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Development of novel pharmaceutical forms for oral administration of bioactive agents

Tese de doutoramento em Ciências Farmacêuticas com especialidade em Tecnologia Farmacêutica, orientada por Professor Doutor Sérgio Simões e Professor Doutor Jorge Coelho e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Development of novel pharmaceutical forms for oral administration of bioactive agents

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“Logic will get you from A to B. Imagination will take you everywhere.”

Albert Einstein **(1879-1955)**

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Abbreviations

ANOVA - Analysis of variance

ATR-FTIR - Attenuated Total Reflection Fourier Transform Infrared Spectroscopy

CDER - Centre for Drug Evaluation and Research

DD – Drug Delivery

DMTA - Dynamic Mechanical Thermal Analysis

DSC - Differential Thermogravimetric Analysis

DoE - Design of Experiments

DS – drug substance

DSC - Differential Scanning Calorimetry

Dt - Disintegration time

Et - Young's modulus

E' - Elastic modulus

E'' - Loss modulus

FDA - Food and Drug Administration

FTIR - Fourier Transform Infrared Spectroscopy

HPC Hydroxypropyl cellulose

HPMC - Hydropropyl Methylcellulose, Hypromellose

HME – Hot Melt Extursion

IR – Infrared

QbD – Quality by Design

MDX- Maltodextrin

MAG – monoammonium glycyrrhizinate

NaCMC – carboxymethylcellulose sodium

ODF – Orodispersible Films

OTC - Over-the-counter

PEG - Polyethylene Glycol

PD – Parkinson Disease

Ph.Eur. - European Pharmacopoeia

PG – propylene glycol, 1,2 - propanediol

PVA – Polyvinyl alcohol

PVAc – Polivinyl acetate

PCA – Principal Component Analysis

PLS – Partial Least Square

Rwc - Residual Water Content (H_2O)

RH - Relative Humidity

TGA - Thermogravimetric Analysis

Tan δ – Damping

TEC – triethyl citrate

Tg - Glass Transition Temperature

T_{onset} - Extrapolated Tonset Temperature

Tm – Melting temperature

USP – United States Pharmacopeia

α - Thermal Transition

β - Thermal Transition

γ - Thermal Transition

εB - Elongation

σB - Tensile stress at break

List of Publications

Patent Application

Borges, AF, Silva, BMA, Silva, C, Coelho, JFJ, Simões, S. Oral dispersible films, in: Bluepharma (Ed.), US20150038594 A1, 2015.

Papers published from the research work presented in this thesis

Borges, AF, Silva, C, Coelho, JFJ, Simões, S (2015). Oral films: Current status and future perspectives: I — Galenical development and quality attributes. Journal of Controlled Release, 206: 1-19.

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Papers published from the collaboration in other projects during the PhD programme

Silva, BMA, Borges, AF, Silva, C, Coelho, JFJ, Simões, S (2015). Mucoadhesive oral films: The potential for unmet needs. International Journal of Pharmaceutics, 494: 537-551.

Contributions to meetings

Poster presentation

Ana Borges, Cláudia Silva, Jorge F.J. Coelho, and Sérgio Simões, Characterization of commercially available oral dispersible films (ODFs), 4th EuPfi Conference, Formulating Better for Children, Prague 2012

Short paper acceptance, entitled Orodispersible films: a deeper sight, to participate in the PBP World Meeting: 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 31st March to 3rd April 2014, Lisbon, Portugal

Short paper acceptance, entitled Oral films: adhesive properties, to participate in the PBP World Meeting: 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 31st March to 3rd April 2014, Lisbon, Portugal

Ana Borges, Filipa Alves, Cláudia Silva, Jorge F.J. Coelho, and Sérgio Simões, Orodispersible films (ODFs): understand it, develop it, 6th EuPfi Conference, Formulating Better for Children, Athens 2014

Summary / Abstract

"Films" or "Oral films" in the US Pharmacopeia monograph are simply defined as single or multi-layer thin sheets with or without drug substance (DS) to be placed in oral cavity. In turn, the European Pharmacopeia adds it as innovative and new dosage form. The oral films are generally prepared by solvent-casting or extrusion, being designed for fast or delayed disintegration and may allow gastrointestinal or mucosal absorption. These differences can be achieved through the modification of the base formulation. This justifies the growing interest of many companies in the development of this dosage form in a perspective of a versatile drug delivery technology. There are also many advantages of this recent and convenient dosage form that also contributed for its rapid growth in the drug delivery market. Also, the clear success of several companies in the field roused the interest of exploring and developing our own conception and technological platform.

An extensive revision of the literature was initially performed in order to gather information about this recent dosage form that allowed the further development of a new and versatile oral film technological platform. This information has been summarized and critically exposed in an extensive literature review divided in two different parts, which covers areas ranging from oral film development appearance to their growth and sustainability on the market.

The output of this broad literature examination led to some considerations and orientations in the experimental part of the thesis. Marketed oral films were deeply analysed and characterized to develop experimental knowledge and suitable quality and process parameters. This work was based on specific statistical tools, as Design of Experiments platforms and Chemometrics analysis. Simultaneously, a wide polymeric screening was performed and 3 new technological platforms were developed, but only the most promising was fully optimized. Once more, this was based on particular tools and systematic approaches that allowed controlling and improving the quality of the product, as Quality by Design concept. This quality and regulatory trend associated with the novelty, particular processing and multicomponent composition unleashed the need of establishing development guidance. Therefore, a quality target product profile (QTPP) was delineated and critical quality attributes (CQAs) stablished to further identify appropriate critical process parameters (CPPs) to function as criterion in new oral film formulations development.

The majority of the fast disintegrating oral films for, commonly designated by orodispersible films (ODFs) are generally based on hydrophilic polymers. This characteristic is usually associated with lower stability, undesirable texture and appearance, especially when exposed to ordinary environment conditions. Considering this aspect and the intellectual property landscape, more stable and robust oral films, were explored, screened and developed. Consequently, oral films based on hydrophobic polymers with a fast disintegration were obtained, which led to a patent application grounded by the polymer nature differentiation, novelty and outcoming advantages.

Finally, two different DS (Pramipexole and ND drug) were incorporated in the developed and optimized ODF, and a small scale-up was performed. Almost 90% of individuals with Parkinson Disease (PD) and more than 33% of Neurodegenerative Disease (ND) patients may develop or already suffer from dysphagia. Pramipexole ODF and ND drug ODF with hydrophobic polymeric matrices, including PVAc, polyvinyl alcohol, triethyl citrate and sodium carboximethylcellulose were developed. The ND drug ODF development was further performed in a larger scale and following Good Manufacturing Practices (GMP) to obtain enough samples to delineate a suitable stability study and lately a bioavailability comparison between ND drug ODF / ND drug capsules (reference product). This approach would function as a proof-of-concept for later scale-up studies. Additionally, research and development challenges and the main issues of the slight scale transposition (manufacturing process and liquid mixture processability) were reported and analysed in a short revision, gathering experimental experience with focused literature examination.

In this thesis, several ODFs were developed and characterized, but importantly some critical knowledge and innovation was generated. For instance, was shown that it is possible to develop ODFs based on hydrophobic polymers without compromising the fast disintegration, breaking an important paradigm in the ODF research field. It was also demonstrated that different characterization techniques and alternative methods of analysis may be very helpful in oral films' development. Another important goal was the conceptual development of a Pramipexole ODF and a relatively stable ND drug ODF that materialize an unmet need of PD and ND therapy, mostly associated to swallowing issues of the drug dosage forms available in the market.

Key words

Oral Films; Orodispersable films; Solvent casting; Quality by Design; Design of Experiments; Chemometrics; Hydrophobic polymers;

Resumo

A forma farmacêutica Película (do inglês "Films") é definida genericamente nas Farmacopeias como uma fina folha composta por uma ou várias camadas com ou sem fármaco, que se destina a ser colocado na cavidade oral. Estas películas são geralmente preparadas por técnicas como *solvent-casting* ou extrusão, podendo ser preparadas com o objetivo de apresentarem desintegração rápida ou lenta e / ou permitirem uma absorção gastrointestinal ou através mucosa oral do fármaco. Estas diferenças podem ser alcançadas por uma simples modificação da composição da formulação base. Esta versatilidade associada a outras vantagens conhecidas como a portabilidade e facilidade de administração justificam o elevado interesse de muitas empresas no desenvolvimento desta forma farmacêutica. Foram estes os motivos que conduziram ao interesse em explorar o conhecimento em torno das películas orodispersíveis.

Inicialmente, foi efetuada uma revisão bibliográfica aprofundada de forma a reunir informação que permitisse o desenvolvimento de uma Película nova e inovadora. Esta informação foi sumariada e criticamente discutida num artigo de revisão dividido em duas partes, descortinando-se desde o seu desenvolvimento primordial até ao seu crescimento e sustentabilidade de mercado.

Esta extensa avaliação conduziu e confluiu para importantes orientações do trabalho experimental. Películas disponíveis comercialmente foram analisadas e caracterizadas para desenvolver conhecimento experimental e parâmetros adequados de processo e qualidade do produto. Este trabalho teve como base ferramentas estatísticas específicas como Desenho de Experiências e Quimiometria. Paralelamente, foi efetuada uma triagem a inúmeros polímeros e 3 novas películas foram desenvolvidas. Mas apenas uma, a que apresentou resultados mais promissores, foi optimizada. Esta optimização foi efetuada com base em instrumentos e abordagens sistemáticas que permitissem o controlo e melhoramento da qualidade do produto, como o conceito *Quality by Design*). Esta tendência regulamentar e de qualidade associada à novidade, processo de fabrico peculiar e composição complexa, desencadeou a necessidade de estabelecer linhas de orientação ou directrizes para o seu desenvolvimento. Assim, o perfil de qualidade do produto alvo foi delineado e os atributos críticos de qualidade estabelecidos para poder definir os parâmetros críticos de processo e servirem como critério de qualidade e aceitação no desenvolvimento de novas películas.

A maioria das películas com rápida desintegração, normalmente designadas por películas orodispersíveis (do inglês "Orodispersible Films") são constituídas por polímeros hidrofílicos. Esta característica costuma estar associada a baixa estabilidade e originar texturas e aparências pouco apelativas e indesejáveis, especialmente quando expostos às condições ambientais. Assim, e considerando o panorama de propriedade intelectual existente na área, películas mais estáveis e robustas foram selecionadas e preparadas. Consequentemente, películas orodispersíveis compostas por polímeros hidrofóbicos foram desenvolvidas, contribuindo para uma aplicação de patente, baseada na novidade dos polímeros utilizados e como solução alternativa para colmatar necessidades tecnológicas e terapêuticas.

Finalmente, 2 fármacos diferentes foram incorporados na película orosdispersível desenvolvida e optimizada, e uma pequena transposição de escala foi também efetuada. Aproximadamente 90% de Doentes de Parkinson (DP) e cerca de 33% de doentes com *Doença Neurodegenerativa (DN)* apresentam ou irão desenvolver disfagia (problemas de deglutição). As películas orodispersíveis desenvolvidas, uma com Pramipexole (tratamento na DP) e outra com fármaco para tratamento de DN, são constituídas por uma matriz hidrofóbica, incluindo acetato de polivinilo, alcóol polivinilico, trietilcitrato e caraboximetilcelulose sódica. A película orodispersível para tratamento de DN foi ainda preparada numa escala ligeiramente superior de acordo com as Boas Práticas de Fabrico, de forma a obter amostras suficientes para delinear um estudo de estabilidade adequado e posteriormente efectuar um estudo de biodisponibilidade comparativa entre películas orodispersíveis e as cápsulas de fármaco para DN disponíveis no mercado (produto de referência). Esta abordagem servirá essencialmente como prova de conceito para testes posteriores de transposição de escala para um nível comercial. Em termo de conclusão, foi ainda elaborada uma pequena revisão que foca os desafios técnicos encontrados durante o processo de investigação e desenvolvimento e transposição de escala; a qual reúne informação da experiência prática, suportada com consulta bibliográfica, sugerindo igualmente possíveis alternativas e soluções para os problemas apontados.

Esta tese inclui o desenvolvimento e caracterização de inúmeras películas orodispersíveis, mas permitiu também gerar conhecimento relevante e inovação. Foi demonstrado que é possível desenvolver películas orodispersíveis constituídas essencialmente por uma matriz hidrofóbica sem comprometer a sua rápida desintegração, destronando um forte paradigma desta área de investigação. Foram ainda elucidadas e sugeridas diferentes técnicas de caracterização e métodos de análise alternativos que podem ser úteis no desenvolvimento

desta forma farmacêutica. Para além disso, foram ainda desenvolvidas películas orodispersíveis de Pramipexole e películas orodispersíveis para tratamento de DN que poderão vir a colmatar as necessidades dos doentes com DP e DN, maioritariamente associadas a problemas de deglutição das formas farmacêuticas atualmente disponíveis.

Palavras Chave

Películas; Películas orodispersíveis; Solvent casting; Quality by Design; Desenho de Experiências; Quimiometria; Polímeros Hidrofóbicos;

Aims of the thesis and motivation

Drug delivery (DD) is a fast growing and highly dynamic segment in the pharmaceutical and biotechnology industry. Pharmaceutical companies are continuously pursuing innovative dosage forms due to the fact that DD technologies are a strategic tool for expanding markets and indications, contributing for extending product life-cycles, generating newer market opportunities and increase the competitive edge and product differentiation. Formulation development is important not only for new chemical entities but also for the improvement of the DD of existing drugs, aiming to improve pharmacoeconomics of drugs (e.g. reducing adverse effects, improving therapy, safety, efficacy, convenience and compliance). Additionally, the oral route administration remains the most preferred by the general population, representing the larger market slice. Therefore, the main goal of this project was the development of a novel and versatile oral fast-dissolving system; namely an oral film drug delivery system designed to dissolve in the mouth within a few seconds after administration. In addition, this development would generate valuable intellectual property to be patentable and allow grant of marketing exclusivity.

The specific aims of the project were:

- To select the most appropriate excipients / ingredients for formulating orodispersible films (ODFs) with the following properties: fast disintegration, high stability, transportability, ease of handling and administration, no water necessary for administration, accuracy of dosage and a pleasant taste.
- To develop a basic understanding of the interplay between the ODFs' components and processing conditions on the final product performance (critical quality attributes, CQAs): physical and mechanical properties, content uniformity, stability, disintegration and dissolution.
- To develop and implement effective and efficient manufacturing technology, with special concern to critical process parameters (CPPs).
- To assure consistency of the manufacturing processes through the: identification and quantification of critical process parameters; characterization of variability; definition of design space; understanding and control over the formulation and manufacturing variables.
- Develop in-house expertise and process know-how of a novel drug delivery technology.

The importance of innovation and new products conception has been increasing in recent years, and the need to generate new technologies is the main core for the business growth.

Outline of the thesis

The present thesis is based on four main parts:

- Introduction to the Oral Films concept – Chapter I
- Oral Films Characterization and Critical Quality attributes outline - Chapter II
- Hydrophobic polymers for oral films: Development and Optimization of novel formulations– Chapter III
- Product formulation overview and development of an Orodispersible Film (ODF) with a Neurodegenerative Disorder drug – Chapter IV

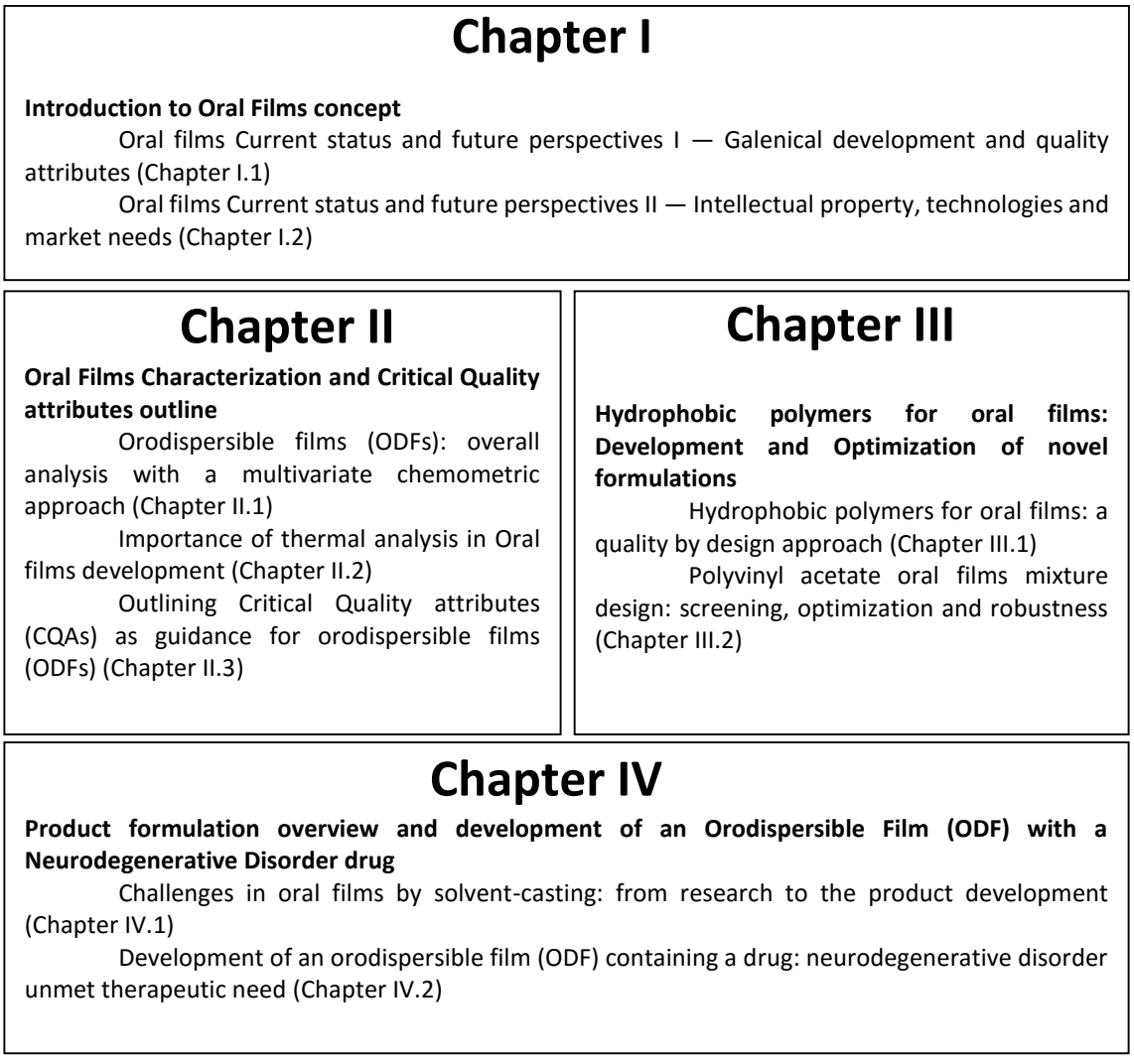

Figure 1 - Overview: outline of thesis.

Oral films are basically a complex polymeric matrix, usually in a stamp shape, which may be used efficiently as drug release platforms. Oral films are relatively recent dosage forms, especially in the pharmaceutical market, in which the first Rx product was only introduced in 2010. Although the recent inclusion of this dosage form in the European Pharmacopeia some research work has been done in the field during the last years.

Chapter I was dedicated to an exhaustive literature revision with an overall examination of the main points of oral film development through their growth and sustainability on the market. This chapter is divided in two different parts: Chapter I.1 and I.2. The first part is dedicated to the galenical development and quality attributes of the oral films (Chapter I.1), while the second part is focused on the main technological platforms developed, intellectual property and market outlook (Chapter I.2).

In Chapter I.1 we may find important information to start the development of a new oral film technological platform. Briefly, oral films are composed by complex polymeric matrices with several components but, generally based on hydrophilic polymers. Both natural (e.g. modified celluloses, modified starches) and synthetic polymers (e.g. polyvinyl alcohol, polyvinylpyrrolidone) are used; and their inherent characteristics (e.g. molecular weight (Mw), degree of substituents), proportions and processing particularities are optimized in order to achieve the desired final product properties. So, a basic understanding of polymers chemistry properties and type are critical for a successful formulation development and quality control. Additional excipients may be added in an attempt to design a suitable product, fitting the quality target product profile (QTTP) that may depend on the drug substance and therapeutic indication. These substances include plasticizers, sweeteners, flavours, colourants, stabilizers, fillers, saliva stimulating agents, buffer systems and others. Although there are several works dedicated to the subject, much work still needs to be done related with the definition of suitable methods for the oral films characterization, quality control and oral films specifications. Therefore, this substantial lack of guidance had lead during the past few years to intensive and somehow scattered work and methods development, always in attempt to hamper the flaw. The two main techniques used to prepare oral films are solvent casting and hot melt extrusion, but in the past few years some developments and innovative techniques emerged, such as casting and extrusion variants and more inventive methods, such as rolling and printing techniques. Chapter I.1 also discriminates oral films evaluation and characterization procedures developed along the years. These may include techniques appropriated for formulation research and development, such as morphological characterization (scanning electron microscopy, near-

infrared chemical imaging) as well as product performance techniques (tensile strength, based on DIN EN ISO 527 or puncture tests; disintegration by thermomechanical analysis, contact angle measurement, petri-dish method; and dissolution profile, through fiber-optic sensor, USP apparatus V, or common and adapted dissolution apparatus).

Chapter I.2 is more centered in the marketing outlook and future prospective. The continuous growing number of patent applications highlights the high competitiveness and fast-evolution of oral films development. More than 132 patent families have been identified and at least 30 companies/institutions are developing these technological platforms. The main players in this field are MonoSol Rx, Kyukyu Pharmaceuticals Co.LTD, LTS Lohmann Therapy-Systems AG, Labtec Pharma SA and Hexal AG. Composition patents are the larger slice in the overall patents filled, claiming the technology composition but essentially the film-forming polymer(s), crucial for the matrix formation. The most patented polymers are polysaccharides, including starch, cellulose and its derivatives. Process patents have also some relevance, but only a few are restricted to a specific drug, therapy or method of use. Generally, the referred top player companies follow a similar business pattern: an innovative and versatile technological platform is developed (e.g. oral film placebo) and several drug candidates are evaluated and considered to be incorporated in oral film. Additionally, partnerships establishment between oral film developers/manufacturers and other pharmaceutical companies researching new chemical entities, developing novel uses for existing drugs (repurposing) or companies looking for innovative formulations for their drugs (life-cycle management) is common. The most prominent oral film technological platforms are the Monosol Pharmfilm®, with nine products on the market, Labtec / APR Rapidfilm®, with four marketed oral films, and KyuKyu Rapid Dissolving Film technology, with at least six available films.

In order to gain some practical experience to be able to develop new and inventive oral films' formulations, marketed oral films were fully analysed and characterized and these results are included in Chapter II. Therefore, a basic understanding of the interplay between the main components of the formulation, possible interactions between them and their effect in oral films properties, was achieved through the study of two marketed films (Chapter II.1 and II.2). This selection was based on their composition, the Listerine Pocket Packs™ composed by Pullulan, described as the most suitable film-forming polymer for oral films technology, and GAS-X ThinStrips®, composed by more than 50% (%w/w) of drug substance (Simethicone). These oral films were evaluated regarding their residual water content (Rwc), disintegration time (Dt), chemical, thermal and mechanical properties. Reconstituted

formulations of both were also prepared based on Design of Experiments (DoE) software. The data was analysed using statistical DoE specific platforms and other multivariate analyses based on Chemometrics fundamentals (Principal component analysis (PCA) and Partial Least Squares regression (PLS)). This type of analysis was very useful to establish a rational understanding that would be harder to find using other common approaches. The PCA allowed a graphical plot differentiation between FTIR spectra differences: all the reconstituted formulations are very different from each other and particularly dissimilar from the commercial formulation. In turn, by PLS analysis the effect of each excipient in the final polymer matrix was highlighted: pullulan, the sweeteners, propylene glycol and menthol have a high influence in the mechanical and thermal properties, whereas the cellulose Mw affects mainly the Rwc and Dt, and simethicone may greatly affect the oral films thermal properties (Chapter II.1).

An extensive thermo-mechanical characterization of GAS-X® and Listerine® marketed films and in-house prepared formulations were performed by TGA, DSC and DMTA. Briefly, GAS-X® films are thermally more stable than Listerine®, evidenced in TGA profiles, whereas DSC and DMTA analyses add complementary information about polymer chains nature and their influence on oral films performance. There is a high impact of the composition on the thermal properties of the oral films, underlining the importance of thermal techniques in the development of this innovative oral dosage. In fact, it was verified and showed that a deep understanding of the mechanical and thermal properties of oral films is very important to develop fundamental knowledge that may be critical to better formulate these polymeric matrices platforms (Chapter II.2).

Allied to these techniques, the statistical tools employed in this study enabled the development of extensive knowledge about the system and the identification of the influence of each excipient in the final product properties as well as the identification of the major interactions in the polymeric matrix. These tools and concepts were recently introduced in the pharmaceutical field by the quality by design (QbD) approach. This is a systematic approach that allows building and improving the quality of the product. It is supported by simple quality concepts as the QTPP that describes the desired product performance by stablishing critical quality attributes (CQAs) and identifying critical process parameters (CPPs). Therefore, another approach was to reach essential information about a clear definition of oral films CQAs, through the analysis of several suitable marketed films. Despite oral films' complexity it was possible to outline suitable acceptance criteria for the

identified CQAs that can work as a reference in the development of new oral film formulations (Chapter II.3).

Chapter III is focused in the preparation of a novel and versatile oral films technological platform. Generally, available oral films are in their majority based on hydrophilic polymers. Additionally these are commonly design for fast oral disintegration, receiving the common designation of orodispersible films (ODFs). However, the ODF hydrophilic nature is frequently related with lower stability, undesirable texture (sticky) and appearance, particularly after exposed to ordinary environments. Therefore in an attempt to circumvent this limitation and considering the intellectual property survey, innovative ODFs were studied and developed. Subsequently, ODFs with a hydrophobic core but with fast disintegration were prepared: polyvinyl acetate (PVAc), methacrylate copolymer and shellac based films (Chapter III.1). The QbD approach was applied to screen the three different formulations based on the previous CQAs established and selection of appropriate CPPs (percentage of the different excipients and plasticizer type). This study lead to a patent application entitled “Orodispersible films”. Briefly, three different formulations generically composed by a hydrophobic polymer (PVAc, methacrylate copolymer and shellac), a stabilizer (polyvinylalcohol (PVA) or hydroxypropylcellulose (HPMC)), a disintegrant (carboxymethylcellulose sodium (NaCMC)) and a plasticizer were developed. These formulations (hydrophobic film-forming polymer) allowed obtaining ODFs with suitable mechanical properties and higher resistance to moisture conditions without compromising the rapid disintegration time. Additionally, with this study it was also found that the same component may behave differently depending on the system: NaCMC and PVA affect differently the mechanical properties of different matrices (Chapter III.1).

The second approach of the formulation development was to prepare an optimized ODF, with suitable performance and capable of incorporating a DS (Chapter III.2). The PVAc formulation demonstrated during the preliminary tests more promising results: easiness to manufacture and best product performance. Therefore, this formulation was selected to further optimization based on a QbD approach. In summary, three different screening / optimization studies were completed: evaluation of the plasticizer type influence, optimization study to obtain a pleasant and moisture resistant polymeric matrix and determination of the capability to incorporate a drug substance (Pramipexole). The formulations were characterized regarding their mechanical properties, residual water content, disintegration time, contact angle, organoleptic and appearance characteristics in attempt to find a suitable ODF that meets the CQAs defined, varying the same CPPs of the

formulation screening (percentage of the different excipients and plasticizer type). It was possible to find a binary taste-masking system, based on a flavour and a sweetener, which allowed obtaining pleasant ODFs. Additionally, it was shown that the incorporation of a drug substance as well as the plasticization effect may be critical for the overall performance and stability of the ODF, and depends on their structure and concentration. An ODF with suitable characteristics, very fast oral disintegration, easy to handle and manufacture, pleasant taste and appearance and likely to become appropriate for drug delivery, was developed (Chapter III.2).

The previous work gave important evidences on the viability of the new technological platform. Afterwards, this was used to incorporate other drug substances directed to therapies with an urgent need of easy to swallow formulations (Chapter IV).

Neurodegenerative Disorder (ND) is a degenerative neurologic disorder, in which more than 33% of the patients have chewing or swallowing problems, and some may also develop permanent dysphagia. Currently, there is no cure for this ND only disease-modifying treatments. The first-line disease modifying drugs include interferons, glatiramer acetate and a ND drug as the first oral treatment alternative. ND drug is an oral sphingosine phosphate receptor modulator marketed in the form of a capsule, which may became a problem in an advanced disease course. Hence, a ND drug ODF may become an alternative to the conventional dosage form available and improve patients' compliance. ND drug ODF with a hydrophobic polymeric matrix, including PVAc, PVA, triethyl citrate and NaCMC was prepared. Exhaustive preliminary tests were performed in an attempt to stabilize the ND drug in the polymeric structure due to its high reactivity and instability. The process to prepare the ODFs was found to deeply influence the DS stability and a structured and organized procedure needed to be followed. A suitable ODF for fast oral disintegration was developed and is likely to become an appropriate and convenient option for oral ND therapy, avoiding the swallowing issues associated with the disease (Chapter IV.1).

Finally, the second part of Chapter IV, reports the main problems found in the slight scale-up used to prepare sufficient samples for suitable stability study and a proof of concept clinical trial. This small scale transposition was performed according to the Good Manufacturing Practices (GMP). Critical issues involving solvent casting (manufacturing process) and liquid mixture processability transposition were identified and surpassed during the process. These challenges were reported and analysed in a short revision that gathered the practical and experimental experience developed with a focus on literature examination (Chapter IV.2). From the industry perspective, the concern of having research

and development equipment similar to the industrial production facilitates the scale transposition. Furthermore, QbD also arises as a conception that favoured the scale-up process by the overall system knowledge. A better understanding and advances in quality, scale up issues, and regulations is important to design and direct efforts for new products development. Firstly, it is important to define the compositional and process variables, the CPPs, which may influence and interfere with the process and product attributes, the CQAs. It is also important to have defined assays that may allow us to evaluate these parameters, namely in vitro tests. These are the main factors that if correctly applied proved to lead to an efficient and successful oral films scale transposition.

Chapter I

Introduction to the Oral Films concept

This chapter is an overview of the state of the art with regard to Oral Films. This literature review points out the different types of Oral Films, describes and explores the oral film technology from its main component to the new and possible market applications, highlighting all the critical and important points of its development. This revision intends to highlight the current status in the Oral films field but simultaneously reveal the main flaws and indicating some suggestions and possible future prospections.

Chapter I.1

Oral films: Current status and future perspectives

I — Galenical development and quality attributes

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1. Introduction

A thin film that readily dissolves in the oral cavity is commonly referred as orodispersible film by the European Medicines Agency (EMA) (Hoffmann et al., 2011) or simply soluble film by the FDA (Food and Drug Administration, 2013). Although, oral films initially appeared as innovative breath freshening formulations, it rapidly evolved to give response to different market needs, namely an easy-to-carry and easy-to-swallow drug delivery system.

The oral films are essentially complex polymeric matrices that may be used efficiently as drug release platforms. These polymeric matrices may be composed by several components in order to achieve well-designed drug-delivery platforms, but usually hydrophilic polymers are its main core. The polymers early entered into the pharmaceutical and biomedical industries as essential components of the formulations and their range of applicability easily spread to several areas, from packaging material to the most sophisticated drug delivery systems and devices. The basic understanding of the role of polymers as excipients, meaning as ingredients in drug products, is critical for formulation development and quality control. Additionally, the knowledge of polymers' basic concepts, as chemistry, properties and types may be critical to develop new or improve conventional drug delivery systems.

Both natural and synthetic polymers can be used in orodispersible dosage forms. The oral films are basically a polymeric matrix which may vary on its composition in order to achieve the desired final product properties. There are several characteristics, such as mucoadhesiveness, disintegration time, % of drug load, mechanical / handling properties (among others) which may be fine-tuned by adjusting the type, amount or grade of the polymers. Additionally, other components may be added in order design the final product according to the target product profile, depending on the drug substance and therapeutic indication. Some of these substances include plasticizers, sweeteners, flavours, colourants, stabilizers, fillers, saliva stimulating agents, buffer systems and others.

Oral films emerged as a very promising and prominent pharmaceutical dosage form in a field subdued to tablets and capsules. The state of the art was also diffused and restrained about the matter until Dixit et al. in 2009 pledge us with a comprehensive overview of the subject, which may probably functioned as a catalyst for several research works. Currently, several original works and patents can be found in literature, but considerable efforts still need to be carried out to optimize the performance of the films (Cilurzo et al., 2008; Dinge and Nagarsenker, 2008; Zerbe et al., 2003). Regarding the pharmaceutical field, there is still a

considerable lack of guidance for the manufacture, characterization and quality control of the oral films.

This review highlights the essential points of oral films development from their appearance through their market growth and formulation key points. To facilitate the readers understanding, the review is divided in two distinct parts. The first part is focused in the galenical development and quality attributes of the oral films whereas the second part covers technological platforms, Intellectual Property protection and a market outlook.

2. Miscellaneous terms

Thin-film, oral film, wafer, oral strip, orodispersible film, oral thin film, oral soluble film, dissofilms, buccal soluble film, mucoadhesive film, buccal film, transmucosal film, are some of the innumerous terms that can be found in literature. Although, the terms seem to be easily differentiated, their meaning can sometimes be misinterpreted and misunderstood.

The oral films were recently introduced in the “Oromucosal Preparations” monograph of the European Pharmacopeia (Ph. Eur. 7.4) with the subchapter “Orodispersible films” whereas the mucoadhesive buccal films are included in the “Mucoadhesive preparations” (Hoffmann et al., 2011). These terms and designations should be carefully read and interpreted to avoid possible misinterpretations.

Orodispersible films should not be confused with buccal films, which should not also be narrowed to the mucoadhesive films designation.

3. Orodispersible films

Non-adhesive fast dissolving films are normally composed by low molecular weight (Mw) (approx. between 1.000 to 9.000 Da) hydrophilic polymers. The majority of the orodispersible films are not necessarily designed to be mucoadhesive, but they may exhibit some degree of mucoadhesiveness, due to the inherent characteristics of the polymers used. This mucoadhesion may also vary depending on the chemical properties and Mw of the film-forming polymer used, as discussed later in this review. However, the Mw of the most common polymers used for this formulation type is usually below 200,000 Da (Myers and Dadey, 2014). Additionally, these films are intended to exhibit a fast disintegration in the

oral cavity, be swallowed and absorbed to the systemic circulation in the gastro-intestinal tract. Actually, this is somehow explicit in both official definitions: “single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly” (Ph. Eur. 7.4, “Orodispersible films”) and a “thin layer or coating which is susceptible to being dissolved when in contact with a liquid” (FDA, dosage form) (Food and Drug Administration, 2013; Hoffmann et al., 2011). Clearly, the high exposition of the drug substance in the oral cavity may influence its absorption through the oral mucosa, but certainly this fact is not the main purpose of the fast dissolving oral films. Indeed, this aspect may lead to another controversial issue, the urgent need of new regulations for oral films, aiming to establish adequately the product differentiation and to eliminate the idea that oral films compete directly with the generics. Additionally, according with the previous, being develop as a generic would not be an easy task due to the interference in the Bioavailability and Bioequivalence Studies (BDBE) related with a possible super-bioavailability and consequently, the failure of these tests. In this case the higher bioavailability may be related with the fast availability of the drug and consequently some oral adsorption. However, if the reference product is already an orodispersible formulation, as the orodispersible tablets, this issue is easily surpassed, being the recent marketed generic oral films good examples.

4. Buccal films

The buccal films are intended to deliver drug substances through the oral mucosa. This goal might be more complex than it seems, since a higher residence time in mouth is far from being the only determining factor. The oral mucosa drug saturation should also be considered, and the one-way absorption should be kept in mind to avoid minimize inter and intra –individual variability. Consequently, multilayer films also appear as a new designation for the buccal films. The advantages of this drug delivery system are very significant. The oral cavity presents many advantages to drug delivery beyond its good acceptably by the patients. The oral mucosa, generally divided in sublingual, gingival, buccal and soft palatal mucosa, is relatively permeable allowing systemic transmucosal drug delivery (Figure 2). For instance drugs that can be rapidly absorbed via buccal delivery do not pass the gastrointestinal tract, which may subject the drug to degradation from stomach acid, bile and other first pass metabolism. As a result, these thin films have the potential to fasten the drug onset of action, to lower the drug strength and enhance the efficacy and safety profile of some drugs. Curiously, the European and USA definition is more consensual regarding

these pharmaceutical dosage form - buccal films. In the European Pharmacopeia they are included in the mucoadhesive preparations, referred as buccal films and defined as “single- or multilayer sheets that adhere to the buccal mucosa and may dissolve” (Figure 3). FDA does not have so clear definition or designation for these films, but buccal soluble film or buccal film, may be acceptable designations if Onsolis® submission is taken as an example.

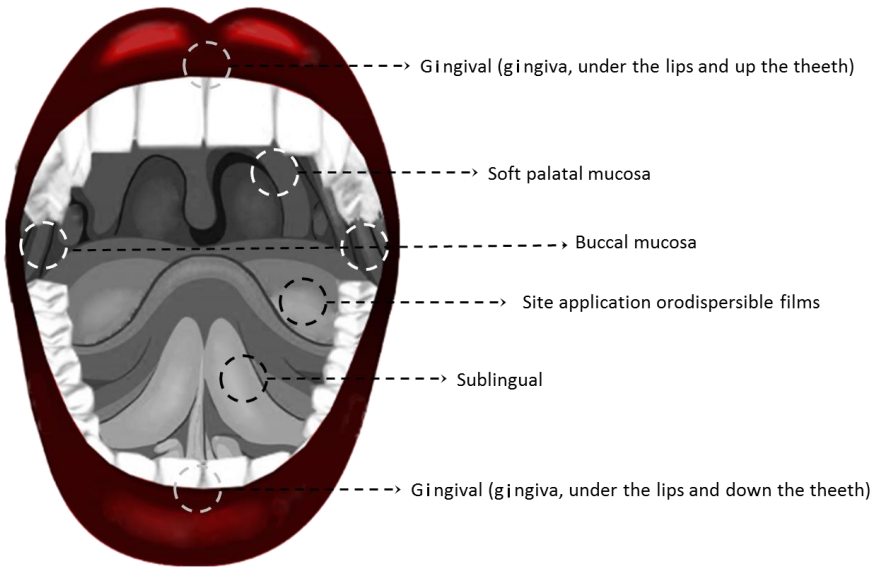

Figure 2 - Different local application sites of the oral films. Depending on the type of film the site of application may vary.

Finally, it is important to consider that additional designations may be used to specify and differentiate the oral film platform technology developed by each company. For example there are also references of some double- or multi- layer orodispersible films and sublingual orodispersible films (Breitenbach et al., 2014; Myers and Dadey, 2014).

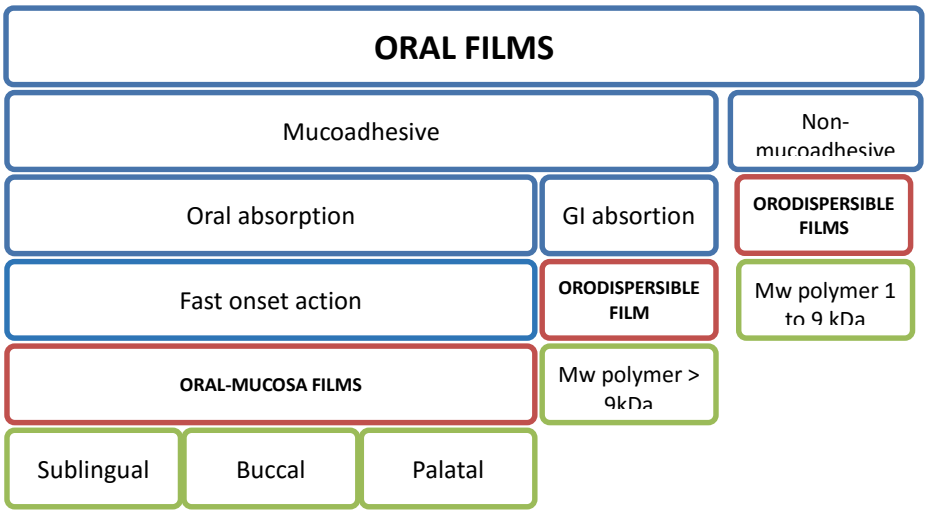

Figure 3 - Simplified scheme with the different terminologies.

5. Why oral films? Particular features for patients and companies

The design of an oral formulation is generally based on two critical factors, drug therapy and the target population. However, the choice of the type of pharmaceutical dosage form may become very difficult when specific target groups include very young children, from birth to 8 - 10 years of age, and geriatric population. Regarding the paediatric segment the major challenge involves the development of a specific type of dosage form suitable for children of all ages. Additionally, for both population groups the size of the dosage form can also be a challenge, essentially due to swallowing issues. The swallowing process involves synchronized actions of several nerves and muscles. It is assumed that a safe swallowing is an ability developed since the 12 years-old (Stegemann et al., 2012; Zajicek et al., 2013). Generally, the swallowing function underlay an aging process, then, some malfunctions may be age-related, normally called as presbyphagia, but also may be due to pathological conditions, usually referred as dysphagia (Stegemann et al., 2012). These conditions are directly related with patients' drug therapy adherence which had led to the huge concern in the development of patient-centered formulations. Therefore, liquid or orally disintegrating dosage forms have been the most preferred and exploited for these population segments. Hence, the oral films appeared as a suitable alternative to patients with swallowing difficulties and also as a more suitable and convenient dosage form when compared to the conventional oral dosage forms.

5.1. Advantages for patients

In fact, orodispersible films promote patient compliance due to its appellative form and inherent ease administration (Dixit and Puthli, 2009). These overall characteristics are especially important for young and elderly patients when proper and complete dosing can be difficult. Additionally, the drug delivery for these groups sometimes needs to be individualized / patient-tailored and may require special delivery devices. Nevertheless, this dosage form can also be beneficial for drugs with small therapeutic windows and for those that need precise dose adaptation in phases of initial dose monitoring; allowing the development of tailored therapeutic drug targets that otherwise may not be possible in conventional formulations. Furthermore, the oral films can be useful for bedridden and non-cooperative patients since they are easily administrated and hardly spited out.

5.2. Advantages over other oral dosage forms

There are also other advantages of the oral films when compared with conventional oral delivery forms. The orodispersible films are a fast dissolving dosage form more stable and resistant in comparison to some orodispersible tablets (ODTs), which are fragile and brittle. Oral films tend to be flexible and portable, whereas ODTs demand special package for transportation. On the other hand, liquid dosage forms are considered very flexible and an alternative to overcome swallowing issues but they are usually associated to some limitations. Generally, liquids should be accurately measured by the care-giver and carefully shaken before administration. The amount of volume is also an important consideration since small amounts may lead to inaccurate measures whereas large amounts may contribute to diminish the adherence of the patients. On contrary, oral films enable improved dosing accuracy once every strip is manufactured to contain a precise amount of the drug. Additionally, depending on the package device is also possible to achieve high dose flexibility, as an electronic tape dispenser can be used that allows to dispense individual strips with adjustable doses simply by controlling an electronic system with a display (Wening and Breitkreutz, 2010). As previously referred, oral films are an easy portable dosage form in contrast to the large liquid bottles and measuring devices that are inconvenient to transport. Besides that, it is also important to consider the poor stability of the liquid formulations, especially the aqueous-based mixtures, that in opposition to the majority of the oral films formulations require the addition of several substance to extend their shelf-life (Hoffmann et al., 2011).

5.3. Market advantages

From the market perspective new drug delivery technologies offer the opportunity to extend revenue life cycles for pharmaceutical companies whose drug patent is about to expire and will soon be vulnerable to generic competition. Moreover, the grant of marketing exclusivity to the new dosage form would help to enlarge the revenue. This type of formulation may also be designed to discourage common methods of tampering associated with misuse and abuse of some prescription drugs (IBISWorld, 2015).

Considering oral films as novel dosage form for drugs already in the market, with a different pharmacokinetic profile, the approval process should be a New Drug Application (NDA) 505(b)(2) for FDA approval, or an Abridged Application, Directive 2001/83/EC, for European Marketing Authorization approval. In this case, especially for the USA market clinical studies would be essential for the FDA granting three marketing exclusivity (3-5 years) (Barei et al., 2013; Dixit and Puthli, 2009).

5.4. Clinical advantages

From the clinical point of view, some oral films may improve the oral bioavailability of drugs with extensive first pass metabolism, by promoting the absorption of the drug substance through the oral mucosa reducing the dose necessary to achieve the therapeutic action, which may contribute also to a reduction of the side effects (Dixit and Puthli, 2009). Nevertheless, this absorption route may also be advantageous in drug therapies where a fast onset action is essential.

5.5. Major limitations

The most common limitations of the oral films are related to their instability in environments with high relative humidity, and the small drug dose that can be incorporated, essentially due to its small size, low weight and thin form. However, some companies had managed to develop oral film technology platforms that can incorporate more than 50% of drug substance (DS) per film weight (GAS-X Strips ®). There are also some types of drugs that should not be selected to incorporate in this pharmaceutical form, such as drugs that are unstable at buccal pH and that may irritate the oral mucosa (Dixit and Puthli, 2009).

Another critical issue is taste-masking since the dosage form is in direct contact with the oral mucosa and may remain in the mouth for long periods of time.

6. Polymers in oral films: the key component

Orodispersible films are basically a polymeric matrix which may be composed by one or more polymers with different physicochemical and functional properties. There are several characteristics that may be controlled depending on the type or grade of polymers: mucoadhesiveness, disintegration time, drug loading capacity, mechanical strength, elasticity, handling properties and others.

The selection of the polymer (or mixtures) for the development of oral film matrices is a critical step and may vary taking into account the desired target product profile. Hydrophilic polymers have been extensively studied and tested for this application.

Table 1, presents a summary of the most widely used polymers in the oral films preparation. Some chemical critical aspects that should be taken in consideration during formulation are revised hereinafter.

6.1. Celluloses

Celluloses, namely cellulose derivatives are widely used. Among those, hydroxypropyl methylcellulose (HPMC) is one of the most used. HPMC is a partly O-methylated and O-(2-hydroxypropylated) cellulose which is available in several grades that differ on their Mw and the amount of substituent groups on the anhydroglucose units (Rowe et al., 2009). The average number of methoxyl and hydroxypropyl groups attached to the ring, usually designated by degree of substitution (DS), influences greatly the oral film properties. There are some references that highlight how these structural and chemical differences may contribute to the final product properties, especially concerning the drug substance release and mechanical and thermal properties. Briefly, hydroxypropyl group, -OCH2CH(OH)CH3 is relatively hydrophilic group contributing to the rate of hydration, whereas the methoxyl group is more hydrophobic. Therefore, polymeric matrices with high hydroxypropoxyl / methoxyl ratio may easily establish a gel barrier (Dow, 2006) This characteristic in polymeric film matrices was found important in the dissolution profile and drug substance release. HPMC grades with higher hydroxypropoxyl / methoxyl ratio were found to delay the release

of the DS from the oral film matrix due to the formation of a thick matrix gel upon contact with the dissolution or biologic media (ElMeshad and El Hagrasy, 2011). Regarding the mechanical properties of the polymeric matrices it is described that methoxyl substitution degree along with the HPMC grade intrinsic viscosity has a remarkable influence. In general, HPMC grades with high viscosity and methoxyl content tend to produce more resistant, stiff and extensible polymeric matrices. High viscosity is possibly associated to higher branching and /or higher Mw related with physical entanglement due to longer chains. This phenomenon may increase the input strength required to disrupt the primary chain interactions (higher tensile strength). In turn, higher methoxyl substitution degrees may lead to an anchoring effect on HPMC chains provided by their larger dimensions compared to the original hydroxyl groups that may also contribute to high tensile strength. The Young's modulus seems not to be significantly affected by methoxyl substitution degree. Concerning the thermal characteristics of the HPMC films, the polarity of the polymer chains conferred by the methoxyl content apparently affects the glass transition temperature (Tg). HPMC grades with lower amount of methoxyl groups present lower polarity that contributes to the reduction of the free space between the polymer chains. The increasing proximity of the polymeric chains will strengthen the secondary interactions between them, which increases the energy required for chain mobility (Otoni et al., 2014).

Additionally, the rearrangement of the methoxyl groups during the film formation could also diminish the polymer inter- and intra-chain hydrogen interactions, thereby suppressing possible hydrophilic hydroxypropyl group actions, which may affect the final product characteristics (Gustafsson et al., 1999).

There are several HPMC grades available and as discussed above their selection should not be random, but evaluated according to the desired product profile. Essentially, there are 2 types of HPMC that are widely used in the oral films formulation, which according to Dow Chemicals grade classification are HPMC type K and E. The HPMC type K contains 22% methoxyl, or a methoxyl DS of 1.4, and 8.1% hydroxypropyl, or a hydroxypropyl DS of 0.21, whereas HPMC type E has 29% methoxyl, or a methoxyl DS of 1.9, and 8.9% hydroxypropyl, or a hydroxypropyl DS of 0.23 (Dow, 2002, 2006). The HPMC K is often used as polymeric matrix but mainly for controlled and / or delayed release of the drug substance (ElMeshad and El Hagrasy, 2011; Kumria et al., 2013; Repka et al., 2005; Wen and Park, 2011), whereas HPMC type E is amply described in literature as film-forming polymer. The E3, E5 and E15 are referred, tested and used intensively, essentially due to their low viscosity and optimal Tg for suitable oral film matrices, 160^{o}C, 170^{o}C and 175^{o}C, respectively. The major difference

between these grades are the polymer chain length, which together with the increasing number of their designation is associated with the increase in the HPMC's Mw (e.g. Mw HPMC E3 < Mw HPMC E5< Mw HPMC E15< Mw HPMC 50). It is reported that low concentration's solutions of E3 and E5 may lead to thin, brittle and non-peelable films. These properties can be ameliorated with the increase of these polymers' concentration, but the films are still referred as tacky (Mahesh A, 2010). Therefore, combinations of the different grades are preferred, especially mixtures with higher HPMCs' Mw (Schobel and Vangala, 2010). Mixtures with other polymers are also described. HPMC E15 is found to have suitable film former properties when mixed with synthetic polymers, as polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP). Also, good film former properties can be achieved when HPMC is blended with microcrystalline cellulose and plasticizers, such as PEG 400 and glycerol (Kulkarni AS, 2010). HPMC was also blended with a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate (Eudragit® E PO), contributing to the formation of films with better clarity and flexibility (Sharma R, 2007). On the other hand, HPMC - Maltodextrin blends, with higher Maltodextrins' concentration, allowed to obtain thin, fast-disintegrating, sweeter and tastier films (Kunte and Tandale, 2010).

It is demonstrated that HPMC origins films with optimal properties depending on its concentration and different blends. This fact is probably the reason why different authors are not consensual regarding the most suitable HPMC to obtain thin films with optimal characteristics. Additionally, it was shown that the drug substance may also have an important impact in the final film properties; some found that HPMC E3 was the most suitable grade to the manufacture cetirizine films (Mishra R), whereas others preferred the E5 to prepare triclosan films (Dinge and Nagarsenker, 2008). It is also described that the mechanical properties of the polymeric matrices are greatly affected by the different grades, and generally, the maximum puncture strength increase with Mw, E3 < E5 < E15 < E50 (Dahiya et al., 2009).

Hydroxypropyl Cellulose (HPC) is another cellulose derivative where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming –OCH2CH(OH)CH3 groups (Rowe R, 2009). HPC has been used as film former due to its good properties to origin films with proper mechanical properties (Alanazi et al., 2007; Bunnelle et al., 2005). HPC films have good carrying capacity, reasonable clarity and moderate bioadhesive properties associated with HPC's swelling capacity (Alanazi et al., 2007; Dahiya M, 2009). An evident advantage of the use of this cellulose is the wide range of solubility (Rowe R, 2009), which

allows a flexible selection of the solvent according to the drug solubility (Yasuda et al., 2011). Interestingly, it is reported that when a combination of HPCs (Klucels EF - Mw 80.000, and KlucelX GF - Mw 300.000) is used to replace synthetic polymers (PVA and PVP) or HPMC in a polymer matrix with modified starch (Maltrin M100, Maltrin M180, Maltrin's QD M550, and Maltrin's QD M600 or Pure-Cote B792) the solubility properties of the films tend to improve (Zerbe and Al-Khalil, 2003).

Carboxymethylcellulose (CMC) is another cellulose derivative that in opposition to the previous non-ionic polymers is an anionic linear polysaccharide, produced by reacting cellulose with sodium monochloroacetate under controlled conditions (Baldwin et al., 1994). CMC, also known as cellulose gum, is an important industrial polymer with a wide range of applications, essentially due to its low cost. In the pharmaceutical field it has a prominent value as thickener and it is ideal for applications requiring a fast dissolving base. It is commercially available with a wide DS range, between 0.4 and 1.5. The DS value of CMC has an important impact on the film-forming solutions properties, since higher DS values are directly related with a decrease in the interchain interactions due to the increase substitution of the hydroxyl sites (Baldwin et al., 1994). CMC had proven to be useful for the preparation of optimal polymeric matrices, produces films with excellent clarity and with the ability of carrying a wide range of active components. CMC oral films with optimal characteristics to be used in oral health biotherapy had also been prepared (Saha et al., 2013). In the preparation of buccal mucoadhesive films it was shown that sodium CMC improved the residence time of HPC and sodium alginate films (Nappinnai et al., 2008). It is also reported that CMC has a good compatibility with starch forming single-phase of polymeric matrix films with improved mechanical and barrier properties (Lu et al., 2009; Tongdeesoontorn et al., 2011). However, some authors showed that HPMC based films are tougher, more elastic and bioadhesive in vivo than sodium CMC based films (Peh and Wong, 1999).

6.2. Starch

Among all natural biopolymers, starch was always considered one of the most promising polymers for this application, due to its wide availability, biodegradability and low cost (Mali S, 2010; Xie et al., 2012). However, pure starch films are usually brittle and tacky. Native starch generally contains 75% of amylopectin and 25% of amylose, a combination that for this application is associated with a lack of strength, water resistibility, thermal stability and processability difficulties (Koch K, 2009; Xie et al., 2012). Therefore, to obtain oral film matrices with optimal properties native starch should be blended with other polymers. The process issues are essentially related with the difficulty of dissolving native starch in water, due to its high molecular size and strong hydrogen bonding. In fact, to dissolve starch, low concentrations and high temperatures need to be used, which is not economically favourable. Thus, in order to overcome this disadvantage and also improve the product performance, several starch derivatives have been developed and are currently available on the market. Examples of modified starches applied to oral films are hydrolysed starches, such as Maltodextrins (MDX) (e.g. MALTRIN®, from Grain Processing Corporation), hydroxypropyl starches (e.g. Lycoat ®, from Roquette), pre-gelatinized starches (e.g. INSTANT PURE-COTE® by Grain Processing Corporation (GPC)) and others, such as Pullulan.

In fact, Maltodextrins have been used blended with other polymers to improve the overall properties of the film, as already discussed, but also as sole film forming polymer (Cilurzo et al., 2011; Cilurzo et al., 2010; Cilurzo et al., 2008; Cilurzo et al., 2012). Chemically, MDX is a mixture of polymers that consists in D-glucose units, with a dextrose equivalent (DE) lower than 20, and are prepared by the partial hydrolysis of a food-grade starch (Rowe R, 2009). MDX origins good quality films (Shamekh et al., 2002) with fast disintegration and low dissolution time (<45 seconds) (Cilurzo et al., 2010; Cilurzo et al., 2012). Low DE MDXs offer higher viscosity and better film formation than higher DE MDXs. It is also referred that low DE MDXs present an improvement on flexibility and reduced cracking compared to modified starch-based films (Chapdelaine et al., 2003). In turn, when blended with microcrystalline cellulose (MC) tends to form non-sticky and smooth polymeric matrices (Cilurzo et al., 2008).

Similarly, Lycoat® can also be used as sole film forming polymer with excellent functionality. Although, it is easily dispersed in cold water, it is suggested the treatment at 70^{o}C in order to improve its film forming ability. In addition, by contrast with native starch solutions, Lycoat® cooked solutions can be immediately cooled down, since the gelation and retrogradation would not be probable to happen due to the high stability of the

hydroxypropylated starch molecules (Parissaux X, 2007). Compared with HPMC, hydroxyethyl cellulose and polyvinyl alcohol, Lycoat® showed faster dissolution time, moderate moisture uptake and satisfactory mechanical properties (El-Setouhy and Abd El-Malak, 2010).

The pre-gelatinized starch is a chemically and/or mechanically processed starch, commercially available in fully or partially pre-gelatinized grades. The first is easily soluble in cold water, whereas partial pre-gelatinization produces a starch with soluble (gelatinized) but also insoluble fractions (Cunningham; Rowe et al., 2009). The knowledge of these differences is critical to obtain formulations with the desired disintegration times.

INSTANT PURE-COTE® is a pre-gelatinized starch, marketed by GPC, with good film-forming capabilities. This polymer origins clear, strong and flexible films using a 15 to 20% solution by solvent-casting process (Business Wire, 2010). GPC offers a broad range of modified starches for pharmaceutical applications including also the PURE-COTE® a corn starch specifically modified to produce clear, flexible, fast drying and tasteless oral polymer matrices (Fadden et al., 2006; GPC, 2014; Kulkarni et al., 2006).

Pullulan, is a modified starch composed by glucose units in maltotriose units connected by α(1→4) glycosidic bonds whereas the consecutive maltotriose units are linked by α(1→6) glycosidic bonds. Pullulan have both suitable processing and film-forming properties that turn it into one of the preferred polymers to be used in the preparation of oral polymeric matrices. It is easily soluble in hot or cold water, and forms a clear and viscous solution that origins smooth, transparent and stable films. Pullulan is obtained from a fermentation process of yeast, the Aureobasidium pullulans, thus, its low availability results in a high cost product (Prajapati et al., 2013). Therefore, Pullulan is usually blended with other compatible polymers that are more abundant and less expensive. For example, other modified starches may be used in combination with Pullulan, to decrease the overall cost. In fact, 50 to 80% of Pullulan can be replaced by starch or modified starch without the loss of its required properties as a good film-former (Dixit and Puthli, 2009). Sodium alginate and CMC, can also be used with the same purpose since they are compatible. In fact, the formation of hydrogen bonds between the COO groups of alginate and CMC with the –OH groups of Pullulan may synergistically enhance the material properties of the resulting film (Dahiya M, 2009; Tong Q, 2008). In addition, it is also reported that Pullulan – HPMC blends, with a HPMC content above 50%, a miscible composition is obtained, and the final polymeric matrix presents improved thermal and mechanical properties (Prasad P, 2008).

The mechanical properties of Pullulan films prepared at various temperatures were also studied. Generally, films prepared at low temperatures are stiffer and more flexible than films prepared at higher temperatures that are brittle and do not have a clear plastic deformation. The Pullulan based films usually present a fast disintegration time (Kawahara M, 2003).

6.3. Semi-synthetic, synthetic and others

There are others natural or semi-synthetic polymers that have been tested as polymeric matrices for drug delivery application, such as: rosin and rosin derivatives, gelatin, sodium alginate, pectin and others (Fulzele S, 2002; Galgatte et al., 2013). Gelatin has excellent properties as film former, but the high viscosity during the processing difficult the handling and limits its applicability in films formulations. On the other hand, the pectin usage limitation is more related with the final product characteristics rather than the manufacturing process. Pectin is a natural polymer obtained from citrus fruits and apples, with a good film forming capacity. Pectin based films have optimal capacity to carry drug substances (Galgatte et al., 2013), but tend to dissolve slowly. This is related with pectin's strong mucoadhesive properties, which is not very useful for fast dissolving films. Thus, modified pectins had also been produced and tested to obtain films with fast dissolution rates (Puri and Zielinski, 2007).

The synthetic polymers have been also intensively explored as film-formers, but the majority converge to PVA, PVP (Alanazi et al., 2007) and methacrylate polymers (Kulkarni AS, 2010).

PVA is a water soluble polymer prepared by partial or complete hydrolysis of polyvinyl acetate that has been successfully used as main film-former polymer (Horstmann and Laux, 2004; Leichs et al., 2008). It is also available a polyvinyl alcohol-g-polyethylene glycol copolymer (PVA–g-PEG), Kollicoat® IR, composed by 75% PVA and 25% PEG units. There are considerable advantages of this copolymer compared to pristine PVA. Regarding the manufacturing process, it is important to consider that PVA is only completely solubilized in hot water and the increase of the PVA hydrolysis is directly proportional to the temperature needed to PVA complete dissolution. In opposition, Kollicoat® IR is freely soluble in water and the presence of the PEG spares the addition of plasticizers to the formulation, simplifying the processability. Additionally, it was shown that the higher ability of Kollicoat® IR to form very flexible films with higher elongation at break values when compared with cellulose derivatives based films. This is probably due to the PVA moiety, combined to the

plasticizing and surfactant properties of the PEG moiety (Bougaret et al., 2009; Mura et al., 2010).

PVP or Povidone is a polymer with linear 1-vinyl-2-pyrrolidinone groups that is available with different molecular weights (Rowe et al., 2009). In general, PVP is described as a good film former (Alanazi et al., 2007; Asari et al., 2011; Centers for Disease Control Prevention, 2009; Chu et al., 2012; El-Setouhy and Abd El-Malak, 2010), but some authors described PVP as a polymer with very poor film forming capacity, which may be improved to an average film former polymer when blended with PVA or HPMC, resulting in transparent and fast disintegration films (Kulkarni AS, 2010). This discrepancy may be due to the different PVP's Mw used in the different studies. PVP has been widely explored as film former because it is an edible polymer that rapidly dissolves in mouth. It is sufficiently soluble in both water and organic solvents enabling the use of the most appropriate solvent during the process and manufacture depending on the drug substance. However, PVP exhibits higher hygroscopicity than HPC, which justify the preference of some authors for this cellulosic derivative polymer (Asari et al., 2011). It is reported that PVP K90 (about Mw 750.000) blended with Ethyl Cellulose and HPC origins films with increased flexibility and softer and tougher properties. It was also verified that the PVP addition, contributes to an increase of the film's swelling rate and extent which results in higher barrier effects that decrease the drug substance diffusion. It is also described that PVP may augment significantly the bioadhesive strength probably due to hydrogen bonding and Van der Wall forces (Alanazi et al., 2007). PVP K90 based films may also present fast disintegration time depending on the formulation composition. However, it is reported that HPMC-PVP K90 based films, when compared with HPMC-MDX and HPMC-PVA blends, had lower dissolution rate, probably due to the viscoelastic properties of PVP K90 (El-Setouhy and Abd El-Malak, 2010). It is also demonstrated that different ratios of PVP - alginate blends can be used to control the drug release: higher amount of PVP contributes to smaller dissolution times whereas higher Mw PVP origins films with increased drug release lags (Chu et al., 2012).

Polyethylene Oxide (PEO) is another synthetic polymer that has been used as main film forming polymer for the preparation of oral films due to its peculiar characteristics (Bruce and Manning, 2011; Chen M, 2006; Myers, 2008; Myers et al., 2011). PEO is a non-ionic hydrophilic PEG with high molecular weight that is commercially known by POLYOX™. Interestingly, PEO can be used as self-plasticizing polymer matrix, due to its low Tg, about -67°C (Dahiya M, 2009), especially for Mw ranging from ~100kDa (Polyox WSR N-10) to ~4,000kDa (Polyox WSR 301). This feature eliminates the need of an additional plasticizer in

the oral films formulation, allowing a higher drug load due to the smaller number of excipients (56% by weight of the film) (Myers, 2008). PEOs with higher Mw, as Polyox WSR Coagulant or WSR 303, may be preferentially used to increase the mucoadhesiveness of the films (Myers, 2008; Rowe et al., 2009).

PEO based films are described as films with good resistance to tearing, minimal or no curling, and fast dissolution rate (Yang et al., 2006). Additionally, it is reported the dissolution time for different POLYOX grades, as expected, increases with the Mw: N-10 (Mw=100kDa) < N-80 (Mw=200kDa) < N-750 (Mw=300 kDa) < WSR 205 (Mw=600 kDa). In fact, POLYOX N-10, N-80 present disintegration times lower than Pullulan films, whereas POLYOX WSR 205 and N-750 have dissolution times similar to the Pullulan films. The same authors also reported that PEO based films have a pleasant mouth feel, without a sticky feeling or formation of a highly viscous gel in the mouth. However, the puncture strength of POLYOX N-750 is reported to be 3,000 kg/m2, slightly lower when compared with some available commercial Pullulan based films (about 10,000 kg/m2) (Chen M, 2006). The desirable characteristics of the resulting oral film can be designed by using different PEOs' grades and concentrations. On this matter, it is possible to balance the tear resistance, dissolution rate, and adhesion tendencies of film compositions combining low Mw PEO from 50% to 75%, with a higher Mw PEO and / or with a cellulosic polymer, as HPC or HPMC (Yang et al., 2006).

There are several polymers that are continuously being explored to develop these matrices for drug delivery. The innumerous types of polymers, the different polymer grades, and the several possible polymer-polymer blend ratios result in an exponential number of possible formulations and a wide range of final product characteristics. Therefore, it is crucial to have a deep understanding of the system under development to avoid undesired and unexpected product profiles.

Although, polymers are the main oral films component, additional excipients may be required in order tailor the target product profile. These excipients include plasticizers, sweeteners, flavour, colourants, stabilizers, fillers, saliva stimulating agents, buffer systems and others.

Table 1 - Most widely used polymers in oral films formulations.

