Filipa Vaz de Carvalho Alves

PREPARATION AND CHARACTERIZATION OF ORODISPERSIBLE FILMS

Master thesis in Pharmaceutical Biotechnology, supervised by Dr Jorge Coelho and by Dr. Sérgio Simões, submitted to the Faculty of Pharmacy of the University of Coimbra.

July 2013

UNIVERSIDADE DE COIMBRA

ACKNOWLEDGMENTS

I would like to thank to my supervisor, Dr Jorge Coelho, for his guidance and support, expertise and availability throughout this work.

Special thanks to Dr. Sérgio Simões for the great opportunity and to whom I am truly indebted.

I would like to give particular thanks to everyone in the lab for the help and support. Ana Borges, Cátia Costa e Branca Silva, many thanks for all the time you spend, for your friendship and availability.

Thank you, Rui for your love. Thank you for your never-ending support, for your patient and motivation during the most difficult times.

To all my friends, because this thesis is the culmination of an academic journey that would not be the same without your friendship. Vanda, Maria João, Luís, Patrícia, Inês, Sara, Licas, Carlinha, Beto and João, to everyone from Spreita: Alex, Pedro, Artur, and Christian. A special thank to all of you.

To my brother Eduardo thanks for being a wonderful friend. And finally but not at least, I would like to thank my parents for all the support and encouragement through these years and to whom I owe everything I've accomplished.

ABSTRACT

In order to achieve maximum patient compliance, pharmaceutical companies have directed their research to the development of innovative delivery systems. As this matter, oral films have been claimed as one of the most promising approaches as a new drug delivery for oral administration, showing great interest and a market opportunity.

As a relatively new pharmaceutical form, there is a lack of information and available studies concerning this technology. Therefore, it is extremely important to investigate the characteristics of commercially available oral films, which can provide essential information to the development of a new product. The main goal of this project was the chemical, thermal and mechanical characterization of two oral films available in the market: Listerine from Pfizer and Gas-X from Novartis.

The characterization of the films was carried out using different techniques: chemical characterization, by FTIR analysis; thermal characterization by TGA, DSC and DMTA; mechanical properties, by tensile tests. Other important characteristics, such as disintegration time and water content were also evaluated.

In order to understand the relationship between the composition, preparation procedures and the final properties of films, an attempt to reproduce Listerine and Gas-X was carried out. Throughout this work, methodologies for characterization of films were established and some relevant conclusions were taken. On the matter, it was possible to develop a formulation with higher similarity to commercial available film (Listerine), which is extremely relevant in the contribution to the development of new technologies for oral films.

The results presented in Listerine revealed the importance of the formulation used in the properties of the oral films.

RESUMO

Muitas indústrias farmacêuticas têm direcionado a sua área de investigação para o desenvolvimento de novos sistemas de entrega de fármacos inovadores. Desta forma, e devido às inúmeras vantagens inerentes a esta tecnologia, os filmes orais têm sido apontados como uma das abordagens mais promissoras como novo sistema para administração oral, revelando-se de grande interesse como oportunidade de mercado.

Sendo uma nova forma farmacêutica, há uma falta de informação disponível e os estudos incidentes sobre este tema são muito limitados e pouco desenvolvidos. Deste modo, é extremamente importante procurar investigar as características dos filmes orais comercialmente disponíveis. Esta informação é fundamental para o desenvolvimento de novas aplicações e tecnologias de administração oral.

O principal objectivo deste trabalho é a caracterização química, térmica e mecânica de dois filmes orais disponíveis actualmente no mercado: Listerine produzido pela Pzifer, e o Gas-X desenvolvido pela Novartis.

A caracterização dos filmes foi realizada recorrendo a diversas técnicas. Caracterização química por análise de FTIR; caracterização térmica por TGA, DSC e DMTA; e caracterização mecânica por testes de tracção. Outras características importantes foram também avaliadas, nomeadamente, o tempo de desintegração dos filmes e o conteúdo de água residual.

De forma a compreender a relação entre a composição, preparação e as propriedades finais dos filmes, procedeu-se a uma tentativa de reprodução dos filmes comerciais Listerine e Gas-X. Ao longo deste trabalho, foram desenvolvidas e estabelecidas metodologias para a caracterização de filmes orais, o que permitiu obter conclusões muito relevantes não só ao nível da influência de excipientes nas propriedades. Na verdade, conseguiu-se obter um filme com grande semelhança ao comercial (Listerine), o que se revela uma mais valia e contribuição para o desenvolvimento de novas tecnologias de filmes orais.

Os resultados apresentados para o Listerine revelam a importância da formulação nas propriedades dos filmes orais.

LIST OF ACRONYMS

API	Active Pharmaceutical Ingredient
ATR	Attenuated Total Reflectance
DMTA	Dynamic Mechanical Thermal Analysis
DTG	Differential Thermogravimetric Analysis
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
E_t	Young's modulus
E'	Elastic modulus
E"	Loss modulus
FDA	Food and Drug Administration
FTIR	Fourier Transform Infrared Spectroscopy
Tan δ	Damping
T_g	Glass Transition Temperature
T_{onset}	Extrapolated T_{onset} Temperature
HPMC	Hydropropyl Methylcellulose, Hypromellose
IR	Infrared
MDX	Maltodextrin
PEG	Polyethylene Glycol
TGA	Thermogravimetric Analysis
UTS	Ultimate Tensile Strength
α	Thermal Transition
β	Thermal Transition
γ	Thermal Transition
ε_B	Elongation
σ_B	Tensile stress at break

CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION

1.1 Oral administration

Due to its ease access and robustness against local stress, oral route is the most preferable way of administration for the general population. Although it is a convenient and flexible route for patients, when administrated in oral cavity, drugs are susceptible of enzymatic degradation and pH variation along the digestive process. Therefore, drugs bioavailability is decreased and high doses of active principle are required to compensate this gap (Mujoriya et. al., 2011; Morales et. al., 2011).

Buccal mucosa has demonstrated an excellent platform for absorption of molecules that have poor dermal penetration, since oral route's permeability is greater than that in the skin by approximately 4-4000 times (Dixit et. al., 2009). On the other hand, besides the greater bioavailability, intestinal epithelium has a larger permeability when compared to buccal mucosa. Because of this, research has been directed to the use of permeation enhancers in order to improve the permeation characteristics of the drug and a large investment has been made in the development of new oral dosage forms, which can lead to eliminate this limitation (Morales et. al., 2011).

To overcome these and other problems associated with patients' compliance, several fast-dissolving drug delivery systems are being developed. Most recently, oral strip technology has been claimed as one of the most promising approaches as a new drug delivery system for oral administration.

Besides being a non-invasive system, oral strips have become an important technology for the application of active pharmaceutical ingredients (API) that are disposed to high level of degradation in the gastrointestinal tract (Dixit et. al., 2009). Drugs can be directly absorbed and then first-hepatic metabolism can be bypassed and stomach's acidic environment can be avoided. Consequently, efficacy and safety profile of the therapeutic agent can be enhanced and bioavailability can be improved. The latter results in the use of lower doses and improved clinical performance through a reduction of side effects (Prajapati et. al., 2009; Garsuch et. al., 2009).

1.2 Oral Strip Technology

In order to achieve maximum patient compliance, many pharmaceutical companies have directed their research to the development of innovative and suitable delivery systems. Hence, oral strips are gaining the interest of these companies due to more flexibility and comfort for patients.

Orodispersible films were introduced in 1970's and have emerged as an advanced alternative to the traditional tablets, capsules and syrups, since this oral forms require swallowing (Mishra et. al., 2011). Pfizer introduced Listerine® PocketPaks in 2001 as the first thin strip for breath freshening. However, only nine years after the first oral film in the market, Zuplenz® was approved in US as the first film accepted for prescription, followed by several (Hoffmann et. al, 2011).

This delivery system consists on a very thin film prepared using hydrophilic polymers and other excipients, which undergo disintegration in the salivary fluids in less than a minute, where the API is released. According to regulatory aspects, all the excipients used in the formulation of oral films should be approved for use in oral pharmaceutical dosage forms. Furthermore, should be Generally Regarded as Safe, i.e. GRAS listed, according to Food and Drug Administration (FDA) (Ravneet et. al., 2012; Dixit et. al., 2009; Mahajan et. al., 2011).

The main advantage of oral strips administration is the rapid dissolution on the oral cavity, without the need of water or chewing. Consequently, geriatric, pediatric and psychiatric patients are the most prone groups for this recent technology, since these patients have special drug administration requirements, e.g. they experience difficulties swallowing traditional oral solid forms. Bedridden, patients with persistent nausea, patients suffering from dysphagia and Parkinson's disease or travelling people are also candidates that can take advantages of this technology.

This technology presents no risks of chocking or suffocation, thus providing improved safety and patient compliance. Furthermore, intake of the films is very discreet due to its excellent musoadhesion, and bioavailability is significantly greater than those observed from conventional tablet dosage form (Siddiqui et. al., 2011; Mahajan et. al., 2011).

Orodispersible films have become very promising in oral drug delivery, facing the traditional oral forms in the market. In spite of dose uniformity is a technical challenge, oral strips offer the convenience of administration and accurate dosing when compared to liquid formulations such as drops or syrups (Arya et. al., 2010).

The greater disadvantage inherent to this technology is the amount of drug that can be incorporated into the strip. High doses of drugs are difficult to formulate into oral films (Hoffmann et. al., 2011). However, researchers have proven that concentration level of API can extend up to 50% per dose weight. Actually, Novartis Consumer Health's Gas-X® thin film has a loading of 62.5mg of API, which corresponds to approximately 60% of the film (Dixit et. al., 2009; Siddiqu et. al., 2011).

As most of the drugs are unpalatable, bitter drugs should be avoided or taste masking is required to improve patient compliance (Siddiqui et. al., 2011).

Due to its hygroscopic nature, this product requires an extra care during consumer handling and storage, since it has a high sensitivity to environmental conditions, namely temperature and moisture (Prajapati et. al., 2009).

1.2.1 Composition

The formulation of oral strips includes a polymer as the essential ingredient for film formation. The other crucial excipients that should be present in its formulation, apart from API and polymer, include film stabilizing agents, plasticizers, sweeteners, flavours and colours, and saliva stimulating agents.

Either alone or in combination to obtain the desired film properties, polymers are used in the preparation of oral strips. As the most essential component of these films, at least 45% of this excipient should be present on total weight (Dixit et. al., 2009). However, typically 60 to 65%w/w are preferred to obtain desired properties (Nagar et. al., 2011).

One of the most critical and important parameter for the success of the development of film formulation is the selection of the polymer. In fact, a right choice in the selection of film formation can lead to improvements in some characteristics of oral films as hydrophilicity, flexibility, mouth feel and solubility (Ravneet et. al., 2012).

Since the primary use of oral disintegrating films relies on their disintegration in saliva, polymers should solubilize on water very easily. Therefore, it is required the use of hydrophilic polymers that will form a strong non covalent bond with the mucin molecules/epithelial surface in the buccal mucosa (Morales et. al., 2011; Mujoriya et. al., 2011).

Polymers employed in oral film preparation should not retard disintegration time of film (Nagar et. al., 2011). In fact, polymers with lower molecular weight dissolve quicker, whereas using a higher molecular weight polymer results in films with better mechanical properties (Hoffmann et. al., 2011). On this matter, it is important to find an optimum comprise between the mechanical properties and the time required for dissolution.

The polymer used in oral strip formulation should be non-toxic, non-irritant, devoid of impurities, should not cause secondary infections in the oral mucosa or dental regions. The strip robustness and stiffness depends on the type of polymer and the amount in the formulation. As referred lately, the final product should be tough enough avoiding extra care during consumer handling and during transportation (Ravneet et. al., 2012).

Another important issue is the cost of the polymers used, which requires that polymers have to be available in large-scale production at an affordable cost.

Presently, both natural and synthetic polymers are used for preparation of fast dissolving oral film. Pullulan, starches and modified starches, gelatin or maltodextrin are some of the natural polymers used in development of strip formulations. On the other hand, hydropropyl methylcellulose (HPMC) and kollicoat are examples of synthetic polymers commonly used (Nagar et al., 2011).

Plasticizer has been reported as a critical excipient that affects mechanical properties of oral strips, such as tensile strength and elongation (Siddiqui et. al., 2011).

The relation between the amount of plasticizer and mechanical properties is dependent on the volatile nature plasticizer and the type of interaction with the polymer backbone. In fact, this excipient interacts with film forming polymers by reducing the glass transition temperature and thereby improving flexibility of the final product. Therefore, selection of the proper plasticizer relies on compatibility with the polymer and also the type of the solvent employed in film's casting. In certain cases, drug molecules themselves can act as a plasticizer (Kumar et. al., 2010).

High concentrations of plasticizers or inappropriate use may result in film cracking, splitting and peeling of the strip. Furthermore, the use of this excipient may affect the solubility of API and the absorption rate of the drug. On the other hand, whereas the brittleness of the films is reduced, the flexibility is improved (Dixit et. al., 2009; Hoffmann et. al., 2011).

Any active pharmaceutical ingredient that can be administered orally or through the buccal mucosa is good candidate for film formulation. However, potent drugs that have high first

pass metabolism and patient non-compliant are the favourites to incorporate onto oral strips. Furthermore, because the drug loading is limited, high potency low-dose drugs are deserved (Mahajan et. al., 2011).

As referred lately, the use of taste masking excipient is often essential since many API have an unpleasant taste. Nevertheless, depending on API physical state in the film and its solubility in saliva, different methods can be used to improve palatability of the formulation. The simplest technique is called obscuration technique and involves the addition of excipients with pleasurable taste, namely flavours or sweeteners. On the other hand, complexation, encapsulation and polymeric coating can be used as barrier methods. The type and the amount of the agents can affect disintegration time, stability and mechanical properties (Dixit et. al., 2009; Hoffmann et.al, 2011).

All these taste-masking techniques affect maximum drug load, hence the rate of drug release varies. Therefore, the selection of the taste-masking agents should be done carefully for each individual case and drug.

In the therapy of paediatric patients, if the formulation is too sweet and too pleasurable like a candy, there is a potential risk for overdosing (Hoffmann et. al., 2011). Consequently, the use of sweeting agents needs to be restricted and carefully evaluated, not only for paediatric population, but also for diabetic patients and people with overweight problems. On this matter, artificial sweeteners have gained popularity in pharmaceutical preparations. Indeed, multiple artificial sweeteners do not contribute to dental caries and required lower concentrations when compared to natural sugars (Dixit et. al., 2009).

In order to improve patient compliant, flavours approved by FDA can also be added to films formulation, alone or in combination. Synthetic flavour oils like peppermint and cinnamon, or fruit essences like apple, cherry and pineapple are some examples of flavours used in oral films. The flavour perception it is an individual feeling, depending upon different factors. Also, the selection of this excipient depends on the type of drug incorporated in formulation and its amount depends on the flavour type and strength.

For the films administration acceptability, Brown (2003) showed that taste and mouth-feel are more important than short disintegration times. However, it is a fact that disintegration rates are a crucial factor in oral strip final product. One strategy to enhance the disintegration rates is based on the use of excipients to improve salivation. As a matter of fact, the purpose of using saliva-stimulating agents is to increase the production of saliva that would help in the faster disintegration of oral films. These agents, generally acids, can be

used either alone or in combination as salivary stimulants (Ravneet et. al., 2012). Other excipients referred lately, as sweeteners, are also used as salivary stimulants.

In some formulations, stability and thickening enhancers are employed to improve the consistency and to prevent particles from sedimentation. Surfactants and emulsifying agents are also used in small amount as solubilising or dispersing agents, to reduce the disintegration times and improve the properties of the strips (Siddiqui et al., 2011).

1.2.2 Methods to prepare oral films

The most commonly used industrial methods to prepare oral film are the film casting and hot melt extrusion methods. In the extrusion process, film-forming polymers, API and other excipients are mixed in solid and dry state. The blend is subjected to heating process where solvents are completely eliminated and then extruded out in molten state. Melt is shaped in films by dies and is further cooled down and cut to film desired size. Due to high temperature used in this process, API can be degraded and this is an important drawback of hot extrusion process (Ravneet et. al., 2012; Dixit et. al., 2009; Hoffmann et. al., 2011). In addition, since extruders are not commonly used in pharmaceutical industry, it is normally required an extra investment in production equipment (Greb, 2009).

Solvent casting is undoubtedly the most widely used method to formulate oral films, mainly due to the easiness of the process (Morales et. al., 2011). Preparation of the casting solution involves the mixing of film-forming polymers and other water-soluble ingredients. Other excipients, including API, are dissolved in a suitable solvent or solvent system, forming a clear viscous solution (Mahajan et. al., 2011). Both solutions are mixed and stirred together and further casted.

During manufacture of the films, some particular factors should be observed with particular attention, since they can jeopardize the quality of the final product. Hence, particular emphasis should be given to desired mass to be cast, content or dosage uniformity, air bubbles entrapped and residual solvents in the final product (Morales et. al., 2011).

The selection of the solvents essentially depends on the API to be incorporated and its physicochemical properties. Therefore, heat sensitivity and compatibility with excipients and solvents are some examples of factors that must be critically studied (Dixit et. al., 2009).

In spite of improving API's solubility and reducing drying time (an important factor in manufacture process), organic solvents are normally questioned when used in oral films. Apart from problems related to environmental safety and health, there are several undesired hazards inherent to the use of organic solvents. Consequently, all residual solvents should be reduced as much as possible, or should be entirely eliminated, trying to reach the specifications required (Hu et. al., 2011). Nevertheless, as many formulations rely on the use of organic solvents, they should be selected from ICH Class 3 guideline: 'impurities: guideline for residual solvents' (Morales et. al.,2011; Hoffmann et. al., 2011).

In order to achieve the complete dissolution and to improve the homogeneity, a controlled heating process may be included during the mixing step. Air bubbles entrapped during the solution preparation tend to produce uneven strips. Therefore, to obtain uniform thickness and surfaces it is required a deaeration step, which is achieved by using specialized stirring systems, and vacuum assisted machines (Hoffmann et. al., 2011). The continuous mixing process is also important in order to keep the viscosity and solution concentration unchanged.

Another important factor to take into consideration in manufacture process is the moisture present in the solution. Therefore, it is required the use of appropriate humidity controls in the manufacturing production area, because this parameter can affect mechanical properties in final product (Dixit et. al., 2009).

The next step in manufacture of the films is the transfer of solution onto a moving inert substrate (an intermediate liner) by suitable rollers, where the film casting process is performed. These rollers can be adjusted to get the desired film thickness, which determine the drug content of the final strip (Hoffmann et. al., 2011). The resulting wet strip is subjected to a drying process, in order to removal solvents before being cut into strips (Prajapati et. al., 2009). After this step, the intermediate liner is removed and the films are packaged in multi-dose or single-dose packaging. In order to avoid accidental overdosing, because films can stick together, single packages should be preferred. Some studies indicate a roll dispenser as a new opportunity for personalized medicine, since films can be cut individually into desired sizes (Hoffmann et. al., 2011; Allen et. al., 1987; Malke et. al., 2011).

Most challenges in production of orally dissolving strips occur when formulation is scaled up from bench scale to production scale. Since speeds of coating and drying process directly influence the production, they are critical steps at this stage. As a matter of fact, physicochemical properties of the coating solution and wet strip's thickness could affect

scale-up process by limiting the drying speed and the thickness of the final product (Greb, 2009). Hence, optimization of these parameters is required for commercial scale throughput. A proper selection of dryers and the number of online dryers should improve the processing times and the scale-up process (Dixit et.al, 2009; Prajapati et. al., 2009; Greb, 2009).

1.2.3 Oral films market

Fast-dissolving drug delivery systems were first developed in the late 1970's as an advanced alternative to traditional tables, capsules and syrups. Oral films were initially introduced in the market as breath fresheners and personal care products, such as soap strips, but were quickly used by pharmaceutical companies for therapeutic benefits.

Nowadays, the most important pharmaceutical companies have recognized the great potential inherent to oral films and the many possibilities for drugs delivery due to poor acceptance of the patients. In fact, patients' compliance is one of the major issues to the healthcare industry and the costs inherent of noncompliance were estimated in $77 to $300billion a year in United States, in 2009 (Rekhi, 2009).

On the other hand, oral films have gained more popularity recently due to the need of non-invasive delivery systems. In fact, a market research report by IBIS*World* (2012) refers an annual growth in last five years (2007-2012) of 30.9% and revenue of one billion dollars. This fact is easily explained for the clearness of changing market trends and the interest of pharmaceutical companies in reformulating existing drugs into new dosage forms. Actually, this strategy has many advantages: not only the cost inherent and time consuming in the development of new chemical entities, but also the competitive and rewarding field of novel drug delivery technologies.

Furthermore, instead of 10 years and $330 million invested in the development of new drugs, the research and the development of a new formulation generally takes only 4 to 5years and also involves considerable lower costs (Rekhi, 2009).

Oral thin films have been seen as an opportunity to pharmaceutical companies extend product life cycles that are expiring and will soon be vulnerable to generic competition. Thus, this delivery drug system shows a great potential in pharmaceutical business.

1.3 Characterization of oral films

Since the performance of orodispersible films is directly affected by their properties, this new technology has been requires a deep knowledge and an extensive study of such properties. Hence, research has been directed to the characterization of oral films, which can help in formulation and processing of these new oral dosage forms.

According to this, it will be described some chemical, thermal and mechanical characterization techniques used on this work.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared (IR) spectroscopy is one of the oldest and well-established experimental techniques used to characterize organic or inorganic compound (Kong et. al., 2007) Over the past seventy years, this technique has been applied to the analysis of solids, liquids and gases, with the main goal of determining the chemical functional groups in samples.

The principles of IR spectroscopy are based in continuously vibration and rotation of the atoms of any molecule. When a sample is passed by an infrared radiation, its atoms acquire a specific vibration. If the frequency of this vibration is equal to the frequency of the IR beam on the molecule, the sample absorbs the incident radiation (Hsu, 1997). The resultant spectrum represents the IR radiation transmitted or absorbed by a sample as a function of wavenumber.

FTIR spectroscopy is the preferred method of IR spectroscopy once it allows rapid data processing and conversion into a spectrum. Actually, FTIR spectroscopy has improved the quality of IR spectra and minimized the time required to obtain data, since FTIR spectrometers uses the well-established mathematical process of Fourier transformation to collect and convert data (Lin et. al., 2012; Stuart, 2004). When accomplished with Attenuated Total Reflectance (ATR) accessories, this technique improved the potential to evaluate and quantify different types of samples.

In FTIR-ATR spectroscopy, the IR beam penetrates the surface of the sample pressed against the ATR crystal. This penetration is called evanescent wave and IR beam's intensity is reduced in IR's spectrum region where the sample absorbs (Hsu, 1997). The resultant attenuated radiation is measured and plotted, resulting in an absorption spectrum characteristic of the sample (Stuart, 2002).

Each peak in an absorption spectrum corresponds to the frequency of a vibration of a part of a molecule, or a chemical functional group. In fact, different functional groups absorb characteristic frequencies of IR radiation, so they can be identified (Stuart, 2004).

Since each material is a unique combination of atoms, no two compounds produce the exact same infrared spectrum. In fact, an IR spectrum is a fingerprint of a particular molecule characterized by the number, shape and intensity of absorption bands (Kendall, 2006). Therefore, IR spectroscopy can be use to positively and qualitatively identify different materials (Lin et. al., 2012).

The peak intensity in resultant spectrum is a direct indication of the amount of the material, i.e., absorbance is proportional to the concentration of the chemical species active (Lin et. al., 2012). Therefore, FTIR spectroscopy allows a quantitative determination of compounds in mixtures, even in small quantities (Hsu, 1997). Adding this to the fact that FTIR spectroscopy is an extremely sensitive and accurate technique, contaminants can be detected and identified, resulting in an invaluable tool for quality control.

During the development of oral films and other solid dosage forms, the incompatibilities between the active pharmaceutical ingredient and other excipients play an important role in formulation stage. FTIR spectroscopy is a powerful tool since it can be used to assess possible drug-excipient interactions (Mahajan et. al., 2011).

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis is a widely used thermal technique for characterization of a variety of materials. Since this analysis involves the measurement of the weight of a sample as a function of temperature or time, TGA can be used to quantify the weight loss associated with degradation or transition processes in polymer analysis (Gabbott, 2008; Stuart, 2002). Therefore, it is a useful tool to provide supplementary information to the most commonly used thermal technique Differential Scanning Calorimetry (DSC).

In TGA, a sample is submitted to a programmed heating sequence and a sensitive balance detects the mass change, in a controlled atmosphere. Different effects or degradation processes can cause weight changes; as evaporation of volatile constituents, drying and uptake or loss of water in humidity controlled experiment. These events originate a step in

TGA curve or a peak in differential thermogravimetric (DTG) curve (alternative and complementary presentation of data results) (Gabbott, 2008).

Once each polymer provides a unique and characteristic TGA curve, it is expected that different polymers can be distinguished from each other's. A typical TGA curve obtained for different polymers can be observed in Figure 1, illustrating how TGA data can be used for qualitative analysis, looking to temperature range and to activation energy of decomposition (Stuart, 2002).

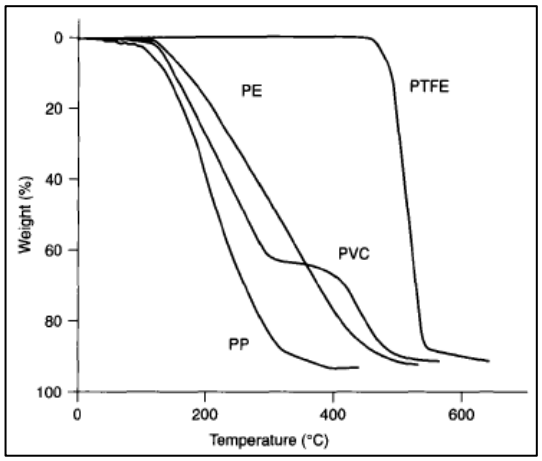


Figure 1: Thermogravimetric profiles obtained for different polymers (Gabbott, 2008).

TGA measurements under controlled humidity are useful to evaluate the interaction of water with polymers, since this factor can have a significant impact on properties of the materials. Thereby, it is a useful test to evaluate the phenomenon of adsorption and desorption of water (Gabbott, 2008). In this particular case, it has proven to be an important factor since it allows evaluating the hygroscopicity of oral strips.

Differential Scanning Calorimetry

Differential Scanning Calorimetry provides a fast and easy method for thermal analysis. This technique is very useful for several types of materials and has become the most used thermo analytical technique. From the single characterization of materials to the investigation of the interaction between excipients, DSC has a wide range of pharmaceutical applications, since most phase transitions are accompanied by a change in heat (Bond et al., 2002).

In this method, the sample and the reference material are subjected to identical temperature conditions in a controlled inert atmosphere and the heat flow associated to thermal events are measured as a function of temperature or time. Therefore, material can be analysed and thermal characterized through the identification of different transitions, such as melting point (Stuart, 2002). In addiction to thermal events, transitions also may be due to chemical reactions such as polymerizations, oxidation or cross-linking (Gabbott, 2008).

These thermal events are represented in DSC plot as peaks associated to endo and exothermic transitions. For example, melting temperature is represented as an endothermic event since the sample absorbs energy in this thermal transition.

There are two different conventions for the display of the heat flow curve: according to the first one, endotherms are represented in the downward direction since endothermic transitions result in a negative temperature differential; on the other hand, endothermic events can be represented upward once the endothermic transitions result in an increase in power supplied to the sample (Gabbott, 2008). Throughout this work, the data is shown with endotherms down.

In addiction to heat capacity, the enthalpy involved in polymer transitions can also be measured. The peak area below the curve is proportional to the enthalpy change in the sample.

Mechanical Properties

There are a number of fundamental techniques used to characterize polymers' mechanical properties. Along this work, tensile strength (σ_B), Young's modulus (E_t), and elongation (ε_B) will be the main focus.

To measure these properties, a experiment is done by a strain-controlled instrument where a test specimen is held between two clamps positioned at a fixed distance: one clamp is fixed and the other one is subjected to a gradually increasing load until the sample breaks. The change in strain is plotted as a function of stress resulting in a stress-strain curve. The area under the curve is often integrated to obtain the energy needed to break the sample and can be used as an indicator of the toughness of the material (Menard, 1999).

If stress and strain are proportional, a linear graph is produced and the corresponding deformation is called elastic deformation. The slope of this region is Young's modulus, which can be seen as the stiffness of the sample in analysis (Stuart, 2002).

In Figure 2, it can be observed a squeme of a stress-strain curve with representation of yield point. Before this point the elongation is reversible. After this, molecules untangled and flow over eachother, and further elongation is irreversible (Stevens, 1999). The Ultimate Tensile Strength (UTS) corresponds to the maximum stress than can be sustained by the material and, if it is maintained, the sample will fracture (Stuart, 2002).

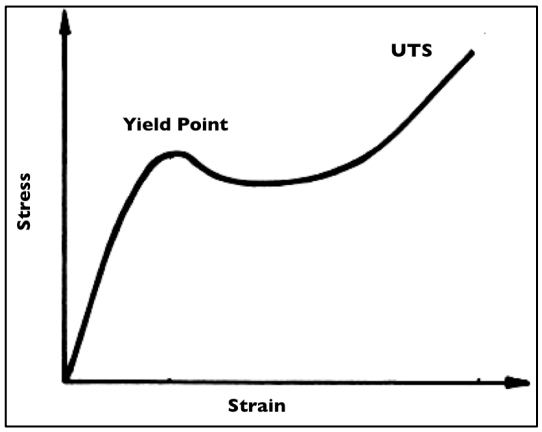


Figure 2: Stress-strain curve with representation of yield point. (Adapted from Blaga, 1973)

The stress-strain curves were determined at constant temperature. However, as these properties are temperature dependent, there is a motivation to relate the mechanical properties with changes in temperature.

Dynamic Mechanical Thermal Analysis (DMTA)

The successful development of polymers applications in drug delivery system and biomedical devices nowadays have been requiring an extensive characterization and comprehensive understanding of such materials. In fact, formulation and processing of pharmaceutical products are directly affected by thermal-mechanical properties, which implicates an accurately optimisation of the design and hence performance in the development of both pharmaceutical and biomedical systems (Jones, 1999; Jones et.al., 2012). Therefore, DMTA has gained increased attention in application for the characterization of pharmaceutical formulations despite being widely employed in polymers and related industries.

Dynamic mechanical analyses generally involve subjecting samples of known dimension and geometry to an oscillating force and assessing the relationship between that force and subsequent deformation (Craig et.al., 1995). This method allows the measurement of material modulus (stiffness) and its mechanical damping behaviour as a function of temperature and frequency (Gabbott, 2008; Stuart, 2004). These parameters are reported as modulus (Storage and Loss) and Tan δ, which are related by the formula:

$$\text{Tan}\,\delta = \frac{E''}{E'} \qquad \text{(Equation 1)}$$

Thus, damping is defined as the ratio between dissipated energy (E'' – viscous modulus) and stored energy (E' – elastic modulus) and allows the measurement of material's capability of store and release energy.

DMTA analysis provides the possibility of determining the glass transition temperature (T_g) with very high accuracy. This transition is related with polymeric chain mobility and determins the transition from a glass-like state to a rubber-like state (Jones, 1999). DMTA is the most sensitive technique used for determination of T_g which is typically taken as the maximum in the damping curve.

Besides T_g, DMTA also provide information about secondary transitions (β and γ). The β transition is particularly interesting, being associated to the impact strength of the material, since it contributes to the dissipation of energy.

Karl Fisher

Karl Fischer titration is an analytical method used to determine traces of water in samples. The reagent used contains all the reactants essential to volumetric titration, which is based in the reaction of iodine and sulphur dioxide in the presence of an alcohol, usually methanol, as describe above:

$$SO_2 + I_2 + 2H_2O \xrightarrow{CH_3OH} 2HI + H_2SO_4 \qquad \text{(Equation 2)}$$

In volumetric titration method, water reacts with iodine until the water is consumed and the endpoint is finally reached. Water determination is based on volumetric measurement of reagent.

Since Karl Fischer titration is not affect by volatile compounds, it is a reliable moisture determination when compared to TGA analyses until 100°C.

Contact Angle Measurement

Contact angle is a method that quantifies the wettability of a solid surface by a liquid. Since surface tensions involve a solid phase, indirect approaches as contact angle are used to estimate this parameter.

