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FCTUC FACULDADE DE CIÊNCIAS
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Conception and implementation of a new facility for the manufacture of a novel dosage form

Dissertation presented to the University of Coimbra to complete the necessary requirements to obtain the degree of Master Biomedical Engineering

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Coimbra, 2015

THIS WORK WAS DEVELOPED IN COLLABORATION WITH:

À minha mãe, à minha avó.

Ao Bruno e ao meu pai.

“É chegado o Fim do Fim

O Fim que até ao Fim

Apesar de não ter Fim

Não deixou, enfim

De ter um princípio, meio e Fim”

Fernando Morgado

Abstract

Studies point that patient adherence to medication is still a big challenge to the pharma industry, since 50-60% of chronic patients in the USA admit not to comply with the prescribed therapy. For this reason pharmaceutical companies have turn their R&D efforts to patient centric dosage forms aiming to improve therapeutic outcomes by improving patient compliance.

One of the most promising technologies in this field are Oral Thin Films (OTFs), a solid dosage form for fast or sustained drug release in the oral cavity. Currently there are almost 10 products in the market and OTFs are generally well accepted by the population, due to their unique advantages. OTFs are easy to swallow, there is no need of water for the administration, they present a good taste and mouth feel and they may improve medicines safety through a reduction in their side effects. Due to these advantages they are particularly suitable for those patients with swallowing difficulties, such as the elderly, children and patients with neuron motor diseases.

In this dissertation it is explored the manufacturing process of OTFs, in order to identify the necessary requisites for the implementation of a new manufacturing facility for the development and commercial scale production of OTFs. Thereby, a specific aim of this work was to understand the types of equipment necessary, how they work and which models are available in the market.

Through an intense research and procurement process it was possible to analyze 39 different types of equipment, to study their critical process attributes and to estimate their capacity. Finally we were able to determine the necessary investment, to outline the design of a manufacturing facility and to trace a road-map for its implementation.

Keywords: Pharma Industry, Manufacturing, Engineering, Oral Thin Films.

Resumo

Estudos mostram que a adesão dos pacientes à medicação é ainda um grande desafio para a indústria farmacêutica, sendo que 50-60% dos pacientes crónicos nos EUA admite não cumprir devidamente a terapêutica prescrita. Desta forma, as empresas farmacêuticas têm direcionado a sua investigação para novas formas farmacêuticas centradas no paciente.

Uma das tecnologias mais promissoras neste campo é os Oral Thin Films (OTFs). Os OTFs são uma forma farmacêutica sólida para libertação rápida ou controlada do medicamento na cavidade oral. Atualmente há já cerca de 10 produtos no mercado, sendo que esta nova forma farmacêutica tem sido bem recebida pela população, devido sobretudo às suas vantagens únicas. São fáceis de engolir e não há necessidade de beber água, têm sabor agradável e podem melhorar a segurança do medicamento, ao reduzir os seus efeitos secundários. Devido a estas vantagens, os OTFs são particularmente adequados para administração em pacientes com dificuldades em engolir, como idosos, crianças e pessoas com doenças neuro-motoras.

Nesta dissertação é explorado o processo de fabricação de OTFs, com o objetivo de identificar os requisitos necessários para a implementação de uma nova unidade de fabrico para o desenvolvimento e produção comercial de OTFs. Assim, uma parte específica deste trabalho foi tentar perceber qual o tipo de equipamento necessário, como funciona e quais são os modelos disponíveis no mercado.

Através de uma intensa pesquisa e procura de mercado, foi possível analisar 39 equipamentos de vários tipos, estudar os seus aspetos críticos e estimar as suas capacidades. Por fim foi possível determinar o investimento necessário, esboçar o desenho da nova unidade e traçar um road-map para a sua implementação.

Acronyms

API – Active Pharmaceutical Ingredient

CMO – Contract Manufacturing Organization

CQA - Critical Quality Attributes

EMA – European Medicine Agency

GMP – Good Manufacturing Practices

HEPA – High Efficiency Particulate Air

OEE – Overall Equipment Effectiveness

OTC – Over-the-Counter medicines (No prescription needed)

OTF – Oral Thin Films

Rx – Prescription Medicine

TDDS – Transdermal Drug Delivery Systems

USA – United States of America

USFDA – Food and Drugs Association of the USA

Table of Contents

List of Tables

List of Graphics

List of Figures

CHAPTER 1

Introduction

1 Introduction

1.1 Scope

This dissertation is the result of the project carried out by the student Ricardo Filipe Morgado de Sousa for the conclusion of the Master's Degree in Biomedical Engineering.

The project started in November of 2014 and corresponded to a trainee of 9 months in the pharmaceutical company Bluepharma, Indústria Farmacêutica S.A.

The supervision of the work developed was in charge of Professor Sérgio Simões from the Faculty of Pharmacy of the University of Coimbra and Dr. Cláudia Silva, Head of Research of Bluepharma.

The project was named "Conception and implementation of a new facility for the manufacture of a novel dosage form".

1.2 Motivation

It was always been an intention of mine to have an enterprise experience while I was studying in the University of Coimbra. It is my vision that we should do different things in college that can contribute to other skills that we will not get inside the classrooms. That's why I choose to go abroad under the Erasmus program, to get involved in Associação Académica de Coimbra and to participate in several national and international programs.

As a future engineer, it was also my intention to try to have an enterprise experience in an industrial company. In addition, I was always interested in the pharmaceutical industry in particular, because of the importance that plays in the World and by the extreme rigor that is associated to this area.

All of this made me send my curriculum vitae to Bluepharma. I knew the success history of this young, prestigious and innovative company in Coimbra and I was sure that it would be the best option to do my Master's project. All of these are the motivations that made me accept such a challenging project, a decision I don't regret at all.

1.3 About Bluepharma

Bluepharma is a privately owned pharmaceutical company, located in Coimbra, Portugal, devoted to the development, manufacturing and distribution of pharmaceutical products. It was launched in 2001 when a group of experienced professionals, all related to the pharmaceutical field, decided to acquire Bayer's industrial unit in Coimbra.

Starting as a pure CMO, Bluepharma rapidly moved into the development of their own generic products and more recently to innovative products and business approaches. We offer an integrated approach on the process of drug discovery and development, including innovative research on new chemical and therapeutic entities, based on novel platforms for the delivery of known drugs, supported by a highly qualified team, with top regulatory expertise in national and international markets, in medicines and medical devices.

The state-of-the-art manufacturing site is dedicated to oral solid dosage forms and is approved by the most demanding regulatory authorities worldwide: FDA (USA), EU-GMP, Korea FDA (MFDS), Taiwan FDA, Iran TGA.