Class Polymer	Polymer ID	Chemical features to consider	Formulation Impact		Examples	Characteristics	Application	References
Celluloses	HPC	Several Mw	Good drug loading capacity		Klucels EF		Used to replace synthetic polymers or HPMC in a polymer matrix with modified starch to improve solubility	(Alanazi et al., 2007; Bunnelle et al., 2005; Rowe R, 2009; Yasuda et al., 2011; Zerbe and Al-Khalil, 2003)
		Degree of substitution	Swelling properties	Moderate bioadhesiveness	KlucelX GF			
			Wide range of solubility	Allows a flexible selection of the solvent according to the drug solubility Simplified processability				
	CMC	DS range, between 0.4 and 1.5	Higher DS values	Decrease in the interchain interactions due to the increase substitution of the hydroxyl sites				(Baldwin et al., 1994; Saha et al., 2013)
			Swelling properties	Mucoadhesive preparations	NaCMC	Films with excellent clarity and with the ability of carrying a wide range of DS	Sodium CMC improved the residence time of HPC and sodium alginate films Good compatibility with starch forming single-phase polymeric matrix films with improved mechanical and barrier properties	(Lu et al., 2009; Nappinnai et al., 2008; Peh and Wong, 1999; Tongdeesoontorn et al., 2011)
Starch	Native starch	Generally contains 75% of amylopectin and 25% of amylose High molecular size Strong hydrogen bonding		Lack of strength, water resistibility, thermal stability and processability difficulties				(Koch K, 2009; Mali S, 2010; Xie et al., 2012)
	Maltodextrins	D-glucose units, with a dextrose equivalent (DE)	Low DE MDXs	Higher viscosity Better film formation	MALTRIN®		Fast disintegration Blended with microcrystalline cellulose (MC) tends to form non-sticky and smooth polymeric matrices	(Chapdelaine et al., 2003; Cilurzo et al., 2010; Cilurzo et al., 2008; Cilurzo et al., 2012; Shamekh et al., 2002)
	Hydrolyzed substituted starches	Hydrolysis degree Substituent type Substitution degree	Hydroxypropylated starch molecules	High stability	Lycoat® (hydroxypropylated pea starch)	Fast dissolution time Moderate moisture uptake Satisfactory mechanical properties		(El-Setouhy and Abd El-Malak, 2010; Parissaux X, 2007)
	Pre-gelatinized starch	Fully or partially pre-gelatinized grades	Partially pre-gelatinized grades	Insoluble fractions Critical to produce formulations with the desired disintegration time	INSTANT PURE-COTE® PURE-COTE®	Clear, strong and flexible films Clear, flexible, fast drying and tasteless oral polymer matrices		(Business Wire, 2010; Cunningham; Fadden et al., 2006; GPC, 2014; Kulkarni et al., 2006)
	Pullulan		Too expensive	50 to 80% of Pullulan can be replaced by starch or modified starch		Smooth, transparent and stable films	Blended with Sodium alginate and / or CMC, may synergistically enhance the properties of the film	(Dahiya M, 2009; Dixit and Puthli, 2009; Kawahara M, 2003; Tong Q, 2008)
			Films prepared at low temperatures	Stiffer and more flexible		Films with fast disintegration	Pullulan – HPMC films, have improved thermal and mechanical properties	
			Higher temperatures	Brittle and do not have a clear plastic deformation				

7. Mucoadhesion: a polymeric inner property?

Although the mucoadhesion concept appeared early during the eighties, it was only ten years later that improved mucoadhesive polymers were introduced in the pharmaceutical field (Laffleur, 2014). There are several theories that may explain the bioadhesion process, but none is able to explain the overall mechanism. The wetting theory is one of the oldest theories and involves notions of thermodynamic work and contact angle. Briefly, the bioadhesion in this theory is defined as the surface tension of the two adherent phases subtracted by their apparent interfacial tensions. On the other hand, the diffusion theory is related with the possible relation between the polymeric chains with the glycoprotein mucin chains. According to this theory depending on the depth of the contact, semi-permanent bonds, between the substrate and polymer adhesive chains, may occur. Therefore, the diffusion coefficient may be influenced by the polymer's Mw and cross-link density. Other theories are associated with attractive forces mediated by electrons transference (electrostatic theory) or by chemisorption due to the formation of van der Waal's, hydrogen and hydrophobic bonding (adsorption theory) and / or fracture strength (fracture theory). Nevertheless, the polymers may be categorized according to the binding type to the mucosa (Laffleur, 2014).

7.1. Ionic polymers

The bioadhesive polymers tend to adhere to the biological substrates mostly by interpenetration followed by secondary non-covalent bonding. These secondary interactions are usually hydrogen bonds between the charged polymers' chains with the oligosaccharide side chains of the mucus proteins. Some of the most effective anionic polymers are the polyacrylates (Carbopols) and carboxymethyl celluloses (CMC) (Andrews et al., 2009; Laffleur, 2014; Morales and McConville, 2011). Carbopols are synthetic high-molecular-weight polymer cross-linked with either allyl sucrose or allyl ethers of pentaerythritol, which present a rapid, high, and stable swelling and good mucoadhesive properties. The NaCMC is also used but normally in combination with other polymers to increase the bioadhesive performance of the oral films. Hydroxyethyl cellulose (HEC) based films generally present high swelling properties and rapid erosion but exhibit poor mucoadhesive properties, therefore NaCMC can be added to enhance this property. The referred mucoadhesive polymers are included in the so called first-generation and have

been intensively used. Their bioadhesion properties come essentially from the H-bonds with their carboxyl functional groups. In addition, the sulfate groups are also characterized by their bioadhesion due to anionic non-covalent and H-bonds. These functional groups are characteristic of the Carrageenans, a gum polymer widely used. There are several types of carrageenan but Carrageenan k, is the most mentioned for the oral films development. This is a strongly gelling polymer with small but stable swelling characteristics and moderate mucoadhesive properties (Andrews et al., 2009; Laffleur, 2014; Morales and McConville, 2011; Preis et al., 2013; Woertz et al., 2013) (Figure 4).

Additionally, cationic polymers can naturally be used as bioadhesive materials since they tend to interact with the anionic substructures present in the mucus, such as sialic acid groups. Chitosan is among all cationic polymers one of the most widely used and tested for biomedical and pharmaceutical applications (Dash et al., 2011; Jayakumar et al., 2010). Chitosan is a natural polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine presenting a high to moderate swelling and mucoadhesive properties (Laffleur, 2014; Morales et al., 2013; Rowe et al., 2009) (Figure 4).

Regarding amphiphilic polymers, non-covalent bonds can also be established. The cationic structures adhere to the mucosa by interacting with negatively charged substructures of the mucus, whereas the anionic parts interact with the oral mucosa essentially through hydrogen bonds.

7.2. Neutral polymers

Non-ionic polymers can also present bioadhesive properties through non-covalent interactions with the surrounding fluids. For instance, the mucoadhesiveness of PEO and Polycarbophil polymers would be promoted by the high entanglement level of their polymer chains followed by possible hydrogen bonds formation (Zhu et al., 2013) (Figure 4).

The concept of chain entanglement emerged early during the nineties in attempt to explain the mechanical properties of amorphous polymers above the Tg. The evidence of its existence is mainly based in the mechanical properties behaviour of the materials. The entangling interactions might be simply resumed as an ability of the molecules to slip to different equilibrium positions promoting somehow temporary links of physical interlocking, distinct from the permanent chemical linkages (Graessley, 1974).

The length and flexibility nature of the polymeric chains may allow the rearrangement through loops that might offer high resistance to deformation for a while, but would eventually slip or be removed and reformed by random thermal motion. Additionally, most prominent effects were observed at high polymer concentrations and Mw, with low crosslink densities and large primary chain lengths (Graessley, 1974).

After the polymer matrix-substrate contact the interpenetration of the polymer chains with the mucus glycoproteins may induce the chain interlocking or physical entanglement, which would be associated with possible conformational changes and followed by secondary chemical interactions.

The mucoadhesiveness measured by rheology comparing different non-ionic polymers, showed that, although weak, the HPMC adhesiveness was superior to the MC. The same authors also reported that PEO with low Mw, inferior to 4000kDa, do not present significant mucoadhesiveness (Madsen et al., 1998).

PEO are polymers with long linear chains in which their length is directly related with de Mw. Low Mw PEOs may not be so favourable to form entanglement conformations able to promote mucoadhesion. Regarding the celluloses, it is also valid the unfavourable conformation for entanglement that is probably more related with the stiffness of their backbone as a result of their inherent chemical nature. The cellulosic anhydroglucose ring is empirically more rigid than the long linear chains of ethylene oxide oligomers (PEO). Furthermore, despite the physical interlocking of the chains, secondary chemical bonds (as hydrogen bonds) may be formed and would contribute to strengthen the links. Therefore, between the celluloses, the high density of available hydrogen bonding groups may contribute to stronger interactions of the polymer chains with the mucin glycoproteins. Nevertheless, the celluloses tested by the authors have significant different viscosities (MC with 4000 cp and HPMC 80000–120000cP, 2% solutions (Dow, 2002) indicative of very distinct Mw, which may turn this mucoadhesiveness comparison unreliable regarding the different type of cellulose.

Other assays with neutral polymers, dextran and PEO, reforced that mucoadhesion could be increased by the polymer concentration, is hardly affected by the pH and may be reduced by the molecular branching and short linear polymer chains (Hassan and Gallo, 1990; Nakamura et al., 1996).

These studies highlight the existence of physical chain entanglement between the polymer chains and glycoproteins and their relevance in the mucoadhesion.

Furthermore, it is important to consider that besides the importance of this mechanism to explain the mucoadhesiveness of the neutral polymers, it may also be relevant in the ionic polymers (Madsen et al., 1998). In fact, the chain entanglement is also described for charged polymers, as poly (acrylic acids). Depending on the polymer chain lengths the entanglement may also favour the chemical reactions between ionic polymers and the mucin proteins as well as to other secondary chemical bonds.

Moreover, the high Mw Poly(methacrylate) with effective entanglement chains exhibit a very poor bioadhesive properties in its non-ionic form, which may only be mitigated when its salt form is used (Cilurzo et al., 2003). Though, the non-covalent adhesive bonds of non-ionic polymers are usually weaker than the non-covalent bonds established by charged polymers (anionic or cationic).

7.3. Thiomers

The majority of the polymers referred are essentially water-soluble and their bioadhesiveness to the mucous membrane arises from their non-covalent bonds after hydration. This property has been widely explored in pharmaceutical technology for several years, but only during the 90s real 'pharmaceutical glue' excipients had been developed. In fact, a clear distinction can be found in literature, a first generation including the mucous-non-covalent-bond polymers and a second generation comprising mucous-covalent-bond polymers. These polymers commonly called thiomers are capable of forming covalent bonds, mainly based on thiol /disulfide exchange reactions. The thiol groups of the polymers bond covalently to the cysteine-rich subdomains of the mucus layer by the formation of disulfide bonds (Figure 4). There are several anionic and cationic thiolated polymers that have already been synthesized: polycarbophil-cysteine, poly(acrylic acid)-cysteine, alginate-cysteine, chitosan-4-thio-butylamidine, chitosan-thioglycolic acid, chitosan-2-mercaptoethylamine (Andrews et al., 2009; Bernkop-Schnurch and Steininger, 2000; Laffleur, 2014).

It is reported that these thioled polymers present improved mucoadhesion characteristics compared to the unmodified counterparts. In addition, a new type of thiomers has been recently developed, the preactivated thiomers, which have better mucoadhesive properties and higher stability: chitosan-thioglycolic acid mercaptonicotin amide, pectin-cysteine-mercaptonicotinic acid and chitosan-4-thiobutylamidine-mercaptonicotinamide.

Generally, these second generation mucoadhesive polymers are usually less sensitive to ionic and pH changes and the disulfide bonds may facilitate controlled drug diffusion due to the higher rigidity and cross-linking. Therefore, these polymers may be preferred to develop modified profile release drug delivery systems whereas the first-generation polymers are preferable to fast onset drug release (Andrews et al., 2009; Bernkop-Schnurch and Steininger, 2000; Laffleur, 2014).

Although many researches have been performed in this area, the application of thiomers in oral films has not been explored to the best of our knowledge. In table 2 it is summarized some of the research work performed with thiomers. There is a wide range of drug delivery systems developed and studied but for buccal or oral delivery, but it is mainly related to tablets. Regarding the first generation thiomers, their usage in the oral films development may also be challenging due to their inherent instability. Thiomers are unstable in aqueous solutions with pH ≥ 5 due to the oxidation of the thiol groups. It is also advisable the production and storage under inert conditions, light and oxygen protection, to avoid thiomer formulations instability. However, the second generation thiomers are more stable in solutions and in a broader pH range (Bonengel and Bernkop-Schnurch, 2014; Ijaz and Bernkop-Schnurch, 2015). Nevertheless, the inclusion of these components in pharmaceutical dosage forms may be still restricted to some applications due to regulatory (e.g. safety assays, registration) and process-production scale-up issues (Ijaz and Bernkop-Schnurch, 2015). Currently, there are only clinical trials for ocular application of chitosan-N-acetylcysteine conjugate (Bonengel and Bernkop-Schnurch, 2014; Garhofer and Medical University of Vienna, 2010, 2012; Ijaz and Bernkop-Schnurch, 2015) and hyaluronic thiomer (Croma-Pharma GmbH, 2013).

Additionally, the inclusion of these compounds in the oral films, especially in buccal films, may also be used as permeation enhancers and protein /peptides stabilizers as already explored by others (Bernkop-Schnurch and Thaler, 2000; Hornof and Bernkop-Schnürch, 2002; Kast et al., 2003; Leitner et al., 2004).

Table 2 - Summary of some of the research work performed with the thiomers.

		Drug Delivery type	Dosage form	Drug substance	Reference
Thiomers	Polycarbophil-cysteine	Buccal	Patch Four layered		(Hoyer et al., 2009)
		Buccal	Tablets	Rifampicin	(Bernkop-Schnurch and Steininger, 2000)
		Oral	Liposomes		(Werle et al., 2009)
		Ocular	Inserts	Diclofenac salts	(Hornof et al., 2003)
	Poly(acrylic acid)-cysteine	Ocular	Microparticles	Bromelain	(Bernkop-Schnurch et al., 2003)
			Tablets		(Guggi et al., 2004; Leitner et al., 2003)
		Ocular	Bilayer inserts	Gatifloxacin	(Aher and Nair, 2014)
	Alginate-cysteine	Oral	Tablets		(Bernkop-Schnurch et al., 2001)
		Oral	Tablets	Tramadol hydrochloride	(Jindal et al., 2010; Roldo et al., 2004)
	Chitosan-4-thio-butylamidine	Oral	Tablet		
			In situ gel-forming system	Protein	(Liu et al., 2014)
		Oral	Tablets	Peptide	(Bernkop-Schnurch et al., 2005)
Preactivated thiomers	Chitosan-N-acetylcysteine conjugate	Ocular	Lacrimera® eye drops	Dry eye syndrome	(Bonengel and Bernkop-Schnurch, 2014; Ijaz and Bernkop-Schnurch, 2015)
	Pectin-cysteine-mercaptonicotinic acid	Oral	Minitablets	Rosuvastatin	(Hauptstein et al., 2013)
		Buccal	Gel delivery	Calcium Lidocaine	(Hauptstein et al., 2014)

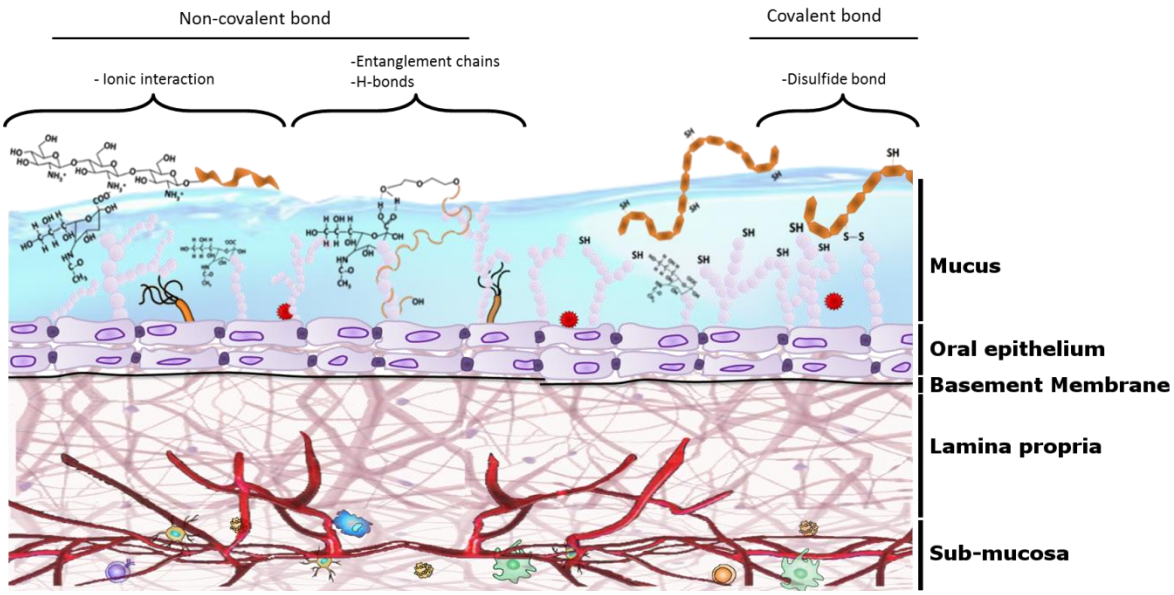

Figure 4 - Bioadhesive interactions. Simplified oral mucosa representation: sub-mucosa with nerves and blood vessels, lamina propria, essentially with connective tissue and with some blood vessels, basement membrane usually a single cell layer lying in the interface of the epithelium and lamina propria; a simplified oral epithelium only for representative purposes; and a mucus layer with mucin and glycoproteins. The mucoadhesiveness of the polymers to the oral mucosa may be explained by the non-covalent and covalent bonds, depending on the polymers' functional groups.

In general, any polymer is capable of establishing electrostatic interactions presenting some degree of bioadhesive properties. Additionally, the majority of polymers used to prepare oral film matrices are rich in hydroxyl groups, which can easily interact with the biological subtracts through H-bonds. This is associated with the natural mucoadhesion of the majority of the hydrophilic polymers used to prepare these platforms. Furthermore, some of these polymers can also be used as adjuvants or modifiers to improve or diminish film's mucoadhesive characteristics. Polymers with small but stable swelling properties characterized by very poor mucoadhesion, such as Agar (hydrophilic colloidal polysaccharide) or Acacia (complex and loose aggregate of sugars and hemicelluloses) can be used to decrease matrices bioadhesion. Another example is the Poly-D,L (lactide-co-glycolide) (PLGA), a synthetic copolymer of lactide and glycolide PLGA, that can be added to the polymeric matrix to confer hydrophobicity to diminish the swelling of other polymers and / or to obtain a prolonged drug release (Cavallari et al., 2013; Dott et al., 2013; Jones et al., 2014; Perugini P, 2003; Rana and Murthy, 2013; Shen et al., 2014).

8. Polymer selection

As discussed on previous sections, the polymer selection during the formulation development of polymeric matrices may be critical and some points should be considered. Several examples were given related the ability of the polymer to affect the mechanical and texture properties of the films and also their influence on the drug release. On the other hand, the inclusion of the drug substance in the polymer matrix may also affect significantly the mechanical properties of the film. Depending on the chemical structure of the DS and the % of drug load the DS may easily interpose between the polymer chains, interfering with the polymer intermolecular bonds. This effect may allow the polymer to move more freely, resulting in matrices with higher flexibility due to a reduction on the elastic modulus and tensile strength parameters (Alanazi et al., 2007). In fact, depending on the drug, the effects may be different, for example, chlorpheniramine maleate has a higher plasticizer effect on HPC based films than indomethacin. Nevertheless this plasticizing effect may also have direct impact in the oral film manufacture, due to chemical modifications of the mixture properties, such as reducing the softening temperature (Low et al., 2013).

Aesthetic and performance characteristics should also be considered during the selection of the polymer. This dosage form is for oral administration and may have some residence time in the oral mucosa. Therefore, polymers that may become unpleasant should be avoided. Therefore some aspects as taste masking, physical appearance and mouth feel should be considered. The hydrophilic polymers are the major choice for the preparation of oral film matrix so the film may smoothly and softly dissolve in the oral cavity. Polymers or combinations that tend to form pastes should be avoided since it may become unpleasant. Regarding the manufacturing process, properties such as good wetting, spreadability, sufficient peel, shear and tensile strengths, should also be taken in consideration.

The mechanical properties of the polymeric matrix are also critical. An ideal oral film should be flexible, elastic and robust enough to resist to handling, transportation and the stress from mouth activities. Generally, low-molecular-weight polymers dissolve quicker, but polymers with higher molecular mass origin films with better mechanical properties. Additionally, the polymer should be preferentially ready-to-use, not toxic or irritant to the oral mucosa and ideally not very expensive. Therefore, a mixture of polymers is preferable used, instead of a one-polymer-based- film, in attempt to improve and optimize the final polymeric matrix characteristics.

9. Critical quality attributes (CQA)

There are general critical quality attributes of the oral films that should be considered during their development. These properties are obviously inherent to the formulation but also significantly influenced by the manufacturing process. Hereinafter, are described briefly some of the most common quality attributes that should be considered during the oral film development.

9.1. Physical strength

Appropriate physical strength, is one of the most evident CQA of the oral films. The product should have suitable mechanical properties so it can be easily manufactured, packaged and handled without damage or break. However, there are no guidelines with the description of the most adequate properties, methods and ranges that should be studied. However, in literature there is a general consensus about the main properties that should be tested: elongation at break, young's modulus and tensile strength (Cao et al., 2009; Dixit and Puthli, 2009; Preis et al., 2014). The literature review highlighted the difficulty of stablishing strict ranges for these parameters (Preis et al., 2014) and a wide variation may be appropriate depending on the polymeric matrix under development. In fact, the appropriate value for the mechanical strength may vary significantly depending on the polymeric matrix and method of manufacture (Nair et al., 2013).

An appropriate balance should be found between these properties. The oral film should be malleable so it can be handled without break but not too flexible that extends easily and deforms during cutting or packaging processes. It should present enough tension so it can be pulled out from the pouch, rolled up after casting, pealed from the release liner, but not too much that may difficult the cutting process. Nevertheless, the mechanical evaluation is particularly important during the product life-time but also for up-scale manufacturing process, since all the process from coiling to the packaging demands robustness (Preis et al., 2013).

9.2. Stability

It is important that the product has the ability to maintain its suitable properties over time, so physical and chemical stability are assured. These characteristics depend on the polymeric matrix and possibly on the manufacturing process. Thus, suitable stability and screening tests should be planned and performed during the development stage. However, proper approaches that may also guarantee the product stability are well-controlled manufacturing conditions, and the selection of an adequate packaging material in an early-development-stage.

Regarding the chemical stability, it is important to consider the polymeric matrix characteristics. The complexity of these matrices is sometimes underestimated and careful attention should be taken during its development. Although the majority of the reaction / interactions need high temperatures to take place, it is found in literature hypothesis of some reactions that may occur at room temperature in polymeric film matrices (Koo et al., 2011; Ortega-Toro et al., 2014). Nevertheless, there are excipients that may inadvertently function as reaction catalysers, compromising the product stability.

Importantly, it is also to assure the drug substance stability incorporated in the polymeric matrix. Although the stability of some drug substances is well known, the change of the pharmaceutical form may interfere with it. The Suboxone® sublingual film is a good example, in which Naloxone may be more easily oxidized in the film compared to the sublingual tablets available. Therefore, the shelf-life is limited to 12 months if the storage temperature is reduced from 30^{o}C to 25^{o}C (Australian Government et al., 2011).

The thermal stability of the product should also be considered since it may influence its long term stability, its storage conditions and possible restrictions.

9.3. Appearance

The appearance of the films is another relevant CQA. The size and the shape should be carefully studied and selected depending on the strength and application site. This has special importance for sublingual formulations which have a small available area to adhere. Moreover, the buccal films, which generally tend to be placed in the mouth for long periods of time, should also have suitable dimensions to be comfortable for the patient.

9.4. Drug release profile

The target drug release profile delivery should be defined early in the development based on the target product profile. The most reliable tests available to this evaluation are the disintegration time and the dissolution profile. Depending on the product, it may be intended to have a bioequivalent oral dosage form or other specific drug-delivery type (e.g. extended or fast release, mucosa or gastrointestinal absorption).

It is also important to consider that according to the FDA guidance a fast disintegration time *in vitro* should be less than 30s (Food and Drug Administration, 2008).

9.5. Residual water content

The residual water content of the films is critical and should also be strictly defined for each specific formulation, since it may influence significantly any of the properties described. It is also crucial to monitor and control the room conditions during production (temperature and relative humidity), and an appropriate primary packaging material should be provided to avoid water transferences between the product and the surrounding room.

An excess or deficit of water content may affect the mechanical properties of the polymeric matrix. The water molecules may interpose in the polymer chains functioning as a plasticizer, so the loss of water content, may contribute for brittle polymeric matrices. In turn, an excess of water absorption by the polymeric matrix may originate sticky films that may adhere to the patient fingers and / or packaging material.

Moreover, the interposition of the water molecules in the polymeric chains may also influence the disintegration / dissolution of the films. The loss of water molecules would contribute to thigh the polymeric chain links, turning difficult the water penetration and therefore the disintegration time.

Furthermore, the free water in the film may also interfere with the stability of the drug substance incorporated and / or with the excipients.

9.6. Organoleptic characteristics

The oral films have a relatively high surface area in contact with the oral mucosa, which makes important to focus some of the development efforts in the formulation of a pleasant and palatable system. Generally, the disagreeable taste is related with the drug substance characteristics (bitterness, particle size / shape, solubility, ionization) and strength in the oral film (Gala and Chauhan, 2014). Therefore, depending on these properties is important to define an efficient strategy to assure an agreeable taste, aftertaste and mouthfeel.

Another important point to consider is the target market, since there may be regional and / or aged group preferences. Different consumers have different preferences and should be captivated by different and independent ways. From the formulation point of view it is important to consider the regional and aged group tastes. For example, children generally prefer fruit and / or sweetener flavours, while adults tend to prefer slightly acid flavours and older people frequently prefer mint or wine flavoured products. Even so, it is important to notice that even flavours' children preferences may vary from country to country and may depend on social and cultural factors (Marriott et al., 2010; Taylor and Linforth, 2010; WHO Expert Committee, 2012). Curiously, even for animals' medicine market is important to record that the choice of the flavour and colour may have impact in the acceptance of the medicine. Actually, these animals' preferences can be surprising. Regarding colours, it is known that iguanas and emus are attracted to red and yellow, respectively. About the flavours, horses may prefer banana instead of apple or molasses, some ferrets may be fond of bubble-gum and rabbits and guinea pigs may prefer pina-colada flavour (Slade, 2012). Despite that, the appropriate choice of flavour is mainly affected by the taste sensation conferred by the drug substance, and the flavours or their combination should mask any bitterness, providing a good balance of acid, salty or sour taste, and covering any unpleasant aftertaste.

9.7. Dose uniformity

The individual weight of the films and the dosage uniformity must be also controlled during the process. It is also important to have a deep knowledge of the process and the product so slightly adjustments may be performed during manufacturing if necessary.

9.8. Others

Additional attributes may also be considered depending on the type of the oral film to develop. For example, adhesion or mucoadhesion tests, for buccal and / or sublingual films and pH values measurements, when the drug absorption or stability depends on it. Moreover the pH assays may also be important to predict possible mucosa irritation, since acidic or alkaline pH may cause some discomfort, and the surface pH should be ideally close to neutral (Kunte and Tandale, 2010).

The CQA must be defined in the beginning of the development according to the target product profile. Moreover, due to the sensitivity / complexity of the product other properties / process parameters involved in the oral films formulation and manufacturing must not be discarded (release liner and packaging material properties). A helpful way to define efficiently the quality attributes of the oral film under development is to consider the quality target product profile and (if possible) previous knowledge of the product and manufacturing process. This should be followed by an appropriate quality risk management to evaluate and highlight the critical and potential attributes that would affect the quality of the drug product (Food and Drug Administration, 2009).

10. Manufacturing processes overview: from the conventional to the innovative

The two main techniques used to prepare oral films are solvent casting (Cilurzo et al., 2011; El-Setouhy and Abd El-Malak, 2010; Garsuch and Breitkreutz, 2010; Kunte and Tandale, 2010; Mashru et al., 2005; Mura et al., 2010; Nishimura et al., 2009; Perumal et al., 2008) and hot melt extrusion (Cilurzo et al., 2008; Cilurzo et al., 2012; Low et al., 2013) (Figure 5). However, during the past few years some developments and innovative techniques have emerged. Some variants of these manufacturing methods of casting and extrusion have also been described and used alone or in combination, such as semisolid casting and solid-dispersion extrusion (Nagaraju et al., 2013). Inventive manufacturing processes as the rolling (Nagaraju et al., 2013; Preis et al., 2013) or printing (Preis et al., 2013).methods have also been described. The first involves essentially the preparation of a pre-mix with a further addition of the drug substance, and the resulting matrix is passed through a metering roller.

The printing method consists literally in printing the drug substance on a placebo oral film with specific techniques (Preis et al., 2013).

10.1. Conventional methods

The solvent-casting method consists essentially in an aqueous or hydro-alcoholic mixture of excipients and drug substance(s) that is casted onto a surface, dried, and cut into a desirable size. On the other hand, hot-melt extrusion consists simply in shaping an adequate mixture of polymer(s), other excipients and drug substance(s) into a film by melting all the components (Mishra and Amin, 2011). Both techniques allow the preparation of films with good characteristics, but generally the solvent casting method is the most widely used, probably due to the special equipment required and high costs associated to the hot melt extrusion method (Dixit and Puthli, 2009).

Regarding the variant methods referred previously, the semisolid casting consists in a gel mass casted using heat controlled drums and obtained by the addition of an acid insoluble polymer to the main liquid mixture in a preferential ratio of 1:4. In turn, the solid dispersion extrusion consists essentially in the dispersion of a drug substance dissolved in an appropriate solvent and its incorporation into polyethylene glycol (PEG) melted. However, the drug substance or the solvent used to dissolve it should be insoluble in polyethylene glycol.

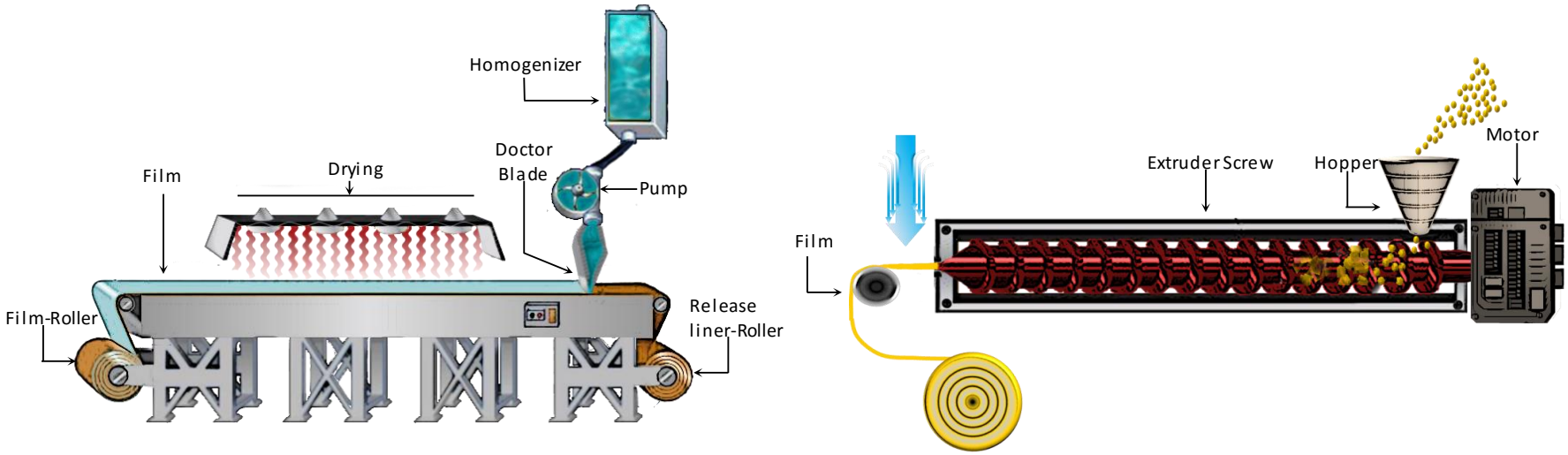

Figure 5 - Most common techniques to prepare oral films. Solvent casting technique (left) and Hot-melt-extrusion method (right).

10.2. Innovative methods

An inventive manufacturing processes is the rolling method which involves the preparation of a pre-mix with a further addition of the drug substance, and the resulting matrix is passed through a metering roller (Nagaraju et al., 2013).

Another, are the drug printing technologies methods, that seemed to be highly flexible and cost-effective (Preis et al., 2013) (Figure 6).

Printing technologies are widely used in the pharmaceutical industry to identify or label the pharmaceutical dosage forms, especially for personalization purposes to be readily identified and to avoid counterfeit production. However, instead of merely printing some identification characters, this technology early started to be adapted to the drug load of pharmaceutical dosage forms. During the 80's, Anhauser, Klein and Nick et al. used screen printing and pad printing to load transdermal patches with drug substances (Janssen et al., 2013) (Figure 6 C, D). Nevertheless, for large production scale, these methods are essentially limited by the low speed production. Later, the inkjet printing started to be explored as a safe and accurate method to produce dosage forms with potent or low-dose drugs. GlaxoSmithKline (GSK) has a GMP Pilot machine since 2005, based on this innovative technology, the Liquid Dispensing Technology, used as a new tablet-manufacturing process that delivers microgram doses with unparalleled precision. GSK is the owner of all intellectual property for this technology until 2028, which was also rewarded in 2012 with a Health and Safety Award by IChmE (IChemE Advancing chemical engineering worldwide, 2012; Richardson and Wilson, 2013). The application of this technology to oral films is not yet much explored. Nevertheless, during 2011, based on printable medicines and with the idea of printing a drug substance onto a carrier (such as a paper strip that can be then inserted into a capsule for an easy administration), a revolutionary concept was established: personalized medicines (Khinast et al., 2011). Although, some references to this concept have emerged in the last years (Buanz et al., 2011; Niklas Sandler, 2011), there is still no reference to the industrial application of these methods for the production of oral films.

GSK technology may achieve a medium output of 20,000 tablets per hour. However, it has no direct correlation with oral films manufacturing production, and some authors consider that inkjet printing is still not suitable for high-throughput industrial production (Figure 6B). Therefore, another printing technology is suggested to be more feasible for oral films industrial production, the flexographic printing technology (Janssen et al., 2013) (Figure 6A). The flexographic printing is a rotary printing process in which the ink (drug substance

solution or suspension) is metered by an anilox roller then transferred to printing cylinder that prints the drug-free-film after unrolling the daughter roll. On the other hand, the drop deposition of the DS solution or suspension with the ink-jet printing may be challenging considering that it is important to avoid the film disintegration or rupturing and simultaneously maintaining the oral film's fast dissolving properties (Janssen et al., 2013).

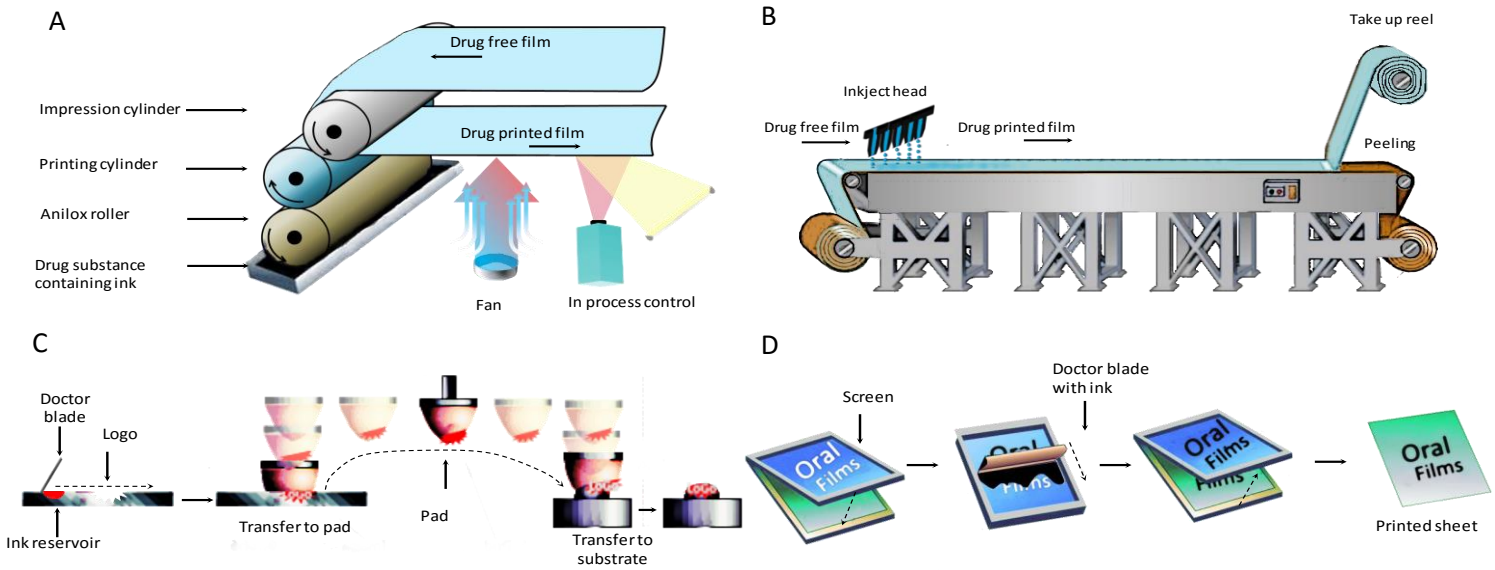

Figure 6 - Printing techniques. Representation of the 4 main printing techniques used in oral films preparation. The two top figures are simplified schemes of possible printing industrial techniques applied to the oral films, flexoprinting (A) and inkjet (B) printing. The two bottom pictures represent two simpler printing methods the pad (C) and screen printing (D).

In theory, any of the printing methods mentioned above would contribute to a more homogeneous distribution and accurate dosage of the drug substance within the film, which by the conventional methods is very challenging. Moreover, dose accuracy and uniform distribution of the drug substance in the films normally depends on the coating mass properties, like viscosity or density, which in turn are affected by the characteristics and amount of the processed drug substances. On this matter, with the conventional methods the formulations have often to be adjusted for each drug substance and dosage strength (Janssen et al., 2013). Hence, the application of these technologies could streamline all the manufacturing process and shorten the time to the market.

In summary, printing drug substances on dosage forms are nowadays a reality and its application in oral films has opened a new world of opportunities when referring to personalized and individualized medicines.

11. Characterization methods

Several efforts have been made to develop suitable techniques for oral films evaluation and characterization, considering their particular characteristics. There are critical parameters that should be evaluated for the quality control of the films. Despite the lack of guidance, the European Pharmacopeia refers the need of a “suitable mechanical strength to resist handling without being damaged” and an appropriate dissolution method “to demonstrate the appropriate release of the active substance”. However, it is advisable to evaluate other critical properties, usually also referred as critical quality attributes that are referred hereinafter.

11.1. Mechanical properties

The variety of dimensions of commercially available oral films difficult the standardization of specific evaluation techniques. The most referred is the determination of mechanical properties based on ASTM or DIN-ISO guidelines, namely DIN EN ISO 527 for foil materials and ASTM D882-01 for tensile properties of thin plastic sheeting. This method consists in the fixation of the sample between two clamps and pull until breaking (Preis et al., 2014). The main limitations of this approach is the unresponsiveness of the apparatus and the preferential use of bone shapes samples to assure that the forces are centred in the middle

of the specimen, which does not match the common small rectangular format (about 2 to 8 cm^2) of the oral films (Garsuch and Breitkreutz, 2009). More suitable methods were developed as the puncture test with a cylindrical probe with a plane flat-faced surface using Texture Analyzer equipment. The probe with the flat face surface allows retrieving the area directly affected by the strain (Preis et al., 2014).

11.2. Dissolution

The dissolution method is also critical, especially concerning the apparatus and media selection. Despite the simple orientation of the Pharmacopeia description, it is important to consider that this assay should be representative and an approach to predict the *in vivo* behaviour.

The majority of the methods described do not mimic the physiological conditions satisfactorily, regarding the dissolution method conditions and apparatus (Garsuch and Breitkreutz, 2009; Xia et al., 2015). Another point to consider is the type of oral film to test, which may include different challenges and limitations. Briefly, the major restrictions in the oral films dissolution methods are the *in vivo* small volume dissolution, the short residence time in mouth (specially fast dissolving films), mucosal absorption (buccal films), composition (e.g. adhesive compounds) and incomplete dissolution (sometimes a complete disintegration is preferred instead of a complete dissolution).

Generally, the apparatus selection would be based on two different assumptions: orodispersible dosage forms (e.g. orodispersible tablets) or transdermal dosage forms, which commonly uses accessories to lock the dosage form in the bottom of the vessel. The paddle apparatus (USP type II) is more used (Arun Arya, 2010; Cilurzo et al., 2010; Gohel et al., 2009; Gupta M.M et al., 2011; Kunte and Tandale, 2010; Liew et al., 2012; Nishimura et al., 2009; Shimoda et al., 2009) than the basket apparatus (USP type I) (Cilurzo et al., 2010; El-Setouhy and Abd El-Malak, 2010; Mahesh A, 2010; Sri et al., 2012). But, due to the limitations of both methods, many researchers have suggested the use of modified apparatus (Dinge and Nagarsenker, 2008; Garsuch and Breitkreutz, 2009; Xia et al., 2015). The majority of the modifications consisted in dissolution media volume reduction (usually including the vessel type modification), stirring accessory modifications (Dinge and Nagarsenker, 2008; Sharma R, 2007; Xia et al., 2015) and type of dissolution medium, such as simulated artificial saliva (Arya et al., 2010; Gohel et al., 2009; Gupta et al., 2011).

Additionally, Gursuch et al. presented a fibre-optic sensor system to overcome the shorter intervals sampling collection (lower than 30s) and the filters clog in apparatus with modified sample withdraw (Garsuch and Breitkreutz, 2009). In fact, fast orodispersible films usually exhibit a rapid disintegration / dissolution, becoming sometimes hard to obtain suitable dissolution profiles with the conventional (manual or automated) sampling collection. Although the online measurement may surge as a suitable alternative for fast dissolvable dosage forms, some points should be considered. The majority of the online fibre optic sensor systems currently available usually use UV spectroscopy, which becomes unviable if there is similar absorption spectrum between drug substance and any other compound of the formulation.

The selection of the correct apparatus and possible adaptive accessories should also be carefully chosen. One-layer fast dissolving films should have both surfaces in contact with the dissolution media, but in multi-layer films this choice may not be the most appropriate. Furthermore, the adhesion of some components of the formulation may also origin trapped disintegrated masses on the accessory / sinker / basket used, resulting in irreproducible dissolution profiles.

Another approach is the usage of the paddle over disk apparatus (USP type V). This dissolution apparatus was used in the development of Zuplenz® along with a gastric pH dissolution media. This may be justified since the primary objective of this fast dissolving film is to disintegrate fast in the mouth to be readily swallowed with the saliva (Warren and Balerna, 2010).

Finally, there are many critical points to consider in the development of the dissolution method and many options are available due to the nonspecific or inexistence of pharmacopeia guidance. However, the method choice should be well grounded and justified.

Table 3 - Summary of the dissolution methods currently used to test oral films.

Apparatus	Dissolution Media	Stirring	Method		Reference
			Sampling	Details	
USP type V	900 mL 0.1N HCl 37.0°C ± 0.5°C	50 rpm	10 minute intervals		(Par Pharmaceutical, 2010)
JP15 paddle apparatus	900 mL of phosphate solution (pH 1.2) 37.0°C ± 0.5°C 50 rpm		Ten-milliliter aliquot from 2 min to 60 min		(Shimoda et al., 2009)
USP type I	400 ml freshly distilled water, 37±0.5°C 100 rpm		2, 4, 6, 8, and 10 min		(El-Setouhy and Abd El-Malak, 2010)
JP15 paddle apparatus	900 mL of phosphate solution (pH 1.2), 37 ± 0.5 C	50 rpm	10 mL from 2 min to 120 min		(Nishimura et al., 2009)
USP type II	300 mL freshly deionized water, 37±1°C	50 rpm			(Cilurzo et al., 2010)
USP type II	300 ml distilled water or simulated saliva (pH 6.8) or 900 mL of simulated gastric fluid (pH 1.2) 37°C ± 0.5°C	50 rpm	5 ml 0-, 1-, 2-, 3-, 5-, 10-, and 20-minute	Simulated saliva:12 mM KH2PO4, 40 mM NaCl, 1.5 mM CaCl2 and NaOH to pH 6.8)	(Gohel et al., 2009)
USP type II	Simulated saliva (phosphate buffer pH 6.4) 37±0.5°C.				(Arun Arya, 2010)
USP type I	300 ml Simulated saliva (phosphate buffer pH 6.8) or 900 ml of simulated gastric fluid (0.1N HCl) 37 ± 0.5°C	50 rpm.	5 mL		(Mahesh A, 2010)
USP type II (?)	900 mL phosphate buffer pH 6.6 37±0.5°C	50 rpm	1 to 30 min		(Kunte and Tandale, 2010)
USP type II	simulated saliva (phosphate buffer pH 6.8) 900 ml phosphate buffer saline (pH6.8) 37°C,	50 rpm	1, 2, 3, 4, 5, 10, 15, 20 and 30 minute	Each film is attached to a glass slide (with glue) that remains in the bottom of the vessel Simulated saliva: 2.38 g Na2HPO4, 0.19 g KH2PO4, and 8.00 g NaCl per liter adjusted with phosphoric acid to pH 6.8).	(Gupta M.M et al., 2011)
USP type II	900 mL 0.1 M HCl 37.0±0.5°C	50 rpm	3 mL 1, 3, 5, 10, 20 and 30 min	Reposition	(Liew et al., 2012)
USP type I	500 mL deionized water 37 ±1°C	25 rpm			(Cilurzo et al., 2011)
USP type I	900 ml buffer pH 6.8 37°C ± 1°C		5 ml	Media reposition	(Sri et al., 2012)
Modified USP-XXIII type1 apparatus	20 ml Phosphate buffer pH 6.4	100 rpm	4 ml 7, 14, 21, 28, 35 and 42 min	Media reposition, film was placed with the help of forceps in a 50 ml glass beaker Without the basket attached with a shaft.	(Dinge and Nagarsenker, 2008)
Modified USP XXIII apparatus (paddle over disk)	1000 ml Distilled water 37.0±0.5°C	100 rpm	5 ml		(Sharma R, 2007)
Third method apparatus Chinese Pharmacopeia (CP 2010, appendix XD modified	100 ml Distilled water	30rpm 50 rpm 100 rpm.	Autosampling	Film samples were sandwiched between two pieces of a sieve mesh and fixed in the right and vertical position	(Xia et al.)

11.3. Mucoadhesiveness

There are no mucoadhesion methods described in any Pharmacopeia. Also, it is complex to define an appropriate method considering the numerous approaches available in literature, the lack of correlation between *in vivo* and *in vitro* tests and the challenge to found intact and fresh buccal mucosa (Nair et al., 2013; Preis et al., 2013). Nair et al. recently compiled the most used in vitro techniques to evaluate the buccal films with a short but relevant section of mucoadhesive studies (Nair et al., 2013).

12. Conclusion

The flexibility of this dissolvable film technology platform offers future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets. It also provides an opportunity to extend revenue life cycles for existing drugs whose patent is expiring and will soon be vulnerable to generic competition. In other words, oral films allow the lifecycle management of the products. Additionally, the majority of the manufacturing approaches used are well understood and easily controlled, prompting a robust and efficient development from bench to market.

There are some important issues that should be taken in consideration regarding the oral films development, manufacturing and marketing. During the development the critical quality attributes should be well-stablished to prevent unfortunate and uncontrolled events. Despite the complexity of the formulation and process, a deep knowledge of the system may be sufficient to control and surpass some inevitable and unpredictable proceedings.

Finally, it is important that the combination of thin film technology with the selected drug substance gain wide consumer acceptance and pave the way for other medicines to move to this portable, exceptionally convenient pharmaceutical form.

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Chapter I.2

Oral films: Current status and future perspectives II

Intellectual property, technologies and market needs

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1. Introduction

The oral route remains the most preferred for the general population (Rosen and Abribat, 2005). It is easier, non-invasive, convenient and flexible, and generally oral formulations have a lower cost of production for the pharmaceutical companies. These facts justify why the oral delivery market holds 52% of the market share remaining the largest sector in the overall drug delivery market (GBI Research, 2010; Research Report, 2013; Vasisht and Finn, 2008). Although the majority of drugs are administered in the form of tablets and capsules, several groups of patients have serious swallowing difficulties. It is estimated that almost 28% of the general population have frequent problems in swallowing medicines that is often the cause of poor patient compliance (Schiele et al., 2013). This is commonly associated to dangerous tablets and capsules' modifications, such as splitting or crushing, related with dosage inaccuracy and drug therapy inefficiency or overdosing (Stegemann et al., 2012). In order to overcome these issues, fast dissolving delivery systems are gaining considerable attention. Among them, oral films have emerged and have been dragged by this urgent market need.

There is no strong evidence or consensus about the date for the first reference of orodispersible delivery systems (Bala et al., 2013) but the most likely pioneer in the conception of orodispersible films was Deadman Frederic in 1960s (Hoffmann et al., 2011). Nevertheless, it remained just a concept until 2001 when Pfizer introduced in the market the major orodispersible film blockbuster, the Listerine® Pocket Packs® (Levinson, 2012).

There is an evident trend that the pharmaceutical field is moving from the conventional and traditional to the innovative and patient-centred developments. There is also an increase demand of the authorities for knowledge, in order to improve the quality of the products, and the optimization and lean of the resources.

This section of the review highlights the Intellectual Property developed in this field, looking over the major players in the area, their platform technologies and all the commercial evolution through a summary market outlook and trends.

2. Intellectual Property

The drug delivery technology is an area with extensive intellectual property protection which is extremely important and required considering the high competitiveness of this fast-evolving field. There are a considerable number of institutions developing oral films, which can be easily confirmed by the constant growing number of patent applications. In fact, the increasing number of patents filled each year is impressive and more than 132 patent families have been identified and at least 30 companies / institutions are developing these technological platforms (Evalueserve, 2011). Until 2011, the majority of the patents were filled in the US and Japan, by the top players such as MonoSol and Kyukyu Pharmaceuticals Co. LTD, with Europe gaining some ground in the recent years with LTS Lohmann Therapy-Systems (LTS), Labtec Pharma, Hexal Pharmaceuticals and others. Additionally, LTS and MonoSol are clearly the major players with a broader technology coverage concerning the intellectual property, highlighting the diversified and fuelled research of these companies in the field (Evalueserve, 2011). At the moment according to the recent published Root Analysis report, MonoSol is the most prominent player in the oral thin films, with nine products already on the market based on its own technology (Ryoo et al., 2012).

Regarding intellectual property protection, an exhaustive search in free patent databases (google patents, Espacenet, WIPO) reveals that the composition patents are the larger slice in the overall patents filled. Among them, few are restricted to a specific therapy or drug substance, and the majority is therapeutically broader and focused in the composition of the technology, claiming essentially the film forming polymer(s), crucial for the matrix formation. The process patents have also some relevance, but only a few are restricted to a specific drug, therapy or method of use.

The most patented polymers are polysaccharides, including starch, cellulose and its derivatives (Figure 7). As already described in the part 1 of this review, these are two large groups of polymers that can be subdivided into subclasses according to the modifications and substituents added to the native natural polymer backbones.

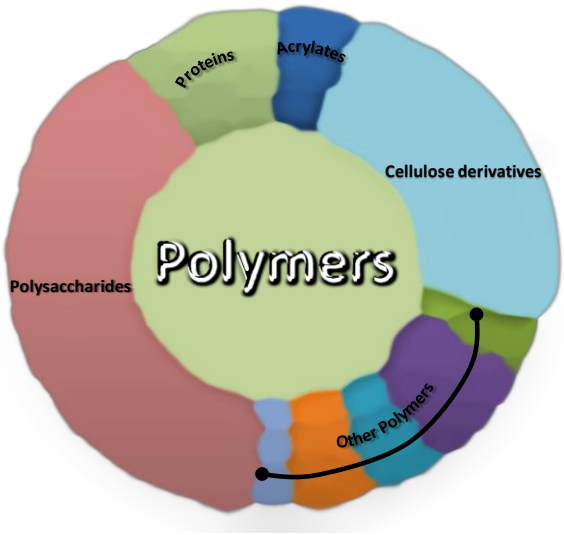

Figure 7 - Overall Scenario of polymers usage. The Polysaccharide group comprises starch derivatives, pectin, gums, dextrans and alginates; other polymers group includes polyvinyl and polyethylene glycol polymers and co-polymers; the proteins groups consists of soy proteins, casein, zein, collagen and others; the acrylates groups refers mainly to methacrylate and polyacrylic polymers.

The use of the majority of hydrophilic polymers in formulations of oral films is already protected by several patents, restricting the possibility of developing formulations that do not infringe existing patents and capable of being protected by new ones. During the last years the development of new polymers suitable to this technological platform was scarce, leading to an increasing number of process patent applications, and patent formulations related with specific drug substances or therapies.

Furthermore, the difficulty in innovating in the formulation composition due to the small number of suitable excipients had probably contributed to new directions in this research field, such as the development of new manufacturing processes (Breitenbach et al., 2013; Janssen et al., 2013) (see part 1 review), or the usage of oral films as drug delivery systems for biotechnology products (e.g. vaccines and insulin) (Cohen et al., 2012; Fierce Drug Delivery, 2012; Pulliam, 2012; Warren, 2012).

3. Technological platforms

The majority of the top player companies referred above followed a similar pattern. Generally, a new and innovative technological platform is developed (like an oral film placebo) and then several drug candidates are evaluated and considered to be incorporated in the film. Obviously, this strategy implies necessarily the development of a versatile oral film platform, which in turn may suffer some modifications depending on the drug substance characteristics and the desired final dosage form performance.

Furthermore, it is common in this market segment the establishment of partnerships between oral film developers / manufacturers and other pharmaceutical companies researching new chemical entities, developing novel uses for existing drugs (repurposing) or companies looking for innovative formulations for their drugs (life-cycle management). This strategy is beneficial to share fixed expenses associated with the product licensing and marketing (Belanger et al., 2009). Therefore, two different major players may be distinguished in this field: the oral film platform developers, usually the technology owners, and the marketing partners.

Several oral film platforms have been already developed, the majority is listed on Table 4 and some are revised herein.

3.1. Pharmfilm®

MonoSol, one of the pioneer companies in the oral film industry owns a protected drug delivery technology, PharmFilm®. MonoSol's film technology is supposed to be more stable and robust than other conventional dosage forms with a loading capacity up to 80 mg. The Pharmfilm® is a polymeric matrix based on polyethylene oxide and hydroxypropylmethyl cellulose, which normally is related with fast dissolution rates and rapid drug absorption (Morales and McConville, 2011). However, MonoSol claims that this technological platform can be used for either fast dissolving system or buccal delivery. In fact, ondansetron hydrochloride had been successfully incorporated into the PharmFilm® technology as fast-dissolving system and others drugs substances such as montelukast sodium, rizatriptan, escitalopram oxalate, donezepil hydrochloride and epinephrine are being considered or under development as oral quick release formulations (Dixit and Puthli, 2009; MonoSol Rx, 2008; Monosol Rx LLC, 2013; NASDAQ OMX, 2013; PRNewswire, 2011; Reuters, 2014).

Additionally, as previously referred, the Pharmfilm® technology is also available as a slower release sublingual formulation (Suboxone® sublingual film) (Monosol Rx LLC, 2013).

Moreover, MonoSol has established strategic partnerships to develop biotechnology sublingual and buccal films based on PharmaFilm® technology, such as anti-diabetic oral films or films to deliver a vaccine for universal flu. Together with Midatech, MonoSol has developed Nanoinsulin (insulin gold nanoparticles, MidaForm insulin) to incorporate in the MonoSol's PharmaFilm® buccal film technology, for the potential treatment of diabetes. In the beginning of 2013, this investigational medicinal product was listed as being in clinical development. Nevertheless, another buccal PharmaFilm® loaded with MidaForm nanoparticles, containing insulin and GLP-1, is also in preclinical development (FierceDrugDelivery, 2012; Monosol Rx LLC, 2013; PRNewswire, 2013).

MonoSol in association with BiondVax Pharmaceuticals is developing a sublingual film formulation for vaccination, with the Multimeric-001 (M-001), for the potential prevention of universal influenza infection. It is expected that this type of formulation will allow the stability of the vaccine at room temperature (Reuters, 2012; Warren, 2012).

3.2. RapidFilm®

RapidFilm® is another patented technology developed by Labtec GmBH. The Rapidfilm® is a fast dissolving thin film based on water soluble polymers, non-mucoadhesive, which can vary from single to multilayer design system. This oral film platform is based in a PVA-Starch mixture plasticized with a medium Mw PEG. The composition used allows its fast dissolution rate when in contact with the oral mucosa (Leichs et al., 2008). It is claimed that RapidFilm® can accommodate up to 30 mg of the drug substances (Dixit and Puthli, 2009; tesa Labtec GmbH, 2015). The ondansetron Rapidfilm® was the first Rx oral film approval worldwide, but at the moment, there are at least three more Rapidfilm® products in the European market (APR Pharma, 2014) (see table 4).

3.3. VersaFilm™

VersaFilm™ technology was developed and patented by IntelGenx Technologies Corp. Initially developed as an edible film for the instant delivery of savoury flavours to food substrates, VersaFilm™ is now used as a system of choice for indications requiring an

immediate onset of action. Thus, the company advances that VersaFilm™'s disintegration time may be wrought from 30 seconds to 10 minutes, and it can be sublingual, depending on the intended application. The maximum drug load claimed is around 40mg. According to IntelGenx pipeline there are several drug substances in consideration or being incorporated in the Versafilm™ technology. However, only one has recently received a complete response letter from FDA, the rizatriptan VersaFilm™, an oral quick release film for migraine, developed together with RedHill Biopharma Ltd (IntelGenx and Biopharma, 2014; IntelGenX Corp., 2006).

3.4. Orally and Adhesive Disintegrating Films

KyuKyu Pharmaceuticals Co. LTD is a Japanese company that also has its own oral film platform technology. Actually, KyuKyu have 2 different technologies the "Orally Disintegrating Film", which dissolves in 10 to 30 seconds and the "Adhesive and Disintegrating Film" that adheres to the oral mucosa and the disintegration time can vary between 30 minutes and 8 hours (KyuKyu Pharmaceuticals Co.). KyuKyu presents a large pipeline with several oral dispersible films in the market, mainly in the Asian market. Recently, it started to develop buccal films for the treatment of cancer-related pain and nicotine dependence. In collaboration with Nippon Kayaku, a buccal formulation of fentanyl is being developed and a phase II trial is being conducted (Pharma & MedTech Business Intelligence, 2009). Regarding to the nicotine mucoadhesive disintegrating film, it was in the fourth quarter of 2013 listed as being in lead optimization.

3.5. SmartFilm®

Seoul Pharma has developed the SmartFilm® technology, an oral film with a high loading dose capacity, over 140 mg, capable of incorporating both hydrophilic and hydrophobic drugs, with unique taste masking technology and an eco-friendly manufacturing process (aqueous solution based). This South Korean pharmaceutical company launched Vultis® in the Korea market in 2012, a 140.45mg film formulation of sildenafil citrate. At the end of the same year, Seoul Pharma licensed it out to Pfizer which rebranded it as (Thomson Reuters Cortellis, 2013a, 2013b). The Sildenafil SmartFilm® technology is a fast dissolving film composition that uses a combination of magnesium oxide and sodium hydroxide to mask the bitter taste of the drug substance. Seoul Pharma is currently seeking and researching

other molecules to incorporate in its own oral film technology (Jeon et al., 2012; Jeong et al., 2013; Seoul Pharma, 2012).

3.6. BEMA®

BioDelivery Sciences International owns the worldwide rights of BEMA®, bio-erodible mucoadhesive, drug delivery technology. This drug delivery technology consists in a bioerodible polymer film which adheres quickly to the oral mucosa (less than 5 seconds) with a backing layer that assures the unidirectional diffusion of the drug substance. This multilayer buccal film technology can rapidly deliver a dose of drug across the oral mucosa and is completely dissolved within 15 to 30 minutes. The BEMA® technology may be developed to incorporate several drug substances, especially if a quick onset of action is required, the oral administration dose is not optimal (low oral bioavailability) or if parental administration is not an option (BioDelivery Sciences International, 2014b). Onsolis®, fentanyl buccal film, was the first product developed and marketed based on BEMA®'s technology, for the management of cancer pain in opioid-tolerant adults. It was launched in 2009 (HighbeamBusiness, 2009), but by March 2012, the Onsolis® production had been temporarily closed in the US, due to FDA concerns regarding the manufacturing process (Pešić, 2010). In January 2014, it was announced that the re-launch of the product is planned to occur in the second half of 2014 (PR Newswire, 2014; PRWeb, 2012). In Europe, the product was approved in October 2010 as Breakyl® (Raleigh, 2010). Currently the BEMA® technology is being applied to improve the delivery of other therapies, as the opioid dependence with Bunavail™, previously referred. The base formulation of the BEMA® layers is very similar. Both the active and the backing layer are composed by hydroxypropyl cellulose, hydroxyethyl cellulose, but the active layer presents additional mucoadhesive polymers, as polycarbophil and carboxymethylcellulose sodium. Interestingly the sweetener and flavour are only present in the backing layer (DataPharm, 2015; Morales and McConville, 2011).

3.7. Bio-FX® Fast-Onset Oral-Cavity ODF

Another technology platform is the Bio-FX® Fast-Onset Oral-Cavity ODF from NAL Pharmaceuticals Ltd. Briefly, it is an oral film formulated with a Bio-FX® absorption enhancer system, which increases the absorption of the drug substances through the oral mucosa with the aim to improve the oral bioavailability of drugs by avoiding the first-pass metabolism

and gastrointestinal degradation. This technology also incorporates a especial designed taste-masking system to improve taste and mouthfeel (NAL Pharma, 2014). Currently, there are no available products on the market with this technology, but several are under development.

3.8. Quicksol®

Quicksol® technology is the oral film platform from SK Chemicals that can accommodate a wide variety of drug substances. According to the company's pipeline, several drug substances were loaded, but only two are already on the market, Montfree (Montelukast) ODF and Mvix-S (Mirodenafil) ODF (SK Chemicals, 2014). Mvix-S is a thin, light and portable 50 mg oral film, available since January 2012, with a mirodenafil rate absorption 16.7% higher than Mvix tablet. Additionally, 15 days after its launch, Mvix-S sold over 1 billion units (SK Chemicals, 2012).

3.9. Fast-onset sublingual bilayer film

Cynapsus developed a fast-onset sublingual bilayer film of apomorphine, the APL-130277. The apomorphine in its neutral form (which may permit its fast mucosal absorption) is easily oxidized making difficult its incorporation in a film. Therefore, the apomorphine non-neutral form is loaded in one film layer, and a neutralizing agent is incorporated in other film layer, physically separated from each other. The neutralizing agent's layer dissolves quickly upon contact with saliva, allowing a fast reaction with the drug substance for a rapidly absorption. Clinical trials demonstrated that the maximum blood levels were reached within 20 minutes of administration, in the majority of subjects, and that it has a good local tolerability (no irritation). The submission of a FDA 505(b) (2) NDA is expected to 2016, since Cynapsus estimate to complete efficacy and safety studies by the end of 2014 and 2015, respectively. This sublingual formulation had already proved to work in the most severe cases of Parkinson's disease. Moreover, it may also present patient benefits and competitive advantages over the subcutaneous injection available and the inhaled and pulmonary approaches that are still in early development stages. According to their patent application the main polymer may be a cellulose, as HEC and / or a modified starch as maltodextrins, or even a mixture thereof (Cynapsus, 2014).

3.10. Biodegradable transmucosal film

In the first quarter of 2005, Auxilium Pharmaceuticals had licensed an oral drug delivery system, based on the PharmaForm technology after their drug delivery platform acquisition. This platform is a biodegradable transmucosal film that adheres to the upper gum, preferentially above the back molar, and after that it completely dissolves. PharmaForm technology may allow a more effective delivery of the substances through a higher rate of drug absorption, contributing to achieve the same therapeutic levels with lower doses when compared with the conventional dosage form, shorter onset of action, reduction of first pass metabolism and probably less frequent dosing. Auxilium was using this technology platform to incorporate drug substances for the treatment of overactive bladder, management of pain and androgen replacement therapy. According to the company information, the overactive bladder transmucosal film candidate was supposed to be moving to phase II studies, after being demonstrated that oxybutynin could be administered using the transmucosal film, but no development has been recently reported. Similarly, Fentanyl Pharmaform film, which was in phase I development in 2011, has no recent updated information. Regarding to testosterone transmucosal film (TestoFilm), it was in a phase III trial in the beginning of 2006. However, in the last quarter of the same year Auxilium discontinued the development claiming that the formulation would not be commercially viable (Auxilium Pharmaceuticals, 2005a, 2005b).

3.11. Eluting Bandage Platform

Pharmedica has an innovative and patented oral film platform, the Eluting Bandage Platform. This is a multiple characteristic platform that can be used as single or multiple layer, with fast or slow disintegration time and for combined or protective treatment. Eluting Bandage Platform is a multi-purpose and multi-functional device that can be used for a large range of products, from fresh breathers to prescription products. Pharmedica was developing oral formulations of insulin for the potential treatment of diabetes which had a launch predicted date for 2013. However, no more information is available, but according to the company's website the insulin, together with cannabinoids, is still listed as a potential product for the Eluting Bandage platform (PharMedica Ltd, 2014).

3.12. Xgel™

Xgel™ film's technology is the basis of Meldex International intellectual property, used in all its film systems: Soluleaves™, Foamburst™ and Wafertab™. Soluleaves™ platform can be designed for fast dissolving release or to adhere to the oral mucosa for a slow release of the drug substance. The Foamburst™ is a variant of the previous technology where an inert gas is passed during the film's manufacture resulting in a honeycomb structure that controls the dissolution rate of the drug substance contributing to a novel mouth sensation. In turn, the Wafertab™ platform is prepared from a placebo Xgel™ film in which the drug substance is added afterwards, thus preventing its exposure to unnecessary heat and moisture. This technology allows the manufacture of unstable drugs and the preparation of multilayer films (Arun Arya, 2010; Dixit and Puthli, 2009). In 2007, Meldex was developing nicotine Soluleaves™, but no recent development has been reported. According to the patent information this is a cellulose derivative based film (Zbygniew and John, 2006).

3.13. Thinsol™

BioEnvelop (or Paladin Labs) has also its own patented technology, the Thinsol™, an oral film based on enzymatically digested carboxymethylcellulose. This platform is a fast dissolving film (from five to 30 seconds) that allows a drug loading up to 60% and can be used to incorporate heat sensitive drugs, since it can be dried at low temperatures(Dixit and Puthli, 2009; Megget, 2007; ODFPharma inc., 2011; Paladin Labs Inc, 2007).

Interestingly, the NeuroHealing Pharmaceuticals Inc. developed an intra-oral slow dissolving mucoadhesive thin film based on the original formulation of Listerine Pocket Packs®. This modified oral film was developed to incorporate 1mg of tropicamide for sialorrhea treatment. In fact, this buccal film platform, designated by the code name NH004, has two main modifications: additional mucoadhesive properties and a slower dissolution capability. Therefore the NH004 easily adheres to the oral mucosa to dissolve slowly, over a period of 60-90 minutes, so the drug can be absorbed locally near the submandibular salivary gland (Neurohealing Pharmaceuticals, 2012). Currently a phase II clinical trial is being conducted in order to evaluate the safety and efficacy of tropicamide thin films in hypersalivation Parkinson's patients treatment (NeuroHealing Pharmaceuticals Inc, 2013).

3.14. Schmelzfilmen

The “Schmelzfilmen”, or melting film, was developed by Hexal and has currently four marketed products: olanzapine, sildenafil, donepezil and risperidone (LTS Lohmann Therapie-Systeme AG, 2014; Medicines and Healthcare products Regulatory Agency, 2013; Siebenand, 2010). Although there are some composition variations between the four formulations, they are mainly cellulose based films. The olanzapine oral film commercially available presents Ethylcellulose as main film forming polymer, plasticized with dibutylsebacate, and apparently according to the patent claims the HPMC is essentially used as gelling agent, although the amounts described may indicate that it can also be used as a film-forming polymer (Heads of Medicines Agencies, 2014; Klokkers et al., 2007; Krekeler and Neumann, 2012; Medicines and Healthcare products Regulatory Agency, 2011, 2013).

3.15. Others

Additionally, other attention-grabbing technology is Nutra3 Complex®, a fast dissolving strip with a high loading capacity around 250 mg per film. Unfortunately, there are no recent reports regarding this product (PR Newswire, 2010).