Establishing the tangent of the angle formed between a liquid and a solid surface easily performs contact angle measurement. This is defined by the mechanical equilibrium of the drop under the action of three interfacial tensions: solid-vapor, solid-liquid and liquid-vapor, which is know as Young's equilibrium (Kwoket. al., 1999). What is relevant to this work is that, if the contact angle is elevated, larger than 90°, samples will be considered hydrophobic and have less capability to retain water. On the other side, if a sample has a low initial contact angle, smaller than 90°, it means that sample has the capability to retain water showing that the solid surface is hydrophilic and film is hygroscopic.

Disintegration

It is critical to determine the time required for a film to be dissolved in the saliva. Disintegration means that an oral film dissolves in a small amount of saliva. Once saliva composition, pressure and temperature, and tongue movements cannot be mimicked, it is difficult to adopt and choose an adequate method to determine disintegration time. However, different methods have been described in literature (Garsuch, 2009a). To determine disintegration time, oral films are placed on a Petri dish with a certain volume of artificial saliva and the time at the disintegration begins is measured.

Although this procedure does not mimic the *in-use* conditions, it can be used to comparison and reference when the analyses are carry on.

II. AIMS OF STUDY

The main goal of this project is the chemical, thermal and mechanical characterization of commercially available oral dosage forms. Although oral films have gained more popularity recently, there are a small number of available studies in the literature. Furthermore, there is no specification or guidance about the specific values or ranges that define the properties of oral films. Due to this fact, it is extremely important to investigate the characteristics of commercially available oral films in the market. With this study, it is possible to provide essential information to the development of a new technology.

The characterization of the films was carried out using different techniques: chemical characterization, by FTIR analysis; thermal characterization by TGA, DSC and DMTA; mechanical properties, by tensile tests. Other important characteristics, such as disintegration time and water content were also evaluated.

The second step of this project involves an attempt to reproduce two commercial available oral films, Listerine and Gas-X, in order to understand de relationship between the composition, preparation procedures and the final properties of these films.

III. MATERIAL AND METHODS

1. Material

1.1 Films preparation

Acessulfame K		Nutrinova, Frankfurt, Germany
Carrageenan	Gelcarin GP-379NF	IMCD UK Ltd, Sutton, UK
FD&C Blue #1		Colorcon, Harleysville, U.S.
HPMC E5	Methocel E5	
HPMC E15	Methocel E15	Colorcon, 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	BASF, 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		Merck, Darmstadt, Germany
Tween 80	Polysorbate 80	Merck, Darmstadt, Germany

1.2 Karl-Fischer Titration

Hydranal Composite 5	Sigma-Aldrich co. LLC, U.S.

2. Methods

2.1 Films preparation

Oral films were prepared according to a standard procedure as displayed in Figure 3.

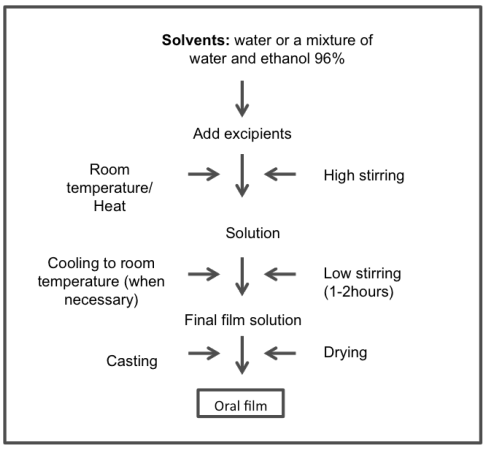


Figure 3: Schematic representation of preparation of oral films

Solutions were prepared in two-neck round bottom-flasks of 50mL and were submitted to a heating process or were kept at room temperature, depending on the excipients used in each formulation.

The process of film formation has been fully described (Alanaz, 2007) and is divided in tree stages: i) solvent evaporation and consequently concentration of polymer particles; ii) coalescence and deformation of polymer particles and, at last, iii) fusion of polymeric molecules of adjacent polymer particles.

Films solutions were cast in PVC release liners with an Erichsen film applicator (Coatmaster 510, Erichsen, Hemer, Germany), with speeds of 18mm.s^{-1}. Films were dried on the heated table at 40°C or at room temperature until dryness, which depends on the properties of each polymer used. Individual samples of each solution were prepared and cut with sharp razor blade in regular dimension for further analysis.

2.2 Storage

After being cut, oral films were stored under controlled conditions at 43% RH with saturated potassium carbonate solution. Before any test being undertaken, films were kept in this conditions for at least five days.

2.3 Characterization

i. FTIR

Commercial films and correspondent excipients were analysed in a FTIR-4200 spectrophotometer by *Jasco*, using the attenuated total reflectance (ATR) technique. For each sample, scans were collected over the wavenumber region 550 and 4000 cm^{-1} with a 4 cm^{-1} resolution.

ii. TGA

TGA analyses were recorded using TGA Q500 (TA instruments). Samples were scanned using a heating rate of 10°C.min^{-1} to a maximum temperature of 500°C. Furthermore, films were heated under a constant nitrogen flow (40 mL.min^{-1}).

iii. DSC

DSC samples were accurately weighed at approximately 5mg and were sealed in aluminium pans and heated with a nitrogen flux of 50mL.min^{-1}. The reference was an empty pan. DSC scans were recorded by using a DSC Q100 (TA instrument).

Films were scanned at 10°C.min^{-1} in two heating runs: first from 25°C to 100°C, in order to eliminate all water content in the films and, after that, from -85°C to 100°C.

iv. Mechanical properties

The mechanical properties of the films were determined using a tensile testing universal apparatus (Zwick, Germany) with a load cell of 100N. Films, free from physical visible imperfections, were held between two clamps positioned at a distance of 50mm and were pulled by the top clamp at a rate of 50mm.min^{-1}. A preload (0.1 MPa) was performed in each assay. The load applied to the film is gradually increased and the corresponding magnitude of elongation is recorded.

Young's modulus, Tensile Strength and Elongation parameters are retrieved from the software TestXpert (TestXpert, Zwick, Germany).

v. DMTA

DMTA analyses ware carried out using a DMA 242 E (Netzsch, Germany) under compression mode. All samples (5.289×0.04×5,61 mm^3 (average value)) were analysed over a temperature range from -150°C to 150°C, at frequencies 1, 5 and 10 Hz, using a heating rate of 3 °C/min.

vi. Karl Fischer Titration

In order to determine the residual water content in orodispersible films, Karl Fischer method was performed in a Karl Fischer 787 KF Titrino (Metrohm AG, Herisau, Schweiz). Each sample was added to the titration flask filled with methanol previously dehydrated with a Karl Fischer reagent (Hydranal Composite 5), with a known determined titer ($mgH_2O.mL^{-1}$). Water content of each film is determined based on the titration volume (mL).

vii. Contact angle measurement

Dynamic contact angle (DCA) measurements were undertaken by an optical contact angle meter (*OCA20 Dataphysics, Filderstadt, Germany)*, at room temperature. Films were fixed on a slide with adhesive tape and a needle with 0.52mm diameter dropped about 10μL of distilled water onto the film surface. The image of the droplet was obtained with an optical microscope with the axis parallel to the sample surface and was sent to the software (SCA20 Dataphysics software, Filderstadt, Germany), which preforms the contact angle calculation.

viii. Disintegration test

In order to evaluate the time needed until the disintegration begins, a simple test was undertaken. 4mL of phosphate buffer (pH=6,8 T=37°C) were added to a Petri dish where films samples were laid on. The time until the film started to disintegrate was recorded, and the average time was determined.

ix. Film thickness

Film thickness was determined using the micrometre screw (Mitutoyo Digimatic Capiler, Mitutoyo Corporation, Japan). Each film sample was measured at five positions: central and the four corners, and the average thickness were calculated.

x. Statistical analysis/ Design of Experiments

Statistical analyses were performed with GraphPadPrism version 6 (GraphPad Software, Inc, San Diego California). Statistic comparisons were made using Analysis of Variance (ANOVA) with Bonferroni test (95% confidence, *$p<0.05$). Results were considered to be significant when $p<0.05$. Mean values are displayed as Meand+SD when repeats number is equal to 3.

Screening and optimization design were performed with JMP 10 (SAS Institute Inc., Cary, NC).

IV. RESULTS

The aim of this work was to understand the influence of formulation used in properties of the films prepared. For this purpose, two commercially available oral films were chosen and were characterized (Listerine PocketPaks from Pfizer and Gas-X from Novartis).

1. Characterization of commercial films

In Table I it is presented the main components used in both commercial films. This information was collected from patents of Leung (2005) and Schobel (2007).

Table I: Main components of commercial oral films evaluated.

	Polymer	Plasticizer	Flavour	Colour	Sweetener	Surfactant	Thickening agent	Drug Substance
Gas-X	Corn Starch Modified HPMC Maltodextrin	PEG	Menthol	FD&Blue#1 Titanium Dioxe	Sorbitol Sucralose	Sorbitol		Simethicone
Listerine Pocket Packs	Pullulan	Propylene Glycol	Menthol Eucalyptol	Green3 Yellow6	Sucralose Acessulfame Potassium	Tween80 Glyceryl Oleate	Chondruscrisp (Carrageeenan Ceratoniasiliqua gum Xantan gum	Copper gluconate Thymol Methyl-salicilate

Chemical structures from all excipients can be seen in appendix A.

i. FTIR analysis

FTIR spectra can be analysed in Figure 4.

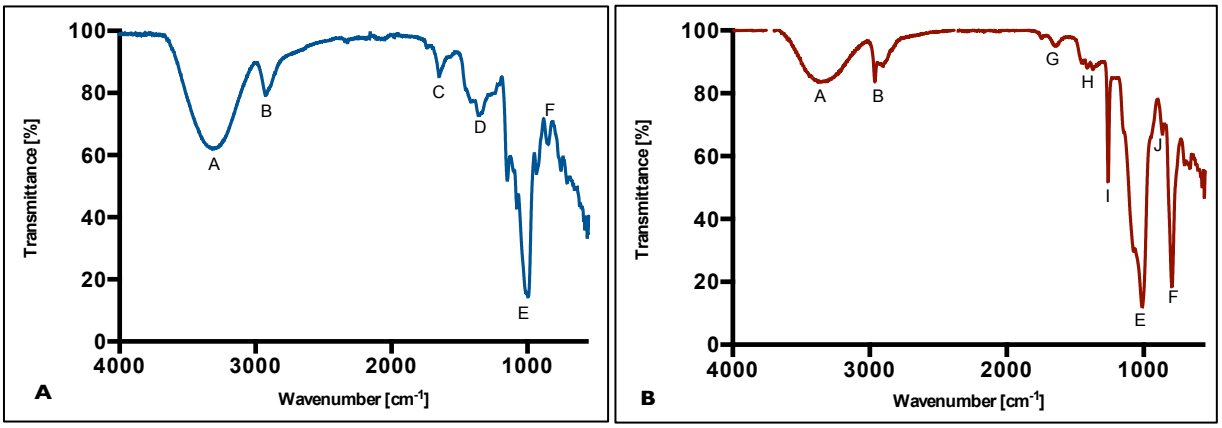


Figure 4: FTIR spectra of commercial films: A - Listerine, B - Gas-X.

The analysis of both obtained spectra (Figure 4) allows the identification of the absorption band characteristic in the region of OH group (3600-2100 cm^{-1}), represented by A letter.

Letter B and letter E present in both spectra, correspond to C—H bonds (2935-2915cm^{-1}) and —O— group (1150-1050 cm^{-1}), respectively, which confirms the presence of components with these bonds. Particularly, C—Cl bond, represented by F letter in 800-700 cm^{-1} region, is only present in Sucralose (Appendix A).

Letter C, only present in Listerine spectrum, indicates the absorption band characteristic of C=C double bond (1680-1600cm^{-1}) and it can be identified in some excipients, namely, acessulfame potassium referred as a sweetener, polysorbate 80 and glyceryl oleate, both referred as a surfactant. Letter D is characteristic of a particular bond only present in acessulfame potassium, a sulfone group R_2SO_2 at 1340-1280cm^{-1}.

Letter G and Letter H, present in Gas-X spectrum, correspond to aromatic compounds and aromatic amine and indicate absorptions bands at 1600-1430cm^{-1} and 1340-1250cm^{-1}, respectively. These characteristics bonds are present in pigment FD&Blue#1. Once intensity of the peaks is directly related with concentration, it is expected that these peaks would not be very intense since concentration of dyes is relatively low when compare to other excipients. According to this, Simethicone is present in higher amount in Gas-X films once its characteristic bond Si—CH_3 represented by I letter, has a considerable intensity when compared to other absorption bands. Following this line, Titanium Dioxe (letter J) is present in Gas-X in small amounts since intensity of absorption band is relatively low.

From the results obtained by FTIR, it is possible to assure the presence of some excipients in both films: sucralose in Gas-X and Listerine, acessulfame potassium in Listerine, and pigment FD&Blue#1 and simethicone in Gas-X.

ii. TGA analyses

Due to the diversity of excipients used in Listerine and Gas-x films, different thermal profiles were obtained, as it can be observe in Figure 5.

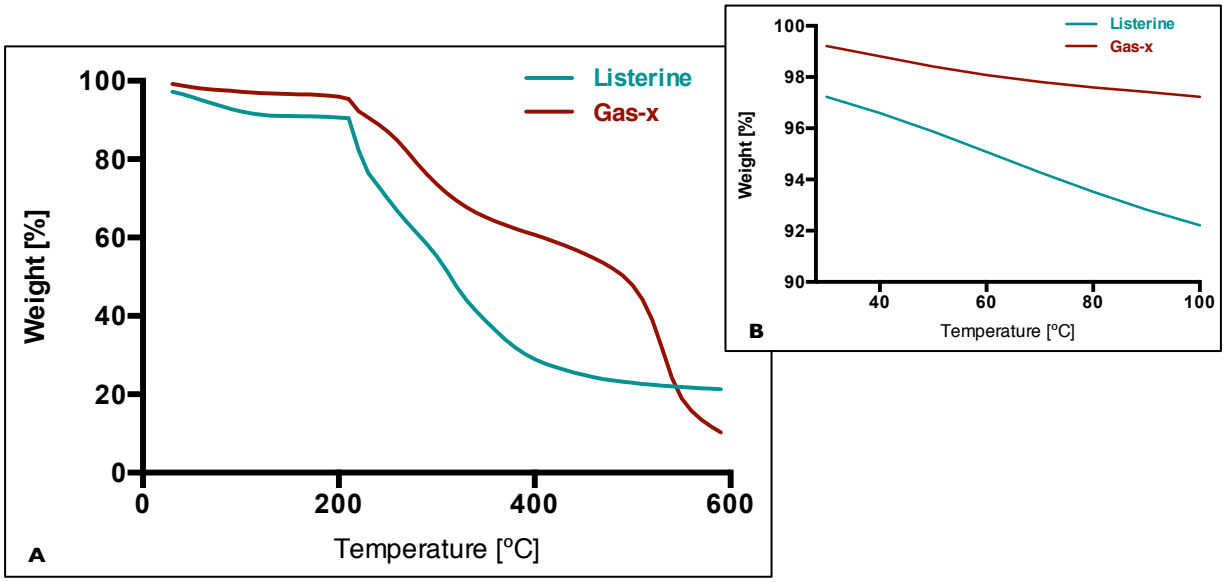


Figure 5: Thermogravimetric analysis of commercial films. A – thermograms, B – weight loss until 100°C.

Gas-X and Listerine start to lose mass approximately at same temperature (about 200°C), despite the differences in their composition. From this temperature, there is a considerable increase in weight loss.

Degradability profiles are related with main excipients. Differences between films can be explained by degradation profiles of the different polymers, which are expected to be the major components of both films.

Table 2 indicates the temperature at occurs a weight loss correspondent to 5% and 10% of the weight, and the extrapolated temperature onset (determined by tangent intersection between the initial degradation point and the slope of the TGA curve).

Table 2: Typical temperatures extracted from TGA curve.

Commercial Film	Weight Loss		T_{onset}
	5%	10%	
Listerine	60,67 °C	216,79°C	216,21°C
Gas-x	211,03 °C	234,54°C	221,60 °C

From Table 2, it is possible to suggest that Gas-X it is relatively more stable than Listerine since it has a higher T_{onset}. Although this difference it is not significant, Gas-X loses 5% of initial weight at 211°C and Listerine at 60°C. This result indicates that Listerine has an initial

weight loss more pronounced than Gas-X. This fact can be corroborated by Figure 5-B, which represents the weight loss until 100°C. The weight decrease observed until this temperature corresponds to the evaporation of volatile substances, as ethanol, flavours and mainly water.

As it can be observed in Figure 5-B, the slope of Listerine's curve is greater than that observe in Gas-X's curve. If we assume that the weight loss until 100°C it is essentially due to water evaporation, it is possible to suggest that Listerine is more hygroscopic than Gas-X.

iii. DSC analysis

Figure 6 presents the DSC traces of Listerine and Gas-X.

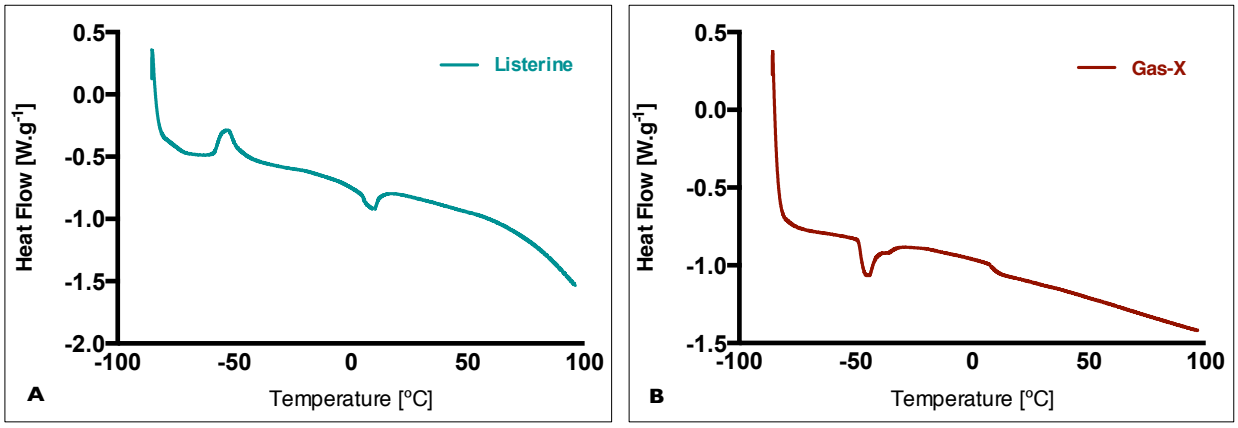


Figure 6: DSC traces of commercial films. A - Listerine, B - Gas-X.

The results present in Figure 6 are not very elucidative. Although some thermal events can be observed in both films, it is very difficult to describe the specific thermal events, probably due to overlapping and the complex formulations used to prepare the films.

iv. Mechanical Properties

Mechanical properties play a crucial role on the physical integrity of orodispersible films. Therefore, elongation, tensile strength and elasticity modulus was determined (Table 3). Stress-strain curves can be evaluated by observing Figure 7.

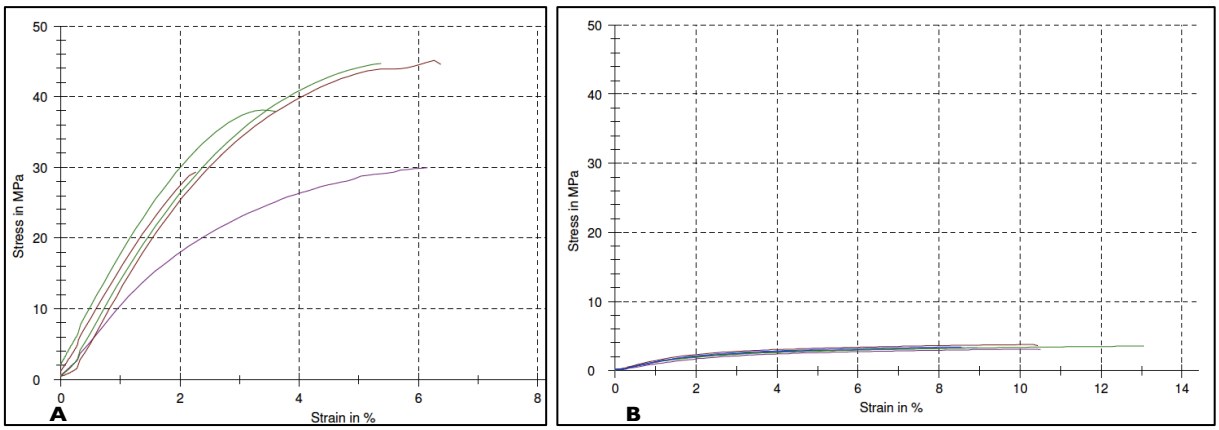


Figure 7: Stress-strain curves of commercial films. A-Listerine, B-Gas-X

From Figure 7, it is possible to observe that Listerine presents high results variability when compared to Gas-X. This observation may indicate that Gas-X presents a more homogenous composition.

Table 3: Summary results of mechanical properties of commercial films.

	Tensile Stress at break (σ_B) [MPa]	Elongation (ε_B) [%]	Young's modulus (E_t) [MPa]	Thickness [μm]
Listerine	35.46	4.35	1105.16	40
Gas-X	9.31	3.301	64.34	110

The results presented in Figure 7 and Table 3 demonstrate the wide variation of mechanical properties of these commercial films. Besides being hard and tough (elevated Young's modulus), Listerine presents higher tensile stress at break. Although Listerine has the smallest film thickness, it is surprising that it broke at the highest force.

On the other hand, Gas-X results in a less ductile film since it presents low tensile strength and moderate elongation. Young's modulus presents a moderate to low value, which means that Gas-X can be described as soft and weak film.

Although the previously described mechanical properties are undoubtedly related with films compositions, formulation and preparation, it is difficult to establish a relationship between excipients and properties. However, considering the main components that theoretically are present in higher concentration and probably contribute more to the mechanical properties, more important information can be taken.

Simethicone is the major component present in Gas-X films, with 62.5mg in each strip, which represents about 60% of film percentage. The high amount of drug can contribute to a weaker structure. Also, films containing modified starch are referred as brittle films having poor mechanical strength (Nagar et al., 2011). This excipient can also justify the soft films obtained for Gas-X.

On the other hand, Pullulan is a natural polymer, referred as a good film-former with excellent mechanical properties (Nagar et al., 2011). Due to its chemical structure, the presence of many available OH groups allows the establishment of intra and inter-molecular hydrogen bonds. This fact can justify the high stiffness and toughness obtained for Listerine.

v. DMTA analysis

DMTA analyses were carried out in order to identify the main thermal events present in commercial films, complementing previous analyses. Although tests have been performed in a multifrequency mode (1, 5 and 10Hz). Figure 8 presents the results at 1Hz.

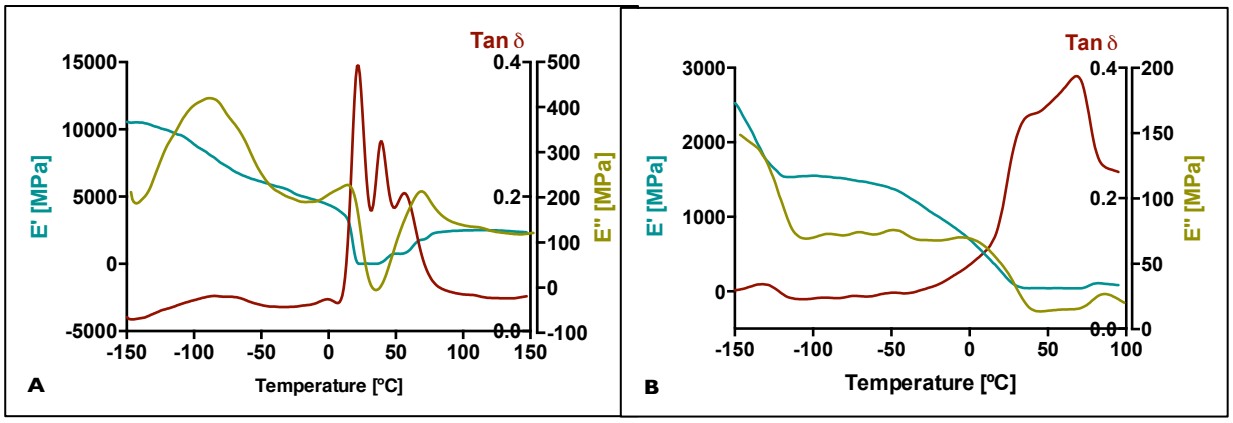


Figure 8: Dynamic mechanical analysis of commercial films: A-Listerine, B-Gas-X.

The viscoelastic properties (E', E" and Tan δ) of both commercial films can be analysed in Figure 8. As mentioned, glass transition temperature can be determined at the Tan δ maximum. In the same region, a sharp decrease in the value of the elastic modulus can also be observed (Jones et al., 2012).

According to this, in Listerine films, T_g can be identified around to room temperature. At 22°C, it can be observed the most intense transition: a peak in Tan δ and in E", and a decrease of large slope in elastic modulus. From 0°C, Listerine starts to lose rigidity and

therefore increases relaxation, once it loses the restricted movement of the polymeric chains.

At around -90°C an evident peak can also be observed in E" and a poorly defined peak can be identified in damping parameter. This peak most probably corresponds to secondary transitions (β).

The same occurs in Gas-X films (Figure 8-B). At around -130°C, a slight peak in Tan δ and a sharp decline in modulus may indicate a movement in lateral chains (β transition). The conversion from glass-like state to rubber-like state probably occurs between 0°C and 50°C. Above this temperature, the viscoelastic behaviour is difficult to explain considering the information available at the moment.

In both commercial films, glass transition occurs in the range of temperatures [0°-50°C], which can lead to modifications in films properties and appearance.

DMTA results can be related with DSC curves and glass transition temperature calculated in both techniques can be compared. As it was said, endothermic steps in the baseline of the DSC curve can be associated to glass transitions. In Listerine an endothermic event can be observed at 10°C (Figure 6-A) and in Gas-X, a slight endothermic slope can also be observed around 10 °C and 16°C (Figure 6-B).

These results are consistent and coherent with T_g calculated by DMTA analysis, although with slightly differences. According to Jones (2012), differences in both techniques can be attributable to operating principles, sensitivity and sample preparation.

vi. Karl Fischer Titration

The residual water content it is an important factor for the performance of oral films. Films with high residual water can be tacky and sticky whereas films with low water content tend to be brittle (Roger, 2004; Garsuch, 2009a).

Figure 9 presents the residual water results for Listerine and Gas-X. Listerine was analysed immediately after the box opening (t=0days) and after 15days, being kept under controlled conditions, at 43% RH.

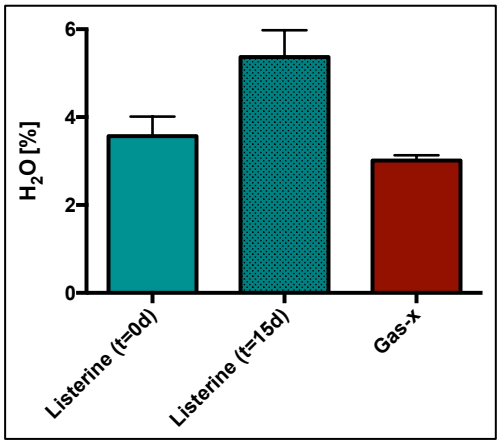


Figure 9: Residual Water Content in commercial films.

After 15days, Listerine retains around 2% more water when compared to Listerine after opening. This result could be mean that Listerine is produced and packaged under relative humidity lower than 43%. Gas-X presents less residual water content when compared to Listerine, around 3%.

vii. Contact Angle Measurement

Contact Angle measurement allows the evaluation of the wettability of the films, which can be a measure of hygroscopicity. Contact Angle of commercial films can be observed in Figure 10.

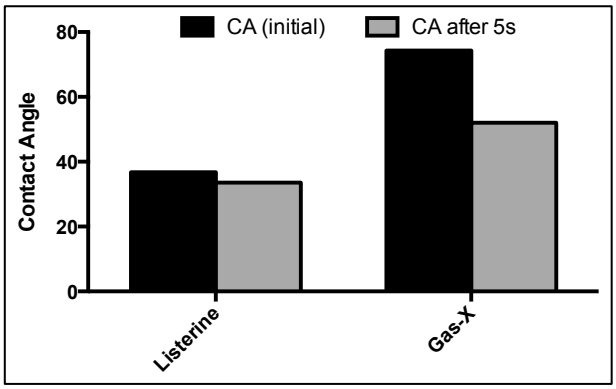


Figure 10: Contact Angle Measurement of commercial films.

Initial contact angle presents different results in both commercial films. Gas-X films have an average angle of approximately 75°, while Listerine has an initial angle of around 35°C. After 5 seconds, Gas-X has a higher decrease in contact angle, whereas Listerine show no notorious change. Lower initial contact angle indicate that water molecules are more attracted to Listerine films since water drops spread more on the surface, unlike Gas-X.

viii.Disintegration

As referred before, it is extremely difficult to mimic the *in-use* conditions. Therefore, the disintegration test can be seen as a preliminary result. In Figure 11, the time at which the films begin to break down can be evaluated and compared.

Listerine starts the disintegration faster when compared to Gas-X. While Listerine begins to break down after 3,3 seconds, Gas-X begins 15 seconds after its contact with phosphate buffer.

Considering that Pullulan is the main component of Listerine and Gas-X consists mainly of Simethicone, it is possible to relate these results based on the composition of the films.

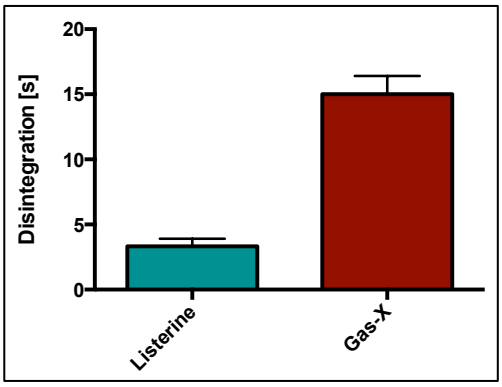


Figure 11: Disintegration time of commercial films

Furthermore, Gas-X presents a higher thickness (110 μm) when compared to Listerine (40 μm). Thickness and disintegration are proportional parameters: as film thickness increased, the disintegration time also increased (Chen et al, 2008). Thus, Gas-X disintegration time relatively to Listerine can be explained by the use of Simethicone as main component and by its thickness.

2. Characterization of developed formulations

The second part of this project involved an attempt to reproduce both commercial films, Listerine and Gas-X. The main objective was to achieve the characteristics of the commercial films, in order to understand the relationship between the formulations used and the performance of the films. For this purpose, several patents were consulted, resulting in the establishment of standard formulations and in the preparation of the films. Several formulations were developed based on this study, and were further characterized.

2.1 Listerine

Based on Listerine's patent (Leung et al., 2005), the main components of this commercial film were selected and their amount %(w/w) in film was changed. In Table 4 it is presented the formulations studied that result from DoE analysis.

Table 4: Developed and characterized formulations based on DoE screening.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	-	3,18%	-	-	-	4,97%
List10	49,36%	15,50%	9,63%	5,46%	6,36%	6,34%	7,35%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

Formulations presented in Table 4 were further characterised, according to commercial film characterisation techniques (Section IV.1). A comparison between Listerine and List formulations were made in order to understand how differences in formulation could affect the final appearance and properties of the films.

i. FTIR analysis

Figure 12 presents the FTIR spectra of the representative formulations studied. The remaining spectra are presented in Appendix B.

From Figure 12 it is possible to observe that the spectra of the different formulations are very similar.

Absorption peaks present in 2200-2400 cm^{-1} region, which can be seen in all spectra with different intensity, are characteristic of CO_2. Apart from this band, all absorption peaks and intensities look approximately similar, indicating that the formulations used should be close to Listerine.

According to Listerine FTIR analysis in Section IV.I, Sucralose and acessulfame potassium were identified in Listerine films. Looking at List2 e List5 composition (Table 4) it can be observe that List2 had both excipients, unlike List5.