Since its launch, Bluepharma has based its activity in four main principals: Innovation, Quality, Internationalization and Investment. To follow this principles we've been building strong relations with major key players of the international pharmaceutical market (pharmaceutical companies, labs, research centers and universities), with whom we established successful partnerships through B2B and B2C models. Bluepharma is chiefly identified for its Research and Development, marketing expertise, lean operational principles, economy of scale and quality standards.

CHAPTER 2

Theoretical Background

2 Theoretical Background

2.1 Patient centric dosage forms

Studies from 2010 show that in the USA the patient adherence to therapies for chronic conditions is low, in the order of 50-60%[1].

There are several types of factors that influence the adherence of a patient to a certain therapy that can be related with the patient himself or even with its social status. Some of those impacts are described in the Figure 1.

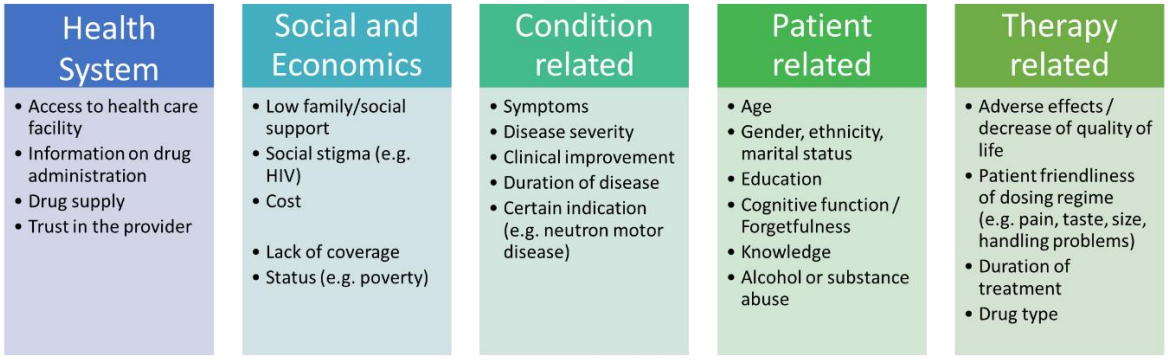


Figure 1 - Factors that influence patient adherence to therapy [2].

To give a response to this problem, the pharmaceutical industry has been seeking new solutions in order to improve the patient compliance to therapy.

Figure 2 - Some examples of strategies to improve patient compliance [3], [4].

In the Figure 2 it can be seen some examples of strategies that have been developed. In this project we will explore a novel oral drug delivery system.

New drug delivery systems represent one of the major research areas in the pharmaceutical and biomedical industries [5]. Nowadays, pharma industry seeks to improve drug stability, oral bioavailability and to decrease the incidence of drug's side effects [6]. Moreover some of these new dosage forms enable to increase its efficiency through a controlled release of the drug and may improve patient compliance.

As commonly known, the oral route of drug administration is the most preferred by the general population [7]. However 28% of the patients have some problems in swallowing tablets and capsules (dysphagia) [8]. These patients include the elderly who have difficulty ingesting conventional oral dosage forms mainly due to hand tremors and dysphagia; children who are afraid to take the solid dosage forms due to the muscular and nervous underdevelopment; mentally ill; patients with developmental delay and / or less cooperative; patients with treatment regimens with low intake of liquids; patients with reduced salivary secretion and travelers who may not have easy access to the water [9]. Also dysphagia is associated with several medical conditions, like AIDS, Parkinson's, head and neck therapy by radiation, thyroidectomy and several other neurological conditions [10].

Oral drug delivery systems represent more than 52% of the global market share of all the drug delivery systems and it is estimated that their market value will reach 90 billion euros by 2016 [11]. All these reasons make the oral drug delivery systems a very appealing area to invest, in a market with strong competition and billions of investments in drug development.

In this project, we will explore the manufacturing process of one particular novel oral dosage form that is currently being developed at Bluepharma, Indústria Farmacêutica, S.A. – Oral Thin Films (OTFs).

2.2 Oral Thin Films

In the late 1970s, the first fast dissolving drug delivery systems were developed, in order to work as an alternative to capsules and tablets, namely for geriatric and pediatric patients [10]. Fast dissolving thin films appeared in 2001, first as breath fresheners, when Pfizer first launched the Listerine® PocketPaks. Nine years would have to pass so the first OTF accepted for medical prescription was released on the market – Zuplenz® was launched in 2010 in the United States [12].

Currently, there are several types of OTFs. Depending on its purpose of action they can be named by the following terms [4]:

- Orodispersible Films:
    - Non-mucoadhesive
    - Mucoadhesive: absorption in the gastrointestinal tract
- Oral-Mucosa Films (Buccal, Sublingual or Palatal Films):
    - Mucoadhesive: absorption in the oral cavity, for fast onset action.

Generally speaking, Oral Thin Films are a solid dosage form for fast or sustained release in the oral cavity. The USFDA describes it as a flexible polymeric strip that contains active pharmaceutical ingredients (APIs), which are intended to be placed on the tongue for fast disintegration for dissolution in the saliva before swallowing for delivery in the gastrointestinal tract [13].

The user-friendly characteristics of OTFs make it a good option for specific target groups, as very young children and geriatric population [4]. Also patients with dysphagia and motor neuron diseases can benefit from this dosage form. Some of the advantages for the patients are [4], [14]:

- No need of water or spoon for administration, compared with tablets or syrups, and no need of chewing;
- Dose accuracy, because each strip as the precise dose that should be administrated;
- Good taste due to taste masking agents in the formulation, that makes it more acceptable for children;

- Easy to carry and to keep, due to its small size, flexibility and packaging options;
- Due to its fast dissolution, it's difficult to spit out, what makes it a suitable option for difficult patients that tend to reject the medication.

Clinically speaking, there are also clear advantages of using OTFs as a delivery system [4], [14]:

- The fast onset action allows the drug to enter in the systemic circulation directly in the mouth;
- Improved oral bioavailability and reduced side effects. Some OTFs promotes the absorption of the drug in the oral mucosa reducing hepatic first pass effects and in these cases the drug dose can be reduced;

Oral Thin Films can also be an advantage to pharmaceutical companies from the market point of view. If an OTF product presents a different pharmacokinetic profile compared with the product already in the market, it is considered a new medicine and it follows the FDA 505(b)(2) approval pathway, where a new clinical study it's required but preclinical toxicity studies are not needed, because the molecule it's the same. This means that the approval process it's faster and plus, an exclusivity marketing authorization of 3 to 5 years it's can be conceded, so no competitor can launch that same drug in OTF dosage form during the defined exclusivity period [4], [15].