Also, FFT Medical presented its own transmucosal drug delivery technology based on a alginate polymeric film, the FFT trans-mucosal film. The company claims that this technology allows delivering a wide variety of substances by a rapid and consistent absorption through the oral mucosa surface directly into the bloodstream. They also refer that the drug dissolution is performed in a controlled rate to avoid the release to the saliva (Cohen et al., 2012).

Additional information about these technology platforms and others are summarized in table 4.

Table 4 - Oral Films' technology platforms, their owners or developers, related patents and associated marketed products.* – means that there is no specific information about the designation and /or status of the technology / product.

Brand name / Designation	Owner / Originator Company	Patent	Active Companies / Partner / Distributor	Commercial products	Drug substance	Phase / Status	Oral Film Type	Polymer	Ref.
Buccal Wafer	LTS Lohman	US-07407669 B2	Pfizer	Listerine ® Pocket Packs®		Launched			
			McNeil-PPC	Sudafed PE™	Phenylephrine	Discontinued	dispersible		(Spence Leung et al., 2001; Susan Banbury and MacGregor, 2011)
			McNeil-PPC	Benadryl ®	Diphemhydramine hcL	Discontinued			
			GlaxoSmithKline	NiQuitin Strips 2.5mg Oral Film	Nicotine	Launched			
VersaFilm™	Intelgenx Technology Corp.	US-20110136815	RedHill Biopharma		Rizatriptan film	Approved by FDA	dispersible		(IntelGenx and Biopharma, 2014; IntelGenX Corp., 2006; Paiement et al., 2011)
					Tadalafil film	Phase 2 Clinical Pilot study planed for Q1 2014	dispersible		
					INT0020 Insomnia	Phase 2 Clinical	dispersible		
					INT-0022; anti-psychotic agent	Phase 2 Clinical	dispersible		
					INT-0023 - Allergy	Phase 1 Clinical	dispersible		
					INT-0025 - Prostate hyperplasia	Phase 1 Clinical	dispersible		
					INT0031 Benign Prostatic Hyperplasia	Pilot study	dispersible		
					INT0030 – Animal health Vetafilm	Pilot study	dispersible		
					INT0036 - CNS	Discovery	dispersible		
Thinsol™	Paladin Labs BioEnvelop's™	WO-2009055923					dispersible		(Bélanger et al., 2009; Dixit and Puthli, 2009; Genevieve; et al., 2009; Labs and INC., 2007; Megget K, 2007; ODFPharma inc., 2011)
Pharmfilm ®	MonoSol Rx LLC	U.S. patent No. 7,824,588	C.B. Fleet Company	Pedia Lax® Quick Dissolve Strips	Sennosides	Discontinued		Polyethylene oxide and HPMC	(Bogue et al., 2012a; Bogue et al., 2012b; Dadey and Schobel, 2013; Dixit and Puthli, 2009; FierceDrugDelivery, 2012; Fuisz and Fuisz, 2012; Mickle, 2013; Mickle, 2008; MonoSol and Rx, 2008; Monosol Rx LLC, 2013; NASDAQ and OMX, 2013; PRNewswire, 2011c; Reuters, 2014; Susan Banbury and MacGregor, 2011; Yang and Fuisz, 2003; Yang et al., 2004, 2006)
		WO-2011017483	Reckitt Benckiser Pharmaceuticals	Suboxone® Sublingual Film	Buprenorphine Hydrochloride +	Launched	dispersible		
				Chloraseptic®	Benzocaine	Discontinued	dispersible		
			Prestige Brands	Little cold sore throat strip	(Pectin) + Ascorbic acid	Discontinued	dispersible		
		WO-2013019187 WO-2008098151	KemPharm's		Methylphenidate prodrug + ligand	Discovery	dispersible		
		WO-2012040262	MonoSol Rx LLC		Montelukast Sodium	Clinical	dispersible		
			MonoSol Rx LLC		Diphenhydramine hydrochloride	*	dispersible		
			MonoSol Rx LLC		Escitalopram	No Development Reported	dispersible		
			MonoSol Rx LLC		Rizatriptan	Discovery	dispersible		
			MonoSol Rx LLC		Epinephrine	No Development Reported	dispersible		
		WO-2013026002	MonoSol Rx LLC		Testosterone	Discovery			
		WO-2012177326	Midatech MidaSol Therapeutics		Insulin nanoparticles (MidaForm insulin)	Phase 1 Clinical	buccal		
			BiondVax		Multimeric-001	Discovery	dispersible		
		WO-2004066986 WO-2006031209; WO-03030881; WO-2012040262	MonoSol Rx LLC; Vestiq Pharmaceuticals Inc	Zuplenz®	Ondansetron Hydrochloride	Launched	dispersible		
			MonoSol/Midatech		GLP-1 peptides	Discovery	buccal		(APR Pharma, 2012)
Rapid Dissolving Film	Kyukyu Pharmaceutical Co Ltd	WO-2005117803; WO-2011108643;	Kyukyu Pharmaceutical Co Ltd;	Amlodipine OD Film	Amlodipine Besilate	Launched	dispersible		(Awamura et al., 2005; Awamura et al., 2010; Awamura et al., 2011; Furusawa, 2005; Intelligence, 2009; Ishise and Nishikawa, 2013; KyuKyu Pharmaceuticals Co.)
			MOCHIDA PHARMACEUTICAL	Voglibose OD Film	Voglibose	Launched	dispersible		
		WO-2010023874	Kyukyu Pharmaceutical Co Ltd		Loperamide	Launched	dispersible		
			Kyukyu Pharmaceutical Co Ltd; Maruho Co.,Ltd.	Olopatadine Hydrochloride OD Film	Olopatadine Hydrochloride	Discovery	dispersible		
		WO-2013121663	Kyukyu Pharmaceutical Co Ltd; Elmed Eisai co.,ltd.	Donepezil Hydrochloride OD film	Donepezil Hydrochloride	Launched	dispersible		
			Mochida Pharmaceutical Co Ltd	Zolpidem Tartrate OD Film	Zolpidem Tartrate	Launched	dispersible		
			Mochida Pharmaceutical Co Ltd	Loratadine OD Film	Loratadine	Launched	dispersible		
			Teva Pharma Japan Inc.	Waplon	Triamcinolone Acetonide		dispersible		
Adhesive and Disintegrating Film (ADF)		US 20040126330 A1 WO-03026654	Kyukyu Pharmaceutical Co Ltd		Nicotine	Discovery	buccal		(Awamura and Sawai, 2003)
			Kyukyu Pharmaceutical Co Ltd; Nippon Kayaku Co Ltd		Fentanyl	Phase 2 Clinical	buccal		

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Patent	Active Companies / Partner / Distributor	Commercial products	Drug substance	Phase / Status	Oral Film Type	Polymer	Ref.
	Novartis Consumer Health	Gas-X®	Simethicone	Launched	dispersible	PVA	(Susan Banbury and MacGregor, 2011)
		Theraflu®Thin Strips®	Dextromethorphan	Discontinued	dispersible	Starch	
		Triaminic® Thin Strips®	Phenylephrine	Discontinued	dispersible	Medium MwPEG	
WO-2008040534; WO-2009043588	Norgine (Europe and Middle East, Africa and Australasia) / SciClone Pharmaceuticals, Inc Takeda Canada (Canada) / Monosol RX §	Setofilm® / Ondansetron Rapidfilm® / Ondissolve™	Ondansetron Hydrochloride	Launched	dispersible dispersible dispersible dispersible		(Dixit and Puthli, 2009; Leichs et al., 2008; Press Release, 2009, 2013; Reiner et al., 2010)
WO-2011124570	APR Applied Pharma Research SA; MonoSol Rx LLC; tesa Labtec GmbH	Zolmitriptan ODF RapidFilm®	Zolmitriptan	Launched	dispersible		(Breitenbach and Schwier, 2012a; Press Release, 2012)
WO-2012110222	APR Applied Pharma Research SA; tesa Labtec GmbH	Aripiprazole ODF Olanzapine ODF	Aripiprazole Olanzapine	No Development Reported Registered	dispersible dispersible		(Breitenbach and Schwier, 2012b)
WO-2009043588; EP-02213278	APR Applied Pharma Research SA; Ferrer Internacional SA; tesa Labtec GmbH	Donepezil ODF	Donepezil	Registered	dispersible		(Breitenbach A et al., 2010)
WO-2007009801	Hexal Sandoz	Olanzapin HEXAL® SF Schmelzfilm	Olanzapine	Launched	orodispersible	Ethylcellulose	(Pharmazie, 2010)
WO-2007009800		Anti-migraine		*		HPMC	
WO-2010115724		Aripiprazole HEXAL® SF Schmelzfilm	Aripiprazole	*	orodispersible		
		Risperidon HEXAL® SF	Risperidon	Launched	orodispersible		
		Donepezil-HCl Hexal®SF	Donepezil	Launched	orodispersible		
WO-2012055947		SildeHEXAL SF (Tornetis)	Sildenafil	Launched	orodispersible	Backing layer – HPC, HEC	
WO-03086345 WO-2008011194;	KunWha Pharmaceutical Co Ltd; Meda AB; TTY Biopharm Co Ltd	Onsolis®	Fentanyl	Launched	Buccal	Active layer – polycarbophi	(A et al., 2003; BioDelivery Sciences International, 2014a; Vasisht and Finn, 2008)
WO-2007070632	BioDelivery Sciences International Inc	BEMA® Granisetron	Granisetron	Discovery	Buccal		
WO-2013096811; WO-2010008863	Endo Pharmaceuticals	BEMA® Buprenorphine	Buprenorphine	Phase 3 clinical	Buccal		
		BUNAVAIL™	Buprenorphine + Naloxone	NDA submitted to FDA on July 2013	Buccal		
WO2005016321	BioDelivery Sciences International Inc	BEMA® Triptan	Triptan	Discovery	Buccal		(Richard and W, 2005)
	Arius Pharmaceuticals Inc	BEMA® Zolpidem	Zolpidem	No Development Reported	Buccal		
					dispersible		(Dixit and Puthli, 2009)
WO-2010002418		Rotavax™	Rotavirus	phase II clinical trials (May 2013)	Buccal		(Auxilium Pharmaceuticals, 2005a; Mao et al., 2010; Zeng and Eleuterius, 2009)
			Testosterone	Discontinued	Buccal		
			Oxybutynin	No Development Reported	Buccal		
WO-2009151574			Fentanyl	No Development Reported	Buccal		
WO-2006114604 (A3)	Meldex International		Nicotine	No Development Reported	Buccal	Cellulose derivative	(Dixit and Puthli, 2009; Zbygniew and John, 2006)
WO-2010062688			Selegiline	Discovery	dispersible		(Chu et al., 2012; Pharma, 2014)
			Rizatriptan Benzoate	Phase 1 Clinical			
			Nicotine	Discovery			
			Levocetirizine	Discovery			
			Zolmitriptan	Discovery			
			Sumatriptan	Discovery			
			Sildenafil citrate	Phase 1 Clinical			
			Tadalafil	Discovery			
			Montelukast	Discovery			
			Fentanyl	Discovery			
			Cetirizine HCl	Discovery			
			Donezepil	Discovery			
			Zolmitriptan	Discovery			

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SmartFilm®	Seoul Pharma Co Ltd	WO-2013129889	Pfizer Inc	Vultis®	Sildenafil citrate	Launched	dispersible		(Choi et al., 2013; Jeong et al., 2013; Lee, 2013; SK Chemicals, 2014; Thomson Reuters Cortellis, 2013a, b)
					SPO-1202 Attention deficit hyperactivity disorder	Discovery			
					SPO-1201 Depression	Discovery			
					SPO-1113 Schizophrenia	Discovery			
					SPO-1108 Asthma	Discovery			
					SPO-1112 - Dementia	Discovery			
Quicksol®	SK Chemicals Co Ltd	WO-2013100564	SK Chemicals Co Ltd		Montelukast	Launched (Korea) Initiated EU development	dispersible		(Choi et al., 2013; Lee, 2013; SK Chemicals, 2014)
		WO-2013085276			Mirodenafil hydrochloride	Launched	dispersible		
Orally Rapid Disintegration Film	AstraZeneca plc			Anastrozole ODF	Anastrozole	Phase 1 Clinical completed	dispersible		(Astra Zeneca, 2012; AstraZeneca, 2012)
Thin film	NeuroHealing Pharmaceuticals Inc	WO-2006078998			Tropicamide	Phase 2 Clinical	Buccal	Pullulan	(Neurohealing Pharmaceuticals, 2012; NeuroHealing Pharmaceuticals Inc, 2013; Ron et al., 2006)
Eluting Bandage Platform	Pharmedica	WO/2012/104834			Insulin	No Development Reported	Buccal		(PharMedica Ltd, 2014; Ron, 2012)
					Cannabinoids	No Development Reported	Buccal		
Fast-onset sublingual bilayer film	Cynapsus Therapeutics	WO-2012083269; WO-2010144817	Cynapsus Therapeutics	APL-130277	Apomorphine	Phase 1 Clinical	dispersible bi-layer sublingual	Cellulose (HEC?) and / or modified starch (MDX)	(Cynapsus, 2014; Giovinazzo et al., 2012; John; et al., 2010)
Transmucosal Matrix Patch	ElSohly Laboratories, Inc				Dronabinol	Discovery	buccal		(Repka M A, 2003)
*	Aoxing Pharmaceutical				Midazolam maleate	No Development Reported	dispersible		(PRNewswire, 2011a)
					Naloxone	No Development Reported	Sublingual		(PRNewswire, 2011b)
*	CHA Bio & Diostech Co Ltd	WO-2010151020							(T; et al., 2010)
		WO-2012121461			Montelukast sodium	Pre-registration	dispersible		(Jun and Jung, 2012)
		WO-2014025206			Aripiprazole				(Kim, 2014)
Oral thin film	CTC Bio Inc	WO-2013002578	CTC Bio Inc; Dong Kook Pharmaceutical Co Ltd; Huons Co Ltd; Jeil Pharmaceutical Co Ltd; Jin Yang Pharm Co Ltd; KunWha Pharmaceutical Co Ltd		Clomipramine	Pre-registration	dispersible		(Jeon et al., 2012; Yoo et al., 2013; Yoon, 2013)
					Tadalafil	Clinical	dispersible		
					Donepezil	Clinical	dispersible		
		WO-2012108738			Sildenafil	Launched	dispersible		
Oral thin Film	CURE Pharmaceutical Inc		CURE Pharmaceutical Inc	PediaSUNATE™	Artesunate and Amodiaquine	Discovery			(PR Newswire, 2012)
Trans-mucosal Drug Delivery	FFT Medical	WO-2007073346			Adrenaline	Pre-clinical		Film-forming agent comprising an alginate salt of monovalent cation	(Cohen et al., 2012; Puri and Zielinski, 2007; Ryoo et al., 2012)
					Cancer Pain	Pending/under negotiation			
					Erectile Dysfunction	Out-licensed			
					Migraine	Out-licensed			
					Parkinson's disease	Under development			
		WO-2013143891			NRT / Nicotine	Out-licensed			(Wood et al., 2013)
Oral Dispersible Film	Aavishkar			Tadalafil	Tadalafil	Launched			(Pulliam, 2012)
				Ondansetron Hcl	Ondansetron Hcl	Launched			
				Simethicone	Simethicone	Launched			
				Dextromethorphan Hbr Phenylephrine Hcl 2.5 mg Strips (Cough & Cold)	Dextromethorphan Hbr Phenylephrine Hcl 2.5 mg	Launched			
				Vitamin B12 strips	Vitamin B12	Launched			
				Vitamin D3 strips	Vitamin D3	Launched			
				Electrolyte Strips	Vitamin B12 + Vitamin C + Sodium + Potassium	Launched			
				Energy strips	Caffeine + Vitamin B12 + Vitamin E + Vitamin B6+ Biotin+ Vitamin B5	Launched			
				Melatonin Strips	Melatonin	Launched			
				Teeth Whitening Strips	6% Hydrogen Peroxide	Launched			
				Breath Freshening Strips		Launched			
					AVISH-01 (AIDS)	Discovery			(Ryoo et al., 2012)
					AVISH-02 (Vaginal infections)	R&D completed			

4. Market overview

The feverous need of launching on the market renewed drug delivery systems of already approved drugs, in order to avoid generic competition, allied with the increased patient's compliance concern, have driven the attention of the industry for the orodispersible technology. There are enormous costs and time consumption in the discovery and development of new chemical entities and at the same time there is a real need to improve the efficacy, safety and compliance of some marketed products (Rekhi, 2009). In fact, almost a quarter of the drugs in the market do not provide the expected commercial returns due to its poor bioavailability and undesirable pharmacokinetics, demanding the development of innovative, better and suitable drug delivery systems (Bajaj and Desai, 2006). Therefore, the field of novel drug delivery technologies is highly competitive, but also very rewarding. The average cost of a new formulation is considerable lower than the cost involving the development of a new chemical entity, in about 40 million dollars, and generally takes also less time to develop (approximately 4 to 5 years). Actually, the changing market trends are very clear, the FDA approvals revealed a majority of reformulations or combinations of current approved products, in contrast with the 25% of new drugs approvals. In 2012, the total drug delivery market (DD) worth $142.5 billion (Vasisht and Finn, 2008), and presently, for the 10 most-popular DD technologies, its estimated market value of $81.5 billion (Richard and W, 2005) and is expected to achieve $92 billion by 2016 (Banbury and MacGregor, 2011).

The oral formulations are the number-one segment of the drug delivery, retaining more the larger sliver of the global market share (Richard and W, 2005). The orodispersible drug delivery systems have found its space as mainstream pharmaceutical products. In fact, eight in ten patients prefer orodispersible dosage forms over the traditional solid oral dosages. Orodispersible films initially emerged as an option for rapid drug delivery, and later with the buccal films as an alternative for low bioavailability drugs. From the market standpoint, oral films were immediately appointed as a successful delivery system probably fuelled by the huge success of Listerine® Pocket Packs®. Actually, oral films proved to be a rewarding commercial platform with a growing rate of 500 million dollars by year since 2006 and reached the 2 billion dollars in 2010 (Dixit and Puthli, 2009). Recent market analyses revealed that the oral film manufacturers have had rapid revenue growth from 2009-2014 and a similar trend is expected at least until 2019. It was estimated an annual growth of 17,1% in the same period for this sector (Belanger et al., 2009)

In 2001, Pfizer launched the Listerine® Pocket Packs® in the market, the first commercial oral film and a blockbuster that in one year exceeded 175 million dollars (Levinson, 2012). Nowadays, under new ownership, it still remains a viable business, although it is a shadow of its initial success. In 2003, Chloraseptic® Relief Strips, the first drug substance loaded oral thin film reached the market (Woolanh, 2003). Chloraseptic® Relief Strips with benzocaine provided an immediate and convenient relief of sore throat pain. In 2004, Novartis debuts in the oral film market with Triaminic® Thin Strips and Theraflu® Thin Strips to treat the most common symptoms of a cold in young children (ages 6-12) and older children (> 12 year old) or adults, respectively. These products were considered the "Best Product of 2004" only three weeks after their official launch, however, they are no longer available in the shelves (Parsippany, 2004). The melts-in-mouth portable delivery platform, with an easy and pleasant administration for children was probably the first multi-symptom cough and cold medicines that provided a fast and accurate dosing. In the beginning of 2012, Novartis decided to discontinue the manufacturing and distribution of Children's Triaminic® Thin Strips “after a careful consideration” (Novartis Consumer Health Inc, 2014). Novartis claimed that this decision was based upon a business need, but there are some suggestions that the removal of these products included production issues and poor sales (Buck, 2013; Cohen, 2013). The latter may probably be a reflection of the decline in the consumption of cough and cold medications due to the implementation of restrictions in 2007 (Freedman, 2014; Hampton et al, 2013).

Nevertheless, Novartis and Pfizer as marketing partners remain as top players in the thin film industry, their capitalization in these success brand products allowed them to gain a strong position in the field (IBISWorld, 2012). The thin film industry exhibits a high level of competition, but until 2010 no prescription oral film product had reached the market. It was a slow ride from the over-the-counter (OTC) market until the first prescription has been approved.

It was only in 2010 that the first Rx oral film, the ondansetron Rapidfilm® (Setofilm®) and the ondansetron Pharmfilm® (Zuplenz®), received European and FDA approval, respectively. Labtec GmBh, *APR Applied Pharma Research SA (APR)* and MonoSol Rx LLC (MonoSol) entered in the market with an ondansetron oral thin film for the prevention of nausea and vomiting, staunch that would capture a broad share of an appellative market that generated 1.9 billion dollars in the same year (Warren, 2011). A month after Zuplenz® launch, MonoSol together with Reckitt Benckiser Pharmaceuticals received FDA approval for Suboxone® sublingual film (Buck, 2013; Richmond, 2010). This thin film, with two drug substances,

buprenorphine and naloxone, approved for the treatment of opioid dependence in adults, was a huge success contributing to boost the oral films market. In 2011, Suboxone® thin film recorded sales of 513 million dollars and accounted for 96 percent of the oral transmucosal film market (PRNewswire, 2013b). In 2012, US sales of Suboxone® sublingual film alone exceeded 1.5 billion dollars and continue with gradual growth (BioDelivery Sciences International, 2014c). During clinical trial the patients seemed to prefer the Suboxone® sublingual film rather than Suboxone® sublingual tablets, due to its fast dissolution and more pleasant taste profile (Richmond, 2010). These factors attracted other companies, as Alvogen Pine Brook, Actavis, Intelgenx and BioDelivery Sciences International (BDSI) to develop similar technologies. In fact, the first three companies have recently filled abbreviated new drug applications (ANDA) for generic products of Suboxone® sublingual film whereas BDSI submitted a NDA with its own buccal film technology, the BUNAVAIL™. BDSI believes that BUNAVAIL™, which adheres to the inside of the cheek, has the potential to offer advantages over Suboxone® sublingual film (BioDelivery Sciences International, 2014c; Raleigh, 2014).

At the moment, none of these competitors' products are on the market since a patent infringement lawsuit against these applicants was submitted by Reckitt Benckiser (Reckitt Benckiser Pharmaceuticals, 2013). The success of the Reckitt Benckiser's prescription thin film proved the viability and value of this pharmaceutical form in the Rx market. In the US the oral films had come into a strong prominence and the prescriptions confirm the preference of these pharmaceutical forms (David S, 2013).

5. Market outlook

It is evident the increasing consumer acceptance of thin films and the market success that can be achieved. Generally, for this dosage form the OTC market is the preferred due to the close proximity with the consumer and the easily advertising. Additionally, in the USA market the convenience store category is extremely important and it has a high sales impact. There are more than 140,000 stores across the US, which achieved a gross sale of 708.2 billion dollars in 2012, with a continuous sale grew every year. Regarding the OTC products, in the Convenience Store News 2013 Industry Report, they are included as health and beauty care products, which in overall had an average gross margin of about 46.89 percent in 2012 (CSNews, 2013; Dixit and Puthli, 2009). It is a very tempting market that may lead to precipitated launches that sometimes may fail the expectations. As example of that, the Sudafed PE™ Quick Dissolve Strips was launched by Pfizer in the middle of 2005, for the relief of sinus pressure and congestion (Drug Store News, 2005; Pfizer, 2005). The brand sales were probably lower than expected due to the intense competition in the cough-and-cold products segment. In fact, considering only Triaminic® and Theraflu®, launched two years earlier, Sudafed PE™ effectively did not leverage a strong point-of-difference, not even in the price (Sudafed PE™ approximately 0,45$/film and Triaminic approximately 0,5$/film) (Parsippany, 2004; uCan Health LLC, 2014). In addition, it should be mentioned also that this segment sale were also off due to the implementation of some constraint measures for cough-and-cold medicines administration.

Nevertheless, all this background experiences are important for planning and develop new oral film. It is crucial to consider that the market success of a new oral film depends on its capacity of differentiate from its competitive set, beyond an attractive new dosage form. A product can achieve a decisive point of difference by its unique characteristics which may engage the customer's attention and bring also some significance. Therefore, considering the Rx market, it would be wise to deliver innovative drug substances, or others that bring additional value, to the oral film platform, otherwise it will be difficult to achieve success.

The manufacturing process of the oral films, when comparing with some complex oral delivery systems, is cost-effective and generally results in affordable end-products (Dixit and Puthli, 2009). However, the majority of the oral films is more expensive than conventional oral dosage forms and may not represent a clear benefit for the consumer. It should be reminded that once the form novelty wears off, it must be found a way to gain advantage over the other competitors / brands that do equal efforts for offering equivalent products.

On the other hand, considering the previous discussion, there is still a poorly explored market with this delivery platform, the veterinary market. It is well known that in general the animals tend to reject, spit out or vomit conventional dosage forms. In fact, giving oral medications to pets can be sometimes a dangerous practice, which can also reduce even the owner compliance, and compromise the treatment. It was evaluated the overall owner-perceived acceptability and the easiness administration of an orodispersible film compared with gelatin capsules in cats. Although there were no significant differences in the general acceptability of the owners, it was shown that the orodispersible films facilitated significantly the administration of the medication (Acton, 2011; Traas et al., 2010). Currently, few companies have developed oral films applied to this segment, and the available products are scarce and limited to OTC products based on blends of herbal extracts (Pace Wellness, 2015; Vet Guru, 2013). Additionally, IntelGenx presents in its pipeline the VetaFilm which rapidly hydrate and adheres upon contact with the tongue. It cannot be spit out and offers appealing flavours and scents to increase the acceptability in pets (IntelGenX Corp., 2006).

The veterinary industry includes several health products such as biologicals, medicated feed additives and veterinary pharmaceuticals that deals with a wide range of products: metabolic drugs, anti-infectives, reproductive aids, feed additives, vaccines, imaging diagnostics, topical solutions, parasite controls, oncologic, cardiovascular, and osteoarthritis drugs (ReportLinker, 2014).

It is estimated that the global animal health care market is worth between 92 and 102 billion dollars (Luke M, 2013). Regarding pets, there is an evident trend of the owners spending more money each year on their pets' health. In the US, it is expected that pet-owners spending will reach 33 billion dollars in 2014. This market segment will always be far from recession, driven by the idea that pets are considered family members. Besides that, the farm animals' health has been in the spotlight as a result of growing awareness of the impact that animal health may have in the human food safety and public health. The current unmet animal health needs, especially in animal disease surveillance, vaccines and lack of drugs in the senior animal veterinary care market (oncology, cognitive dysfunction syndrome, antidepressants) may also fuel the veterinary market growth (ReportLinker, 2014). Although, US remain the largest regional market for animal medication, Asia-Pacific is the fastest growing regional market. Regarding the products segment, the nutritional chemicals and parasiticides have the majority share in the total dollar sale, whereas vaccines and diagnostics are the fastest growing products segments (Freedonia, 2013; Global Industry Analysts, 2012).

It is clear that animal health is far to be little and insignificant health care niche. Actually, keeping pets and farm animals healthy might be a huge business. Therefore, innovative delivery platforms such as the orodispersible films, that quickly dissolve and become sticky in contact with saliva, can easily become valued by pet owners and animal caregivers.

Another unexplored market with these technology platforms is the biologics products. There are some references and efforts in the development of these type of products especially in immunotherapy, but at the moment no product had already reached the market. For example, vaccines in oral film formulations may have significant advantages. Despite of the needle free delivery, which may increase patient compliance, the higher stability may simplify the worldwide storage and distribution. The simplification of the logistic would also favour the mass immunization campaigns (Levine, 2010; Wang and Coppel, 2008). In fact, this type of small and stable vaccines could be easily sent by mail. Furthermore, it is expected that the human vaccine industry forecast reaches 41.85 billion dollars by 2018 (Lucintel insights that matter, 2013), with a CARG growth of 62.81 percent from 2013 to 2018 (Business Wire, 2014).

In addition to the quick-dissolving oral film influenza vaccine, under development by BiondVax - MonoSol Rx, others had already reported the development of oral film vaccines. During 2007, Johns Hopkins students had reported the development of an oral film vaccine, the rotavirus thin film delivery system which may surpass the drawbacks of the liquid vaccine. The original idea came from Aridis Pharmaceuticals that owns the rotavirus vaccine stable at room temperature and gave the challenge to the researchers from the Johns Hopkins School of Medicine. The oral film system is composed by a FDA-approved biocompatible polymer, which is pH-responsive. This composition design avoids the degradation of the vaccine in the stomach acid, allowing its release in the small intestine, triggering the immune response. According to their patent application these pH-sensitive microparticles are composed by a complex polymeric mixture, a copolymer of methacrylic acid or acrylic acid, as an Eudragit®- like copolymer, a pluronic polymer, a chitosan or a derivative or a combination thereof; and possible additional components as a surfactant, a sugar, a buffering salt and or a combination thereof (Mao et al., 2010). The Eudragit® polymers are an Evonik Industries AG trademark that offer a full flexibility of pH-dependent drug release (Evonik Industries AG, 2014). In fact, the manufacture method to prepare these microparticles includes the blend of two different grades of Eudragit®, possibly to accurately define the pH release of the drug. An anionic copolymer of methacrylic acid with ethyl acrylate is balanced with an anionic copolymer of methacrylic acid with methyl

methacrylate, so the drug release pH may be achieved somewhere between 5.5 and 7. The oral film composition is based on water-soluble polymers, as PVP or PVA, mucoadhesive polymers, as PEO and / or sodium alginate. Therefore, this composition allows that Rotavax™ vaccine melts quickly in a children's mouth, prompting them to swallow it. Unfortunately, no additional developments had been reported since then (Dixit and Puthli, 2009; Sneiderman, 2007). Currently, the Johns Hopkins School of Medicine also has a clinical trial ongoing to evaluate the Safety and Efficacy of a sublingual dissolving film for Peanut Allergy. The estimated date for the completion of the study is in the beginning of 2015 and it is expected that this sublingual immunotherapy with a dissolving peanut extract film has the potential to improve the efficacy of this type of treatment (Clinicaltrials.gov, 2013; Wood et al., 2013).

It has been an increasing interest in the development of micro- and / or nano- drug delivery systems associated to buccal polymeric matrices for a transmucosal delivery (Cavallari et al., 2013; Dott et al., 2013; Giovino et al., 2012; Jones et al., 2014; Morales et al., 2013; Rana and Murthy, 2013; Shen et al., 2014). These nanoparticle systems for oral absorption have been recently explored to incorporate poorly soluble drugs, to extend and improve the buccal release, to provide an improvement in the drug targeting and also to increase drug stability. These systems generally include nanosuspensions (Cavallari et al., 2013; Rana and Murthy, 2013; Shen et al., 2014), nanofibrous matrix system (Dott et al., 2013), solid lipid nanoparticles (Giovino et al., 2012; Jones et al., 2014), PEG-b-PLA nanoparticles (Giovino et al., 2012), submicron and nanosized particles of lysozyme (Lys)-loaded d , l –valine (Val) (Morales et al., 2013). The majority of these studies were initially applied to the proteins, especially due to its large size, low oral bioavaibility and poor stability, but they are currently extended to non-biologic drugs. Nevertheless, for the development of this type of systems it is important to consider the size of the coating particles. The size and shape of the particles may lead to undesirable aggregation and loss in the homogeneity, which could compromise the physical stability of the films in terms of both mechanical and mucoadhesive properties.

6. Conclusion

The main catalysts of the drug-delivery market are the patent cliff and more informed and autonomous consumers (Vasisht and Finn, 2008). Therefore, the demand side for pharmaceutical treatments has been changing and nowadays the approach is more patient - centred and quality- based.

Recent reports refer that in the next five-year period, many oral film drug producers will focus on extend their drug pipeline through other therapeutic classes (Belanger et al., 2009). At the same time it is expected that the formulation complexity may contribute to technical, manufacturing and regulatory barriers that may lessen the growth of the oral film market (Vasisht and Finn, 2008). So, it is critical that the value added by any new delivery platform boosts its own growth by the continuous improvement of consumer compliance and by enticing new consumers.

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Chapter II

Oral Films Characterization and Critical Quality attributes outline

There are no standardized methods for characterization or analysis of the oral films. The absence of guidance leads to the application of several and alternative techniques and statistical tools based on a Quality by Design approach that contributed to the development of extensive knowledge about this technological platform. Critical quality attributes (CQAs) were stablished to be used as reference and facilitate the identification of critical process parameters (CPPs).

Chapter II.1

Orodispersible films (ODFs): overall analysis with a multivariate Chemometric approach

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Submitted

Abstract

The main goal of the present work concerned the use the fundamentals of Chemometrics to analyse commercial orodispersible films (ODFs) aiming to develop basic understanding of the interplay between their main components, possible interactions and influence in the final product properties. GAS-X ® and Listerine ® ODFs were evaluated regarding their residual water content (Rwc), disintegration time (Dt), as well as chemical, thermal and mechanical properties. Reconstituted formulations were prepared based on a Mixture Design and the data were analysed by Principal component analysis (PCA) and Partial Least Squares regression (PLS). PCA analysis allowed the identification of fourier transform infrared spectroscopy (FTIR) spectra differences: all the reconstituted formulations are very different from each other and particularly dissimilar from the commercial formulation. PLS showed the effect of each excipient in the final polymer matrix: Pullulan, sweeteners, propylene glycol and menthol were found to have a high influence in the mechanical and thermal properties; the molecular weight (Mw) of cellulose derivatives effect on the Rwc and Dt and simethicone may affect greatly the thermal properties.

Although ODFs present a very complex composition the use of these tools allows the development of important knowledge about the system and the identification of the influence of each excipient in the final product properties as well as the major interactions in the polymeric matrix.

Keywords

Chemometrics; orodispersible films; galenical development

1. Introduction

In the past few years there has been an increasing concern to enhance patient compliance in order to improve health outcomes. Although, the oral route is the most preferred for the general population, several groups of patients have serious swallowing difficulties regarding the conventional dosage forms (Kelly et al., 2009). To overcome these problems, several fast-dissolving drug delivery systems have been developed. The Orodispersible films (ODFs) are a type of delivery system especially indicated for dysphagic patients and children. In fact, in some cases the ODFs may be acceptable for children below 2-year-old (Zajicek et al., 2013).

ODFs were introduced in the market by Pfizer in 2001 with Listerine ® Pocket Packs™. Since then ODFs have gained popularity in the US and are currently a well-accepted delivery system. Pharmaceutical dosage forms must follow strict regulations according to a set of quality criteria defined by the regulatory health authorities (Qiu et al., 2009). Although the main processes involved in the pharmaceutical development are well known, each development may represent a new challenge. Therefore, a regulatory framework based mainly on a risk-control and science-based approach has been introduced since 2002 (Qiu et al., 2009). These pharmaceutical regulations focusing on the quality by design (QbD) are essentially based on careful risk management and quality systems. QbD is a systematic study that provides the strategy, methods and tools for developing the data and information needed for a good product, process understanding and control (Qiu et al., 2009; Visser et al., 2015; Yu et al., 2014). Generally, the unit operations involved in the manufacturing of a dosage form have a significant influence on the final product properties. It is important to assure that the uncertainty and risk is minimized during all the processes and also assures some leeway to freely operate within a well-designed and structured working space. Therefore, several chemometric tools have emerged and are intensively used during the different stages of pharmaceutical development and manufacture, such as Design of Experiments (DoE) and multivariate analysis (El-Gindy and Hadad, 2012; Singh et al., 2013; Wesolowski et al., 2012; Yu et al., 2014).

DoE involves planning, conducting, analysing and interpreting controlled experiments to provide a mechanistic understanding of the relationship between critical process parameters (CPP), raw material attributes and critical quality attributes (CQA) of the product. Therefore, DoE is especially useful when dealing with multiple factors to understand and optimize the formulation system to achieve the desired target product profile (TPP) (Hwang and Kowalski, 2005; Visser et al., 2015). On the other hand, multivariate

data projection, such as Principal Component Analysis (PCA) and Partial Least Squares (PLS), may be used in combination with DoE during formulation or process development for the screening of a large number of parameters and further optimization. PCA provides an overview about the interactions, while PLS quantifies the correlation between excipient characteristics and product properties (Singh et al., 2013; Wold et al., 2006). In fact, these methods allow us to map different components which may be very useful in mixture design studies (Singh et al., 2013). Additionally with PCA, it becomes easier to identify the sources of variation in the data set and the patterns or trends in large data matrixes. The use of PCA during pharmaceutical development can be quite broad involving the search of new drugs, mapping and patterning closely related drugs' pharmacological, and chemical properties (Konieczna et al., 2012), or to evaluate the incompatibility between formulation components, by mapping thermogravimetric analysis (TGA) (Wesolowski et al., 2012). Recently PCA analysis was used to evaluate the correlation of several processing parameters of ODF solvent casting method in Loperamide and Ibuprofen cellulose based films. The analyses allowed to highlight the strongest influence of the thickness and mass in the studied systems (Woertz and Kleinebudde, 2015). Regarding the ODFs there is a considerable lack of guidance information, namely the influence of each component on the properties of the formulations and quality control. Furthermore, for dosage forms with such a complex composition, it can be very difficult to retrieve significant and meaningful information using conventional analysis only. PCA analysis was used to map the main composition differences in two commercial available ODFs, by the individual analysis of each formulation excipient, and the prepared formulations based on the correspondent patents. Hierarchical clustering was also used as a PCA complement to facilitate the analysis of the TGA data. This test allowed the organization of the data into clusters whose values are close to each other relative to those of other clusters (Institute, 2015) . The PLS method was used to evaluate the impact of each excipient on the final product properties (Leung et al., 2008; Schobel and Vangala, 2010).

This work intended to develop a basic understanding of the interplay between the main components of the formulation, possible interactions between them and their influence on ODF properties. The commercial ODFs selection was based on their composition, Listerine ® Pocket Packs™ composed of Pullulan, described as the most suitable film-forming polymer for ODF technology (Choudhary et al., 2011), and GAS-X ThinStrips® (GAS-X ®), composed of more than 50% (%w/w) of drug substance (Simethicone).

2. Material and Methods

2.1. Material

Acessulfame K (Nutrinova, Frankfurt, Germany); Carrageenan k, Gelcarin GP-379NF (IMCD UK Ltd, Sutton, UK); FD&C Blue #1 (Colorcon, Harleysville, U.S.); HPMC E5, Methocel E5 (Colorcon, Harleysville, U.S.); HPMC E15, Methocel E15 (Colorcon, Harleysville, U.S.); HPMC E50, Methocel E50 (Colorcon, Harleysville, U.S.); Maltodextrin (MDX) Maltrin M180 (LEHVOSS UK Limited, Cheshire, UK); Menthol (-)-Menthol (Merck, Darmstadt, Germany), Modified starch, Pure Cote B793 (LEHVOSS UK Limited, Cheshire, UK); Polyethylene Glycol (PEG), Lutrol 400 (BTC, Ludwigshafen, Germany); Propylene Glycol 1,2-propanediol (Merck, Darmstadt, Germany); Pullulan (Hayashibara Co., Ltd, Okayama, Japan); Simethicone (Resil chemicals Pvt. Ltd., Bangalore, India); Sorbitol (Colorcon, Harleysville, U.S.); Sucralose, Splenda (Merck, Darmstadt, Germany); Polysorbate 80, Tween 80 (Merck, Darmstadt, Germany); Hydranal Composite 5 (Sigma-Aldrich co. LLC, U.S.).

2.2. Methods

2.2.1. Preparation of the ODFs

The ODFs were prepared according to a general procedure displayed in Figure 8.

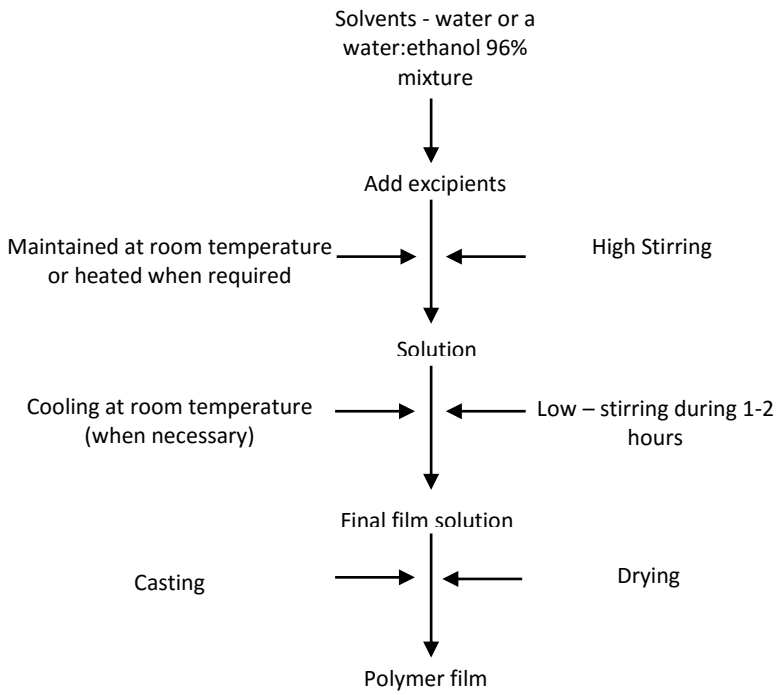

Figure 8 - Schematic representation of the general preparation procedure of the ODFs.

The solutions were prepared in two-neck round bottom-flasks (50 mL). The system was kept at room temperature or at elevated temperatures (60^{o}C - 90^{o}C) depending on the excipient used in each formulation. The film solutions were cast in polyvinyl chloride (PVC) foils, used as release liner / substrate with an Erichsen film applicator (Coatmaster 510, Erichsen, Hemer, Germany). To obtain different heights a vertically adjustable doctor knife was used and the film solutions were cast with speeds of 18 mm/s. The ODFs were cast with a gap of 300 (GAS-X ® formulations) or 500 µm (Listerine ® formulations). This height gap was selected based on some casts previously performed with each liquid mixture.

The cast ODFs are dried on the heated table of the Erichsen film applicator at 40 °C until dryness. The duration of dryness depends on the composition of each formulation.

To further characterize the ODFs, individual samples were prepared by cutting strips of regular dimension (60 mm^2, 2mm x 3mm) with a surgical scalpel.

2.2.2. Storage

The individual ODFs were stored under controlled conditions (43 % RH, room temperature), using a saturated solution of potassium carbonate for at least 5 days before testing.

2.2.3. Film mass

The ODFs were weighed using an analytical balance (Mettler Toledo AGXS, Mettler-Toledo Inc., Columbus, US) and the average weight was calculated (n=3).

2.2.4. Film thickness

The thickness of the ODFs was measured with a micrometer screw (Mitutoyo Digimatic Capiler, Mitutoyo Corporation, Japan) (n=3).

2.2.5. Tensile Strength

The mechanical properties of the ODFs were determined using a tensile testing universal apparatus (Zwick, Germany) with a load cell of 10 N. The measurements were performed similarly as described elsewhere. Briefly, ODFs with the dimensions of 60x20 mm and free from air bubbles or physical imperfections, were held between two clamps positioned at a distance of 40 or 50 mm. Firstly, a preload was applied in each assay and then the strips were pulled by the top clamp at a rate of 10,0 mm/min. The load automatically applied to the film was gradually increased and the corresponding magnitude of elongation was recorded until the break point of the film was finally reached. The parameters were directly retrieved from the software TestXpert (TestXpert, Zwick, Germany), namely Young's modulus (Et), tensile strength (σB) and elongation (εB). Measurements were run at least in three samples for each film.

2.2.6. Disintegration time

The ODFs were laid on a Petri dish and 4 mL of a phosphate buffer pH=6.8 (artificial saliva) at 37^{o}C was added. The time at the film samples disintegrate was recorded.

2.2.7. Karl-Fisher

The Karl Fischer Method was used to determine the residual water content of the ODFs. This technique basically consists in the quantitative reaction of iodine and sulfur dioxide by the addition of water, in the presence of a lower alcohol such as methanol:

$$SO_2 + I_2 + 2H_2O \xrightarrow{CH_3OH} 2HI + H_2SO_4$$

A sample was added to the titration flask filled with methanol previously dehydrated with a Karl Fischer reagent (Hydranal Composite 5, Sigma-Aldrich Co. LLC). Titration was then carried out using the Karl Fischer reagent with a known determined titer (mgH_2O/ml). Water content was determined based on the titration volume (ml). The polarization-current potential-difference method was employed as an end-point detection method.

These tests were performed in a Karl Fisher 787 KF Titrino (*Metrohm AG*, Herisau, Schweiz).

2.2.8. FTIR

To investigate any possible interactions between the excipients used in the preparation of the ODFs, infrared spectroscopy (IR) was used similarly as described by other authors (Alanazi FK 2007). Fourier Transform Infrared (FTIR) spectroscopy was carried out in a FTIR-4200 spectrophotometer (Jasco) recorded at a wave number comprised between 550 and 4000 cm^{-1} and with 4 cm^{-1} resolution. Attenuated Total Reflection (ATR) mode was used.

2.2.9. Thermogravimetric Analysis (TGA)

Thermogravimetric Analysis (TGA) was used to analyse the thermal stability of the polymer samples. TGA technique quantifies the weight variation/loss of the sample as a function of temperature. TGA test was performed in a TGA Q500 (TA instruments), at a heating rate of $10^{o}C$/min, from $0^{o}C$ to $500^{o}C$, under a constant nitrogen flow.

2.2.10. Statistical analysis

The screening and optimization designs were performed with JMP 10 (SAS Institute Inc., Cary, NC). The Custom Design platform was used to generate the mixture design performed, by introducing the factors as mixture variables and apply a model for the evaluation of the main factors and if possible the second interactions.

The Multivariate analysis (PCA and PLS) was performed with a Demo version of SIMCA 13 (Umetrics, San Jose, CA, USA) and the hierarchical clusters were performed with JMP11, based on Ward's minimum variance method (SAS Institute Inc., Cary, NC).

3. Results and Discussion

The composition of the evaluated ODFs is described in Table 5. Both commercial formulations (Listerine ® and GAS-X ®) are composed by a high number of excipients. Thus, to perform an adequate design of experiments, only the some of the excipients were used to prepare the test ODFs. This selection was assumed based mainly on the amount and functionality of each excipient in the final product.

Table 5 - Main components of Listerine ® and GAS-X ®, the commercial ODFs evaluated.

	Polymers	Plasticizers	Flavors	Colorants	Sweeteners	Surfactants	Thickening agents	Drug substance / Strength
GAS-X ®	Corn Starch modified Hypromellose Maltodextrin	Polyethyleneglycol Sorbitol	Menthol Flavor	FD&Blue#1 Titanium dioxide	Sorbitol Sucralose			Simethicone / 62,5 mg
Listerine ®	Pullulan	Polyethyleneglycol	Menthol Eucalyptol Aroma Orange oil	Green 3 Yellow 6	Sucralose PotassiumAcesulfame	Polysorbate 80 Glyceryln Oleate	Chondruscrispus (carrageenan) ceratoniasiliquagum Xanthan gum	Coppergluconate Thymol Methylsalicilate

The omission of some components was necessary to simplify the mixture design study. The introduction of several variables would imply a high complexity of the design that could lead to inconclusive and misinterpretation of the results.

Table 6 - Composition of the different test ODFs based on Listerine ® Pocket Packs composition (List) that were prepared and characterized based on a mixture design (%).

Film ID	Pullan	Propylene Glycol	Menthol	Carrageenan	Acessulfame	Sucralose	Tween 80
Selected ranges	49-92%	0-17%	0-10%	0-5.5%	0-6%	0-6%,	0.1-7%
List1	65.6	13.4	8.6	1.8	5.2	5.3	0.1
List2	79.0	15.1	3.7	2.0	0	0	0.2
List3	77.4	0	5.9	5.0	5.0	0	6.7
List4	58.4	15.7	9.2	0	5.9	5.9	4.9
List5	91.8	0	3.2	0	0	0	5.0
List6	49.4	15.5	9.6	5.5	6.4	6.3	7.3
List7	88.4	0	9.4	2.1	0	0	0.1
List8	68.3	16.1	0	2.1	0	6.2	7.3
List9	70.2	16.7	0	1.6	6.6	-	4.9
List10	66.5	15.7	3.9	1.1	6.3	6.4	0.1
List11	89.6	0	3.5	0.9	5.9	0	0.1
List12	80.8	0	0	2.1	6.5	3.9	6.6
List13	73.4	16.0	2.0	1.3	3.6	3.6	0.1

The ranges used to prepare the mixture design (Tables 6 and 7) were based on the formulation examples of the patents (Leung et al., 2008; Schobel and Vangala, 2010). The ODFs are singular dosage forms mainly composed by a film-forming polymer, usually the main component that allows the formation of the core matrix. In this design a constraint was introduced, the usage of Methocel E50 implied the absence of Methocel E15 and vice-versa, because it was not clear in the patent the most suitable Methocel grade to use.

Table 7 - Composition of the different test ODFs based on GAS-X ® composition (GAS) that were prepared and characterized based on a mixture design (%).

Film ID	Methocel E5	Methocel E15	Methocel E50	Maltrin	Starch	PEG 400	Sorbitol	Sucralose	Simeticone
Selected ranges	0-60%	0-75%	0-55%	0-35%	0-45%	0-18%	0-11%,	0-4.5%	5-60%
GAS1	43.3	0	0	0	43.5	0	0	0	13.2
GAS2	43.5	43.3	0	0	0	0	0	0	13.2
GAS3	56	0	0	33.7	0	0	0	0	10.3
GAS4	15.7	15.7	0	15.4	15.4	18.2	9.9	4.6	5.1
GAS5	76.6	0	0	0	0	0	0	0	23.4
GAS6	0	41	0	0	24.6	18.1	0	0	16.2
GAS7	0	76.2	0	0	0	0	0	0	23.8
GAS8	41.1	0	10.3	13.7	13.7	0	7.4	0	13.7
GAS9	59.1	0	14.8	0	0	0	11.2	5	10.0
GAS10	59.8	0	15.0	20.1	0	0	0	0	5.2
GAS11	13.7	0	54.4	0	18.1	0	0	0	13.8
GAS12	15.0	0	14.9	0	0	0	10.6	0	59.4
GAS13	12.4	0	33.0	16.5	0	0	9.2	4.2	24.6
GAS14	15.7	0	47.1	0	0	0	8.8	3.9	24.4
GAS15	13.5	0	49.6	0	18.0	0	0	4.5	14.3
GAS16	14.8	0	14.9	0	19.8	0	0	0	50.5
GAS17	12.0	0	47.5	0	0	16.5	0	0	24.0

3.1. FTIR analysis

The direct analysis of the FTIR spectra allows the identification of some specific chemical groups (Figures 9 and 10). This analysis is usually employed to evaluate the drug-excipients or excipient-excipient interactions (Cilurzo et al., 2008; Kumar et al., 2014). This evaluation is normally based on known and characteristic stretching regions of the FTIR spectra that usually are missing or diminished in intensity due to electrostatic interactions and / or hydrogen bonds between the components. Kumar et al., was able to relate the probable drug-polymer interactions present in the FTIR spectra with the drug dissolution parameters (Kumar et al., 2014). Others have also used this assay to evaluate the suitability of some plasticizers for specific polymers through miscibility evaluation shown by slight modifications of the polymer main bands. These may correspond to shift stretching regions and/or band intensity (Cilurzo et al., 2008).

The prepared ODF formulations present a very complex composition (see Table 5) which difficult the FTIR spectra analysis. Nevertheless, specific functional groups were identified.

The –OH band (band A, Figure 9) was observed in all spectra as expected, since this functional group is very characteristic and abundant in hydrophilic polymers, such as starches and cellulose. The C-H bonds, very common in organic compounds, are also presented in all spectra (band B, Figure 9). The –O- group is detected in different formulations and corresponds to the sharp band identified with the letter E. Other characteristic bands of some excipients, like C-Cl of Sucralose (band F, Figure 9) can be found in Listerine ® and GAS-X ® spectra.

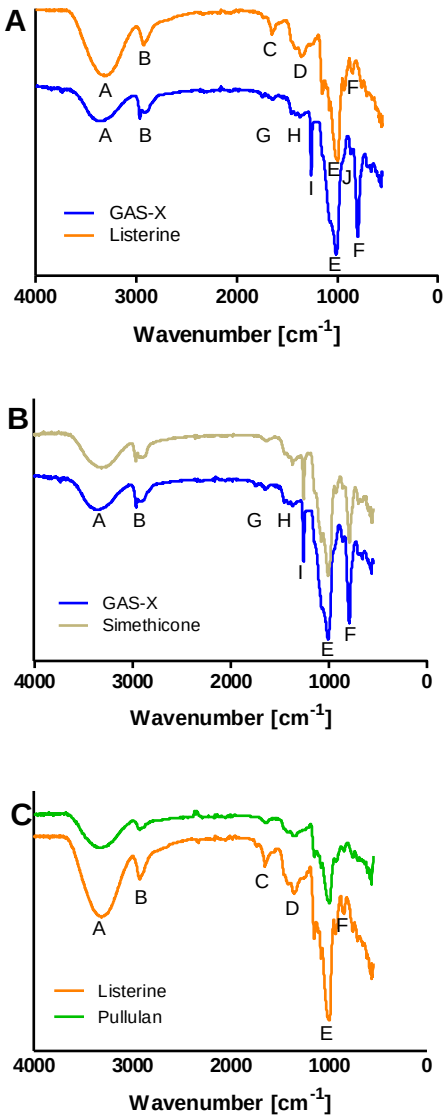

Figure 9 - FTIR spectra of the marketed formulation and its main components. (A) Represents GAS-X ® and Listerine ® Pocket Packs. (B) Represent GAS-X ® and Simethicone. (C) Represent Listerine® and Pullulan. Absorption peaks of 2200- 2400 cm^{-1} region (CO_2 band) were not considered in the analysis.

Besides the bands identified above there are others specific bands of each formulation. In the Listerine ® FTIR spectra (Figure 9), it is possible to identify the C=C band (1680-1600cm^{-1}), the double bond present in the sweetener acessulfame K and in the surfactants polysorbate 80 and glyceryl oleate (band C, Figure 9). The sulfone group (R_2SO_2) of the acessulfame K is identified by letter D (1340-1280cm^{-1}) (Figure 9) (Yadav, 2005).

It is important to consider that the conformation and hydration of the polymers may influence their FTIR bands. These band modifications for the majority of biopolymers are usually observed in a specific absorbance region, at 1200-950 cm^{-1} (Xiao et al., 2014). Xiao et al. showed the band changes of pullulan spectrum during drying and film formation. As expected, the most prominent changes were verified in the 1200-950 cm^{-1} region. Briefly, the drying time contributed to an overall increase of absorbance probably due to the higher vibration of specific pullulan groups, C-O-C, C-O, C-C and C-O-H. It was also shown that the drying process contributes to the formation of more-ordered molecular structure, because the shape of the peaks continuously became larger and the area ratio increases. This process is accompanied by the inter-chain interactions increase between pullulan molecules that have a less-ordered conformation in solution (Xiao et al., 2014). There are no clear shift variations of the pullulan characteristic bands in our studied formulations and the commercial film. This observation may suggest that there are no strong bonding between the pullulan molecules and the other excipients, and probably they simply interpose between the polymers net without a stronger linkage. The differences in the intensity of the bands absorbance are probably due to the different pullulan concentration between formulations.

Regarding GAS-X ® FTIR spectra (Figure 9) it is clear the presence of the bands of general aromatic (1600-1430cm^{-1}) and aromatic amine compounds (1340-1250 cm^{-1}) from the colorant used in this formulation, FD&Blue#1. Also, the characteristic band of the titanium dioxide (TiO_2) is represented by letter J (Figure 9A). The simethicone band is identified in all spectra, especially in the commercial ODFs due to its high concentration and characteristic bond Si-CH_3, identified by letter I (Figure 9A) (Alavi et al., 2014; Yadav, 2005). Additionally, there is no evident shift of the simethicone bands in the formulations analysed indicating a weak interaction of this component with the other excipients.

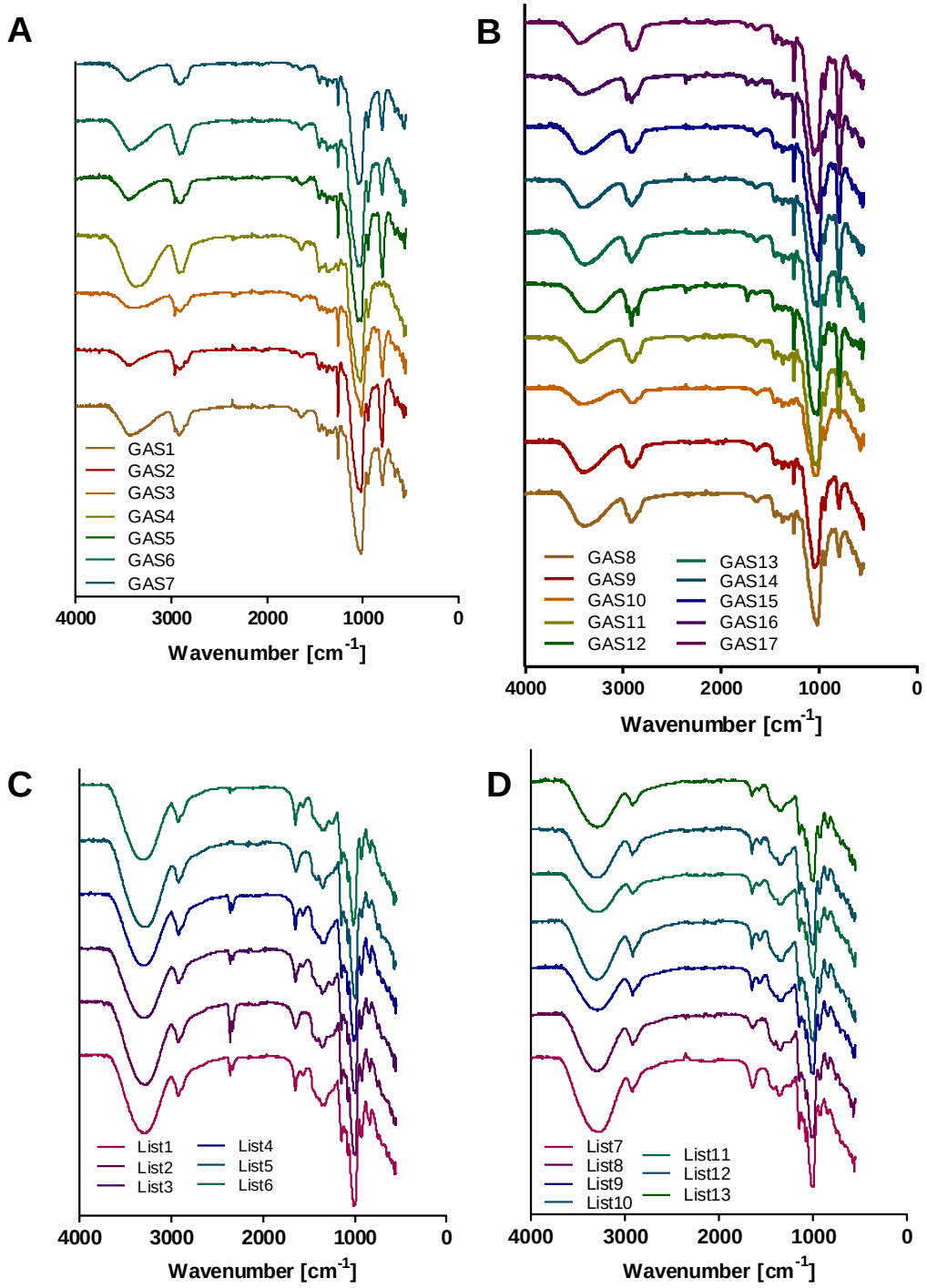

Figure 10 - FTIR spectra of screened GAS-X ® and Listerine ® formulations. Absorption peaks of 2200-2400 cm^{-1} region (CO_2 band) were not considered in the analysis. (A and B) Represent the GAS-X ® formulations evaluation. (C and D) Represent the Listerine ® formulations evaluation.

The analyses of these spectra allow inferring about the possible presence of some components in the formulations and their relative concentration, since the band intensity is directly proportional to its concentration. This aspect is particularly clear in the dyes bands, which due to its lower amount in the formulation have a much lower intensity comparing with other components such as Simethicone, for example. Moreover, it becomes difficult to distinguish differences between the spectra of the prepared formulations (Figure 10) from the commercial ODFs spectra or even the commercial ODFs spectra with the main component spectrum (Pullulan in Listerine ® ODFs – Figure 9C and Simethicone in GAS-X ® ODFs – Figure 9B) using only to the FTIR spectra bands and frequency shifts. On the contrary, using multivariate analysis it is possible to highlight spectra differences related with the composition of the formulations (Figure 11).

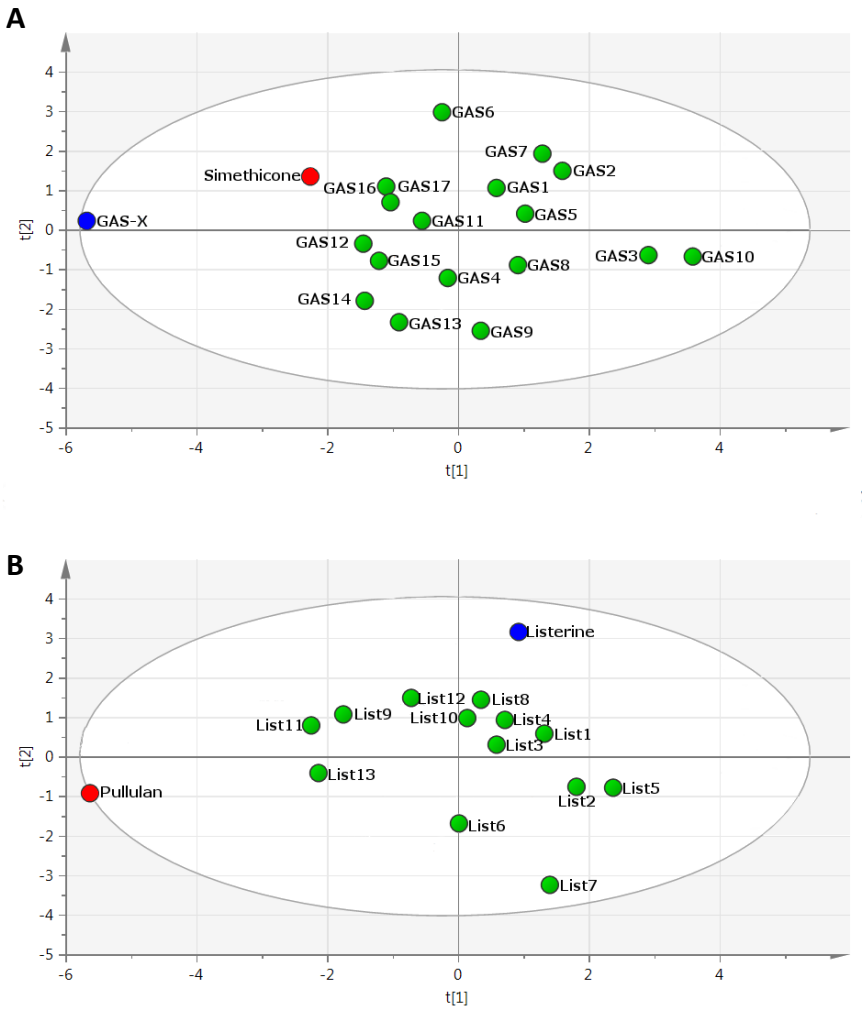

Figure 11 - Scores Scatter Plot: shows the possible presence of outliers, groups, similarities and other patterns. (A) Represents the GAS-X ® formulations evaluation. (B) Represents the Listerine ® formulations evaluation. The red dots represent the main component of each formulation (Pullulan in (A) and Simethicone in (B)) and the blue dots correspond to the Commercial film spectra (Listerine ® in (A) and GAS-X ® in (B)). The green dots correspond to the screened formulations. t[1] and t[2] are the two vectors calculated by the Principal component analysis (PCA) of a data table, which summarize all the variables entering the analysis.

The PCA was used to map the different FTIR spectra. It is clear that there are significant differences in the formulations especially when compared to the commercial ODFs and main excipient (Figure 11). Regarding Listerine ® formulation (Figure 11 A), it is notorious that the Pullulan spectrum is very different from others since it is plotted as an outlier (outside the ellipse). Therefore, it can be concluded that the diversity of functional groups of this polymer, contributes to several bands along the spectra turning difficult to distinguish specific bands that result from excipient-excipient interactions. The Listerine ® spectrum is slightly different from the prepared formulations, which can be explained by the reduced number of excipients used in the preparation of the film formulations and their percentage.

The GAS-X ® formulations spectra are all very different from each other and particularly different from the commercial formulation, which is plotted almost as an outlier (Figure 11 B). These results highlight the complexity of the formulations and the importance of each excipient in the overall properties of the ODFs. Furthermore, other important aspects to take into account that may be related with the differences found, concern the method and preparation conditions in a large scale, involving strictly and highly controlled procedure conditions (e.g. drying and blending time, etc.).

The distance between the scattered points in Figure 11 suggests a significant difference from each formulation that may be explained by the concept of the experiments purposely generated for the analysis. The construction of the mixture design assumes that the experiments are designed to cover a surrounding space implying that the formulations tend to be representative of the entire system and therefore with a different composition from each other. However, probably due to the high concentration of some components, it is possible to show some similarities (FTIR spectra).

3.2. Disintegration time, Residual water content, Mechanical and thermal properties analyses

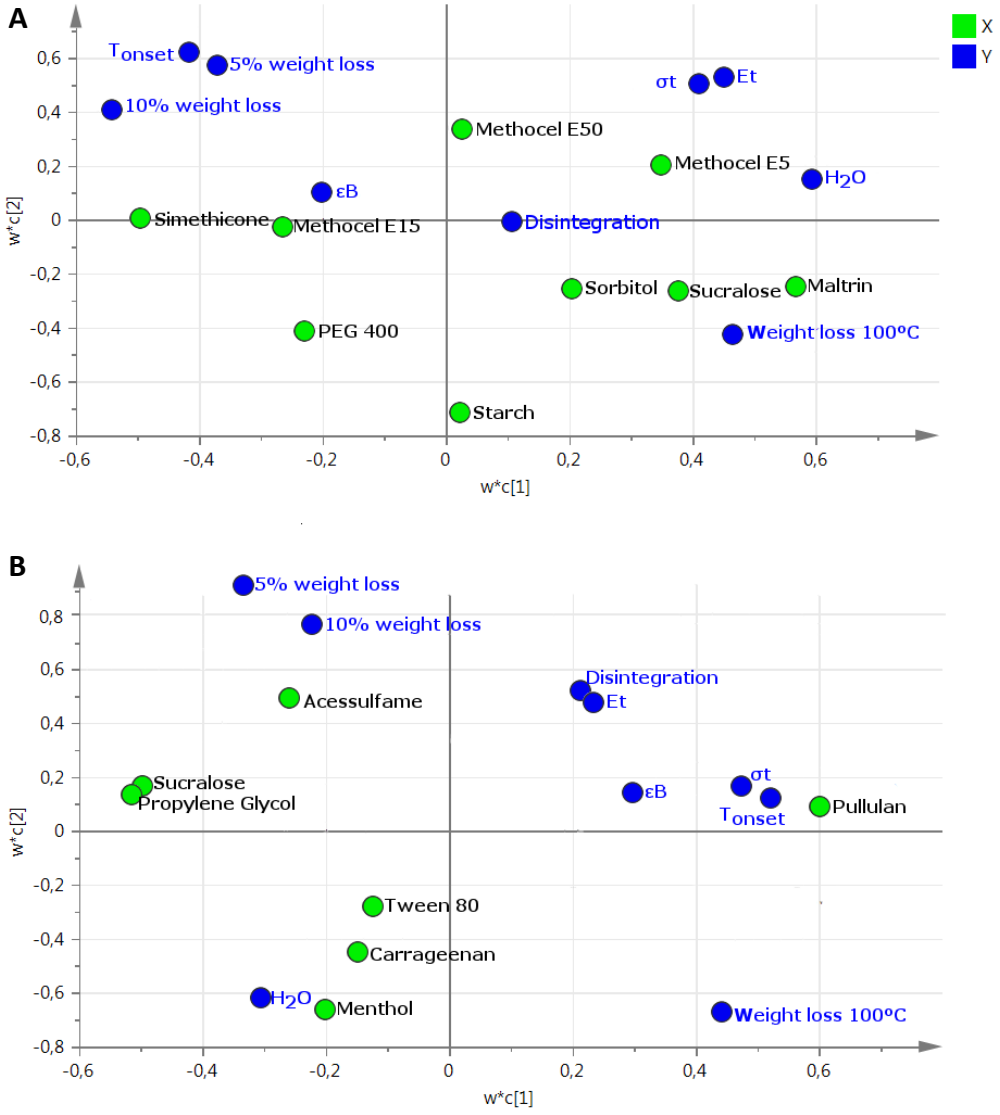

Figure 12 - Loadings Scatter plot: highlights the relation between the excipients studied, green dots, and the characterization parameters evaluated, blue dots. (A) Represents GAS-X ® formulations. (B) Represents Listerine ® formulations. Evaluated parameters: σB (MPa) - tensile strength, εB (%) - elongation at break, Et (MPa) - Young's Modulus, H2O (%) - residual water content, Disintegration (s) time, Tonset (ºC), Weight loss at 100ºC (%), 5% weight loss (ºC), 10% weight loss (ºC). The above w*c is a superimposition of the w* plot (loading weights that combine the X-variables) and the c plot (Y-loading weights) of one PLS component against another, 1 and 2. To analyse this plot, imagine a line through the origin and project other X- and Y- variables on this line. Variables opposite to each other are negatively correlated and positively correlated to variable situated near them.