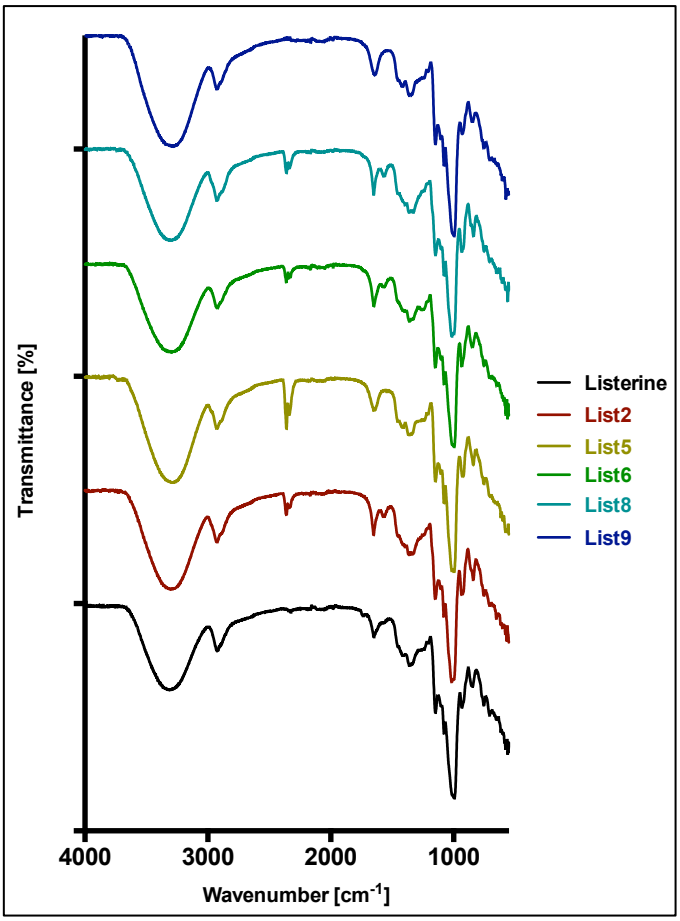


Figure12: FTIR analysis of representative formulations.

Table 5: Developed formulations with and without Sucralose and acessulfame potassium (Adapted from Table 4).

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%

Therefore, it is expected that List2 spectrum had an absorption band in 800-700 cm^{-1} region (corresponding to sucralose) and other at 1340-1280cm^{-1}region, characteristic of acessulfame potassium. Inversely, none of these peaks should be seen in List5. However, the analysis of Figure 12 reveals no differences between these two spectra.

Once Pullulan is the main component in all developed formulations, it can "mask" the other excipients and this could be the reason behind the fact no other excipients are detected. This conclusion can be confirmed by Figure 13, which represents pullulan and Listerine FTIR spectra.

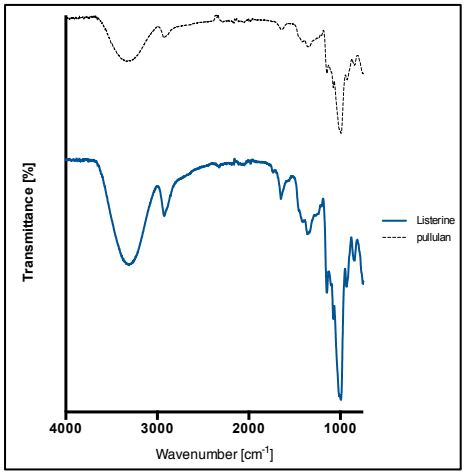


Figure 13: Pullulan and Listerine FTIR spectra.

ii. TGA analyses

In order to study thermal stability of developed formulations, TGA analyses were carried out. Figure 14 shows examples of films with and without plasticizer. In appendix C, all curves corresponded to developed formulations analysed could be observed.

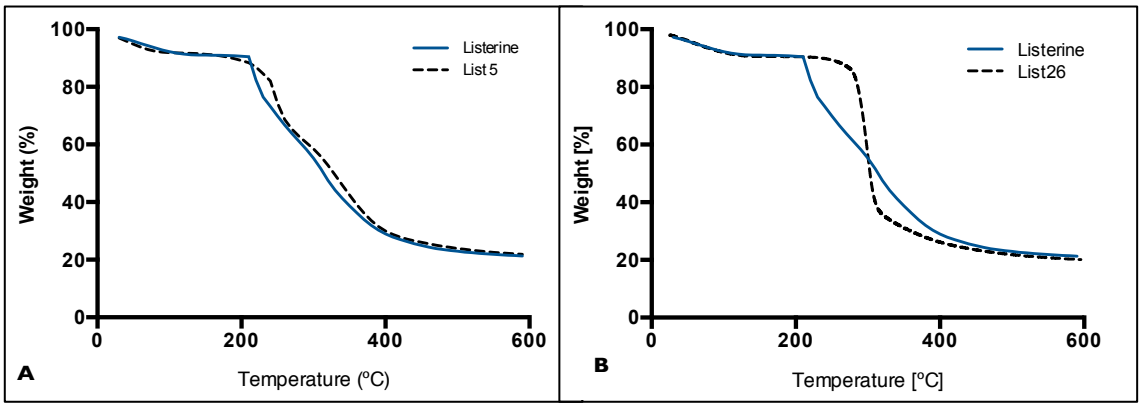


Figure 14: TGA profiles of representative formulations: A - with and B - without plasticizer.

According to Figure 14, films with plasticizer in their composition have a similar behaviour to Listerine, until 200°C. Around this temperature, thermal degradation is initiated in developed formulations and in commercial films. However, films with no propylene glycol are thermally more stable than Listerine but behaviour until 200°C is different. This fact can be justified by TGA profile of propylene glycol (Figure 15). In fact, propylene glycol stars the thermal degradation at lower temperature than films. Therefore, films with this excipient in its composition have a higher initial weight loss.

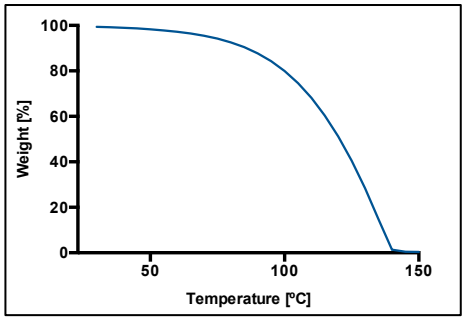


Figure 15: TGA profile of propylene glycol.

Considering that the films with plasticizer have similar behaviour to Listerine, the amount of propylene glycol used in the commercial sample can be about 15%-16%.

Table 6 presents the thermogravimetric data obtained for the films.

Table 6: Temperatures extracted from TGA curve. Grey – higher values, Blue- lower values.

Film ID	Temp. at Weight loss		T_{onset}
	5%	10%	
List2	54,17°C	175,24°C	212,4°C
List5	48,57°C	184,96°C	233,52°C
List6	34,46°C	78,13°C	265,98°C
List8	62,8°C	190,89°C	215,04°C
List9	44,07°C	105,81°C	299,73°C
List14	39,15°C	96,43°C	253,92°C
List18	57,59°C	176,05°C	205,41°C
List20	64,74°C	164,81°C	278,01°C
List25	73,96°C	187,17°C	215,06°C
List26	61,64°C	237,6°C	283,14°C
List27	58,56°C	182,48°C	200,83°C
List29	64,11°C	226,74°C	227,58°C
Listerine	**60,67°C**	**216,79°C**	**216,21°C**

In order to disclose the results it is important to analyse compositions used for each film (Table 7).

Table 7: Main formulations discussed in TGA analysis.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	-	3,18%	-	-	-	4,97%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

Evaluating T_{onset} of all developed formulations, there is a wide range of values. The combination of the information present in Table 6 and Table 7 suggest that films with higher T_{onset} (highlight in grey) tend to have higher percentage of pullulan in its composition.

Thermal degradation of pullulan starts at approximately 300°C, unlike Listerine which degradation temperature is around 200°C

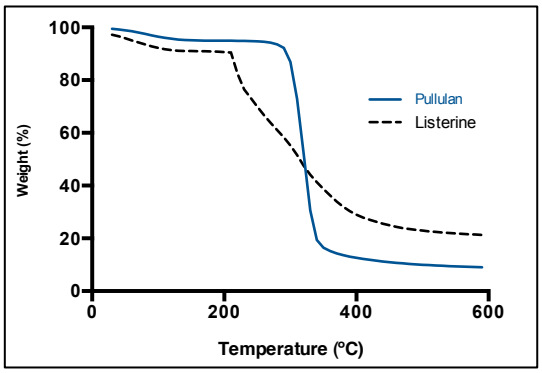


Figure 16: TGA profiles of pullulan and Listerine.

(Figure 16). Hence, it is logical that films with higher percentage of this polymer in its composition have higher degradation temperature. However, this conclusion is not general once films with lower pullulan percentage do not present the lowest T_{onset}.

Nevertheless, films that present lower T_{onset} (highlight in blue) have a feature, the sucralose is present in the formulation. Based on that and corroborated by DoE software, sucralose influences the T_{onset} parameter. This means that films with higher percentage of sucralose have lower degradation temperature. This conclusion can be confirmed from Figure 17, showing that sucralose starts to lose weight around 130°C.

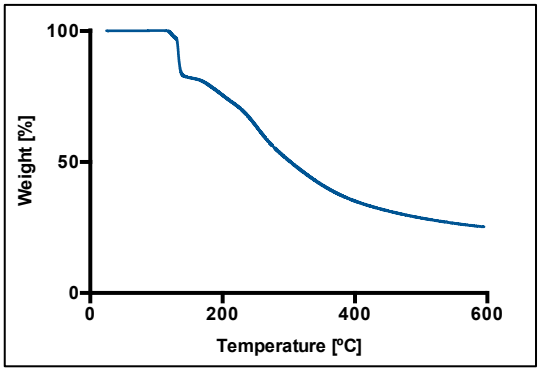


Figure 17: TGA profile of sucralose.

Films highlight in grey colour (higher T_{onset}) do not have propylene glycol in their composition. This result is consistent with the observation made before (Figure 14), where films without plasticizer have tendency to degrade later than films with plasticizer. Although List29 (highlight in dark blue) have no propylene glycol in its composition, it has a relatively lower T_{onset}. This result may be due to the presence of sucralose in composition.

As oral films are strongly influenced by moisture, it is important to evaluate the weight loss until 100°C. Until this temperature, weight loss is due to evaporation of volatile substances as ethanol, flavours, but mainly water. Films with steeper slope have greater water retaining capacity, which means, they are more hygroscopic. Weight loss until 100°C for all developed formulations is presented in Figure 18.

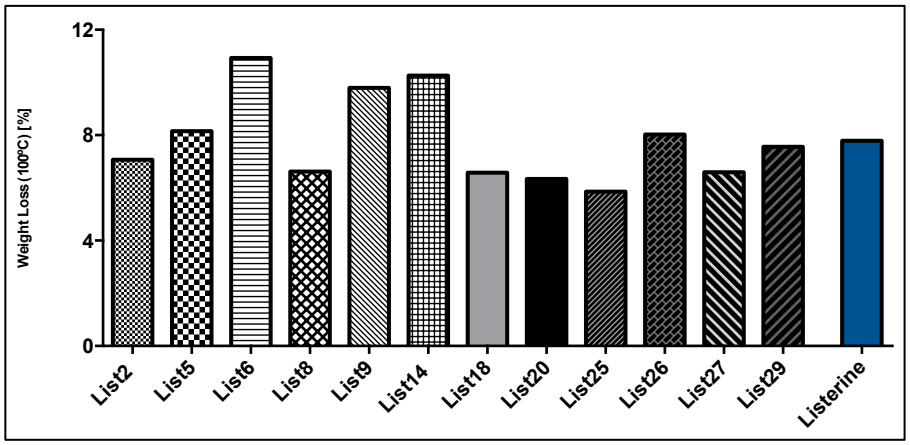


Figure 18: Weight loss until 100°C

From the results present in Figure 18, there are three films that can be stressed. List6, List 9 and List14 have clearly a pronounced weight loss until 100°C. On the other hand, List 18, List20 and List25 have the lowest percentage of weight loss. List8 and List27 have approximately the same weigh loss as the last mentioned. In Table 8, it is presented the composition of the reference formulations.

Table 8: Composition of developed formulations. Grey- higher values of weight loss.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	0,00%	3,18%	-	-	-	4,97%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

List6, List9 and List14, are the films with higher weight loss until 100°C, and have no plasticizer in its composition. List 26 and List 29 have the same particularity and have also higher values until this temperature. On the other hand, films with higher percentage of propylene glycol in its composition have lower percentage of weight loss. This means that films without plasticizer in composition have a greater capacity for water retention.

Films without propylene glycol haver higher percentage of pullulan. It is expected that pullulan has a higher capacity for water absorption than this plasticizer, and by that means that films without propylene glycol absorb more water.

From Table 6, List8 and List25 have approximately the same degradation temperature as Listerine. However, taking into account the TGA profiles of the different formulations, List5 and List18 are more similar to this commercial film. Figure 19 and Table 9 shows the TGA curves and formulation of these films.

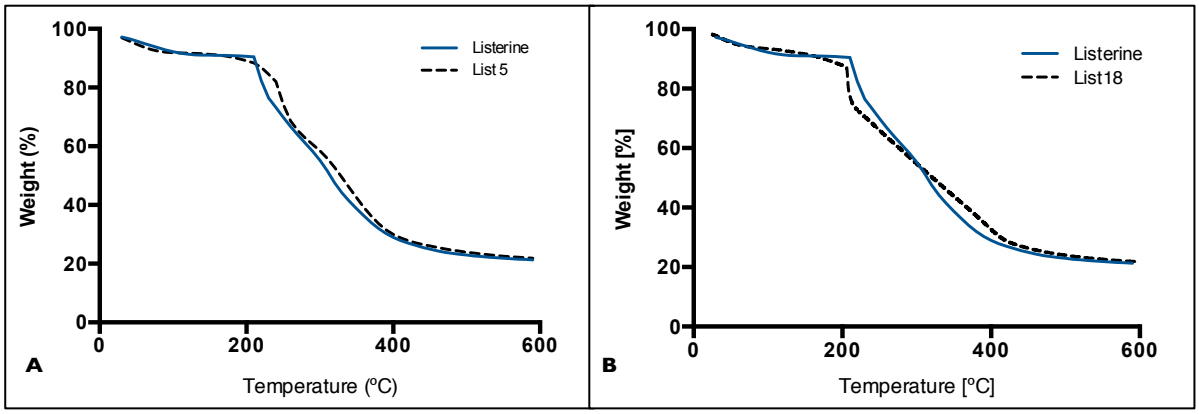


Figure 19: TGA profiles similar to Listerine. A – List5, B – List18.

Table 9: Composition of films with TGA profile similar to Listerine.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%

If films with sucralose start thermal degradation earlier than films without this excipient, it is understandable that List18 have a lower T_{onset} when compared to List5, since the latter have no sucralose in its composition (Table 6 and Table 9). However, Listerine has a degradation temperature between these two films. This result may suggest that the amount of sucralose in Listerine should be less than 6% (%w/w) in film.

From TGA analyses it is possible to set some concentration ranges for different excipients, namely: sucralose between 0 and 6% and propylene glycol between 15 and 16%. As List5 and List18 are similar to Listerine and the amount of menthol varies between 0 and 3,73%, this interval can also be used as indicative. The amount of tween80 in formulation does not influence TGA analysis since its degradation temperature it is much higher than films analysed (Appendix C).

iii. DSC analyses

Figure 20 present some DSC traces obtained for representative films. In Appendix D all DSC results can be consulted.

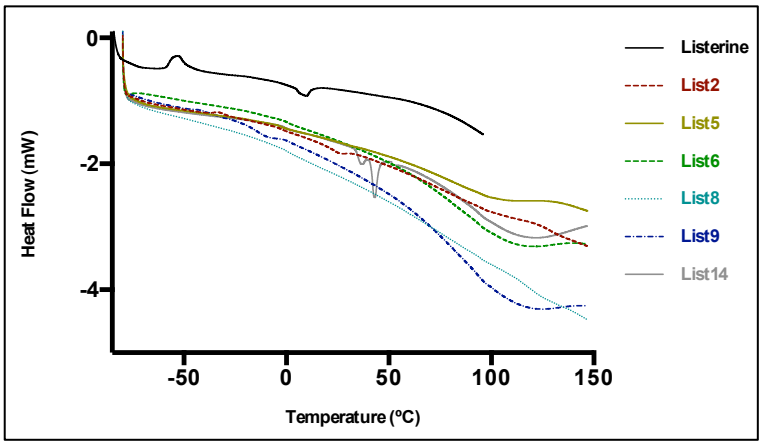


Figure 20: DSC traces of List formulations

From the results present in Figure 20, it is possible to observe a discrepancy between developed formulations and Listerine film.

List14 is the only developed formulation that demonstrates some evident thermal events near 50°C. However, and similarly to the commercial films, the DSC curves are not very elucidative and thermal events are hard to disclose.

iv. Mechanical Properties

Mechanical properties were evaluated in developed formulations in order to understand how differences in formulation can affect the film properties. It is known that these differences result in a wide variation of mechanical properties. Additionally, there is no specification or guidance available in literature about the specific values or ranges that define the proper mechanical properties of oral films. In this section, developed formulations are compared with commercial films.

In Figure 21, an average value of mechanical properties of developed films is presented and these values are summarized in adjacent Table 10.

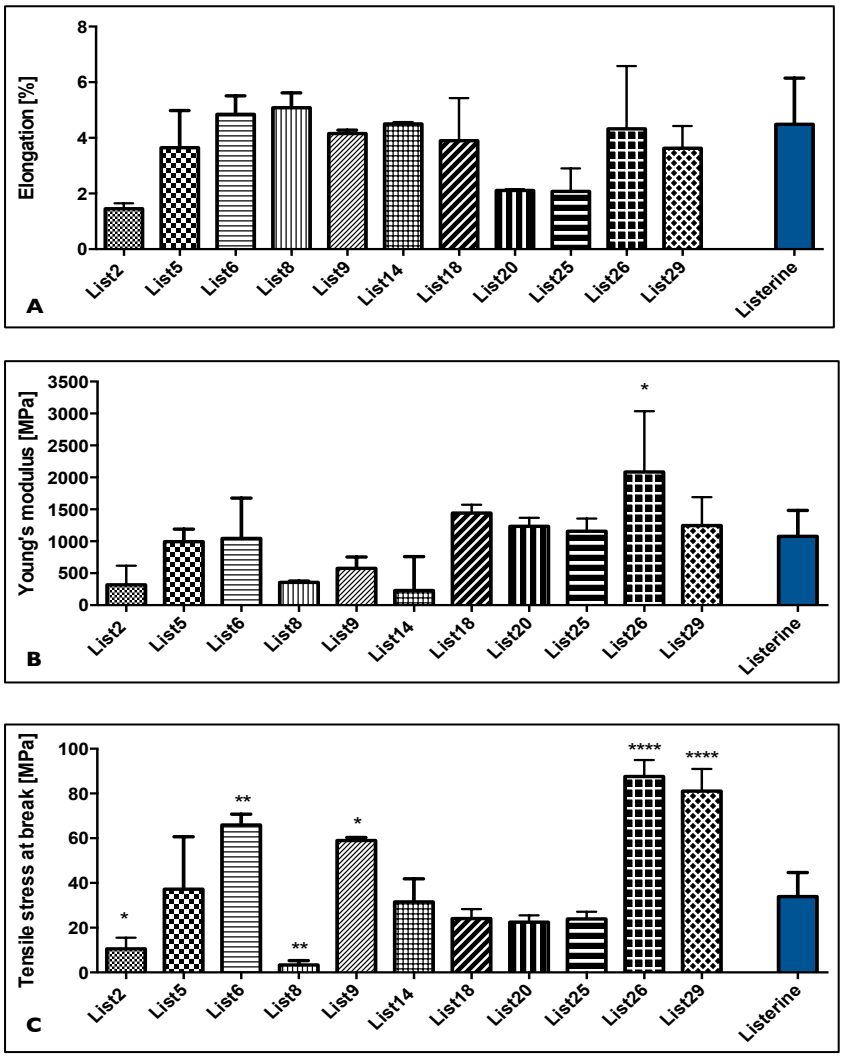


Figure 21: Summary results of mechanical properties of developed formulations. A - Elongation, B - Young's Modulus, C - Tensile Stress at Break.

Table 10: Summary results of developed formulations. Blue-Similar to Listerine; Red – Low E_t; Yellow – Low σ_B ; Grey- High σ_B.

Film ID	ε_B [%]	E_t [MPa]	σ_B [MPa]	Thickness (μm)
List2	1,177	404,2	9,447	30
List5	3,9	984	43,82	30
List6	4,555	1255	61,54	10
List8	5,085	357,1	3,345	50
List9	4,06	599,6	59,04	20
List14	4,143	495,6	33	30
List18	3,895	1441	24,07	20
List20	2,11	1234	22,5	20
List25	4,407	1128	22,64	30
List26	4,37	2088	82,55	20
List29	3,625	1246	81,09	20
Listerine	**4,345**	**1105**	**35,46**	**40**

According to results presented in Figure 21 and Table 10, it is possible to identify a wide variation of mechanical properties and even in the thickness.

The different formulations have an average elongation similar to Listerine. However, it is possible to identify that List2, List20 e List25 have a smaller percentage of tensile strain than other films. Although these differences are not statistically significant, no relationship can be found between formulation and elongation value (Table 4 and Figure 21-A).

In what concerns to Young's modulus, only List26 present differences that are statistically significant when compared to Listerine. List2, List8, List9 and List14 show a low average value for this parameter. On the contrary, the other films except List26 present a Young's modulus relatively similar to Listerine (E_t = 1105 MPa). The most similar are List5 (E_t = 984 MPa), List25 (E_t = 1128 MPa) and List20 (E_t = 1234 MPa). List5 had already been shown as the most similar film in TGA analysis.

In Table 11 it is presented the formulations used.

Table 11: Developed Formulations. Blue- E_t similar to Listerine; Red– Lower E_t

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	-	3,18%	-	-	-	4,97%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

Films highlighted in red have lower elastic modulus, being considered ductile films. Except List9, all these films present higher percentage of menthol in its composition, which may indicate that menthol is responsible for a softening effect. In fact, it is known that plasticizers have a strong influence in mechanical properties (Saini et al., 2012) and, although menthol is used as a flavouring agent, it can also act as a salivary stimulant and a plasticizer (Sharma et al., 2007).

List26 have the highest value of Young's modulus and show a high stiffness when compared to Listerine, being the more rigid film obtained. Although the amount of menthol is relatively

low, this formulation does not have propylene glycol in its composition. Therefore, it is understandable that this formulation origins a rigid film.

The films that are more similar to Listerine are highlighted in blue. Considering that menthol has an important role on stiffness, it is possible to suggest that the percentage of this excipient in Listerine films should be in the interval [0-3,87%]. Following the same idea, higher percentage of propylene glycol should also be considered: [15.08-16.22%]. Also, the percentage of pullulan in similar films is in a limited range, between [67-80%].

As shown in Figure 21-C, analogously to Young's modulus, List2 e List 8 present the lower tensile stress at break. On the contrary, List26 e List29 show the highest value of this parameter with a high level of significance. Once again, List5 show similar results to Listerine, along with List14.

In Table 12, this reference films are highlighted in different colours to better understand the influence of formulation.

Table 12: Developed Formulations. Blue- σ_B similar to Listerine; Yellow – Lower σ_B ; Grey- Higher σ_B.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	-	3,18%	-	-	-	4,97%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

Comparing Figure 21-C and Table 12 it is possible to identify that films with propylene glycol in their formulation present lower tensile stress at break, having a value close to Listerine (Table 10). Contrary, films without plasticizer show high values of this parameter.

According to Young's modulus analysis, menthol should also act as a plasticizer, so it is expected that its presence also influence tensile strength. Indeed, List2 and List8 (lower σ_B - yellow) present higher percentage of menthol in their constitution. On the contrary, List26 and List29 (higher σ_B - grey) show lower percentage of this excipient.

Although List14 also present higher percentage of menthol in constitution (9.44%), its tensile strength it is not so small as List2 and List8. This fact can be justified by the absence of propylene glycol, which allows obtaining films with high tensile break.

List5 (σ_B= 43.82 MPa) and List14 (σ_B= 33 MPa) present similar behaviour to Listerine (σ_B =35.46 MPa). Assuming that films with lower percentage of menthol are more comparable with Listerine, and that the percentage of this excipient in List14 is not considerable, the quantity of menthol should be between 0 and 3.75% to reproduce a film similar to Listerine. These range are consistent with those defined previously.

As List5 is similar to Listerine in TGA analysis and in mechanical properties, stress-strain curve is only presented for this formulation (Figure 22). In Appendix E, all stress-strain curves for all developed formulation can be consulted.

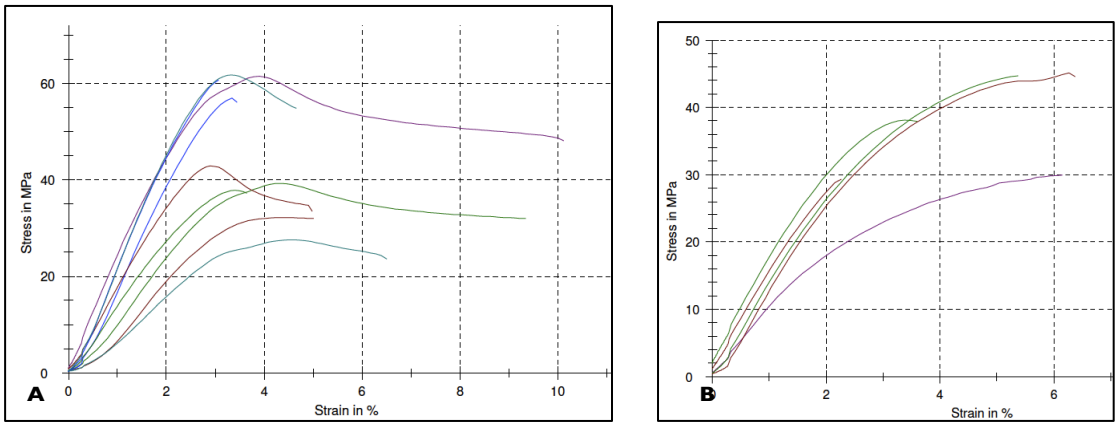


Figure 22: Stress-strain curves of Listerine and most similar film. A- List5, B- Listerine

From the results present in Figure 22, it is possible to observe an high variability of the results for List5 when compared to Listerine. However, both present values in the same order of magnitude.

v. DMTA

DMTA analyses were performed for List formulations and for Listerine films. Only films that presented similarity with Listerine in other techniques were chosen to be analysed by DMTA. The comparison between films can be analysed in Figure 23.

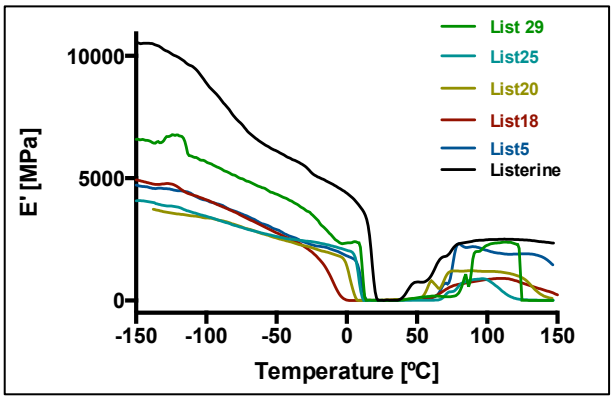


Figure 23: DMTA traces (1Hz) of List formulations and comparison with Listerine.

In general, all developed formulations present similar behaviour to Listerine films. In the glass transition region (0-25°C), a sharp decrease in the elastic modulus can be identified in all formulations and commercial film (Figure 23). When comparing developed formulations and Listerine, it is possible to see that the glass transition occurs at lower temperatures in developed films, once the decrease in E' begins first in these films than in Listerine. However, in List18 the decrease in E' starts below 0°C which indicates that the T_g is lower in this films than in the remaining.

Another important aspect to stress is the elasticity of the films. At glass transition range, developed films are less elastic than Listerine once, at this temperature, they all present lower value of elastic modulus than commercial film.

vi. Karl Fischer Titration

In order to evaluate residual water content in developed oral films, some Karl Fischer tests were carried out. Figure 24 presents the results obtained for the different films.

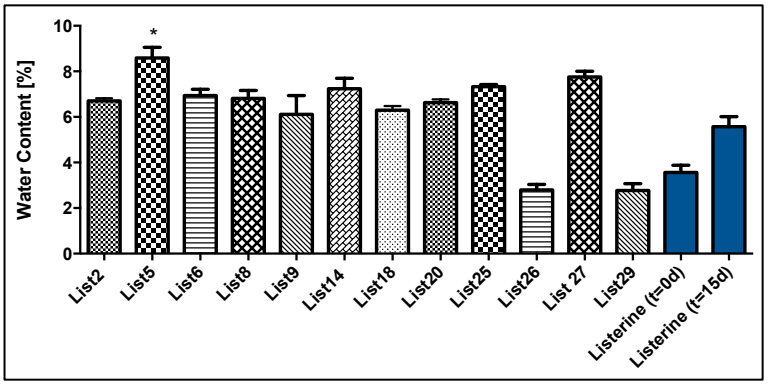


Figure 24: Residual water content determined by Karl Fischer Titration

Listerine was analysed immediately after the box opening (t=0days) and after 15days (t=15d), being kept under controlled conditions, at 43% HR. As both assays present differences in water content, it is presumable that Listerine is produced and packaged under different conditions from that used to store it. Therefore, the developed formulations should be compared to Listerine t=15d, since they were kept under some condition.

Although all developed films and Listerine t=15d were preserved under the same conditions, developed films have higher average in water content than Listerine.

The lowest average in water content was detected in List26 and List29, which are more similar to Listerine t=0d. Inversely, the highest residual water content was identified in List5 (statistically significant) and List27. However, all developed formulations present similar water content, except List26 and List29.

Although List5 have presented similar behaviour in the analyses above (TGA, Young's modulus and tensile strength), the List9, List18 and List20 are similar to Listerine in water content.

Once Karl Fischer results and the differences in formulations are hard to relate, DoE was used to help this interpretation. pullulan is the major component responsible for water content although with low confidence interval. Films with higher percentage of pullulan have less residual water than films with low percentage of this excipient.

Formulations with higher and lower average water content are presented in Table 13.

Table 13: Relevant formulations analysed by Karl-Fischer. Blue – Higher %, Grey – Lower %

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

According to DoE, films with higher percentage of pullulan have lower residual water content (List26 and List29). However, List5 have approximately the same percentage of pullulan in film as List29 and it is the developed formulation with higher water content. This means that this conclusion cannot be fully validate and should be considered carefully.

Something important to point out is the fact that films with low water content have no propylene glycol in its composition, but present acessulfame K. On the contrary, films with high water content have plasticizer in composition and not acessulfame K.

Karl-Fischer results can be compared to TGA curves until 100°C. In Figure 25 this relationship can be evaluated and in Table 14 the formulations can be analysed.

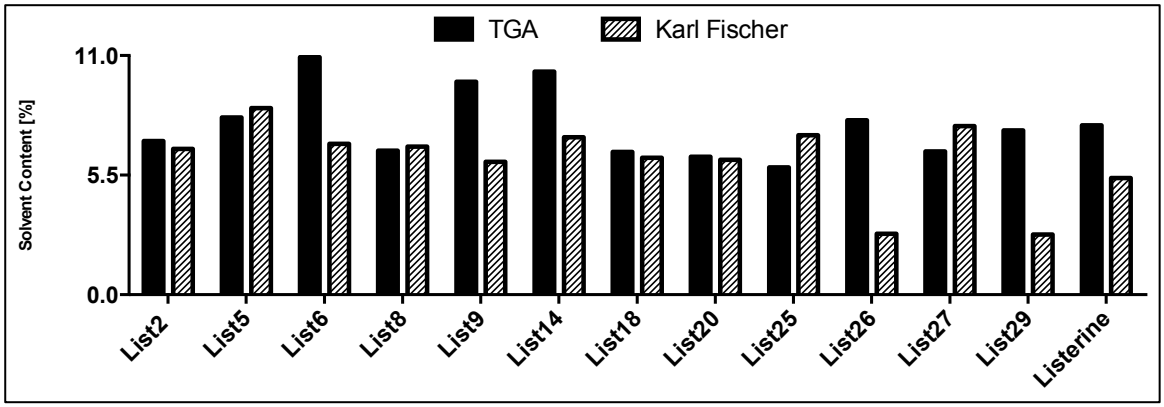


Figure 25: Comparison of two methods for determination of residual solvent.

From Figure 25 it is possible to highlight some particularities. List6, List9, List14, List26 and List29 present some discrepancy between TGA and Karl Fischer results. In other films, no significant differences between both methods can be observed. Only in List25 the average solvent content is higher in Karl-Fischer method than in TGA. At 100°C, bound water is still present within the film matrix, which justifies the reason for less water content in TGA than in Karl-Fischer technique in these films.