Nonetheless, as all dosage forms, OTFs have also some limitations.

The main limitation is the small amount of drug that may be incorporated per OTF. Although some companies managed to introduce up to 50% of drug substance per film weight, the best case reported was Novartis Gas-X Strips® with 62,5mg of drug substance into a strip [4], [14]. This means that high doses medicines cannot be developed in OTFs.

2.2.1 Formulation

One key component of OTFs is the film forming polymer. In fact, OTFs are basically a polymeric matrix that can have one or more polymers with different properties, depending on the characteristics that we want to incorporate in them, like the drug load

capacity, disintegration time, mucoadhesiveness, elasticity and others. Currently, the polymers used can be natural derivative polymers of cellulose or starch but can also be used semi-synthetic or synthetic polymers [4]. The choice of the most suitable polymer it's one of the most important steps in the development of OTFs.

Beside the drug substance and the polymer, other ingredients are normally used in the formulation of OTFs, like sweetening agents or plasticizers. The Table 1 resumes the ingredients and their usual percentage in a typical OTF.

Water soluble polymer	45% ww
Drug	5 % to 30% ww
Plasticizers	0-20% ww
Surfactants	q.s.
Sweetening agent	3% to 6% ww
Saliva stimulating agent	2% to 6% ww
Fillers, colorants, flavors, etc.	q.s.

Table 1 - Typical composition of an oral thin film [16]**.**

In both formulation and manufacturing processes there are several critical quality attributes (CQA) that should be considered in the development of OTFs. These parameters must be defined in the beginning of the development process. Some of those CQAs are [4]:

- **Physical strength**: the OTF must present suitable mechanical properties so it can easily resist to the manufacturing process and consequently handling of the product. Properties like tensile strength or elongation at break must be tested and the appropriate values mostly depends on the polymer that is being used;
- **Stability**: drug substance stability (physical, chemical and thermal) is very important and can directly influence, for example, the manufacturing process, its conditions and the choice of the polymeric matrix and the packaging material. The stability of the product will determine, among other things, its shelf-life and the storage conditions;
- **Appearance**: characteristics like the size, the color and shape must be considered. For example, for OTFs that are intended to be placed under the patient's tongue, the

size should be small enough to be comfortable because the area available is very small;

- **Drug release profile**: it depends if the OTF is supposed to be dissolved quickly or to be slowly released, or if the absorption should occur in the oral mucosa or in the gastro intestinal tract;
- **Residual water content**: an excess or lack of water can interfere with the mechanical properties of the OTF. Each formulation should have the right amount of water to ensure the desired mechanical properties. Suitable packaging material should be taken into account to avoid water transference between the OTF and the surrounding environment;
- **Organoleptic characteristics**: OTFs can be delivered with a certain flavor incorporated, what make it a good option for pediatric patients. However, the choice of a pleasant option depends on the taste of the drug substance. Also, the market target must be considered because flavor preferences can vary from region to region and from age to age;
- **Dose uniformity**: the dose uniformity depends on the formulation but also on the size and thickness of the product. These parameters should be constantly controlled in the manufacturing process so slight adjustments may be carried out.

2.2.2 Manufacturing Process

There are different manufacturing processes which are well documented in the literature:

- Solvent casting;
- Hot melt extrusion;
- Semisolid casting;
- Solid dispersion extrusion;
- Rolling.

Solvent casting and hot melt extrusion are the most commonly used.

Solvent casting

Solvent casting, also known as film casting, is the most used manufacturing process for OTF, being a relatively simple and low cost method [17]. In this process, an aqueous or hydro-alcoholic mixture of excipients and drug substance(s) is casted on a surface, where the solvents evaporate so the mixture becomes a solid thin film. After this, the film is cut in strips with the desired size and shape [4]. During the internship in Bluepharma, I had the possibility to see the manufacturing of OTFs in the laboratory, using this method. The process goes as described below:

- The mixture is prepared;
- A sheet of a release liner is placed in the casting machine;
- The mixture is spread along the substrate (release liner) with a proper slot or knife with a uniform thickness;
- The casting machine is heated in order to transfer the necessary energy to the solvents evaporation;
- In the end, the release liner with the OTF on top is removed from the coating equipment and it is cut into individual OTF with the desired dimensions;
- Finally, the release liner it's peeled off manually from every strip and each individual OTF is placed into an individual pouch that is sealed by heat.

In a higher scale, the casting machines are more complex, as showed in Figure 3.

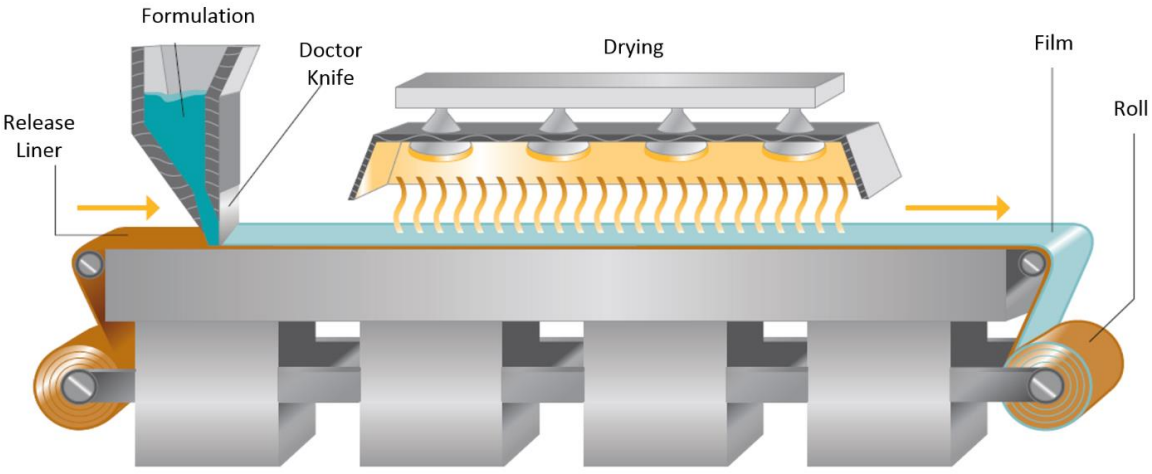


Figure 3 -Schematic of the solvent casting method in a continuous machine [18]**.**

Like the image displays, the release liner roll is placed on the left and it is slowly unwinded. Then it passes through an applicator that contains the formulation where the mixture passes through a small clearance that makes the mixture to be spread with the same thickness along the release liner. The release liner continues moving and enters in a drying zone where the solvents are evaporated. Finally, the liner with the solid film is winded in a new roll.

This method is appropriate for OTFs with high sensitive APIs, namely because the drying process is made under relative low temperatures [18].