The formulations prepared allowed to retrieve some important conclusions about the influence of the different components in the ODFs properties (Figure 12). Regarding the Listerine ® formulation (Figure 12B), it is clear the strong and direct correlation between Pullulan with the mechanical (σB and Et) and thermal (Tonset and Weight loss until 100^{o}C) properties. Therefore, these properties are highly dependent on Pullulan's amount in the film (also confirmed by PLS regression coefficients, data not shown). Indeed, Pullulan films have been already reported as films with high elastic modulus and moderate to high tensile strength (Kawahara et al., 2003). On the other hand, menthol affects negatively the elasticity modulus and the thermal stability of the films. In fact, the small relative size of the menthol molecule, may allow it to interpose between the polymer chains playing also the role of a common plasticizer. These compounds are an important class of low molecular weight non-volatile compounds that are widely used in pharmaceutical industry. These substances are mainly used to improve the flexibility, workability or processability of polymers by lowering the glass transition temperature (Tg) (Vieira et al., 2011). The possible presence of menthol between polymer chains may reduce the polymer-polymer interactions contributing to a higher degree of freedom of motion between the polymer strands. Under this condition, there is a reduction in the deformation and hardness tension and probably in the electrostatic charge of the polymer. Hence, menthol is known to be able to reduce the elastic modulus by increasing the polymer matrix flexibility and simultaneously the resistance to fracture (Vieira et al., 2011). Similarly the increase of propylene glycol is also associated with the decrease of the tensile strength (σB) and the ODF thermal stability (lower Tonset). It would be expectable that propylene glycol may influence the film mechanical properties, since it is used mainly as plasticizer in the pharmaceutical industry (Vieira et al., 2011). Additionally, it is reported by others the effect of this compound as plasticizer, contributing to the decrease of tensile strength and Young's modulus, and the increase in the % elongation, turning the films from brittle to flexible (Jagadeesh et al., 2013). Curiously, the Sucralose seems also to be associated with a decrease in the tensile at break. According to these results it may be possible to conjecture that sucralose molecules probably have the ability to break some of the secondary bonds associated with the polymers' crystallinity.

It was also verified in this polymeric system that the added sweeteners in general tend to enhance the polymer thermal stability. Acessulfame increases the temperature required to lose 5% of weight and Sucralose increases the temperature necessary to lose 10% of weight. This result may be related with the chemical properties of each excipient. The sucralose is described as being stable until 119°C (Bannach et al., 2009), whereas Acessulfame does not

have a consensus value in literature. However, it is reported that Acessulfame decomposition temperature is usually observed at 200°C. Even so, it is also reported that the surrounding environment, such as the pH, may also influence this property (Mayer, 1991; O'Brien-Nabors, 2001). The high thermal stability of these excipients at lower temperatures may have a positive effect on the polymeric matrix. Contrarily, menthol decreases the temperature necessary to lose 5% of the film's weight. For this excipient, it is difficult to find thermal profiles reported in the literature. The melting point described is around 34°C, which may contribute to the decrease of the matrix mechanical stability at room temperature (Rowe et al., 2012). Curiously, sucralose is also associated with a decrease of the degradation temperature, similarly to menthol and propylene glycol. This highlights that the influence of sucralose is not linear because this compound help to stabilize the matrix until a certain temperature but it can also contribute to diminish it.

The thermal profile of the different formulations were grouped according to their similarities, based on clustering statistical analysis (Figure 13)

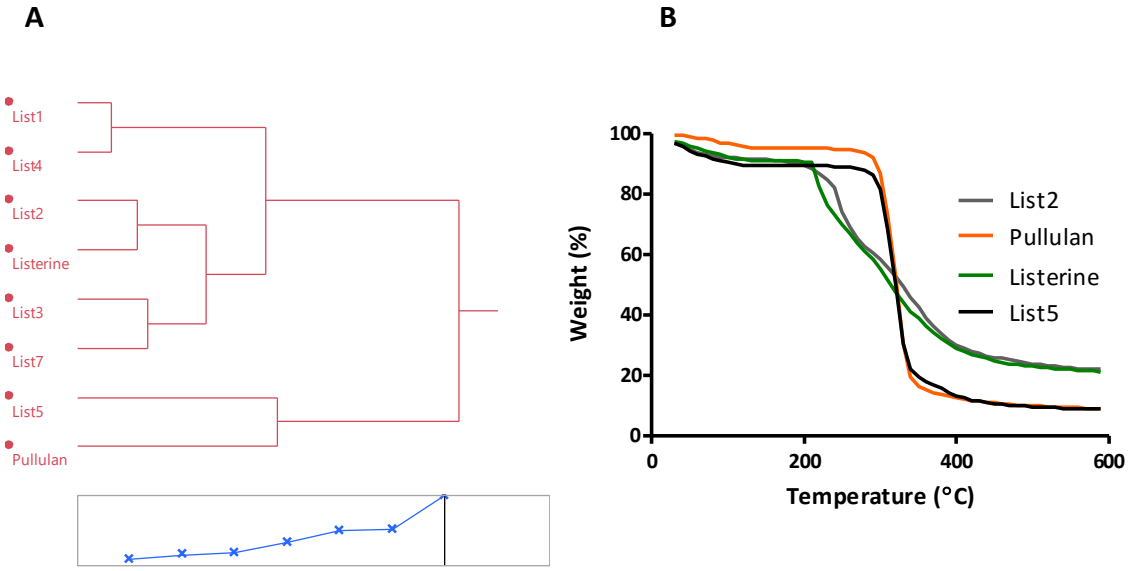

Figure 13 - TGA data profiles analysed by Hierarchical cluster test (A) and TGA data profile (B). (A) Represents a dendrogram that lists and group each observation based on its similarity (by Ward's method).of the Commercial film tested. (B) Represents the TGA profiles of the Listerine ® film-forming polymer (pullulan) and two relevant formulations tested (List2 and List5).

According to Figure 13, the thermal behaviour of List2 is very similar to the commercial film; both belong to the same cluster and have analogous TGA curves. This data confirms the prepositions assumed before for the effect of each excipient on the thermal stability. Based on the List2 and List 5 compositions (Table 6) it is evident that the addition of propylene glycol and menthol to the polymeric matrix contributes to a decrease on the thermal stability. List 5 is the formulation with the thermal profile more similar to pullulan, which is expected since it corresponds to the film formulation with the highest amount of this excipient.

Regarding GAS-X ® formulations (Figure 12 A), it was also clear the influence of the plasticizer, PEG 400, in the mechanical properties of the polymeric matrix. The increase of PEG 400 contributes for the decrease of Young's Modulus and tensile strength, due to the reasons pointed out above involving the main characteristics of the plasticizers. The decrease in the Et is associated with a reduction of the rigidity of polymer matrix due to the lower number of polymer-polymer interactions (Wypych, 2012). On the other hand, the increase of Methocel E5 seems to have a more significant influence in the increase of Et and σB, than the other higher Mw based celluloses (Methocel E15 and E50). In literature, it is commonly reported the direct and linear correlation between the Mw and mechanical properties (Carstensen, 2000). However, the results obtained for these complex polymeric matrices suggest opposite conclusions. Although this result seems surprising, it should be pointed out that the elastic modulus also depends on the chain organization and draw ratio. The glassy or amorphous nature of the polymer may origin non-linear behaviour of the elastic modulus values, being sometimes unpredictable (Swallowe, 1999). For semi-crystalline polymers, such as HPMC, it is described that its elastic limit (yield strength) may at times increase with the Mw, due to second-order effects of crystallinity Mw degree (Akinosho, 2012; Swallowe, 1999). These facts may justify the lower polymeric matrix rigidity results obtained for high molecular weight Methocel. Hence, the tendency observed may not only be associated with Methocel increase but also related with the increase of modified starch in the same formulations (GAS9, GAS11, GAS2, GAS3). The interactions between the starch and cellulose chains may cause a decrease of their own mobility contributing for an increase of the Et. The hydrogen bounds that may be established between starch and cellulose hydroxyl groups might contribute to increase the rigidity of the polymeric film contributing for the elevated Young's modulus observed.

Regarding the thermal properties, the sweeteners, maltodextrins and simethicone may play also an important role. The increase of simethicone contributes to a high thermal stability,

showed by the higher temperatures for 5% and 10% weight loss. The simethicone is an inert mixture of polydimethylsiloxane and hydrated silica gel (Watson, 2014). These polymers are very stable, retaining their own properties when exposed during long periods at higher temperatures, compared with the majority of organic polymers. In fact, the Tg of polydimethylsiloxanes depends on the particular substituent groups to the main -(Si-O)x- chain backbone. Generally, Tg values of these polymers vary between -150 to -70°C and the onset temperature for irreversible degradation may be up to 300-350 ^{o}C. On the contrary, the majority of the organic -C-C- type polymers, rarely present Tg values below -70°C and the onset temperatures hardly exceed 150-200°C. Therefore, the inclusion of the simethicone in the formulation provide to the polymeric matrix desirable properties, higher flexibility at room temperatures, due to the low Tg, and higher thermal stability (Jones et al., 2001).

On the other hand, the increase of Maltodextrins (Maltrin) (MDX) contributes to a high weight loss when the temperature is elevated at 100^{o}C and lower temperature are needed to achieve 5% or 10% weight loss. These evidences may be related with the hygroscopicity of MDX already described in literature and verified by the Karl-Fisher test (data not shown) (Embuscado and Huber, 2009). The ability to retain high amount of water in the polymeric matrix is associated with the increase of weight loss at lower temperatures, especially up to 100^{o}C.

The increase of Sorbitol and Sucralose contribute to lower the temperature for 10 % weight loss (poor thermal stability). Additionally, the increase of Maltodextrins, sorbitol and / or sucralose contributes for a decrease of the degradation temperature (T_{onset}), also associated with poor thermal stability. Generally, it is advisable to store sucralose below room temperature, since under high temperatures it may easily break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride (Rowe et al., 2012). This poor time-temperature resistance of sucralose may be related with the same influence in the final polymeric matrix. On the contrary, sorbitol is described as being chemically inert and relatively stable at elevated temperatures but when combined with other excipients its thermal stability may be altered. In fact, it is known that this phenomenon is common in some excipients, as for example liquid polyethylene glycols, like PEG400, which alter its melting point from ca. 100^{o}C to around 35–40^{o}C when added to a excipient mixture (Rowe et al., 2012).

The disintegration time increases with Methocel E50, but tends to decrease with the increase of sorbitol. The higher amount of Methocel E50 (Mw 45,000) in the film

composition is mainly compensated by a reduction of the Methocel E5 (Mw 10,000) quantity used. This fact justifies the high disintegration time, which normally increases with the increase of the polymer molecular weight. This assumption is confirmed by the faster disintegration time of the formulations in which the Methocel E50 is replaced by Methocel E15. The amount of sorbitol can lead to a decrease of the disintegration time, which may be related with its ability to interpose between the individual strands of polymer associated with breakdown of polymer-polymer interactions. This effect facilitates the entrance of water molecules that posteriorly would be favourable to the disintegration of the polymeric matrix. In fact, it is already described that the sorbitol molecules are easily inserted between the HPMC strands that due to increase of hydrogen bonds leads to the reduction of intermolecular forces (Somashekarappa et al., 2013).

Finally, the residual water content tend to increase with Methocel E50 and Maltodextrins, but decreases with the presence of Methocel E15 (Mw 30,000). The higher Mw of Methocel E50 implies longer polymer chains with hydrophilic groups (e.g. –OH), which may be related to the higher retention of water in the film matrix, when compared with Methocel E15 films. In the case of maltodextrins, it is associated with the inherent hygroscopicity as described earlier.

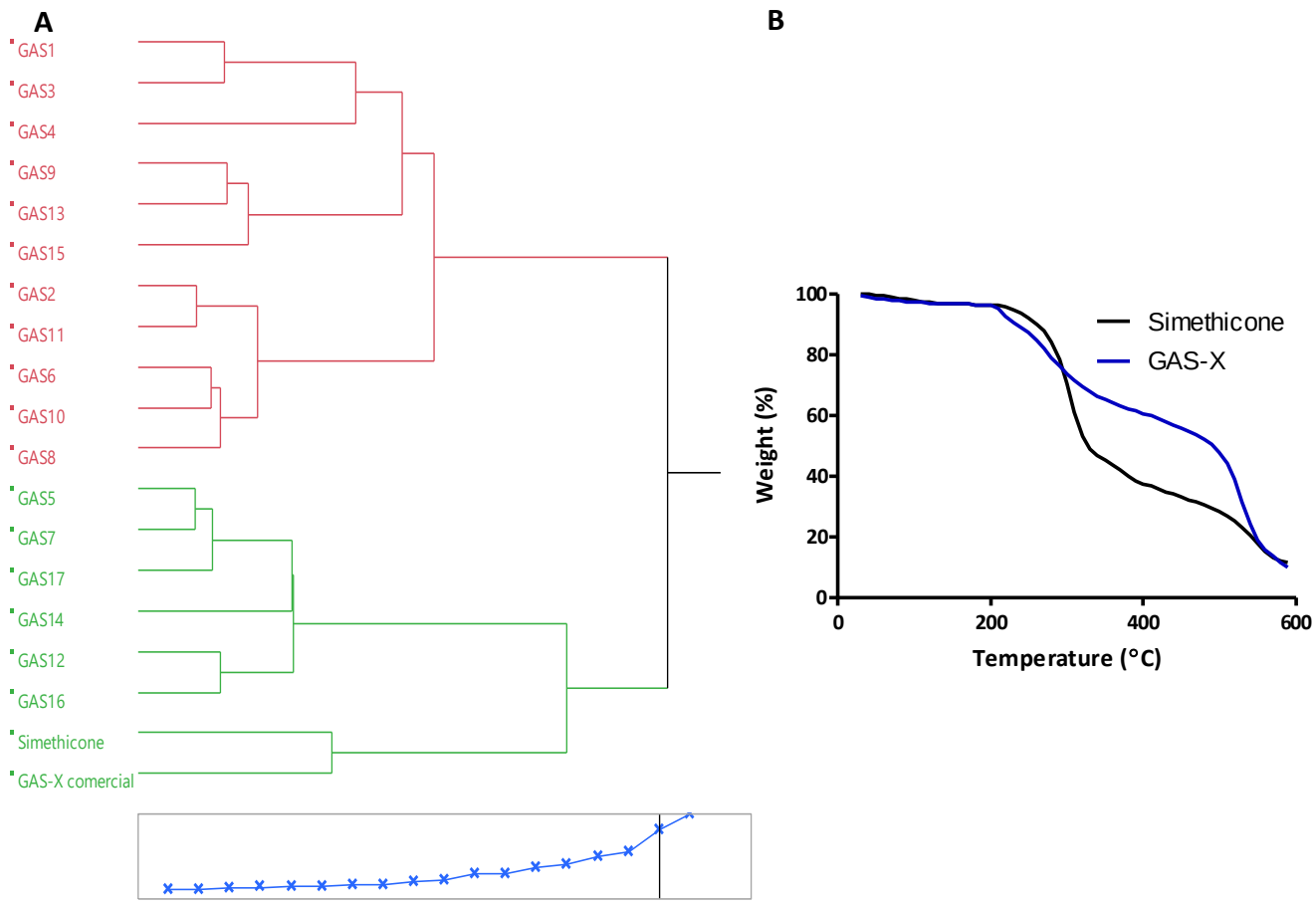

Figure 14 - TGA data profiles analysed by Hierarchical cluster test (A) TGA data profile (B). (A) Represents a dendrogram that lists and group each observation based on its similarity (by Ward's method). (B) Represents the TGA profiles of GAS-X ® and its major component (simethicone).

The clustering analysis of the GAS-X ® formulations showed that the prepared formulations have very different thermal behaviour compared to the commercial film. The formulations with more resemblances with the commercial formulation are presented in the same cluster (green cluster, Figure 14) and are the ones that present higher amounts of simethicone as described in Table 7. Considering that the GAS-X ® commercial film presents more than 50% of simethicone, it is not surprising that the TGA profiles of the formulations with higher amounts of simethicone are the most similar to the commercial film. However, the particular TGA curve of the GAS-X ® commercial ODFs was not possible to be reproduced with the prepared formulations. There are probably specific excipient combinations that may lead to the observed profile, which were not possible to achieve in this study.

It is also interesting to notice that the sweeteners used in the tested formulations seem to have opposite effects in the ODFs studied. In the commercial ODFs evaluated, sucralose that apparently have a positive effect on the thermal stability of the Listerine ® ODFs, have opposite effect on the GAS-X ® ODFs. However, it is important to consider that this discrepancy is only observed until certain extent, since sucralose seem to increase thermal stability, due to the higher temperature necessary to lose 10% of weight, but is further verified that the degradation temperature (T_{onset}) decreases with the sucralose increase. This observation may be related with sucralose structure and interactions. Briefly, sucralose is obtained from sucrose by the replacement of the three hydroxyl groups by three chlorine atoms. The major stability added by this compound to the formulation may be due to its stability until the first endothermic event. Afterwards the molecule modifications decreases its stability and the continuous increase of temperature easily conduct to sucralose decomposition, which may be linked with the polymeric matrix decomposition at similar temperatures (Bannach et al., 2009).

4. Conclusions

To the best of our knowledge only one very recent study (Woertz and Kleinebudde, 2015) used PLS and PCA analysis to evaluate ODFs**.** In the present work, Chemometric multivariate analysis was used to extensively evaluate a pharmaceutical dosage form, especially marketed ODFs. The analysis performed was very useful to generate wide formulation knowledge essential for ODF matrix development.

The complex composition of the ODFs makes their characterization and standardization of their unique parameters very difficult. This work demonstrates the high importance of each excipient in the ODF matrix and also highlights their inter-dependence and interaction.

This work reinforces that each film, depending on the type and concentration of the excipients, presents unique characteristics. The sweeteners exhibited an opposite effect in both formulations, and propylene glycol, which was proved in the present work as being a suitable plasticizer, was already described as having an anti-plasticization effect in chitosan films (Suyatma et al., 2005). Moreover, the preparation of ODFs by solvent casting may be influenced by several other technical and galenical factors. For instance, it is important to consider the concentration of solids in the casting liquid mixture. In fact, the amount of solids is critical, to select cast height, which in turn would influence the polymeric matrix rearrangement and finally its properties. There are evidences that casting solution properties, as viscosity influences reasonably the mechanical properties. It is described that the tensile strength of the ODF may decrease with the solution's viscosity (Dow, 2002).

Finally, the techniques and analysis performed appears to be a suitable approach to provide a comprehensive of the relationship between raw material attributes and critical quality attributes of the pharmaceutical product.

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Chapter II.2

Importance of thermal analysis in Oral films development

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Submitted

Abstract

Polymers have a key role in the pharmaceutical field. Polymeric matrices have been widely explored to obtain different and desirable outcomes in drug releasing kinetics. Thin polymeric matrices for oral administration, commonly designated by oral films, had been developed during the past years. These innovative dosage forms have gained some relevance due to their several advantages and application in unmet medical needs. A deep analysis of the complex formulation used in the development of oral films is highly desirable to facilitate the final product properties prediction and allow its successful development. This work is focused in an extensive thermo-mechanical characterization of marketed oral films (GAS-X® and Listerine® films) and in-house prepared thin films by solvent casting using the available information about these commercial products. The films were stored under controlled conditions and evaluated by TGA, DSC and DMTA. Generally, the GAS-X® films are thermally more stable than Listerine® as evidenced in TGA profiles. At least, two distinct thermal events were observed in both marketed films at similar temperatures, around -50^{o}C and 10^{o}C. The DMTA analyses corroborate the DSC results and provided additional information about polymer chains nature and influence of the formulations. These results demonstrate the high impact of the composition on the thermal properties of the oral films, highlighting the importance of these techniques development this innovative oral dosage.

Keywords

Thermal analysis, oral films, DSC, DMTA, TGA

1. Introduction

Polymers have a key role in pharmaceutical development. These macromolecules made up of repeating units can have several functions in the pharmaceutical dosage forms. Their usage may go simply from a tablet binder, to a more complex role such as taste masking, modified release matrices, or even as polymeric drug delivery platforms itself (Omidian et al., 2011). Polymeric matrices used as drug delivery systems have evolved along the years, and their use in oral administration has been extensively explored. Orodispersible films (ODFs) were originally introduced in the market as a breath-freshener, gaining very recently, a relevant position in the Rx market. However, the complexity of this type of formulations hampers the outline of specifications and methods standardization for their proper development, characterization and quality control.

There are different inherent polymer characteristics that may affect the final product performance, such as: viscoelasticity, rheology, mechanical properties, swelling as well as gelling and adhesive capacity. These properties may be evaluated using a range of techniques, specially thermal and / or mechanical analysis (Jones et al., 2012). Thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA) are the most common methods used for studying the thermal behaviour of polymers.

TGA may be used to evaluate the thermal stability of different compositions including polymeric film matrices. It allows obtaining decomposition temperatures (T_{onset}), moisture and volatile compounds determination in complex compositions. In pharmaceutical development, TGA can be also used to evaluate the incompatibility between formulation components (Australian National Fabrication Facility, 2015; Wesolowski et al., 2012)..

The DSC is widely used in the pharmaceutical industry because this equipment provides important information for drug and galenical developments (Bond et al., 2002; Clas et al., 1999; Feldstein et al., 2003; Giron, 2002; Okhamafe and York, 1985). This technique allows the characterization of the components and multicomponent mixtures, regarding to their melting points, enthalpy of fusion, purity, crystallinity, polymorphism, degradation, decomposition, stability, glass transition and heat capacity (Bond et al., 2002; Clas et al., 1999). Additionally, DSC is particularly useful for the fast screening of excipients' compatibility, namely those concerning drug–excipient compatibility. In fact, this type of study is very advantageous since it does not require long-term stability studies, only small

amounts of samples are required for each assay in early formulation studies and to predict possible interactions in the final product.

Another useful technique for thermal analysis of polymers is DMTA. DSC and DMTA are perhaps the most used methods to determine the glass transition temperature (Tg), but the last is much more sensitive in the detection of this relaxation phenomenon (Jones et al., 2012). Different Tgs values may be obtained from these two techniques due to different operating principles. DSC is essentially based in variation of the specific heat capacity of the sample during the analysis, whereas in DMTA, the strain of the material is measured as result of an applied sinusoidal stress. This technique is very useful and efficient to evaluate the thermos-mechanical behaviour polymers that typically have amorphous and crystalline phases (Australian National Fabrication Facility, 2015; Jones et al., 2012; Soutari et al., 2012). Although DMTA is an easy, rapid and non-destructive method to evaluate the viscoelastic properties of polymers, it has not been widely used in pharmaceutical development essentially due to sample preparation issues. Nevertheless, during the last years DMTA has gained increasing interest for the characterization of drug delivery systems and biomedical platforms (Jones et al., 2012).

The references available regarding the determination of mechanical properties of polymeric films involve mostly the use of standard tensile equipment based in stress-strain, puncturing or creep-recovery and stress-relaxation tests. DMTA emerges as a suitable alternative to these classical techniques with the advantage of additional information about viscoelasticity and temperature induced transitions over a broad range of temperatures and frequencies (Cespi et al., 2011; Jones et al., 2012).

The aim of this work is to perform a comprehensive thermal and mechanical analysis of two marketed oral films, GAS-X® and Listerine® pocket packs, as well as ODFs prepared using the same excipients in different proportions. A deep understanding of the mechanical and thermal properties of these films is very important to develop fundamental knowledge that may be critical for future advancements in the development of this novel dosage form.

2. Material and Methods

2.1. Material

Acessulfame K (Nutrinova, Frankfurt, Germany), Carrageenan k, Gelcarin GP-379NF (IMCD UK Ltd, Sutton, UK), FD&C Blue #1 (Colorcon, Harleysville, U.S.), HPMC E5, Methocel E5 (Colorcon), HPMC E15 Methocel E15 (Orpington, UK), HPMC E50 Methocel E50, Maltrin M180 (LEHVOSS UK Limited, Cheshire, UK), Menthol (-)-Menthol (Merck, Darmstadt, Germany), Modified starch, Pure Cote B793 (LEHVOSS UK Limited, Cheshire, UK), Polyethylene Glycol, Lutrol 400 (BTC, Ludwigshafen, Germany), Propylene Glycol 1,2-propanediol (Merck, Darmstadt, Germany), Pullulan (Hayashibara Co., Ltd, Okayama, Japan), Simethicone (Resil chemicals Pvt. Ltd., Bangalore, India), Sorbitol (Colorcon, Orpington, UK), Sucralose, Splenda (Merck, Darmstadt, Germany), Polysorbate 80, Tween 80 (Merck, Darmstadt, Germany); Hydranal Composite 5 (Sigma-Aldrich co. LLC, U.S.).

2.2. Methods

2.2.1. Preparation of the ODF samples

ODFs were prepared according to a standard procedure as displayed in Figure 15.

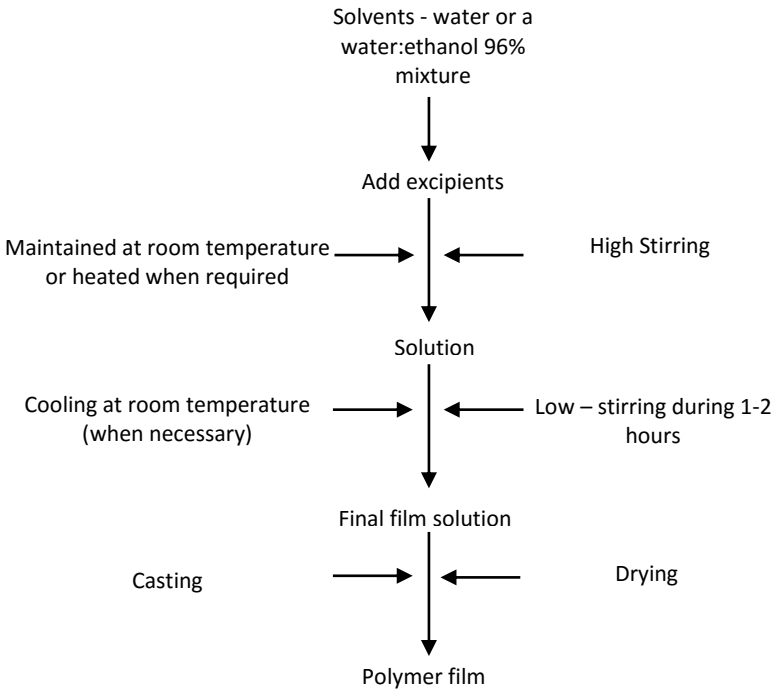

Figure 15 - Schematic representation of the preparation procedure of the orodispersible films (ODFs)**.**

The solutions were prepared in two-neck round bottom-flasks (50mL). The system was kept at room temperature or at higher temperatures (60-90^{o}C) depending on the excipient used in each formulation. For formulations kept at high temperatures that contained ethanol as solvent, a condenser was used. The film solutions were cast in PVC release liners (substrate) with an Erichsen film applicator (Coatmaster 510, Erichsen, Hemer, Germany). To adjust to different heights a vertically adjustable doctor knife was used and the film solutions were cast at 18 mm/s. The films were cast with a gap of 250-500 µm. The process of film formation has been thoroughly described (Alanazi et al., 2007) and is divided into three stages: (a) evaporation of the solvent and subsequent concentration of polymer particles, (b) deformation and coalescence of polymer particles and (c) further fusion by inter-diffusion of polymeric molecules of adjacent polymer particles. The cast films were dried on the heated table of the Erichsen film applicator at 40 °C or at room temperature until dryness.

To further characterize the ODF, individual samples are prepared by cutting strips of regular dimension (60 mm^2, 2mm x 3mm) with a surgical scalpel.

The mixture designs were performed with JMP 10 (SAS Institute Inc., Cary, NC), to obtain experiments that were representative and randomly chosen within the ranges selected.

2.2.2. Storage

The individual films are stored under controlled conditions (43 % RH, room temperature), by means of a saturated solution of potassium carbonate for at least 5 days before testing.

2.2.3. Differential Scanning Calorimetry (DSC)

DSC measurements were performed in a DSC Q100 (TA instrument). The tests were carried out using two heating runs, from 25 to 100°C and -85 to 100°C with the temperature increase rate of 10°C/min and with constant nitrogen flow.

2.2.4. Modulated DSC

Modulated differential scanning calorimetry of each sample was carried out in a TA Instruments (Q100 model). The heat flow was calibrated using indium, whereas for the heat capacity, a sapphire standard was employed. The samples were analysed in aluminium pans with an ordinary aluminium lid loosely placed from 25 to 100°C and -85 to 100°C. A heating rate of 10°C/min, a modulation period of 40 s, and a temperature modulation period of ±0.50° C were used. A dry nitrogen purge flow of 50 mL/min was used in all measurements.

2.2.5. Thermogravimetric Analysis (TGA)

TGA test was performed in a TGA Q500 (TA instruments), at a heating rate of 10°C/min, from 0°C to 500°C, under a constant nitrogen flow.

2.2.6. Dynamic Mechanical Thermal Analysis (DMTA)

DMTA analyses ware carried out using a DMA 242 E (Netzsch, Germany) under tensile mode. All samples (5.29 ×0.04×5,61 mm^3 (average value)) were analysed over a temperature range from -150°C to 150°C, at frequencies of 1, 5 and 10 Hz, using a heating rate of 3 °C/min.

2.2.7. Data analysis

The graphs were prepared using GraphPadPrism version 5.01 (GraphPad Software, Inc, San Diego California) and the Plotly (Plotly, Inc, Montréal, Canada).

The screening and optimization designs were performed with JMP 10 (SAS Institute Inc., Cary, NC). The Custom Design platform was used to generate the mixture design performed, by introducing the factors as mixture variables and apply a model for the evaluation of the main factors and if possible the second interactions.

3. Results and Discussion

The composition of the studied films is summarized in Table 8. The components selected to be used in the formulations resulted from the information available to the consumer, usually presented on the package. In order to perform a suitable set of experiments, only the most critical components of both formulations were selected.

Table 8 - Main components of the commercial ODFs evaluated, GAS-X and Listerine® Fresh Burst.

	Polymer	Plasticizer	Flavor	Color	Sweetener	Surfactant	Thickening agent	Drug substance / Strength
GAS-X®	Modified Corn Starch Hypromellose Maltoextrin	Propylene glycol Sorbitol	Menthol Flavor	FD&Blue#1 Titanium dioxide	Sucralose			Simethicone / 62,5 mg
Listerine® PocketPacks	Pullulan	Propylene glycol	Menthol Eucalyptol Aroma Orange oil	Green 3 Yellow 6	Sucralose Potassium Acesulfame	Polysorbate 80 Glyceryl Oleate	Chondruscrispus (carrageenan) Ceratoniasiliqua gum Xanthan gum	Coppergluconate Thymol Methylsalicilate

This information was used to prepare the mixture design experiments presented in Table 9 and Table 10.

Table 9 - Composition of the different test films based on Listerine® Pocket Packs composition (List) that were prepared and characterized based on a mixture design (%).

Film ID	Pullan	Propylene Glycol	Menthol	Carrageenan	Acessulfame	Sucralose	Tween 80
Selected ranges	49-92%	0-17%	0-10%	0-5.5%	0-6%	0-6%,	0.1-7%
List1	65.6	13.4	8.6	1.8	5.2	5.3	0.1
List2	79.0	15.1	3.7	2.0	0	0	0.2
List3	77.4	0	5.9	5.0	5.0	0	6.7
List4	58.4	15.7	9.2	0	5.9	5.9	4.9
List5	91.8	0	3.2	0	0	0	5.0
List6	49.4	15.5	9.6	5.5	6.4	6.3	7.3
List7	88.4	0	9.4	2.1	0	0	0.1
List8	68.3	16.1	0	2.1	0	6.2	7.3
List9	70.2	16.7	0	1.6	6.6	-	4.9
List10	66.5	15.7	3.9	1.1	6.3	6.4	0.1
List11	89.6	0	3.5	0.9	5.9	0	0.1
List12	80.8	0	0	2.1	6.5	3.9	6.6
List13	73.4	16.0	2.0	1.3	3.6	3.6	0.1

The intervals used to define the different experiments were based on the marketed films patent references (Leung et al., 2008; Schobel and Vangala, 2010).

Table 10 - Composition of the different test films based on GAS-X® composition (GAS) that were prepared and characterized based on a mixture design (%).

Film ID	Methocel E5	Methocel E15	Methocel E50	Maltrin	Starch	PEG 400	Sorbitol	Sucralose	Simeticone
Selected ranges	0-60%	0-75%	0-55%	0-35%	0-45%	0-18%	0-11%,	0-4.5%	5-60%
GAS1	43.3	0	0	0	43.5	0	0	0	13.2
GAS2	43.5	43.3	0	0	0	0	0	0	13.2
GAS3	56	0	0	33.7	0	0	0	0	10.3
GAS4	15.7	15.7	0	15.4	15.4	18.2	9.9	4.6	5.1
GAS5	76.6	0	0	0	0	0	0	0	23.4
GAS6	0	41	0	0	24.6	18.1	0	0	16.2
GAS7	0	76.2	0	0	0	0	0	0	23.8
GAS8	41.1	0	10.3	13.7	13.7	0	7.4	0	13.7
GAS9	59.1	0	14.8	0	0	0	11.2	5	10.0
GAS10	59.8	0	15.0	20.1	0	0	0	0	5.2
GAS11	13.7	0	54.4	0	18.1	0	0	0	13.8
GAS12	15.0	0	14.9	0	0	0	10.6	0	59.4
GAS13	12.4	0	33.0	16.5	0	0	9.2	4.2	24.6
GAS14	15.7	0	47.1	0	0	0	8.8	3.9	24.4
GAS15	13.5	0	49.6	0	18.0	0	0	4.5	14.3
GAS16	14.8	0	14.9	0	19.8	0	0	0	50.5
GAS17	12.0	0	47.5	0	0	16.5	0	0	24.0

3.1. Thermal analysis

3.1.1. TGA

An overall analysis of Figure 16 indicates that GAS-X® and Listerine® have similar thermal profiles regarding the maximum loss of mass because it starts approximately at same temperature, about 200^{o}C. However, a closer observation (Figure 16) suggests that GAS-X® may present better thermal stability than Listerine® visualized by the higher T_{onset}, and the initial sharp decrease of the Listerine® weight. The temperature that corresponds to 5% weight loss is around 60^{o}C for Listerine®, whereas for GAS-X® is at 211^{o}C.

There is a clear difference in the thermal behaviour of the polymeric matrices until the 100^{o}C. Generally, it is assumed that the weight decrease up to this temperature corresponds to the evaporation of volatile substances, such as ethanol, flavours and water. Therefore,

the initial weight loss is not related with any polymer degradation but mainly to water evaporation, suggesting that Listerine® is more hygroscopic than GAS-X® polymeric matrix.

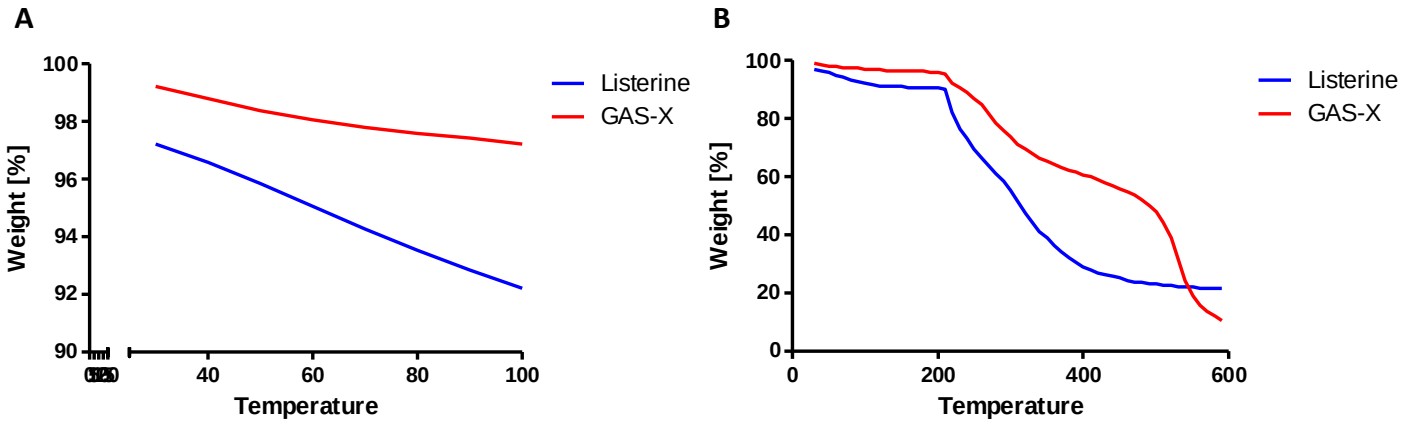

Figure 16 - TGA profile of marketed formulations, Listerine® (blue line) and GAS-X® (red line). (A) Represents the TGA profile up to 100°C. (B) Represents the overall TGA profile.

The prepared ODF based on Listerine® composition that have shown similar thermal behaviour compared with the marketed product were the ones prepared with propylene glycol (plasticizer) and lower % of menthol (flavour) (List 2, List 7 and List 9 in Figure 17). In fact, until 200°C, all the films with plasticizer present a very similar thermal profile to the marketed product (List1, List2, List4, List7, List8, List9 and List11 in Figure 17).

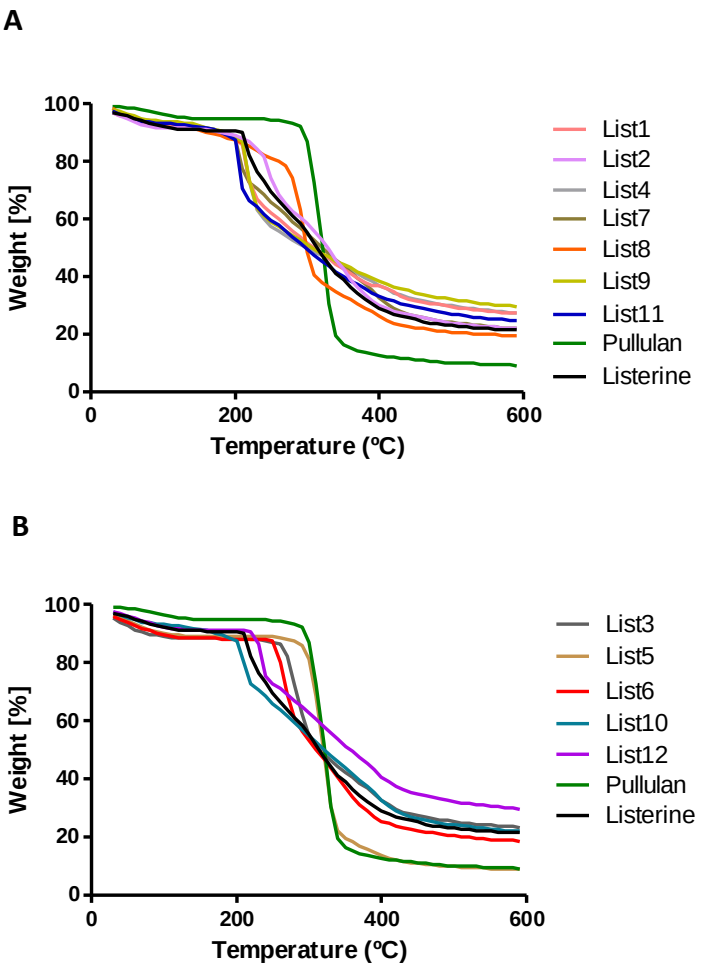

Figure 17 - TGA analysis of marketed and prepared films. (A) Represent the films without plasticizer. (B) Represent the films with plasticizer.

Pullulan, the main component of the formulations is very stable until 200°C, and its degradation starts around 300°C (Figure 17). Menthol and propylene glycol have very similar thermal profiles, with a starting sharp weight loss around 100°C (Figure 18). This poor thermal stability justifies the modified profile of pullulan when propylene glycol and / or menthol are included in the matrix formulation. Moreover, the thermal degradation starts earlier for matrices with higher menthol concentration, above 3.7% (List1, List4 and List11). Additionally, this pullulan matrices with propylene glycol and high level of menthol in their composition present lower thermal stability even compared with the Listerine® marketed formulation. On the contrary, List2 present a very similar profile. On the other hand, the pullulan - menthol matrices, without plasticizer, tend to have a higher thermal stability than the polymeric systems discussed above (List3, List5, List6, List10 and List12). This result is probably related to the fact that without plasticizer, the polymeric films have more pullulan, contributing for the higher T_{onset}.

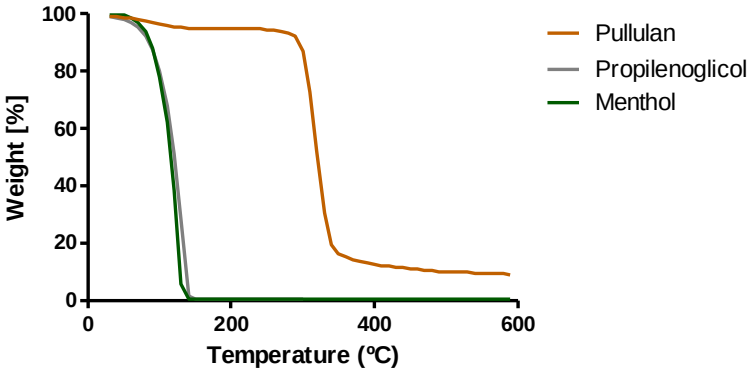

Figure 18 - TGA profile of Pullulan, Menthol and Propylene glycol.

The oral films matrices are generally based on hydrophilic polymers, and consequently strongly influenced by moisture. The amount of free water molecules in the polymeric matrix may be easily analysed by TGA thermal profiles through the weight loss up to 100ºC (Leung et al., 2008). The polymeric matrices with sharper decrease in this region are probably due to a higher hygroscopicity (Figure 19).

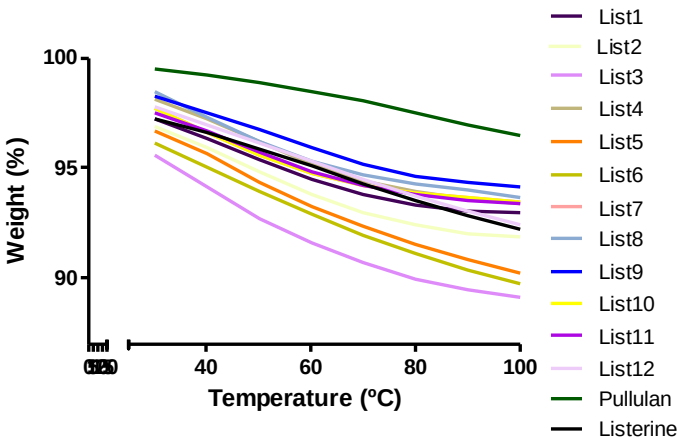

Figure 19 - TGA profiles of weight loss up to 100ºC of the prepared formulations compared with Listerine®.

List3, List 5 and List 6 have a pronounced weight loss until 100^{o}C, whereas List7, List8 and List9 have the lowest percentage of loss. There is a clear trend that the films with higher Pullulan amount in their composition exhibit a sharper decrease in the weight up to this temperature, which is probably related with the capacity of this polymer to absorb water. However, it is important to notice that up to 100^{o}C other volatile substances, such as menthol, may also evaporate contributing to the observed weight loss in this region (Zhang et al., 2011). The complexity of the formulations in the polymeric matrix difficult the analysis.

Among the prepared films, List5 is apparently the one with a higher thermal stability with a higher T_{onset}, while, List7 and List11 are the polymeric matrices with lower degradation temperature (Figure 17). The high degradation temperature observed for List 5 is probably related with the high pullulan concentration (higher than 90%). The lower thermal stability of List7 and List 11 is more difficult to ascribe due to the complexity of the formulations. According to the previous analysis, it may be possible to corroborate that pullulan contributes to improve the thermal stability, while propylene glycol and menthol could be the main components responsible for a decrease in the thermal stability of the prepared samples. Sucralose is another excipient that is present in the formulations with lower thermal stability (Figure 17, List1, List4, List7, List9, List11 and List12). Sucralose is described as being thermally stable up to 119°C (Bannach et al., 2009) but an opposite effect was observed here.

TGA thermal profiles of the GAS-X® based formulations is very different from the marketed formulation (Figure 20). Despite the complex composition of the GAS-X® formulation, its main component is simethicone and accounts for ~60% of the film weight, which was never achieved in the prepared formulations due to technical limitations that involved the preparation of homogeneous films with this high drug load.

The hydrophilic polymers present in the composition of GAS-X® films are less hygroscopic than the Pullulan polymer matrices evaluated in the Listerine® based formulations. In general, up to 100^{o}C none of the films lose more than 6.5% of weight and the majority of the films, especially the films with HPMC E50, do not reach the 5% of weight loss (Figure 20, Gas8 to Gas19). The films with higher weight loss, above 5%, correspond to formulations based on HPMC E5 with a modified starch (Figure 20 and Table 10, Gas1 and Gas3). In fact, the hygroscopicity of maltodextrins (Maltrin) (MDX) are already described in literature (Embuscado and Huber, 2009), and its presence could contribute to 5% or 10% weight loss at lower temperatures.

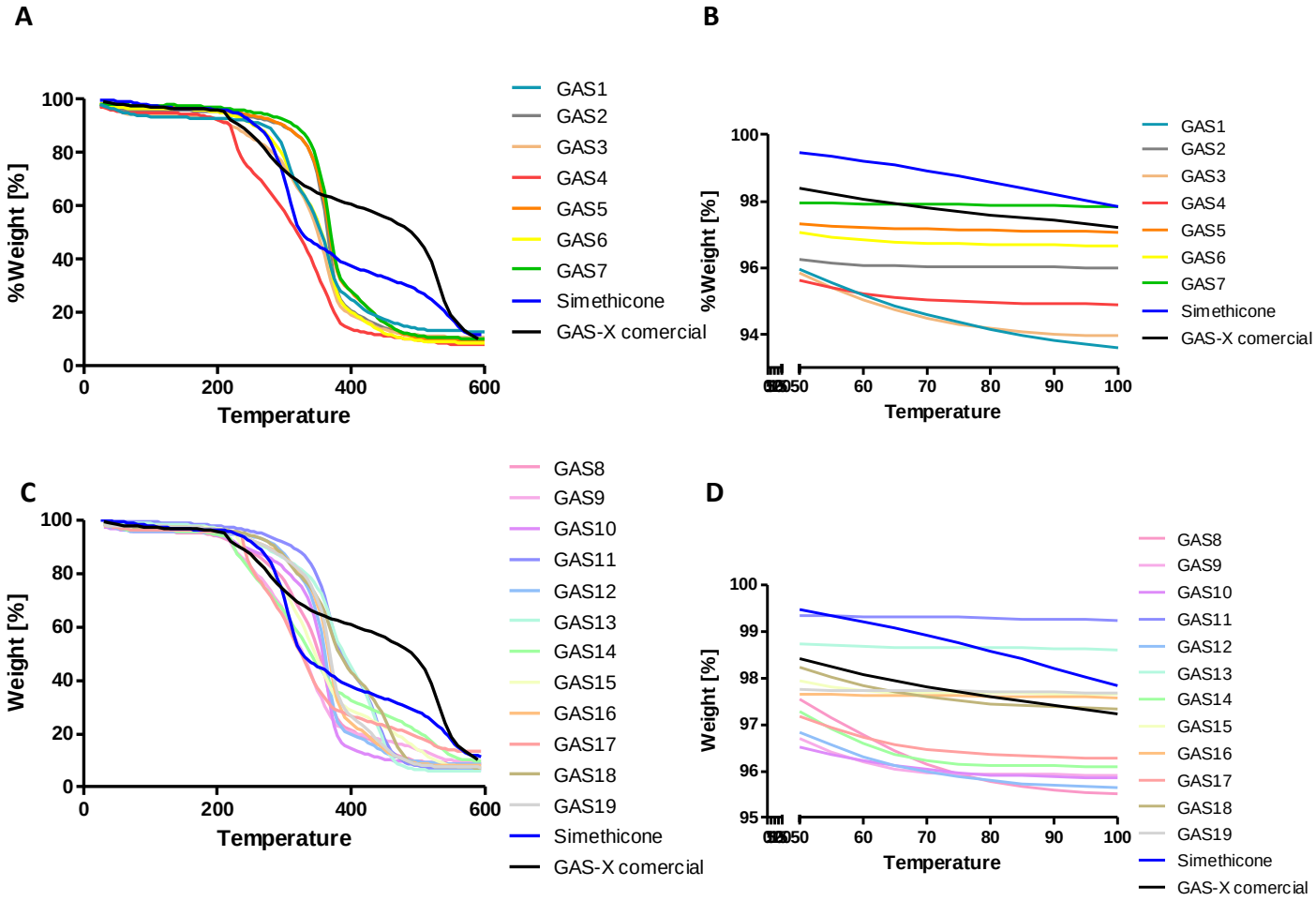

Figure 20 - TGA analysis of marketed and prepared ODFs (A) TGA profiles of prepared films with HPMC E15. (B and D)TGA profiles of weight loss up to 100°C of the prepared formulations compared with GAS-X®and (C) TGA profiles of prepared films with HPMC E50.

Additionally, a lower thermal stability is also observed in the thermal profiles of formulations with higher amounts of sorbitol (Figure 20, GAS4, GAS13 and GAS14) and sucralose (Figure 20, GAS4, GAS9, GAS13, GAS14 and GAS17). However, there is a tendency to higher thermal stability for formulations with higher HPMC contents, probably related with the high thermal stability of this polymer (Figure 20, GAS1, GAS3 and GAS11). Additionally, it is also verified a notorious trend to a higher thermal stability with the increase of simethicone content confirmed by the small weight loss until temperatures up to 100^{o}C (Figure 20, GAS7, GAS11, GAS13, GAS16, GAS18 and GAS19). Chemically, simethicone is a mixture of polydimethylsiloxane and hydrated silica gel (Watson, 2014). Polysiloxanes are known to be very stable and to retain their characteristic properties when exposed during long periods to higher temperatures, compared with the majority of organic polymers. Typically, polydimethylsiloxanes have degradation temperatures around 300-350 ^{o}C. This fact may be associated to the higher thermal stability of these formulations (Jones et al., 2001).

3.1.2. DSC

The thermal behaviour of samples can be a powerful approach to access relevant information such as: purity, chiral purification and miscibility issues.

The absence of interactions in the solid state and immiscibility in the liquid state would result in DSC curve profiles correspondent to the combination of each individual thermal curve (Giron, 2002). On the other hand, any possible miscibility would result in a single transition temperature (Feldstein et al., 2003).

Figure 21 (blue line) present two thermal events in the GAS-X® DSC trace, approximately at -46^{o}C and 10^{o}C.The first event is an endothermic peak typically ascribed to a melting temperature (Tm). The event at 10^{o}C may be attributed to a Tg. The form of the peak at approximately -46^{o}C is characteristic of a Tm event, which according to the GAS-X composition that may be attributed to two different substances: simethicone and / or polyethylene glycol (PEG) (Tejwani et al., 2000; United States Pharmacopeia, 2013). Both substances are referred as having very low Tm, simethicone lower than -50^{o}C and PEGs from -60^{o}C to +40^{o}C depending on their Mw. Therefore, such lower Tm for PEG is only valid for specific Mw polymers, especially low Mw PEGs. Even for the same grade, low Mw PEGs may have slightly different characteristics, due to minor variations on the carbonated chain. The Tm ranges found in literature for PEG 200 vary from -60 to -45^{o}C (Dow, 2011a; JHD Fine Chemicals, 2008). It is not specified on the marketed product the PEG grade used in GAS-X

composition. Nevertheless, it should be mentioned that in the patent of the product the examples are presented only PEG 400 (Schobel and Vangala, 2010) (Tm~4-8^{o}C (Dow, 2011b)), which was also used for the prepared formulations in the present work. In turn, the simethicone is described to have a Tm around -58^{o}C (United States Pharmacopeia, 2013). It is important to highlight that these characterization temperatures may vary depending on the purity and the moisture content of the compounds. The prepared formulations carried out to replicate the GAS-X® marketed formulation, have the same endothermic peak independently of the PEG presence (Figure 22, GAS1 to GAS5, Gas 13 and GAS17). Hence, this endothermic event may be attributed to simethicone, which is also corroborated by simethicone DSC profile (Figure 22). There is also another event, not very clear, at approximately -36^{o}C, that may be related with a Tg. However, there are no components in the formulation that could justify this transition at this temperature. PEG 400 is described to have a Tg around -70^{o}C to -60^{o}C (Feldstein et al., 2003; Okhamafe and York, 1985; Pillin et al., 2006) and GAS13 and GAS17 also have a similar endothermic profile and are PEG-free (Figure 22). As described previously, another subtle endothermic event may be identified at 10^{o}C with a shape coherent with a Tg transition. This event is also observed for other formulations. Although, it is not possible to identify a specific component that may justify this event, this peak may result from the physical interaction between the polymers in the formulation and the other components. As mentioned above, the good miscibility of the components would result in a DSC profile with a single Tg. Therefore, despite the high Tgs of the polymers used (Table 8) (HPMC Tg=170-180^{o}C (Rowe et al., 2012) and modified corn starch Tg= 40-50^{o}C (Lim et al., 2001)), the plasticization effect of PEG 400 and sorbitol (anhydrous Sorbitol Tg= -9 to -1,7^{o}C (Netzsch, 2015; Rahman, 2009)) may have depreciated the Tg of the mixture to values around 10^{o}C.

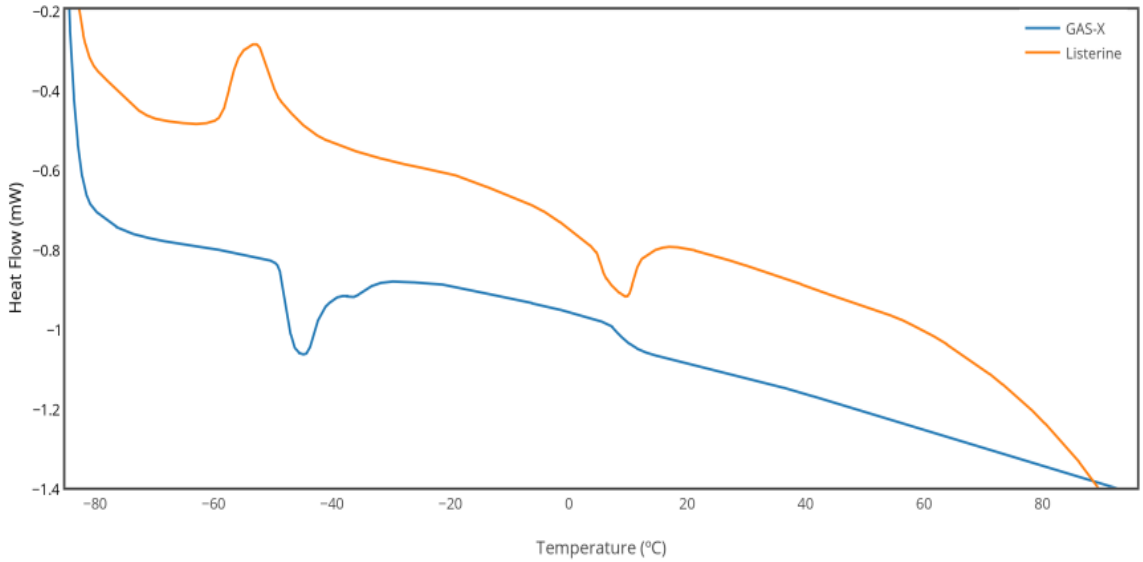

Figure 21 - DSC profile of Listerine ® (orange line) and GAS-X® (blue line) marketed films.

Simethicone is mainly composed by polydimethylsiloxane (PDMS), which presents a very low Tg, around -127°C (Ringsdorf and Schneller, 1982). Due to technical limitation of the DSC equipment, it was not possible to start the tests below -80°C, and verify the presence of this Tg. Therefore, no conclusions regarding its miscibility within the polymeric matrix can be drawn. However, a DSC analysis of the simethicone used in the formulations was performed, and a very close profile was obtained, compared to GAS-X marketed film (Figure 22D). This result reveals that a similar silicone mixture is probably used to prepare the original GAS-X® commercial film. Additionally, the majority of the prepared GAS-X® based formulations present the same endothermic event. In fact, the formulations with lower simethicone amount, GAS4, GAS10 and GAS15, present also this small variation in the heat flow in the same region. On the other hand, the formulations GAS13 and GAS18, which have around 50-60% of simethicone, have a pronounced endothermic peak at this temperature. The possibility of the existence of two simultaneous thermal events with different nature cannot be excluded, since each may be related with two independent sub-systems that may be formed within the overall polymeric matrix (for example starch-based polymeric system and cellulose-based matrix system that are not completely miscible). But, analysing the formulations prepared, similar DSC profiles are verified in cellulose based matrices (Figure

22, GAS13), which rebuts any of the previous theory. In order to clarify the obtained profiles a modulated DSC was performed.

In Listerine®, two different thermal events were also identified, an apparent exothermic event, around -53^{o}C, and an endothermic one visible at around 10^{o}C (Figure 21). The exothermic peaks are usually related with crystallization or oxidative decomposition (Ahuja and Scypinski, 2010; Sepe, 1997). However, crystallization peaks are usually preceded by Tg events (Sepe, 1997), and the oxidative events are associated with higher temperatures (Ahuja and Scypinski, 2010). In turn, the second peak of Listerine® DSC curve has the shape of a melting transition. However, within the formulation components, none of them has a Tm around 10^{o}C. Nevertheless, it is important to consider that miscible blends may contribute to lower Tm of each single component (Zhang et al., 1998). Indeed, the complexity of the system and the wide range of Tm values of the different components, difficult the clear interpretation of the traces. However, as discussed before, it is possible to consider the formation of a blend that due to its good miscibility may behave as a single component with in-between characteristics of the different components used in the formulation. In fact, it is already described in literature that an optimal miscibility between the oral film components pullulan-based polymeric matrices is possible (Bhavya, 2013; Bumbu et al., 2002; Diab et al., 2001; Prasad et al., 2012; Wesolowski et al., 2012).

A modulated DSC was also performed for the Listerine® marketed films, in an attempt to clarify the thermal events presented.

The information regarding DSC profiles of pure pullulan available in literature is very scarce and contradictory because some references indicate very different Tg values (94^{o}C (Bhavya, 2013) and 160^{o}C (Bumbu et al., 2002)). There is an evident discrepancy between the reported results and also with the Tg obtained in the present work, around 120^{o}C (pullulan DSC curve, Figure 23). These differences may be related with the fact that pullulan is a natural polymer, and different sources or suppliers, may have influence in the purity of the raw material. Additionally, it is important to consider that this biopolymer due to its hydrophilic nature, has a high affinity for water, which is known to function as a plasticizer that may contribute to lower the Tg values.

Regarding the prepared Listerine® formulations, the differences to the commercial film DSC profile are clear. In fact, in the prepared formulations, it is very difficult to identify clearly specific thermal events, only very slight changes in the heat flow curves are observed, except in formulation List6. This last formulation presents an unexpected DSC profile with two

endothermic events. In this specific formulation the profile obtained may be related with the high content of menthol. Therefore, a part of the menthol interacting with the polymeric matrix may functioning as a plasticizer, as previously described, and may contribute for the matrix-endothermic peak event observed around 50^{o}C; whereas the menthol that remains free in the polymeric matrix may contribute for the first-endothermic peak, which could correspond to its Tm, around 40^{o}C (Rowe et al., 2012).

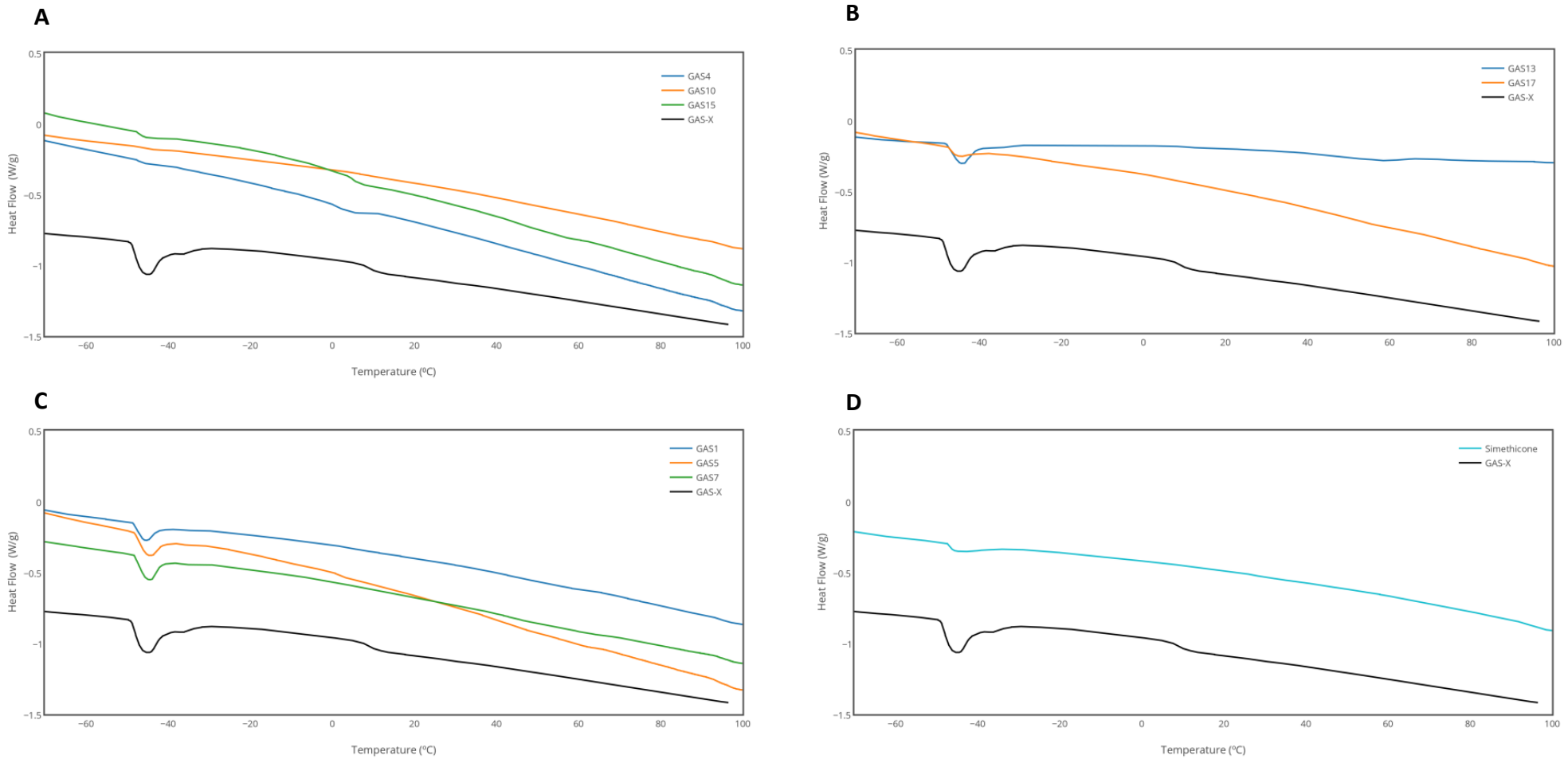

Figure 22 - DSC traces of GAS-X® prepared formulations compared with GAS-X® marketed film. (A), (B) and (C) Represent DSC profile of GAS-X® formulations. (D) Represents DSC profile of marketed GAS-X® and Simethicone.

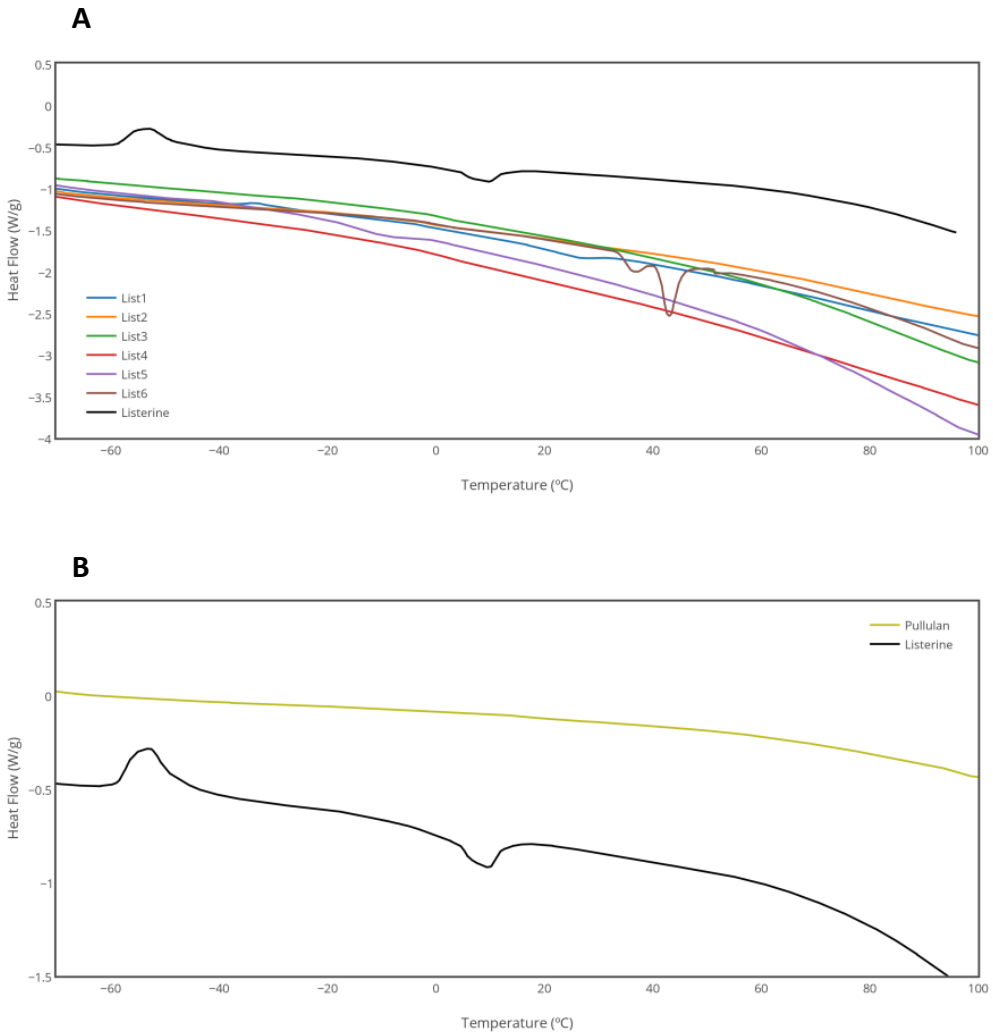

Figure 23 - DSC traces of Listerine® prepared formulations compared Listerine® marketed film. (A) DSC profile of Listerine® prepared formulations. (B) Represents DSC profile of Listerine® marketed film and pullulan.