Differences between these two methods could be expected since weight loss until 100°C in TGA is not only due to water evaporation. Until this temperature, there are some other excipients that can evaporate and be degraded. On the other side, since film matrices did not completely dissolve within the solvent used in Karl-Fischer titration, some water may not be available. However, since some films present consistent results in both methods, the results can be considered reliable.

In Table 14 the formulations of all films analysed can be evaluated. Films highlight in blue correspond to films that show some difference between TGA and Karl-Fischer.

Table 14: Developed formulations. Blue- Different results in Karl-Fischer and TGA.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	-	3,18%	-	-	-	4,97%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

According to Table 14, films highlight in blue colour show different results in both methods. All these films have no propylene glycol in its composition. As this excipient starts its thermal degradation below 100°C (Figure 15), it would make sense that films with this excipient had different results in TGA and Karl-Fischer. However, the opposite was observed. Films with propylene glycol present higher percentage of residual solvent by TGA than by Karl-Fischer.

The TGA analyses results indicated that films without plasticizer have higher percentage of pullulan. Due to its chemical structure, the presence of many available OH groups allows the establishment of hydrogen bonds with water molecules. For this reason, films with higher percentage of this excipient retain more water and, consequently, have more residual water content, when compared to other films.

vii. Contact Angle Measurement

In the Figure 26, it is presented the contact angle results obtained for some developed formulations.

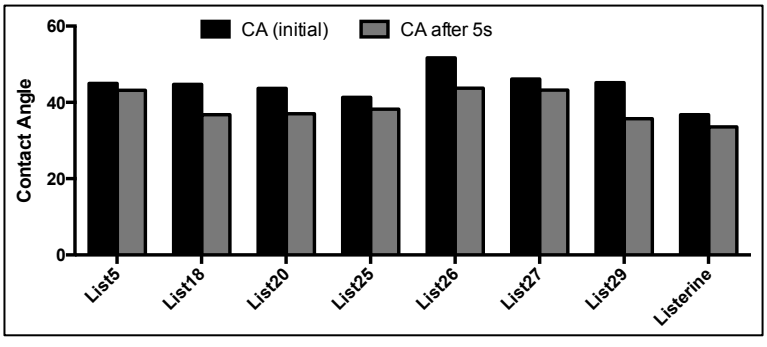


Figure 26: Contact Angle of representative films.

In general, studied formulations have higher initial contact angle than Listerine films, which means that commercial film is more hygroscopic than the developed ones. List26 stands out from the other films because it presents the highest average angle (51.60°), unlike List25 that shows the lowest initial contact angle (41.31°).

No relation between films formulations and contact angle value was possible to establish.

viii.Disintegration

Figure 27 represents the disintegration time of developed films.

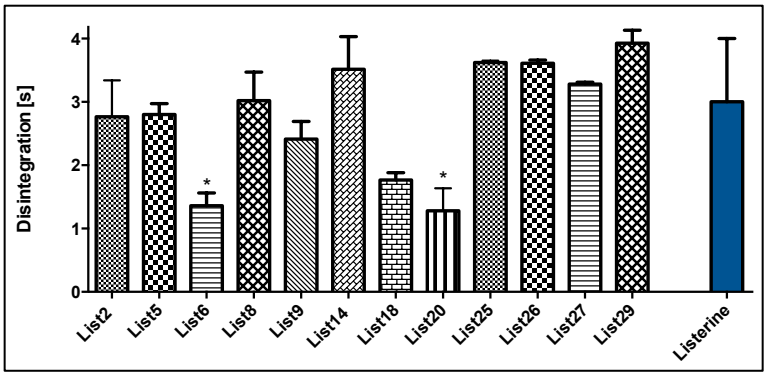


Figure 27: Disintegration time of developed formulations.

According to Figure 27, all developed formulations start to disintegrate in less than four seconds. List6, List18 and List20 present the lowest disintegration time. In fact, the difference between List6, List20 and Listerine was statistically significant. When compared to other films, there are no significant differences. List18 and List20 also present a lower initial contact angle when compared to other films, which means that they are more hygroscopic, so they take less time to disintegrate.

List26, List27 and List 29 show an initial contact angle with higher average value. This mean that they are less hygroscopic that other films. Therefore longer disintegration times were expected. Disintegration results obtained are consistent with previous analyses.

Even so, it should be mentioned that the results of this test are too relative. The differences between the developed formulations are too small and it is difficult to define the precise time to be considered. Based on that, the results should be considered only for comparison purposes.

Table 15: Developed formulations. Blue - films with lower disintegration time.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List6	77,35%	-	5,88%	4,99%	5,03%	-	6,75%
List8	58,43%	15,68%	9,12%	-	5,92%	5,94%	4,92%
List9	91,85%	0,00%	3,18%	-	-	-	4,97%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List18	68,32%	16,11%	-	2,11%	-	6,25%	7,21%
List20	70,21%	16,22%	-	2,10%	6,55%	-	4,91%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List26	89,59%	-	3,47%	0,93%	5,88%	-	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%
List29	80,88%	-	-	2,08%	6,48%	3,87%	6,68%

Films highlight in Table 15 with blue colour represent films that start to disintegrate faster. Apparently, films with higher percentage of carrageenan seem to have tendency to disintegrate first.

According to AlHusban (2011), carrageenan is used to drastically increase the viscosity of solutions and, consequently form orally disintegrating tablets with higher resistance to disintegration. This excipient is known to have a prime influence on this parameter, suggesting that increasing the concentration of carrageenan increases disintegration time.

This assumption is corroborated by another research using pullulan and carrageenan gum. As reported by AlHusban (2011), due to gel forming property, carrageenan led to high disintegration times and to low mechanical properties (Choudhary, 2012). However, experimental results are not consistent with these studies.

Although films with higher percentage of carrageenan tend to present lower disintegration times, this is not a linear conclusion. List27 and List29 have higher amount of this thickness agent and present higher disintegration times. Therefore, at this stage no more conclusion can be drawn regarding this matter, and more tests will be required.

Films highlighted in blue have also a particularity since they present high percentage of tween 80, which acts as a surfactant. According to DoE screening, as carrageenan, tween 80 also influences the disintegration time; films with higher percentage of tween starts to disintegrate first. This is not a linear conclusion since it is taken with a low confidence interval. In fact, List29 shows the higher disintegration time and, in this formulation, tween 80 represents almost 6.5% (w/w) on film.

As referred by Poluri (2013), adding tween 80 to the formulations means a reduction in disintegration time. However, Chantrainea (2006) refers surfactants should retard the disintegration once this excipient creates weak inter-particle bonds with other excipients, limiting water uptake responsible for disintegration. This observation is not in agreement with the main experimental results, except for List29.

List2, List5, List8, List14, List25, List 26 and List 27 present similar disintegration time to Listerine. Except List8, all referred formulations have lower percentage of tween. Therefore, the results suggest that the percentage of this excipient in commercial film should be between 0.13% and 0.17%.

In Table 16, similar formulations to Listerine can be analysed.

Table 16: Developed formulation with disintegration time similar to Listerine.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List2	65,57%	13,36%	8,57%	1,78%	5,25%	5,30%	0,17%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%
List14	88,36%	-	9,44%	2,07%	-	-	0,13%
List25	66,56%	15,66%	3,87%	1,08%	6,32%	6,38%	0,13%
List27	66,68%	15,98%	8,77%	2,05%	-	6,35%	0,16%

Following the same tendency, and as carrageenan also influences disintegration time, it is possible to find indicative values for the range of concentration of this excipient in Listerine. According to Table 16, it is possible to assume that the percentage of thickness agent should be between 1.08% and 2.05%.

2.1.1 Listerine – summary

Listerine results are summarized in the Table 17.

Table 17: Summary of characterization of List formulations.

	Excipient	Property	Influence
TGA	**Propylene Glycol**	Tonset	Decreases
		Weight Loss (100°C)	Decreases
	Pullulan	Tonset	Increases
		Weight Loss (100°C)	Increases
	Sucralose	Tonset	Decreases
Mechanical Properties	**Propylene Glycol**	Tensile stress at break	Decreases
	Menthol	Tensile stress at break	Decreases
		Young's modulus	Decreases
Disintegration	**Carrageenan**	Disint. Time	Decreases
	Tween 80	Disint. Time	Decreases

Taking into account the data collected in this work, Table 18 indicates the lower and higher limits for the main compounds made used in the production of Listerine.

Table 18: Defined ranges for concentration %(w/w) on Listerine and respective technique where these conclusions where taken.

	Lower Limit	Upper Limit	Technique
Pullulan	67%	80%	E_t
Propylene Glycol	15%	16.22%	TGA, E_t
Carrageenan	1.08%	2.05%	Disintegration
Menthol	0%	3.87%	TGA, E_t, σ_B
Tween 80	0.13%	0.17%	Disintegration
Sucralose	0%	6%	TGA

In order to validate the conclusions presented in Table 18, a new formulation was studied using the middle values for the intervals defined (Table 19).

Table 19: Desirable formulation developed.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List D	73,86%	15,27%	1,99%	1,54%	3,56%	3,58%	0,19%

Observing Table 19, we can see that the percentage of tween 80 doesn't feet on defined range. This is explained by the difficulty in pipetting such small quantities. However, we assume that there is no big difference in results.

i. FTIR analysis

Considering that FTIR analysis did not show relevant results in previous Listerine formulations (Section 2.2), no FTIR analysis was carried out to desired formulation.

ii. TGA analysis

TGA analysis of Listerine and List D is presented in Figure 28-A. List5 is also presented due to its similarity in previous TGA results (Figure 28-B).

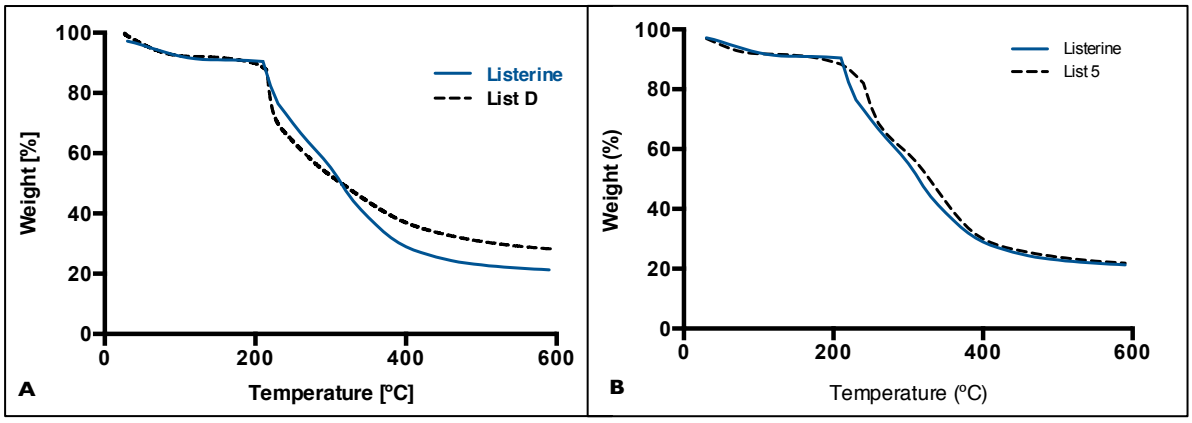


Figure 28: TGA profile of List D (A) and List 5 (B) and its comparison with Listerine.

List D presents a thermal behaviour similar to Listerine until degradation temperature. However, above this value the similarity is not maintained. Regarding List 5 (Figure 28-B), it is possible to observe that the profile obtained for this film resembles more the Listerine.

Table 20: List D and List5 formulations.

Film ID	Pullulan	Propylene Glycol	Menthol	Carrageenan	Acessulfame K	Sucralose	Tween80
List D	73,86%	15,27%	1,99%	1,54%	3,56%	3,58%	0,19%
List5	79,03%	15,08%	3,73%	1,99%	-	-	0,17%

Based on data presented (Table 20) it is possible to identify sucralose and menthol as the compounds that influence degradation before 200°C (they degrade below this temperature). Above this temperature, it is impossible at this stage to ascribe the compound(s) that define the degradation profile obtained.

iii. DSC analysis

DSC trace of List D can be observed in Figure 29.

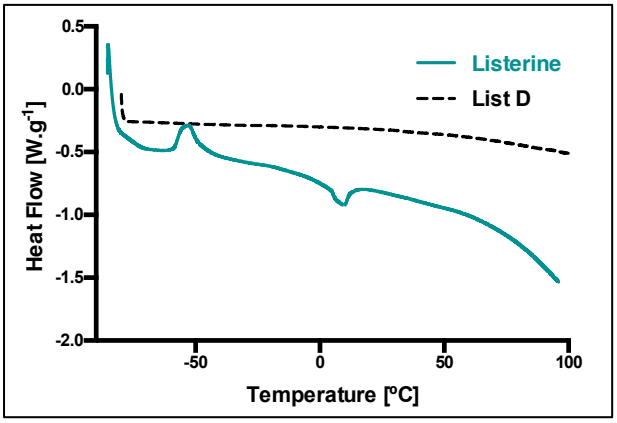


Figure 29: DSC curve of List D and comparison with Listerine.

As observed in previous analysed, DSC trace of List D did not allowed to draw any conclusion.

iv. Mechanical Properties

Table 21 and Figure 30 summarize the mechanical properties obtained to List D.

Table 21: Summary results of properties of desirable formulation.

Film ID	ε_B [%]	E_t [MPa]	σ_B [MPa]	Thickness (μm)
List D	4,605	1274	31,6	30
Listerine	4,345	1105	35,46	40

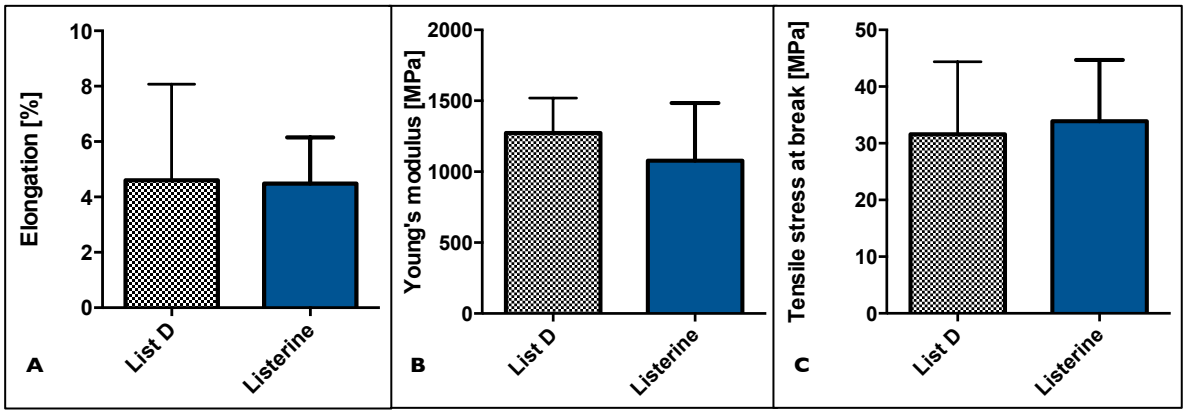


Figure 30: Summary results of mechanical properties of desirable formulation. A - Elongation, B - Young's Modulus, C - Tensile Stress at Break

The present results show that the formulation leads to a film that has very similar mechanical properties to Listerine. This result suggest that the formulation stand to be very close to Listerine and that the defined ranges were valid. However, comparing stress-strain curves, it is possible to identify some variability in results but in the same order of magnitude.

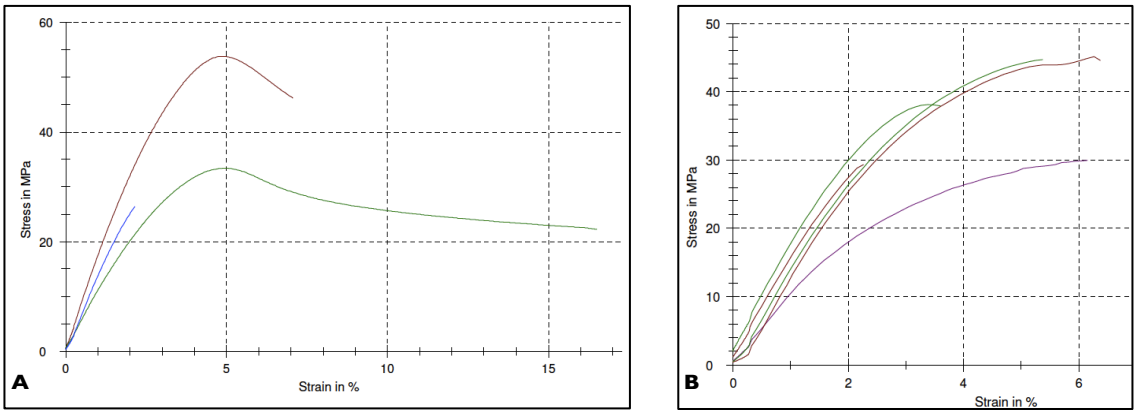


Figure 31: Stress-strain curves for: A- Desirable formulation, B-Listerine

v. DMTA

DMTA analyses were performed for desired formulation and for Listerine. Once List5 also present relevant similarity with this commercial film, it was analysed by DMTA and compared with List D. The comparison between films can be analysed in Figure 32.

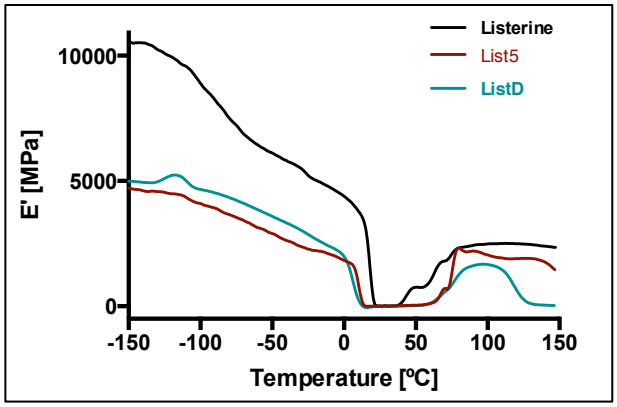


Figure 32: DMTA traces of List D, List5 and Listerine.

Developed formulations have a similar behaviour in E' curves. When compared to Listerine, the resemblance is not so obvious but it is possible to verify the same trend in E' profile. List D presents higher values in E' trace than in List5 which suggests that the desired formulation is closer to Listerine. Elastic modulus presents higher values in commercial film than in developed formulations, which indicates that Listerine is more elastic than List5 and List D (Figure 32).

Glass transition temperature occurs at lower temperatures in developed films and in Listerine; the slope in elastic modulus begins around 0°C, unlike Listerine that initiates the decrease of this parameter near room temperature.

vi. Karl Fischer Titration

Karl Fischer results can be observed in Figure 33.

A small difference in List D and Listerine (t=15d) can be observed, which can be due to handling during cut and storage. In general, formulations analysed previously (Figure 27) also have similar water content. Therefore, there is no significant variability in results this difference is not significant.

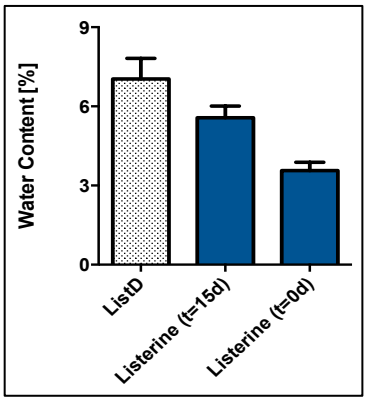


Figure 33: Residual water in List D and Listerine.

vii. Contact Angle Measurement

Contact angle analysis was also performed to desired formulation (Figure 34).

As observed in developed formulations, List D has higher average contact angle than Listerine film. This result suggests that the developed formulation has lower capacity to retain water. The same behaviour can be observed after 5sec, since both analysed films practically maintain the initial contact angle.

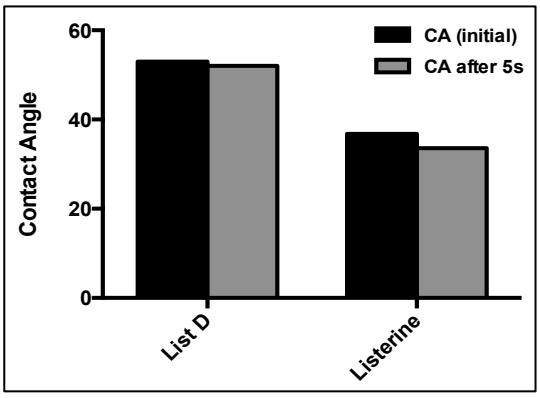


Figure 34: Contact angle of List D and Listerine.

This desired formulation presents the higher average angle when compared to other developed formulations (52.95°), very close to List26 with an initial contact angle of 51.69°.

viii.Disintegration

Figure 35 indicates that List D starts its disintegration later than Listerine. In fact, this formulation have the highest disintegration time when compared to developed formulations analysed previously.

These results are consistent with contact angle analysis, where List D presents the higher initial contact angle when compared to other formulations. For this reason, it is understandable that List D also presents the highest disintegration time.

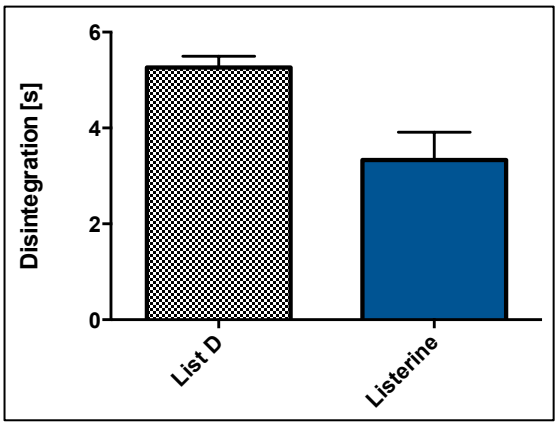


Figure 35: Disintegration time of List D and Listerine.

2.2 Gas-X I

The main components of this commercial film were selected from the patent (Schobel et al., 2007).

Two different grades of HPMC were indicated: Methocel E5 and Methocel E50. Their viscosity in 2%(w/v) aqueous solution at 20°C is 5 and 50 MPa.s^{-s}, respectively. At this stage of the work Methocel E50 was not available, therefore Methocel E15 was used for the preliminary tests.

Table 22 presents the list of formulations defined using a DoE method.

Table 22: Developed and characterized formulations.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.1.	43,3%	0,0%	0,0%	43,5%	0,0%	0,0%	0,0%	13,2%
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.6	15,7%	15,7%	15,4%	15,4%	18,2%	9,9%	4,6%	5,1%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%

Formulations presented in Table 22 were deeply characterized, according to commercial film characterization techniques (Section IV.1). The comparison between Gas-X and Gas I. formulations is presented in this section.

i. FTIR analysis

FTIR analysis was carried out to try understanding films composition and the influence of formulation in peaks absorption. The results of this analysis can be observed in Figure 36.

Although it should be possible identify different compounds in FTIR spectra, looking carefully to Figure 36 it is possible to observe that all spectra are very similar, which indicates that regarding the main components the formulation used is very close to Gas-X.

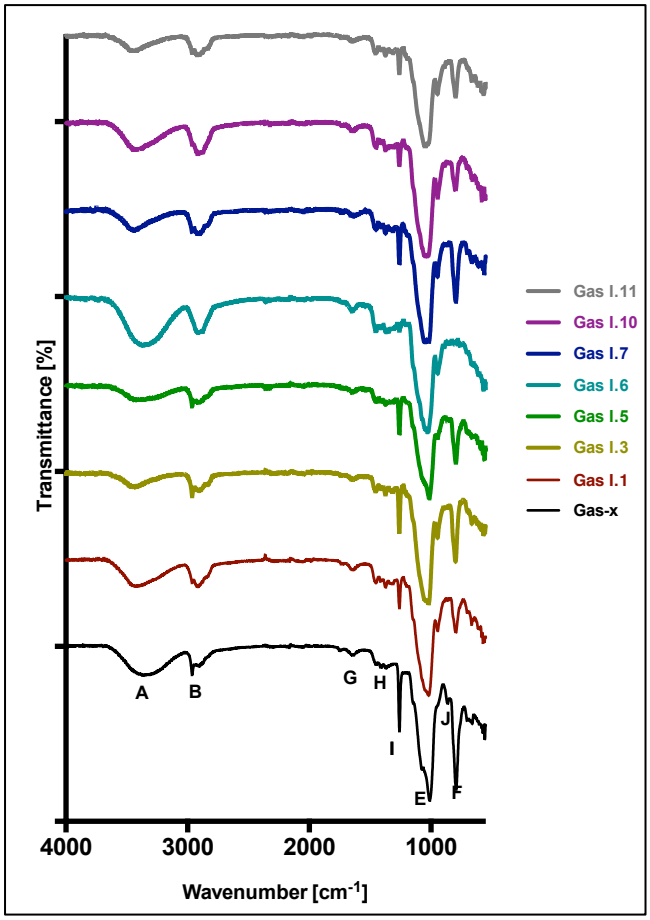


Figure 36: FTIR analysis of Gas I developed formulations

However, once Gas-X has around 60% of simethicone in composition, this component "masks" other excipients present in lower amounts. Figure 37 represents simethicone and Gas-X FTIR spectra.

Simethicone present a similar spectrum to Gas-X (Figure 37). This result confirms that API mainly composes this commercial film.

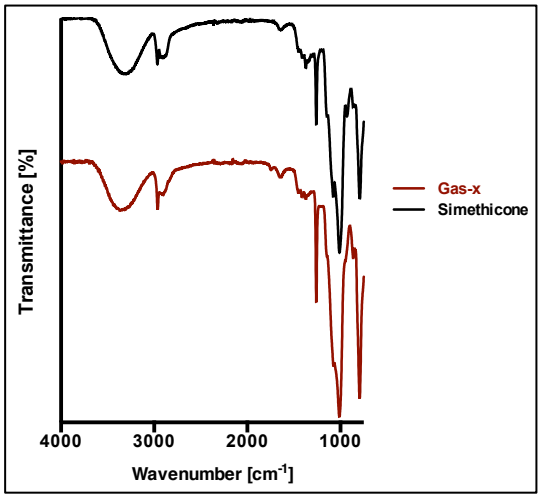


Figure 37: FTIR analysis of Gas-X and simethicone

The analysis of obtained spectra allows the identification of the absorption band characteristic in the region of alcohol group (A) (3600-2100 cm^{-1}). In all developed formulations this peak can be identified. However, in Gas I.11, Gas I.7, Gas I.5 and Gas I.3 this peak is less evident than in the remaining formulations. Once intensity is also related with concentration, it can be assumed that in these formulations there is one excipient with OH groups in less concentration than in the other formulations. Formulations can be analysed in Table 23.

Table 23: Developed formulations Gas I. Blue – peak characteristic of OH group less evident.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.1.	43,3%	0,0%	0,0%	43,5%	0,0%	0,0%	0,0%	13,2%
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.6	15,7%	15,7%	15,4%	15,4%	18,2%	9,9%	4,6%	5,1%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%

The mentioned films are highlighted in blue and have no modified starch in composition. This excipient has several available OH groups and, once it is absence in these films, it makes sense that the peak that corresponds to this structure has lower intensity than the remaining.

Letter F in 800-700 cm^{-1} region is characteristic of C—Cl bond, and was defined previously as characteristic of sucralose. Once Gas I.6 is the only film with sucralose in composition, it does not make sense that it is the only FTIR spectrum where this absorption band cannot be identified. So, Letter F does not correspond to C—Cl bond.

Peak I was defined as Si—CH_3 bond, characteristic of simethicone. Gas I.6 presents the lowest percentage of this excipient in composition, and the absorption peak is not easily detected in this formulation. Contrary, Gas-X films have higher intensity in this region. This could indicate that the developed formulations have lower percentage of simethicone than the commercial film.

Letter B and letter E present in spectra, correspond to C—H bonds (2935-2915) and —O— group (1150-1050 cm^{-1}), respectively, which confirms the presence of these bonds in formulations.

Letter G and Letter H, present in Gas-X spectrum, were ascribed to aromatic compounds and aromatic amine (absorptions bands at 1600-1430cm^{-1} and 1340-1250cm^{-1}, respectively). These characteristics bonds are present in pigment FD&Blue#1. As these bonds are also present in simethicone FTIR, and because none formulation presents pigment in composition, it is not possible to confirm that this pigment is really present in Gas-X formulation.

ii. TGA analyses

Figure 38 present some representative results obtained for the formulations studied. In Appendix C, TGA curves of all developed formulations can be observed. Gas I.12 was not evaluated.

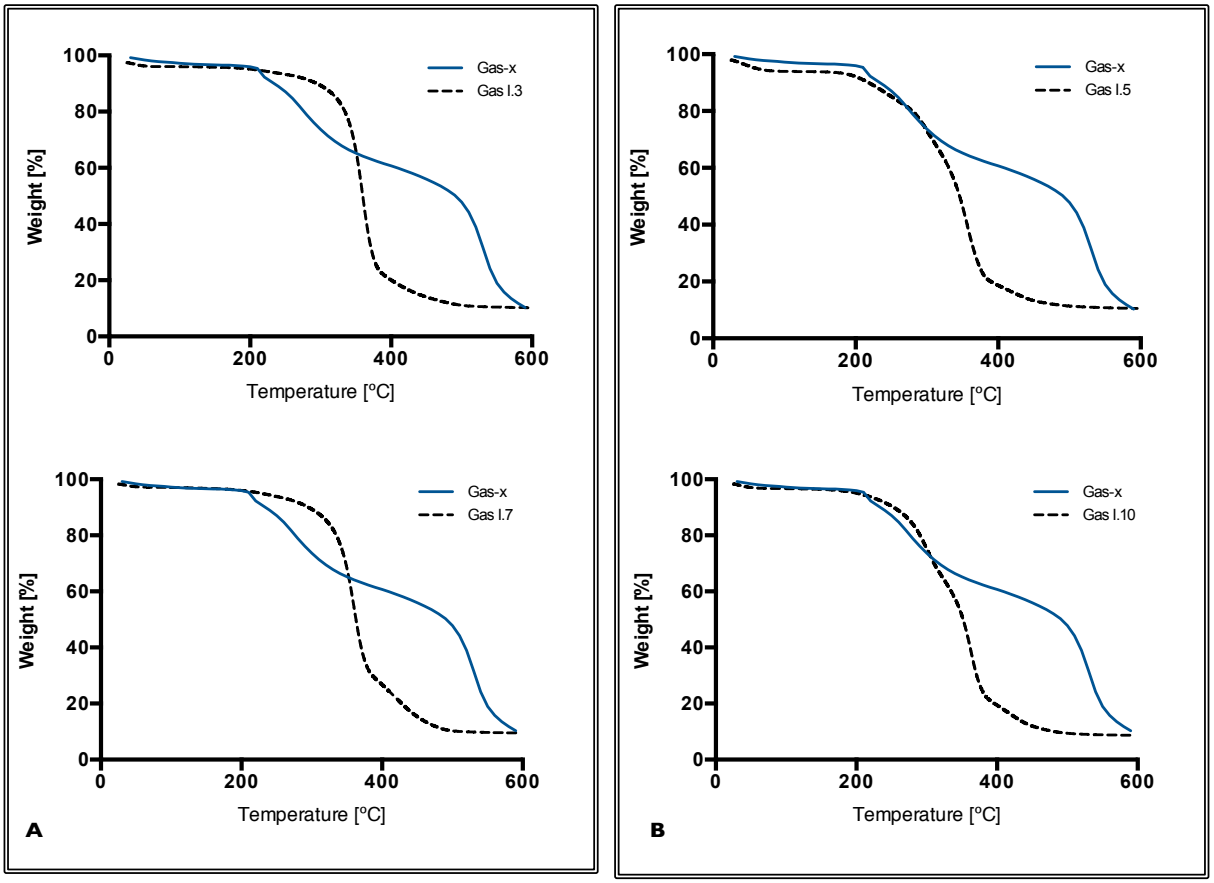


Figure 38: TGA profiles of representative formulations.

The thermograms obtained for Gas I and Gas-X are different result. This observation can be due to the fact that HPMC E15 was used instead of HPMC E50. It is known that the viscosity solution is altered and it has impact in films properties. Besides, this commercial film is known by the percentage of API included in one thin strip: Gas-X has a loading of 62.5mg of simethicone, which corresponds to approximately 60% of this excipient in film (Siddiqui, et al, 2011). However, the quantity used in the commercial film is also higher than the formulations tested.

The temperatures at occur a weight loss of 5% and 10% are presented in Table 24.

Table 24: Temperatures extracted from TGA curve. Blue – similar to Gas-X. Grey – higher than Gas-X.