The machines responsible for this process at high production scales are called coating machines. Thereby this process it's commonly known as coating process, definition that we will use in this dissertation.

Hot melt extrusion

This method consists in shaping a mixture of polymers, drug substance and other ingredients into a film strip through a melting process that melts all components [4].

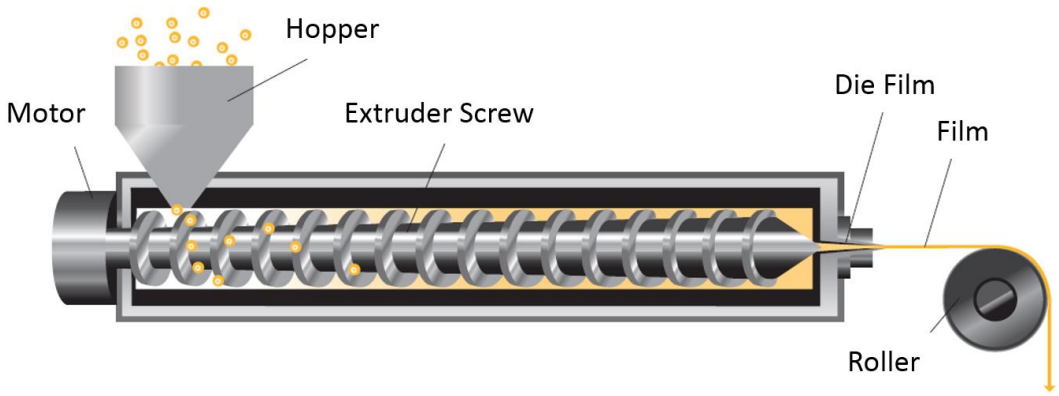


Figure 4 - Diagram of the hot melt extrusion process for the production of OTFs [18]**.**

As seen in the Figure 4, the drug and the other ingredients are added in the solid state. The extruder then homogenizes and heat the ingredients by the action of the extruder screw that moves itself thanks to the motor, so the ingredients are mixed and fused. Finally, the melted material is forced to pass by a flat die that presses the resulting film into the desired shape [18], [19].

There are some limitations in this method, mainly because the ingredients are subject to high temperatures which can cause thermal degradation. Plus, all the ingredients

must be completely devoid of water or other volatile solvents. If not, the uniformity of the film can be affected [18]. From the advantages point of view, this method is appropriate for anhydrous processes and it tend to present better results in terms of content uniformity [19].

Semisolid casting, Solid dispersion and Rolling

The semisolid casting is a method where a solution of a water-soluble polymer is added to a solution of acid insoluble polymer, previously prepared under certain conditions. Finally a gel mass is prepared by the addiction of a plasticizer and it is casted into films using a heat source [15].

The solid dispersion method consists in the extrusion of immiscible components with the drug, so a solid dispersion is obtained [19].

Finally, in the rolling method a solution or suspension composed mainly of water and alcohol, also containing the drug, is rolled on a carrier. The films are then dried on the rolls [15].

2.2.3 Packaging of OTFs

OTFs can be packaged in single units or multiple dose packages. Figure 5 shows some examples of how OTFs can be packed.

Figure 5 - One OTF and different types of packaging material.

Some examples of multiple unit options are the dispensers and the continuous roll dispensers. Some of these solutions are even patented [14].

There are advantages and disadvantages in the way the films are packed. A single unit package offers more stability and avoid possible fusion of the strips when compared with multi dose solutions. Nevertheless, it is more expensive to produce single unit solutions, mainly because more packaging material is necessary increasing the cost. The multiple dose packaging solutions are more expensive to develop, but less expensive to produce in high quantities [20].

Web Converting and Primary Packaging

Web converting and primary packaging are two different processes, although they occur in the same equipment in the case of OTFs. The process it's described in the Figure 6.

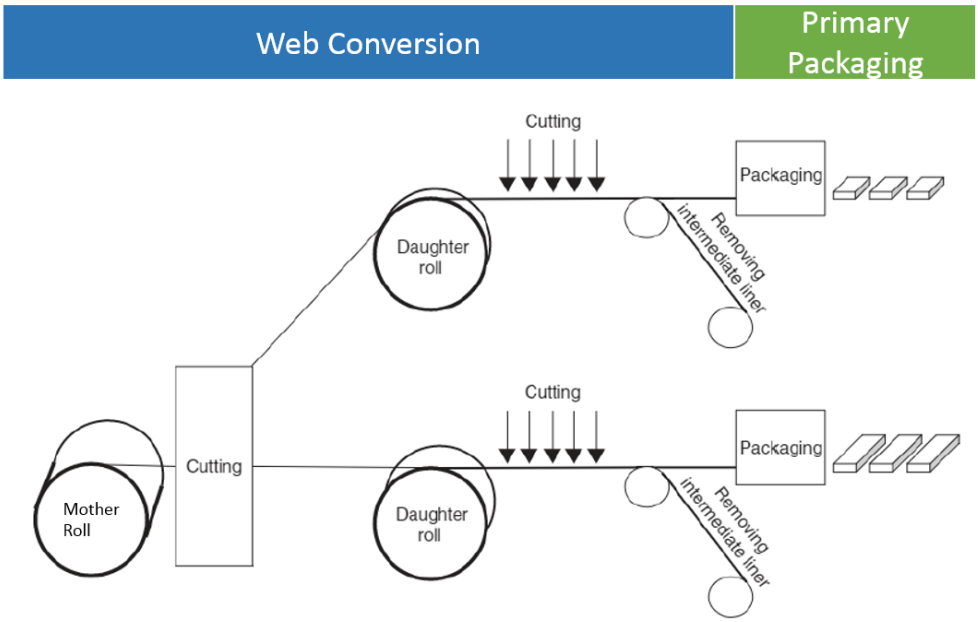


Figure 6 - Diagram of the web conversion and packaging in a primary packaging machine [20]**.**

Figure 6 represents a web converting and primary packaging machine. At the laboratory scale the cut and packaging of the OTFs may be done manually.

The mother roll is the roll that comes from the solvent casting machine, as seen before. In the first step this roll is divided in two or more lanes, which operate simultaneously. Pilot machines, as we will see, normally just operate with one lane. The web keeps running and then it is cut into individual strips with the desired size and shape. The release liner is then peeled off from the cut film. All this process is called web conversion, because the film roll is converted into small strips.

After that, each strip is placed into a small individual pouch, which is then sealed. This, of course, in the case of single packaging process.

Secondary packaging

The secondary packaging is the process were the products are packed in the final packaging format, conventionally in a carton box. It is done normally by cartoning machines placed in the end of the primary packaging line. This equipment it's similar to the ones used in the production of other more conventional solid dosage forms, like capsules or tablets.