3.1.3. Modulated DSC

Modulated DSC allows the separation of reverse and non-reverse thermal events. This approach allows the separation of specific events into individual signals, which can be very helpful to identify peaks that are overlapped. The reverse component allows highlighting important transitions as crystal melting and glass transition, whereas the non-reversing component may allow identify, recrystallization and enthalpy relaxation (Artiaga et al., 2011; Sepe, 1997).

A

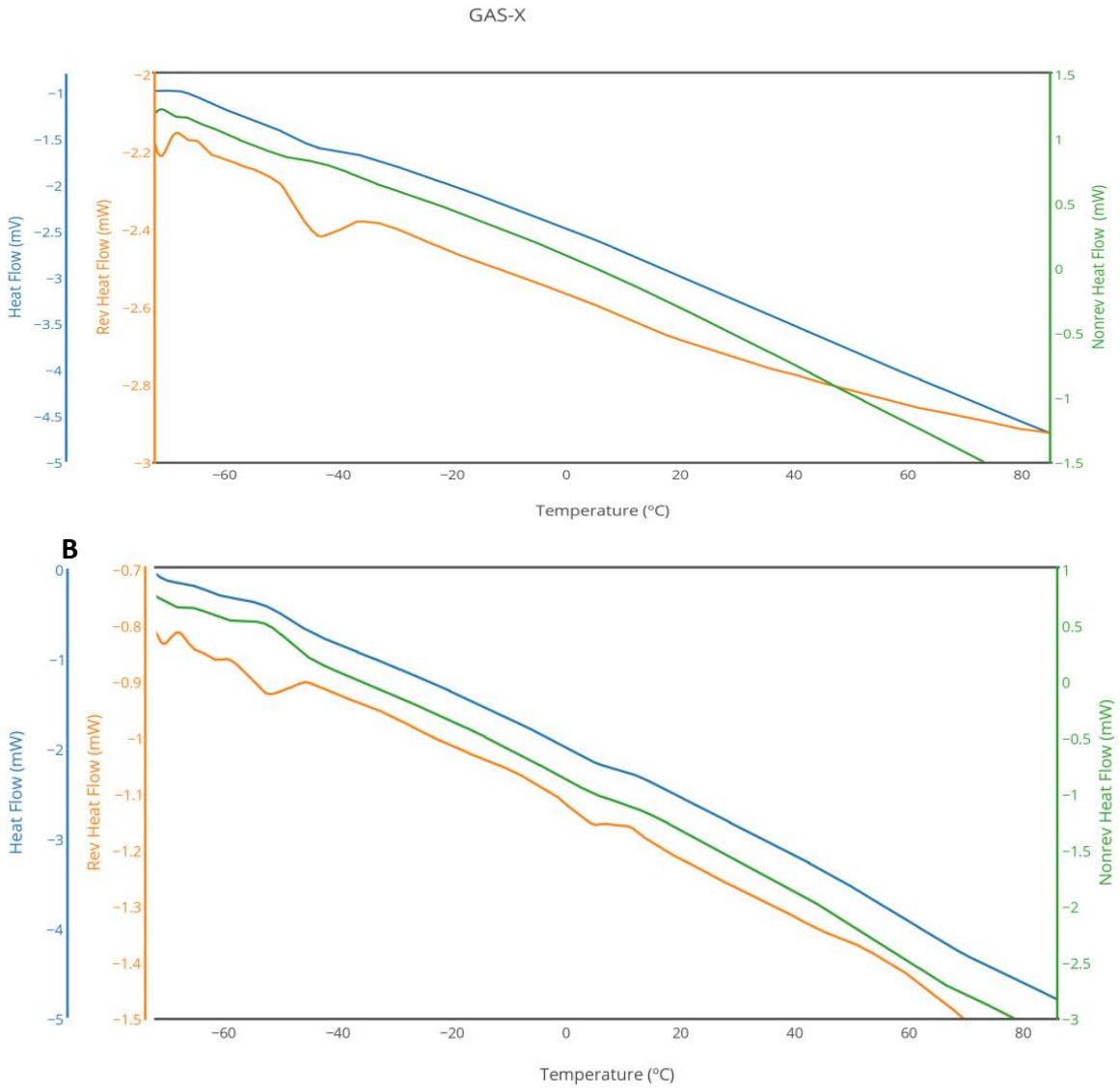

Figure 24 - Modulated DSC for GAS-X® (A) and Listerine® (B) marketed products (Exothermic events Up).

In the GAS-X® analysis, it is possible to verify the presence of a melting event around -44^{o}C (Figure 24A, orange line). The slight elevation at the same temperature in the non-reverse heat flow curve (Figure 24A green line) may also indicate a Tg. However, this last is not so obvious and is difficult to assure this event due to the very slight variation. Similarly, the possible Tg identified in the previous DSC results, at 10^{o}C, is also not so evident in this profile. No significant change is verified in the non-reverse heat flow curve that represents a Tg at this temperature. As already discussed the event at negative temperatures probably results from simethicone melting.

In the Listerine® profile, it is easier to identify the transition events, two possible Tms, around -52^{o}C and 5^{o}C (Figure 24B, orange line). The peak form is related with the enthalpy energy, since the overlapping of events contributed to an energy release, masking the real genesis of the event. At this negative temperature it is possible that the Tm results from the propylene glycol, which is described to melt at -59^{o}C (Rowe et al., 2012). However, to present an unchanged Tm profile compared with the pure substance, in such complex system, it may have to be immiscible with the other components and / or have an excess amount non-linked / interaction-free with the polymeric matrix.

The DSC analysis is very useful to evaluate and characterize galenical formulations, but the interpretation of the thermal data is not always simple and several external / environmental factors may lead to results' misinterpretation and misleading. In fact, it should be considered that if the DSC experiment is performed in non-equilibrium conditions, some interactions may not be predicted and confirmation methods should be used (Clas et al., 1999). In addition, the complexity of the formulations highlights the limitation of this technique to obtain structural-properties characteristics in these matrices. Therefore, a dynamical mechanical thermal technique (DMTA or DMA) was also used to evaluate the oral thin films in attempt to discriminate some of the dubious thermal events verified in DSC traces.

3.1.4. DMTA

DMTA analyses were carried out to complement the previous thermal analyses. Thermal relaxation events as Tg and secondary transitions (β and γ) can be accurately identified with this technique.

The tests were performed in a multifrequency mode (1, 5 and 10Hz) and the results are presented at 1 and 10 Hz for the marketed formulations and at 1Hz for the others. The viscoelastic properties (elastic modulus - E', viscous modulus - E'' and damping - Tan δ) are represented for both commercial films (Figure 25). The DMTA analysis was performed for the developed formulations that apparently present some similarities with the commercial form (Figure 25).

The complexity of the DMTA traces is obviously associated with the blending complexity of the polymeric matrix. However, there are some basic features that can be always retrieved from the profiles obtained. The Tg value may be estimated assuming the events combination in the same region: maximum peak of the Tan δ curve and elastic modulus (E') sharp decrease (Jones et al., 2012).

Regarding the Listerine®, there is an unusual profile of the viscoelastic properties of the films in the beginning of the thermal profile, around -100^{o}C, with an evident peak of the viscous modulus (E'') along with a slight decrease of the storage modulus (E'). The next thermal transition evident assumes the profile of a Tg, at approximately at 10^{o}C (not observed in the DSC). This event is shown by very intense transitions, a Tan δ peak and a sharp decrease of the storage modulus. Above this temperature the samples becomes too soft avoiding the analysis to continue.

The Listerine® developed formulations have similar behaviour when compared with commercial Listerine® films. In fact, in the Tg region (0-25^{o}C), a sharp decrease in the E' is observed for all formulations. However, this phenomenon occurs slightly earlier in the developed formulations than in commercial Listerine®. Therefore, the Tg is lower in these formulations. Actually, the Tg is around 0^{o}C for the majority of the formulations, except for List7, in which the E' curve starts to decrease at negative temperatures, indicating a higher flexibility of this polymeric matrix at lower temperatures. The complexity of the formulations that involve the use of different compounds/quantities turn extremely difficult to ascribe the differences observed.

The majority of the Listerine® formulations prepared has half of the E' values compared with the commercial films and present a longer rubbery plateau. In general higher storage modulus is indicative of higher crystallinity or lower plasticization of the polymer chains. The storage modulus of a semi crystalline polymer is always higher than the modulus of a similar amorphous polymer above the Tg (Menard, 1999; Menczel and Prime, 2014).

The differences of E' observed between the commercial and the prepared formulations can be also ascribed to the number of excipients used that in the latter case are smaller.

The analysis of the GAS-X® DMTA show two regions with major E' drops. This unusual profile has been already reported for some complex film matrices, due to thermal events overlap (Menard, 1999). The first sharp decrease of E' occurs around -125^{o}C. This event is ascribed to the presence of simethicone that has a Tg around -127^{o}C (Ringsdorf and Schneller, 1982). This thermal transition was not observed in the DSC profile, since the equipment could not be used at such low temperatures. The very slight transition observed at -50^{o}C is consistent with the results observed in DSC regarding the presence of Tm of this simethicone, which has been reported at -50^{o}C.

The second Tanδ peak is at 30^{o}C that depends on the frequency of analysis may be related to the thermal event that was observed at about 10^{o}C in the DSC trace. This transition corresponds to the main Tg of the film resulting from the formulation used. Several reports in the literature describe differences between the Tg values obtained by DSC and DMTA that can be between 10-20^{o}C (Menard, 1999). Also, the mentioned difference is usually higher in the DMTA assays because the differences on the time scale of the methods and frequency effect of the DMTA (Cheng, 2002).

The prepared GAS-X® formulations present a DMTA profile different from the commercial film (Figure 25). In fact, comparing their storage modulus it is easier to identify the thermal event at - 50^{o}C, which probably corresponds to simethicone Tm. In the GAS6 formulation it is also possible to identify a second Tg around 10^{o}C that corresponds to the film resulting from the formulation used. The E' peaks above Tg transition are well-marked in GAS6 and more subtle in GAS13. This formulation presents significantly higher values of E' in negative temperatures, however with the temperature increase these values rapidly drop. In fact, around -50^{o}C, presumably the simethicone's Tm, a sharp decrease is verified in formulation GAS6.

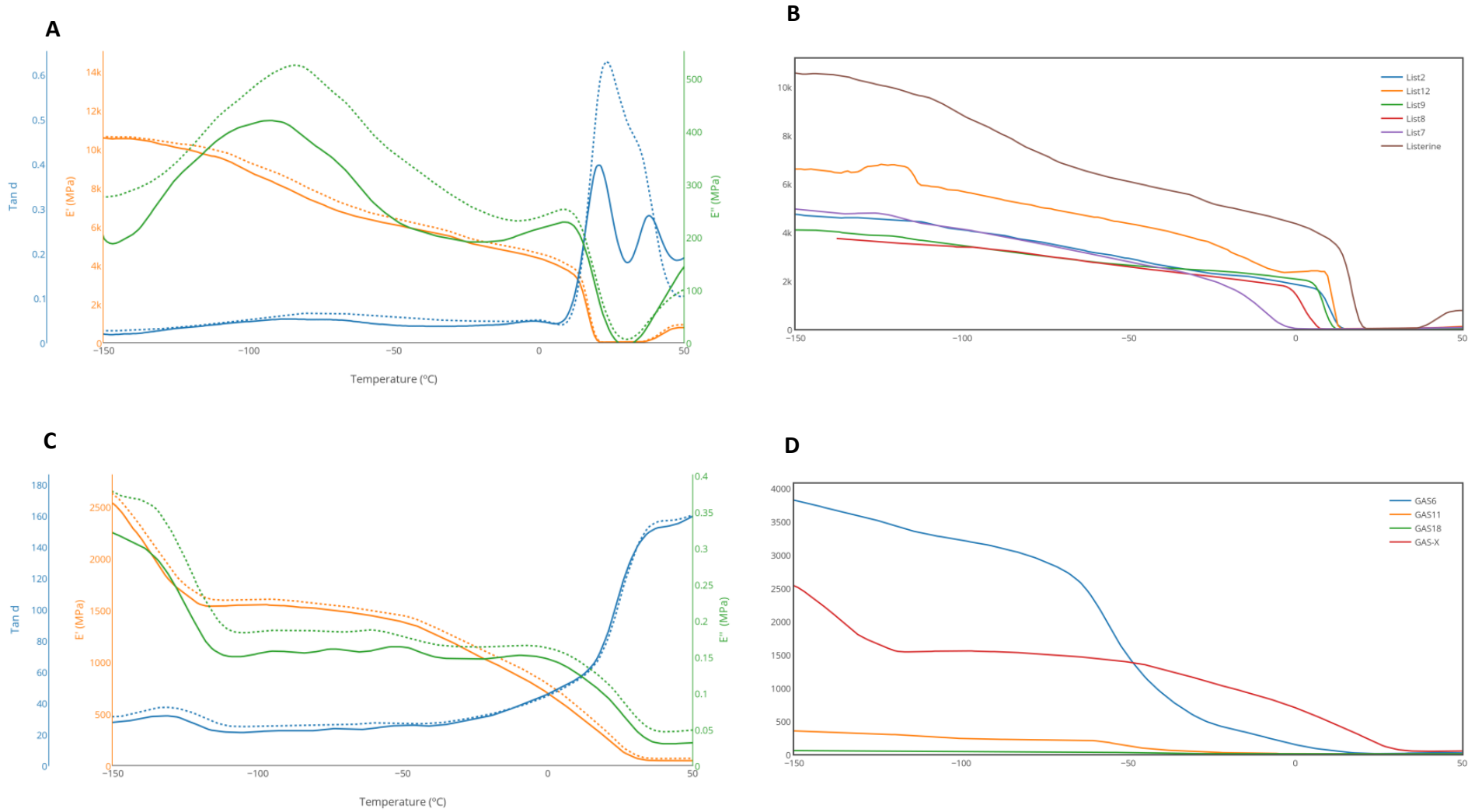

Figure 25 - DMTA analysis traces of the marketed films (1Hz, full line and 10Hz, dashed trace) of the prepared formulation and marketed films. (A) and (C) Represent DMTA profile of marketed films Listerine® and GAS-X®; (B) and (D) Represent Storage modulus (E') of prepared formulations, top Listerine® formulations and bottom GAS-X® formulations.

4. Conclusion

A complete thermo-mechanical analysis was performed in a novel dosage form (ODFs) in an attempt to relate its composition to the final product characteristics. This data may be extremely relevant to retrieve information that may be helpful to the development of new oral films platforms. Currently, to the best of our knowledge, it is not available any similar approach or such complete thermo-mechanical study in highly complex polymeric systems.

Despite of the formulations' composition complexity, very simple curve profiles were observed, which may be related with the optimal interaction between the components or thermal events overlapping. It was also obvious that the fewer amount of components in the prepared formulations diminished the overlap events in the thermal analysis methods allowing the easier identification of some events.

The TGA analysis was very useful to evaluate the thermal stability profile of the different components, which may be very useful to predict the formulations stability subjected to different temperatures.

The DSC analyses allow retrieving some relevant information about some components interactions and behaviour in the polymeric matrix. But, the complexity of the formulations hampered a complete understanding of role of the different components used in the formulations, and highlighted the limitation of this technique to obtain structural-properties characteristics in these matrices. Therefore, the DMTA evaluation was very helpful to obtain additional information about matrix-composition and product properties. Despite of some differences observed regarding the values obtained by DSC, both results are consistent and coherent regarding the Tg determination.

Although DMTA application is still limited in pharmaceutical industry its application in this polymeric film systems would be very useful to understand the performance, stability behaviour and some quality attributes of the final product (Jones et al., 2012; Perfetti et al., 2010).

In the present work it was shown that the main polymers / components presented in the film are responsible by the majority of the characteristic trends verified in the final product. Even the minimal amount of other excipients can change greatly the matrix film properties. It was also demonstrated that there is no need to have a perfect miscible system to obtain marketed viable products, with suitable handling, stability and performance properties.

Therefore, the compatibility or immiscibility of the components may be sometimes desirable depending on the drug delivery system under development (Mura et al., 1995).

Finally, in the development of these systems each excipient's properties added to the matrix should not be considered individually or independently. Several complex interactions may occur and each component of the oral film functions as a fingerprint for final product identification and behaviour.

5. References

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Chapter II.3

Outlining Critical Quality attributes (CQAs) as guidance for oral films

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Abstract

Oral films have gained increasing relevance as a novel dosage form the pharmaceutical market. Associated to their particular processing and multicomponent composition, there are a vast number of reasons to establish helpful development guidance, gathering simultaneously the recent pharmaceutical regulatory trends. This study aimed at characterizing marketed oral films in order to provide essential information about a clear definition of product CQAs. Several commercial oral films were evaluated in terms of thickness, residual water content, disintegration time and mechanical and thermal properties. The oral films exhibit a very broad range of thickness values [40-140µm], which is probably associated with the height gap used on the cast of oral films production. The majority of oral films dissolved within 60 seconds [32-105s]. In general, a broad range of values were found for all the properties studied, residual water content [2.91- 9.75 %], Young's Modulus [51.25 – 1827 Mpa], tensile strength [1.47 - 33.91Mpa] and tensile strain [0.32 – 38.2 %]. Despite the oral films' complex composition, it was possible to establish some important correlations about the impact of the main excipients on the final product characteristics. Additionally, it was also defined a range of acceptable values for the CQAs evaluated that may work as an acceptance criterion in the development of new oral film formulations.

Keywords

Orodispersible films, Quality by Design, Critical Process parameters, Critical Quality Attributes

1. Introduction

Oral drug delivery still holds the major share in the drug delivery market (Borges et al., 2015; De Robertis et al., 2015; Research, 2010). This fact is mainly driven by the convenience of the administration and lower production costs. Therefore, innovative oral dosage forms for very fast or controlled release, have been developed, with the focus on patient's compliance by addressing swallowing problems, multi-dose prescriptions, and for improving safety and / or efficacy (Kelly et al., 2009; Patel et al., 2010; Yang et al., 2010).

Orodispersible films (ODF) are a pharmaceutical dosage form that may be developed to have a fast or tailor drug release profile, and the interest of the pharmaceutical industry in this dosage form has significantly increased during the past years. ODFs were firstly introduced in the market as breath fresheners with the Listerine Pocket Packs®. This important landmark was followed by other OTC ODFs and later by the Rx products, in 2009 with the launch of Onsolis® and in 2010 with Zuplenz® (Borges et al., 2015; CenterWatch, 2015).

Currently, ODFs already have a solid and growing presence in the pharmaceutical market. However, there is still some lack of guidance for the development and manufacture of ODFs with suitable properties, particularly for medical use. These difficulties are mainly driven by the inexistence of well-defined characterization procedures, standard evaluation parameters, guidance on appropriate final product properties and specifications.

In literature, several techniques are described for the characterization of this dosage form. Garsuch et al. tested a set of very convenient techniques for oral films characterization with high relevance for the development phase, such as morphological characterization (scanning electron microscopy, near-infrared chemical imaging) as well as other techniques more indicated for the evaluation of product performance, tensile strength (based on DIN EN ISO 527), disintegration (thermomechanical analysis, contact angle measurement), and dissolution profile (fibre-optic sensor, common and adapted dissolution apparatus) (Garsuch and Breitkreutz, 2009).

Gaisford et al. also described a very interesting technique based on near-infrared chemical imaging (NIR-CI) to investigate the expected crystallization of the drug substances in the polymeric matrix (Gaisford et al., 2009). This non-invasive approach allows the analysis of the drug substances distribution within the matrix, after previous calibration with pure substances. As result, vibrational bands for selective imaging are obtained. The verification may be performed visualizing the possible substance crystallization by a homogeneous or

nonhomogeneous appearance (Gaisford et al., 2009). This information may have extreme importance during formulation development and optimization to evaluate possible incompatibilities between the drug substance and the polymeric matrix and to evaluate the product long-term stability.

Although these advanced techniques may be very helpful during formulation development, they are not easily carried out during routine procedures like in-process control and quality control. On the other hand, there is a lack of standard methods to evaluate relevant critical properties that are mandatory to control the product quality and at the same time are appropriate to evaluate such relative small-size dosage form. In this context, alternative methods have been studied and developed to be specifically applied to ODFs. For example, texture analyzer (TA) instruments enable the determination of ODFs' mechanical strength based on puncture tests (Preis et al., 2014b). This equipment has a holder clamp systems, special weights, an electronic end-point detection that enable the determination of the disintegration time (Preis et al., 2014a). Also, millifluidic continuous flow-through dissolution devices to mimic more closely mouth physiological conditions (the place where the disintegration and dissolution of oral films occurs) have been developed (Adrover et al., 2015).

Currently, scarce information is still available on the Pharmacopeia's regarding ODFs. The USP presents a complete definition for the characterization of films depending on its application site (European Pharmacopoeia Commission, 2015), but has no specific tests or any dedicated monograph requirements to apply (European Pharmacopoeia Commission, 2015). On the other hand, the European Pharmacopeia (EP) present a brief description of the dosage form and also mention that oral films should have an adequate drug release and mechanical strength (European Pharmacopoeia Commission, 2015). Therefore, there is an urgent need to study techniques and characteristics that may be critical to obtain ODFs products with optimal quality and performance properties, during the development and product quality control stages. Visser et al. recently enumerated some critical quality attributes (CQAs) that ODFs should present to be easily handled and quickly dissolved in the oral cavity, those include: tensile strength, elongation at break, Young's modulus and disintegration time (Visser et al., 2015).

Nevertheless, besides the brief guidance provided by EP (suitable mechanical strength and appropriate dissolution method), it was not possible to find more detailed information regarding advisable procedures for oral films characterization /quality control or to define suitable specification limits (Preis et al., 2014). For this reason, there is still much work to be

done in this area aiming to contribute to the knowledge and understanding of the CQAs of this new pharmaceutical dosage form.

The aim of this work was to perform an extensive characterization of several different commercial films, using different techniques, in order to correlate their main properties with major composition components and to evaluate the possibility of defining acceptance criteria for oral films' CQAs that may constitute valuable information to boost the development of new ODF formulations.

ODFs were evaluated regarding their structure, disintegration time, residual water content, mechanical and thermal properties. The methods used to characterize the films were selected based on the most widely described in literature and their suitability for the specific purpose.

2. Material and methods

2.1. Materials

Ten marketed products with orodispersible films technology were investigated: Gas-X®, Novartis Consumer Health, Inc; Snoreeze, Passion For Life Healthcare (International) Ltd; Re:balance, Boots Pharmaceuticals; Stop Snoring, Essential Health Products Ltd; Zentrip, Sato Pharmaceutical Co., ltd; B12 strips, Essencial Source, Inc; Hunger Strips, Now Slim Ltd; Listerine® Fresh Burst and Listerine® Cool Heat, Johnson & Johnson Healthcare Products; Snore Relief, CNS Inc.

2.2. Methods

2.2.1. Film mass

The films were weighed using an analytical balance (Mettler Toledo AGXS, Mettler-Toledo Inc., Columbus, US) and the average weight was calculated (n=3).

2.2.2. Film thickness

The thickness of the films was measured with a micrometer screw (Mitutoyo Digimatic Capiler, Mitutoyo Corporation, Japan) (n=5).

2.2.3. Tensile Strength

The mechanical properties of the films were determined using a tensile testing universal apparatus (Zwick, Germany) equipped with a load cell of 10 N. Briefly, oral films were held between two clamps positioned at a distance of 15 mm. Firstly, a preload was performed in each assay and then the strips were pulled by the top clamp at a rate of 10,0 mm/min.

The load automatically applied to the film is gradually increased and the corresponding magnitude of elongation is recorded until the break point of the film is finally reached. The

parameters are directly retrieved from the software TestXpert (TestXpert, Zwick, Germany), namely Young's modulus, tensile srength and elongation. Measurements were run at least in three replicates for each film.

2.2.4. Disintegration time

A simple test was used to evaluate the time needed until the disintegration starts. The oral films were laid on a Petri dish and 4 mL of water at room temperature or a phosphate buffer pH=6.8 (artificial saliva) was added. The time until the film samples started to disintegrate was recorded.

2.2.5. Karl-Fisher

The Karl Fischer Method was used to determine the residual water content in the oral films. This technique basically consists in the quantitative reaction of iodine and sulfur dioxide by the addition of water, in the presence of an alcohol (methanol).

$$SO_2 + I_2 + 2H_2O \xrightarrow{CH_3OH} 2HI + H_2SO_4$$

A sample was added to the titration flask filled with methanol previously dehydrated with a Karl Fischer reagent (Hydranal Composite 5, Sigma-Aldrich Co. LLC). Titration was carried out using Karl Fischer reagent with a known determined titer (mgH_2O/ml). Water content was determined based on the titration volume (ml). The polarization-current potential-difference method was employed as an end-point detection method.

These tests were performed in a Karl Fisher 787 KF Titrino (*Metrohm AG*, Herisau, Schweiz).

2.2.6. Differential Scanning Calorimetry (DSC)

DSC measurements were performed in a DSC Q100 (TA instrument). The tests were performed in two heating runs, from 50 to 100°C and -90 to 100°C with a heating rate of 10°C/min under constant nitrogen flow.

2.2.7. Thermogravimetric Analysis (TGA)

TGA was used to analyse the thermal stability of the sample by measuring the weight loss of the sample as a function of temperature, when the sample is submitted to a significant temperature variation. Generally, the TGA derivative, known as DTG curve, is used to mark the different peaks associated to each TGA steps, which represents the maximum rate of mass loss.

TGA test was performed in a TGA Q500 (TA instruments), at a heating rate of 10^{o}C/min, from 0^{o}C to 500^{o}C, under a constant nitrogen flow.

2.2.8. Statistical analysis

The number of samples tested was too small (n<7) to perform the normality test. Therefore, it was used the Kruskal-Wallis test to compare the different groups, or the Mann-Whitney test to compare 2 groups. The values in tables and graphs are presented as median (25% quartile – 75% quartile). These analyses were performed with GraphPadPrism version 5.01 (GraphPad Software, Inc, San Diego California).

3. Results and discussion

The compositions of the different marketed products were taken from the available information on the packaging boxes and are presented in Table 11. Excluding Listerine® oral films, all the products have modified hydrophilic cellulose. The complexity of their composition is well illustrated by the significant number of excipients used in each formulation.

The samples were kept at room conditions in their primary packaging material until the moment to perform the different characterization tests.

Table 11 - Main components of the commercial oral films evaluated - Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief.

Commercial Name	Polymers	Plasticizers	Flavors	Color	Sweetener	Surfactant	Thickening agent	Desintegrant	Anti-oxidant	Drug substance / Strength
Gas-X	Corn Starch modified Hypromellose Maltoextrin	Polyethyleno glycol Sorbitol	Menthol Flavor	FD&Blue#1 Titaniumdioxid e	Sorbitol Maltodextrins Sucralose					Simethicone / 62,5 mg
ListerinePocket Packs	Pullulan	Propylenogl ycol	Menthol Eucalyptol Aroma	Green 3 Yellow 6	Sucralose Potassium Acesulfame	Polysorbate 80 Glyceryl Oleate	Chondruscrispus (carrageenan) Ceratoniasiliquagu m xanthangum			Coppergluconate Thymol Methylsalicilate
Stop Snoring Oral Strips	Sodium alginate Modified starch Modified cellulose	Glycerol	Essential oils of peppermint, lemon, pine, fennel, lemon balm, eucalyptus, lavander, mastic, sage, thyme, clve	FDC Blue	Sucralose Potassium Acesulfame	sorbitol Polysorbate 80	Soylecithin			
B12 Strips	Hypromellose ModifiedStarch	Glycerol	Peppermint Flavor Menthol		Stevia	Polysorbate 80	GumArabic	Sodium Carboxymethyl Cellulose Microcrystalline Cellulose		B12 / 1000mcg
Zentrip	Hypromellose	Polyethylene glycol 400	Menthol Orange oil	Ferric Oxide	Mannitol	Sucrose esters of fatty acids				MeclizineHCl 25mg
SnoreRelief	Hypromellose Polyethylene Oxide Pectin		Menthol Wintergreenflavour	FD&Blue#1 FD&Yellow#5	Polydextrose Sucralose			Butylatedhydroxytoluene		
Hunger Strips	Cornstarch Cellulose	Glycerol	Natural MintFlavour	BrilliantBlue	Maltitol Acessulfame K	AlginicAcid (stabilizer)				GuaranaSeedextract
Snoreeze	Pectin Cellulose	Glycerol	Peppermintoil Menthol	Blue FCF	Aspartame Sodium saccharin Acessulfame K	Sorbitan Stearate Polysorbate 60	Guargum	Tocopherylacetate Hyaluronicacid Potassiumsorbate (preservative) Citricacid		
Re:Balance	Pectin Cellulose	Glycerol	Peppermintoil Menthol	Blue FCF	Aspartame Sodiumsaccharin Acessulfame K	Sorbitan Stearate Polysorbate 60	Guargum	Tocopherylacetate Hyaluronicacid Potassiumsorbate (preservative) Citricacid		

3.1. Tensile Strength

The mechanical properties were analysed in commercially available films in order to evaluate the possibility of defining standard ranges for these properties. These tests were restricted to the original shape of the films. The tests performed provided important insights about their mechanical characteristics.

Table 12 - Mechanical properties of commercially available oral films. The values are presented as median (25% quartile – 75% quartile). ϭB - tensile stress at break; εB - tensile strain; Et– Young's modulus.

Commercial films	E_t (MPa)	εB (%)	ϭB (Mpa)	Thick. (μm)	Nature
B12 Strips	692.5 (554.3-803.9)	7.815 (6.4-10.07)	33.78 (31.43-35.45)	60	Soft - Tough
Gas-X	51.25 (45.89-56.54)	3.160 (3.160-3.710)	1.470 (1.440-1.610)	110	Soft- Weak
Hunger strips	1003 (956.4-1437)	0.3200 (0.3100-0.3400)	4.570 (3.830-5.450)	40	Hard - Brittle
ListerineFreshBurst	1077 (797.7-1440)	4.485 (2.595-5.955)	33.91 (29.45-43.01)	40	Hard - Tough
Listerine Cool Heat	1724 (1677-1729)	3.380 (2.940-3.710)	27 (26.89-27.20)	40	Hard - Tough
Stop Snoring	236.2 (145.0-277.2)	6.340 (4.943-6.958)	10.39 (9.032-13.17)	60	Soft - Tough
SnoreRelief	1827 (1753-1871)	3.810 (2.990-4.420)	29.94 (24.04-31.87)	60	Hard - Tough
Zentrip	223.8 (218.7-228.4)	2.485 (2.288-2.570)	3.960 (3.953-4.103)	140	Soft - Weak
Snooreze	90.47 (39.42-91.77)	38.20 (32.80-44.44)	14.84 (12.94-17.06)	80	Soft - Tough
Re:balance	186.2 (157.3-204.2)	31.59 (25.01-33.38)	12.44 (10.62-13.65)	80	Soft - Tough

The Young's modulus (Et) of the marketed ODFs varied between 51.25MPa and 1827 MPa (Table 12 and Figure 26). In the present study, it was not possible to correlate the Et with the films thickness, due to the high variability and multicomponent complexity of the studied films. The GAS-X® samples correspond to the less stiffeness films (lower Et) but are the second samples in terms of thickness, whereas the SnoreRelief samples correspond to the most rigid films (higher Et) and are the second thinner films. Although the elastic modulus is affected by the cross sectional area of the sample, the gauge length of the test specimen was maintained constant in order to minimize the impact of having samples with different cross sectional areas, since samples with higher cross sectional area tend to be stiffer. Therefore, the main differences observed between the different oral films are probably related with the different nature of the polymeric matrices (Table 11). Interestingly, the majority of the films are based on modified cellulose, despite the discrepancy of results. This observation suggests that besides the polymeric matrix, the other components used in the formulation have also an important role on the mechanical properties.

Listerine® films, mainly based on Pullulan are clearly stiffer than the majority of cellulose based films, except for Snorerelief® and Hunger strips®. Considering the structures of hypromellose and pullulan, the latter presents more available hydroxyl groups to establish intra-and inter-polymer chains hydrogen bonds, which could justify the higher rigidity of the Pullulan based films.

It is also interesting to notice that Listerine® films with distinct flavours (Listerine® Fresh Burst menthol flavour, and the Listerine® Cool Heat, cinnamon flavour) present slight differences in the elastic modulus. Their mechanical properties are probably mainly affected by Pullulan and propylene glycol, but the differences found may indicate that components present in very small amounts can also have some influence on the product properties, in this case, different flavours. Nevertheless, the mechanical properties of Listerine films evaluated are consistent with the mechanical properties of Pullulan films reported: higher elastic modulus and moderate to high tensile strength (Kawahara M, 2003). The tensile strain at break reflects the elongation ability of the products. Regarding this property, a wide range of possible values were observed from 0.32 % to 38.20% for Hunger strips® and Snooreze®, respectively (Table 12 and Figure 26).

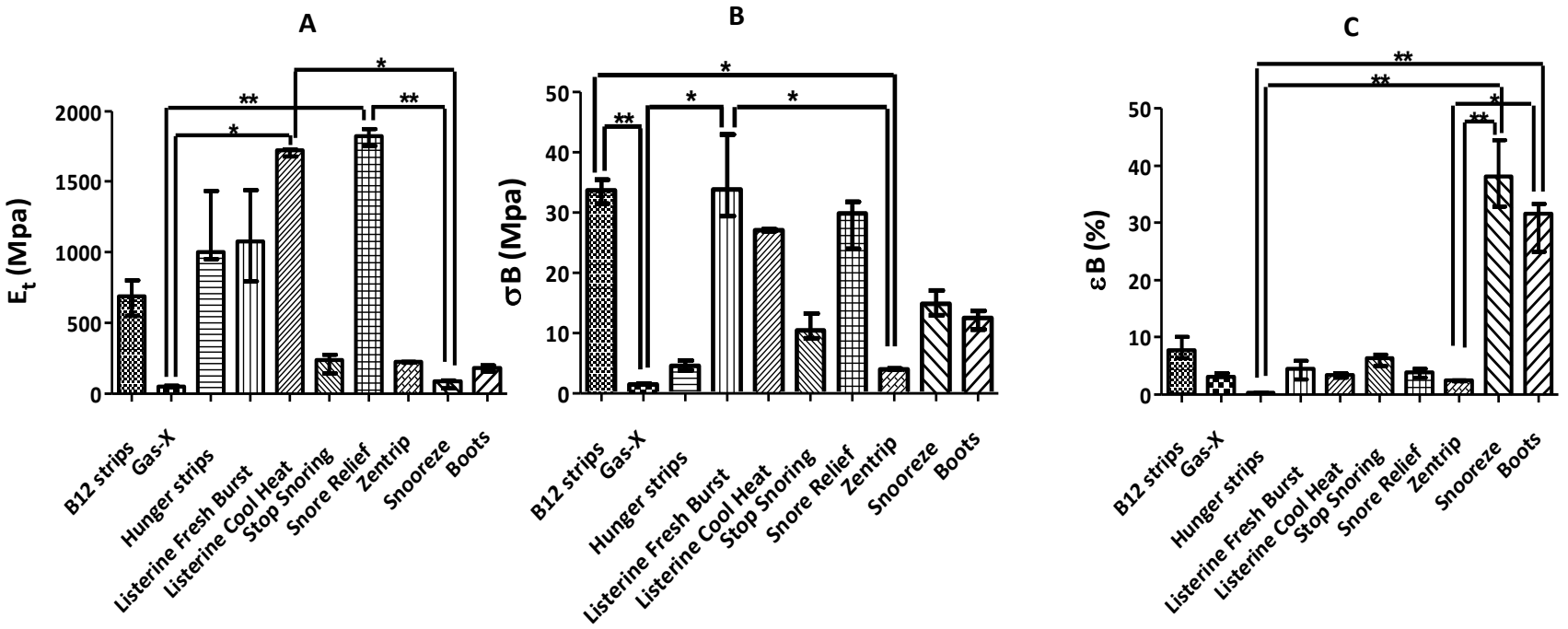

Figure 26 - Mechanical properties of commercially available oral films (Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief). (A) Represent Et, Young's modulus. (B) Represents ϬB, tensile stress at break. (C) Represents εB, tensile strain. * $p<0.05$; ** $p<0.01$.

The tensile stress at break (Breaking force, σB) also varies significantly between the tested products (Table 12 and Figure 26). Gas-X® tears easily with 1.47 MPa while Listerine Fresh Burst requires 33.91 MPa to break. It was also verified that the majority of the films with high rigidity (high Et) tend to have higher tensile stress to break (Listerine®, Snore Relief® and B12 strips®). However, this is not observed for the Hunger strips®, that are hard (high Et) and brittle (low σB). Snooreze ® and Rebalance® films are less stiffness (low Et) but also though (medium σB values).

In general, the results demonstrate that the several marketed films studied have a wide variation of the mechanical properties. Moreover, it is clear that the overall composition should be the main reason for the observed differences. Therefore, it would be very important to evaluate the role of each component and its influence in the matrix. It is expected that the major contributors to the mechanical properties are due to the film forming polymers, the plasticizer and the drug substance (Cilurzo et al., 2010; Mishra and Amin, 2009).

Hydrophilic modified cellulose compose the majority of the films studied, being hydroxypropylmethyl cellulose (HPMC or hypromellose) and hydroxypropyl cellulose (HPC) the most widely used, since these polymers have a fast dissolution in aqueous media (Bourtoom, 2008).

Generally, HPMC is referred as a strong polymer with good physical integrity and as a film-former (Chen M, 2006; Meenu Dahiya, 2009). Thus, these properties are highly dependent on HPMC grade and also can be influenced by formulation characteristics, e.g. concentration of HPMC used or possible excipients blends. In fact, it is reported that the maximum puncture strength of HPMC increases with the molecular weight, E3 (Mw 9,000) < E5 (Mw 10,000) < E15 (Mw 30,000) < E50 (Mw 45,000) (Cherukuri and Ravella, 2009; Meenu Dahiya, 2009). It is also known that HPMC E-15 has better film forming properties when blended with other polymers such as microcrystalline cellulose or synthetic polymers (PVA and PVP) (Kulkarni et al., 2010), while solutions with lower HPMC concentration became thin, brittle and non-peelable (Mahesh et al., 2010).

The films evaluated that have cellulose as film-former are mainly soft (moderate Young's modulus) and tough (moderate tensile strength). However, there are some exceptions such as Zentrip® and Gas-X® that are soft and weak (low elongation and very low tensile strength). Hunger strips® are hard and brittle (high Et and very low elongation), whereas Snore Relief®

is hard and tough (high E_t). One half of the films under study have hypromellose as matrix component, while the other half have solely cellulose or modified cellulose. Therefore, based on the moderate E_t that favours the softener handling properties observed, hypromellose may be the polymer used. The exceptions are Snore Relief® and the Hunger strips®, that normally are tougher. This fact may be related with different cellulose grades used or excipient-excipient interactions between different components. For example, HPC based films were shown to be stiffer than HPMC films, due to the high elastic modulus, and were found to have a brittle fracture and a very low elongation (Priyanka et al., 2011). The higher rigidity could be explained by the relatively high glass transition temperature (Tg) of HPC comparing to hypromellose. Low substituted HPC presents a Tg of 220^{o}C, whereas HPMC may vary typically between 170-198^{o}C (Gómez-Carracedo et al., 2003). The hydroxypropyl side groups on both celluloses increase the interactions (via hydrogen bonding) between substituents, raising the Tg, whereas the methoxyl groups presented on the hypromellose reduce the ability of the polymer to form hydrogen bonds. This fact increases the amorphous content of the polymer, resulting in the mentioned Tg differences. Therefore, HPC has a relatively strong intermolecular force and consequently a higher crystallinity which results in tougher but brittle materials. Additionally, it has been demonstrated that in thin films both mechanical and thermal properties have a strong dependence, and the Young's modulus and *T*g are likely to follow a similar trend (S. Rivero, 2010). Furthermore, hypromellose thin films demonstrated different mechanical properties when blended with other film-forming polymers. As referred before, Snore Relief® films, contrarily to the other hypromellose based films, present a significantly higher E_t ($p< 0.01$: Snore Relief® / Gas-X®) (Figure 26) that is comparable with the Pullulan based films (Listerine® films) (Figure 26). These results can be explained by the presence of the poly (Ethylene Oxide) (PEO) that is known as a polymer with good film-forming properties (Chen M, 2006; Myers, 2008; Myers et al., 2013), with the additional and valuable characteristic of being a self-plasticizing polymer. This PEO feature eliminates the need of adding a plasticizer to the film formulation, which is absent in Snore Relief® films, and enables the incorporation of a higher percentage of the drug substance (Chen M, 2006; Myers, 2008). It is worth to mention that the commonly used plasticizers, are small molecules that easily embed themselves between the polymer's chains, increasing the free volume and chains' movements, lowering significantly the Tg and turning the polymer matrix softer. On the contrary, despite of the sufficient plasticizing effect of PEO in the film, due to its high molecular weight (Mw) that can range from around 100,000 (Polyox WSR N-10) to 4,000,000 (Polyox WSR 301) (Myers, 2008; Rowe R, 2009), probably do not interlace between

hypromellose chains so easily, and therefore work essentially as an additional film-forming polymer. Consequently, the addition of another polymer restricts the polymer chain motions in the polymer-polymer complex, particularly due to the hydrogen bonds established between the primary hydroxyl groups on cellulose with the oxygen in the ether groups of PEO (Pawar et al., 2013), contributing to the higher rigidity and tensile strength.

Regarding Gas-X® films, the mechanical behaviour can be ascribed to the high percentage of drug substance (Simethicone) presented on the film (at least 60 % w/w). This high amount of drug contributes to a weaker structure of the polymer matrix that has a deleterious effect on the mechanical parameters. The Zentrip® soft and weak mechanical performance can be related to the mannitol presence, which has demonstrated the ability to increase the crystallinity of polymeric films turning the structures more brittle (Lakshmi et al., 2011).

3.2. Disintegration

It is important to consider that this test is used only for comparison purposes, because it does not mimic properly the *in-use* conditions, namely: the complex saliva composition, the physiological temperature, the possible tongue movements and the pressure. Nevertheless, the results are very consistent with the literature (Borges et al., 2015). Briefly, the pullulan and HPMC based films tend to dissolve faster comparing to the films that contain Pectin as film forming agent (Snooreze, Boots and Snore Relief) (Borges et al., 2015).

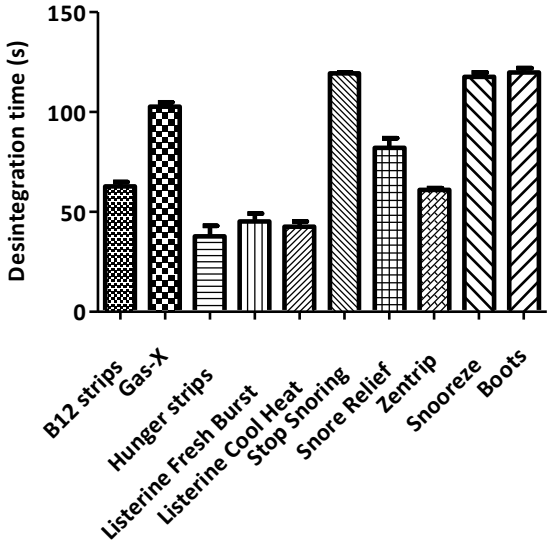

Figure 27 - Disintegration time of commercially available oral films (Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief).

At least half of the marketed tested films dissolved within 60 seconds (Figure 27). Pullulan based films (Listerine® films) present fast disintegration time compared with HPMC based films (Chen M, 2006). Boots® and Snoreeze® films showed higher disintegration time probably due to pectin, which is known by its mucoadhesive properties and slowly dissolution, even in oral cavity (Dahiya et al., 2009). Zentrip® films do not completely dissolve; instead they rapidly disintegrate in small pieces. This behaviour could be explained by the presence of Mannitol, which facilitates the fast disintegration times (Kadajji and Betageri, 2011) and the insoluble components presented in the formulation including the drug substance, Meclizine HCl (approximately 34% w/w film). Regarding the hypromellose based films, the difference observed between samples is not statistically significant, being the slight variations probably related to the different hypromellose grades used (Chen M, 2006).

3.3. Residual Water content

The evaluation of the residual water content is important parameter to establish an optimal amount that would allow obtaining flexible films. Higher water contents are known to induce the formation of tacky films (Hoffmann et al., 2011).

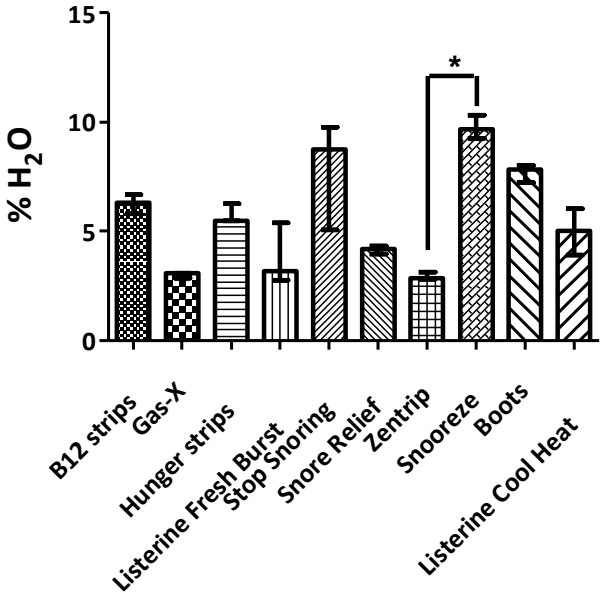

Figure 28 - Residual water content of commercially available oral films (Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief). % H_2O, residual water content. * $p<0.05$.

All commercial films analysed exhibited residual water content below 10% and the majority below 5% (Figure 28). There were no significant differences between the films, except for Snoreeze® and Zentrip® ($p<0.05$). In fact Snoreeze®, Boots® and Stop Snoring® films are the ones with higher water content. This observation could be explained by the high hydrophilic nature of sodium alginate and pectin used in the formulation of these films, or eventually due to the use of glycerol as plasticizer. In fact, all formulations with more than 5% of water content (with no exceptions) have glycerol as a plasticizer: Stop Snoring®, B12 strips®, Hunger Strips®, Snoreeze® and Rebalance®; whereas the others have poly(ethylenoglycol) or propylene glycol as plasticizer (Table 1, Figure 3). In addition, it is described that the water retention depends not only on hygroscopicity of the polymer but also on the amount and type of plasticizer. In fact, polymers plasticized with hydrophilic compounds tend to absorb more water from surrounding medium. For instance, an increase on the plasticizer content,

from 1 to 3 %, can induce an increase of about 68% of the water retention by the polymer (Meenu Dahiya, 2009).

3.4. TGA and DSC Analysis

TGA and DSC allow the characterization of individual components and multicomponent mixtures (Bond et al., 2002; Clas et al., 1999) and also a fast screening excipients' compatibility, specially concerning to drug–excipient compatibility (Feldstein et al., 2003; Giron, 2002; Wesolowski et al., 2012). These techniques are very advantageous since they can be used for quick stability screening evaluation that may be performed in early development stage and with small amount of sample.

Probably due to the complex composition of the films analysed very different thermal profiles were obtained (Figure 29 and Figure 30) because the TGA thermogram is not only dependent on the polymer's degradation mechanism but also on oral film components, such as water content, plasticizers and volatile substances.

3.4.1. TGA

TGA in the pharmaceutical development is mainly used for the characterization of excipients and drug substances. This method essentially evaluates the thermal decomposition reactions, dehydrations as well as the nature of excipient-water interactions (Craig and Reading, 2006). Thereby, it is also an useful test to evaluate the phenomenon of adsorption and desorption of water (Gabbott, 2008).

TGA consists in the continuous measurement of the sample weight with increasing temperature. The weight loss is easily quantified and associated with degradation or transition processes (Gabbott, 2008; Stuart, 2004).

In this particular case, TGA was very helpful to evaluate the composition in volatile substances, including water molecules, and the thermal stability of the oral films studied.

The Hunger strips were apparently the more unstable formulation avoiding valid assays, whereas the Snore Relief seems to be more thermal stable composition, with higher $T_{onset.}$. However, considering the weight loss percentage, Gas-X would be the more thermal stable

oral films. Temperatures above 200°C are needed for 5% or 10% of weight loss in GAS-X films.

Table 13 - TGA results of the commercial films: Gas-X, Re:balance, Boots Pharmaceuticals, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief. T(5%), represents the temperature at each oral dispersible film have 5% of weight loss. T(10%), represents the temperature at each oral dispersible film have 10% of weight loss. T_{onset}, is the maximum tolerated temperature before degradation. (* - the film swelled during the analysis, it was not possible to perform valid assays).

	T(5%)	T(10%)	T_{onset}
B12	51.44	145.61	158.85
Snore Relief	78.60	202.31	297.94
Zentrip	125.24	201.52	236.40
Snoreeze	56.82	101.89	157.86
Listerine	62.62	168.61	210.38
Gas-X	210.02	231.05	207.59
Hunger Strips*	-	-	-
Re Balance	60.61	109.25	159.98
Stop Snoring	58.55	132.54	188.06

The weight decrease observed in the beginning of the curve (until 100°C) corresponds essentially to the evaporation of volatile substances, such as ethanol, flavours and water. Gas-X®, Zentrip® and Snore Relief® are the films with lower weight loss in this region, which is consistent with the previous results (% of residual content) (Figure 29). In fact, Gas-X® is the film with lower % of residual water, followed by Zentrip® and Snore Relief® (Figure 28). On the other hand, the highlighted decrease of weight observed in the Re balance® (Boots) and Snoreeze® curves indicate that these films have higher residual water content as already demonstrated by Karl-Fisher results (Figure 29).

Above the 200°C, there is an accentuated weight loss that corresponds to the decomposition of the polymers that are the main components of the oral films.

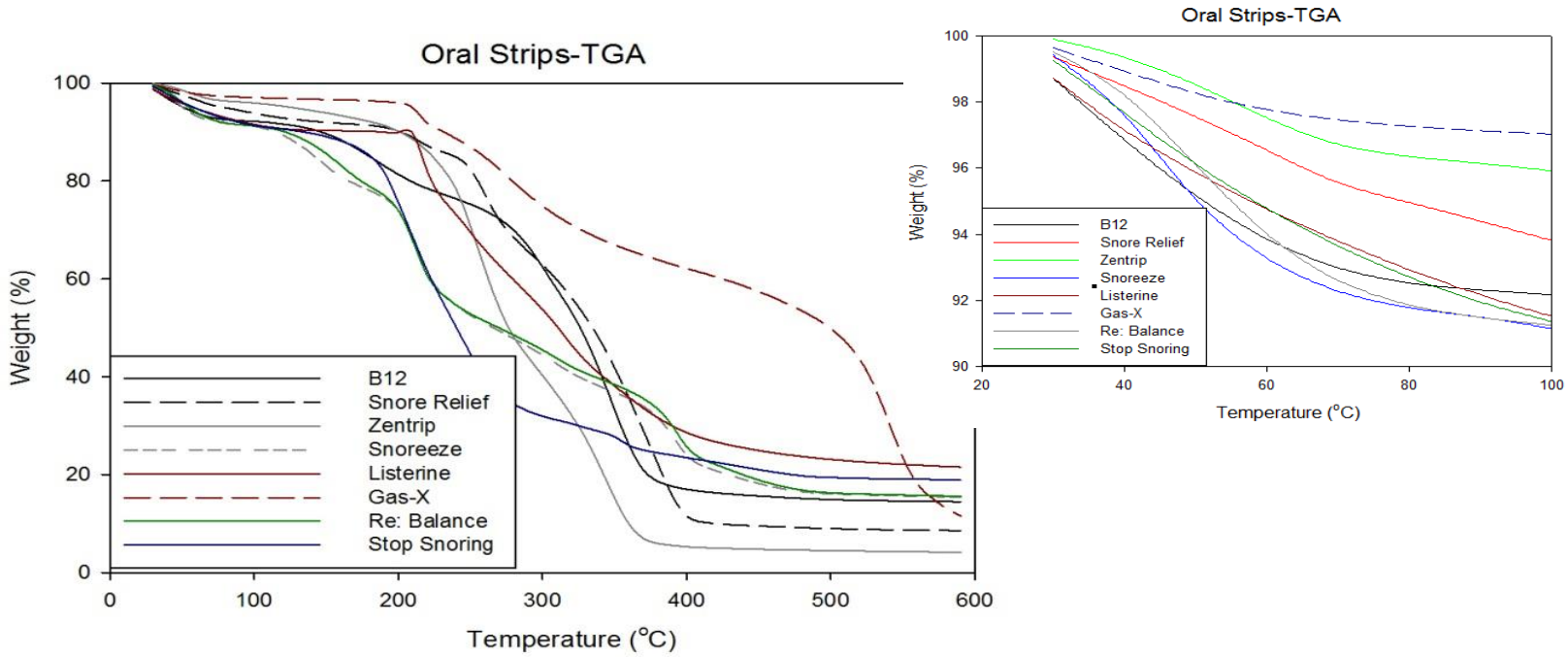

Figure 29 - TGA analysis of commercially available oral films (Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief).

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Finally, it is possible to conclude that, despite the very different thermal profiles, Gas-X® is the most thermal stable film, followed by Zentrip® (Table 13 and Figure 29). This result can be explained taking into account the film composition, which influences the polymer-polymer and polymer-plasticizer interactions.

3.4.2. DSC

As can be observed in Figure 30, two distinct thermal events are identified: one from Stop Snoring® and other from Snore Relief®. However, even these events are hard to disclose due to the complexity of the formulations. Stop Snoring® is composed by a complex polymer matrix: a modified cellulose (Tg~ 100 °C (Gómez-Carracedo et al., 2003)), a modified starch and sodium alginate (Tg ~ 95-158°C (Roger et al., 2007)). The Tg of these polymers are very high compared to the possible Tg event observed for this film (Figure 30), suggesting that this event may occur due to complex interactions between the film components. The Snore Relief® films have as main components HPMC (Tg ~ 170-198°C (Gómez-Carracedo et al., 2003)), PEO (Tg ~ -67°C (Meenu Dahiya, 2009)) and pectin (Tg ~95°C) without any plasticizer. The endothermic event observed at 60°C, may correspond to the PEO melting temperature (Tm), as reported by others (Money and Swenson, 2013).

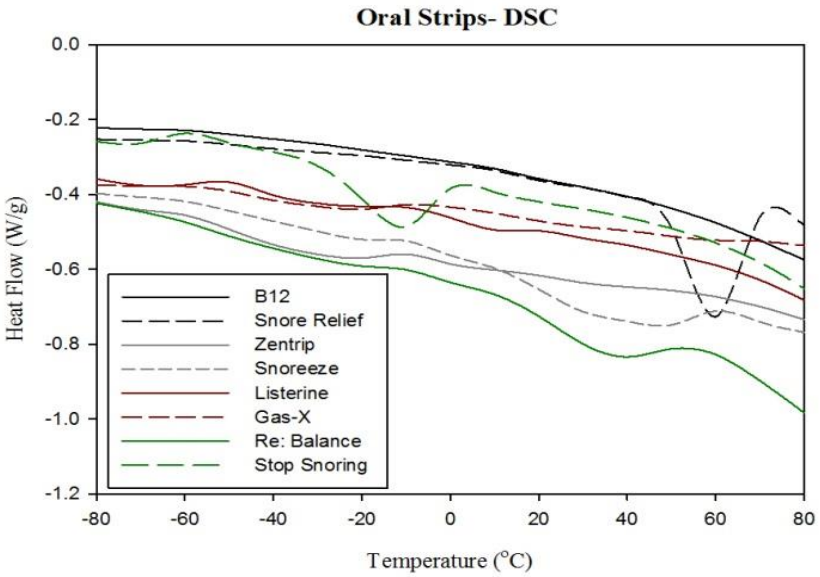

Figure 30 - DSC analysis of commercially available oral films (Gas-X, Re:balance, Stop Snoring, Zentrip, B12 strips, Hunger Strips, Listerine Fresh Burst and Listerine Cool Heat and Snore Relief)**.**

Regarding the other marketed films analysed it is not possible to draw any effective conclusion. Despite of formulations' composition complexity, very simple curve profiles are observed, which may be related with the optimal interaction between the components or overlapping of some thermal events.

3.5. Critical Quality attributes (CQAs)

The data presented above allowed defining acceptance criteria for CQAs that may be used to develop oral film platforms with appropriate properties for the intended use (Table 14). These ranges of values were defined considering that a wide selection of polymeric matrixes may be done to prepare this dosage form and each may be singular with its own performance behaviour. Although the broad range values determined, all the studied films present acceptable features to be processed, manufactured, marketed and handled.

Table 14 - Critical Quality attributes acceptance criteria for ODF development.

CQA	Acceptance criteria
ϭB (Mpa)	15-35
εB (%)	5-40
E_t (Mpa)	100-1500
Residual water content (%)	3-6%
Disintegration time (s)	<60 seconds (target 30 seconds)

The difficulty to establish thermal specifications is mainly related with the inherent characteristics of the assays and the complex formulation of the polymeric matrices. These are very specific tests used to characterize materials normally with completely different parameters compared to oral films (Craig and Reading, 2006; Gabbott, 2008; Stuart, 2004). In turn, this pharmaceutical dosage is a multicomponent matrix that may behave as a new material depending on the components miscibility (Bond et al., 2002; Clas et al., 1999). Therefore, the results obtained are a very own feature of each formulation, which turns difficult a universal standardization. The thermal stability may be assumed and extrapolated for higher stabilization through time by assessing a kinetic degradation model for each

system (Clas et al., 1999; Yoshida et al., 2010). Additionally a good excipient-excipient or drug-excipient compatibility would correspond to a good miscibility, and the multicomponent matrix would behave as a single component. Therefore, this information would be related with a suitable dispersion of the drug substance within the polymeric chains that may avoid possible instability of the drug and also its premature crystallization. In fact, polymers that may inhibit the crystallization if drug-polymer interactions are more favourable than those present in the crystalline drug (Shah et al., 2014).

4. Conclusions

To the best of our knowledge there is no study that enabled the definition of acceptance criteria for oral films CQAs. The relative wide range of values determined for each CQA are justified by the variety oral films composition, especially regarding the additives. Nonetheless, the definition of acceptance criteria for these quality attributes can be translated into a very important contribution to the future development of new oral films formulations.

This work highlights the complexity involving the characterization of oral films and the urgent need of have development guidance and suitable quality standards. Although it was not possible, with this approach, to define a strict correlation between a single component and the selected CQAs, the general analysis allowed to conclude that the same polymer based films may have significantly different behaviours. However, it is also important to consider that these differences may be caused not only by the composition but also by the processing and manufacturing methods.

Finally, the acceptance criteria values should be preferentially used for initial screening tests during the development of a new, soft and tough oral film. Nevertheless, based on a pre-defined polymeric matrix composition, optimization tests should be performed in order to define less broad acceptance criteria for each specific oral film formulation in order to obtain a desirable and robust final product.

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Chapter III

Hydrophobic polymers for oral films: Development and Optimization

This Chapter is dedicated to the preparation of a novel and versatile oral film technological platform. The Quality by Design approach was applied to screen the different formulations developed based on the previous critical quality attributes established and selection of appropriate critical process parameters. The optimization was only performed in one formulation that apparently demonstrated more promising results.

This study led to a patent application entitled “Orodispersible films”.

Chapter III.1

Hydrophobic polymers for oral films: a quality by design approach

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Patent application US20150038594 A1

Abstract

Orodispersible films (ODF) for fast oral disintegration are generally based on hydrophilic polymers, which when exposed to ordinary environmental humidity conditions may become sticky, with low stability, undesirable texture and appearance. The aim of present study was to develop ODF based on hydrophobic polymers with a fast disintegration time. A quality by design (QbD) approach was applied to screen three different formulations each one based on a different hydrophobic polymer: polyvinyl acetate (PVAc), methacrylate based copolymer and shellac.

The screening formulations were characterized regarding their mechanical properties, residual water content, disintegration time and appearance, in order to find a suitable ODF formulation according to established critical quality attributes (CQAs). The selected critical process parameters (CPP) for the selection of appropriate ODF formulations were the percentage of the different excipients and the plasticizer type. Three hydrophobic based matrices with fast disintegration were developed. These were generically composed by a hydrophobic polymer, a stabilizer, a disintegrant and a plasticizer. Interestingly, it was found that the same component may behave differently depending on the overall system composition. It was shown that it is possible to develop oral films based on hydrophobic polymers with fast disintegration time, good texture and appearance, breaking a paradigm of the ODF research field.

Keywords

Oral Films; Hydrophobic Polymers; Critical Quality Attributes; Critical Process Parameters, Polyvinyl acetate; Methacrylate copolymer; Shellac

1. Introduction

Orodispersible films (ODF) have been introduced in the market as an alternative to conventional oral dosage forms. The fast dissolution in the oral cavity is useful to overcome the swallowing problems associated with capsules or tablets and for non-cooperative patients, promoting patient compliance.

The majority of the oral films available in the market and under development are based in hydrophilic film forming polymers (Borges et al., 2015; Dixit and Puthli, 2009; Hoffmann et al., 2011; Irfan et al., 2015). By definition, hydrophilic substances have higher affinity to water when compared to hydrophobic components. Therefore, mechanical and physical properties of hydrophilic polymeric matrices may vary significantly with the water presence in the surrounding environment, which could lead to the premature disintegration of the polymeric matrix (Ping et al., 2001). In fact, these structures tend to become sticky over time when exposed to ordinary environmental humidity conditions, leading to low stability ODFs, undesirable texture and bad appearance. Nevertheless, additional changes at molecular level may occur, since small or less perfect crystalline polymeric structures might be lost contributing to a decrease of the glass transition temperature (*T*g) (Ping et al., 2001). In turn, it is known that hydrophobic polymers tend to absorb very small quantities of water at equilibrium even at high moisture contents at room temperature.

Polyvinyl acetate (PVAc) is an atactic, non-crystalline and non-ionisable polymer, synthesized by a free radical polymerization. It presents high flexibility and low toxicity, making it very appropriate to use in the food and pharmaceutical industry (BASF, 2010; Kolter et al., 2013). PVAc is available in a 30% w/w aqueous colloidal dispersion by BTC, known as Kollicoat® SR 30 D, with an optimal low minimum film forming temperature (MFT) of 18^{o}C (BASF, 2010). This characteristic may allow the application of the suspension to form a polymeric matrix without the need of a plasticizer when above 35^{o}C (BASF, 2010). Additionally, this polymer is an interesting choice for the development of film matrices with low tendency to absorb water when exposed to the environment RH (Ping et al., 2001). The high molecular weight (Mw) of the polymer (around450 kDa), contributes to the formation of films with suitable mechanical polymeric properties (Kolter et al., 2013).

Ammonium Methacrylate Copolymers are acrylic polymers widely used as film forming polymers in modified drug release dosage formulations due to their hydrophobic properties (Qiu et al., 2009), and are also available as aqueous suspensions, e.g. Eudragit RL or RS from Evonik®. These copolymers of poly(ethylacrylate), poly(methyl methacrylate) and

poly(trimethyl aminoethyl methacrylate chloride) are insoluble in water, but easily permeable to drugs' incorporation, depending on the relative proportion of the quaternary ammonium groups. The increase of these charged chemical groups may enhance the amount of loaded drug. Eudragit RL (10%) has twice the amount of this functional quaternary ammonium groups when compared to Eudragit RS (5%) (Derakhshandeh and Soleymani, 2010).

In opposition to the previous synthetic polymers, shellac is a purified product of lac, a natural resinous oligomer (Mw ≈ 1000 D) secreted by an insect. Shellac is composed by polyesters of mainly aleuritic acid, shellolic acid, and a small amount of free aliphatic acids (Leopold, 2009). In its pure form this polymer is insoluble in water. The development of shellac aqueous ammoniacal solutions turned this polymer very important for pharmaceutical dosage forms, being commonly used as an enteric coating material (Farag and Leopold, 2009). Shellac ammonium salt solutions are easy to handle even at high concentrations and present higher stability than its acid form (Farag and Leopold, 2009). It is described that shellac-coated tablets have lower water uptake than HPMC-coated systems, indicating higher shellac's moisture protection, especially at high RH (Pearnchob et al., 2003).

Hydrophobic polymers usually origin insoluble matrices widely used for controlled drug release formulations due to their inertness and high drug loading capacity. Although, the hydrophobic nature seems to be incompatible with oral fast disintegration, the association of a channelling agent may facilitate the liquid penetration and consequently the disintegration (Derakhshandeh and Soleymani, 2010).

The development process of pharmaceutical preparations has changed in recent years. A systematic approach for the optimization of pharmaceutical dosage forms and processes able to improve the quality prediction and control has been amply adopted (Quality by Design) (ICH Harmonised Tripartite, 2009). A very common tool used in the QbD is the definition of a quality target product profile (QTPP), a dynamic product description that summarizes the quality characteristics expected to guarantee the product performance, stability, safety and efficiency. Generally, the QTPP includes the different dosage form characteristics (e.g. route of administration, strength, therapeutic indication, drug release profile, pharmacokinetics, the critical quality attributes (CQAs) and the critical process parameters (CPPs) (Rathore and Winkle, 2009; Visser et al., 2015). The CQAs may be resumed as the characteristics that define the product quality, and CPPs refers to the process variables that can influence these characteristics (Rathore and Winkle, 2009). Therefore, the combination of the CQAs and CPPS allow the definition of the design space (Rathore and

Winkle, 2009; Visser et al., 2015). The construction of an oral film QTPP may be roughly structured based on the available literature describing the suitable oral films requirements and the characterization methods available to access the film properties (Borges et al., 2015; Dixit and Puthli, 2009; Hoffmann et al., 2011; Irfan et al., 2015). An ideal oral film should be handled without being damaged, should be physically stable and provide an easy and pleasant administration. These properties may be translated into product quality attributes, such as appropriate mechanical properties and organoleptic evaluation (Visser et al., 2015).