Film ID	Temp. at Weight loss		T_{onset}
	5%	10%	
Gas I.1	62,86	267,95	279,19
Gas I.3	204,85	294,13	334,74
Gas I.5	60,77	217,69	261,69
Gas I.6	74,72	217,28	214,71
Gas I.7	228,15	294,85	333,87
Gas I.10	201,07	252,61	261,2
Gas I.11	257,48	312,16	339,19
Gas-X	211,03	234,54	221,6

Films represented in Figure 38-A have a higher thermal degradation temperature than Gas-X (Table 24 – Grey). Contrary, films represented Figure 38-B have a T_{onset} similar to Gas-X (Table 24 – Blue). Formulations can be analysed in Table 25.

Table 25: Developed formulations. Blue - T_{onset} similar to Gas-X, Grey- higher T_{onset} than Gas-X.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.1.	43,3%	0,0%	0,0%	43,5%	0,0%	0,0%	0,0%	13,2%
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.6	15,7%	15,7%	15,4%	15,4%	18,2%	9,9%	4,6%	5,1%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%

Gas I.3, Gas I.7 and other formulations with degradation temperature higher than Gas-X are composed primarily of polymers. For example, Gas I.3, Gas I.7 and Gas I.11 have around 80% of HPMC in composition. Figure 39 presents the TGA curve of HPMC.

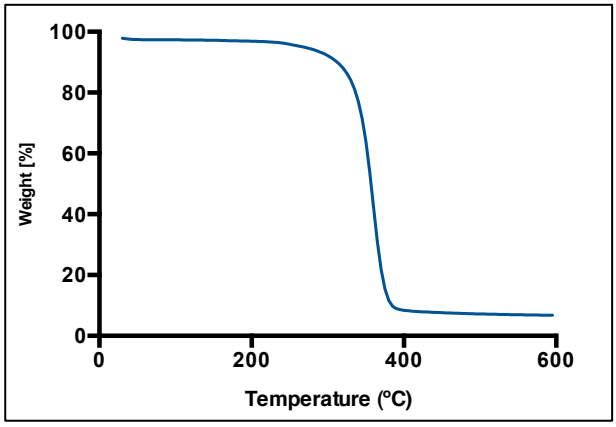


Figure 39: TGA curve of HPMC.

From Figure 39, it is possible to conclude that HPMC starts its thermal degradation process around 350°C. Once this polymer is the main component of the formulations, it is understandable that they have a T_{onset} value around this temperature.

According to DoE software, sorbitol has an influence in T_{onset} parameter. Higher percentage of this excipient implies higher T_{onset} value. Taking into account the information of Table 24 and Table 25, it is possible to observe that Gas I.6 have higher percentage of sorbitol in composition, but the film presents lower T_{onset}. As DoE provides these results with lower confidence level, and considering that Gas I.6 is the only film with sorbitol in composition, more tests should be required to draw any conclusion.

On the other hand, Gas I.6 has the lower percentage of simethicone. This may suggest that this excipient can also influence T_{onset} and lead to film with less thermal stability. However, there are no enough data to support this conclusion.

As referred before, oral films are deeply influenced by moisture. Therefore, it is important to evaluate the weight loss until 100°C. These results are presented in Figure 40.

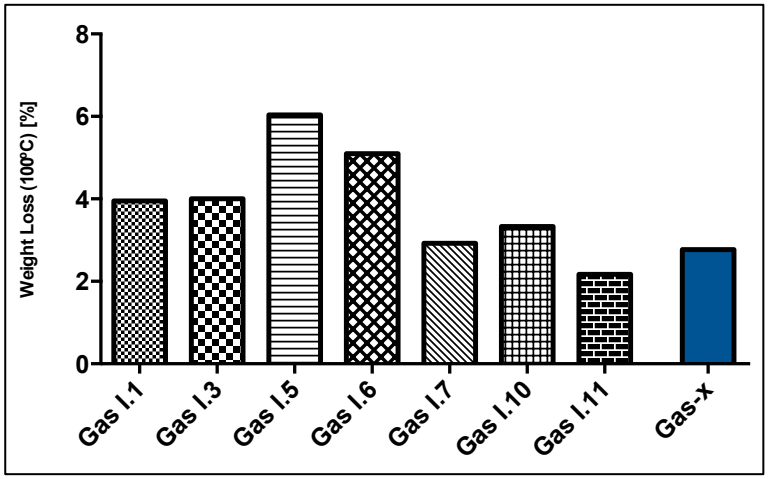


Figure 40: Weight loss until 100°C

From Figure 40 it is possible to verify that Gas I.5 and Gas I.6 are the films with higher percentage of weight loss. Until 100°C, this percentage is mainly due to water evaporation. Therefore, these films retain more water than the remaining.

On the contrary, Gas I.11 presents the lower percentage of weight loss when compared to the remaining formulations. The most similar to Gas-X are Gas I.7 and Gas I.10.

It is interesting to note that films with higher percentage of weight loss until 100°C have maltodextrin in their composition (Table 25). This observation can suggest that films with maltodextrin have a greater capacity for water retention. Consequently, they are more hygroscopic.

iii. DSC analyses

Figure 41 presents the DSC results for selected films that represent the different formulations. In Appendix D, all DSC results can be analysed.

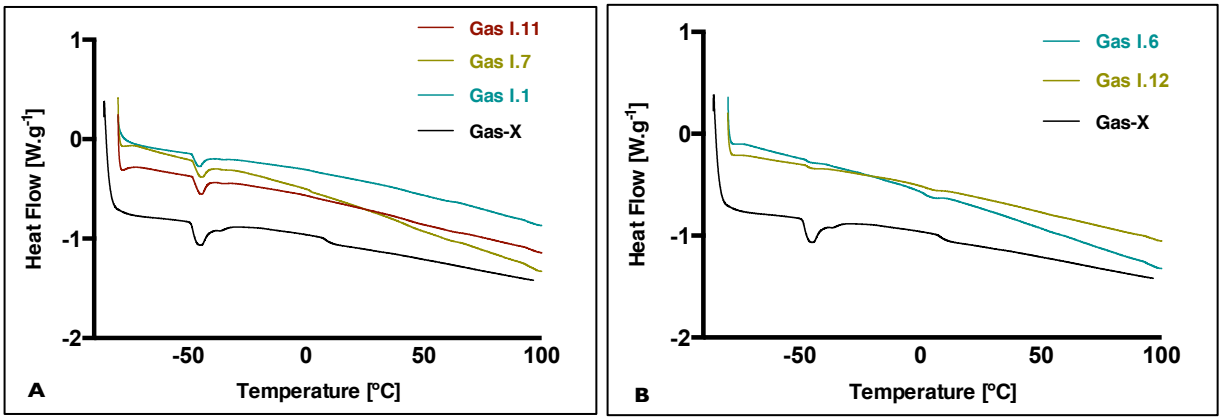


Figure 41: DSC curves of some Gas I. developed formulations. A – similar to Gas-X, B- some differences from Gas-X.

Although we have defined that Gas-X events are difficult to ascribed, it is possible to identify in Figure 41-A that the formulations present the same thermal event around -50°C. This endothermic event is common for the developed formulations, except in Gas I.6 and Gas I.12 (Figure 41-B). In these formulations, there is a variation in heat flow around this temperature, but not so pronounced as in the other ones.

Gas I.6 and Gas I.12 have lower percentage of HPMC when compared to other formulations. This result may suggest that the percentage of HPMC in Gas-X is higher than 30%. These films have also lower percentage of simethicone.

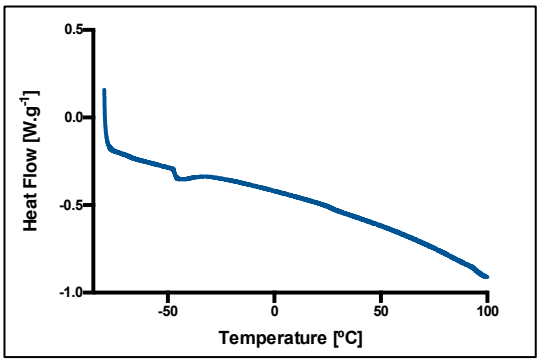


Figure 42: DSC curve of simethicone

Comparing simethicone and Gas-X DSC curves (Figure 42), it is possible to identify that simethicone present the same thermal event around -50°C as Gas-X. This result confirms the present of this excipient in the formulation.

iv. Mechanical Properties

Figure 43 presents the average values of mechanical properties for developed films. It was not possible to evaluate the mechanical properties of Gas I.6 due to its fragility.

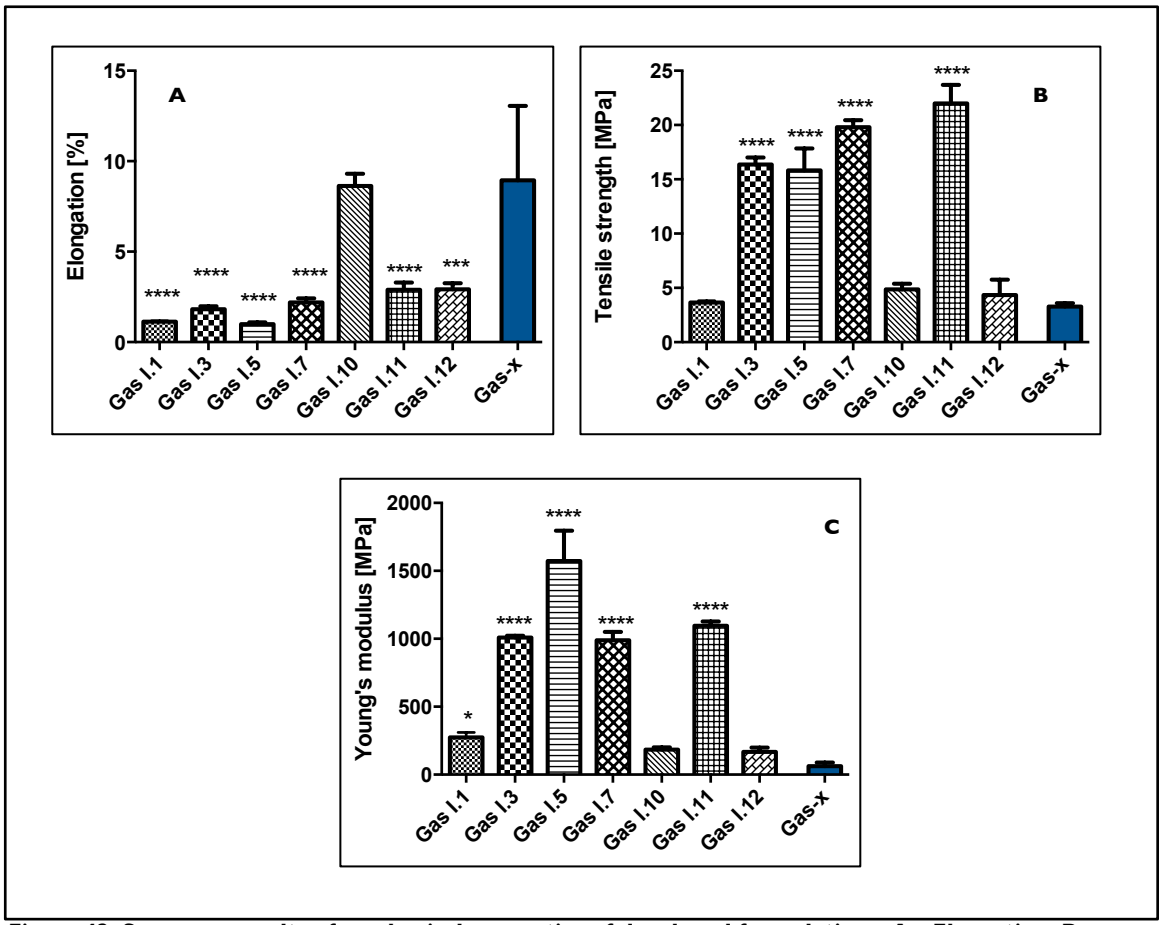


Figure 43: Summary results of mechanical properties of developed formulations. A - Elongation, B Tensile Stress at Break, C - Young's Modulus.

Table 26 summarizes the mechanical properties obtained for the films.

Table 26: Summary results of mechanical properties of formulations. Red – Lower values; Grey- Higher values.

Film ID	ε_B [%]	E_t [MPa]	σ_B [MPa]	Thickness (μm)
Gas I.1	1,12	273,5	3,65	90
Gas I.3	1,627	992,9	14,45	40
Gas I.5	0,99	1572	15,82	40
Gas I.7	2,193	987,1	18,87	40
Gas I.10	8,427	181,7	4,74	40
Gas I.11	2,833	1089	21,86	30
Gas I.12	2,92	168.1	4,345	45
Gas-X	**9,311**	**64,34**	**3,301**	**110**

According to results presented (Table 26), it is possible to identify a wide variation in the mechanical properties and even in the thickness.

From the results available in Figure 43-A, it is possible to identify Gas I.10 as the film with more elongation, almost 3-fold the value of the remaining formulations. This is the one with similar elongation to Gas-X.

Table 27: Developed formulations. Grey- similar elongation to Gas-X.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.1.	43,3%	0,0%	0,0%	43,5%	0,0%	0,0%	0,0%	13,2%
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%
Gas I.12.	16,2%	16,0%	16,0%	16,0%	14,8%	11,2%	4,8%	5,1%

Taking into account the information of Table 27, it is possible to suggest that PEG400 is the excipient that provides the elongation observed for Gas I.10. This film has highest percentage of plasticizer, which should be responsible for the elongation represented.

Gas I.10 and Gas I.12 have the lower Young's modulus value, which is also justified by the amount of plasticizer in their composition. According to Dixit (2009), this excipient improves the flexibility and reduces the brittleness of the strip, as observed in the presented results.

Gas I.1, Gas I.10 and Gas I.12 have the lower tensile stress at break and the value is similar to commercial film. These formulations differ from the remaining because they have modified starch in formulation. DoE software supports this statement: this excipient influences negatively this parameter. Higher percentage of modified starch leads to lower tensile strength value.

The results extracted from software have lower confidence intervals, which means that to take more reliable conclusions, more experiments should be done.

As Gas I.10 is similar to Gas-X in the different mechanical properties, stress-strain curve is only presented for this formulation (Figure 44). In Appendix E, stress-strain curves for all developed formulation can be consulted.

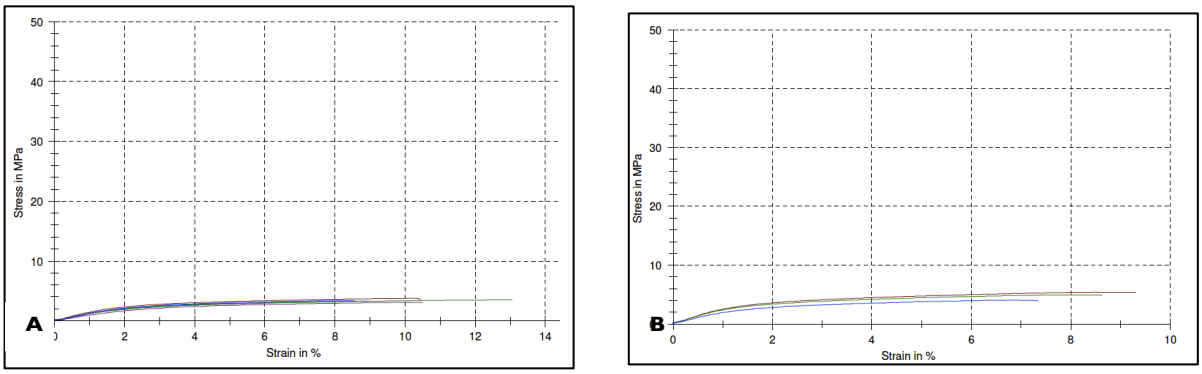


Figure 44: Stress-strain curves of Gas-x and most similar. A- Gas-X, B- Gas I.10

From the results present in Figure 44 it is possible to identify that the stress-strain curves of Gas I.10 and Gas-X are very similar. Even so, Gas I.10 has a higher tensile strength and smaller elongation percentage. The results suggest a correspondence between Gas I.10 formulation as Gas-X film.

v. DMTA

Once Gas I.10 presented similar behaviour to Gas-X in mechanical properties, this was the only film evaluated by DMTA analysis. The comparison between these both films will be made in next Section, with Gas III formulations.

vi. Karl Fischer Titration

Figure 45 presents the Karl Fischer results obtained for the formulations.

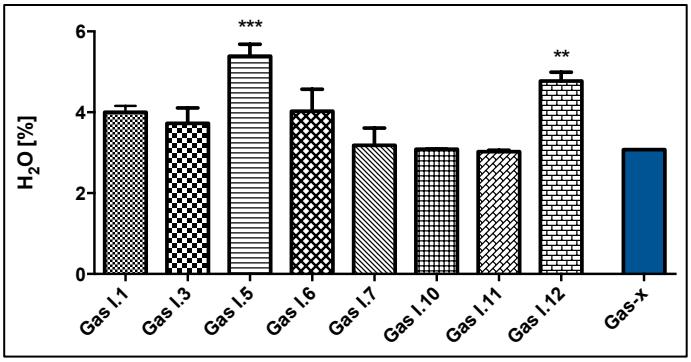


Figure 45: Residual water content determined by Karl Fischer Titration.

The water content obtained for Gas I.5 and Gas I.12 are significantly different from that in Gas-X. Formulations Gas I.7, Gas I.10 and Gas I.11 have approximately the same residual water as this commercial film and have the lower value when compared to others. The remaining films retain more water, but the difference is not statistically significant.

In Table 28, formulations can be analysed in order to find a possible relationship between the amount of excipient used and the water content.

Table 28: Developed formulation. Grey – higher % of water content.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.1.	43,3%	0,0%	0,0%	43,5%	0,0%	0,0%	0,0%	13,2%
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.6	15,7%	15,7%	15,4%	15,4%	18,2%	9,9%	4,6%	5,1%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%
Gas I.12.	16,2%	16,0%	16,0%	16,0%	14,8%	11,2%	4,8%	5,1%

Films with higher water content are highlighted in colour grey and are the only films with maltodextrin in composition. According to this observation and obtaining information from DoE software, maltodextrin has a strong influence in the residual water content. This result corroborates the weight loss until 100°C, where maltodextrin was found to have an important role in the water content.

Karl-Fischer results were compared to TGA curves until 100°C in Figure 46.

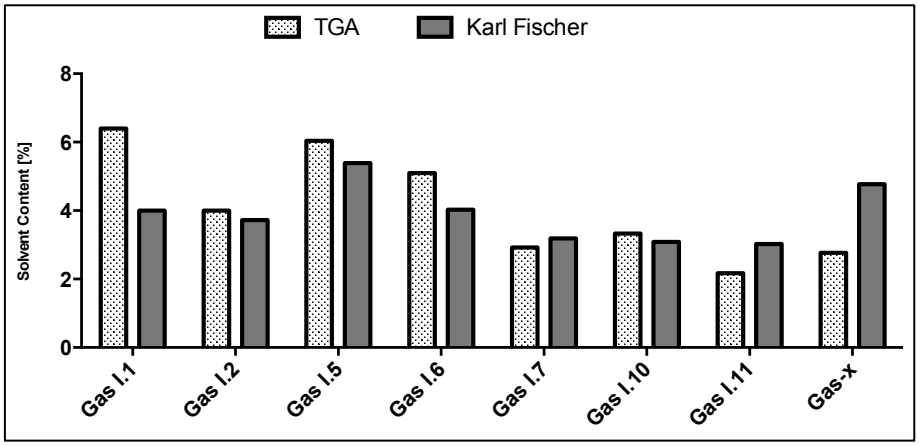


Figure 46: Comparison between two methods for determination of residual solvent.

Comparing solvent content in TGA analysis and in Karl Fischer technique, it is possible to observe that in some cases there are some discrepancies between both methods, namely in Gas I.1, Gas I.5, Gas I.6 and Gas I.11. In other films, no significant differences can be

observed. Only in Gas I.11 the average solvent content is higher in Karl-Fischer method than in TGA. At 100°C, bound water is still present within the film matrix, which justifies the lower water content in TGA than in Karl-Fischer technique in this film.

Differences between these two methods could be expected since weight loss until 100°C in TGA is not only due to water evaporation. Until this temperature, there are some other excipients that can evaporate or suffer degradation. On the other side, since film matrices did not completely dissolve within the solvent used in Karl-Fischer titration, the amount of water could be underestimated. However, since some films present consistent results in both methods, the data can be considered reliable.

Considering the results from Figure 46 and the formulations in Table 28, it is possible to conclude that the films that have maltodextrin and modified starch are the ones that show higher differences between the TGA and water context.

vii. Disintegration

Gas I.6 and Gas I.12 presented some difficult to peeling off the substrate and started to crack and split. This fact can be justified by inappropriate use of plasticizer in formulation (Dixit, 2009). Figure 47 represents the disintegration time of each formulation.

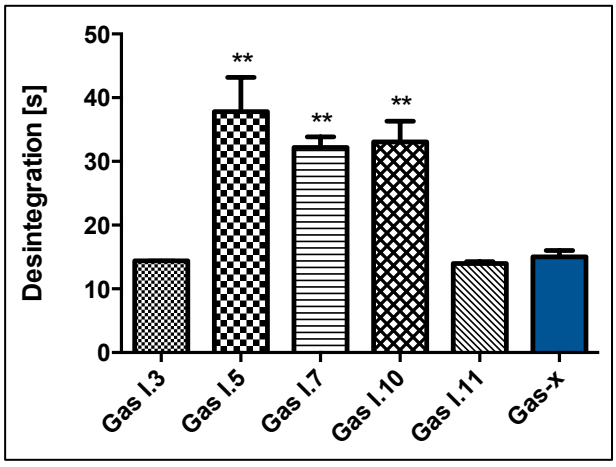


Figure 47: Disintegration time of developed formulations.

Gas I.3 and Gas I.11 starts their disintegration process at approximately the same time as Gas-X, around 15seconds. On the contrary, Gas I.5, Gas I.7 and Gas I.10 have a disintegration time statistically different from this commercial film.

In Table 29 the formulations can be related with disintegration time.

Table 29: Developed formulations. Grey- higher disintegration time

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	Simethicone
Gas I.3.	43,5%	43,3%	0,0%	0,0%	0,0%	0,0%	0,0%	13,2%
Gas I.5.	56,0%	0,0%	33,7%	0,0%	0,0%	0,0%	0,0%	10,3%
Gas I.7.	76,6%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	23,4%
Gas I.10	0,0%	41,0%	0,0%	24,6%	18,1%	0,0%	0,0%	16,2%
Gas I.11.	0,0%	76,2%	0,0%	0,0%	0,0%	0,0%	0,0%	23,8%

Gas I.5 is the film having maltodextrin in its composition and present the higher disintegration time. In previous analyses, this excipient was already pointed as having influence in water absorption.

As referred by Chen, higher loading of API leads to lower disintegration time (Chen et al.,2008). This can be confirmed by Gas I.11 which starts its disintegration process first than other film analysed.

2.3 Gas-X II

Formulations denominated Gas-X II were prepared using solutions of HPMC E5 10% (%w/w) and HPMC E50 2% (%w/w). Some films became fragile, brittle and powdery, and others crumbled into pieces. Consequently, it was impossible to fully characterize these films.

This phenomenon happens due to excess of water in films preparation, which leads to brittle films. Formulation has a high influence in films final look and in films properties.

2.4 Gas-X III.

Formulations denominated Gas III. were prepared using polymers in powder form.

In Table 30 it is presented the developed formulations resulting from a DoE screening.

Table 30: Developed and characterized Gas III. formulations.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	API
Gas III.4	41,1%	10,3%	13,7%	13,7%	0,0%	7,4%	0,0%	13,7%
Gas III.5	59,1%	14,8%	0,0%	0,0%	0,0%	11,2%	5,0%	10,0%
Gas III.6	59,8%	15,0%	20,1%	0,0%	0,0%	0,0%	0,0%	5,2%
Gas III.7	14,9%	15,0%	19,7%	0,0%	20,6%	10,4%	0,0%	19,5%
Gas III.10	13,7%	54,4%	0,0%	18,1%	0,0%	0,0%	0,0%	13,8%
Gas III.11	15,0%	14,9%	0,0%	0,0%	0,0%	10,6%	0,0%	59,4%
Gas III.12	12,4%	33,0%	16,5%	0,0%	0,0%	9,2%	4,2%	24,6%
Gas III.14	15,7%	47,1%	0,0%	0,0%	0,0%	8,8%	3,9%	24,4%
Gas III.15	50,7%	12,7%	0,0%	0,0%	17,5%	0,0%	0,0%	19,2%
Gas III.18	13,5%	49,6%	0,0%	18,0%	0,0%	0,0%	4,5%	14,3%
Gas III.19	14,8%	14,9%	0,0%	19,8%	0,0%	0,0%	0,0%	50,5%
Gas III.20	12,0%	47,5%	0,0%	0,0%	16,5%	0,0%	0,0%	24,0%

i. FTIR analysis

The FTIR spectra of representative formulations are presented in Figure 48.

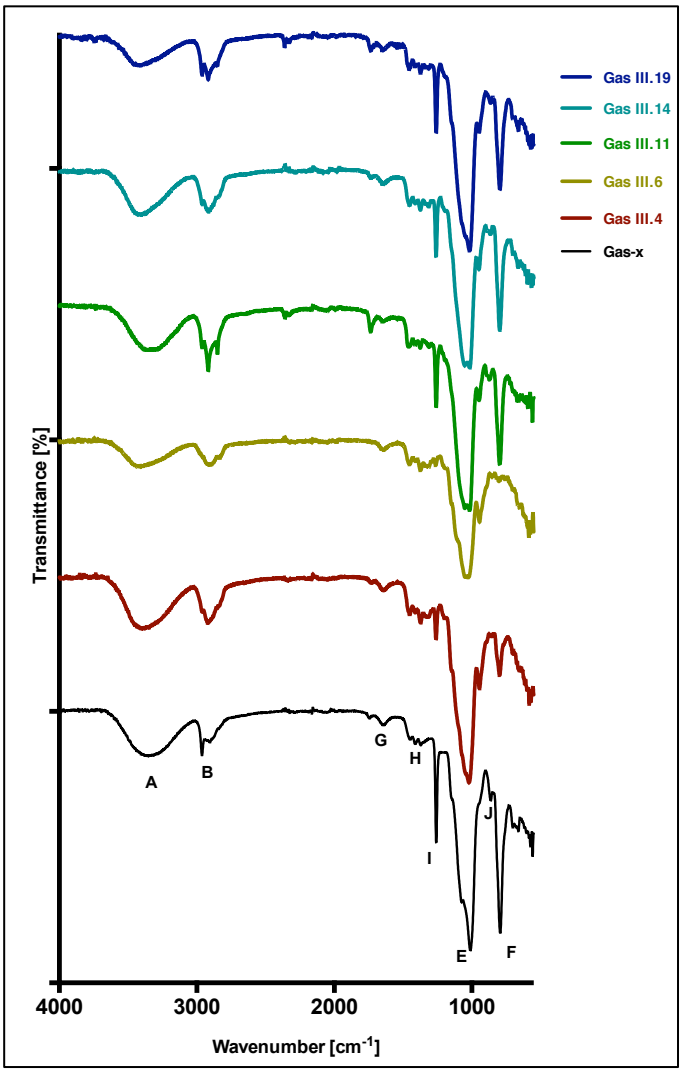


Figure 48: FTIR analysis of Gas III developed formulations

As in previous Sections, FTIR spectra of the different films are masked by the main excipient in composition. As in Gas I FTIR analysis, also simethicone masks Gas III films and no other excipients can be identified. However, it can be observed some differences in peaks intensity. Formulations can be observed in Table 31.

Table 31: Formulations representative of FTIR analysis. Blue – Different from Gas-X.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	API
Gas III.4	41,1%	10,3%	13,7%	13,7%	0,0%	7,4%	0,0%	13,7%
Gas III.6	59,8%	15,0%	20,1%	0,0%	0,0%	0,0%	0,0%	5,2%
Gas III.11	15,0%	14,9%	0,0%	0,0%	0,0%	10,6%	0,0%	59,4%
Gas III.14	15,7%	47,1%	0,0%	0,0%	0,0%	8,8%	3,9%	24,4%
Gas III.19	14,8%	14,9%	0,0%	19,8%	0,0%	0,0%	0,0%	50,5%

Previously FTIR analysis identified modified starch as the responsible for the intensity of the absorption band characteristic by OH group (Letter A). Considering Table 31 and Figure 48, it could be expected that Gas III.6, Gas III.11 and Gas III.14 have lower intensity in this region since they have no modified starch in composition. However, this cannot be confirmed in these results. Only Gas III.6 has an absorption peak with lower intensity in this region, which can be justified by the amount of simethicone in film.

Peak I was ascribed to Si—CH_3 bond, characteristic of simethicone. Gas III.4 and Gas III.6 present the lower intensity of this band, which is justified by the amount of this excipient in composition (Table 31). In fact, Gas III.6 not even presents an evident peak in this region once it only has 5% of API in film. The same situation occurs with the absorption peak represented by Letter F. It has already been demonstrated that this peak may not correspond to C—Cl bond characteristic of sucralose. Contrary, it is also related with the amount of API in composition. On this matter, Gas III.4 and Gas III.6 have lower intensity in this region and, once again, it is because they have the lower percentage of simethicone.

The remaining peaks have already been identified in Section IV.2.2.

ii. TGA analyses

In Figure 49, some representative TGA curves are presented. In Appendix C, all curves corresponded to developed formulations can be analysed.

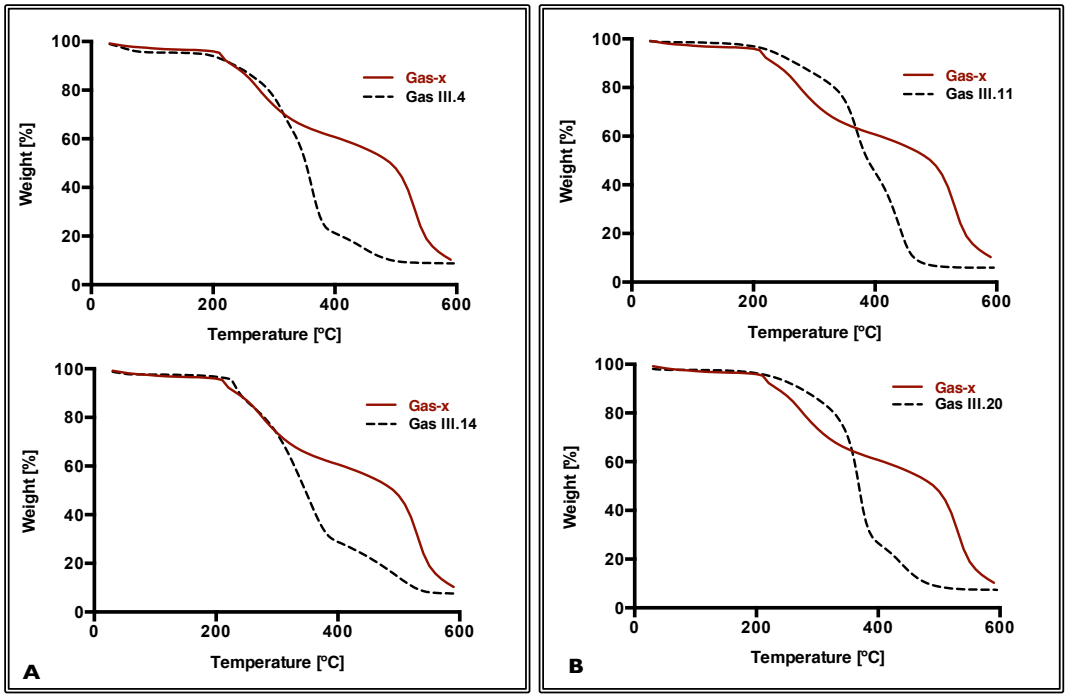


Figure 49: TGA curves representative of all Gas III. Formulations. A – T_{onset} similar to Gas-X, B – Higher T_{onset} than Gas-X

Although none of these films have a similar behaviour to Gas-X, it is possible to identify particular similarity in some of them. In films presented in Figure 49-A, thermal degradation process starts at approximately the same temperature of the Gas-X film (around 200°C). Films represented by Gas III.11 and Gas III.20 begins they degradation process after Gas-X (Figure 49-B).

To complete TGA analysis, temperatures at occur a weight loss of 5% and 10% and the T_{onset} are presented in Table32.