2.2.4 Market Perspectives

Since 2013, more than 80 OTFs brands were launched, mainly in the USA and Asia. However, most of this brands launched are Over-the-Counter (OTC) products. As we have seen, just in 2010 was launched the first OTF for prescription (Rx) [14]. This first product, Zuplenz ® (Ondansetron PharmFilm®) in the USA and Setofilm® (Ondansetron RapidFilm®) in Europe, is an OTF for the prevention of nausea and vomiting and in its first year it conquered a wide share of a market that generated 1.9 billion dollars in that year [21]. The second Rx product launched was approved one month later. The Suboxone® sublingual film, is an OTF with two drug substances (buprenorphine and naloxone) for the opioid addiction, and was the confirmation of the success that OTFs can have in the Rx market, generating sales of 513 million and 1.5 billion in 2011 and 2012 in the USA, respectively.

It was estimated that OTF Rx market experimented an annual growth of 17.1% from 2009 to 2014. Also, during the period from 2009 to 2019 it is expected that the industry value added (IVA), an indicator that measures the contribute of an industry to the overall

economy, will represent an annual growth of 13.6% in the USA [22]. This is explained by the crescent number of companies investing on this new dosage form. Currently there are 10 products launched in the market and 29 are in different stages of development [23].

There are many advantages, as seen, in this technology. The principal therapeutically areas where companies are investing are [19]:

- Pediatrics;
- Geriatrics;
- Gastrointestinal diseases;
- Nausea;
- Pain;
- Drug Addiction;
- Motor-Neuron Diseases.

This is a market of partnerships between companies dedicated to the manufacturing of films, contract manufacturing organizations (CMOs), companies dedicated to the discovery of new chemical entities or developing new uses for existing drugs and also companies searching for new ways to extend their drugs lifecycle. This strategy results in lower risk of investment but also shared revenues. It can be said that there are two main players in the OTF market, the technology owners and the marketing partners [21].

The main players and their technologies are [21], [23]:

- MonoSol Rx LLC: PharmFilm®;
- Applied Pharma Research (APR) and Tesa Labtec: RapidFilm®;
- BioDelivery Sciences: BEMA®;
- FFT Medical: Oral Transmucosal Film;
- IntelGenx: VesalFilm®.

All these facts demonstrate that OTF delivering systems are a trending technology in the pharmaceutical market. However, the competition will probably grow as the market becomes more receptive to it. Thereby it's important to understand deeply the

necessities and opportunities of the market and present solutions that can represent a differentiate factor rot e company.

Also it must be considered that OTFs manufacturing is a less expensive process when compared with other complex oral delivery systems, but it is more expensive that the manufacturing processes of more conventional dosage forms [21].

CHAPTER 3

Objectives

3 Objectives

The aim of this project was to identify all the necessary requirements for the implementation of a new manufacturing facility for a novel oral dosage. Moreover the specific objectives of this project were:

- To identify the main manufacturers (CMOs) of OTFs;
- To identify the major suppliers of mixing equipment, coating equipment and web converting and primary packaging equipment;
- To make a procurement process in order to obtain the specifications and budgetary quotations of the equipment mentioned on the previous point, for pilot and commercial scale;
- To analyze each equipment in order to determine their critical quality and process attributes and to estimate their annual capacities;
- To determine the necessary capacity of the new manufacturing facility in order to meet Bluepharma's OTF forecasts;
- To trace a road-map for the acquisition of equipment and to estimate the necessary investment;
- To outline a manufacturing facility of OTFs that have laboratory, pilot and industrial scale.

CHAPTER 4

Methodology

4 Methodology

Oral Thin Films are a novel dosage forms with a particular manufacturing process that is different to the manufacturing process of tablets or capsules, the conventional ones. For this reason it is very important to identify the type of equipment used, and to understand the critical process parameters in order to be able to design a new manufacturing facility dedicated to this dosage form.

The first step was to look to the competitors in this area in order to find the right companies with suitable equipment solutions for the three phases of OTF manufacturing process: Mixing, Coating web converting and Primary Packaging.

In the end, it's our hope to answer to three simple but crucial questions:

- What do we need in terms of equipment?
- How does it work?
- When do we need it?

4.1 Search Method

To answer the first question, it's important to study and characterize OTF market. Moreover, the study of this particular environment allowed us to understand who is investing in this technology and who are the main suppliers of equipment for the production of OTFs.

Thereby, it is important to have a suitable end efficient search methodology in order to get proper, reliable and traceable information.

First of all, we divided our search in Macro Data and Micro Data.

By Macro Data we mean non-specific information that characterizes OTF technology, its manufacturing and development processes and its market as a whole. For this part of our search several web sites dedicated to this kind of information were used (see Table 2).

Scientific	Technology and Manufacturing	Economic	Others
PubMed B-On	FiercePharma PharmaTek PharmTech in-Pharma Drugs.com	IBIS World Root Analysis Frost & Sullivan Markets and Markets CMO Locator	LinkedIn (discussion groups)

Table 2 – List of websites and platforms used for macro data search, divided by area.

Through this engines, we were able to find studies, reports, news and articles containing very important scientific, technological and economical know-how.

In what concerns Micro Data, a specific research was used in order to obtain information about OTF products, competitors and equipment suppliers. The list of sources can be found on Table 3.

Databases	Suppliers and CMOs	Exhibitions / Websites	Others
Cortellis Newport	Press Releases Products overall specifications Annual Reports	Interpack PharmTech CPhI FCE Pharma InterPhex Pharm Complex ACHEMA European Coating Show	Google LinkedIn (companies profiles) YouTube (equipment videos)

Table 3 - List of websites and platforms used for micro data search, divided by area.

It's important to make a reference to Cortellis and Newport databases. These engines are products of Thomson Reuters, one of the biggest media and information group of the world. These tools allowed to retrieve precise information on pharmaceutical products, such as medical indications, sales forecasts, deals, companies' involved, patent information, press releases and analysis reports, stage of development and others. In the Figure 7 it's possible to see a print screen of the Cortellis database.