In the present work, three different hydrophobic polymers (polyvinyl acetate, methacrylate copolymer and shellac), generally regarded as safe (GRAS) and suitable for oral administration were selected for the development of ODFs, based on a QbD approach. The main aim of this work was to demonstrate that hydrophobic polymers can be used in the manufacture of ODFs with suitable mechanical properties and higher resistance to moisture conditions without compromising the rapid disintegration time, which breaks a paradigm in the ODF research field.

2. Material and methods

2.1. Material

Polyvinyl acetate (PVAc) (Kollicoat® SR 30D) (BTC, Ludwigshafen, Germany), Polyvinyl alcohol 4-88 (Merck, Darmstadt, Germany), Ammonium Methacrylate Copolymer, Type A (Eudragit® RL 30D) (Evonik Nutrition & Care GmbH, Essen, Germany), Shellac (HARKE Pharma GmbH, Mülheim an der Ruhr, Germany), Hydroxypropylmethyl cellulose, Methocel E5 (Colorcon, Harleysville, U.S.), Sodium Carboxymethylcellulose (Aqualon France BV, Alizay, France), Maltodextrins (Grain Processing Corporation, Iowa, USA), Monoammonium glycyrrhizinate (Mafco, NJ, USA), Citric acid (Merck, Darmstadt, Germany), Glycerol (Merck, Darmstadt, Germany), Triethyl citrate (Merck, Darmstadt, Germany), Polyethylene Glycol 400, Lutrol 400 (BTC, Ludwigshafen, Germany), Polyethylene Glycol 4000, Macrogol 4000 (Clariant Burgkirchen, Deutschland GmbH), Polyethylene Glycol 6000, Macrogol 6000 (Clariant Burgkirchen, Deutschland GmbH), Propylene Glycol 1,2-propanediol (Merck, Darmstadt, Germany), Polysorbate 80, Tween 80 (Merck, Darmstadt, Germany), Red Iron Oxide (Huntsman Pigment S.p.A, Torino, Italy),

2.2. Methods

2.2.1. Choice of design and experimental Layout

The software JMP 10 (SAS Institute Inc., Cary, NC) was used to construct custom designs. This platform was used instead of classical designs, since different types of factors were studied, including mixture and categorical variables. The defined experiments carried out in this work are presented on Tables 15, 16 and 17. They were run in random order within each formulation type. The analysis was performed using the screening designer platform, so the software adds automatically the interactions and crossed effects.

The selection of the ranges for the CPPS (factors) (e.g. amount of excipients and plasticizer type) was based on preliminary tests and theoretical intervals for each excipient-function described in literature (Dixit and Puthli, 2009; Hoffmann et al., 2011). The continuous factors were introduced as mixture factors in order to identify the proportions within the different

components that maximize the defined responses (CQAs). The factors are constituent proportions of a mixture which sums to 1 (100%) and the last component percentage is determined by the sum of all the others. Therefore, factors are not independent, but the software methodology for this type of designs is the same as for classical designs. The Plasticizer type is a categorical factor and was introduced as a nominal variable.

The screening platform used to evaluate the results basically uses the n values in the response vector and rotates them into n new values. The rotated values are then mapped by the space of the factors and their interactions. The screening report generated shows a list of coefficients with their contrasts and p-values. Mathematically, the contracts are: Contrasts = T' × Responses. T is an orthonormalised set of values which starting with the intercept and goes in descendent order through the main effects, two-way, three-way interactions, and so on, until n values have been obtained. T is orthogonal, the contrasts are the parameters estimated in a linear model. The significant terms are usually associated with low *p*-values, which are generated based on Lenth *t*-ratios that are created through a Monte Carlo simulation of 10,000 runs of $n - 1$ purely random value. The t-ratios are obtained from the *Lenth Pseudo Standard Error* (*PSE*) by the Lenth's method that identifies inactive effects and constructs an estimate of the residual standard error. The most significant terms that may lead to the best Model to explain the variable in study are selected.

The best fit Model was selected based on the higher and proximal RSquare and RSquare Adjusted, the overall *F*-value and the associated *p*-value of the Analysis of Variance for the entire model (Goupy and Creighton, 2007; SAS Institute, 2013).

2.2.2. Design Selection and experimental layout

The QTPP was constructed with previous knowledge of the dosage form, acquired from previous laboratorial work on marketed oral films; but also based on literature support (Hoffmann et al., 2011; Preis et al., 2014; Visser et al., 2015) (Figure 31). The QTPP includes the outline of the CQA that should be carefully selected and evaluated to establish limits that allow obtaining suitable oral films without compromising its performance. In turn, the CPPs are subsequently chosen according to its influence and effect on the CQAs. Figure 31 summarizes the CQAs and CPPs selected in the present work. The aim of the work, screening and develop innovative oral film platforms, lead to a careful and limited selection of the quality parameters and attributes. Therefore, the CQAs were restricted to features that are characteristic and essential of this dosage form: mechanical properties, due to the handling

and manufacturing process; disintegration time, the slow or fast disintegration of the dosage form determines its performance; residual water content, may determine the stability of the product.

Subsequently, the most critical process parameters (CPPs) that may influence the attributes described were chosen: film forming polymer amount, %weight /weight (%w/w) per film (PVAc, methacrylate copolymer or shellac); stabilizer amount, %w/w per film (PVA, HPMC and / or tween 80); disintegrant amount, %w/w per film (NaCMC); plasticizer amount, %w/w per film (triethyl citrate, 1,2 -propanediol, glycerol, polyethylene glycol 400, polyethylene glycol 1000 and / or polyethylene glycol 6000); plasticizer type.

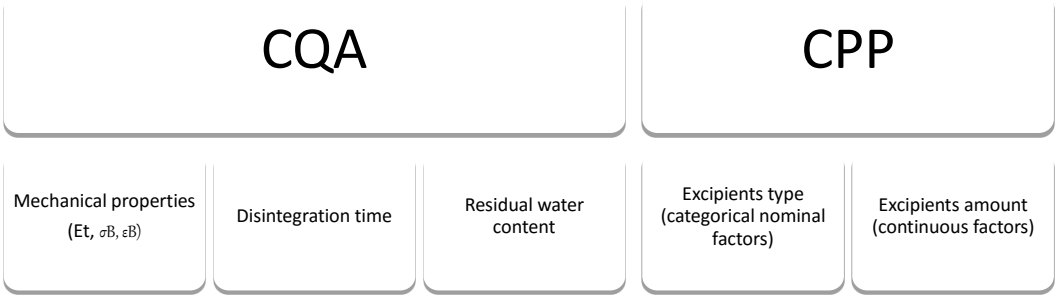


Figure 31 - Control Quality Attributes (CQA) and Control Process Parameter (CPP) selected. QTPP - Quality Target Product Profile; Et – Young's modulus; εB –Elongation at break; σB – tensile strength.

2.2.3. Selection of excipients

The selection of other excipients, in particular the plasticizers and stabilizers (PVA and HPMC), was mainly based on manufactures indication and some literature available (BASF, 2010; Evonik, 2011; Freed et al., 2007; Kolter et al., 2013). Based on this information some preliminary tests were performed, in which the main concern was to confirm the ability of these systems to form suitable films (PVAc – system A; Ammonium Methacrylate – system B; Shellac – system C). In these screening tests the selection was based on a qualitative analysis according to their ability to form films. In summary, within the 6 disintegrant tested (sodium carboxymethyl starch, croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium alginate, NaCMC), NaCMC revealed to be compatible with all systems and is the only common excipient in the 3 different types of polymeric matrixes. PVA and HPMC were tested as stabilizer in the three systems. Although, it was possible to obtain ODF with HPMC and PVA in the three systems, PVA was selected as stabilizer for methacrylate and

PVAc formulations and HPMC as stabilizer for Shellac ODF because they contributed to formulations with a better visual appearance than the other alternatives.

2.2.4. ODF Appearance characterization

ODFs were evaluated by a test panel based on their appearance and handling properties. The appearance parameters evaluated were the existence of lumps, phase segregation and the visual homogeneity of the oral films. The handling properties considered were the detachment ability from the release liner, the touch sensitivity, and the mechanical integrity to allow further characterization. It was used a 1 to 5 scale, where the global evaluation value corresponds to the average of the referred parameters, all with equivalent degree of importance (14% of importance) except for the detachment from the release liner (30% of importance).

2.2.5. Preparation of the ODFs

The liquid mixtures were prepared in two-neck round bottom-flasks (50mL). The system was kept overnight at room temperature under slow agitation to obtain free-bubble-liquid. Each excipient was added after ensuring that a homogeneous liquid mixture was formed. The liquid mixtures were cast in PVC release liners (substrate) with an Erichsen film applicator (Coatmaster 510, Erichsen, Hemer, Germany). To adjust different heights a vertically adjustable doctor knife was used and the film mixtures are cast with speeds of 6 mm/s. The casted films were dried on the heated table of the Erichsen film applicator at 40 °C or at room temperature until dryness. The drying time depended on the composition of each formulation evaluated.

To further characterize the films, individual samples were prepared by cutting strips of regular and equal dimension with a bench manual press (Tinius Olsen, Horsham, USA).

2.2.6. Storage

The individual films were stored under controlled conditions (43 % RH, room temperature), by means of a saturated solution of potassium carbonate for at least 5 days before testing.

2.2.7. Film mass

The films were weighed using an analytical balance (Mettler Toledo AGXS, Mettler-Toledo Inc., Columbus, US) and the average weight was calculated (n=3).

2.2.8. Film thickness

The thickness of the films was measured with a micrometer screw (Mitutoyo Digimatic Capiler, Mitutoyo Corporation, Japan) (n=5).

2.2.9. Tensile Strength

The mechanical properties of the films were determined using a tensile testing universal apparatus (Zwick, Germany) with a load cell of 10 N. The measurements were performed similarly as described elsewhere (11, 12). Briefly, ODFs with the dimensions of 60x20 mm and free of air bubbles or physical imperfections, were held between two clamps positioned at a distance of 40 or 50 mm. Firstly, a preload was applied in each assay, and then the strips were pulled by the top clamp at a rate of 10.0 mm/min. The load automatically applied to the film was gradually increased and the corresponding magnitude of elongation was recorded until the break point of the film was finally reached corresponding magnitude of elongation was recorded until the break point of the film was finally reached. The parameters were directly retrieved from the software TestXpert (TestXpert, Zwick, Germany), namely Young's modulus (Et, MPa), tensile strength (σB, MPa) and elongation at Break (εB, %). Measurements were run at least in three samples for each film.

2.2.10. Disintegration time

Approximately 4 mL of a phosphate buffer pH=6.8 (artificial saliva) was added on a Petri dish and the ODFs were laid on. The time at which the film samples disintegrate was recorded.

2.2.11. Karl-Fisher

The Karl Fischer Method was used to determine the residual water content in the ODFs. This technique basically consists in the quantitative reaction of iodine and sulfur dioxide by the addition of water, in the presence of methanol:

$$SO_2 + I_2 + 2H_2O \xrightarrow{CH_3OH} 2HI + H_2SO_4$$

A sample was added to the titration flask filled with methanol previously dehydrated with a Karl Fischer reagent (Hydranal Composite 5, Sigma-Aldrich Co. LLC). Titration was then carried out using the Karl Fischer reagent with a known determined titer (mgH_2O/ml). Water content was determined based on the titration volume (ml). The polarization-current potential-difference method was employed as an end-point detection method.

These tests were performed in a Karl Fisher 787 KF Titrino (*Metrohm AG*, Herisau, Schweiz).

2.2.12. Contact angle

Drop shape analysis was used to determine contact angles. Time-dependent contact angles were measured by an optical contact angle meter (OCA20 Dataphysics equipment, Filderstadt, Germany) at room temperature. An approximate volume of 10 µL of distilled water was dropped onto the film surface, initially fixed in a slide on a planar position. The contact angle was determined right after the drop addition (t=0s) and after 20 or 30 seconds (t=20s or t=30s, depending of the film characteristics) by using the supplied software (SCA20 Dataphysics software, Filderstadt, Germany).

3. Results

The information regarding the different components of each systems were introduced in the DoE software and a custom design was generated. In total, 58 oral films were prepared with different percentages of main film-forming polymer (PVAc, system A; methacrylate Copolymer, system B; and shellac, system C), stabilizer (PVA or HPMC), disintegrant (NaCMC) and plasticizer (triethyl citrate, propanediol, glycerol, polyethylene glycol 400, polyethylene glycol 1000, and polyethylene glycol 6000). The different runs are presented on the CPPs columns of Tables 15, 16 and 17, whereas the results of their evaluation are on the CQAs columns on the same tables. Even though the excipients were previously selected in the screening tests described previously, 9 of the films prepared exhibited very poor characteristics that hampered the characterization of these samples (samples marked with an * on Tables 15, 16 and 17).

Table 15 - Disintegration time, % of H2O, qualitative evaluation, Et, εB and σB. Ranges of CPPs (amount of PVAc, PVA, NaCMC, tween 80, plasticizer and plasticizer type) for formulations based on PVAc. . The amount of each excipient is presented as rational values where the sum of the components is 1. The missing values are identified (*) and are related with the poor films characteristics t hat prevented the execution of valid characterization tests. The median values of the CQAs were introduced in the software to perform the analysis. TEC - Triethyl citrate; PG - Propylene glycol; H_2O - Residual water content; Et – Young's modulus; εB –Elongation at break; σB – tensile strength.

Run	CPPs						CQA					
	PVAc	PVA	NaCMC	Tween 80	Plasticizer	Plasticizer Type	Disintegration time (s)	H_2O (%)	Et (MPa)	εB (MPa)	σB (%)	Global evaluation (1-5)
Range tested	0,5-0,75	0,1-0,40	0,05-0,2	0,001-0,05	0,05-0,2							
A1	0,469	0,248	0,053	0,05	0,18	TEC	25 (24 - 26)	4,6 (4,5 - 4,8)	81,4 (53,7 - 83,1)	113,2 (101,8 - 129,5)	1,9 (1,7 - 2,8)	3
A2	0,726	0,093	0,134	9,00E-04	0,046	TEC	49,5 (47,3 - 51,8)		220,8 (208,3 - 233,3)	46,0 (38,3 - 53,8)	6,3 (5,2 - 7,3)	3,8
A3	0,224	0,374	0,139	0,06	0,201	PG	14,5 (14,3 - 14,8)	7,8 (7,6 - 8,0)	171,2 (158,1 - 184,2)	19,1 (18,3 - 19,9)	7,0 (7,0 - 7,0)	3,5
A4	0,443	0,405	0,051	0,05	0,051	TEC	10 (9,5 - 10,5)	6,4 (6,2 - 6,6)	41,5 (33,4 - 49,6)	80,7 (76,6 - 84,7)	3,2 (2,7 - 3,6)	3,5
A5	0,464	0,103	0,184	0,05	0,199	PG	60 (60 - 60)	8,0 (7,9 - 8,1)	328,6 (315,3 - 341,9)	1,3 (1,3 - 1,4)	8,1 (7,9 - 8,4)	2,5
A6	0,34	0,406	0,203	1,00E-03	0,051	TEC	9 (8,5 - 9,5)	7,3 (7,1 - 7,4)	433,7 (381,6 - 485,8)	27,8 (26,4 - 29,3)	19,1 (19,1 - 19,2)	3,5
A7	0,512	0,282	0,05	1,00E-03	0,154	PG	60 (60 - 60)	5,3 (5,1 - 5,4)	99,2 (85,3 - 105,0)	85,5 (80,6 - 99,9)	4,8 (3,3 - 5,7)	3
A8	0,752	0,099	0,05	0,05	0,049	PG	60 (60 - 60)	4,1 (4,0 - 4,2)	71,1 (69,4 - 72,8)	5,6 (5,4 - 5,8)	7,1 (6,9 - 7,3)	2,5
A9	0,367	0,253	0,17	0,04	0,167	TEC	7,5 (7,25 - 7,75)	7,3 (7,3 - 7,3)	325,8 (316,7 - 337,5)	11,4 (11,0 - 12,5)	11,2 (10,1 - 11,3)	4
A10	0,636	0,146	0,073	0,07	0,072	TEC	60 (60 - 60)	4,1 (4,1 - 4,1)	34,2 (33,8 - 34,6)	55,2 (41,6 - 68,8)	1,8 (1,3 - 2,3)	3
A11	0,395	0,23	0,164	0,05	0,165	PG	34 (33,5 - 34,5)	6,8 (6,3 - 7,3)	38,6 (38,3 - 42,0)	28,0 (26,9 - 30,5)	5,8 (5,5 - 6,0)	2
A12	0,255	0,426	0,053	0,05	0,213	PG	16,5 (16,3 - 16,8)	6,5 (6,4 - 6,6)	47,2 (42,6 - 51,9)	170,9 (168,4 - 173,3)	9,1 (8,7 - 9,5)	1,5
A13	0,494	0,102	0,202	1,00E-03	0,201	TEC	17 (17 - 17)	5,4 (5,4 - 5,5)	238,3 (231,5 - 245,1)	20,8 (20,2 - 21,3)	3,7 (3,1 - 4,3)	3
A14	0,3	0,4	0,051	0,05	0,2	TEC	29 (28 - 30)	5,1 (5,0 - 5,2)	50,9 (47,9 - 55,8)	141,9 (139,9 - 145,5)	5,7 (5,2 - 5,7)	3,5
A15	0,304	0,398	0,199	0,05	0,05	PG	9 (9 - 9)	7,3 (7,2 - 7,5)	269,1 (237,1 - 291,5)	13,0 (12,5 - 13,0)	12,1 (10,9 - 12,9)	2
A16	0,49	0,407	0,051	1,00E-03	0,051	PG	21 (20,5 - 21,5)	5,3 (5,2 - 5,4)	78,8 (76,6 - 80,9)	178,0 (177,6 - 178,5)	10,5 (10,4 - 10,6)	4
A17	0,239	0,355	0,202	1,00E-03	0,203	TEC	10 (9 - 11)	7,5 (7,5 - 7,6)	326,3 (323,3 - 333,1)	20,2 (18,5 - 20,8)	14,0 (13,3 - 14,0)	3,8
Selected range	0,50-0,57	0,07-0,17	0,07-0,17	0-0,01	0,06-0,10	TEC						

Table 16 - Disintegration time, % of H2O, qualitative evaluation, Et, εB and σB. Ranges of CPPs (amount of PVAc, PVA, NaCMC, tween 80, plasticizer and plasticizer type) for formulations based on Methacrylate Copolymer. The amount of each component is presented as rational values where the sum of the components is 1. The range used to delineate the design is present on the excipients row. The missing values are identified (*) and are related with the poor films characteristics that does not allowed to perform some valid tests. The value in the CQAs column corresponds to the median value introduced in the software to perform the analysis. H_2O - Residual water content; Et – Young's modulus; εB –Elongation at break; σB – tensile strength.

Run	CPPs				CQA										
	Ammonio Methacrylate Copolymer	Glycerol	NaCMC	PVA	Disintegration time (s)		H_2O (%)		Et (MPa)		εB (MPa)		σB (%)		Global evaluation (1-5)
Range tested	0,5-0,65	0,1-0,2	0,07-0,2	0,1-0,2											
B1	0,559	0,14	0,1	0,201	>60	(60,0 - 70,0)	6,48	(6,3 - 6,7)	115,2	(90,6 - 139,9)	3,9	(3,3 - 4,5)	3,6	(3,1 - 4,0)	4,28
B2	0,55	0,152	0,149	0,148	51	(48,0 - 54,0)	7,27	(7,1 - 7,4)	227,5	(227,5 - 227,5)	8,1	(8,1 - 8,1)	12,4	(12,4 - 12,4)	3,38
B3	0,597	0,205	0,099	0,099	*		*		*		*		*		2,66
B4	0,498	0,205	0,099	0,198	35	(30,0 - 40,0)	7,355	(7,1 - 7,6)	85,6	(82,0 - 92,0)	3,7	(3,6 - 3,9)	12,1	(11,1 - 13,1)	4,56
B5	0,545	0,204	0,101	0,149	46	(44,0 - 48,0)	8,34	(8 - 8,7)	107,7	(101,1 - 114,2)	4,7	(4,7 - 4,7)	13,0	(12,0 - 14,0)	3,66
B6	0,497	0,101	0,201	0,201	43	(38,0 - 48,0)	7,815	(7,8 - 7,8)	251,9	(245,6 - 458,4)	14,4	(8,3 - 14,8)	6,5	(5,4 - 8,2)	4,28
B7	0,606	0,152	0,142	0,1	51	(49,0 - 53,0)	6,62	(6,6 - 6,7)	226,8	(226,8 - 226,8)	8,4	(8,4 - 8,4)	7,7	(7,7 - 7,7)	3,38
B8	0,51	0,196	0,197	0,098	25	(10,0 - 36,0)	6,74	(6,5 - 7,4)	*		*		*		2,54
B9	0,547	0,153	0,15	0,15	>60		7,07	(6 - 7,8)	236,3	(220,5 - 252,1)	7,0	(6,1 - 7,9)	3,8	(2,6 - 5,1)	3,38
B10	0,598	0,105	0,198	0,098	33	(32,0 - 70,0)	6,45	(6,1 - 6,8)	488,2	(488,2 - 488,2)	4,0	(4,0 - 4,0)	0,6	(0,6 - 0,6)	4,28
B11	0,6	0,1	0,12	0,179	25	(21,0 - 29,0)	6,44	(6,3 - 6,6)	239,5	(228,2 - 270,9)	6,5	(6,4 - 6,8)	2,5	(2,5 - 3,6)	3,66
B12	0,499	0,152	0,198	0,151	26	(24,0 - 28,0)	6,68	(6,7 - 6,7)	151,3	(123,7 - 178,8)	7,1	(6,7 - 7,5)	8,6	(8,0 - 9,3)	3,38
B13	0,5857	0,1136	0,143	0,1578	35	(30,0 - 40,0)	7,045	(6,9 - 7,2)	407,3	(407,3 - 407,3)	11,8	(11,8 - 11,8)	2,8	(2,8 - 2,8)	4,28
B14	0,6299	0,1019	0,0679	0,2002	23,5	(17,0 - 30,0)	6,455	(6,3 - 6,6)	423,1	(379,5 - 466,8)	6,0	(4,9 - 7,0)	1,1	(0,8 - 1,3)	3,66
B15	0,6206	0,2083	0,0688	0,1023	*		*		*		*		*		2,66
B16	0,5404	0,2144	0,1417	0,1035	7,5	(5,0 - 10,0)	8,25	(8,2 - 8,4)	78,6	(78,6 - 78,6)	6,8	(6,8 - 6,8)	14,4	(14,4 - 14,4)	2,96
B17	0,6285	0,1526	0,0682	0,1507	23,5	(23,0 - 24,0)	*		*		*		*		3,1
B18	0,5812	0,1053	0,1032	0,2103	19	(16,0 - 22,0)	5,975	(6,0 - 6,0)	450,7	(445,5 - 455,8)	11,7	(11,2 - 12,2)	3,0	(2,5 - 3,5)	4,56
B19	0,5309	0,1133	0,142	0,2139	>60		6,17	(5,9 - 6,8)	473,1	(458,1 - 488,1)	14,7	(14,1 - 15,2)	6,9	(5,9 - 7,9)	4,56
B20	0,6487	0,1074	0,1402	0,1037	>60		6,00	(5,6 - 6,4)	*		*		*		3,12
B21	0,5163	0,2057	0,0674	0,2106	19	(6,0 - 21,0)	5,95	(5,9 - 6)	161,2	(147,3 - 175,1)	7,0	(6,5 - 7,5)	31,6	(28,1 - 35,1)	4,56
B22	0,5235	0,2173	0,1087	0,1505	51	(42,0 - 60,0)	7,13	(6,9 - 7,4)	*		*		*		3,4
B23	0,526	0,1549	0,1064	0,2128	44,5	(37,0 - 52,0)	5,285	(5,2 - 5,4)	219,5	(188,4 - 220,1)	7,5	(6,3 - 8,0)	7,3	(6,0 - 7,8)	4,42
B24	0,5896	0,1638	0,1434	0,1031	>60		5,825	(5,8 - 5,9)	*		*		*		4
Selected range	0,52-0,58	0,10-0,15	0,15-0,17	0,15-0,20											

Table 17 - Disintegration time, % of H2O, qualitative evaluation, Et, εB and σB. . Ranges of CPPs (amount of Shellac, HPMC, NaCMC, plasticizer and plasticizer type) for formulations based on Shellac. The amount of each component is presented as rational values where the sum of the components is 1. The range used to delineate the design is present on the excipients row. The missing values are identified (*) and are related with the poor films characteristics that does not allowed to perform some valid tests. The value in the CQAs column corresponds to the median value introduced in the software to perform the analysis. H2O - Residual water content; Et – Young's modulus; εB –Elongation at break; σB – tensile strength; PG - Propylene glycol.

Run	CPPs					CQA					
	Shellac	HPMC	NaCMC	Plasticizer Amount	Plasticizer Type	Disintegration time (s)	H_2O (%)	Et (MPa)	εB (MPa)	σB (%)	Global evaluation (1-5)
Range tested	0,4-0,8	0,2-0,5	0,01-0,2	0,01-02							
C1	0,4	0,389	0,011	0,2	PEG 1000	>60	3,51 (3,3 - 11)	315 (309 - 321)	13,7 (14 - 14)	10,5 (10 - 11)	4,14
C2	0,585	0,202	0,011	0,202	Glycerol	>60	5,46 (5 - 5,9)	56,9 (55,8 - 58,1)	24,6 (25 - 25)	5,04 (4,8 - 5,3)	3,44
C3	0,575	0,196	0,218	0,011	PG	7 (4 - 10)	4,64 (3 - 5,6)	997 (946 - 1048)	0,48 (0,3 - 0,6)	5,39 (3,6 - 7,2)	2,84
C4	0,393	0,498	0,098	0,011	PEG 6000	18,5 (17 - 20)	4,7 (4,2 - 5,2)	1181 (1142 - 1220)	0,57 (0,5 - 0,6)	7,29 (6,9 - 7,7)	3,54
C5	0,778	0,2	0,011	0,011	PEG 6000	>60	2,98 (2,7 - 3,2)	*	*	*	2,26
C6	0,462	0,244	0,077	0,217	PEG 400	>60	4,24 (4,2 - 4,3)	541 (496 - 556)	1,22 (1 - 1,3)	7,12 (6 - 8,6)	2,84
C7	0,398	0,197	0,209	0,195	PEG 6000	>60	4,69 (3,6 - 5,5)	875 (776 - 912)	1,04 (1 - 1,2)	11,3 (8,9 - 12)	3,72
C8	0,516	0,303	0,095	0,087	Glycerol	>60	5,01 (4,6 - 5,4)	570 (563 - 577)	0,96 (1 - 1)	6,39 (6,3 - 6,5)	3,72
C9	0,398	0,488	0,096	0,018	Glycerol	50,5 (47 - 54)	3,94 (3,8 - 4,1)	1254 (1221 - 1287)	0,85 (0,8 - 0,9)	12,3 (11 - 14)	3,26
C10	0,398	0,389	0,011	0,202	PG	>60	4,58 (4,4 - 4,7)	125 (121 - 130)	27 (23 - 31)	5,98 (5,6 - 6,3)	4,28
C11	0,598	0,189	0,205	0,008	PEG 1000	6,5 (5 - 8)	5,26 (3,5 - 5,6)	774 (683 - 930)	0,48 (0,5 - 0,6)	3,81 (3,5 - 5,7)	3,26
C12	0,783	0,197	0,011	0,009	PEG 400	>60	3,3 (3,2 - 3,4)	*	*	*	2,28
C13	0,639	0,198	0	0,163	PEG 400	>60	3,16 (3,1 - 3,2)	139 (124 - 155)	12,6 (11 - 14)	6,59 (6,2 - 7)	3,72
C14	0,641	0,199	0	0,16	PEG 1000	>60	3,61 (3,5 - 3,8)	324 (324 - 324)	1,55 (1,6 - 1,6)	7,05 (7,1 - 7,1)	3,44
C15	0,646	0,199	0	0,155	PEG 6000	>60	3,41 (3,2 - 3,7)	391 (386 - 396)	1,22 (1,2 - 1,3)	7,29 (7 - 7,5)	4,56
C16	0,646	0,199	0	0,156	Glycerol	>60	5,38 (5,1 - 5,6)	87,1 (81,4 - 88,7)	19,9 (20 - 22)	6,92 (6,2 - 7)	3,58
C17	0,657	0,196	0	0,148	PG	>60	4,32 (3,9 - 4,6)	30,7 (29,5 - 33,1)	37,7 (32 - 42)	1,65 (1,6 - 2,6)	3,3
Selected range	0,50-0,57	0,16-0,20	0,10-0,20	0,01-0,15	PG or glycerol						

The obtained results were examined via DoE study according to the CQAs acceptance criteria defined by the analysis and evaluation of several marketed products in a previous study (see Table 18).

Table 18 - Critical Quality attributes acceptance criteria.

Desirability	
σB (MPa)	15-35
εB (%)	5-40
Et (MPa)	100-1500
Residual H_2O content (%)	[3-6%]
Disintegration time (s)	<30
Global evaluation (1-5)	>3,5

3.1. Screening results: model selection and profiler creation

The JMP screening platform was used to analyse the data of the set of experiments designed before. The best Fit models were selected and generated based on their statistical significance. This information was based on the analysis of variance (ANOVA) F-test. The results are depicted on Figures 32, 34 and 35.

The prediction profiler is a simplified way of representing the response surface and gives the settings that according with the software origin the best formulation composition based on the target response (see Figures 32, 33 and 34). The main advantage of the prediction profiler concerns the ability of the user to predict the values which were not actually examined as long as they are within the experimental space. The individual plots in each row of plots show the prediction traces for each CPP. This prediction trace shows the expected variance of the response according to the change in each variable while the others are constant (SAS Institute, 2013). Therefore, parallel lines to the x-axis represent the absence of parameter's influence in the correspondent y-variable (response). On the other hand, nonlinear traces indicate the influence of the x-variable in the response that may be more or less complex depending on the shape of the line. The profile visualization presented in Figures 32, 33 and 34 is related with the defined acceptance criteria for CQAs referred before and with the range that allows a better visualization of the curves.

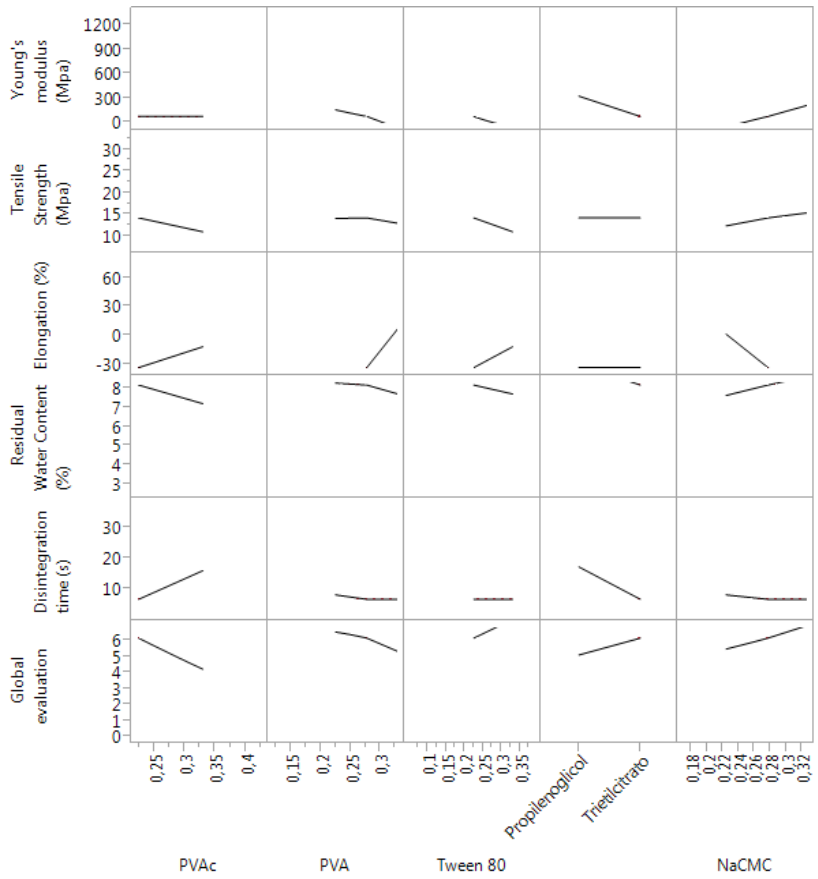
Next to each prediction profiler a summary of the model significance is presented for each CQA. The ANOVA through the p-value allowed to evaluate the whole model, and a significance probabilities of 0.05 or less are often considered evidence that there is at least one significant regression factor in the model (SAS Institute, 2012). The RSquare (R^2) that estimates the proportion of the variation in the response around the mean and the Rsquare Adj which adjusts R^2 (to make it more comparable over models with different numbers of parameters) are also presented (SAS Institute, 2012). The RSquare also represents the square of the correlation between the actual and predicted response, meaning that if equal to 1, a perfect fit (errors are all zero) is observed, whereas 0 means that the fit predicts the response no better than the overall response mean. In this way, an ideal model should present a p value lower than 0.05 (for 95% of confidence), the RSquare closer to 1 and an RSquare Adj value similar to the RSquare (SAS Institute, 2012).

Therefore, the analysis of the models should be done carefully (Tables 15, 16 and 17, first row). In theory, models with very low p-value and high and similar Rsquare are very robust

(Figures 32, 33 and 34 with green boarder evaluation). On the contrary, more caution should be take when analysing models with high p-values and low Rsquare (Figures 32, 33 and 34 with yellow and red boarder evaluation).

3.2. PVAc based films

PVAc formulation models seem to be less complex than the other tested systems (B and C). The plasticizer amount seems to have very little influence in the parameters tested since it was not included in any model and consequently does not appear in the profiler (Figure 32).



Model	ANOVA	RSquare	RSquare Adj
Et	p=0.0058	0.790	0.664
σB	p=0.0029	0.648	0.566
εB	p=0.0009	0.894	0.812
% H_2O	p=0.0079	0.854	0.725
Disintegration time	p=0.0041	0.544	0.479
Global evaluation	p=0.0178	0.785	0.617

Figure 32 - Prediction profiler of PVAc screened formulations. It is represented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green solid border means very good fit models p value <0.01) and high (>0.6) and proximal Rsquare; Yellow dashed border means good fit models (p value <0.05) and Rsquare values between 0.4-0.6; Red square dotted border means poor fit models, (p-value >0.05) and very low Rsquare values.

The majorities of the models present a more linear profile and are generally very good models (Figure 32), with very small p-values, $p \leq 0.01$. Only, disintegration time has a less robust model, but even though, the p-value is very low, and the RSquare indicates that there is more than 55% of possibilities that the response effect observed is correct (Figure 32). In addition, the models for the other CQAs are more robust, with very low p-values and higher Rsquare values.

General views of the models are presented in Table 5.

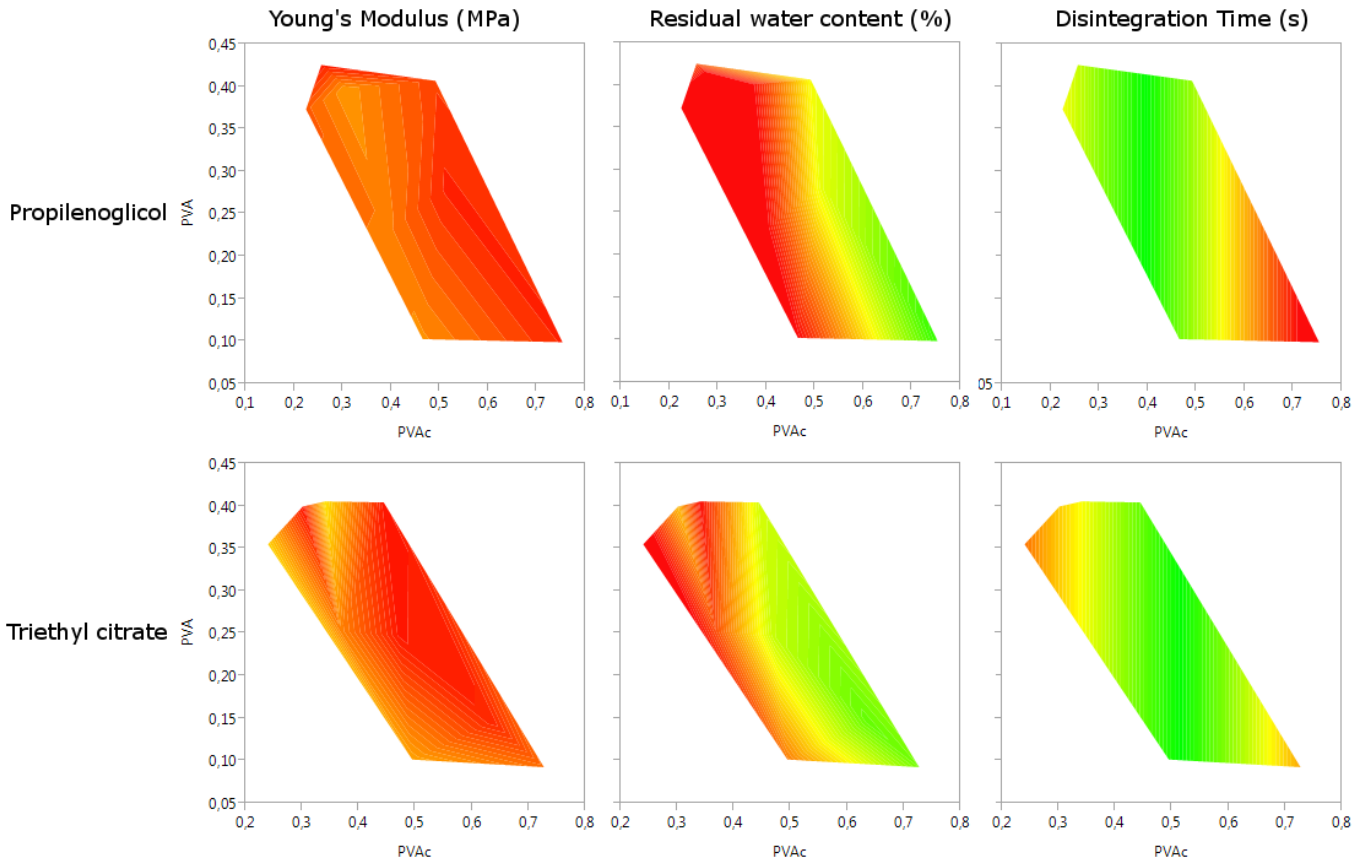


Figure 33 - Plasticizer type influence in the Young's modulus, Residual water content and disintegration time on the PVAc polymeric matrices. The influence of the plasticizer may be visualized based on the two main components of the formulation, PVA and PVAc. The grade of colours range from the desirable (green) to the unsuitable (red) effect in each CQA evaluated.

The plasticizing effect on the Young's modulus, residual water content and disintegration time of the PVAc formulation was also evaluated according with the type of plasticizer evaluated. The two main components of the formulation were selected, and the effect of each plasticizer was analysed (Figure 33).

As previously described the grade of colours is related with the CQA limits defined in Table 18. Briefly, green is the desirable zone, yellow-orange correspond to values close to the limits and the red zone out of the CQAs acceptance criteria (out of limit data).

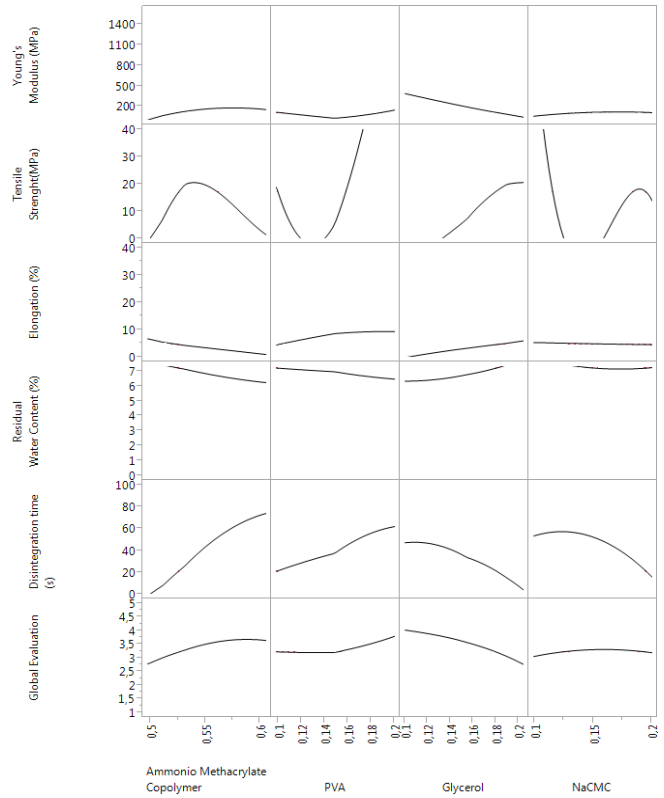
Young's modulus varies in a similar way with both plasticizers (Figure 33, column 1). Independently, of the PVAc-PVA ratio a yellow-orange is obtained. However, there is also a trend to be out of the limits with the increase of PVAc, above 55% (% w/w), with medium values of PVA, between 20 to 30%. Regarding the other properties, it is verified that TEC origins larger green areas, but the trend of the effect is similar with both plasticizers. The use of TEC demonstrates that there is a higher probability of having films within the CQAs limits. However, for both, higher PVAc contents in all the range of PVA amount contribute to desirable values of residual water content, whereas lower amount of PVAc within almost all PVA ranges used contributed to lower disintegration times.

The plasticizer effect that allows obtaining green areas based on PVA-PVAc proportion within the limits studied (coloured area) is summarized in table 20.

According to the obtained results, PVAc based films should be preferentially composed by: PVAc (50-57%), PVA (7-17%), NaCMC (7-17%) and Tween 80 (0-1%) (Table 15). Unfortunately, it was not possible to define a definite range for the triethyl citrate with this model, but from the literature is possible to retrieve a probable range of concentration for triethyl citrate (6-10%) (Kolter et al., 2013)).

3.3. Methacrylate Copolymer based films

The different CPPs evaluated using methacrylate copolymer based films influence all CQAs under analysis (Figure 34).



Model	ANOVA	RSquare	RSquare Adj
Et	p=0.0012	0.731	0.614
σB	p=0.0254	0.483	0.340
εB	p=0.0013	0.728	0.609
% H_2O	p=0.0420	0.617	0.411
Disintegration time	p=0.1969	0.507	0.204
Global evaluation	p=0.0011	0.934	0.832

Figure 34 - Prediction profiler of methacrylate screened formulations. It is represented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green solid border means very good fit models p value <0.01) and high (>0.6) and proximal Rsquare; Yellow dashed border means good fit models (p value <0.05) and Rsquare values between 0.4-0.6; Red square dotted border means poor fit models, (p-value >0.05) and very low Rsquare values.

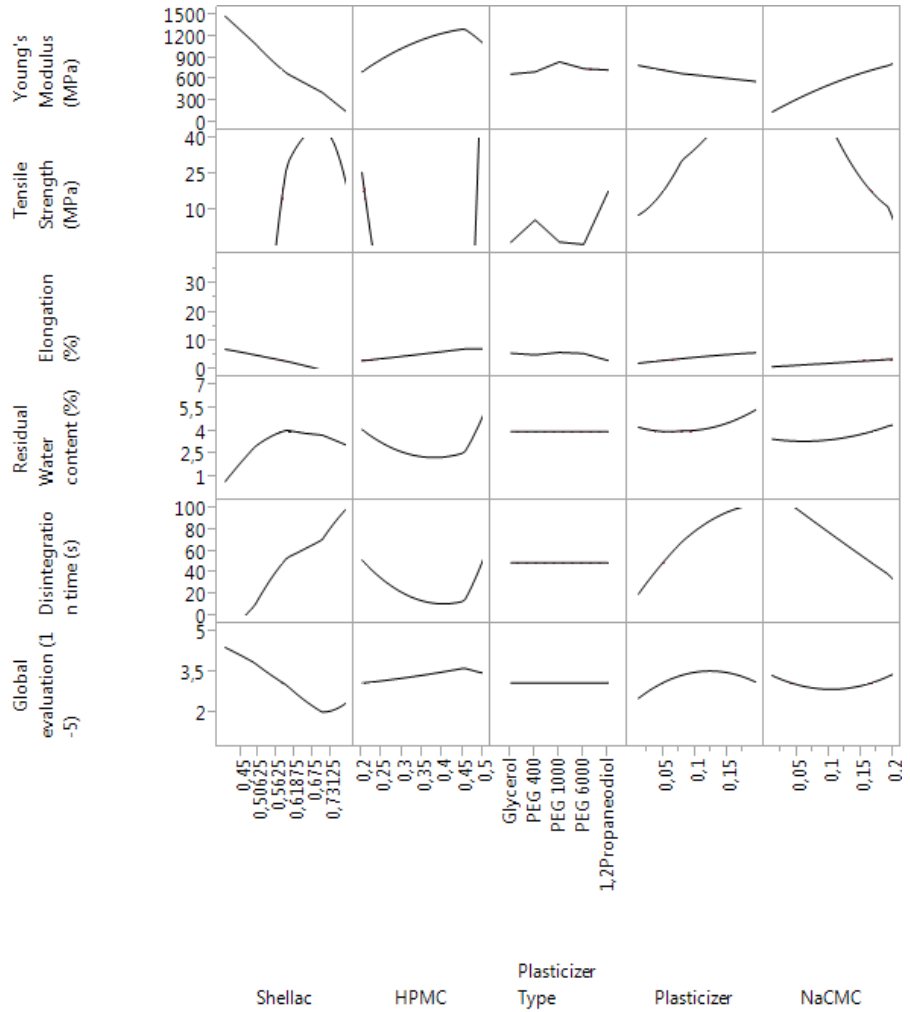
For the methacrylate copolymer model the majority of the variations are nonlinear, although according with the shape of the prediction profiler fit models, the effect seems to be less complex when compared to shellac fit models (Figure 34). However, 3 excellent models were obtained (Et, εB and global evaluation) with very low p-values, 2 models with reasonable characteristics (p-values closer to 0.05) and a non-significant statistical model (disintegration time) (Figure 34). Regarding the elongation, despite the significant p-value ($p<0.05$) the RSquares are very low and different (Figure 34). Therefore, there are less than 50% of chance of having a reliable model (RSquare<0.5) where the response (CQA) is attributed to the factors (CPPs) included in the model rather than to random error.

A general view of the models obtained can be visualized in Table 19.

Finally, based on the results obtained a methacrylate based films should be preferentially composed by: methacrylate copolymer (52-58%), PVA (15-20%), NaCMC (7-17%) and glycerol (10-15%) (Table 16).

3.4. Shellac based films

In the Shellac formulation the CQAs (y-variables) are influenced by the majority of all the CPPs tested except by the plasticizer type that seems to influence only the mechanical properties in the range of concentration used (Figure 35).



Model	ANOVA	RSquare	RSquare Adj
Et	p=0.0002	0.929	0.875
σB	p=0.0567	0.992	0.933
εB	p=0.0387	0.791	0.582
% H_2O	p=0.0469	0.724	0.509
Disintegration time	p<0.0001	0.974	0.948
Global evaluation	p=0.0031	0.767	0.661

Figure 35 - Prediction profiler of Shellac based formulations. It is represented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter are on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green solid border means very good fit models p value <0.01) and high (>0.6) and proximal Rsquare; Yellow dashed border means good fit models (p value <0.05) and Rsquare values between 0.4-0.6; Red square dotted border means poor fit models, (p-value >0.05) and very low Rsquare values.

It is easily seen by the curves of the prediction profile that the fit models are complex and non-linear. Nevertheless, some very good prediction models were obtained (Figure 35, green border). Some of the values predicted by the model should be analysed with more caution (Figure 35, yellow and red border), e.g.the ones related with tensile strength, elongation at break and residual water content.

An overall summary of the model is presented in Table 19.

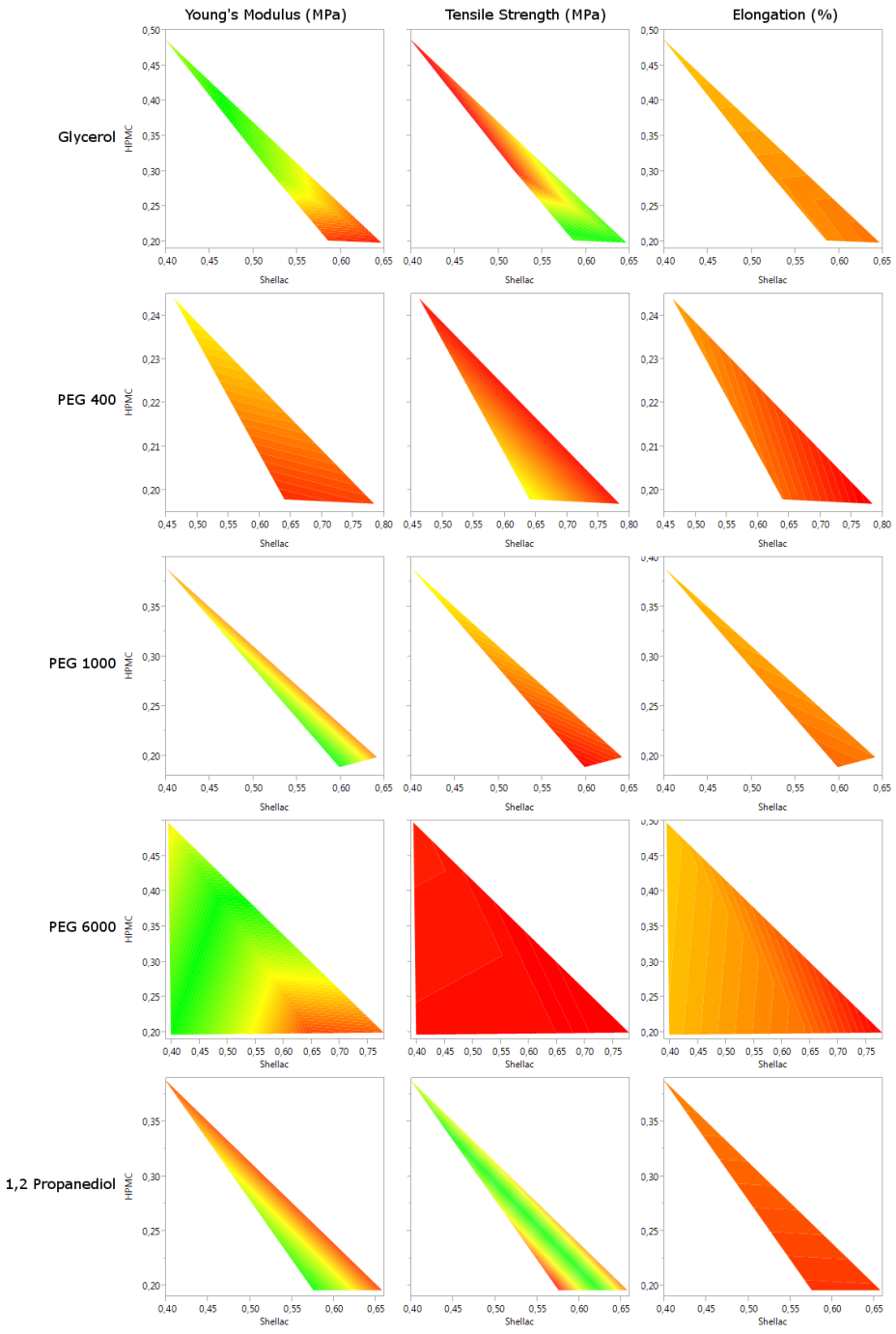


Figure 36 - Plasticizer type influence in the mechanical properties of the Shellac polymeric matrices. The influence of the plasticizer may be visualized based on the two main components of the formulation, HPMC and Shellac. The grade of colours range from the desirable (green) to the unsuitable (red) effect in each CQA evaluated. Only the coloured area represents the range of the CPPs studied. The white zone is out of range values that were not studied.

The effect of the different plasticizers on the mechanical properties of the Shellac based formulations was also evaluated. However, to facilitate the analyses, only the two main components of the formulation were considered (Figure 33).

The grade of colours is related with the CQA limits defined previously, and used in the screening evaluation of the formulations (Table 18). The green area corresponds to the desirable zone that allows obtaining suitable response effect for the correspondent CQA: Young's modulus, tensile strength or elongation (Figure 36). In turn, the yellow-orange area is related with values close to the limits and the red zone out of limit data.

Acceptable Young's modulus values are possible to obtain with the majority of the plasticizers, except with PEG 400. The values obtained for Young Modulus with PEG 400 for any HPMC-Shellac combination are always on the boarder limits of the acceptance criteria (100-1500MPa, Table 18). By the contrary with PEG 6000 a large green area is obtained and only with high shellac concentration (above 55%) a smaller yellow-orange zone is verified. Regarding the tensile strength effect this plasticizer is associated with poor characteristics (big red zone, Figure 36). For this property, glycerol and 1,2 propanediol are the only plasticizers that allow obtaining green areas. In turn, any plasticizer allowed obtaining a green area for the elongation, but mainly orange zones.

The percentage of each plasticizer that allows obtaining green areas based on HPMC-Shellac proportion within the limits studied (coloured area) are in Table 20.

Therefore based on the obtained results a proper selection to obtain suitable shellac films seems to be: Shellac (50-57%), HPMC (16-20%), NaCMC (10-20%), PG or glycerol (1-15%) (Table 17).

Table 19 - Summary of the influence of the tested components on the different system evaluated. Only the major effects are presented.

CQA	PVAc formulations	Methacrylate Copolymer formulations	Shellac formulations
Stiffer films (higher Et)	↑ PVAc	↑ Methacrylate Copolymer	↓ Shellac
	↑ NaCMC	↑ NaCMC	↑celluloses (NaCMC and HPMC)
	↓ PVA	↑ PVA from 16% (%w/w per film)	Choose PG or PEG 400
	PG	↓ Glycerol	
Resilient films (higher σB)	↑NaCMC	↑ Methacrylate Copolymer	↑ Shellac up to 60% (%w/w per film)
		↑ PVA	↑ celluloses (NaCMC and HPMC) from 30% (%w/w per film)
			Choose PG or PEG 400
Deformable films (higher εB)	↓ NaCMC	↓ Methacrylate Copolymer	↑ celluloses (NaCMC and HPMC)
	↑ PVA	↑ PVA	
	↑ tween 80	↑ Glycerol	
Higher residual water content	↓ PVAc	↓ Methacrylate Copolymer	↑ Shellac up to 60% (%w/w per film)
	↑ NaCMC	↑ NaCMC from 15% (%w/w per film)	↑ celluloses (NaCMC and HPMC) from 30% (%w/w per film)
	↓ tween 80	↓ PVA	Choose PG or PEG 400
	PG	↑ Glycerol	
Fast disintegration	↓ PVAc	↓ Methacrylate Copolymer	↓ Shellac
	TEC	↑ NaCMC	↑celluloses (NaCMC and HPMC)
		↓ PVA ↓ Shellac ↑celluloses (NaCMC and HPMC)	
		↑ Glycerol	
Better appearance	↓ PVAc	↑ Methacrylate Copolymer	↓ Shellac
	↑ NaCMC	↓ NaCMC from 15% (%w/w per film)	↑celluloses (NaCMC and HPMC)
	↓ PVA	↑ PVA	↓ plasticizer amount
	TEC	↓ Glycerol	

Table 20 - Desirable zones (green areas) obtained from the plasticization effect on PVAc and Shellac based films. The clear cells indicate that there are no green zones for the referred properties.

	Green areas	
	PVAc based films	**Shellac based films**
Young's modulus		Glycerol: Shellac < 50% and HPMC >30% PEG 1000: Shellac < 60% and HPMC <30% PEG 6000: Shellac < 55% and HPMC <45% 1,2 – Propanediol (Propilenoglicol): Shellac < 60% and HPMC <25%
Tensile Strength		Glycerol: Shellac < 65% and HPMC <25% 1,2 – Propanediol (Propilenoglicol):: 60% <Shellac < 65% and HPMC <30%
Residual water content	1,2 – Propanediol (Propilenoglicol): PVAc > 65% Triethyl citrate: PVAc > 55%	
Disintegration time	1,2 – Propanediol (Propilenoglicol): 30% < PVAc < 50% Triethyl citrate: 35% < PVAc < 65%	

3.5. Contact angle evaluation in the best screened formulations

Based on the screening results, 3 additional formulations of each hydrophobic polymer with a composition within the ranges determined to be appropriate for ensuring ODFs with good properties, to test and evaluate the contact angle (Table 21). The contact angle assay was used to determine the hydrophobicity of the systems when compared with a well-known commercial hydrophilic polymeric matrix oral film (Listerine Pocket Packs).

Based on the previous results, the PVAc system was apparently the most promising. Therefore, this polymer was used to prepare more complex formulation (additives addition) to test the film-forming ability of this system with complex composition (Table 21). Additionally, optimized formulations of system B and C were also prepared and characterized.

Table 21 - Optimized ODF formulations with hydrophobic behavior.

	PVAc formulations			Methacrylate formulations			Shellac formulations			
	A18	**A19**	**A20**	**B25**	**B26**	**B27**	**C18**	**C19**	**C20**	
PVAc	52,80%	58,90%	59,90%							
Methacrylate Copolymer				58,10%	51,60%	52,60%				
Shellac							51,40%	57,40%	57,50%	
PVA	16,80%	7,00%	15,20%	21,00%	21,10%	21,30%				
HPMC							19,60%	17,00%	19,60%	
NaCMC	17,40%	14,50%	6,90%	10,30%	6,70%	10,60%	17,60%	10,10%	21,80%	
Triethylcitrate	6,90%	10,60%	10,00%							
Glycerol				10,50%	20,60%	15,50%				
1,2 - Propanediol							11,40%	15,50%	1,10%	
Citric acid	6,00%	5,00%	5,00%							Listerine Pocket Packs ®
Mono-ammonium glycyrrhizinate		0,50%								
Maltodextrins		3,00%	3,00%							
Red Iron Oxide		0,40%								
Young's Modulus (Mpa)	457,4	330,2	901,4	450,7	161,2	219,5	306,46	106,75	997,1	
Elongation (%)	25,68	38,65	6,795	11,67	6,98	7,49	1,01	2,69	0,475	
Tensile Strength (Mpa)	10,07	2,44	23,39	2,99	31,58	7,25	4,31	4	5,39	
Water Content (%)	4,66	3,73	4,255	5,98	5,95	5,29	5,15	4,69	4,64	
Disintegration time (s)	13,5	17,06	46,22	19	19	44,5	4	18	7	
Contact Angle (°)	58,8	64,2	74,4	61,12	61,24	63,54	66,28	41,48	50,31	38,34

Contact angles higher than 65^{o} are characteristic of hydrophobic surfaces (Vogler, 1998). All the prepared formulations had revealed contact angles significantly superior to the ones of the pullulan hydrophilic films (Listerine® marketed films). The PVAc based films (Table 20, A18-A20) exhibited values between 58.8 - 74.4^{o}, the methacrylate copolymer based films (Table 20, B25-B27) presented angles between 61.12 - 63.54^{o} and shellac based films within 41.48 – 66.28^{o}.

4. Discussion

Each polymeric matrix has its own inherent properties that affect greatly the CQAs of the final product. Each system depending on its composition exhibits different behaviour. Nevertheless, these Designs with smaller number of experiments are useful to screen a high number of process parameters in order to find which ones have a significant effect on the responses evaluated (in this case CQAs) such the one used in this study (fractional factorial design). These designs are commonly designated by screening designs. Three independent screening designs, one for each system, were performed in attempt to have an overall view of the influence of each process component in the CQAs of the 3 systems (Goupy and Creighton, 2007).

The number of experiments depended on the number of CPP (x-variables) being evaluated.

4.1. Critical Quality Attributes

The CQAs of the oral films have been already described by others (Preis et al., 2014; Visser et al., 2015). The most studied characteristics are the mechanical properties and the disintegration time. Since the free water molecules in the polymeric matrix are known to have a plasticizing effect, the percentage of the residual water content was also evaluated in this work. In solvent casting method the remaining percentage of water is dependent on the formulation composition, the drying temperature and drying time during films' preparation, but may also change depending on the storage environment and primary packaging material. For that reason, these parameters were controlled.

In previous works, it was demonstrated the difficulty to define with precision the ideal mechanical properties for ODF (Preis et al., 2014). Even so, considering ODFs usage and purpose, the polymeric matrix should be soft (moderate Young's modulus) to avoid becoming uncomfortable and difficult to handle. On the other hand, it should be though enough to resist during the entire manufacturing process and also handling at the moment of administration (moderate to high tensile strength and elongation).

4.2. PVAc based films

The PVAc based films present a peculiar pattern concerning the influence of each excipient in the CQAs studied (Figures 32 and 33). Interesting to notice is the small influence of the amount of plasticizer in these films in the range of concentration evaluated. The plasticizer amount is not included in any model justifying its absence on the profiler (Figure 32). Theoretically, this situation occurs when the factor being studied does not have any significant effect in the responses evaluated. Even so, it is well known that plasticizer amount influences greatly the films properties. This result is contrary to the results of other authors that described a significant influence of the plasticizer nature and amount in PVAc matrices (Kolter et al., 2013).

The PVAc aqueous suspension used (Kollicoat® SR 30 D) is known by its low film forming temperature (MFT), that allows the formation of film matrices without plasticizers (Kolter et al., 2013). Most probably due to the presence of the disintegrant in the formulation it was impossible to obtain a suitable film without a plasticizer and a stabilizer (PVA). Two different plasticizers were tested, triethyl citrate (TEC) and 1,2 – propanediol (propilenoglicol). As already described by others, more lipophilic plasticizers, such as TEC, contributed to obtain PVAc films with better characteristics (Kolter et al., 2013). Although, the plasticizer amount was not included in the profiler, it is described that the plasticization of PVAc films contributes to the decrease of MFT (especially for medium lipophilic plasticizers) and to increase sharply the flexibility (εB) even in small amounts (Kolter et al., 2013). Nevertheless, the recommended amount of plasticizer for PVAc based films is 5–10% w/w based on polymer mass (Kolter et al., 2013).

NaCMC demonstrated a strong and positive influence in the Young's modulus (Figure 32, 1st row). Hence, also in the PVAc based films the increase of the percentage of charged polymer chains in the matrix contributes to increase the rigidity of the films. Similarly, NaCMC-PVA films are already described as being stiffer with the NaCMC increase (Knyazeva et al., 2006). The COO^- groups and non-substituted OH groups of NaCMC promote the chemical interaction with other chemical groups, especially OH and $COCH_3$ groups through hydrogen bonding (Xiao et al., 2001). Therefore, the increase of NaCMC in this system leads to the formation of stronger linkages that are associated with more resilient (higher tensile strength) and non-deformable films (lower elongation at break) (Figure 32, 1st row). Apparently, these results seem to contradict some literature references describing that NaCMC may increase elongation and flexibility and decrease the tensile strength when

blended with polymers more brittle than NaCMC (Kundu et al., 2011). However, this effects were more prominent and significant for NaCMC concentrations on the films above 30% (%w/w per film) (Kundu et al., 2011). Nevertheless, it is also referred by others that the mechanical properties effect of NaCMC on polymeric binary systems is nonlinear (Xiao et al., 2001). Therefore, NaCMC addition effectively changes the mechanical properties of the matrices, creating new materials with different behaviour. Both stabilizers, tween 80 and PVA, contribute to increase the elongation and decrease the tensile strength and rigidity (Figure 32, 2nd and 3rd rows). In literature, it is found that tween 80 in starch based films at 2% (%w/w per film) may behave as a plasticizer (Brandelero et al., 2010), which is in accordance with the obtained results (Figure 32, 3rd column). PVA has a different behaviour in this system compared to the methacrylate based films (Figure 32, 2nd column). Although the elongation increases, the elasticity and toughness of the polymeric matrix decreases with PVA augmentation (Figure 32, 2nd column). This profile corresponds to a plasticizing effect, which may be possible considering the low molecular weight of the PVA used (approximately 31 kDa (Clariant, 1999)) and the optimal miscibility between PVA-PVAc chains (Jelinska et al., 2010).

Regarding the plasticizer nature, in accordance to the results described above, the higher lipophilicity of the plasticizer, such as triethyl citrate compared to propylene glycol, lead to the formation of more elastic films (Figure 32, 4th column, 1st row). The other mechanical properties did not changed significantly with the nature of the plasticizer (Figure 32, 4th column, 2nd and 3rd row). However, the predominant red zone in Figure 33 for Young's Modulus, crossed with the profiler trace (Figure 32, 1st row), indicates that both plasticizers contribute to low Et values, close to the CQAs limits defined.

The residual water content is affected in a similar manner in the other polymeric systems. The hydrophobic polymer (PVAc) diminishes significantly the free water molecules in the polymer matrix, and the disintegrant increases it sharply (Figure 32, 4th row). Triethyl citrate, probably due to its lipophilicity and the absence of polar groups available for water retention (Rowe et al., 2009), contributes to lower the residual water content when compared to propylene glycol (Figure 32, 4th row). In addition, the residual water content (Figure 33) column presents a higher green zone when TEC is used, meaning that a larger operational space for these attribute may be obtained using TEC as plasticizer.

The interposition of tween 80 amphiphilic molecule between the polymer chains contribute to increase the free volume between the polymer chains, which besides the plasticizing effect, could also increase the water sorption capacity due do tween 80 polar region

(Brandelero et al., 2010). However, this effect was not observed in this system, where the increase of tween 80 decreases the residual water content (Figure 32, 4th row). This result is probably due to the hydrogen bond interactions between the surfactant polar groups and the hydrophilic groups of the matrix, reducing the number of polar groups available to retain water molecules (Villalobos et al., 2006).

Curiously, the disintegration time was only significantly affected by the main polymer and the nature of the plasticizer used (plasticizer type) (Figure 32, 5th row, Figure 33 column 3). The increase of PVAc contributes to delay the disintegration time and triethyl citrate origins fast disintegrating films when compared to propylene glycol. The slower disintegration behaviour with the increase of the % PVAc may be easily explained by its hydrophobic nature, which difficult the water permeation to the polymeric matrix breaks. Considering the triethyl citrate, although it is more lipophilic than propilenoglycol, the faster disintegration may be explained by the higher efficiency of triethyl citrate to interpose between the PVAc chains. This effect may lead to higher free volume that may function as channels allowing a more efficient water penetration and faster matrix disintegration. In Figure 36, it is also shown that using TEC as plasticizer allows to have a larger operational range for these attribute, demonstrated by the larger green area.

In this system, the films with better appearance have triethyl citrate, higher amount of disintegrant and lower concentration of PVA and PVAc (Figure 32, 6th row).

4.3. Methacrylate based films

In the Methacrylate based films there is an evident influence of the excipients (CPPs) in all the studied CQAs (Figure 34). Young's modulus is affected in a nonlinear way by the main polymer, the disintegrant (NaCMC) and the stabilizer (PVA) (Figure 34, 1st row). The higher concentration of charged polymers such as NaCMC and the ammonium methacrylate copolymer, could be associated with the higher rigidity and stiffness of the material. On the other hand, a tensile strength decrease is observed with an increase of Methacrylate %, which may be related with the concomitant PVA proportion decrease in the polymeric matrix (Figure 34, 2nd row). In fact, the results show that PVA increase contributes to higher tensile strength and elongation (Figure 34, 3rd row). This behaviour is commonly verified in other PVA based films reported (Clariant, 1999).