Table 32: Temperatures extracted from TGA curve. Blue – similar to Gas-X; Grey – similar behaviour until 300°C

Film ID	Temp. at Weight loss		T_{onset}
	5%	10%	
Gas III.4	179,16	236,89	271,26
Gas IIII.5	221,23	223,17	215,24
Gas III.6	190,7	240,6	326,17
Gas III.7	264,93	311,89	341,39
Gas III.10	212,97	289,07	329,2
Gas III.11	228,92	269,86	324,57
Gas III.12	193,36	224,86	223,86
Gas III.14	227,88	238,02	284,66
Gas III.15	224,75	274,67	333,61
Gas III.18	235,04	239,6	234,66
Gas III.19	240,32	286,3	320,03
Gas III.20	224,91	272,63	333,31
Gas-X	**211,03**	**234,54**	**221,6**

Formulations Gas III.5, Gas III.12 and Gas III.18 (highlighted in blue) have a similar T_{onset} to Gas-X, and represent the lowest values of all developed formulations. Although formulations represented in Figure 49-A do not have T_{onset} similar to Gas-X, their behaviour until 300°C are almost identical. Furthermore, their T_{onset} values are included at the lower of all developed formulations (highlighted in grey).

Table 33: Developed formulations. Blue- T_{onset} similar to Gas-X. Grey – similar behaviour until 300°C.

Film ID	HPMC E5	HPMC E15	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	API
Gas III.4	41,1%	10,3%	13,7%	13,7%	0,0%	7,4%	0,0%	13,7%
Gas III.5	59,1%	14,8%	0,0%	0,0%	0,0%	11,2%	5,0%	10,0%
Gas III.6	59,8%	15,0%	20,1%	0,0%	0,0%	0,0%	0,0%	5,2%
Gas III.7	14,9%	15,0%	19,7%	0,0%	20,6%	10,4%	0,0%	19,5%
Gas III.10	13,7%	54,4%	0,0%	18,1%	0,0%	0,0%	0,0%	13,8%
Gas III.11	15,0%	14,9%	0,0%	0,0%	0,0%	10,6%	0,0%	59,4%
Gas III.12	12,4%	33,0%	16,5%	0,0%	0,0%	9,2%	4,2%	24,6%
Gas III.14	15,7%	47,1%	0,0%	0,0%	0,0%	8,8%	3,9%	24,4%
Gas III.15	50,7%	12,7%	0,0%	0,0%	17,5%	0,0%	0,0%	19,2%
Gas III.18	13,5%	49,6%	0,0%	18,0%	0,0%	0,0%	4,5%	14,3%
Gas III.19	14,8%	14,9%	0,0%	19,8%	0,0%	0,0%	0,0%	50,5%
Gas III.20	12,0%	47,5%	0,0%	0,0%	16,5%	0,0%	0,0%	24,0%

Formulations highlighted in blue and grey colours represent the films with lower thermal degradation temperature. According to Table 33 and DoE software it is possible to identify that sucralose is present in all formulations, except in Gas III.4. So, films with higher percentage of sucralose in composition have a lower T_{onset} and, consequently, they are thermally less stable than films without sucralose. This can be validated by Gas III.5 that has the highest percentage of this excipient (5%) and have the lowest T_{onset} value (215,24°C) (Table 32).

Sucralose is an essential excipient in Gas-X films and it is possible to suggest that its percentage in films should be between 0 and 5%.

The weight loss up to 100°C is presented in Figure 50.

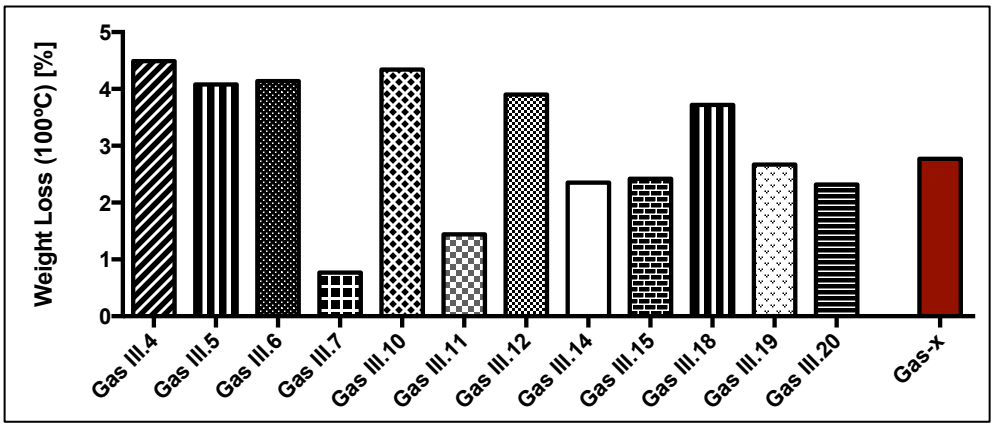


Figure 50: Weight loss until 100°C of Gas III. formulations

Taking into account Figure 50 and the formulations (Table 33), it is possible to verify that films with higher percentage of weight loss until 100°C have lowest percentage of simethicone. Except Gas III.12, all the others with higher solvent content have percentage of API inferior to 15%. Contrary, all other films with lower percentage of weight loss have a percentage of API higher than 20%. This result suggests that simethicone is responsible for water retention.

According to DoE software, PEG 400 also influences this parameter. Films with plasticizer in composition (Gas III.7, Gas III.15 and Gas III.20) have lower percentage of weight loss. This means that PEG 400 is responsible for water retention, which is easily justified by the hygroscopicity of this excipient.

Film with a similar weight loss until 100°C to Gas-X is Gas III.19. This film presents a percentage of API of 50.5% and no plasticizer in composition.

iii. DSC analyses

DSC curves of representative films can be observed in Figure 52. In Appendix D all DSC results can be analysed.

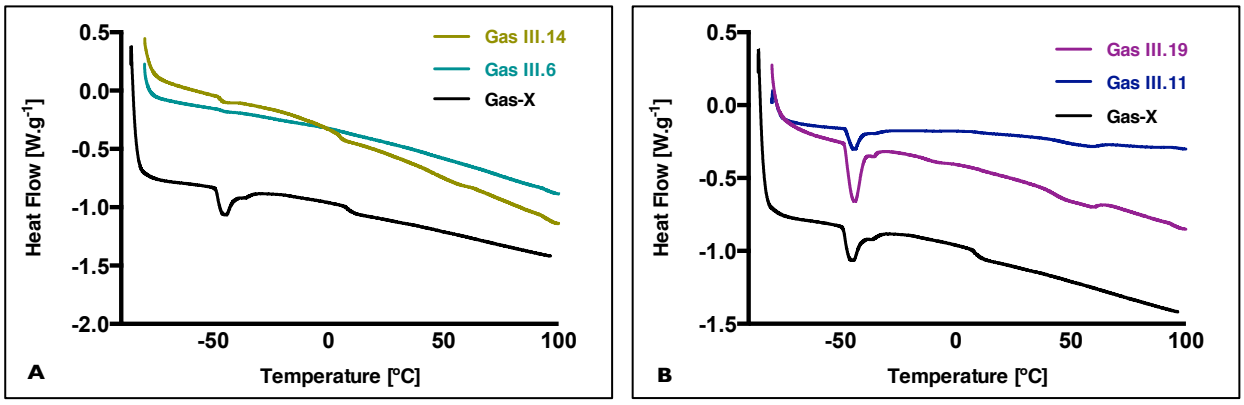


Figure 51: DSC curves for some Gas III. Formulations. A – discrete events, B – highlighted events.

The formulations were divided in two groups according the presence of a peak around -50°C. In Figure 51-A, films present no peak in this region. In opposition, films in Figure 51-B have an evident peak at this temperature and also present a glass transition at higher temperature. Differences between both groups are in the amount of simethicone in formulation. Films with higher percentage of API have lower percentage of polymers in composition. Gas III.11 and Gas III.19 have around 30% of HPMC and 50-60% of API.

Contrary, all other formulations have a percentage of HPMC above 50% and lower percentages of simethicone. (Table 33)

In Section IV.1, Gas I was referred that films with lower percentage of simethicone does not present evident thermal events (Figure 41-B). In this Section, results are consistent with previous analyses: films with higher percentage of simethicone have clear and evident events.

iv. Mechanical Properties

In Figure 52 an average value of mechanical properties of developed films is presented and these values are summarized in Table 34.

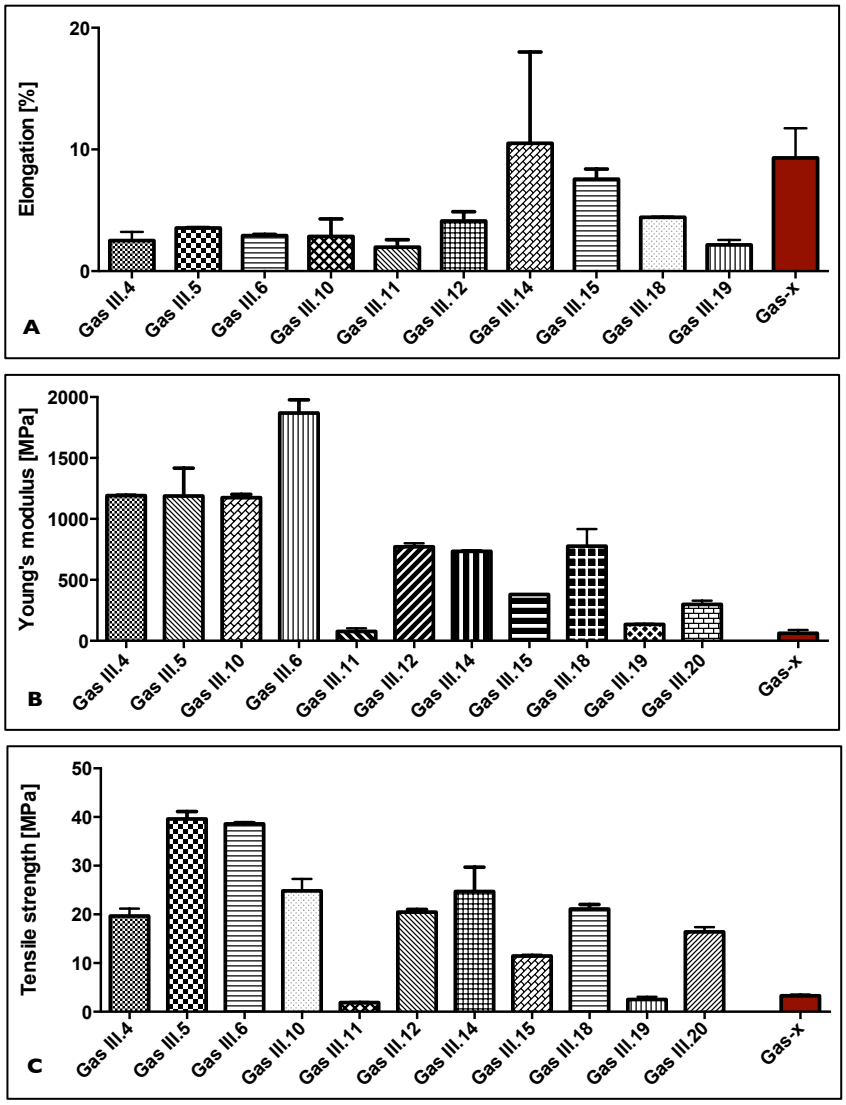


Figure 52: Summary results of mechanical properties of developed formulations. A-Elongation, B-Young's Modulus, C – Tensile Stress at Break.

Table 34: Summary results of properties of developed formulations. Grey – Higher ε_B; Blue-Similar to Gas-X; Red – Higher E_t Yellow – Higher σ_B.

Film ID	ε_B [%]	E_t [MPa]	σ_B [MPa]	Thickness (μm)
Gas III.4	2.68	1159	19.5	70
Gas III.5	3.56	1252	39.43	30
Gas III.6	2.843	1900	38.31	50
Gas III.10	3.203	1165	24.85	40
Gas III.11	2.16	83.89	1.763	70
Gas III.12	4.21	779.3	20.53	50
Gas III.14	10.51	734.8	24.7	50
Gas III.15	7.467	373.2	11,39	50
Gas III.18	4.433	795.8	20.55	60
Gas III.19	2.16	130.7	2.54	70
Gas III.20	55.7	293.5	16.42	50
Gas-X	**9.311**	**64,34**	**3,301**	**110**

According to results summarized in Table 34, it is possible to observe a wide variation of mechanical properties and thickness. Poluri (2013) referred that thickness of films increased with the viscosity grade of the film-forming agent. This parameter influences these properties, but this fact should not be considered in general evaluation.

Gas III.20 was not represented in Figure 52-A once its percentage of elongation is too high (56%), which is much higher than the other films elongation.

Gas III.14 and Gas III.15 present high percentages of elongation, being significantly different from the remaining films analysed. Gas-X elongation is set between these two films. In Table 35 formulations can be analysed in order to understand which excipients are affecting elongation parameter. Films with higher percentage of elasticity are highlighted in grey.

Table 35: Developed Gas III formulations. Grey – Higher ε_B; Blue-Similar to Gas-X; Red – Higher E_t Yellow – Higher σ_B.

Film ID	HPMC E5	HPMC E50	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	API
Gas III.4	41,1%	10,3%	13,7%	13,7%	0,0%	7,4%	0,0%	13,7%
Gas III.5	59,1%	14,8%	0,0%	0,0%	0,0%	11,2%	5,0%	10,0%
Gas III.6	59,8%	15,0%	20,1%	0,0%	0,0%	0,0%	0,0%	5,2%
Gas III.10	13,7%	54,4%	0,0%	18,1%	0,0%	0,0%	0,0%	13,8%
Gas III.11	15,0%	14,9%	0,0%	0,0%	0,0%	10,6%	0,0%	59,4%
Gas III.12	12,4%	33,0%	16,5%	0,0%	0,0%	9,2%	4,2%	24,6%
Gas III.14	15,7%	47,1%	0,0%	0,0%	0,0%	8,8%	3,9%	24,4%
Gas III.15	50,7%	12,7%	0,0%	0,0%	17,5%	0,0%	0,0%	19,2%
Gas III.18	13,5%	49,6%	0,0%	18,0%	0,0%	0,0%	4,5%	14,3%
Gas III.19	14,8%	14,9%	0,0%	19,8%	0,0%	0,0%	0,0%	50,5%
Gas III.20	12,0%	47,5%	0,0%	0,0%	16,5%	0,0%	0,0%	24,0%

By analysing results presented in Table 35 as well as the DoE, some conclusion can be drawn. Films with higher percentage of elongation have PEG 400 in composition and/or have higher percentage of HPMC E50. Gas III.20, referred as the one with highest elongation, have around 48% of HPMC and 16.5% of plasticizer. The combination of these two excipients and both in large quantities leads to a film with a much higher elongation rate than the remaining formulations.

Although Gas III.4 does not have plasticizer in composition, the percentage of HPMC E50 is around 47% (w/w), which contribute for a film with higher elongation rate. All films with amounts of this excipient around this value stand out from the others, although with lower difference.

In what concerns to stiffness, Gas III.6 stands out from the other films presenting the highest Young's Modulus, followed by Gas III.4, III.5 and Gas III.10. Comparing this observation with formulations in Table 35, it is possible to notice that these films, highlighted in red, have the lowest percentage of API. Otherwise, as the amount of simethicone increases, the stiffness of films decreases (Gas III.11and Gas III.19). Both films have 50-60% of this excipient and their Young's modulus is similar to Gas-X. This result could suggest that simethicone is responsible for weaker structure, which lead to weak and soft films. This conclusion is consistent with previous results analysed in other sections.

Gas III.5 and Gas III.6 present the higher values of tensile strength. Gas III.11 and Gas III.19 present similar tensile strength to Gas-X.

Films highlighted in blue in Table 35 present some similarity to Gas-X relatively to mechanical properties. Except for elongation parameter, they show an analogous behaviour that is important to point out. As referred, Gas-X is known by the amount of API in composition. Since both developed formulation present high percentage of this excipient, it would be expected to see some similarity in most characterization techniques. In this particularly case, it could be understandable than they do not present elongation rates equivalent to Gas-X. If we look carefully to formulations table (Table 35), it is possible to confirm that none of them has plasticizer in composition. As this excipient is essential for elongation behaviour, it would be expected that if Gas III.11 and Gas III.19 would have PEG 400 in composition, these films would show a higher elongation rate.

Figure 53 presents stress-strain curves for Gas III.11, Gas III.19 and Gas-X.

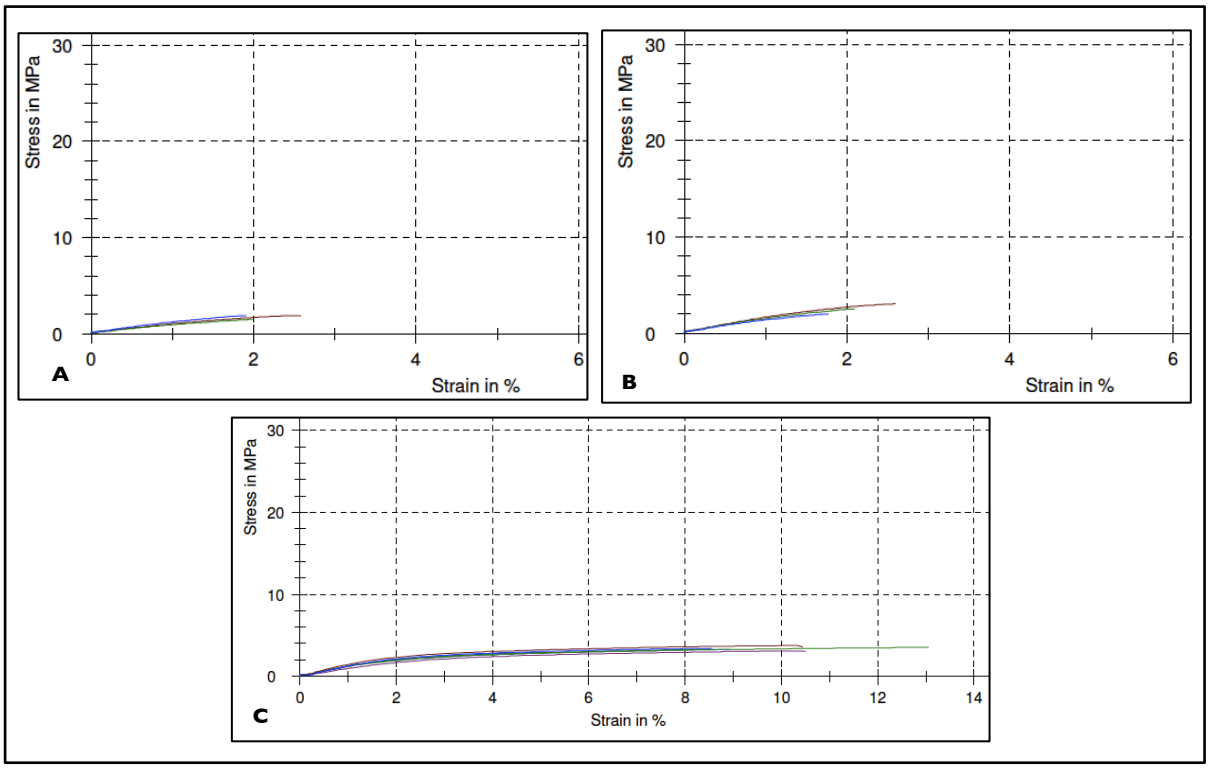


Figure 53: Stress Strain curves of Gas-X and similar films. A- Gas III.11, B-Gas III.19 and C - Gas-X

As referred before, the similarity between developed formulations and commercial film is quite evident, except in elongation parameter. It can be seen the same tendency in Figure 54–A and Figure 54-B for the tensile strength at break, but the maximum stress are different.

v. DMTA

Once only Gas III.11 and Gas III.19 presented similar behaviour to Gas-X in mechanical properties, these were the only two films evaluated by DMTA analysis. Gas I.10 from Section 2.2 will be analysed in this section. The comparison between these films is represented in Figure 54.

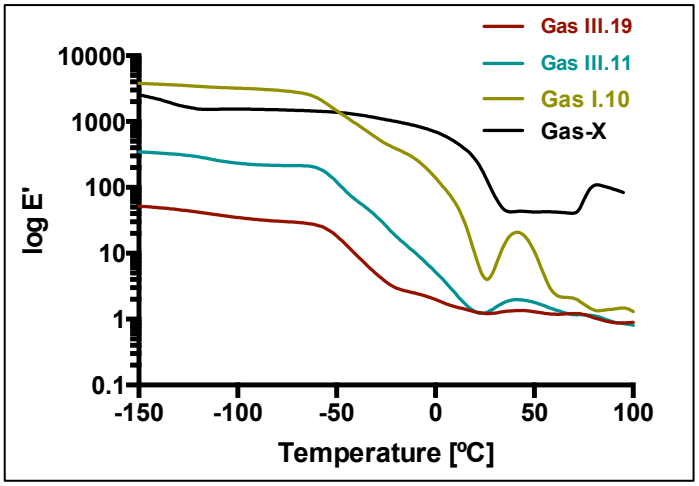


Figure 54: DMTA traces (1Hz) of Gas III formulations, Gas I.10 and Gas-X.

Similar profiles between developed formulations and Gas-X films can be observed in Figure 54. However, elastic modulus has different values in all analysed films. Glass transition is not so evident in developed films, once the sharp decrease in this parameter starts around -50°C and extends until room temperature (Figure 54).

vi. Karl Fischer Titration

The Karl-Fischer results are presented in Figure 55.

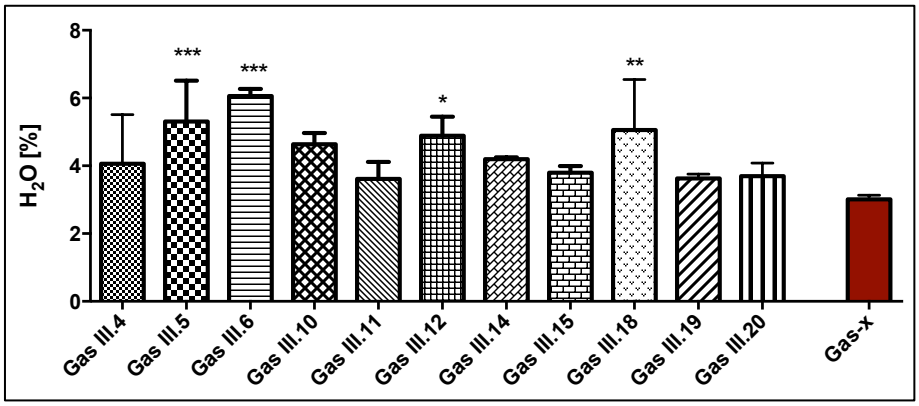


Figure 55: Percentage of water content determined by Karl-Fischer technique.

Gas III.5, Gas III.6, Gas III.12 and Gas III.18 present some differences, statistically significant, when compared to Gas-X. All the other films analysed have water content around 4 and 5%, which is approximately the same value as Gas-X. Nevertheless, this commercial film still has a residual water of about 3%. This small difference can be justified by different condition used for packaging and storage of commercial films.

In order to understand differences in solvent content between Karl-Fischer Titration and TGA analysis, both results are compared in Figure 56.

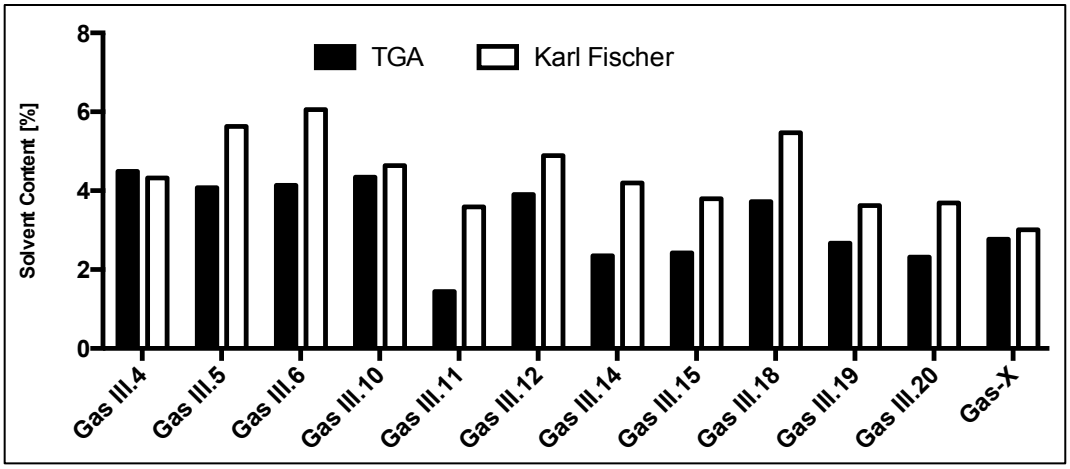


Figure 56: Comparison between two methods for determination of residual solvent

The comparison between the different methods shows some differences in results. Only Gas III.4 and Gas III.10 have approximately the same results in both methods. All the remaining films present higher percentage of water content in Karl-Fischer than in TGA. In previous Sections, TGA always presented a higher value than Karl-Fischer titration, which is justified by the insolubility of films in methanol medium used in Karl-Fischer.

Since the amount of determined water in titration is higher than that in TGA, it is possible to assume that at 100°C bound water is still present within the film matrix and for that reason is not detected during the analysis. Contrary to what happened in previous Sections, the relationship between this fact and the formulation was shown fruitless.

vii. Contact Angle Measurement

Figure 57 present the contact angles obtained for the different films.

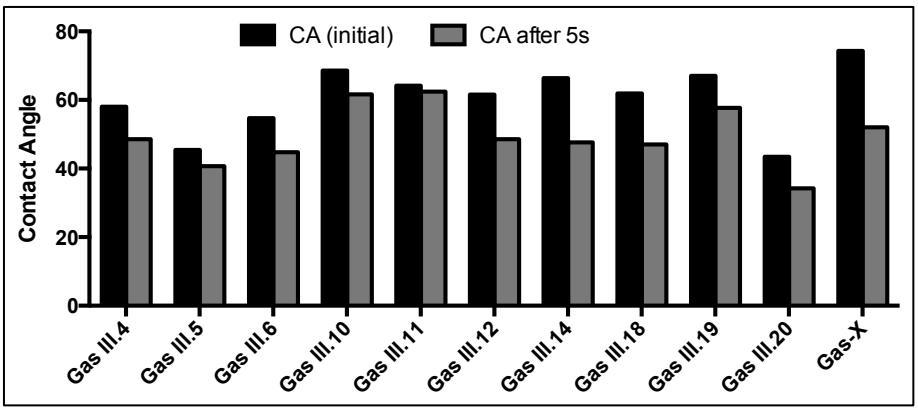


Figure 57: Contact angle of developed formulations.

Gas III.4, Gas III.5, Gas III.6 and Gas III.20 present lower average contact angle than the remaining films. Gas III.5 and Gas III.20 present the lowest angle, around 45°. The other films have an initial contact angle a closer to Gas-X. However, commercial film still has the higher

average contact angle (74.33°). This means that developed formulations are more hygroscopic than correspondent commercial film.

No relation between contact angle and formulations can be made, using the available data.

viii.Disintegration

The time at they begin to break down was measured and represented in Figure 58.

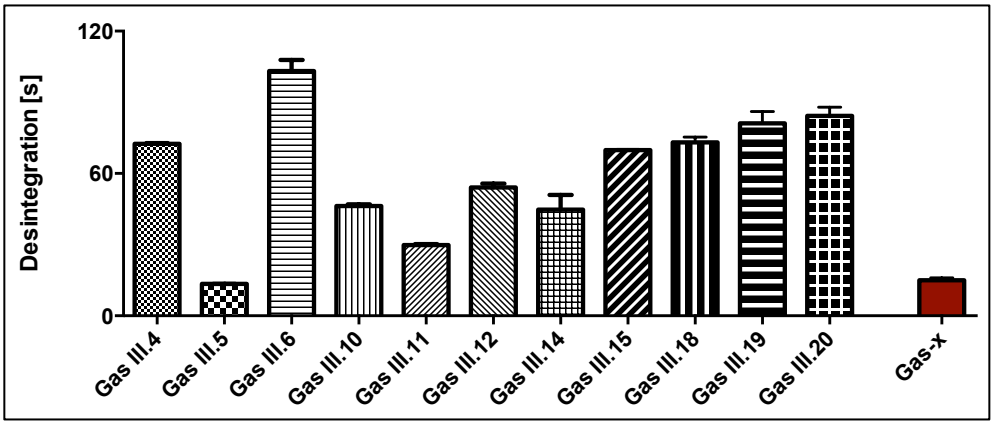


Figure 58: Disintegration time for Gas III. formulations

Regarding disintegration time (Figure 58), Gas III.6 stands out from the remaining formulations once it has higher disintegration times, around 100 seconds. Instead, Gas III.5 present similar disintegration time to Gas-X, and represent the lower value when compared to others.

Formulations can be analysed in Table 36, in order to understand which excipients affect this parameter. Films with higher disintegration times are highlighted in blue and films with lower disintegration time are highlighted in grey.

Table 36: Developed formulations. Blue – higher disintegration time; Grey – lower disintegration time.

Film ID	HPMC E5	HPMC E50	MDx	Modified Starch	PEG 400	Sorbitol	Sucralose	API
Gas III.4	41,1%	10,3%	13,7%	13,7%	0,0%	7,4%	0,0%	13,7%
Gas III.5	59,1%	14,8%	0,0%	0,0%	0,0%	11,2%	5,0%	10,0%
Gas III.6	59,8%	15,0%	20,1%	0,0%	0,0%	0,0%	0,0%	5,2%
Gas III.10	13,7%	54,4%	0,0%	18,1%	0,0%	0,0%	0,0%	13,8%
Gas III.11	15,0%	14,9%	0,0%	0,0%	0,0%	10,6%	0,0%	59,4%
Gas III.12	12,4%	33,0%	16,5%	0,0%	0,0%	9,2%	4,2%	24,6%
Gas III.14	15,7%	47,1%	0,0%	0,0%	0,0%	8,8%	3,9%	24,4%
Gas III.15	50,7%	12,7%	0,0%	0,0%	17,5%	0,0%	0,0%	19,2%
Gas III.18	13,5%	49,6%	0,0%	18,0%	0,0%	0,0%	4,5%	14,3%
Gas III.19	14,8%	14,9%	0,0%	19,8%	0,0%	0,0%	0,0%	50,5%
Gas III.20	12,0%	47,5%	0,0%	0,0%	16,5%	0,0%	0,0%	24,0%

Films that start they disintegration process earlier have sorbitol in composition. Sorbitol is pointed as a surfactant in Gas-X composition. As in List formulations, also films with tween 80 (excipient with the same function) lead to films with lower disintegration time. The same effect was represented by Poluri (2013)

Design of Experiments software also point out maltodextrin as responsible for disintegration process. Films with higher percentage of this excipient (as Gas III.6), present higher disintegration times. In previous Gas I. formulations, this excipient was also indicated as increasing disintegration time. In Karl-Fischer titration, weight loss until 100°C and in disintegration process of Gas I formulation, maltodextrin showed its influence in having greater capacity for water retention.

2.4.1 Gas-x summary

Gas III results are summarized in the Table 37.

Table 37: Summary of Gas III characterization.

	Excipient	Property	Influence
TGA	**Sucralose**	T_{onset}	Decrease
	Simethicone	Weight loss (100°C)	Decrease
	PEG 400	Weight loss (100°C)	Decrease
Mechanical Properties	**PEG 400**	Elongation	Increase
	HPMC E50	Elongation	Increase
	Simethicone	Young's modulus	Decrease
		Tensile stress at break	Decrease
Disintegration	**Sorbitol**	Disint. Time	Decrease
	Maltodextrin	Disint. Time	Increase

V. CONCLUSIONS

The overall analyses of Gas-X and Listerine films showed the impact of complexity of formulations in films properties. Despite being commercially available, it is evident the wide variation in both films properties which allows us to understand that is possible to obtain acceptable films in a broad range of values.

The attempt to reproduce commercial films revealed the influence of some excipients in films properties. In both films, sucralose showed an influence in thermal properties, namely in the decrease of T_{onset} of the degradation. The main polymers in both films (pullulan and HPMC) also showed an influence in this parameter. Films with plasticizer in composition revealed a decrease in weight loss (until 100°C), which allows us to consider that plasticizers, beside the mechanical properties, also affect the water retention.

Sorbitol and tween 80 act as surfactants in both films. With the addition of this excipient, the disintegration time decreases: films start to disintegrate first with increasing of concentration. Thickness agents, showed different results in this property: in Gas-X films, maltodextrin increases disintegration time, whereas in Listerine, carrageenan leads to films, which start to disintegrate earlier.