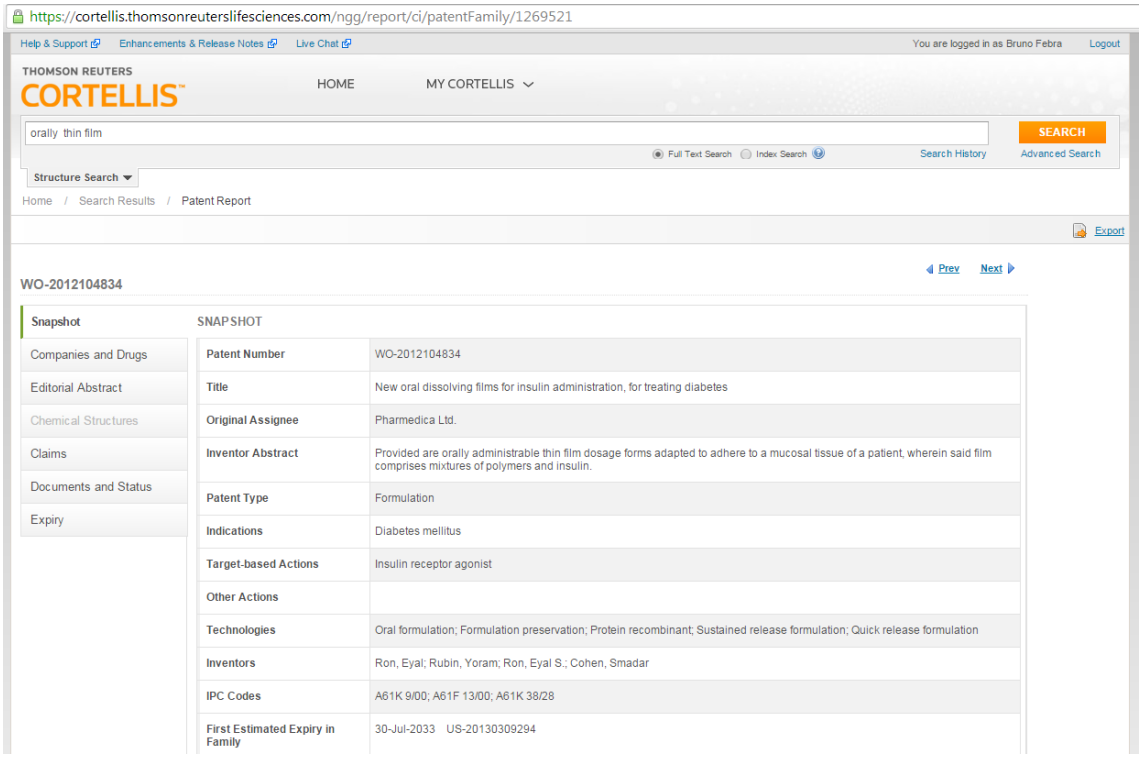


Figure 7 - Snapshot of Cortellis database.

The biggest difference between these two platforms is that Cortellis has information about products still in development, while Newport presents information about products already in the market.

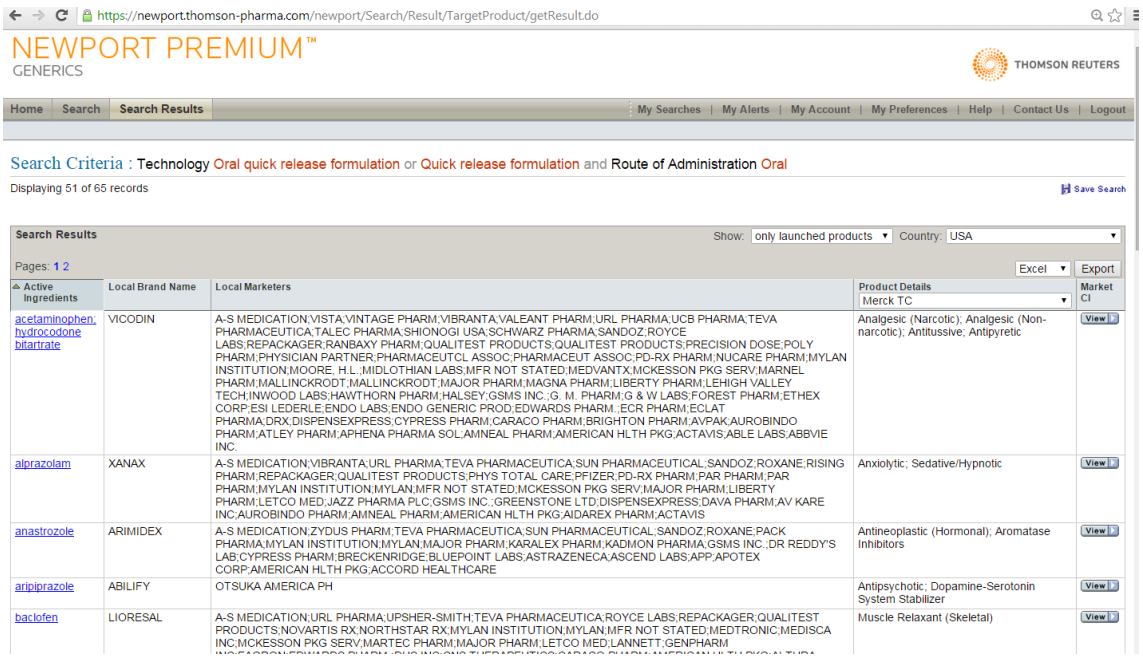


Figure 8 - Snapshot of Newport database.

The Figure 8 it's a print screen of Newport. These tools were used with the needed permission, once they are not license-free.

Moreover, we visited the websites of some of the biggest pharma events in the world. This quest was very helpful, because it is possible to search for exhibitors by area of interest and retrieve information about them.

At last, but not least, we lead an individual investigation to the identification of possible CMO's and suppliers that we identified in the previous steps.

A note also for the more common and social engines, such as LinkedIn, Google or YouTube, that were also a precious help to get information. On LinkedIn we found discussion groups about OTFs, were people connected to this area post and share information about this technology. In what concerns YouTube we used it to watch some videos of the equipment working, founded in some of the suppliers' pages.

Finally, relevant data was selected and then analyzed among an enormous amount of information.

4.2 Procurement Process

After the initial search, we identified a group of possible suppliers for the equipment necessary to the production of Oral Thin Films. After this we followed the following method to reach the final group of suppliers:

- Research phase: identification of possible suppliers and CMOs;
- Individual Analysis of the identified suppliers: First Selection;
- Direct contact with the first selected suppliers: Final Group of Suppliers.

We followed this three step method in order to reach a final group of suppliers that fulfilled the following requirements:

- Suitable equipment for our needs: mixing, coating, web converting and primary packaging equipment;
- Experience with OTFs and TDDS;
- Experience in the pharma and medical industry;

- Compliance with quality requirements, namely FDA and EU GMP requisites.