The glycerol increase origins polymeric matrices with a peculiar behaviour (Figure 34, 3rd column). As described above, the plasticizers would contribute to more deformable films, with higher elongation and lower tensile strength. The opposite profile was observed in this work within the range of concentration tested (Figure 34, 3rd column). Glycerol is a small molecule with three hydroxyl groups, which may facilitate the interposition between the polymeric chains. It should be mention that higher concentration of hydroxyl groups may also promote hydrogen bonding. In fact, the behaviour observed indicates a probable strong interaction between the chemical groups, which may explain the tougher and less deformable films. However, the free space available between the polymer chains by the glycerol interposition also originated less rigid films, lower Et (Figure 34, 3rd column, 1st row).

Regarding the residual water content variation, more hydrophilic substances (glycerol and NaCMC) tend to increase this parameter, although in a nonlinear way (Figure 34, 4th row). Glycerol is a very hygroscopic substance (Rowe et al., 2009), and its increase in the matrix increases significantly the retention of water, as already described by others (Baldwin et al., 2011). The matrix moisture increase is not so evident with the NaCMC variation and surprisingly, below 15% of NaCMC there is also a decrease on the residual water content (Figure 34, 4th column, 4th row). This result may be justified by the diffusion or dilution of this polymer in a more concentrated methacrylate/PVA matrix, wrapping NaCMC chemical hygroscopic groups responsible for water molecules retention. In turn, NaCMC increase may lead to a higher accessibility of these groups and more residual water content is present in the films (Figure 34, 4th column, 4th row). Contrarily, methacrylate copolymers and PVA contribute to diminish the water retention in the polymeric matrix (Figure 34, 4th row).

Methacrylate copolymers are considered hydrophobic, which by definition do not tend to absorb water (Derakhshandeh and Soleymani, 2010; Qiu et al., 2009), and PVA based films are also described as non-hygroscopic (Clariant, 1999). Hence, the same components have opposite effects in the disintegration time: PVA and methacrylate copolymers increase sharply the time to disintegrate the films whereas glycerol and NaCMC contribute to a faster disintegration of the films (Figure 34, 5th row). Curiously, a similar pattern is verified in the qualitative evaluation of the appearance (Figure 34, 6th row). The appearance of the film tends to ameliorate significantly with methacrylate and PVA increase but diminish with the augmentation of the plasticizer and NaCMC (Figure 34, 6th row).

4.4. Shellac based films

Although other works related with shellac based films are scarce, it was possible to find some information regarding their properties and behaviour. Increasing amounts of shellac, particularly above 45%, contributes to a sharp decrease of the young's modulus (Figure 35, 1st row) whereas the addition of celluloses, NaCMC and HPMC, as well as their interaction, significantly contributes to its increase (Figure 35, 1st row). The Young's modulus translates the elasticity of the polymeric matrix that also depends on the polymeric chain orientation and interactions. Therefore, considering the usage of shellac ammonium salts, it would be expectable that some ionic interactions may occur contributing to the stiffness of the films (higher Et). The opposite effect was verified in the present study, probably due to the formation of less ionized shellac films during the process. Ammonium ion is a weak acid, therefore a possible explanation for this result, is that during the drying time the ammonium ions protonate the carboxylate anion of the shellac (Al-Gousous et al., 2015). Consequently, more protonated shellac films are formed and the resulting ammonia evaporates, during the process (Al-Gousous et al., 2015). A possible evidence of the carboxylate protonation is the lightly yellow films obtained, similar to the shellac free acid films (Al-Gousous et al., 2015). Nevertheless, the increase of shellac is associated with the reduction on the proportion of HPMC (Table 17) and consequently more elastic films were obtained. In fact, it is already described that the addition of HPMC may contribute to stiffer films (Borges et al., 2015). Additionally, the increase of the films rigidity with the NaCMC increase may also be related with its ionic nature and possible interactions with other polymer matrix components leading to a higher stiffness of the matrix (Figure 35, 1st row).

The tensile strength is strongly affected by all the CPP tested, and the majority exhibits a nonlinear influence. The Shellac effect on the tensile strength (Figure 35, 2nd row, sharp increase up to 60% Shellac followed by an accentuated decrease) may be related with the Shellac / HPMC ratio in the matrix composition, since HPMC concentration has the opposite effect on the films. Cellulose values up to 30% contribute to brittle films (Figure 35, 2nd row) although for higher amounts of stiffer films are obtained probably due to the augment of chemical interactions that turn the polymeric matrix less deformable and stiffer (Figure 35, 2nd row).

The elongation is also negatively influenced by the main polymer but tends to increase slightly with the increase of celluloses concentration (Figure 35, 3rd row). The addition of the celluloses, which also implies the decrease of shellac in the matrix (Table 17) may increase

the free volume between shellac chains contributing to higher mobility and higher elongation. On the other hand the increase of hydrophilic polymers, particularly NaCMC, in the polymeric matrix may promote the increase of the moisture content. The water molecules are known to act as external plasticizers, promoting an elongation rise and a decrease in the tear strength (Figure 35, 3rd row) (Clariant, 1999).

Among the plasticizers tested (Glycerol, PEG 400, PEG 1000, PEG 600, 1,2 Propanediol) (Figure 35, 3rd column), PG and PEG 400 contribute to higher tensile strength values (Figure 35, 2nd row), but low and unsuitable elongation values (Figure 35, 3rd row). A deeper analysis of the plasticizing effect is presented in Figure 36. It is easily seen by the orange and red zones, that suitable elongation values are hard to obtain with any of the plasticizers tested (Figure 36, column 3) and ODF with PG or PEG 400 have predominant red zones compared to the other plasticizers for this attribute.

Amongst the plasticizers tested, glycerol and PG are probable the most alike (chemically and in structure), and it is notorious their different effects (Figure 35, column 3 and Figure 36, 1st and 5th rows). The additional hydroxyl group of the glycerol is probably enough to interpose more efficiently between the polymeric matrix chains. In fact, the good miscibility of glycerol with shellac was already described due to the thermal and mechanical properties modifications with glycerol increase (e.g. reduction of melting temperature, elasticity improvement) (Stummer et al., 2010). It is also described that glycerol plasticizing effect on shellac films is due to its diffusion within the polymer chains and hydrogen bonds formation (Stummer et al., 2010).

Regarding the PEGs, the differences found are probably related with their different molecular weight (Figure 35, column 3 and Figure 36, 2nd, 3rd and 4th rows). Higher Mw PEGs present long carbonated chains (Al-Nasassrah et al., 1998; Rowe et al., 2009) that may be more prone to entangle within the polymer matrix chains, increasing the free volume between them and consequently diminish the tensile strength and increase the elongation.

Nevertheless, considering the overall results of the plasticizer type analysis (Figure 35, column 3 and Figure 36), it is possible to select Glycerol and PG as the most appropriate plasticizers for the shellac based films within the group studied. This conclusion is mainly retrieved from the major green areas presented in Figure 33 for this two plasticizers compared with the others. However, Figure 36 should be analysed with caution since it is not presented the whole system, but only the plasticizing effects considering only the two main components (Shellac and HPMC). On the other hand, the results obtained are in

accordance with the literature, which describes that plasticizers with lower Mw and more hydrophilic functional groups have better plasticizing effect on shellac films (Stummer et al., 2010). Glycerol and 1, 2 - propanediol have lower Mw (Glycerol Mw is 92.09 g/mol and 1,2 Propanediol 76.09 g/mol (Rowe et al., 2009)) compared to the lowest Mw PEG (PEG 400 Mw 380-420 g/mol (Rowe et al., 2009)).

Surprisingly, in this system the type of plasticizer appears to have no significant impact on the residual water content and disintegration time, in the range of concentrations tested (Figure 35, 4th and 5th rows). However, Shellac and HPMC have a nonlinear and predictable influence in these properties, considering their chemical nature (Figure 35, 4th and 5th rows). Higher shellac concentration is associated with smaller residual water content and a sharp increase of the disintegration time, whereas the modified celluloses have the opposite effect (Figure 35, 4th and 5th rows).

The overall appearance of the film seems to be related with every component tested except with the plasticizer type (Figure 35, 6th row). The amount of polymers affects greatly the film appearance (Figure 35, 6th row). High amount of shellac has a deleterious effect on the oral films appearance, whereas high cellulose amount origin films with better appearance (Figure 32, 6th row).

4.5. Hydrophobicity of maximized desirability formulations

The contact angle (CA) is a parameter that may be used to measure the hydrophobicity of a surface (Oun and Rhim, 2015). A marketed oral film with a hydrophilic polymer was used as reference.

It is described that the addition of hydrophilic polymers to the matrix usually contributes to lower the CA due to the increase of the hydrophilicity of the film surface. This may be chemically explained by the exclusion of non-polar components of the hydrophobic polymers and the exposure of hydroxyl groups from the hydrophilic structures (Oun and Rhim, 2015). Therefore, the polar groups are more prone to absorb and retain water that may favour the polymeric matrix disintegration.

The PVAc based films had higher contact angles with the PVAc increase, as expected. The major proportion of non-polar groups of PVAc tend to repel the water contributing to the higher contact angles verified. However, at the same time the disintegration time increases.

The contact angles obtained for the methacrylate polymer films were very consistent, and had very slightly variations with the increase of glycerol. This is probably due to the compensation with NaCMC decrease, also known by being hygroscopic when dried (Rowe et al., 2009).

The shellac based films presented the lower contact angles. This result is probably due to the usage of the shellac as an ammonium salt. Although during the drying the majority of these ammonium salts may be converted in shellac non-ionic form, some of the ionic forms may still remain and contribute to increase the water affinity of the films. Additionally, these films are prepared with HPMC as stabilizer of the main polymer instead of PVA, which is known to have better moisture protection (Edsall et al.).

The contact angle of the marketed pullulan film (Listerine® pocket packs) is in accordance to values available in literature, lower than 35^{o} (Farris et al., 2011; Garsuch and Breitkreutz, 2009). Therefore, the majority of the tested formulations present a contact angle significantly higher, representative of a more hydrophobic nature of the polymeric matrix that was one of the aims of the present work.

4.6. Systems overall comparison

It is not clear if the different hydrophobic behaviour of each system was due to the specific hydrophobic polymer used or mainly due to the overall system composition. However, it was possible to verify that the same component may have a different influence on the ODF properties depending on the overall system composition (Table 22).

As a general evaluation, considering the previous discussion and the compositions studied, it was possible to observe that PG is probably a more efficient plasticizer for PVAc based films than for shellac (medium-low Et and medium σB), whereas glycerol is better for shellac than methacrylate copolymer formulations (medium Et, low σB and higher εB) (Table 22, columns propylene glycol and glycerol). Theoretically, the plasticizers interpose between the polymer chains increasing their free volume, which contributes to a more freely motion and rotation of the chains. This phenomenon would be associated to a higher flexibility and more prone to deformation ODF. Therefore, lower tensile strength, lower Young's modulus and higher elongation are expected (Lim and Hoag, 2013). However, these effects are completely dependent on the plasticizer nature and its miscibility with the main polymer (Boateng et al., 2009). It is likely that the effects described above, occur mainly if the plasticizer is fully miscible or compatible with the polymeric matrix. Ideally, the plasticizers should be compatible with the polymer to plasticize, hydrophilic polymers usually are well plasticized by hydroxyl-containing compounds, which may not be valid for hydrophobic polymers. Therefore, the distinct effects of the plasticizers on the polymeric matrix reflect the different interactions that each have with the polymeric matrix.

Additionally, the influence of NaCMC and PVA on PVAc and methacrylate copolymer formulations was also evaluated and summarized in Table 22. The most evident influences are on Et, σB and disintegration time. NaCMC contributes to stiffer, resilient and fast disintegration films in PVAc systems. These observations are probably related with chemical interactions between the polymer chains. NaCMC and Methacrylate are charged polymers, and chemical bounds between them may be related with the different results obtained when compared to the neutral PVAc.

PVA allows obtaining more elastic and deformable films using methacrylate copolymers based formulations. This effect may not be strictly related with the PVA addition but also with the film-forming polymer characteristics. PVAc is known to form high flexible films (Kolter et al., 2013) whereas methacrylate copolymers are described to origin brittle films in the dry state (Bodmeier and Paeratakul, 1994). Therefore, these significant differences may

be also related with the PVAc and methacrylate copolymers inherent film-forming properties.

Table 22 - Summary of the influence of common excipients used in the different systems. This information is retrieved form the profilers, considering the excipients increase (a right to left reading of each square of the profilers).

	Propilenoglycol		Glycerol		NaCMC			PVA	
	Shellac	**PVAc**	**Shellac**	**Methacrylate**	**Shellac**	**Methacrylate**	**PVAc**	**Methacrylate**	**PVAc**
Et	Medium-high ~900MPa	Medium-low ~450MPa	Medium ~600MPa	Medium-low <500MPa	↑↑ 10-400MPa	↑ 40-100MPa	↑↑ 0-300MPa	↓ 200-40 MPa (up to 16 % PVA) ↑ 40-200MPa (from 16% PVA)	↓↓ <300MPa
σB	Medium ~25MPa	Medium <20MPa	Low <5MPa	Medium <20MPa	↑↑ 10-40MPa	↓↓ 40-0 MPa (up to 12 % NaCMC) and <20MPa (from 18 % NaCMC) ↑↑ 0-20MPa (12-18% NaCMC)	↑ 12-18MPa	↓↓ 20-0 MPa (up to 12 % PVA) ↑↑ 0-30MPa (from 12% PVA)	↓ <15MPa
εB	Low <10%	Low <10%	Low <10%	Low <5%	↑ 0-5%	- ~5%	↓↓ <5%	↑↑ 5-10%	↑↑ > 0%
%H_2O	-	High > 6 %	-	High > 6 %	↑ 3-4%	↑ >7%	↑ >7%	↓ 7 - 6 %	↓ 8 - 7 %
Disintegration	-	Low ~20s	-	Medium <40s	↓↓ 100-40s	↓↓ 60-20s	↓ <10s	↑↑ 20-60s	↓ 20-60s

5. Conclusions

This work demonstrates that orodispersible films can also be prepared based on hydrophobic polymers, and not only hydrophilic polymers, breaking a paradigm of the research of this novel dosage form. Three different formulations were developed, which may be optimized and used to embed drug substances for oral delivery. Additionally, there is a similar pattern in the three formulations: a hydrophobic polymer, a stabilizer, a disintegrant and a plasticizer. Despite the need of a disintegrant, for the fast disintegration, it was also shown that other components may also contribute to this property. In fact, the DoE approach for initial screening was very useful to determine the influence that each excipient could have in the overall system. The generation of the profilers and counter graphs is helpful for the graphic visualization of these influences.

In general, it was not possible to clearly define if the differences in the hydrophobic nature of the 3 systems was due to the specific hydrophobic polymer used alone or due to the overall system composition. However, it was possible to determine the effect of each component in the different polymeric matrices CQAs and to detect some common trends.

In the future, the incorporation of drug substances in this type of ODFs (more hydrophobic in nature) should be performed as well as stability studies as the final proof of concept.

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Chapter III.2

Polyvinyl acetate oral films mixture design: screening, optimization and robustness

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Abstract

Orodispersible films (ODFs) emerged as an effective alternative for conventional oral dosage forms. ODFs, based on a hydrophobic polymer were developed and optimized. The quality by design approach was applied to a pre-defined polyvinyl acetate (PVAc) formulation to perform three different studies: evaluation of the influence of the plasticizer type, determination of the maximum drug loading capacity (Pramipexole) and optimization design to obtain an ODF with the target product profile. The formulations were characterized regarding their mechanical properties, residual water content, disintegration time, contact angle, organoleptic and appearance characteristics in attempt to find out a suitable ODF that could meet the critical quality attributes (CQAs) defined. The selected critical process parameters (CPP) for the formulation screening were the percentage of the different excipients and the plasticizer type. It was found that the plasticizing effect is critical for the overall performance and stability of the product. Also, a binary taste-masking system, based on a flavour and a sweetener, to obtain agreeable ODFs was accomplished. Additionally, the drug substance effect may be very significant and greatly dependent on its concentration. Finally, an ODF with suitable characteristics, such as: very fast oral disintegration; easy to handle and manufacture; pleasant taste and appearance; and likely to become appropriate for drug delivery, was developed.

Keywords

Orodispersible Films; Hydrophobic Polymers; Critical Quality Attributes; Critical Process Parameters, Polyvinyl acetate

1. Introduction

Orodispersible films (ODF) have been introduced in the market as a patient centric alternative to conventional oral dosage forms. ODFs are a pharmaceutical dosage form based on a polymeric matrix that may be developed to disintegrate almost immediately in the oral cavity. This dosage may be very helpful for some patients that refuse conventional oral dosage forms due to swallowing disorders (dysphagia) or fear of chocking. Therefore, the development of an ODF orientated for diseases associated with dysphagia, such as Parkinson's disease (PD), will most likely improve patient compliance due to the easier administration. PD is the second most common neurodegenerative disorder and is estimated that may affect 7 to 10 million people worldwide (Ballard et al., 2015; Foundation, 2015; Miller and O'Callaghan, 2015; Olanow et al., 2009; Sapir et al., 2008). PD is progressive and it is characterized by motor disabilities including bradykinesia, hypokinesia, muscle rigidity, resting tremor, speech and swallowing disorders (dysphagia), autonomic dysfunction and, non-motor symptoms such as olfactory disturbances, oral cavity problems, fatigue, pain, sleep fragmentation, depression, and dementia (Sapir et al., 2008; Zlotnik et al., 2015). Nearly 90% of individuals with PD suffer from dysphagia during the course of the disease, which is becoming a major problem in patient compliance to therapy (Sapir et al., 2008; Zlotnik et al., 2015). Therefore, unmet needs in PD therapy include improved efficacy, tolerability and ease of drug use/compliance due to the problems associated to swallowing of drug dosage forms available in the market.

For the development and optimization of every novel dosage form, a deep knowledge of the product and its process parameters should be established very early stage of the development process of the product, essentially to build quality in. This understanding is the base of the Quality by design (QbD) concept, a systematic approach that allows controlling and improving the quality of the product. The most common tool used for pharmaceutical development is the definition of the quality target product profile (QTPP), which is critical to describe the desired product performance, delimit the CQAs and then identify the critical process parameters (CPPs) (Rathore and Winkle, 2009; Visser et al., 2015).

In the case of ODF, the mechanical characteristics, the water molecules retained, the disintegration and dissolution time are all critical quality attributes (CQAs) that may affect the drug release and bioavailability of the drug as well as the stability of the final product. Additionally, the mechanical resistance of the ODF is also associated with its ability to be properly processed and manufactured; and with its handling capacity, that allied to

appropriate organoleptic characteristics, may compromise the patient compliance (Hoffmann et al., 2011; Visser et al., 2015).

The aim of the present work was to use the QbD approach for the optimization of an ODF for the treatment of PD. The CQAs considered to obtain a suitable ODF were the mechanical properties, residual water content and disintegration time. The critical process parameters were outlined based on the variables that may influence the previous parameters, such as the type of plasticizer, the amount of excipients and drug substance. From a pre-defined PVAc formulation (Borges et al., 2015) three independent, but consecutive tests were performed: an initial screening design, a second screening study to evaluate the ability of the matrix to incorporate a PD drug and, finally, an optimization study to obtain a pleasant and moisture resistant polymeric matrix.

2. Material and methods

2.1. Materials

Polyvinyl acetate (PVAc) (Kollicoat® SR 30D) (BTC, Ludwigshafen, Germany), Polyvinyl alcohol 4-88 (PVA) (Merck, Darmstadt, Germany), Sodium Carboxymethylcellulose (NaCMC) (Aqualon France BV, Alizay, France), Maltodextrins (Grain Processing Corporation, Iowa, USA), Glycerol (Merck, Darmstadt, Germany), Triethyl citrate (TEC) (Merck, Darmstadt, Germany), Polyethylene Glycol 400, Lutrol 400 (BTC, Ludwigshafen, Germany), Polyethylene Glycol 6000, Macrogol 6000 (Clariant Burgkirchen, Deutschland GmbH), 1,2-Propanediol (PG) (Merck, Darmstadt, Germany), FD&C Blue #1 (Colorcon, Harleysville, U.S.), Red and Yellow Iron Oxide (Huntsman Pigment S.p.A, Torino, Italy), Indigotine Lake (Colorcon, West Point, US), Menthol (-)-Menthol (Merck, Darmstadt, Germany), Lemon Flavour, Passion Fruit Flavour, Wildberry Flavour (IFF, Haverhill, UK), Mannitol (Merck, Darmstadt, Germany), Sucralose, Splenda (Merck, Darmstadt, Germany), Monoammonium glycyrrhizinate (MAG) (Mafco, NJ, USA), Citric acid (Merck, Darmstadt, Germany), Pramipexole Dihydrochloride (Crystal Pharma S.A.U, Boecillo, Spain).

2.2. Methods

2.2.1. Choice of design and experimental layout

The software JMP 10 (SAS Institute Inc., Cary, NC) was used to construct Custom designs. This platform was used instead of classical designs, since different types of variables were studied including mixture and nominal variables. The defined experiments to run are presented in Table 23. The experiments were carried out following a random order within each formulation type. The analysis was performed using the screening designer platform, meaning that the software adds automatically the interactions and crossed effects.

The selection of the ranges for the CPPs (process variables, the amount of excipients and plasticizer type) was based on preliminary tests and ranges of concentration for each excipient-function described in literature (Dixit and Puthli, 2009; Hoffmann et al., 2011). The continuous variables were introduced as mixture factors in order to identify the proportions

within the different components that maximize the defined responses (CQAs). The factors are constituent proportions of a mixture which sums to 1 (100%) and the last component percent is determined by the sum of the others. Therefore, the factors are not independent, but the software methodology for this type of designs is the same as for classical designs. The nominal factor evaluated was the plasticizer type.

The screening platform used to evaluate the results basically uses n values in the response vector and rotates them into n new values. The rotated values are then mapped by the space of the factors and their interactions. The screening report generated shows a list of coefficients with their contrasts and p-values. Mathematically, the contracts are: Contrasts = T' × Responses. T is an orthonormalized set of values that starts at the intercept and goes in descendent order through the main effects, two-way, three-way interactions, etc., until n values have been obtained. T is orthogonal and the contrasts are the parameters estimated in a linear model. The significant terms are usually associated low *p*-values, which are generated based on Lenth *t*-ratios that are created through a Monte Carlo simulation of 1-runs of $n - 1$ purely random value. The t-ratios are obtained from the *Lenth Pseudo Standard Error* (*PSE*) by the Lenth's method that identifies inactive effects and constructs an estimate of the residual standard error. The most significant terms that may lead to the best fit model to explain the variable in study were manually selected. The best fit model was selected based on the higher and proximal RSquare and RSquare Adjusted, the overall *F*-value and the associated *p*-value of the Analysis of Variance for the entire model (Goupy and Creighton, 2007; SAS Institute, 2013).

2.2.2. Design Selection and experimental layout

The QTPP implies the definition of the CQAs, which stablish the limits to obtain suitable ODFs without compromising product's performance, and the CPPs that should be selected according to the effect that may have on the CQAs. The CQAs and CPPs outlined for this work are summarized in Figure 37.

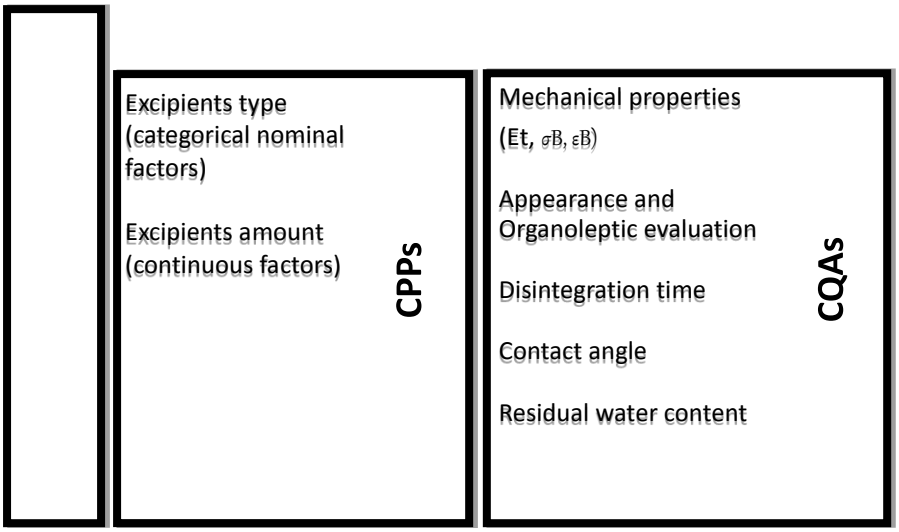


Figure 37 - Control Quality Attributes (CQA) and Control Process Parameter (CPP) selected. QTPP - Quality Target Product Profile; Et – Young's modulus; εB –Elongation at break; σB – tensile strength.

In general, this work consists mainly in the optimization of an ODF platform for the treatment of PD. Therefore CQAs and CPPs were selected based on the main features and characteristics essential for this dosage form, these include: mechanical properties; disintegration time; residual water content; appearance and organoleptic evaluation and contact angle.

Successively, the most critical components and parameters (CPPs) that would influence the CQAs above were selected, such as: the film forming polymer (PVAc) amount, %weight /weight (%w/w) per film; stabilizer amount (PVA), %w/w per film; disintegrant amount (NaCMC), %w/w per film; plasticizer amount, %w/w per film and plasticizer type (triethyl citrate, 1,2 -propanediol, glycerol, polyethylene glycol 400, polyethylene glycol 1000 and / or polyethylene glycol 6000).

2.2.3. Preparation of the oral films

The formulation used as starting point for this work was previously described (Borges et al., 2015). The liquid mixtures were prepared in two-neck round bottom-flasks (50mL). The system was kept overnight at room temperature under agitation to obtain free-bubble-liquid. Each excipient was added only after assuring that a homogeneous liquid mixture had been formed. The PVA and NaCMC were added as pre-prepared solutions of 25% w/w and 7% w/w, respectively. In the more complex mixtures, involving the use of flavours, MAG, colourant and sucralose, these compounds were previously solubilized in the PVA solution before being added to the mixture. The PVAc was always the last compound to be added in the mixture. The liquid mixtures were cast in PVC release liners (substrate) with an Erichsen film applicator (Coatmaster 510, Erichsen, Hemer, Germany). To adjust to different heights a vertically adjustable doctor knife was used and the film mixtures were cast with speed of 6 mm/s. The films were cast with a gap of 300 µm. The process of film formation has been thoroughly described (Alanazi et al., 2007) and it is divided into three stages: (a) evaporation of the solvent and subsequent concentration of polymer particles, (b) deformation and coalescence of polymer particles and (c) further fusion by interdiffusion of polymeric molecules of adjacent polymer particles. The cast films were dried on the heated table of the Erichsen film applicator at 40 °C or at room temperature until dryness. The drying time depended on the properties of each polymer.

To further characterize the films, individual samples were prepared by cutting strips of regular and equal dimension with a bench manual press (Tinius Olsen, Horsham, USA).

2.2.4. Film mass

The films were weighed using an analytical balance (Mettler Toledo AGXS, Mettler-Toledo Inc., Columbus, US) and the average weight was calculated (n=3).

2.2.5. Film thickness

The thickness of the films was measured with a micrometer screw (Mitutoyo Digimatic Capiler, Mitutoyo Corporation, Japan) (n=5)

2.2.6. Tensile Strength

The mechanical properties of the films were determined using a tensile testing universal apparatus (Zwick, Germany) with a load cell of 10 N. The measurements were performed similarly as described elsewhere (11, 12). Briefly, ODFs with the dimensions of 60x20 mm and free from air bubbles or physical imperfections, were held between two clamps positioned at a distance of 40 or 50 mm. Firstly, a preload was applied in each assay and then the strips were pulled by the top clamp at a rate of 10.0 mm/min. The load automatically applied to the film was gradually increased and the corresponding magnitude of elongation was recorded until the break point of the film was finally reached. The parameters were directly retrieved from the software TestXpert (TestXpert, Zwick, Germany), namely Young's modulus (Et, MPa), tensile strength (σB, MPa) and elongation at Break (εB, %). Measurements were run at least in three samples for each film.

2.2.7. Disintegration time

Approximately 4 mL of a phosphate buffer pH=6.8 (artificial saliva) was added on a Petri dish and the ODFs were laid on. The time at which the film samples disintegrate was recorded.

2.2.8. Karl-Fisher

The Karl Fischer Method was used to determine the residual water content in the ODFs. This technique basically consists in the quantitative reaction of iodine and sulfur dioxide by the addition of water, in the presence of a lower alcohol such as methanol.

$$SO_2 + I_2 + 2H_2O \xrightarrow{CH_3OH} 2HI + H_2SO_4$$

A sample was added to the titration flask filled with methanol previously dehydrated with a Karl Fischer reagent (Hydranal Composite 5, Sigma-Aldrich Co. LLC). Titration was then carried out using Karl Fischer reagent with a known determined titer (mgH_2O/ml). The water

content is determined based on the titration volume (ml). The polarization-current potential-difference method is employed as an end-point detection method.

These tests were performed in a Karl Fisher 787 KF Titrino (*Metrohm AG*, Herisau, Schweiz).

2.2.9. Contact angle

Drop shape analysis is used to determine contact angles. Time-dependent contact angles were measured by an optical contact angle meter (OCA20 Dataphysics equipment, Filderstadt, Germany) at room temperature. An approximate volume of 10 µL of distilled water was dropped onto the film surface initially fixed in a slide on a planar position. The contact angle was determined right after the drop addition (t=0s) and after 20 or 30 seconds (t=20s or t=30s, depending of the film characteristics) by using the supplied software (SCA20 Dataphysics software, Filderstadt, Germany).

2.2.10. Storage

The individual films were stored under controlled conditions (43 % RH, room temperature) by means of a saturated solution of potassium carbonate for at least 5 days before testing.

2.2.11. Appearance and handling characterization

The oral films obtained from each run were also evaluated by a test panel based on their appearance and handling properties. The test panel was created to select appearance and handling properties of the films that allow its evaluation and classification. The appearance parameters evaluated were the existence of lumps, phase segregation and the homogeneity of the oral films. The handling properties considered were: the detachment ability from the release liner; the touch sensitivity; and the integrity of the sample to be characterized. It was used a 1 to 5 scale, where the Global Evaluation value corresponds to the average of the referred parameters, all with equivalent degree of importance (14% of importance) except for the detachment from the release liner (30% of importance).

2.2.12. Organoleptic characterization

The placebo ODF obtained from each run were also evaluated by a test panel based on taste and mouthfeel characteristics. The initial taste sensation, aftertaste and mouthfeel were evaluated based on a 0 to 5 scale, 0-bad, 1-unconfortable, 2-indiferent, 3-reasonable, 4-agreeable and 5- very agreeable. It was also evaluated if the triethyl citrate taste was detectable or uncomfortable in the prepared oral films based also in a 0 to 5 scale, where 0 – too uncomfortable, 1- uncomfortable with aftertaste, 2 - uncomfortable without aftertaste, 3- detectable and still a bit uncomfortable, 4- detectable but not uncomfortable, 5- not detectable. The final evaluation value corresponded to the average of the referred parameters, all with equivalent degree of importance (20% of importance) except for the aftertaste (40% of importance).

3. Results

3.1. Screening results: experimental design with CPPs range and CQAs studied

A QbD approach was followed essentially by using the Design of Experiments (DoE) tool. The QTPP was constructed based on practical knowledge of the dosage form, from previous works and from literature support (Hoffmann et al., 2011; Preis et al., 2014; Visser et al., 2015).

The different factors under study (CPPs) were introduced in the DoE software and a custom design was outlined for each different test. In total, 123 oral films were prepared with different percentages of main film-forming polymer (PVAc), stabilizer (PVA), disintegrant (NaCMC) and plasticizer (triethyl citrate and / or propanediol, glycerol, polyethylene glycol 400, polyethylene glycol 1000, polyethylene glycol 6000) (Table 23). For the taste masking optimization (Table 24) and DS incorporation (Table 25) additional additives were tested: mannitol, citric acid, sweeteners (sucralose, MAG), flavour (strawberry flavour) and /or colourant (iron oxide). The different runs are presented on the CPPs columns of Tables 23, 24 and 25, whereas the results of their evaluation are on the CQAs columns on the same tables.

Table 23 - Ranges of CPPs (amount of PVAc, PVA, Plasticizer, NaCMC and Plasticizer type) for plasticizer selection formulations. The amount of each compound is presented as rational values where the sum of the components is 1. The range used to delineate the design is present on the excipients row. The missing values are identified (*) and are related with the poor films characteristics that did not allowed to perform some valid tests. The value in the CQAs column corresponds to the median value introduced in the software to perform the analysis.

Run	CPPs					CQAs					
	PVAc	PVA	Plasticizer	NaCMC	Plasticizer type	Young's modulus (Et) (Mpa)	Tensile Strength (σB) (Mpa)	Elongation (εB) (%)	Residual water content (%)	Disintegration time (s)	Global evaluation (1-5)
Range tested	0,25-0,80	0,1-0,40	0,01-0,2	0,01-0,20							
A1	0,5	0,2	0,2	0,1	PEG 400	9,42 (8,6 - 10,23)	2,41 (2,3 - 2,5)	80,8 (75 - 87)	6,16 (5,7 - 6,6)	*	3,4
A2	0,67	0,2	0,01	0,12	Propylene glycol	*	*	*	5,03 (4,2 - 5,8)	*	1,98
A3	0,67	0,01	0,2	0,12	Propylene glycol	*	*	*	5,19 (4,7 - 5,7)	>60	1,98
A4	0,69	0,11	0,01	0,19	Glycerol	*	*	*	5,82 (5,5 - 6,1)	>60	1,86
A5	0,6	0,01	0,2	0,19	Glycerol	*	*	*	*	*	1,54
A6	0,69	0,01	0,1	0,2	PEG 6000	621 (618,7 - 622,8)	6,47 (5,5 - 7,4)	0,66 (0,6 - 0,7)	6,89 (6,4 - 7,4)	>60	2,42
A7	0,82	0,06	0,1	0,01	PEG 400	3,19 (2,39 - 3,98)	6,96 (6,9 - 7)	391 (380 - 402)	2,99 (2,7 - 3,3)	>60	3,16
A8	0,82	0,01	0,06	0,12	PEG 400	58,2 (44,16 - 72,16)	4,22 (3,2 - 5,3)	58,8 (55 - 63)	5,02 (4,9 - 5,2)	>60	2,68
A9	0,95	0,03	0,01	0,01	Propylene glycol	656 (653,9 - 669,8)	9,84 (9,8 - 24)	1,19 (1,1 - 3,6)	3,11 (2,9 - 3,3)	>60	3,96
A10	0,93	0,01	0,01	0,05	PEG 6000				3,91 (3,5 - 4,3)	>60	2,42
A11	0,72	0,06	0,06	0,16	PEG 6000	1366 (990,6 - 1552)	13,2 (12 - 28)	0,76 (0,7 - 1,9)	4,56 (4,2 - 4,9)	>60	2,98
A12	0,67	0,09	0,2	0,04	Glycerol	*			*	*	2,1
A13	0,46	0,2	0,15	0,2	Glycerol	*			*	*	2,12
A14	0,68	0,14	0,14	0,05	PEG 6000	939 (829 - 1049)	6,6 (5,6 - 7,6)	0,58 (0,6 - 0,6)	3,14 (2,7 - 3,5)	>60	3,58
A15	0,67	0,18	0,01	0,14	Glycerol	0,5 (0,5 - 0,5)	0,01 (0 - 0)	0,01 (0 - 0)	5,32 (5 - 5,6)	>60	2,42
A16	0,7	0,19	0,07	0,04	PEG 6000	1361 (1128 - 1473)	4,36 (3,7 - 8,8)	0,3 (0,3 - 0,5)	3,49 (3,3 - 3,7)	>60	2,98
A17	0,4	0,2	0,2	0,2	PEG 6000	833 (692,9 - 973,9)	8,81 (8,2 - 9,4)	0,69 (0,7 - 0,7)	7,19 (6,7 - 7,7)	26 (15 - 31)	3,58
A18	0,68	0,11	0,11	0,1	PEG 400	23,9 (23,33 - 24,54)	6,9 (6,1 - 7,7)	221 (187 - 255)	5,34 (5,3 - 5,4)	>60	2,6
A19	0,79	0,01	0,01	0,19	Propylene glycol	1521 (1513 - 1529)	16,5 (16 - 17)	0,88 (0,9 - 0,9)	5,12 (4,8 - 5,5)	>60	3,58
A20	0,9	0,03	0,07	0,01	Glycerol	696 (696,3 - 696,3)	10 (10 - 10)	1,42 (1,4 - 1,4)	3,68 (3,6 - 3,7)		2,54
A21	0,49	0,17	0,18	0,17	PEG 400	0,5 (0,5 - 0,5)	0,01 (0 - 0)	0,01 (0 - 0)	6,28 (6,3 - 6,3)	>60	1,42
A22	0,64	0,2	0,15	0,01	Propylene glycol	*	0,47 (0,3 - 0,7)	49,5 (16 - 83)	4,32 (4 - 4,6)	>60	1,98
A23	0,78	0,01	0,2	0,01	PEG 6000	1766 (1766 - 1766)	11,2 (11 - 11)	2,08 (0,6 - 3,6)	2,53 (2,5 - 2,6)	>60	2,84
A24	0,82	0,12	0,02	0,05	Propylene glycol	*	*	*		>60	2,42
A25	0,57	0,19	0,23	0,01	Propylene glycol	*	*	*	6,14 (6,1 - 6,2)	>60	1,42
A26	0,8	0,01	0,14	0,05	Propylene glycol	*	*	*	4,78 (4,6 - 4,9)	>60	1,42
A27	0,58	0,22	0,01	0,2	PEG 6000	1488 (1168 - 1543)	16,6 (13 - 30)	0,93 (0,9 - 2,3)	5,92 (5,9 - 5,9)	60 (19 - 67)	3,58
A28	0,59	0,11	0,19	0,12	Propylene glycol	0,5 (0,5 - 0,5)	0,01 (0 - 0)	0,01 (0 - 0)	* (-)	>60	1,7
A29	0,6	0,16	0,08	0,16	PEG 400	228 (224,4 - 240,5)	10,8 (11 - 12)	11 (11 - 13)	6,75 (6,7 - 6,8)	>60	3,44
A30	0,7	0,1	0,12	0,08	Glycerol	*	*	*	*	*	1,68

Table 24 - Ranges of CPPs (amount of PVAc, PVA, Triethyl citrate, NaCMC, Mannitol, Citric acid, Sucralose, MAG, Flavour and colourant) for taste masking optimization formulations. The amount of each compound is presented as rational values where the sum of the components is 1. The range used to delineate the design is present on the excipients row. The missing values are identified (*) and are related with the poor films characteristics that did not allowed to perform some valid tests. The value in the CQAs column corresponds to the median value introduced in the software to perform the analysis.

Run	CPPs										CQAs							
	PVAc	PVA	Triethyl citrate	NaCMC	Mannitol	Citric acid	Sucralose	MAG	Flavour	Colorant	Young's modulus (Et) (Mpa)	Tensile Strength (σB) (Mpa)	Elongation (εB) (%)	Residual water content (%)	Disintegration time (s)	Contact angle (º)	Organoleptic evaluation (1-5)	Global evaluation (1-5)
Range tested	0,45-0,60	0,1-0,20	0-0,1	0,05-0,20	0-0,10	0-0,20	0-0,05	0-0,05	0-0,05	0-0,005								
B1	0,435	0,2	0,174	0,196	-	-	-	-	-	-	577,3 (484 - 655)	7,04 (6,07 - 8,13)	9,53 (9,14 - 14,7)	6,88 (6,42 - 7,33)	5 (5 - 5)	88,01 (87,5 - 90,2)	0	4
B2	0,552	0,17	0,107	0,171	-	-	-	-	-	-	678,5 (667 - 682)	9,8 (7,71 - 12,9)	45,8 (44,6 - 49,3)	5,47 (5,14 - 5,8)	7 (7 - 7)	69,05 (68,6 - 75)	0,2 (0 - 0,2)	3,6
B3	0,46	0,19	0,163	0,188	-	-	-	-	-	-	743 (712 - 972)	14,6 (11,8 - 16,3)	2,42 (2,29 - 2,47)	5,01 (5,01 - 5,01)	6,5 (6 - 7)	54,41 (53,1 - 56,5)	0	4,3
B4	0,426	0,21	-	0,199	-	0,17	-	-	-	-	1401 (1337 - 1465)	13,6 (4,49 - 22,6)	0,68 (0,27 - 1,09)	3,22 (3,14 - 3,3)	26 (25 - 26)	*	2,8 (2,2 - 3,4)	3,7
B5	0,543	0,15	-	0,201	-	0,11	-	-	-	-	2285 (2244 - 2327)	17 (14,5 - 19,4)	0,63 (0,55 - 0,71)	4,49 (3,77 - 5,19)	25 (25 - 25)	*	2,2 (2,2 - 2,4)	3,7
B6	0,587	0,16	-	0,201	-	0,05	-	-	-	-	2537 (2463 - 2610)	13,1 (7,41 - 18,7)	0,47 (0,28 - 0,66)	5,27 (4,88 - 7,06)	19 (16 - 21)	*	2,2 (2,2 - 2,8)	3,7
B7	0,498	0,15	0,056	0,149	0,085	0,05	-	0,01	-	-	73,1 (69,1 - 81,8)	8,69 (7,61 - 8,74)	42,6 (42,2 - 50,4)	3,91 (3,87 - 3,95)	17 (17 - 17)	63,44 (62,3 - 63,7)	1,8 (1,8 - 2,6)	3,6
B8	0,528	0,17	0,069	0,174	-	0,06	-	-	-	-	457,4 (435 - 460)	10,1 (7,99 - 10,1)	25,7 (16,9 - 32,1)	4,66 (4,07 - 5,25)	14 (13 - 14)	59,48 (58,1 - 59,9)	1 (1 - 2,6)	1,5
B9	0,491	0,15	0,056	0,174	0,058	0,01	-	0,01	-	-	488,3 (383 - 515)	16 (12,3 - 17,6)	15,3 (14 - 25,5)	3,97 (3,59 - 4,34)	13 (12 - 14)	*	2,4 (2,4 - 3,4)	2,3
B10	0,529	0,15	0,072	0,144	0,058	0,02	-	0,03	-	-	274,8 (266 - 354)	8,47 (7,91 - 9,09)	21,4 (16,8 - 22,4)	4,54 (4,34 - 4,73)	5,5 (5 - 6)	68,02 (64,9 - 68,2)	2,2 (2,2 - 2,2)	3,2
B11	0,553	0,15	0,071	0,151	0,04	0,01	-	0,01	-	-	172,3 (148 - 197)	4,75 (3,44 - 6,05)	61,2 (54,1 - 68,3)	4,41 (4,25 - 4,56)	7 (7 - 13)	59,36 (59,3 - 60,4)	1 (1 - 2,8)	4,3
B12	0,494	0,16	0,052	0,133	0,049	0,01	0,02	0,01	0,043	0,005	824,1 (684 - 952)	20,4 (14,4 - 21,6)	24,8 (21,5 - 25,9)	5,33 (5,22 - 5,44)	4 (4 - 4)	65,08 (59,6 - 65,8)	4,4 (4 - 4,4)	4,6
B13	0,511	0,15	0,05	0,147	0,026	0,01	0,039	0,01	0,051	0,005	897,3 (692 - 1049)	16,9 (16,2 - 25,8)	12,7 (7,06 - 17,1)	4,94 (4,9 - 4,98)	3,5 (3 - 4)	67,37 (63 - 67,5)	4 (3 - 4)	4,6
B14	0,477	0,13	0,099	0,143	0,048	0,01	0,041	0,01	0,039	0,005	607,7 (551 - 724)	11,5 (4,19 - 11,8)	28,2 (25,1 - 37,8)	5,23 (5,18 - 5,28)	6,5 (5 - 8)	61,84 (61,7 - 62,4)	3,2 (3,2 - 3,2)	4,6
B15	0,544	0,14	0,017	0,144	0,048	0,05	-	-	0,048	0,005	629,6 (345 - 914)	24,6 (24,6 - 24,6)	10,4 (9,76 - 11,1)	4,02 (3,9 - 4,13)	29 (23 - 34,4)	65,93 (65,4 - 68,6)	3 (3 - 3)	4,3
B16	0,49	0,15	0,103	0,082	0,051	0,05	0,04	0,01	-	-	154,6 (110 - 199)	10 (9,32 - 10,7)	106 (104 - 108)	3,97 (3,75 - 4,18)	21 (18 - 22,8)	64,78 (63,7 - 65,7)	2 (1,8 - 2)	3,9
B17	0,563	0,15	0,104	0,084	0,049	-	-	0,01	0,049	-	206,4 (130 - 256)	6,34 (1,98 - 7)	61,1 (37,6 - 101)	3,82 (3,49 - 4,78)	20 (15 - 24,8)	56,8 (56 - 58,7)	0,8 (0,4 - 0,8)	3,6
B18	0,492	0,15	0,083	0,147	-	-	0,04	0,01	0,05	0,005	748,5 (660 - 837)	3,92 (3,59 - 4,25)	23,4 (23,3 - 23,4)	4,18 (4,07 - 4,29)	9,7 (9,3 - 10,1)	59,98 (59,4 - 60)	2,6 (2,4 - 2,6)	4,6
B19	0,45	0,14	0,094	0,138	0,047	0,05	0,037	-	0,047	-	405,6 (388 - 424)	10,1 (7,63 - 12,5)	22,6 (19,8 - 25,3)	2,76 (2,6 - 2,91)	13 (13 - 13,3)	65,82 (62,3 - 69,9)	3,8 (2,6 - 3,8)	4,6
B20	0,6	0,14	0,012	0,149	-	0,05	0,04	0,01	-	-	2282 (2282 - 2282)	12,4 (12,4 - 12,4)	0,48 (0,48 - 0,48)	3,28 (3,11 - 3,45)	35 (31 - 38,4)	56,53 (56 - 58,1)	3,2 (3,2 - 3,2)	3,7
B21	0,599	0,09	0,012	0,068	0,05	0,05	0,04	0,01	0,05	0,005	421,5 (341 - 502)	6,42 (4,39 - 8,45)	0,6 (0,48 - 0,71)	3,93 (3,91 - 3,95)	22 (20 - 24,8)	61,86 (60,4 - 64,1)	3,8 (3,8 - 4)	3,7
B22	0,599	0,15	0,1	0,069	-	0,05	-	-	-	-	292,4 (277 - 355)	3,54 (2,55 - 7,22)	81,9 (71,6 - 85,4)	3,1 (3,03 - 3,16)	17 (16 - 18,7)	58,84 (56,2 - 59,4)	1 (0,8 - 1)	4,3
B23	0,599	0,07	0,013	0,145	0,051	-	0,04	-	0,05	-	901,4 (870 - 933)	23,4 (22,2 - 24,6)	6,8 (5,89 - 7,7)	4,26 (4,15 - 4,36)	46 (25 - 100)	77,54 (72,4 - 78)	3,6 (2,8 - 3,6)	4,3
B24	0,6	0,07	0,105	0,08	-	0,05	0,039	0,01	0,049	0,005	438,9 (415 - 463)	2,89 (2,06 - 3,71)	59,5 (37,7 - 81,2)	3,02 (2,65 - 3,92)	30 (30 - 31,2)	57,83 (56,2 - 59,2)	2,8 (2,2 - 3,6)	4,3
B25	0,582	0,15	0,106	0,067	0,05	-	0,04	-	-	0,005	286,5 (218 - 292)	3,35 (3,24 - 3,64)	94,4 (93,6 - 111)	3,31 (3,03 - 3,59)	15 (12 - 17,6)	59,43 (58,7 - 62,1)	2,4 (0,8 - 2,6)	4,3
B26	0,589	0,07	0,106	0,145	0,05	-	-	0,01	-	0,004	330,2 (310 - 339)	2,44 (2,36 - 2,49)	38,7 (23,9 - 41,7)	3,73 (3,33 - 4,13)	17 (17 - 17,5)	63,72 (62,5 - 65,6)	1,8 (1,8 - 2,4)	3,6
B27	0,432	0,15	-	0,145	0,095	0,09	0,039	0,05	-	0,005	585,9 (568 - 604)	9,44 (9,38 - 9,5)	1,12 (1,05 - 1,18)	5,45 (5,3 - 5,59)	29 (20 - 37)	79,84 (79,8 - 79,8)	*	2,7
B28	0,483	0,18	-	0,075	0,107	0,05	-	0,05	0,054	-	528,6 (514 - 543)	4,91 (4,27 - 5,55)	0,66 (0,56 - 0,75)	*	*	*	*	1,7
B29	0,554	0,16	-	0,142	0,093	-	-	0,05	-	0,005	*	*	*	*	*	*	*	1,5
B30	0,624	0,16	0,019	0,131	-	-	-	0,01	0,054	0,005	627,2 (601 - 668)	14,8 (11,1 - 16,8)	34,1 (30,9 - 39,7)	5,52 (5,39 - 5,64)	28 (25 - 30)	63,78 (63,7 - 65,2)	*	3,6
B31	0,638	0,19	0,006	0,051	-	0,11	-	0,01	-	-	420,4 (364 - 477)	7,15 (3,42 - 10,9)	0,74 (0,46 - 1,01)	*	*	*	*	2,7
B32	0,64	0,07	0,006	0,071	0,038	0,11	0,043	0,01	0,016	-	270,2 (238 - 302)	7,78 (5,68 - 9,87)	19,8 (1,37 - 38,2)	4,39 (4,38 - 4,4)	100 (100 - 100)	58,45 (56,6 - 59,2)	*	2,7
B33	0,537	0,05	0,058	0,15	0,099	-	0,049	0,05	-	0,005	231,2 (187 - 255)	11,9 (11,3 - 12,9)	42,1 (35 - 55,1)	5,32 (4,83 - 6,19)	6 (6 - 6)	60,7 (59,4 - 63,2)	*	3,6
B34	0,567	0,05	0,095	0,145	-	-	0,048	0,05	0,048	-	439,7 (426 - 447)	3,92 (2,84 - 5,88)	33,7 (30,8 - 36,4)	5,82 (5,72 - 5,91)	9 (9 - 9)	61,66 (60,7 - 61,7)	*	3
B35	0,595	0,17	0,035	0,05	-	-	0,048	0,05	0,05	-	633,3 (631 - 635)	10 (4,9 - 15,1)	44,9 (23,9 - 66)	4,05 (4,04 - 4,06)	20 (18 - 21)	61,66 (61,5 - 61,8)	*	4
B36	0,456	0,17	0,036	0,055	0,1	0,08	-	0,05	0,05	0,005	*	*	*	4,79 (4,73 - 4,85)	7,5 (6 - 9)	68,36 (64,6 - 69,4)	*	3,7
B37	0,452	0,05	0,082	0,139	0,099	0,07	0,05	-	0,05	-	91,3 (90,7 - 91,9)	9,33 (9,25 - 9,41)	93,3 (89,4 - 97,1)	4,18 (4,09 - 4,27)	10 (9 - 11)	58,08 (55,4 - 59,6)	*	3,6
B38	0,504	0,21	0,089	0,044	0,085	0,06	-	-	-	0,004	203,5 (154 - 253)	3,08 (2,83 - 3,33)	60,7 (56,2 - 65,1)	2,41 (2,31 - 2,5)	100 (100 - 100)	62,78 (62,5 - 64,7)	*	4,6
B39	0,443	0,06	0,1	0,15	0,099	0,05	0,049	0,01	0,049	-	172,4 (161 - 180)	9,78 (9,34 - 10,1)	50,8 (47,6 - 53,7)	4,55 (4,3 - 4,79)	7,5 (6 - 9)	60,5 (60,2 - 63,2)	*	3,9
B40	0,467	0,18	0,048	0,164	-	0,08	0,052	0,01	-	0,005	1054 (1002 - 1114)	28,3 (27,2 - 30,7)	6,78 (5,12 - 9,32)	3,55 (3,39 - 3,7)	16 (12 - 19)	64,51 (60,5 - 64,9)	*	3,6

Table 25 - Ranges of CPPs (amount of PVAc, PVA, Triethyl citrate, NaCMC, Mannitol, Citric acid and Pramipexole) for formulations with drug substance incorporated. The amount of each compound is presented as rational values where the sum of the components is 1. The range used to delineate the design is present on the excipients row. The missing values are identified (*) and are related with the poor films characteristics that did not allowed to perform some valid tests. The value in the CQAs column corresponds to the median value introduced in the software to perform the analysis.

Run	CPPs							CQAs											
	PVAc	PVA	Triethyl citrate	NaCMC	Mannitol	Citric acid	Pramipexole	Young's modulus (Et) (Mpa)			Tensile Strength (σB) (Mpa)			Elongation (εB) (%)			Residual water content (%)			Disintegration time (s)			Global evaluation (1-5)
Range tested	0,5-0,6	0,1-0,17	0,025-0,075	0,1-0,15	0-0,06	0,01-0,05	0,004-0,5																
C1	0,593	0,099	0,045	0,099	0,03	0,05	0,084	70,8	(68 -	73,54)	5,55	(4,2 -	6,9)	37,3	(34,6 -	40,1)	4,87	(4,81 -	4,92)	34	(33 -	35)	2,54
C2	0,6	0,102	0,03	0,139	0,05	0,05	0,03	260	(246 -	274,8)	14,7	(14 -	16)	22,1	(12,9 -	31,4)	4,45	(4,2 -	4,7)	39	(27 -	40)	2,96
C3	0,597	0,151	0,048	0,1	0,05	0,01	0,045	102	(89 -	104,2)	10,2	(7,7 -	10)	61,4	(47 -	77,1)	4,85	(4,51 -	5,92)	11	(10 -	25)	3,72
C4	0,526	0,131	0,031	0,141	0,031	0,01	0,131	260	(223 -	296,3)	12,9	(12 -	14)	8,9	(4,14 -	13,7)	5,76	(5,57 -	5,95)	24	(24 -	24)	3,52
C5	0,531	0,131	0,063	0,135	0,065	0,045	0,031	89,4	(80,4 -	98,44)	10,1	(9,6 -	11)	42,6	(40,3 -	44,9)	4,75	(4,45 -	5,04)	12,5	(12 -	13)	4,56
C6	0,536	0,141	0,075	0,138	0,031	0,046	0,032	134	(119 -	149,2)	4,94	(3,8 -	6)	43,7	(39,2 -	48,2)	4,03	(4,03 -	4,03)	21	(18 -	24)	3,58
C7	0,509	0,1	0,03	0,1	0,03	0,05	0,181	*			*			*			*			*			2,66
C8	0,598	0,149	0,03	0,102	0,03	0,01	0,081	193	(191 -	194,5)	10,2	(9 -	11)	31,2	(28,1 -	34,4)	*			*			2,52
C9	0,53	0,132	0,062	0,135	0,064	0,045	0,032	51,5	(50,5 -	52,48)	8	(6,4 -	9,6)	90,1	(69,6 -	111)	4,69	(4,68 -	4,7)	17	(15 -	19)	2,84
C10	0,553	0,091	0,042	0,092	0,028	0,009	0,186	38,2	(37,6 -	38,8)	3,68	(3,4 -	3,9)	65,6	(64,3 -	66,8)	6,75	(6,74 -	6,76)	13,5	(11 -	16)	3,58
C11	0,574	0,149	0,045	0,141	0,03	0,05	0,01	211	(209 -	214,1)	10,8	(9,7 -	12)	34,8	(33,1 -	36,6)	4,04	(3,81 -	4,26)	15	(10 -	22)	4,28
C12	0,511	0,149	0,03	0,1	0,05	0,05	0,11	90	(74,8 -	105,2)	8,43	(7,6 -	9,3)	41,9	(38,7 -	45,1)	5	(4,84 -	6,08)	12,5	(11 -	14)	4,56
C13	0,556	0,109	0,039	0,153	0,055	0,011	0,077	123	(103 -	125,6)	8,85	(8,7 -	9,8)	21,1	(19,5 -	33,9)	4,68	(4,47 -	4,89)	17,5	(16 -	19)	2,98
C14	0,569	0,15	0,046	0,142	0,045	0,045	0,004	131	(106 -	131,9)	9	(8,1 -	9,2)	43,4	(39,6 -	46,4)	4,43	(4,35 -	4,5)	13,5	(11 -	16)	3,44
C15	0,275	0,075	0,025	0,075	0,025	0,025	0,5	*			*			*			*			*			1,54
C16	0,535	0,146	0,045	0,151	0,045	0,045	0,033	103	(102 -	109,1)	8,91	(8,1 -	9,1)	20	(14,8 -	20,1)	4,56	(4,39 -	4,73)	8	(7 -	9)	3,3
C17	0,548	0,147	0,046	0,153	0,045	0,045	0,017	115	(96,5 -	122,4)	8,08	(7,9 -	8,9)	19,7	(19,6 -	25,7)	5,88	(5,67 -	6,08)	6	(5 -	7)	3,44
C18	0,513	0,148	0,047	0,152	0,045	0,045	0,05	87,4	(70,4 -	94,54)	7,45	(6,3 -	8,2)	23,6	(17 -	27,5)	5,78	(5,57 -	5,98)	7	(7 -	7)	3,58
C19	0,514	0,15	0,044	0,151	0,045	0,045	0,05	67,4	(160 -	169,7)	7,33	(7,5 -	7,6)	26,2	(28,4 -	34,6)	5,43	(5,4 -	6,19)	8	(14 -	15)	4,14
C20	0,562	0,149	0,046	0,15	-	0,045	0,05	165	(202 -	221)	7,56	(8,6 -	10)	31,5	(13,9 -	19,5)	5,45	(5,2 -	5,51)	14,5	(9 -	13)	3,58
C21	0,557	0,151	0,042	0,15	-	0,05	0,05	218	(215 -	221,1)	10	(8,3 -	12)	16,3	(10,3 -	14,7)	5,36	(6,04 -	6,28)	11	(4 -	6)	3,12
C22	0,534	0,168	0,046	0,153	-	0,05	0,05	218	(63,9 -	82,52)	10,3	(6,4 -	7,8)	12,5	(23,1 -	29,3)	6,16	(5,14 -	5,72)	5	(8 -	8)	3,3
C23	0,55	0,155	0,041	0,155	-	0,05	0,05	208	(200 -	212,5)	12	(10 -	12)	20,6	(10,2 -	20,7)	5,62	(5,59 -	5,65)	10,5	(8 -	13)	3,58

The components used in each experiment are presented in its rational value being their sum always equal to 1. The oral films were prepared by solvent casting and tested with the appropriate techniques to evaluate the CQAs (target vales on Table 26). The obtained results were evaluated according to the CQAs limits previously defined. The global and organoleptic evaluations, as well as the contact angle, were added and the limits were stablished according to the test panel used and literature reference (Vogler, 1998).

Table 26 - Critical Quality attributes acceptance criteria defined for the initial screening studies. * - Not applicable in all the optimization design.

	Target values
σB (MPa)	15-35
εB (%)	4-50
Et (MPa)	100-1500
Residual H_2O content (%)	[3-6%]
Disintegration time (s)	<30
Global evaluation (1-5)	>3,5
Organoleptic evaluation (1-5)*	>3,5
Contact Angle (º)*	>65º

The JMP screening platform was used to analyse the data of the set of experiments designed before. The models selection was based on their statistical significance, p-value and RSquare analysis. The p-value was obtained through the analysis of variance (ANOVA) and allows evaluating the whole model. Significance probabilities of 0.05 or less were considered to be an evidence that there is at least one significant regression factor in the model (Institute, 2012). In turn, the RSquare (R^2) estimates the proportion of the variation in the response around the mean. Additionally, the Rsquare Adj was also considered because it corresponds to the adjustment of R^2 to make it more comparable with other models with different numbers of parameters (Institute, 2012). The RSquare is also the square of the correlation between the actual and predicted response. If R^2 = 1 (errors are all zero) a perfect fit is observed, whereas R^2 = 0 occurs when the response prediction of the model is not different from the mean response. Nonetheless, a good model should present a low p-value (lower than 0.05 for 95% of confidence), a RSquare closer to 1 and an RSquare Adj similar to the RSquare (Institute, 2012).

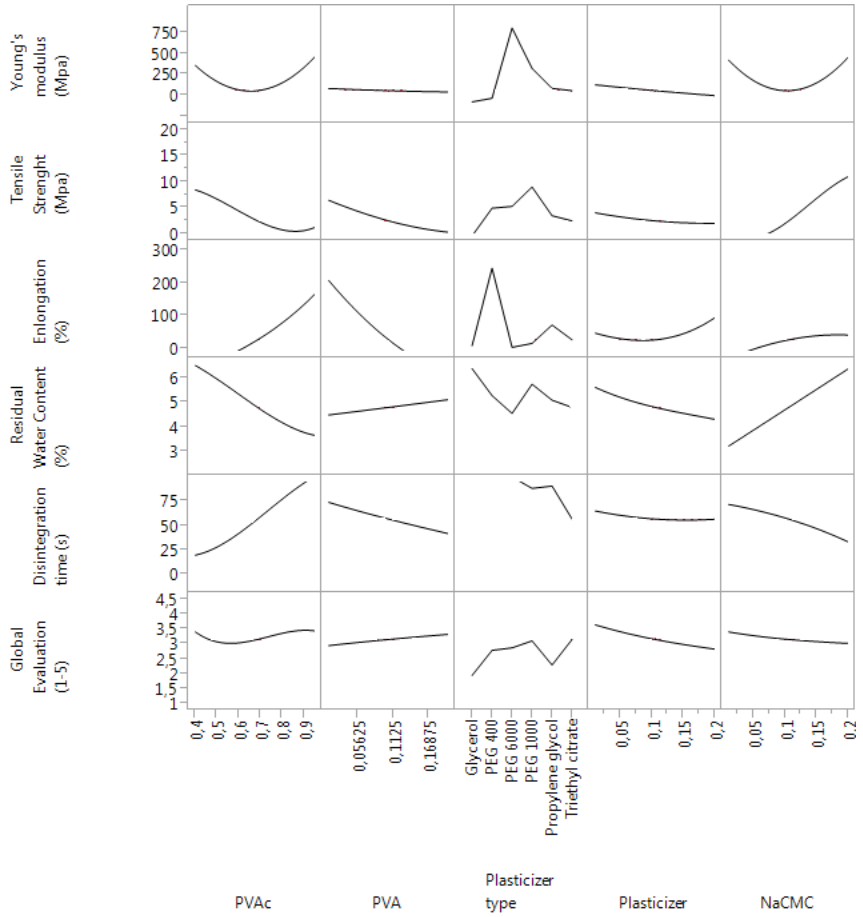
The analysis of the models should be carefully performed considering the statistical data obtained for the parameters presented above. Theoretically, models with very low p-value and high and similar Rsquare are very robust models (Figures 38, 39 and 40 with green border evaluation), whereas higher p-values and low RSquare models indicate that more caution should be taken in their analysis (Figures 38, 39 and 40 with yellow and red boarder evaluation). In addition, the results should only be considered reliable if within the real range studied (Tables 23, 24 and 25, first row).

The model selection lead to the creation of prediction profilers that show graphically the influence of each excipient on the CQAs tested (Figures 38, 39 and 40). The prediction profiler is a simplified way of representing the response surface and verifies the settings that may origin the best response target (see Figures 38, 39 and 40). The individual plots in each row of plots show the prediction traces for each CPP. This prediction trace shows the predictable variance of the response according to the change in each variable while the others are constant (SAS Institute, 2013). Therefore, parallel lines to the x-axis represent the absence of parameter's influence in the correspondent y-variable (response). On the other hand, nonlinear traces indicate the influence of the x-variable in the response that may be more or less complex depending on the shape of the line. The profile visualization presented in Figures 38, 39 and 40 is related with the defined limits for CQAs and / or with the range that allows to obtain better curve variations.

3.2. Screening of possible alternative plasticizers

Although the optimal formulation was obtained using TEC in previous work, its bitter flavour was considered and screening tests with alternative plasticizers were performed (Shimizu et al., 2003; Taylor and Linforth, 2009). The tested plasticizers were chosen based on the previous knowledge that they would not present unpleasant taste: glycerol(Koseki et al., 2004), polyethylene glycols (Clariant, 2014) and propylene glycol (Todd, 1992).

Approximately 60 test solutions were prepared and the results are summarized in the profiler graph (Figure 38).



Model	ANOVA	RSquare	RSquare Adj
Et	p<0.0001	0.660	0.498
σB	p=0.0008	0.673	0.464
εB	p<0.0137	0.883	0.570
% H_2O	p<0.0001	0.885	0.822
Disintegration time	p<0.0001	0.907	0.828
Global evaluation	p=0.0014	0.558	0.379

Figure 38 - Prediction Profiler of different types of plasticizers. It is represented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green solid border means good fit models, with very low p value (<0.01) and high (>0.6) and proximal Rsquare; Yellow dashed border means reasonable fit models, with low p value (<0.05) and medium Rsquare values (0.4-0.6); Red square dotted border means poor models, with no significant p-value (>0.05) and very low Rsquare values. The vertical axis present the evaluated properties in function of the amount and type of component tested in each formulation (horizontal axis).

The majority of the effects obtained do not have a linear trend and it was possible to obtain essentially good models (Figure 38 green border summary). However, two weaker models, that should be carefully analysed (Elongation and Global evaluation, Figure 38 yellow summary), were also obtained.

Briefly, an overall summary of the model is presented in Table 27, column 1.

Table 27 - Summary of the influence of the components on the different testes performed. Only the most evident influences are presented.