In Listerine films, plasticizer and menthol have an important influence in mechanical properties. Once intermolecular bonds and mobility of the polymer chains are increased, the stiffness and the tensile stress at break are reduced. Regarding Gas-X films, its mechanical behaviour can be justified by the amount of drug substance in formulation (at least 60% (w/w)). The high percentage of simethicone contributes to obtaining weak and soft films.

This study allowed us to establish the influence of main excipients in oral films properties. Furthermore, as a relatively new pharmaceutical form, there is a lack of information concerning this theme. Due to this, it was extremely important to deeply investigate the characteristics of these two commercially available oral films. With a complete characterization of the developed films, we establish methodologies for the characterization of such materials, which will constitute to the development of new formulations and oral technologies.

FUTURE WORK

This project has created a basis for new studies aiming the development of new oral films. Although some methodologies for characterization of such materials were established, some other techniques could be carried out, such as: Nuclear Magnetic Resonance (NMR), Size Exclusion Chromatography (SEC), Gas Chromatography (GC) and stability studies.

The formulations developed to Listerine and Gas-X should be optimized.

Further studies regarding the understanding of the molecular interactions between excipients should be carried out in the future.

REFERENCES

ABIAD, Mohamad G. et. al. - **A novel method to mesure the glass and melting transitions of pharmaceutical powders**. International Journal of Pharmaceutics, 2010: 23-29.

ALHUSBAN, F., PERRIE, Y., MOHAMMED, A.R. - **Formulation of multiparticulate systems as lyophilised orally disintegrating tablets**. European Journal of Pharmaceutics and Biopharmaceutics 79, 2011: 627-634.

ALLEN, Jimmy D. - **Integrated drug dosage form and metering system.** Patent 4,712,460. Dec 15, 1987.

ARYA, A. et. al. - **Fast Dissolving Oral films: and innovative drug delivery system and dosage form**. International Journal of ChemTech Research 2, no. 1 (Jan-Mar 2010): 576-583.

BLAGA, A. – **Properties and behaviour of plastics in:** National Research Council Canada, 1973 [Accessed 28 June 2013]: http://archive.nrc-cnrc.gc.ca/eng/ibp/irc/cbd/building-digest-157.html

BOND, L. et al. - **Differential scanning calorimetry and scanning thermal microscopy analysis of pharmaceutical materials.** International Journal of Pharmaceutics 243, 2002: 71-82.

BROWN, D. - **Orally disintegrating tablets - taste over speed**. Drug Delivery Technology 3, no. 6 (2003): 58-61.

CHANTRAINE, F. et al. - **Parametric Study of Surfactant Effect on Mechanical and Dissolution Properties of Detergent Tablets**. Journal of surfactants and detergents, *9*, 2006.

CHEN, M. et al. - **Castable edible pharmaceutical films**. Drug Del Tech , 8 (6), 2008: 35-41.

CHOUDHARY, D.R. et al – **Natural polysaccharides as film fomer: a feasibility study for development of rapid sissolving films of ondasentron hydrochloride.** International Journal of Pharmacy and Pharmaceutical Sciences 4, 2012: 78-85.

CRAIG, Duncan Q.M.; JOHNSON, Fiona A. "- **Pharmaceutical applications of dynamic mechanical thermal analysis.** Thermochimica Acta, 1995: 97-115.

DIXIT, R. P.; PUTHLI, S. P. - **Oral strip technology: Overview and future potential**. Journal of Controlled Release 139 (2009): 94-107.

GABBOTT, Paul - **Principles and Applications of Thermal Analysis**. Oxford: Blackwell Publishing Ltd, 2008. ISBN-13: 978-1-4051-3171-1.

GARSUCH, Verena; BREITKREUTZ, Jörg - **Novel analytical methods for the characterization of oral wafers**. European Journal of Pharmaceutics and Biopharmaceutics 73 (2009): 195-201.

GARSUCH, Verena Ingeborg - **Preparation and Characterization of fast-dissolving oral films for pediatric use**. Düsseldorf: Heinrich Heine University, 2009. PhD thesis

GREB, Erik - **Are Orally Dissolving Strips Easy for Manufacturers to Swallow?** *PharmTech.* January 21, 2009. [Accessed April 18, 2013]. http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=576124

HOFFMANN, Eva Maria; BREITENBACH, Armin; BREITKREUTZ, Jörg - **Advances in orodispersible films for drug delivery**. Expert Opinion Drug Delivery 8, no. 3 (2011): 299-316.

HSU, C.P. Sherman - **Infrared Spectroscopy.** In SETTLE, Frank A., Handbook of Instrumental Techniques for Analytical Chemistry, Arlington, Virginia: Prentice Hall PTR (ECS Professional), 1997. 247-283

HU, Changqin; LIU, Ying - **Quality Control in Pharmaceuticals: Residual Solvents Testing and Analysis**. In AKYAR, Isin, Wide Spectra of Quality Control. Beijing: Intech, 2011. ISBN 978-953-307-683-6,183-210.

IBISWorld - **Thin Film Drug Manufacturing in the US: Market Research Report.** 2012. [accessed April 3, 2013]. http://www.ibisworld.com/industry/thin-film-drug-manufacturing.html

JONES, David S. - **Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance**. International journal of pharmaceutics, 1999: 167-178.

JONES, David S. et. al. - **Pharmaceutical applications of dynamic mecanical thermal analysis**. Advanced drug delivery reviews, 2012: 440-448.

KENDALL, Douglas S. **Infrared Spectroscopy of Coatings**. In Coatings Technology Handbook. Taylor & Francis Group, 2006.

KONG, Jilie; YU, Shanoning - **Fourier Transform Infrared Spectroscopic Analysis of Protein Secondary Structures**. Acta Biochimica et Biophysica Sinica, no. 39(8) (2007): 549-559.

KUMAR, Subash Vijaya - **Overview on fact dissolving films**. International Journal of Pharmacy and Pharmaceutical Sciences 2, no. 3 (2010).

KWOK, D.Y.; NEUMANN, A.W. - **Contact angle measurement and contact angle interpretation**. Advances in Colloid and Interface Science 81 (1999): 167-249.

LEUNG et al. **Fast dissolving orally consumable films** (2005), *Patent No. US 6,923,981 B2*.

LIN, Shan-Yang; WANG, Shung-Li - **Advances in simultaneous DSC-FTIR microspectroscopy for rapid solid-state chemical stability studies: some dipeptide drugs as examples**. Advanced Drug Delivery Reviews 64 (2012): 461-478.

MAHAJAN, Apoorva; CHHABRA, Neha; AGGWARWAL, Geeta - **Formulation and Characterization of Fast Dissolving Buccal Films: a Review**. Shcolars Research Library 3, no. 1 (2011): 152-165.

MALI, G.M., YAMASHITA, F. – **Starch films: production, properties and potential of utilization (Review)**, Semina: Ciências Agrárias, (2010): 137-156.

MALKE, S.; SHIDHAYE, S.; DESAI, J. - **Oral films - patient compliant dosage form for pediatrics.** The Internet Journal of Pediatrics and Neonatology 11, no. 2 (2011).

MENARD, Kevin P. - **Dynamic Mechanical Analysis: A practical introduction**. Florida: CRC Press, 1999.

MISHRA, Renuka; AMIN, Avani - **Formulation and Characterzation of Rapidly Dissolving Films of Cetirizine hydrochloride using Pullulan as a Film Forming Agent**. Indian Journal of Pharmaceutical Education and Research 45, no. 1 (2011): 71-77.

MORALES, Javier O.; MCCONVILLE, Jason T. - **Manufacture and Characterization of mucoadhesive buccal films**. European Journal of Pharmaceutics and Biopharmaceutics 77 (2011): 187-199.

MUJORIYA, Rahesh - **A Review on study of Buccal Drug Delivery System**. Innovative Systems Design and Engineering 2, no. 3 (2011): 29-33.

NAGAR, Priyanka; CHAUHAN, Iti; YASIR, Mohd - **Inghights into polymers: Film formers in mouth dissolving films**. Drug Invention Today 3, no. 12 (2011): 280-289.

POLURI, K. – **Formulation development and evaluation of novel oral soluble films of ziprasidone hydrochloride in the treatment of schizophrenia.** International Journal of Pharmacy and Pharmaceutical Sciences , 5 (2), (2013): 619-627.

PRAJAPATI, Bhupendra G.; RATNAKAR, Nayan - **A Review on Recent patents on Fast Dissolving Drug Delivery System**. International Journal of PharmTech Research 1, no. 3 (July-Sept 2009): 790-798.

REKHI, G.S. - **Novel technologies improve oral drug delivery performance, in: Formulation| The Leader of the Pack.** June 2009. [accessed April 3, 2013]. http://www.pharmaquality.com/me2/Audiences/dirmod.asp?nm=Browse+Articles&type=Publishing&mod=Publications%3A%3AArticle&mid=D3E3C719D8D44216836DCA4F4144BEC4&tier=4&id=41C41043EA4C451DBC28743E31E04755&AudID=5648A5C28C97462DBBDB309539B820EF.

ROGER, B.S. - **Physical and mechanical properties of alginate films containing calcium cations and ferrofluids**. Fifth International Conderence Polymer-Solvent Complexes & Intercalates. Lorient, France, 2004.

RAVNEET, Kaur; BALA, Rajni; MALIK, Dhruv- **A novel approach in oral fast dissolving drug delivery system - a review**. American journal of pharmatech research, December 2012.

SAINI, P., KUMAR, A., & VISHT, S. - **Fast Disintegrating Oral Films: A Recent Trend of Drug Delivery.** International Journal of Drug Development & Research , 4 (4), 2012: 80-94.

SCHOBEL et al. - **Solid dosage form containing a taste masked active agent (2007)** *Patent No. US 2007/0292515.*

SHARMA R., et al. – **Development of taste masked film of vasdecoxib for oral use**. Indian J. Pharm Sci 2007; 69: 320-3

SIDDIQUI, M.D. Nehal; GARG, Garima; SHARMA, Pramod Kuma - **A short review on "a novel approach in oral fast dissolving drug delivery system and their patents"**. Advances in Biological Research 5, no. 6 (2011): 291-303.

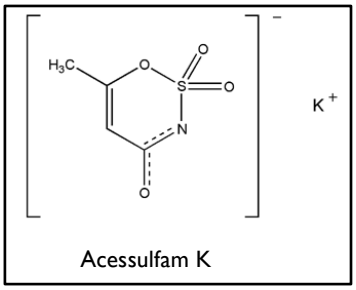
STEVENS, Malcom P. - **Polymer Chemistry: An introduction**. 3rd edition. NewYork: Oxford University Press, 1999.

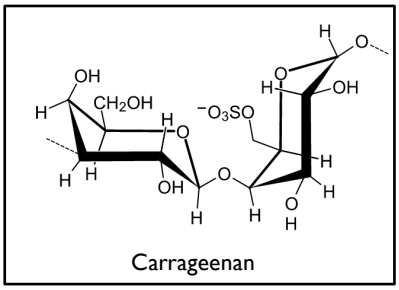
STUART, Barbara H. - **Infrared Spectroscopy: fundamentals and applications**. Chichester: John Wiley & Sons Ltd, 2004. ISBN 0-470-85428-6.

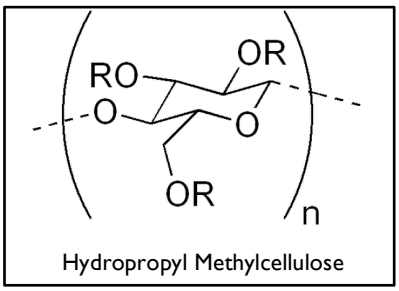
STUART, Barbara - **Polymer Analysis**. Chichester: John Wiley & Sons, Ltd, 2002. ISBN 047 18 1363X.

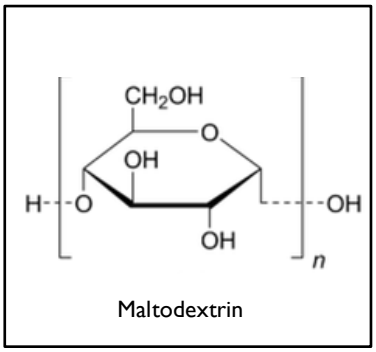
APPENDIX A

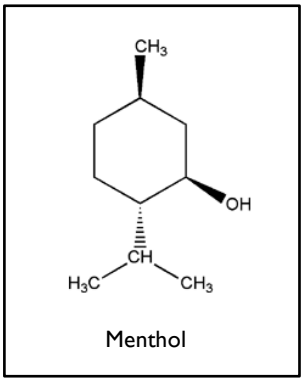
1. CHEMICAL STRUCTURES OF EXCIPIENTS

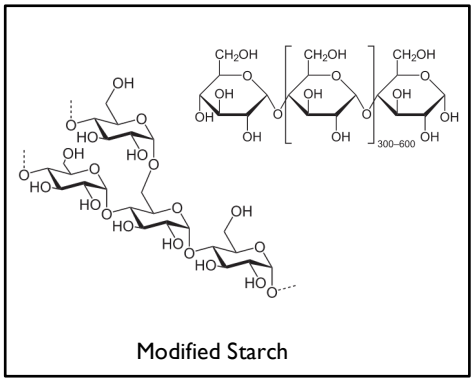

Acessulfam K

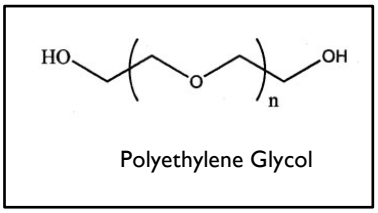

Carrageenan

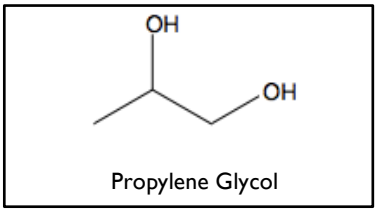

Hydropropyl Methylcellulose

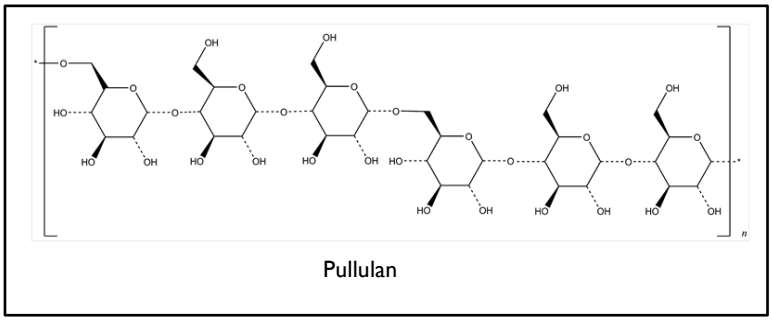

Maltodextrin

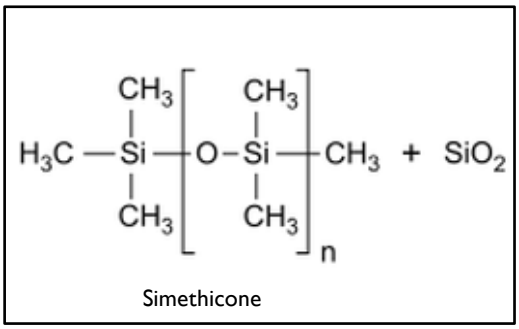

Menthol

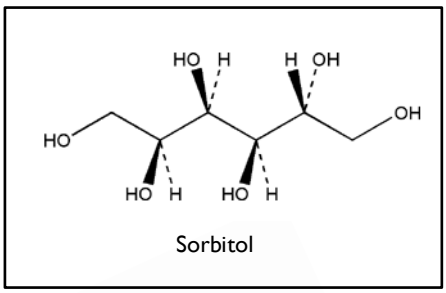

Modified Starch

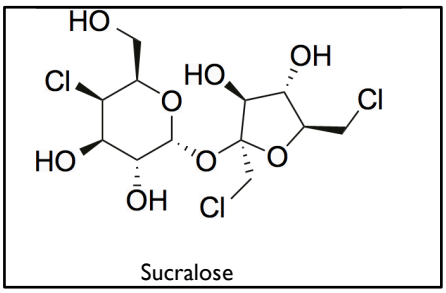

Polyethylene Glycol

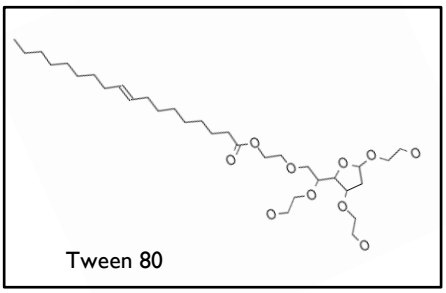

Propylene Glycol


Pullulan


Simethicone

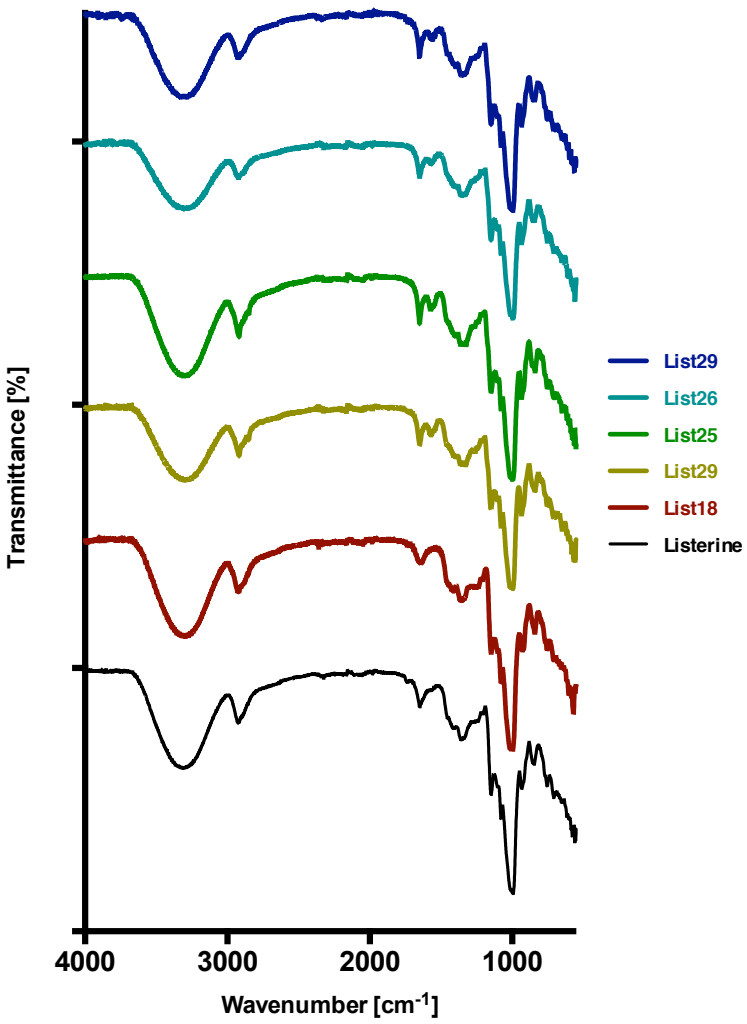

Sorbitol


Sucralose

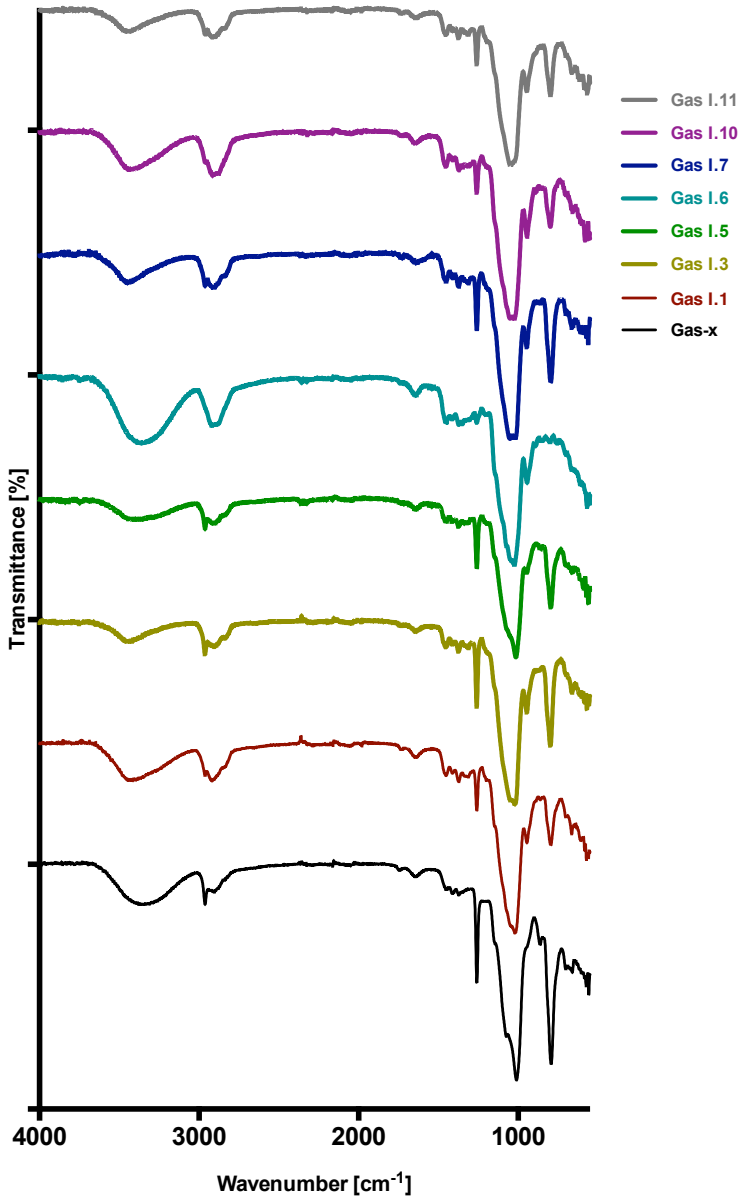

Tween 80

APPENDIX B

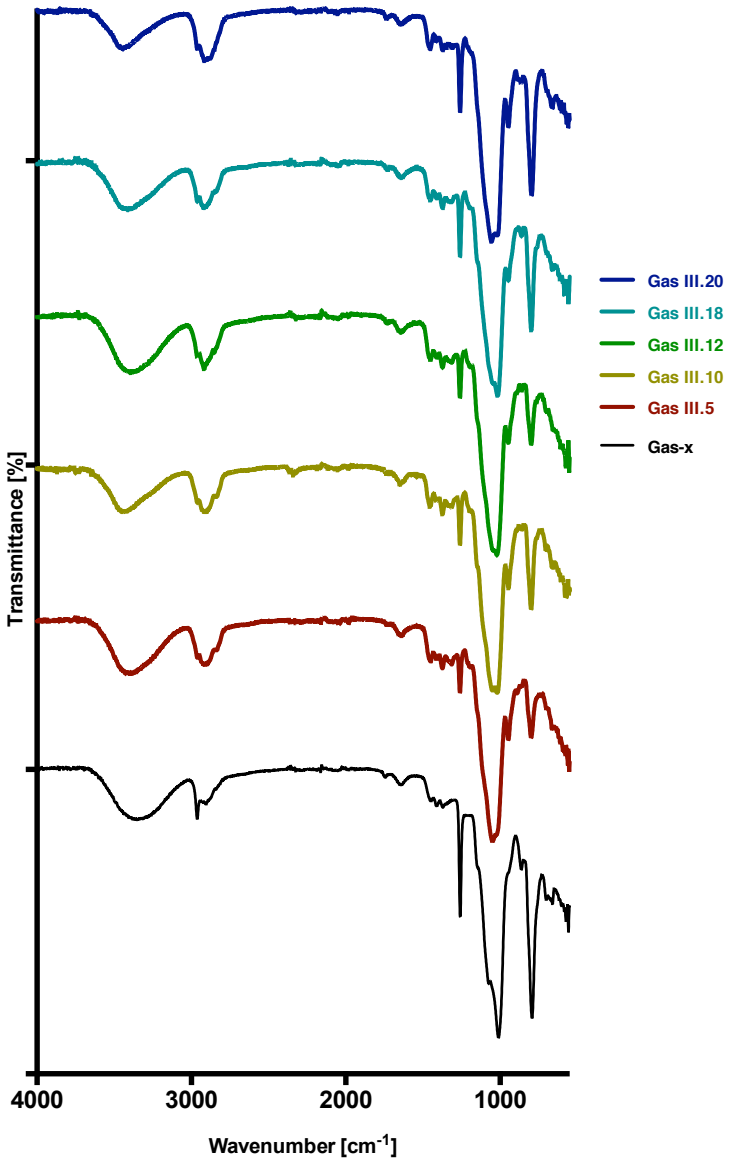
2. FTIR ANALYSES OF LIST FORMULATIONS



3. FTIR ANALYSES OF GAS I FORMULATIONS

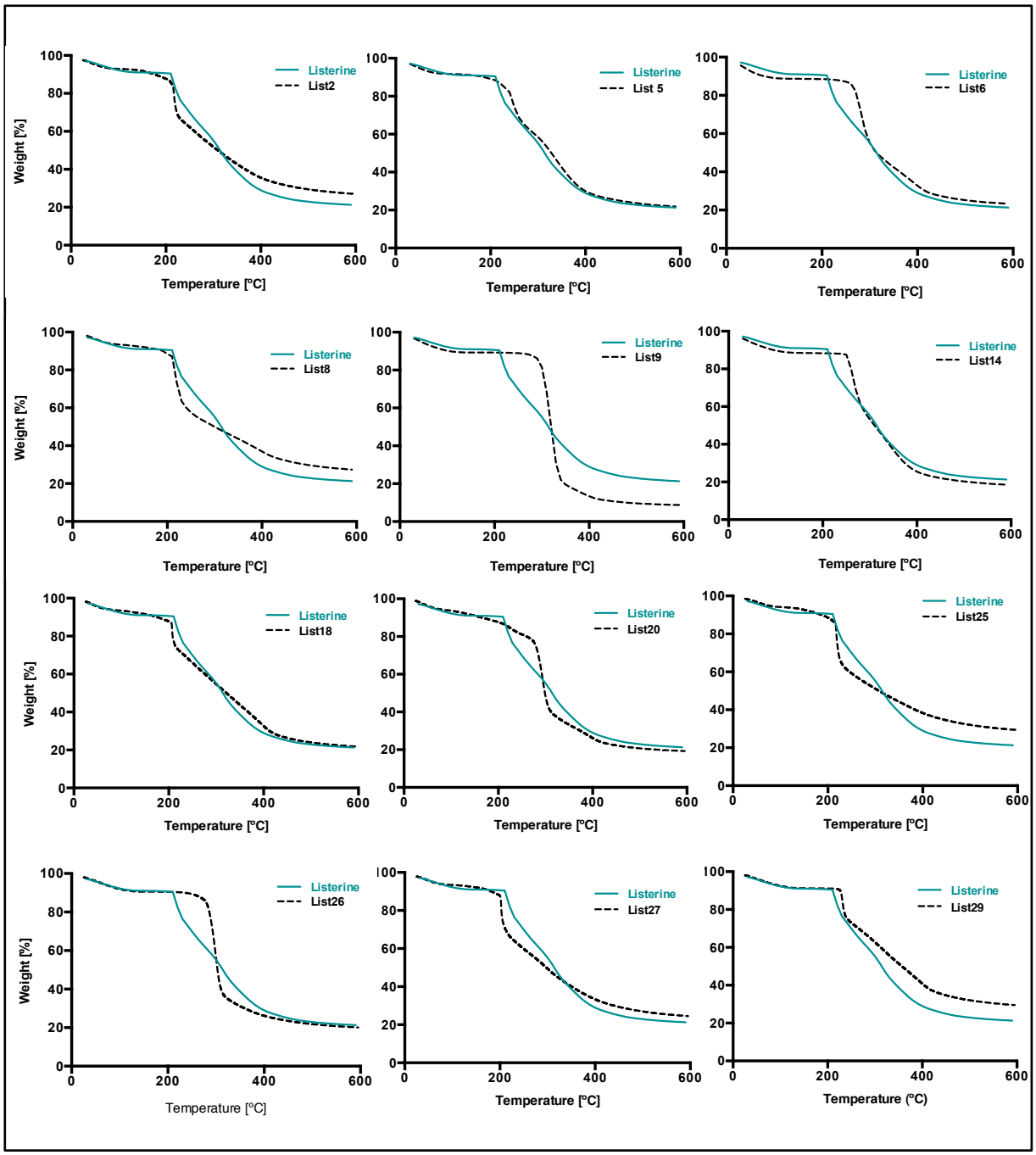


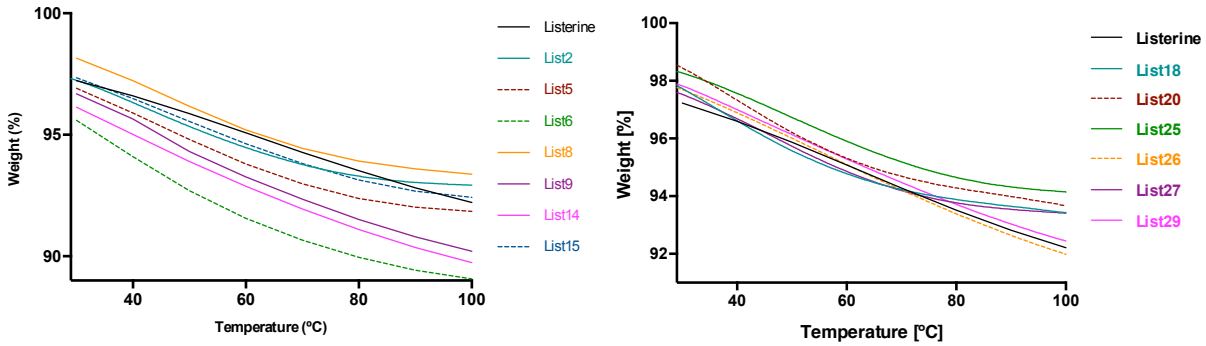
4. FTIR ANALYSES OF GAS III FORMULATIONS