After the identification of the possible suppliers, we embarked in a more profound individual analysis by investigating each supplier profile. We searched the information available on their websites, the industry databases and press releases. We also analyzed each competing CMO with the expectation of perceiving their equipment suppliers. This search was more difficult by the fact that pharmaceutical companies are much closed about their processes and technologies. Some of these information can be seen in the appendix A. Nevertheless we found some important information in some press releases and internal reports. In the end of this step, we had selected a group of 21 companies as potential suppliers for the OTF manufacturing equipment.

The next step was to contact all these companies via e-email (see Appendix). In this first contact we presented Bluepharma and the technology for which we needed the equipment and we asked for:

- Available equipment for pilot scale and commercial scale;
- Technical specifications including output and total capacity for a standard sized strip;
- Lead time, budget quotation and payment conditions for each equipment;
- Type of support (e.g. training, installation, documentation, validation, qualification, etc.).

This was a continuous process and along the way companies were excluded for several reasons. In the end we had a final group of 13 suppliers that presented official proposals for analysis.

4.3 Identification of the Critical Requisites

It was an objective of this project to deeply how the three types of equipment work and what are the critical aspects that determine their performance and output. It's important to say that the vast majority of the input information come directly from the suppliers that were selected.

4.4 Capacities Estimation

To determine the capacity of each equipment we followed a rigorous method that is defined in the next pages. This work was performed for the coating and primary packaging equipment.

4.4.1 Coating Equipment

As seen before, this equipment is used to coat the liquid mixture of excipients and drug substance in a release liner to form a film.

As we can easily understand, it's the velocity that determines the output of the equipment. But as we'll see in the next chapter, the velocity in the coating machines is determined by the drying process.

Every supplier gave us their claimed process velocity. The problem was that they were considering different type of formulations, so these velocities were not possible to compare. Each formulation will behave differently. For example, a formulation with a high percentage of water will take more time to dry than one with less amount of water. So, if it takes more time to dry the velocity will be slower and the output smaller.

Once all the equipment used the same drying technology (hot hair in a closed system dryer), we applied the knowledge that we had about our formulation in order to get a drying time that we could use in our predictions.

We knew at this point that Bluepharma's formulation takes 20 to 30 minutes to dry a sample at 40ºC by contact heating from bellow. We crossed this information with the opinions of our suppliers for this type of situation, in order to get a realistic time value to dry our formulation.

Thereby we considered a time of $T = 10\,min$ to dry our formulation in a coating machine.

As we will see further, the factor that is directly related with the increase of the capacity is the dryer length. It is easy to understand, the higher is the drying path we have the faster the process can go.

If we consider X as the dryer length of the equipment and Xi the beginning of the dryer (zero), we can relate it with the drying time in order to get the velocity of the process for each equipment:

$$X = Xi + V \text{ x } T$$

Eq. 1

If we consider $Xi = 0\ m$,

$$V = \frac{X}{T}$$

So,

$$Velocity = \frac{Dryer\ lenght\ (X)}{Drying\ time\ (T)}$$

Eq. 2

We this information we were able to calculate the area produced by a coating equipment, by applying the following equation:

$$Area\ of\ film = Working\ time \text{ x } Velocity \text{ x } Web\ Width$$

Eq. 3

Where the Web Width is the accepted release liner width of the equipment and the Working Time the time that the machine operates.

Working Time

The objective of these estimations was to know if the equipment being analyzed had the necessary capacity to ensure the production of the Bluepharma's OTFs according to the internal forecasts (on a year basis). All the suppliers informed us that both pilot and industrial equipment can run 24 hours per day, and that it's normal that the production run in 2 or 3 shifts per day, normally of 8 hours each. Also, in Bluepharma the production stops during weekends, so we didn't considered them. These information lead us to the scheme in the Table 4:

Years	Weeks per Year	Days per Week	Shifts per Day	Hours per Shift
1	50	5	2 or 3	8

Table 4 - Available working time considered to estimate the equipment capacity.

As we can see we considered 2 weeks of complete stop of the company. Plus, we made calculations for 2 and 3 shifts of operation.

During this time, the machines need to stop working for several reasons: for maintenance, changing of the material, cleaning, product changing, etc. We call this the downtime of the machines. This downtime varies from machine to machine and depends also on the production planning. Nevertheless, the contact with the suppliers gave us important information to set a transversal downtime calculation for the coating equipment.

Heating and Calibration	Cooling down	Cleaning	Coils change per shift	Maintenance per year
90 min	90 min	45 min	30 min	2 days

Table 5 - Considered downtime for the coating machines. This values result from the conversations with the suppliers.

The downtime of the machines, in the Table 5, was considered the same for all machines because we had very similar answers from the different suppliers. Nevertheless, it was not always easy to get this type of information from the manufacturers.

We applied these downtimes differently for 2 shift and 3 shift operation:

- 2 shift operation: Heating, cooling and cleaning happens every day.
- 3 shift operation: Heating happens in the beginning of the week, and cooling and cleaning in the end of the working week.

The equipment is prepared to work continuously. If we assume they work 24 hours per day, it is only necessary to heat when the production starts (in the beginning of the week) and to cool in the end of the journey. We also considered that for a 3 shift operation, only one product is produced per week. Product change just happens from one week to the next. That's why it is only necessary to clean the machine in the end of the journey. On the contrary, for the 2 shift operation system there is the need to heat

and cool the machine every day and also to clean it, because it is not an acceptable practice in the pharmaceutical industry not to clean the equipment when there is a planned interruption of the production.

Translating this to a mathematical equation we have for a 2 shift operation:

$$DT(2) = (Ht + CLt + Ct) * Nd + (CHt * Nd * Nsh) + M$$

Eq. 4

While for a 3 shift operation we have:

$$DT(3) = (Ht + CLt + Ct) * Nw + (CHt * Nd * Nsh) + M$$

Eq. 5

In Eq. 4 and Eq. 5 Ht is the heating time, CLt the cleaning time, Ct the cooling time, CHt the time for coil changes, Nd the total number of working days, Nw the total number of working weeks, Nsh the number of shifts per day and M the maintenance time of the machine.