	Plasticizers evaluation	Organoleptic optimization	Pramipexole incorporation
Stiffer films (higher Et)	↑PVAc from 65% (%w/w per film)	↓TEC	↑PVAc
	↓ Plasticizer	↑NaCMC	↓PVA
	Choose PEG 600 or PEG 1000	↓Mannitol	↓TEC
	↑NaCMC from 12% (%w/w per film)	↓Citric Acid	↑NaCMC
		↑Sucralose	↓Pramipexole
Resilient films (higher σB)	↓PVAc	↑TEC	↑PVAc
	↓PVA	↓NaCMC	↓TEC
	↓ Plasticizer	↑Mannitol	↑NaCMC
	Choose PEG 600 or PEG 1000	↓Flavor	↑Citric acid from 3% (%w/w per film)
		↓Colorant	↓Pramipexole up to 20%(%w/w per film)
Deformable films (higher εB)	↑PVAc	↓PVAc	↑PVAc
	↓PVA	↑PVA	↑TEC
	↑ Plasticizer	↑TEC	↓NaCMC
	Choose PEG 400 or PG	↑NaCMC	↑Mannitol
	↑NaCMC	↑Sucralose	↓Citric acid
		↑Flavor up to 3% (%w/w per film)	↓Pramipexole
More hygroscopic (Higher residual water retention)	↓PVAc	↓PVAc	↓PVAc
	↑PVA	↑PVA	↑PVA
	Choose Glycerol, PEG 400 or PEG 100	↓TEC	↓TEC
	↑NaCMC	↑NaCMC	↑Mannitol
		↑Sucralose	↑Pramipexole
		↑MAG	
Fast disintegration	↓PVAc	↓PVAc	↓PVAc
	↑PVA	↑PVA	↑PVA
	Choose PEG 1000 or TEC	↑TEC	↑TEC
	↑NaCMC	↑NaCMC	↑NaCMC
		↓Citric acid	↑Mannitol
		↑MAG	↑Citric acid
Better appearance	↑PVA	↓PVAc	↓PVAc
	Choose PEG 1000 or TEC	↑PVA	↑PVA
		↑TEC	↑ Mannitol
		↑Sucralose	↓Pramipexole from 20%(%w/w per film)
		↑Colorant up to 0.03% (%w/w per film)	
Better organoleptic characteristics	-	↓TEC ↑NaCMC ↑Mannitol ↑Citric acid ↑Sucralose up to 3% (%w/w per film) ↑MAG ↑Flavor ↑Colorant	-
More Hydrophobic (higher contact angle)	-	↑PVAc from 52.2% (%w/w per film) ↑PVA from 10% (%w/w per film) ↓Citric acid	-

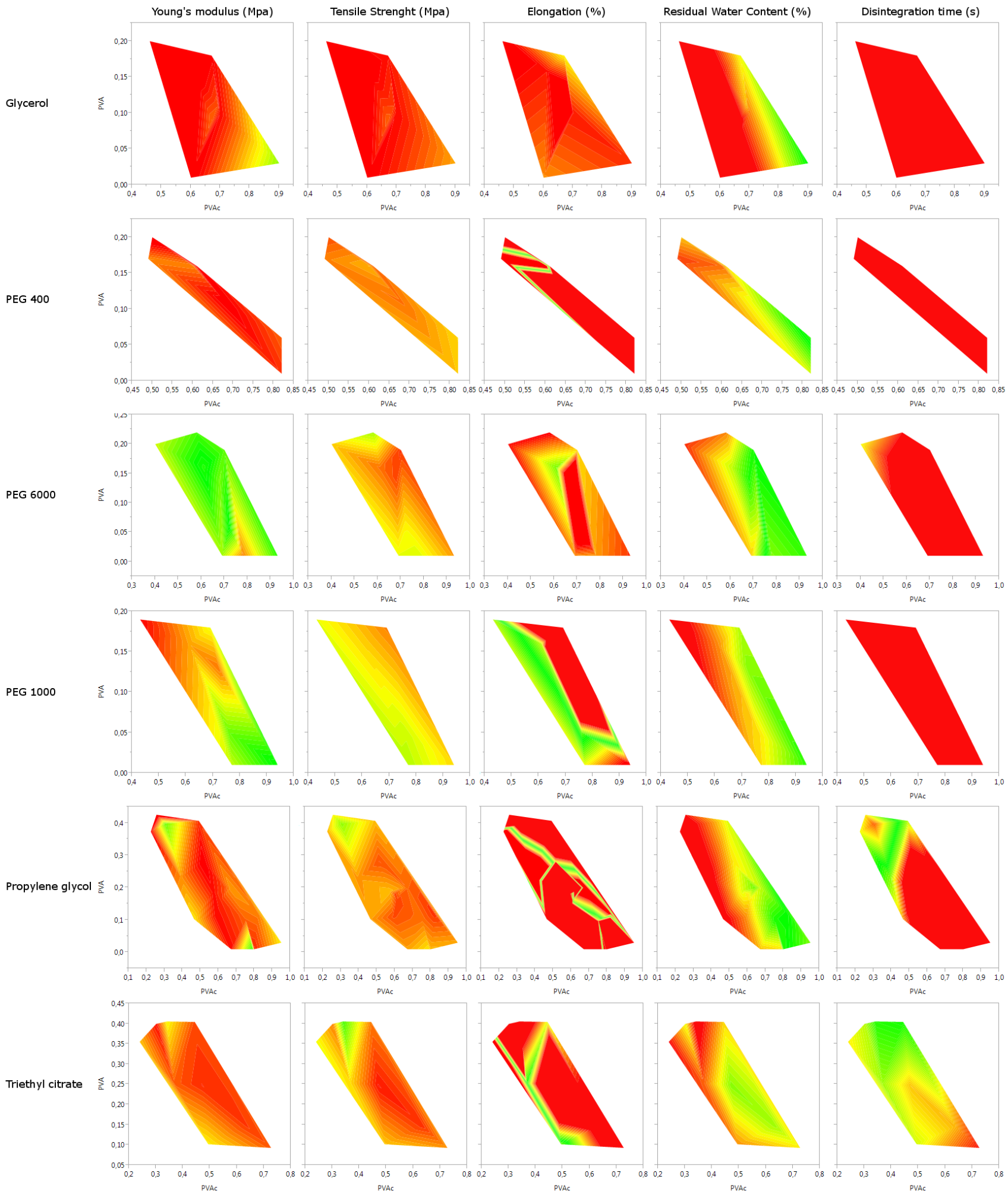


Figure 39 - Plasticizer type influence in the studied CQAs. The influence of the plasticizer may be visualized based on the two main components of the formulation, PVA and PVAc. The grade of colours range from the desirable (green) to the unsuitable (red) effect in each CQA evaluated. Only the coloured area represents the range of the CPPs studied. The white zone is out of range values that were not studied.

The effect of each plasticizer was also analysed through counter plots (Figure 39). In order to facilitate the analyses only the two main components of the formulation were considered (Figure 39).

The grade of colours is related with the CQAs limits defined (Table 26). The green area corresponds to the desirable zone, yellow-orange area is related with values that are close to the limits and the red zone is out of limit range.

In general, almost every plasticizer allows obtaining acceptable values for the majority of the CQAs tested, except for disintegration time. Only TEC, PG and PEG 6000 allow to afford ODF that quickly disintegrate (in less than 30 seconds). Nevertheless, a more suitable operational range was obtained with TEC (no red areas, Figure 39), whereas with PEG 6000 there is an elevated risk to be out of the limits (small yellow-orange area, when PVAc<50% and PVA> 15%, Figure 39).

It is also possible to retrieve that both glycerol and PEG 400 are the worst plasticizers for this system according to the outlined CQAs. This conclusion was taken based on the large and predominant red areas in Figure 39.

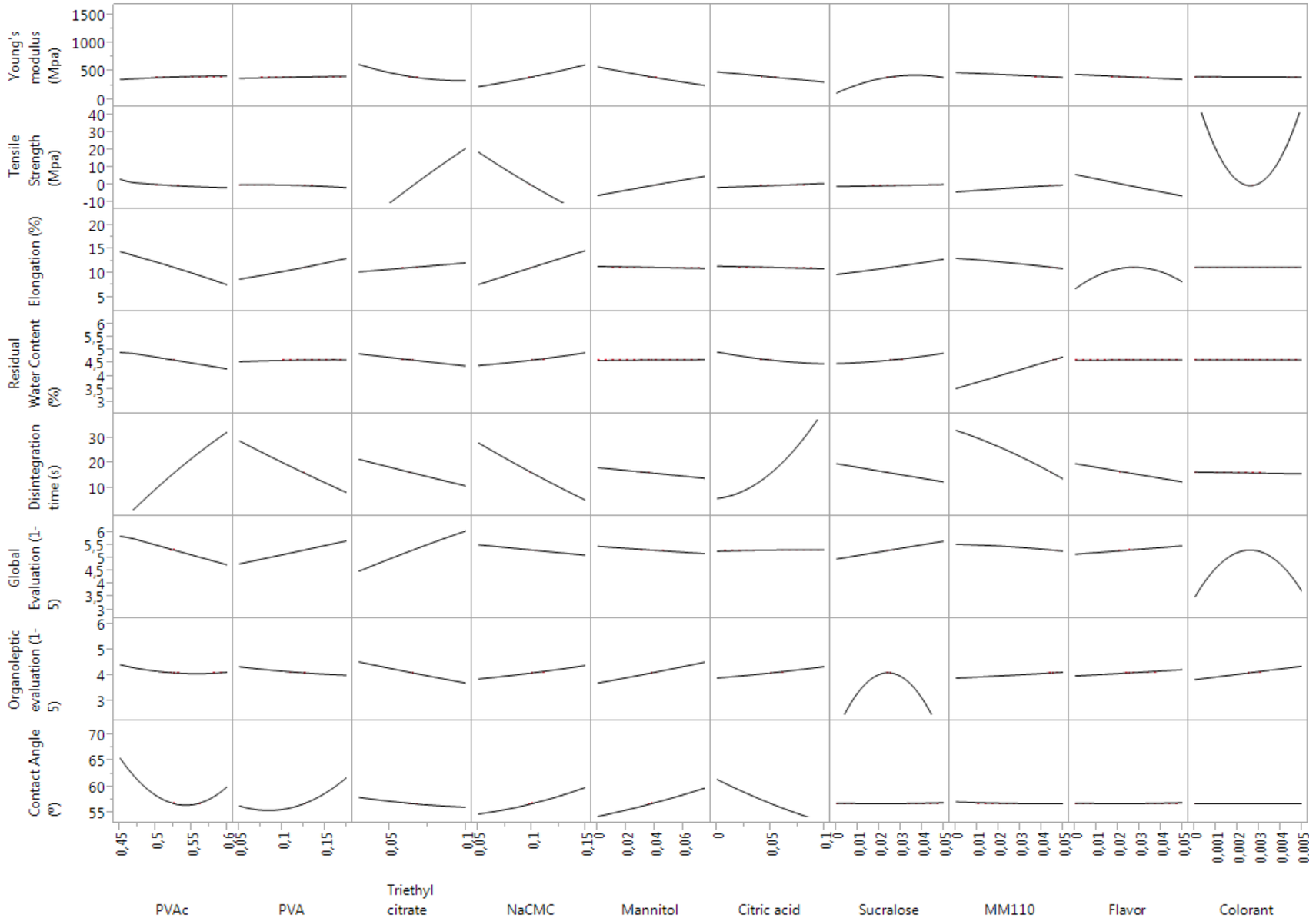
Briefly, the plasticizer effect for each plasticizer tested that allows obtaining green areas based on PVAc-PVA proportion within the limits studied (coloured area) are summarized in Table 28.

Table 28 - Desirable zones (green areas) obtained from the plasticization effect on PVAc-PVA system.

	Green areas
Young's modulus	Glycerol: PVAc > 85% and PVA < 5% PEG 6000: 40% < PVAc < 90% and 5% <PVA < 20% PEG 1000: 75% > PVAc > 90% and PVA < 10% 1,2 – Propanediol (Propilenoglicol): 40% < PVAc < 50% and 30% < PVA < 40%; plus 75% < PVAc < 80% and PVA < 10%
Tensile Strength	PEG 6000: 55% < PVAc < 60% and PVA > 20% plus 70% < PVAc < 80% and PVA < 5% PEG 1000: PVAc < 80% and PVA < 10% 1,2 – Propanediol (Propilenoglicol): 30% < PVAc < 50% and PVA > 30% Triethyl citrate: 30% < PVAc < 40% and PVA > 25%
Elongation	PEG 400: Diffuse zones when PVAc < 60% and PVA > 10% with very narrow operational ranges PEG 6000: 50% < PVAc < 70% and 8% < PVA < 18% PEG 1000: PVAc < 80% and PVA > 5% plus PVAc > 80% and 2,5% < PVA < 5% 1,2 – Propanediol (Propilenoglicol): Diffuse zones within all the range evaluated, but with very narrow operational ranges Triethyl citrate: Diffuse zones in all PVA range when PVAc < 60%
Residual water content	Glycerol: 75% < PVAc < 90% and PVA > 5% PEG 400: 70% < PVAc < 82,5% and 5% < PVA < 12,5% PEG 6000: 65% < PVAc < 90% and 5% < PVA < 20% PEG 1000: 75% < PVAc < 90% and 5% < PVA < 20% 1,2 – Propanediol (Propilenoglicol): 65% < PVAc < 90% and 5% < PVA < 40% Triethyl citrate: 45% < PVAc < 70% and 10% < PVA < 35%
Disintegration time	1,2 – Propanediol (Propilenoglicol): 35% < PVAc < 55% and PVA > 40% Triethyl citrate: PVAc < 50% and PVA > 25%

3.3. Optimization complexes to ameliorate the organoleptic characteristics

Another important goal of this work concerned the development of a formulation with a pleasant taste. For that purpose, additional screening tests were performed with specific sweeteners and flavours.



Model	ANOVA	RSquare	RSquare Adj
Et	p<0.0001	0.789	0.713
σB	p=0.001	0.711	0.542
εB	p<0.0001	0.845	0.745
% H_2O	p=0.0022	0.662	0.492
Disintegration time	p=0.008	0.641	0.502
Global evaluation	p=0.010	0.618	0.405
Oraganoleptic evaluation	p<0.0001	0.946	0.910
Contact angle	p=0.0405	0.453	0.270

Figure 40 - Prediction Profiler of different sweeteners / flavours for taste masking. It is represented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green border means good fit models, with very low p value (<0.01) and high (>0.6) and proximal Rsquare; Yellow border means reasonable fit models, with low p value (<0.05) and medium Rsquare values (0.4-0.6); Red border means poor models, with no significant p-value (>0.05) and very low Rsquare values. The vertical axis present the evaluated properties in function of the amount and type of component tested in each formulation (horizontal axis).

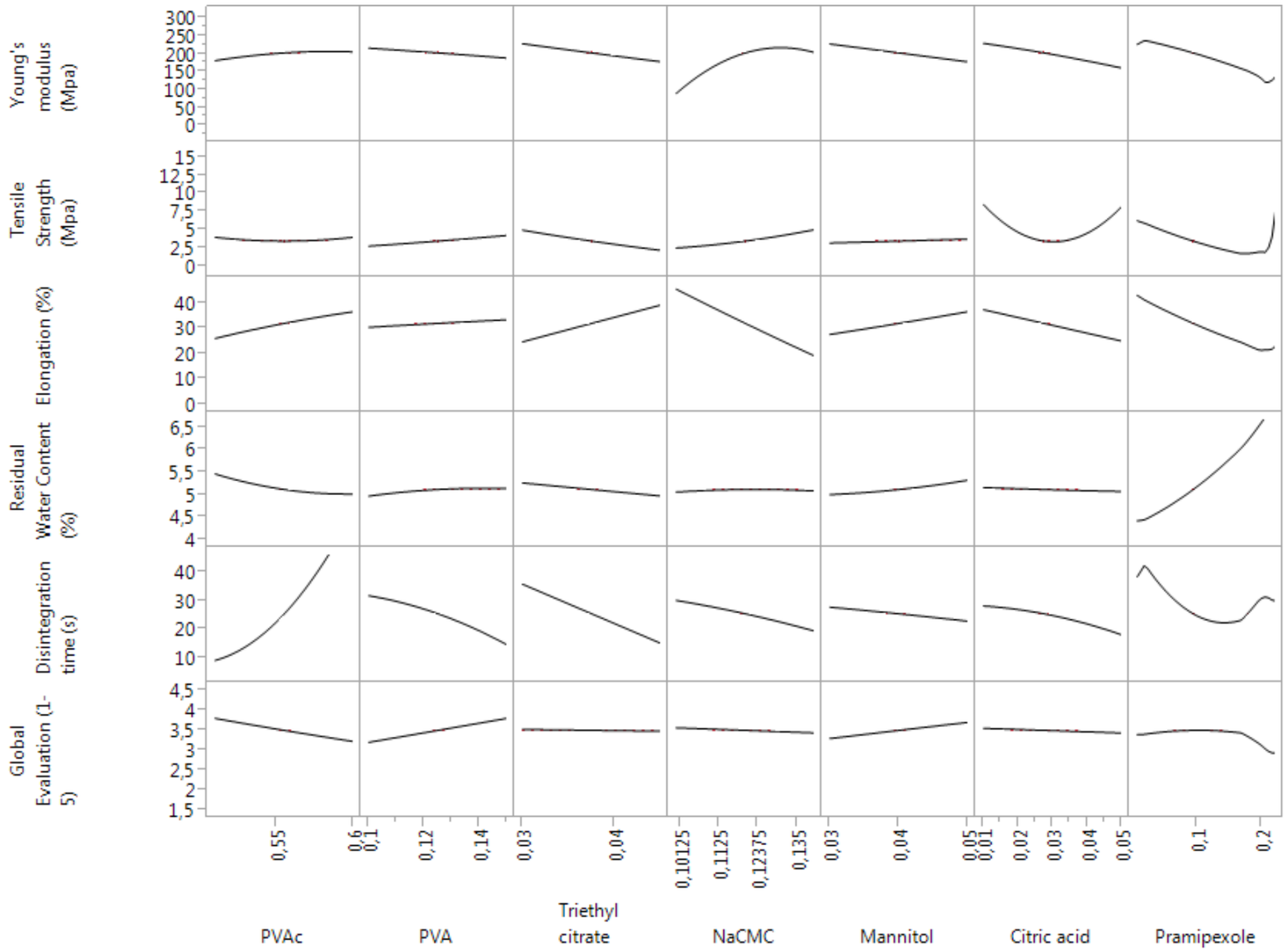
The majority of the models present a linear profile and in general are good models, except for the contact angle (Figure 40). However, despite the relatively moderate RSquare, the model is still statistically significant, since the possibility of 45% of the response effect observed not being by chance remains (Figure 40). The models for the other CQAs are relatively robust, with very low p-values and moderate to high RSquare values.

A general graphical analysis of the models are presented in Table 27 column 2.

3.4. Incorporation in the ODF of a drug used in the treatment of Parkinson's disease (PD)

It was verified previously that an ODF formulation with suitable organoleptic characteristics was possible to achieve with the PVAc-NaCMC-PVA-triethyl citrate system when a taste masking complex is incorporated. The suitability of this system to incorporate a drug substance was also evaluated.

Several formulations were tested and the results are summarized in a profiler graph (Figure 41).



Model	ANOVA	RSquare	RSquare Adj
Et	p<0.0001	0.941	0.892
σB	p<0.0001	0.851	0.752
εB	P=0.0082	0.639	0.422
% H_2O	p<0.0001	0.921	0.828
Disintegration time	p<0.0001	0.931	0.900
Global evaluation	p=0.0014	0.614	0.449

Figure 41 - Prediction Profiler of PD drug loaded films. It is presented the effect of each CPP in the CQAs. Parallel lines to the x-axis mean that there is no effect of the parameter on the evaluated attribute. The significance of the selected model for each CQA evaluated is summarized and presented in the correspondent row. The border colour of each summary is related with the model significance. Green solid border means good fit models, with very low p value (<0.01) and high (>0.6) and proximal Rsquare; Yellow dashed border means reasonable fit models, with low p value (<0.05) and medium Rsquare values (0.4-0.6); Red square dotted border means poor models, with no significant p-value (>0.05) and very low Rsquare values. The vertical axis present the evaluated properties in function of the amount and type of component tested in each formulation (horizontal axis).

The majority of the models obtained are linear and the more peculiar traces are obtained by pramipexole influence (Figure 41). All the models obtained were considered good models, since the p-value was always low (<0.01) and the RSquare above relatively high (>0,6).

A general view and effect of each component in the model is presented in Table 27, column 3.

4. Discussion

4.1. Screening of possible alternative plasticizers

Although an optimal formulation was obtained with TEC in a previous work, its unpleasant taste could affect patient compliance (Shimizu et al., 2003; Taylor and Linforth, 2009). Therefore, screening tests with other plasticizers were performed in an attempt to find a suitable alternative. The tested plasticizers were chosen based on the available references that suggested compounds with no unpleasant taste: glycerol (Koseki et al., 2004), polyethylene glycols (Clariant, 2014) and propylene glycol (Todd, 1992).

Sixty test solutions were prepared and the results are summarized in the profiler graph (Table 23 and graphically in Figures 38 and 39). It is clear the influence of the type of plasticizer in the general properties of the films (Figure 38, 3rd column and Figure 39), as well as the amount of plasticizer used (Figure 38, 4th column). According to the CQAs defined, the most suitable mechanical properties were obtained with polyethylene glycol of higher molecular weight (Mw): PEG 6000 and PEG 1000 (larger green areas in Figure 39). The polymeric matrix with these polyethylene glycols are more rigid (higher Young's modulus) are tougher (higher tensile strength) but less deformable (lower Elongation) (Figure 38, 3rd column). It should be mentioned that this behaviour is unexpected for a plasticizer (Lim and Hoag, 2013). In general, plasticizers are molecules that may interpose between the polymer chains allowing them to tilt and rotate freely. This is commonly observed by the achievement of films with high elongation, low tensile strength and young's modulus (Lim and Hoag, 2013). The high Mw PEGs have a reverse behaviour, which could be justified considering the complexity of the system. It is already described that for simpler binary system with microcrystalline cellulose or gelatin, the increase of PEGs molecular weight contribute to a less efficient plasticizing effect (Cao et al., 2009; Turhan et al., 2001). This effect is explained by the decrease of the polar (hydroxyl) groups per mole influenced by the increase non-polar substitutes of the PEG skeletal related with the higher Mw. This leads to solubility and polarity decrease and consequently to a decrease in the number of hydrogen bound interactions and their ability to interpose and interact easily with hydrophilic polymer chains (Cao et al., 2009; Turhan et al., 2001). The same authors also refer that low polarity PEGs may be easily included in these systems when an interface (e.g. amphiphilic molecule) between both is created (Laboulfie et al., 2013). Additionally, the large polymer chains of

the high Mw PEGs may also have a block effect that may difficult other polymer-polymer interactions (Turhan et al., 2001).

The PVAc based formulation proposed in this work is mainly hydrophobic, due to the hydrophobic nature of the film-forming polymer (PVAc) and represents a significant content of the formulation composition. PVAc is known to have an elevated flexibility and plasticity (Kolter et al., 2013). Therefore, the inclusion of high Mw PEGs in the PVAc matrices probably exert a blocking effect due to the interposition of its long carbonated skeletal between the non-polar polymeric chains contributing to increase the matrix rigidity and lack of resilience (Figure 38, 3rd column).

On the other hand, PEG 400, the lower Mw PEG tested in this system, originate matrices with very high elongation values (Figure 38, 3rd column). The smaller carbonated skeletal of this PEG probably facilitates its penetration between the polymer matrix, leading to a more freely chains movement and consequently easier deformable films. This characteristic makes the films less suitable to process and/or manufacture.

Glycerol revealed to be a very weak plasticizer to this system, probably due to its small size and hydrophilic nature (Figure 38, 3rd column and Figure 39). In turn, the additional methyl groups in the PG backbone seems to be sufficient to increase the non-polar properties of the molecule and to ameliorate its plasticizer properties in this hydrophobic polymeric matrix (Figure 38, 3rd column and Figure 39). Similarly, the triethyl citrate non-polar groups can also easily interpose between the polymeric matrix and origin suitable mechanical properties (Figure 38, 3rd column and Figure 39). Additionally, it is described in literature that triethyl citrate is one of the most suitable plasticizers for PVAc matrix systems (Kolter et al., 2013).

The influence of the polymers (PVAc, PVA and NaCMC) in the matrix mechanical properties is essentially nonlinear (Figure 38, 1st, 2nd and 5th column). The rigidity of the film tends to increase with high PVAc concentration (higher young's modulus), starting at 65% (% w/w per film) (Figure 38, 1st column, 1st row) and decrease with lower concentration of NaCMC in the matrix, up to 12,5% (%w/w per film) (Figure 38, 5th column, 1st row). The higher rigidity of the samples with higher PVAc concentrations in the polymeric matrix is probably related to proportional decrease of the other compounds in the formulation, especially PVA (Figure 38, 2nd column, 1st row). On the other hand, the initial decrease of the rigidity with NaCMC increase may be due the hygroscopic nature of this polymer that enhances the water absorption and retention. The water molecules have high affinity for polar and charged groups, and when diluted in the macromolecules decrease its intermolecular interactions

and increase their free volume. These factors turn the water molecules good plasticizers (Blum et al., 2011). On the contrary, saturation of NaCMC groups probably contributes to the further increase of the matrix rigidity. The influence of these compounds in the other mechanical properties is also complex and somehow difficult to explain (Figure 38, 1st, 2nd and 5th column).

The residual water content decrease is associated with the lower polarity of the tested plasticizers, as expected (Figure 38, 4th row). The less polar components are associated with lower affinity for water molecules, which may contribute to a decrease in the water retention (Blum et al., 2011). According to the chemical structures of the hydrophilic plasticizers tested, and their polar groups per mole (mainly hydroxyl groups), glycerol is probably the most hygroscopic component followed by propylene glycol, PEG 400, PEG 1000 and then PEG 6000. Therefore, the residual water content behaviour obtained for the different compounds follow the same order, more hygroscopic and polar components contribute to retain more water molecules in the polymeric matrix (Figure 38, 4th row and Figure 39). Triethyl citrate a lipophilic compound, presents a similar behaviour compared to the high Mw PEGs tested regarding water retention in this polymeric matrix, probably due to their nonpolar characteristics (Figure 38, 3rd column, 4th row and Figure 39). Glycerol presents a limited green area which only occurs when there is a higher concentration of the hydrophobic polymer in the composition, at least 85% (%w/w per film). Regarding the other plasticizers PEG 6000 has the larger green zone, highlighting its non-hygroscopic properties.

The residual water content sharply increases with the disintegrant concentration (NaCMC), whereas the PVAc concentration origins a sharp decrease (Figure 38, 4th row). This effect is easily explained by the nature of the components. The increase of PVAc in the polymeric matrix contributes to higher non-polar groups that tend to repel the water, whereas the increase of the charged and polar (NaCMC) promote the water adsorption and retention.

Curiously, regarding the disintegration time, the more hydrophilic plasticizers (Glycerol and low Mw PEGs), except PG, contribute to increase this parameter (Figure 38, 5th row). This observation may be related with a more efficient ability of the less polar components to interpose between the PVAc chains that may contribute to form channels that facilitate the water movement and the disruption of the hydrophobic polymeric matrix (Emeje et al., 2006; Tajrin et al., 2015). Additionally, high Mw PEGs, as PEG 6000, are usually used as channeling agents either in hydrophilic or hydrophobic matrices to improve the fast release profile (Emeje et al., 2006; Tajrin et al., 2015). The PG may promote easily the disintegration compared to glycerol, possibly due to its apolar group, and to PEG 400, probably due to PG

lower Mw (PG=76.09 g/mol; PEG400 = 380-420 g/mol) (Rowe et al., 2009) that may ease its interposition between the PVAc chains. Nevertheless, only for TEC or PG was possible to obtain suitable working zones (green areas, Figure 39). In fact with TEC, the probability of being out of the limits (red area, Figure 39) is very low, and may only happen for very high PVAc concentrations (> 65% (%w/w per film)).

The disintegration time is slightly affected by NaCMC and PVA, and both contribute to originate fast dissolving films. Moreover, the PVAc augment is related with sharp increase of the disintegration time. This result is associated with the high concentration of non-polar groups in the polymeric matrix that tend to repel the water molecules, delaying the disintegration time.

The general appearance of the films do not vary significantly with compounds' amount, but mainly with plasticizer type. High Mw PEGs and the triethyl citrate led to films with an acceptable appearance.

Finally, it is easily verified that the plasticizer type influences greatly the overall system and the defined CQAs. However, among the plasticizers tested, TEC showed to be the most suitable plasticizer to use considering the general performance of the obtained films, especially due to larger operational working ranges (it presents less red areas than the others, Figure 39) and the fast disintegration time (<30s).

4.2. Optimization complexes to ameliorate the organoleptic characteristics

The plasticizer screening allowed us to verify the different profiles of the system when diverse plasticizers were used. It was obvious that the modification of a single component may be critical and can change completely the polymeric matrix behaviour. Triethyl citrate remains the plasticizer that allowed meeting more efficiently the CQAs defined for the ODF developed, especially regarding the fast disintegration time. Therefore the unpleasant triethyl citrate aftertaste has to be masked.

Around sixty formulations were tested and the results are summarized in a profiler graph (Figure 40).

An efficient taste masking complex to improve the organoleptic properties of a formulation may be composed by a combination of sweeteners and flavours (Preis et al., 2015). However, the choice of flavour should not be random and some criteria must be considered: the target population, its application and the unpleasant taste to mask (Marriott, 2010). The bitter taste is preferably masked by anise, chocolate, mint, passion fruit and wild berry (Marriott, 2010). Additionally, the bitter aftertaste may also be reduced by the addition of flavour enhancers. Other additives, such as citric acid, may also be used to mitigate some bitter taste (Marriott, 2010). The correct combination of flavours and sweeteners may origin interesting masking profiles that might function as suitable palatable and pleasant taste. An attempt to mask the bitter and unpleasant taste with a masking system was carried out, which was not intended only to cover the initial bitter taste but also to be protracted over the tasting experience (Roger E. Stier, 2007). A two-fold approach was followed: sweetness profiling and flavour creation. The first was achieved using sucralose for initial sweetness burst and monoammonium glycyrrhizinate (MAG) as natural sweetener enhancer. A citrus flavour combining lemon flavour, citric acid and mannitol was studied. The mannitol was added because of the cooling effect that may be used to mitigate the organoleptic effects involving a bitter taste (Rowe et al., 2009; Stier, 2007).

The impact of these flavours on the mechanical properties was not evident for most of the molecules tested. The absence of evidences of influence in these parameters might be related with the complexity of the system. Such complex formulation may demand the preparation of more experiments to obtain more data to be analysed. The components that showed more prominent influence on the mechanical characteristics were the plasticizer (triethyl citrate) and the disintegrant (NaCMC). Both present antagonistic effects, except for

the elongation at break (Figure 40, 1st - 3rd row). Triethyl citrate contributes to a reduce the rigidity of the matrix (Et decrease), in a non-linear way (Figure 40, 3rd column, 1st row) probably by an increase in the free volume between the polymer chains. However, at the same time triethyl citrate seems to increase the film toughness, probably its interposition between the polymer chains contributes to the formation of a more organized structure (Figure 40, 3rd column, 2nd row). NaCMC contributes to increase the Young's modulus (Figure 40, 4th column, 1st row), perhaps due to the augment of charged and long polymer chains. On the other hand, the influence on the tensile strength and elongation is very similar to that of a plasticizer (Figure 40, 4th column, 2nd and 3rd row). This effect may be due to the hygroscopicity of this polymer that promote the absorption of water molecules absorption that is then responsible for this plasticizing effect. In this system, it is showed that PVA may also contribute to a more deformable matrix, as expected (Clariant, 1999). In turn, the PVAc leads to a less resilient structure, probably due to proportional reduction of NaCMC and PVA (Figure 40, 1st column, 2nd row).

Regarding the taste-masking complex, some influences were possible to identify with the design performed (Figure 40, 5th - 9th column, 1st - 3rd row).

MAG seems to have a slight influence on the mechanical properties of the films, especially on their ability to be deformed (Figure 40, 8th column, 3rd row). The MAG used in this system is a MAG-glycerol solution. Previously, it was seen that glycerol contributed to diminish the elongation of the matrix, therefore the similar behaviour observed may be due to its effect. Mannitol seems to influence the rigidity and the hardness of the structure (Figure 40, 5th column, 2nd row). The small molecule of mannitol (Rowe et al., 2009), with several hydroxyl groups, might facilitate its interposition between the polymer chains, enhancing the free volume that contributes to increase the flexibility of the matrix. However, this interposition may occur in a way that, at the same time, a more organized chain orientation and probable chemical bounding would also contribute to harder matrices. The increase of sucralose content also presents a peculiar pattern (Figure 40, 7th column, 1st and 3rd row) with a slight non-linear increase of the matrix rigidity that tends to a plateau for higher sucralose concentrations. At the same time, an increase of elongation is observed. This result could be related with sucralose complex structure with a closed ring structure and chlorine groups.

The flavour exerts a non-linear effect on the matrix deformability (Figure 40, 9th column, 3rd row). Initially contributes to the elongation increase but, above 3%, it seems to decrease this property. Usually, flavours correspond to complex compound mixtures, which may be the reason for observed effect. At low concentrations the interposition of some components in

the matrix contribute to an increase in the free volume between chains and exert its effect as plasticizer, whereas at high concentrations these components begin to have a reverse effect turning the matrix more weak and less robust.

The colourant has a peculiar influence on the polymeric matrix toughness (Figure 40, 10th column, 2nd row). At lower concentrations of pigment it is possible to obtain more flexible films but with the increase of its concentration, the polymeric matrix starts to become harder. This observation is probably related with the insolubility of the colourant used, higher concentrations lead to poor dispersions that contribute to its precipitation within the matrix.

The residual water content has a similar pattern to the previous results (Figure 40, 4th row). The lipophilicity of some molecules, such as triethyl citrate and PVAc, contribute to diminish the residual water content. Their non-polar groups tend to repel the water molecules, contributing for less water absorption. Other components (such as NaCMC, Sucralose, PVA and MAG) contribute to increase the residual water content probably due to their hydrophilic nature. Citric acid does not tend to increase this parameter probably because its hydrophilic groups are not available to absorb water molecules.

Regarding the disintegration time triethyl citrate contributes to fast disintegrating matrices, possibly by the reason already pointed. The NaCMC (super disintegrant) also leads to a decrease of the disintegration time. Additionally, PVA also have a significant impact on this parameter contributing to its decrease. Despite its hydrophilic nature, the observed effect is probably related with the lower proportion of PVAc in the matrix with the PVA increase. The PVAc increase contributes to higher disintegration time, as expected considering its lipophilicity. MAG and citric acid seem to have a strong impact on this property, although with opposite effects. The MAG contributes to boost the matrix disintegration, probably functioning as a channelling agent on the polymeric structure. On the other hand, citric acid exerts a non-linear influence with an increase trend of this parameter. Some authors showed that elevated concentrations of citric acid in polymer structures may lead to free citric acid molecules (non-linked molecules within the matrix). These free molecules are then able interact with other compounds in the formulation even at room temperature. Additionally, it was shown that non-bonded citric acid may react with the hydroxyl groups through time, leading to the formation of esters bonds. These bonds are susceptible to suffer hydrolysis at low pH (Ortega-Toro et al., 2014). Both effects are associated to disintegration time increase through the formation of more hydrophobic component or crystalline structures. The PVA polymer chains are also known to undergo esterification reactions with citric acid, and may

also go through hydrolysis by pH decrease. PVA esterification is commonly used to improve films properties and / or to ameliorate polymers compatibility (Park et al., 2005; Wang et al., 2014). Although, it is not very common at lower temperatures, this type of chemical reactions should not be discarded, considering the limited knowledge of the system under study, and the observation of this chemical reaction during storage at room temperature between HPMC-citric acid (Ortega-Toro et al., 2014). In turn, the higher degree of PVA hydrolysis is probably associated with an increase of crystallinity due to a greater extent of hydrogen bounding (Chanda and Roy, 2006; Koo et al., 2011). This phenomenon is similar to what occurs in the natural unmodified cellulose. The abundant hydrophilic groups, lead to a polymer chain conformation that promotes hydrogen bonding systems increasing tendency to form crystalline aggregates, which are responsible for its insolubility in water (Wertz et al., 2010). Additionally, the pH decrease may also lead to the protonation of the NaCMC, decreasing its hydrophilicity, and consequently slowing the disintegration time (Akar et al., 2012).

The organoleptic evaluation tends to ameliorate with the addition of sweeteners and flavours but becomes worse with increasing amounts of triethyl citrate (Figure 40, 6th row). However, it was shown that sucralose may perform a dual effect on this parameter, but besides triethyl citrate and sucralose, the other components linearly contributed to improve the organoleptic characteristics. The increase of triethyl citrate concentration in the polymeric matrix contributes to enhance the unpleasant taste. Interestingly, sucralose has a non-linear influence in the system: smaller amounts, up to 3% (%w/w per film), contribute to an improvement of the taste, while higher sucralose amounts contribute to unpleasant flavour (Figure 40, 7th column, 6th row). Sucralose is widely used as a sweetening agent in the pharmaceutical industry. It is strongly sweet, approximately 600 times more than sucrose and has no aftertaste (Magnasweet, 2015; Rowe et al., 2009), but it seems to present an upper limit to origin pleasant tasteful films. All the other components have a more linear and slight influence on this parameter (Figure 40, 6th row). Nevertheless, it is observed that mannitol also tend to ameliorate the organoleptic characteristics, which may be associated with its negative heat of solution, sweetness, and 'mouth feel' (Rowe et al., 2009).

Regarding films appearance (Figure 40, 7th row), the most evident influence is associated with the colourant concentration. Its non-linear and abrupt influence on this property is probably related with the usage of an insoluble colourant. At low concentrations it is easy to disperse within the liquid mixture, contributing to improve the films appearance, whereas higher concentrations may lead to deficient dispersions and poor films appearance.

The contact angle presents an interesting pattern varying mainly with the polymers used, PVAc, PVA and NaCMC, with the plasticizer, mannitol and citric acid (Figure 40, 8th row). Oddly, the NaCMC seems to increase the contact angle in this system despite its known hygroscopicity. This result may indicate that the polar groups of NaCMC polymer chains are not available at the surface, which could contribute to the lower contact angles. The PVA and PVAc present a non-linear influence on this parameter but with a trend to increase it with their concentration on the matrix. Up to 50% of PVAc (%w/w per film) it is clear a decrease on the contact angle. Probably above this concentration, the polymer chains disposition do not allow the prevalence of the non-polar groups of PVAc at the matrix surface. Therefore, this polymer matrix rearrangement with more available polar groups on the exterior do not favour the water repelling and smaller contact angles are obtained. Above 50%, the apolar concentration would be sufficiently high to contribute to the increase of the angle between the water drop and the polymeric matrix surface. The PVA and mannitol contribute to higher contact angles (Figure 40, 8th column). Both are known as non-hygroscopic substances, and the influence on this parameter would also be associated with the non-disposition of the polar groups at the matrix surface (Rowe et al., 2009).

The high number of variables tested increased the complexity of the system, which may be the reason for the observed differences obtained for each component that fall outside of the initial prediction. In order to have more details and robust models, more experiments would be required. However, it should be stressed that the formulations tested had organoleptic properties good enough to obtain a final ODF with satisfactory properties.

4.3. Incorporation in the ODF of a drug used in the treatment of Parkinson's disease (PD)

An ODF formulation based on a PVAc-NaCMC-PVA-triethyl citrate with an additional taste masking complex was developed with suitable organoleptic characteristics. In addition, it is also important to evaluate if this system is suitable to embed a drug substance for the treatment of PD and its impact on the properties of the film.

Several formulations were tested and the results are summarized in a profiler graph (Figure 41).

Different amounts of a PD drug were incorporated in the ODF formulation (Table 25, Figure 41). It is interesting to observe the influence of the PD drug in PVAc polymeric matrix. There

is a complex interaction of this between the drug and the polymer matrix (Figure 41). In general all the CQAs evaluated are affected significantly by the PD drug (Pramipexole) incorporated in the matrix. This substance tends to decrease the rigidity, the deformability and the toughness until 20% w/w. However, above this value it starts to have an opposite effect that is the rigidity, toughness and the deformity starts to increase (Figure 41, 7th column). The residual water content increases sharply with the increase in the % of the drug substance, whereas the disintegration time tends to decrease with a particular behaviour. It is observed a short and fast increase of the disintegration time up to 2,5% of Pramipexole, then a fast decrease up to 12% and a small plateau until de 15%, followed by a slight increase up 20% of drug substance. The global appearance of the films had a slightly increase up to 20% of DS incorporation, but tends to worsen sharply for higher amounts.

Regarding the other components, the majority have similar profiles to the other systems DS-free analysed (Figure 41). The higher differences are observed in the PVA, NaCMC and citric acid, which may be related to the higher interaction of these components with the drug substance. Other important feature concerns the ranges that were narrowed in this system, based on the previous screening results. The rigidity and deformability of the film varies in completely different way with NaCMC and in an opposite direction of the drug substance (Figure 41, 4th column). In PVA there are opposite differences when compared to the previous systems regarding lower rigidity and more rigid polymeric matrices (Figure 41, 2nd column). The citric acid presents a completely different behaviour than the previous study (Figure 41, 6th column). This observation may related with the narrow ranges values selected that would influence the pH and the surrounding environment, which may also contribute to the other differences verified.

It is expectable that drug substance incorporated in the film can contribute to the alteration of the matrix behaviour, due chemical interactions. As any other used compound, it was obvious the effect of the DS in the polymeric system, which in this case may be more evident considering the high content used. Additionally, it was already described that Pramipexole tend to modify the polymeric systems characteristics, e.g. the decrease of glass transition temperature (Tg) with the increase of its concentration (Papadimitriou et al., 2008).

5. Conclusions

The overall analyses emphasized, once more, the complexity of the ODFs' formulations and their impact on the properties of the film. However, it was shown that each film, depending on the type and concentration of the excipients, presents unique characteristics. Finally, all the techniques and methodologies of analysis used allowed the generation of an extensive knowledge of this type of formulation that lack in the available literature. This type of know-how is essential for ODF matrix research, development and manufacturing, according to the Quality by Design principles.

Three main conclusions were possible to retrieve from these tests:

- Specific functional excipients have significant effect on the overall polymeric matrix;
- Binary taste-masking complex (sweetener and flavour) allows to obtain ODFs with satisfactory taste;
- There are Complex interactions of the drug substance with the polymeric matrix that may be critical for the ODFs properties.

It was also verified that the addition of pH modifiers may be critical and influence considerably the product characteristics, since parallel reactions may interfere with film performance and chemical stability.

Nonetheless, it is difficult to assume that a single excipient combination can be defined to incorporate any different drug substance. Modifications and adjustments to the formulation composition must be performed for each different DS to incorporate, due to different physic-chemical properties and its specific behaviour in the matrix.

Although these types of studies are laborious and time consuming, they give a deep knowledge of the system and the influence that each component and drug substance may have in the polymer matrix and the film properties. This type of information becomes very useful to predict and overcome eventual problems in the product production and will certainty facilitate the scale-up process.

Finally, a new, soft and tough oral dispersible film with PD DS was developed. However, to evaluate its suitability as an optional drug delivery system, additional *in vitro* (e.g. dissolution, content uniformity, accelerated stability) and *in vivo* (e.g. pharmacokinetic tests) tests should be performed in future work.

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Chapter IV

Product formulation overview and development of an Orodispersible Film (ODF) with a Neurodegenerative Disorder drug

This chapter is focused in the problems and challenges found during the research and development of this new dosage form, in a perspective to discuss and suggest solutions that may allow surpassing similar difficulties

It also reports the development of an oral film for fast oral disintegration, aiming to become suitable and feasible alternative for oral Neurodegenerative Disorder therapy.

Chapter IV.1

Challenges in Oral films by solvent-casting: from research to the product development

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Abstract

The oral films emerged as an alternative dosage form for old and new prescription drugs in the pharmaceutical field. There are relevant advantages of this dosage form, mainly due to its portability, handling and administration easiness. Additionally, from the industrial standpoint it is also favourable, since diverse formulations may allow different bioavailability and pharmacokinetic profiles. Recently, there is a concern to use research and development (R&D) equipments that are similar to the industrial production to avoid some main critical challenges and to facilitate the scale up. Additionally, the Quality by Design (QbD) arose as an assisting approach to facilitate the scale-up process, through the definition of the quality product profile. This includes the delineation of the critical quality attributes (CQAs), which are influenced by the critical process parameters (CPPs). The CQAs include the main characteristics that may interfere with product performance, especially focused on the efficiency and safety. The CPPs are defined based on the process unit operations and the critical attributes previously outlined. A focused overview about oral films preparation and manufacturing challenges is presented and discussed. Furthermore, some suggestions are pointed out but, generally, the correct application of QbD concepts and usage of equivalent manufacturing processes may lead to an efficient and successful scale-transposition.

Keywords

Orodispersible films; scale-up; Quality by Design; critical quality attributes; critical process parameters; quality target product profile; solvent-casting

1. Introduction

The oral route is the most popular and usually the preferred administration route of the patients (Sastry et al., 2000). Recently, orodispersible films (ODF) have gained relevance as a patient centric formulation.

ODF are complex multicomponent matrixes, mainly composed by a plasticized film-forming polymer with additional additives to improve the product performance in terms of patient acceptance / compliance (Borges et al., 2015). Moreover, ODF may be developed in order to obtain different release profiles, to obtain single or multi-layer dosage forms and to achieve gastro-intestinal or mucosal drug absorption (Borges et al., 2015).

Changes in formulation composition including solvents, thickeners, main polymer matrix, pH environment and also the DS may have a significant impact in the dosage form characteristics and performance. For this reason, the influence and variability of the formulation components should be early investigated and understood and a better understanding and more knowledge associated with quality issues, scale up hurdles and other specificities regarding this particular dosage form are fundamental to advance in the development of new products.

Scale-up is commonly defined as the process to increase the batch-size. The control of this process generally demands a deep understanding of the critical quality attributes (CQA) and the critical process parameters (CPP). It is crucial the control of these critical variables, as well as the definition of in process control tests and final product quality control tests in order to obtain a reproducible product with the highest standard of quality (Levin, 2001; Swarbrick and Boylan, 2000).

In this short report, the most critical points to consider during the development of ODF manufactured using the solvent-casting method are reviewed, based on practical experience and literature revision.

2. Formulation variables

Generally, ODFs may be roughly categorized in different types including (Borges et al., 2015; Garg et al., 2010):

- fast disintegrating films;
- non-disintegrating mucoadhesive films;
- slow disintegrating (mucoadhesive) films.

Normally, ODFs are composed by water-soluble polymers matrices and are usually designed to dissolve or disintegrate in the oral cavity. Additionally, the polymeric matrix is also composed by other excipients that may also be critical for the oral film performance, such as plasticizers, fillers, thickeners, pH modifiers and stabilizers (Dixit and Puthli, 2009; Hoffmann et al., 2011).

All excipients used in the formulation should be Generally Regarded as Safe (GRAS) (i.e. GRAS-listed) and should be listed in the FDA Inactive Ingredients list as being used in the same pharmaceutical dosage form if the medicine is intended to get a Marketing Authorization.

The main parameters to consider during the excipients selection and product development are:

- Drug delivery profile (fast or controlled release);
- Drug absorption (local or systemic absorption and mechanism of drug absorption);
- System design (simple or multi-layer, size, thickness, strength, combination with other drug delivery strategies);
- Local tolerability;
- Moisture content;
- Packaging requirements and characteristics;
- Mechanical properties under demanding climate zones (e.g., tropical climates, WHO Zones IVa and IVb).

Also, the proportion between the components cannot be neglected in particular the % of drug load. The % of drug load is dependent on 3 main factors:

- minimal amount (%w/w) of polymer required to create a matrix with appropriate mechanical strength;
- % w/v of polymers in the coating suspension, which is limited by the desired viscosity range.
- Drug / excipients interactions.

2.1. Polymers

The ideal properties of the film forming polymer are: film-forming ability, safe and non-irritant, without leachable impurities, good wetting and spreadability, acceptable peel / shear / mechanical properties and inexpensive to manufacture and package.

Since the film-forming polymer has a significant impact the product's performance (mechanical strength, disintegration time, stability, compatibility / miscibility with the drug substance), all the polymer characteristics must be considered, from its chemical nature to single and slight modifications of polymer's molecular weight, during the selection process.

2.2. Plasticizers

Many polymers used form rigid and brittle matrix which require the addition of plasticizers. These additives are essential to provide flexibility, appropriate tensile properties and also to ensure an acceptable texture. Oral films should be tough enough to avoid damages while manufacturing, packaging, handling and during transportation. Nevertheless, inappropriate use of plasticizers may lead to film cracking, splitting and peeling. Additionally, it is important to consider that the plasticizer type may also influence the disintegration time, the drug absorption rate, the water absorption capacity and the final product stability.

2.3. Additives

Depending on the Quality Target Product Profile (QTPP) different additives may be necessary in order to achieve the desired product performance. For example, disintegrants can be used to reduce the disintegration time of the final product(Garg et al., 2010) and cross-linked and / or swellable polymers may be used to delay the drug substance release.

The pH modifiers may be incorporated for several reasons including stability improvement, promotion of specific pH environments related with drug release and / or drug absorption, enhancement of organoleptic or to control / fine-tune the extent of the drug substance absorption. That is the case in Suboxone® sublingual film and in the fast-onset sublingual bilayer film from Cynapsus Therapeutics (Borges et al., 2015; Myers et al., 2011; Silva et al., 2015). In the first product, a specific buffer system is used to maintain a local pH environment that ensures appropriate buprenorphine absorption while reducing for the mucosal absorption of naloxone. In the case of the Cynapsus technology, the pH modifier is used to deionize the Apomorphine and, in this way, promote its mucosal absorption (Myers et al., 2011; Silva et al., 2015). Moreover, pH modifier substances may be used to mask unpleasant tastes or promote fast disintegration profiles through saliva stimulation (Dixit and Puthli, 2009). Acidic substances, such as citric acid, may be used as saliva stimulant agents and to mask bitter tastes (Marriott, 2010).

Taste masking complexes, based on sweeteners, flavours and coating or competitors taste receptors substances (Stier, 2007) should be used. Although it may increase the formulation complexity, the product's residence time in the oral cavity demands ODF with pleasant taste and good mouthfeel. This aspect becomes critical considering that a high number of DS have bitter taste. For ODF, liquid flavours should be preferentially used rather than powder flavours to avoid its sedimentation that may originate poor film appearance and texture and may induce disruption of particles during drying.

Some drug substances, depending on their chemical characteristics, may need stabilizers such as surfactants or pH modifier agents, to achieve an appropriate shelf-life.

It should also be considered that not all drugs can be incorporated into this dosage form, smaller and potent drugs are preferred, since the loading capacity and cross-sectional area available are limited. Additionally, physicochemical properties of the DS should be critically evaluated, including: heat and shear sensitivity (but may not be a critical factor) (Garg et al., 2010), polymorphic form, stability at the local pH, compatibility with solvent and other excipients and non-irritant to the mucosa.

2.4. Manufacturing process

The additives added to the formulation may not only be critical to the product performance, but also to the processing method. There are two main manufacturing processes used to prepare oral films, solvent casting and hot-melt extrusion (HME), but valuing the experimental practice only the first method will be addressed (Borges et al., 2015).

Solvent-casting involves the preparation of liquid mixtures in which some thickeners, gelling agents, fillers and / or thixotropic agents may be added, to stabilize and or to give enough consistency / density to the liquid mixture. Viscosity must be high enough to avoid the precipitation of suspended solids during liquid preparation and coating operation, essential to achieve uniformity of drug content. On the other hand, the viscosity should not be too high to avoid mixing problems and film defects due to poor spreadability.

3. Process variables

Oral films preparation involves several unit operations (see table 29) and vary depending on the manufacturing process used. Nevertheless, the DS and excipients are usually dissolved or dispersed in a liquid and the final liquid mixture is then coated on a platform substrate (commonly designed by release liner) to be dried. Normally, in oral films this release liner is removed before packaging and is not used as backing layer like in the case of transdermal drug delivery systems. However, the development of multilayer ODFs is common, and in this case the one-layer coated release liner can be used again as raw material for another casting before punching and pouching.

In each unit operation some key variables must be controlled and specific parameters determined (quantification / measure to access control). Some are summarized in table 29. Considering the industrial process perspective the unique manufacturing method of the oral films may be advantageous, but from the development perspective the singular manufacturing process may become challenging (Garg et al., 2010).

In sum, the oral films manufacturing process might include the following steps:

- Preparation of the liquid mixture,
- Coating or casting process,
- Drying,
- Cutting,
- Packaging.

3.1. Liquid mixture

The preparation of the liquid mixture is more complex and challenging than it could seem at a first glance. Firstly, the components of the mixture, including the solvents, need to be well characterized to predict and easily understand the impact that each may have on the system performance. In the same way, their interaction (e.g. compatibility, solubility) should also be considered since it is likely the possible occurrence of chemical interaction. Therefore, the individual components may start to behave as mixture with singular properties and characteristics (e.g. eutectic mixtures, crystallization, gel structures) due to specific modifications (e.g. plasticization, cross-linking, hydration, (de)protonation, gelification) that could have significant impact on product performance (e.g. drug release, swelling, adhesion,

tensile strength). On the other hand, the preparation method parameters may also influence greatly the mixture characteristics which are summarized in table 29.

Table 29 - Oral films manufacturing process summary by unit operation. The critical process parameters (CPPs) are identified.

Unit operation	Critical Process Parameters (CPPs)		CQAs of output materials	Challenges
Mixture	mixing type	· mechanical · magnetic stirring	· drug content · homogeneity	· shear stress · correct formulation ratio
	mixing conditions	· temperature · time · speed	· viscosity · solids content · flowability	· excipients incompatibility · air bubbles inside the mixture · agglomerates
	mixing device	· mixer or homogenizer		· homogeneity
	mixture accessory head and blade	· shape, design, size (e.g. propeller, U-paddle)		
	mixture vessel	· shape · size · occupancy		
	components	· polymer hydration · order of addition · proportion · inherent characteristics · compatibility		
Casting	speed		· appearance · coat weight per unit area · coat uniformity	· drug loss · excipient loss · air entrapment
	feeding	· speed, nozzle characteristics		· control of film thickness
	micrometer accuracy	· gap height precision		
	release liner	· coating mass and dried film adherence, interaction, compatibility		
Drying	air temperature air circulation line speed time		· residual solvents · impurities profile	· moisture control · water activity · film thickness
	type	gradual or continuous		
Cut	degree of precision		· dimensional accuracy · appearance · unit weight variation	· yield · roll tension · storage time effect
	die	shape, size		· defects detection
	pressure			· pouch integrity
Package	type	single- or multi-unit	· external conditions tolerability	· stability · shelf life · target market · moisture control
	material	composition, number of layers		· selection of the appropriate container

The liquid mixture parameters are very important and should be tightly controlled. Depending on the conditions (e.g. pH, order and velocity of addition) there are some chemical and/or physical interactions that may be favoured as well as molecular modifications. It is also important to have a tight control of room's temperature and moisture in the manufacturing area to prevent their incorporation into the product and avoid possible interferences that might impact on the final product quality attributes.

3.2. Casting and drying

The casting process is a critical step in ODF manufacturing process, since the initial coating mass feeding (e.g. speed, nozzle characteristics) to the selection of the film substrate (release liner). The release liner should allow the formation of an optimal web in order to avoid delamination during handling and, at the same time, allow its easy separation prior to packaging. The micrometer precision, which promotes the coating mass spreadability, has a direct impact in the DS dose accuracy since the oral films weight and strength are generally low. The speed of casting should be optimal to assure appropriate levels for commercial-scale throughput and obtain thickness uniformity. In addition, the thickness of the coated mass and the physicochemical properties of the liquid mixture affect the scale-up by limiting the drying speed of product and final thickness of the dried film. These properties should be carefully adjusted to enable efficient commercial scale production.

The type of drying process also affects the final product performance. The dryness could be performed from the bottom, from the top or both, depending on the machine used. Therefore, the parameters adjustment should be performed according to type of equipment, the minimum-film-forming-temperature of the liquid mixture developed and thermal stability of its components. If necessary, the drying time can be shorten by incorporating extra dryers into the line and by temperature gradients along the process.

3.3. Cutting and Package

The oral films should be cut and packed immediately, ideally right after its preparation. If this is not possible, the casted and dried film should be properly conditioned in specific rooms with controlled and monitored conditions. The packaging of the oral films may be done in single-unit or multiple-unit dosage packaging. The majority of the Rx products are in single unit packaging, usually in individual pouches, to ensure higher product stability, being more suitable for severe climate zones. Curiously, the multiple dose packaging tends to be more expensive to develop but it is less expensive to manufacture in large quantities (Garg et al., 2010). Nevertheless, it demands the use of a more robust secondary package to provide larger shelf life stability, until the first-opening. Still, the product stability during usage becomes more critical with the multi dosage packaging. (Garg et al., 2010). The packaging container should have suitable mechanical strength to protect the film during shipping and it has to provide protection from external factors such as temperature and moisture. Therefore, the selection of the type of packaging material and their specific characteristics should not be neglected. The packaging could be critical for product stability and should be treated as part of the formulation.

Although there is no specific guidance for the parameters discussed above, their control is important, since the working components are usually hygroscopic. Therefore, companies are increasingly adopting continuous-coating equipment and dryers in their research and development (R&D) laboratories that are similar to the commercial scale production technology. This strategy allows the proper simulation of the process and turns easier the later scale-up. Moreover, it allows the initial interplay with machine controllers that give the necessary information for high-capacity production. In fact, the major challenges of switching from R&D to commercial-scale production generally results from coating speeds and drying operations (Greb, 2009).

In resume, the manufacturing techniques must be deeply understood and exceptionally tight tolerances through the process should be established, in such way that the scale-up would not be more challenging compared to other conventional dosage forms.

4. In vitro tests for Oral films

In vitro tests are important tools to guide the product development, for quality control of the final product and to study the product stability. These tests may also be used as *in process control* (IPC) for process monitoring and control and / or alternatively as integrant part of the *Process Analytical Technology* (PAT) (De Beer et al., 2011). These tests may be differentiated in physical, mechanical, and chemical characterization and the number os tests used depend on the product's development stage, formulation type (e.g. orodispersible, mucoadhesive, single- or multilayer) and the characterization purpose. The physical tests usually include size, shape, appearance, weight and thickness. The mechanical characterization usually includes tensile strength, % of elongation, Young's modulus (Preis et al., 2014) and might be completed with additional determinations of tear resistance, fold endurance and peel strength (Dixit and Puthli, 2009; Garg et al., 2010). The chemical evaluation could include swelling index, bioadhesion, drug release / permeation, dissolution profile, drug content uniformity, impurities content, residual water content, disintegration time, thermal stability and components compatibility (Garg et al., 2010).

It is important to consider that good experimental data require a proper number of replicates. Additionally, the delineation of algorithms to confirm properties determinations and predict toxicity, bioactivity, safety and efficacy assessments could be developed and used (Garg et al., 2010). The *in vitro* release and / or *in vitro* absorption (when applicable) should be used to evaluate probable correlations with *in vivo* bioavailability.

Finally, the success of the products development may be related with detailed characterization. On this matter, in early stages, a careful characterization should be performed to gain a broad knowledge of the system, but in a later stage only the most critical and representative are possible to carry out as routine procedure (Garg et al., 2010).

5. Summary

Due to the complexity of ODF drug delivery systems several points must be considered during product development. During the scale-up, adjustments in the percentage of the different compounds may be made in order to maintain the products stability and performance. During the development, it should be clearly distinguished and identified the excipients that have minor impact and those that are critical for the product quality and performance. The operational ranges should be defined for all the components of the formulation. The operational ranges must be outlined by experimental data showing the impact and effects of any change and its effecton the CQA or CPP (e.g. mechanical properties, disintegration time, residual water content, crystallinity, solubility, adhesion, dissolution profile, stability). In this line, the Quality by Design (QbD) emerged as an optimal approach to predict the product's quality, performance and stability.

The most common tool used in the QbD is the description of a quality target product profile (QTPP) that includes all the dosage form characteristics (e.g. route of administration, strength, therapeutic application, drug release profile, pharmacokinetics), the characterization of the CQAs and the CPPs (Rathore and Winkle, 2009; Visser et al., 2015). The CQAs may be resumed as the characteristics that define the product quality, whereas the CPPs are the process variables that could influence these characteristics (Rathore and Winkle, 2009). In table 30 a generic resume of a possible QTPP for an oral film is presented and possible CQAs are listed and explained by critical level in table 31. In turn, the CPPs are discriminated in table 29.

Table 30 - Quality Target product profile (QTPP) for an oral film. OTR, oxygen transmission rate. WTR, water transmission rate**.**

Features	Target	Observations
Dosage form	Oral Film	
Dosage form design	Fast or slow disintegration Single- or multi-layer Sublingual / Mucoadhesive	
Route of administration	Oral – systemic, local or through GI	
Pharmacokinetics	Drug release profile: Immediate Controlled / delayed	Meet the reference characteristics (if applicable)
Dimensions / shape	25-40 mm in length and 20-30 mm in width (stamp size) Rectangular /square / round film	
Dry thickness	50 – 200 µm	
Unit weight	≤ 150 mg	
Dosage strength	0.01 up to 60%, %w/w per film	It should have the same strength as the reference (if applicable) New manufacturing technologies or formulations may allow higher % per film
Upper limit for drug loading	Usually 60-80 mg (max. 120 mg)	
Oral disintegration/dissolution	< 30 s for orodispersible films > 30-60 s for others	
Stability / shelf life in package	At least 24-month shelf-life at room temperature	Ideally equivalent to or better than the reference
Container closure system	Triple laminated aluminum child resistant pouch	Needed to achieve the target shelf-life Preferentially with Low OTR and WTR
Administration / Accordance with labeling	Therapeutically target Indications to correct use	Pharmaceutical equivalence requirement

In-process and / or in-real-time control may be used during the manufacturing as an assurance mechanism of finish product consistency and reproducibility. The use of PAT tools allows the manufacturing control in real-time on the identified CPPs during a specific or across the span of unit-operations of the process. Therefore, the PAT tools can be used as part of the quality control strategy for the manufacturing process if the impact of the CPPs on the CQAs is already understood (Çelik, 2011).

Table 31 - Critical quality attributes for an oral film.

CQA	Target	Critical level	Rationale
Appearance	Suitable color and shape No visual film defects Ensure patient acceptability	Low	Not directly linked to safety and efficacy
Odor	No unpleasant odor	Medium	
Size	Suitable for the site application and target population	Low	For ease of administration to oral cavity
Flavor and taste	No unpleasant taste Suitable for the target population	Medium	May influence patient compliance
Disintegration time	Suitable for the therapeutically target Appropriate to the application site	High	May have direct impact in the safety and efficacy due to the onset action
Assay	Must comply with pharmacopoeia specification 100 % (95-105%) %w/w per film	High	May have direct impact in the safety and efficacy due to the inaccuracy of dosage
Uniformity of weight and content	Must comply with pharmacopoeia specification	High	
Dissolution profile	Should be characterized and defined according to the therapeutically target and application site	High	May have direct impact in the safety and efficacy due to influences in the products' bioavailability
Degradation products	Must comply with pharmacopoeia specification or ICH requirements	High	May have direct impact in the safety and efficacy due to the presence of
Residual water content	Should be defined according to the system characteristics	High	The water content may interfere with the product performance May alter the stability and the physical characteristics of the film
Mechanical Properties	Suitable properties to handle and process Should be defined according to the system characteristics	High	Unappropriated mechanical properties may lead to films that may easily break or may difficult the cut and packaging

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Chapter IV.2

Development of an orodispersible film (ODF) containing a drug: neurodegenerative disorder unmet therapeutic need

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This chapter is presented separately for confidentiality reasons.

Main conclusions and Future perspectives

Chapter I: Introduction to the Oral Films concept

Oral films are a relatively new and very promising drug delivery system. Their versatility offer future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets. Although, it is already included in the Pharmacopeias, there is still a lack of information regarding their development, characterization and quality features.

Chapter II: Oral Films Characterization and Critical Quality attributes outline

The results showed that the multivariate analysis may be very useful to generate wide formulation knowledge essential for ODF matrix development. It was also clear that the complex composition of the ODFs makes their characterization and standardization very challenging. In this thesis, it is demonstrated the high importance of each excipient in the ODF matrix and also highlighted their inter-dependence and interaction. Moreover, it was seen that the manufacturing process should be deeply known and carefully controlled, since slight variation in the process parameters may also influence the polymeric matrix rearrangement and product properties.

Thermo-mechanical analysis was also found very useful to generate relevant data to the development of new oral films platforms. The TGA may be very useful to predict the formulations stability, whereas the DSC analyses allow retrieving relevant information about some components interactions and behavior in the polymeric matrix. In turn, DMTA evaluation was very helpful to obtain additional information about matrix-composition and product properties, especially to understand the performance, stability behavior and some quality attributes of the product.

The second approach of this chapter allowed defining a range of acceptable values for the CQAs that could be used as acceptance criteria for the development of new oral film formulations.

In sum, during the development of oral film systems each excipient property should not be considered individually, since complex interactions may occur and each component may function as a fingerprint in the polymeric matrix. The characterization and analysis techniques appeared as a suitable approach to provide a mechanistic understanding of the relationship between raw material attributes and critical quality attributes of the pharmaceutical product. Nevertheless, based on a pre-defined polymeric matrix composition, optimization tests should be performed in order to define less broad acceptance criteria for each formulation aiming obtain a desirable and robust oral film.

Chapter III: Hydrophobic polymers for oral films: Development and Optimization of novel formulations

The results of the present thesis revealed the successful design of ODFs based on hydrophobic polymers with fast disintegration. Three different formulations with a similar pattern (a hydrophobic polymer, a stabilizer, a disintegrant and a plasticizer) were developed. These could be posteriorly optimized and used to embed drug substances for oral delivery.

It was also demonstrated, once more, that each film depending on the type and concentration of the excipients, presents unique characteristics. In fact, specific functional excipients and complex interactions of the drug substance could have significant effect on the overall product's performance. Therefore, it may be presumed that each film may be designed with singular and focused specific desirable target (e.g fast / slow disintegration, mucoadhesive) depending mainly on the excipients, proportions and possibly processing parameters.

Nonetheless, it is difficult to assume that a single excipient combination can be defined to incorporate any different drug substance, some adjustments would be necessary due to different physico-chemical properties and peculiar behavior within the matrix.

This work also revealed that the initial usage of QbD principles and tools may be laborious but rewarding. The use of specific statistical platforms such as the Design of Experiments

was very useful for initial screening and optimization. This methodology of analysis allowed the generation of an extensive know-how essential for ODF matrix research, development and manufacturing. Moreover, this type of information is very scarce in the literature.

Finally, this data becomes very useful to predict and overcome eventual problems in the product production and will certainty facilitate the scale-up process.

Chapter IV: Product formulation overview and development of an Orodispersible Film (ODF) with a Neurodegenerative Disorder drug

Finally, the work of the present thesis allowed obtaining a stable ND drug ODF, apparently with good uniformity and fast oral disintegration. This constitutes an alternative for MS patients with swallowing issues, being helpful to ameliorate patients' compliance and life's quality.

This thesis work also endorses the major challenges of the solvent casting, mainly focused in the liquid mixture preparation and process parameters. The main issues are pointed, critically discussed and circumvent alternatives or solutions were suggested.

Future perspectives

Numerous features regarding characterization (by several methods and distinct analysis), formulation development (based on QbD tools) and final product production (including stability and a small scale-up tests) were discriminated in this thesis.

The oral films market is an emergent area, a newborn field that still needs to be spread and be more explored. Additionally, it is notorious some unawareness or probably some reluctance of European consumers regarding the usage of this dosage form. Therefore, it is important that the oral films technology breakthrough the health market, probably through a properly caregivers' approach, which may incite and easily gain consumers acceptance. Eventually, it would only be necessary to evidence properly their peculiar valuable advantages as portable and exceptionally convenient pharmaceutical form.

There is a need to surpass some technical, manufacturing and regulatory barriers to avoid the downturn growth of the oral film's market. The correct application of the QbD approach, as well as, the specific characterization and analysis techniques may be helpful for this goal. This thesis aimed to propose the application of potential characterization tests and statistical tools that may be used to evaluate available products and support the development of new oral films. Thus, it is highlighted the crucial need of standardized procedures and reliable guidelines to promote a more efficient and feasible development, processing and quality evaluation.

Considering formulation development it is expected that some common guidance may be outlined to facilitate the technical hurdles. Regarding product performance, hopefully, in a near future, it is expected to have defined and standardized solutions for the mechanical strength evaluation, suitable and consistent methods / equipment for disintegration and dissolution evaluation. In time, it would also be needed the development of reliable and standard adhesive testing techniques (e.g novel synthetic material, new equipment accessories – Texture analyzer) and organoleptic assessment test (e.g. electronic tongues).

The demand side for pharmaceutical treatments has been changing and nowadays the approach is more patient-centered and quality- based. One of the main goals of this thesis was to develop successfully an ODF that could meet and fulfil specific patients' needs. This objective was materialized by the conception of one ODF product that answers an unmet therapeutic need, which expectably could be soon on the market; and hopefully would be the first of many.