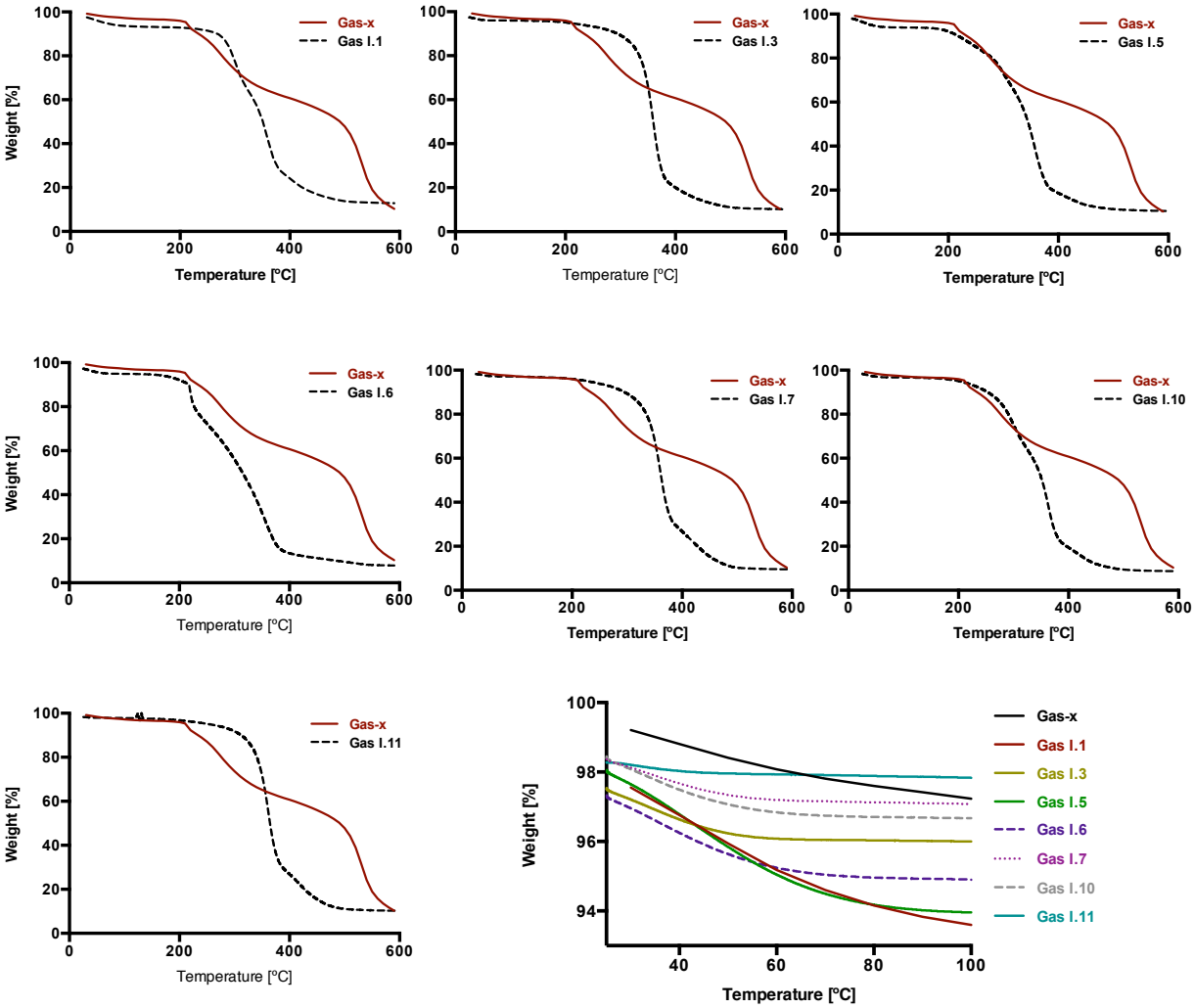
APPENDIX C

1. TGA CURVES OF LIST FORMULATIONS

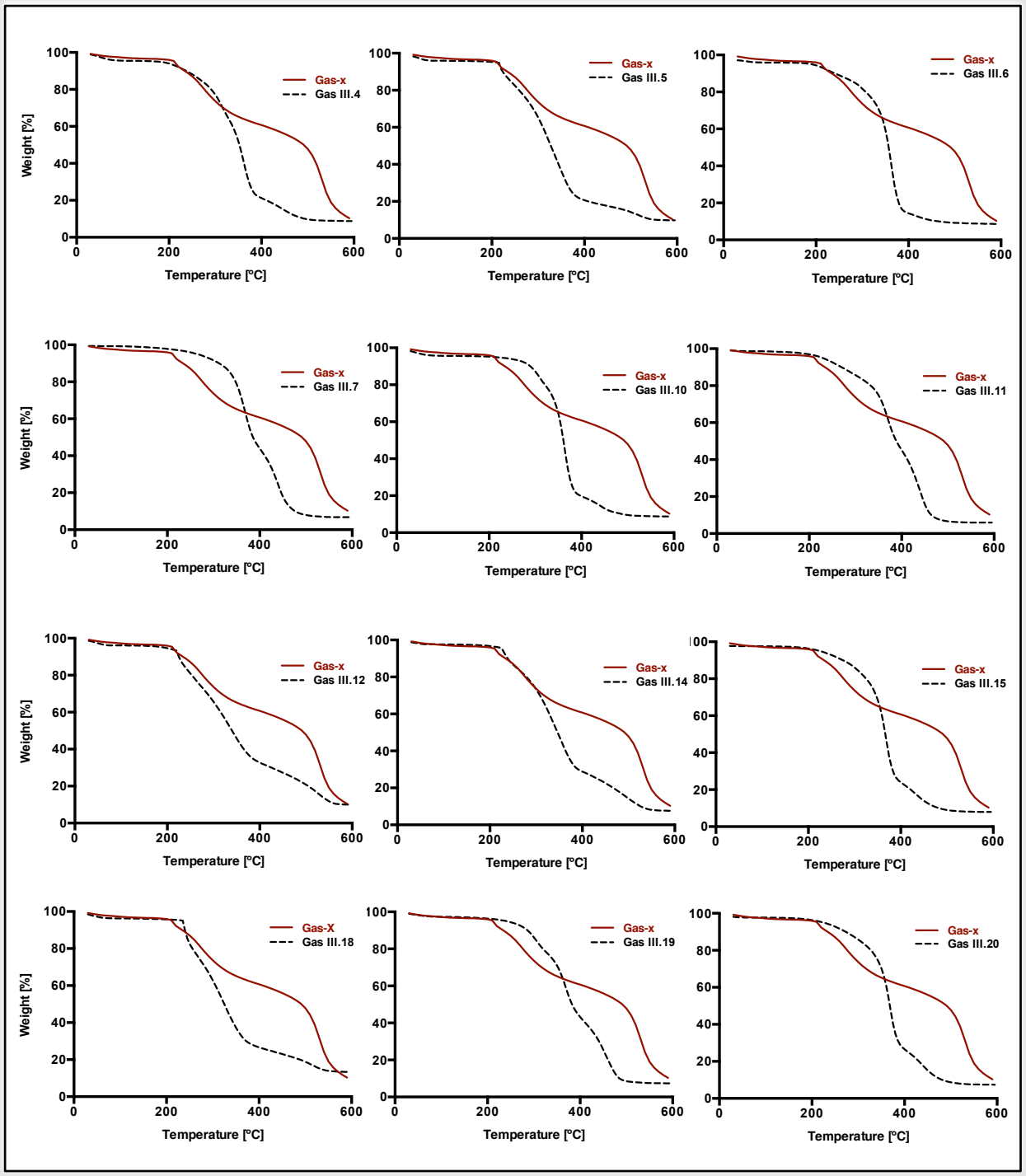


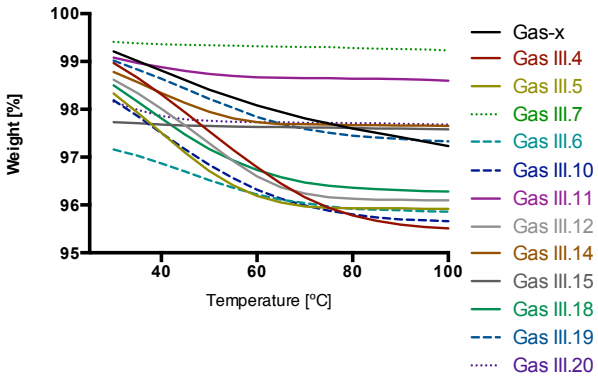


2. TGA CURVES OF GAS I FORMULATIONS

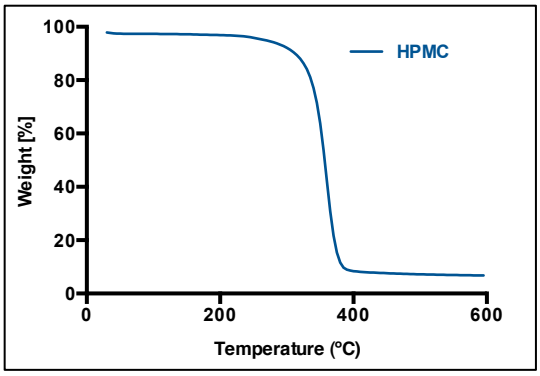


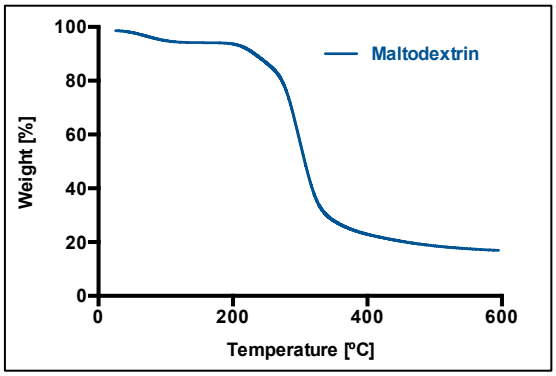
3. TGA CURVES OF GAS III FORMULATIONS

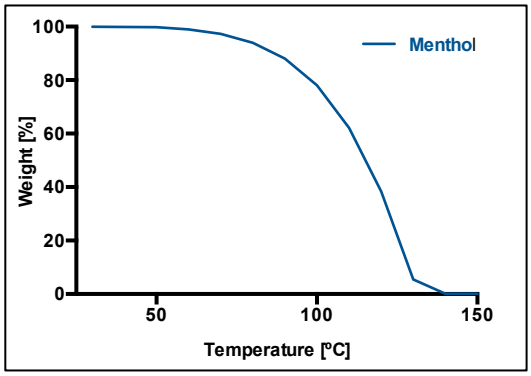


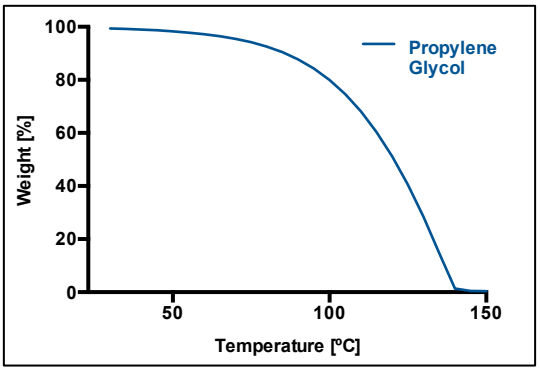


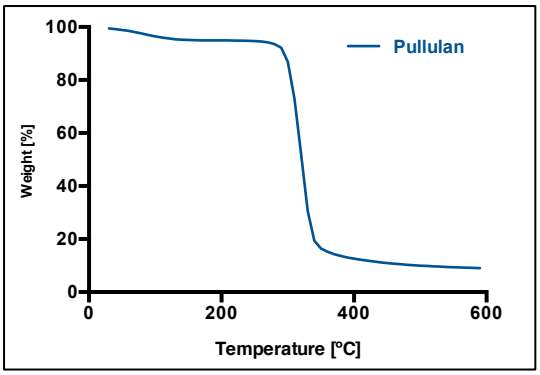
4. TGA CURVES OF EXCIPIENTS

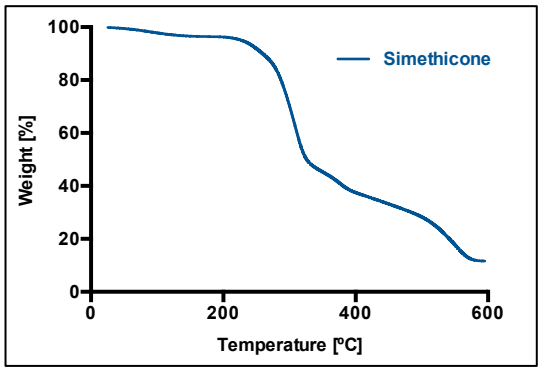


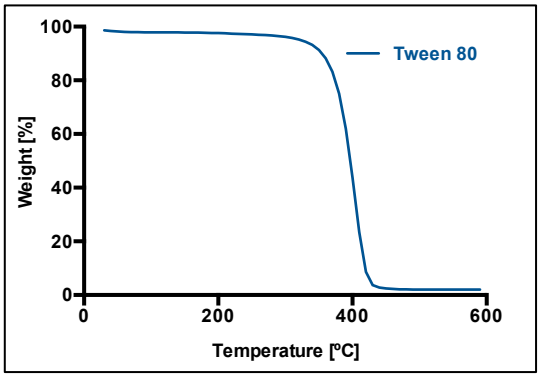






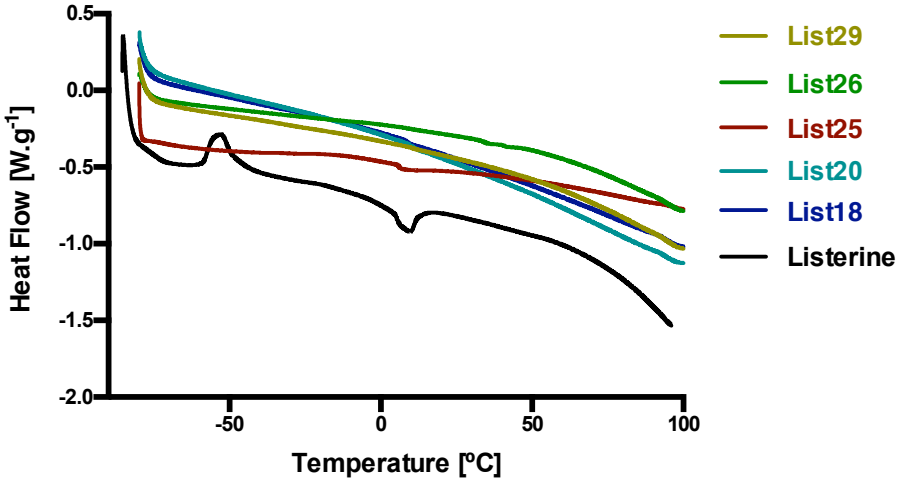




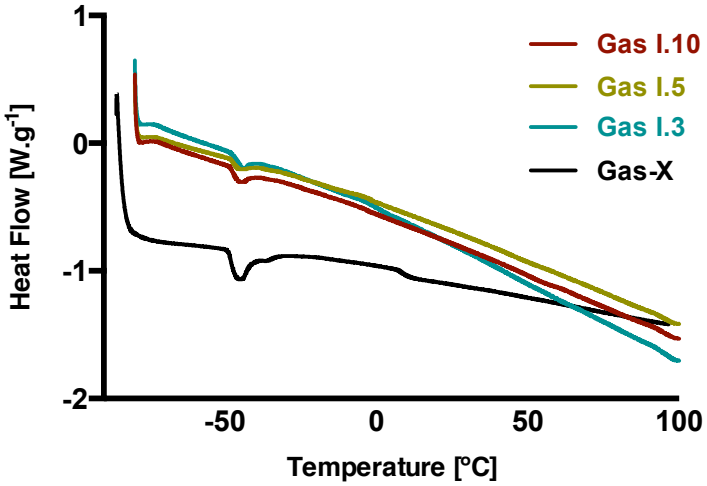


APPENDIX D

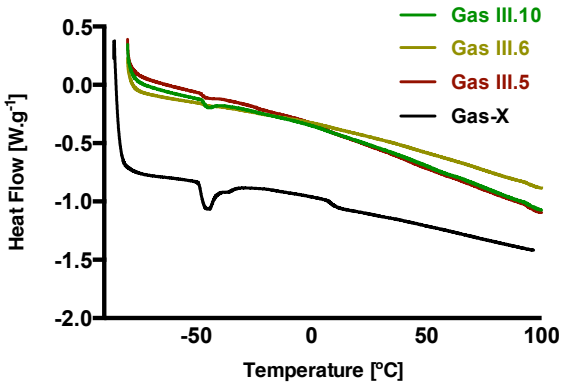
1. DSC CURVES OF LIST FORMULATIONS

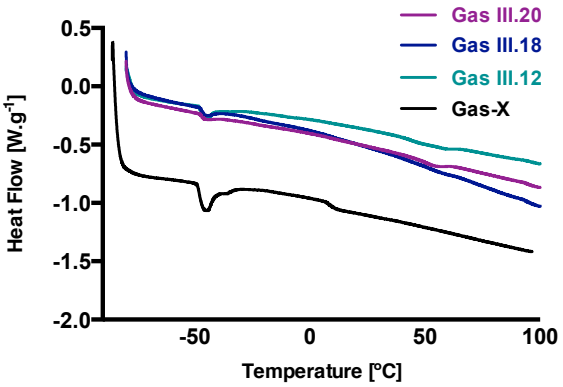


2. DSC CURVES OF GAS I FORMULATIONS



3. DSC CURVES OF GAS III FORMULATION

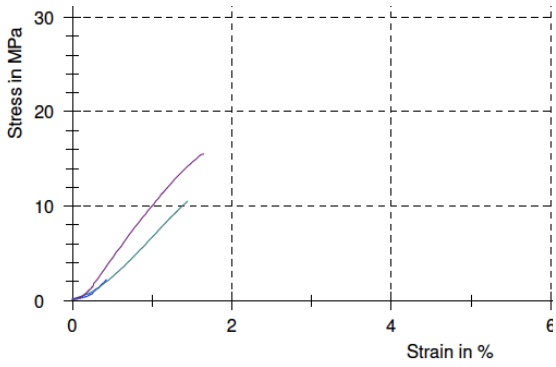




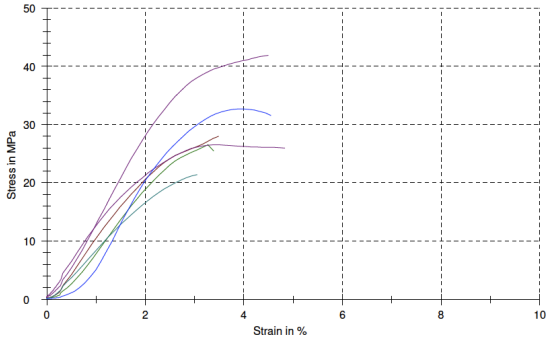
APPENDIX E

1. STRESS-STRAIN CURVES OF LIST FORMULATIONS

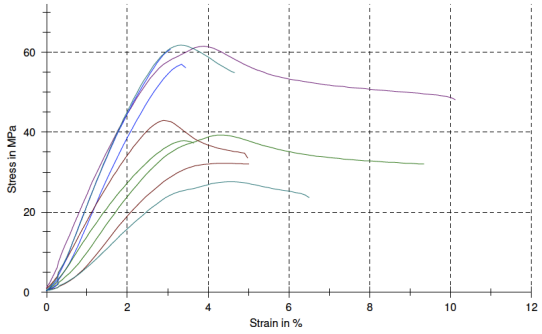
LIST2



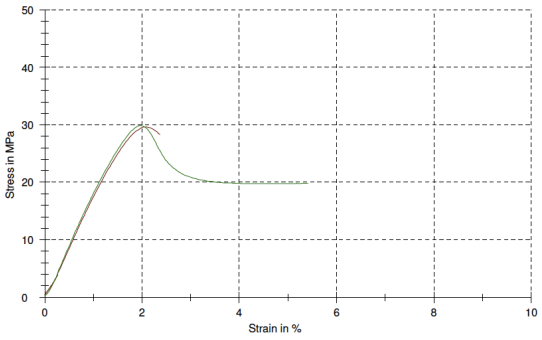
LIST14



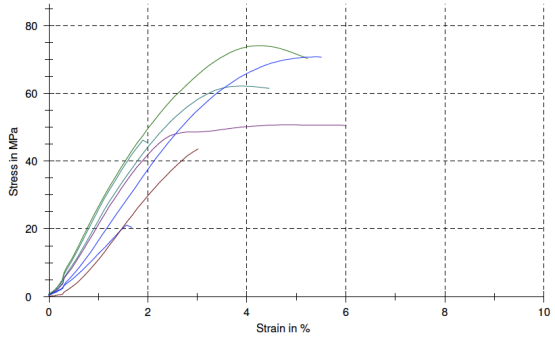
LIST5



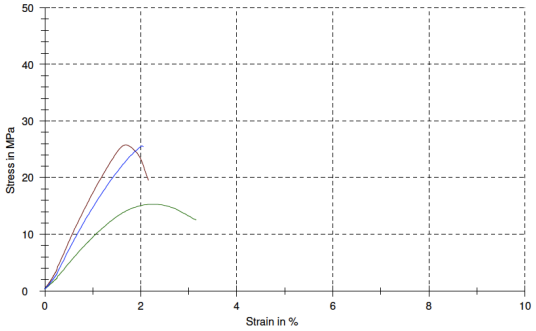
LIST18



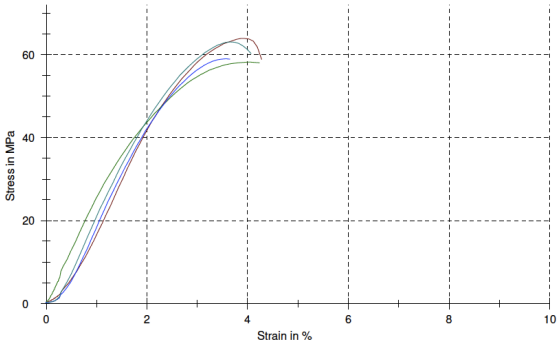
LIST6



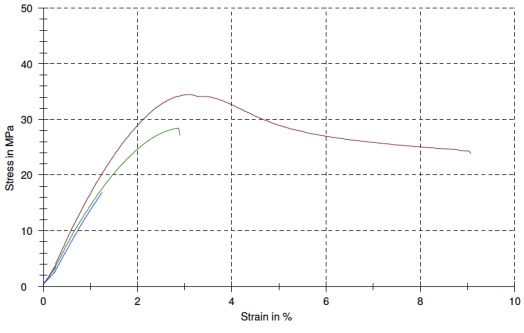
LIST20



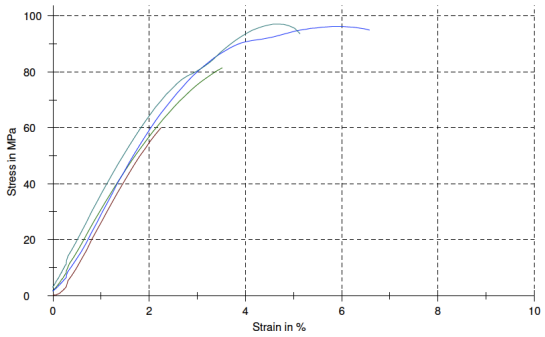
LIST8



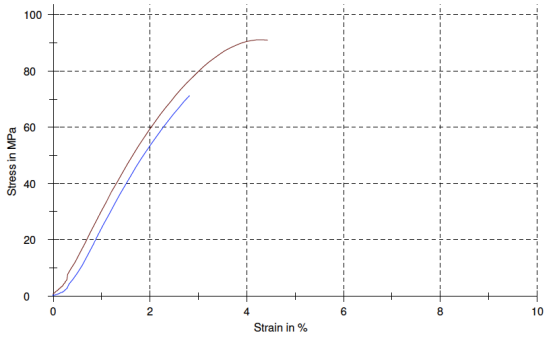
LIST25



LIST26

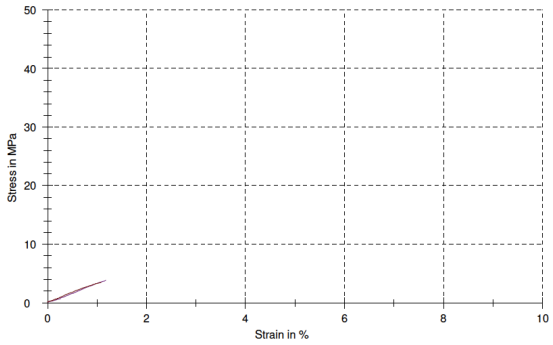


LIST29

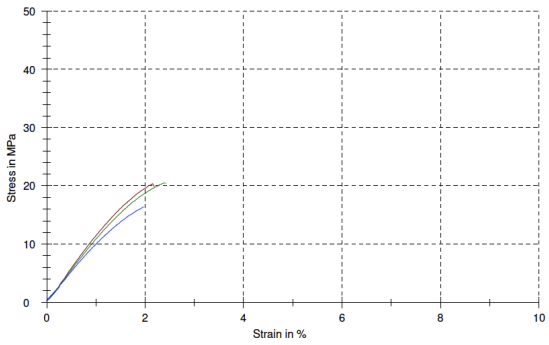


2. STRESS-STRAIN CURVES OF GAS I FORMULATIONS

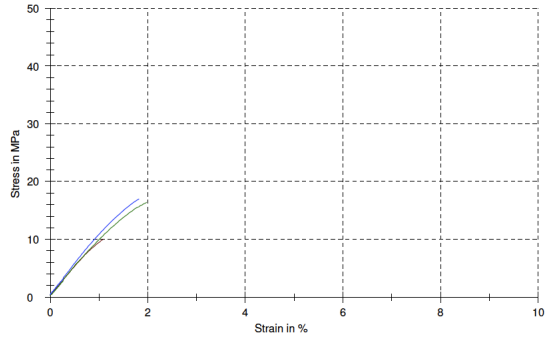
GAS I.1



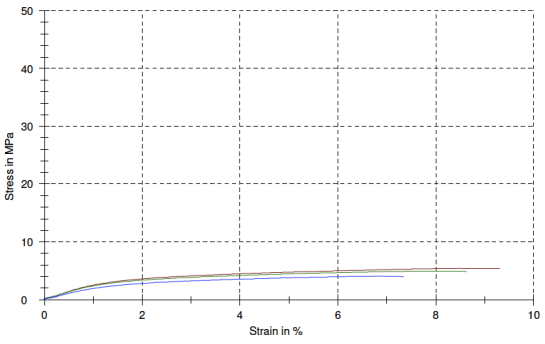
GAS I.7



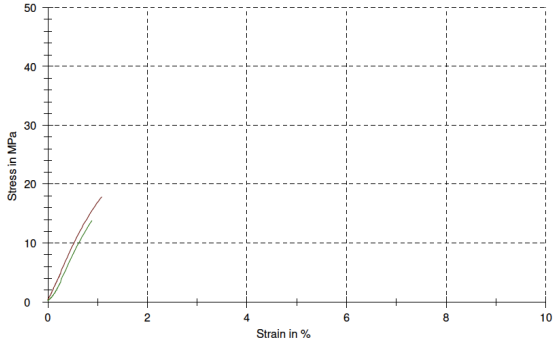
GAS I.3



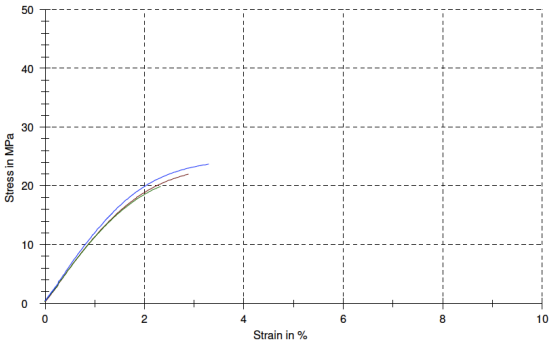
GAS I.10



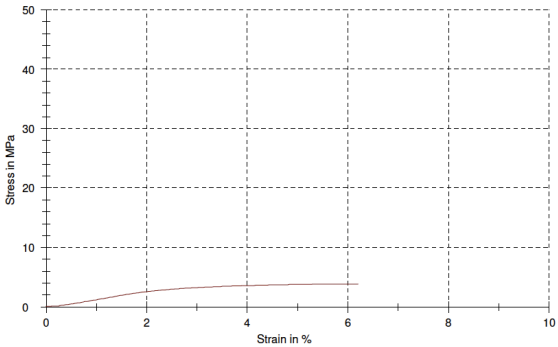
GAS I.5



GAS I.11

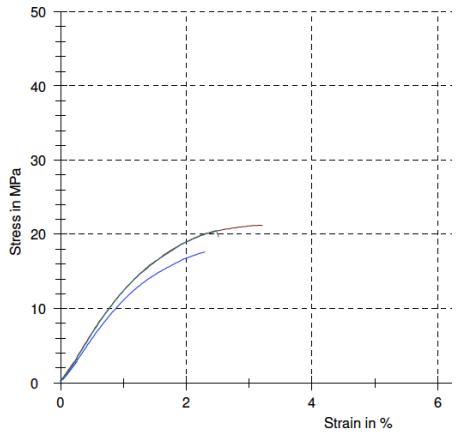


GAS I.6

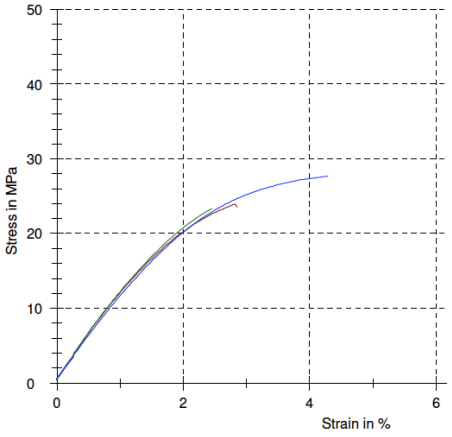


3. STRESS-STRAIN CURVES OF GAS III FORMULATIONS

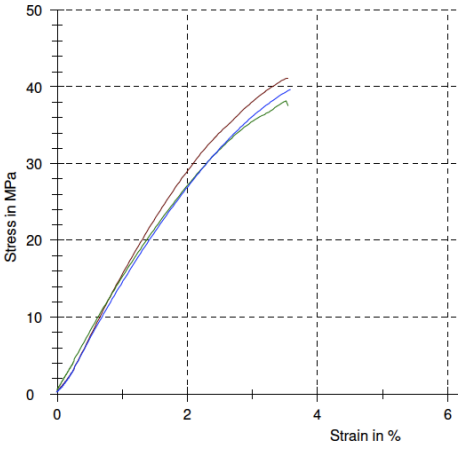
Gas III.4



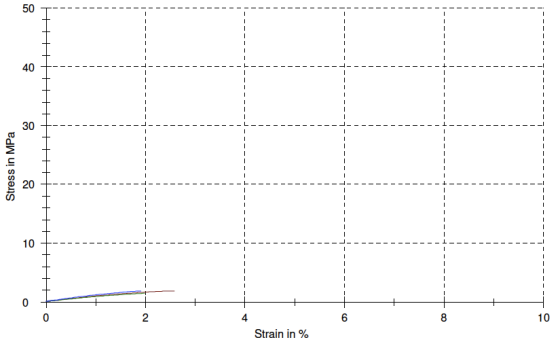
Gas III.10



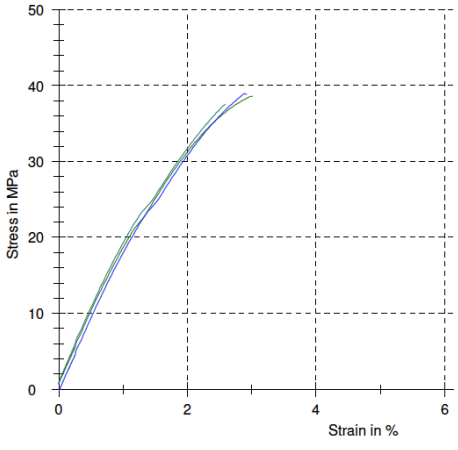
Gas III.5



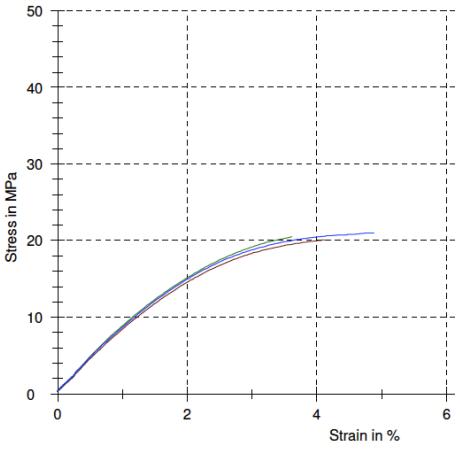
Gas III.11



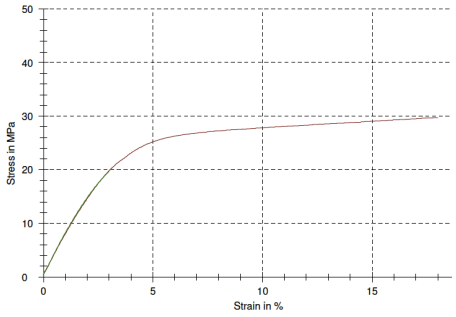
Gas III.6



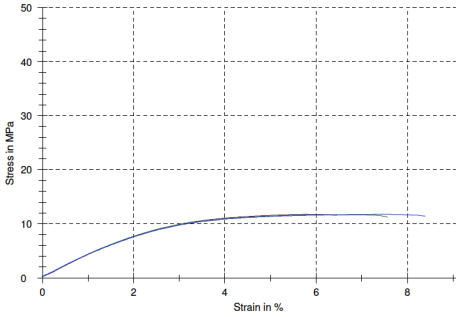
Gas III.12



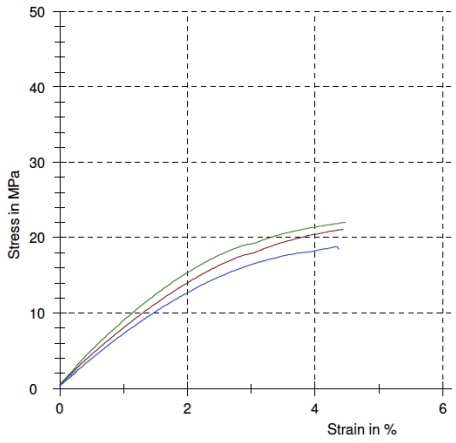
Gas III.14



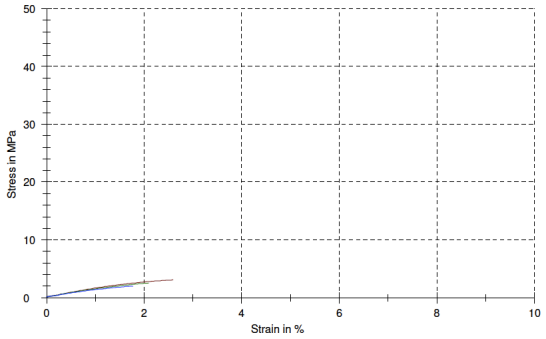
Gas III.15



Gas III.18



Gas III.19



Gas III.20