Overall Equipment Effectiveness (OEE)

In order to have more accurate and realistic results, we decided to use one of the most known efficiency indicators in the manufacturing industries, namely in the pharma industry. The Overall Equipment Effectiveness (OEE) can be defined as a best practice measurement that shows the truly productive time of the planned production.[24]

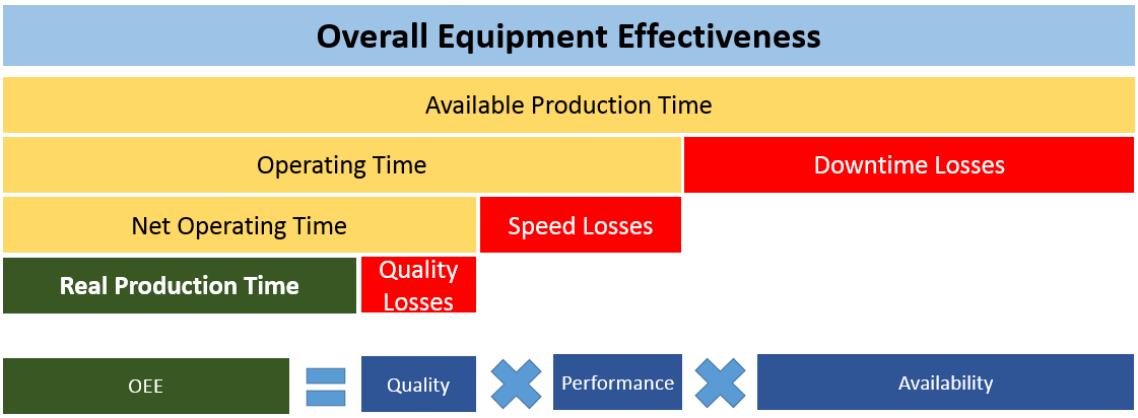


Figure 9 - Illustration of the Overall Equipment Effectiveness (OEE) logics.

As we can see in the Figure 9 there are 3 concepts that define OEE. These concepts are rates and can be defined as:

$$Availability = \frac{Operating\ Time}{Planned\ Production\ Time}$$

Eq. 6

$$Performance = \frac{Parts\ Produced\ *\ Ideal\ Velocity}{Operating\ Time}$$

Eq. 7

$$Quality = \frac{Good\ Parts}{Parts\ Produced}$$

Eq. 8

The availability takes into account the planned downtime of the machines, as we have seen before in Table 5. The Performance measures the behavior of the machine during the available operating time, and can be seen as a confrontation between the theoretical output and the real output. For example, if the velocity of the machine is supposed to be 10m/s and the corresponding output 100 m^2, but the final result it's just 50 m^2 of output, this means that the medium velocity during the operating time was just 5m/s, and so, the performance was just 50% of the expected. According with the suppliers' information, this happens mostly due to unplanned stops, short stops or lack of material for example. The Quality factor it's given by the number of good parts (or good product). In any industrial process there is always defects in the production and it also affects the final efficiency.

In the Table 6 we can see the major loss causes for each OEE factor.

OEE	Availability	Performance	Quality
Major Loss Causes	Planned maintenance, training, cleaning, changeover	Lower speed, short stops, underutilization	Startup losses, rejects, rework

Table 6 - Principal causes that affect directly the OEE.

The OEE is a dynamic tool, and it should be used "on-time" in order to understand where a manufacturing process can be improved and how. In what concerns this project, it's easy to understand that we cannot know how many short stops or how many reject products we will have. Nevertheless, it is possible, assuming some hypothesis, to have an acceptable OEE model, and this was what we've done.

It's good to remind that we are estimating the full capacity of the machines for one year of production. Has we have seen before, we considered 50 weeks of 5 days as the available time, and 2 and 3 shifts per day. Also as showed before, we know the habitual downtimes for this type of machines and we know how to calculate it. So, knowing the Downtime and the Available Time, we can easily calculate the Availability (Eq. 6).

$$Availability = \frac{Operating\ Time}{Planned\ Production\ Time}$$

In the Table 7 it's possible to see the different values of the OEE ant its factors for the different number of shifts.

	Availability	**Performance**	**Quality**	**OEE**
2 Shift Operation	69,1%	75,0%	95,0%	49,24%
3 Shift Operation	89,8%	75,0%	95,0%	64,00%

Table 7 - Considered values for each OEE factor and the respective OEE result, for an operation of 2 and 3 shifts.

As we can notice, the OEE it's approx. 20% lower for a 2 shift operation due to the fact, that the number of planned stops is higher if the equipment doesn't work continuously during the entire week.

The values of the Performance and Quality were assumed by us. As we said, it's not possible to know them at this point. Thereby, we asked directly every supplier about the OEE performance and quality rates for their machines, and almost all answers were those values or very near them. The maximum value given by one of the suppliers was 80%, while the minimum was 65%.

With the OEE estimated for every machine, we were then in conditions to estimate the capacity of each equipment, by applying the following formula:

$$C(m2) = Time\ (min) * OEE * Velocity(m/min) * Web\ Width(m)$$

Eq. 9

4.4.2 Primary Packaging Equipment

As we have seen in the second chapter, the primary packaging equipment combine both production and packaging processes:

- Web Converting (Production): the coated film is cut into small strips with de desired size.
- Primary Packaging (Packaging): the small strips are packed into a small pouch by hot sealing.

The limiting step of these manufacturing phase is the primary packaging of each individual film strip into a pouch. It is the size and the material of the pouch that has the most important impact on the final output of the equipment. This happens because OTFs don't vary very much in terms of size, and once they are small, size variations don't significantly affect the web converting process velocity. On the contrary, variations in the pouch size can have a significant impact on the output of the machine. Also the pouch material has a very important influence. For example, if a certain material takes more time to seal than other, we'll have a lower output.

At this stage of the project the primary packaging material is not known nor the size of the pouches.

Thereby, we used the claimed capacity of each supplier to estimate the maximum capacity for each equipment. Contrary to the coating machines where the output is given by the velocity that in turns depends on the formulation, in this case it is given by the maximum number of pouches per minute.

Taking all this into account and considering the principles referred before the following formula was applied for this estimation:

$$C(number\ of\ OTFs) = T(\min) * OEE * Notf(\frac{OTF}{min}) * Nl$$

Eq. 10

The capacity C is then equal to the multiplication of the working time T by the OEE, the number of strips, $Notf$, produced per minute in each lane and the number lanes Nl. As we have seen, machines can have one to several production lanes embedded. Once we are estimating the maximum capacity, we considered the total number of lanes of each equipment.

4.5 Outline Design of the Manufacturing Facility

One of the challenges of this project was to outline the manufacturing facility for OTF production in terms of space, building requirements and overall investment needed.

This projection should include laboratorial, pilot and commercial scale equipment, in order to gather all phases of the product development, since the lab until the commercial scale manufacturing.

The first step consisted in searching information regarding other facilities used to the same purpose. We then collect information from inside the company that lead us to a first design that was several times improved until we reach the final draw that is presented in this dissertation.

4.6 Bluepharma Forecast and Road-Map

At this point we already could answer to these two questions: what we need? How does it work? But to answer to the question, “when do we need it?” we have to look to the company’ sales forecast.

First of all it’s important to say that the forecasts were provided by Bluepharma. As we will see in the confrontation between the capacities estimated and the sales forecast, these sales predictions are represented in number of OTFs per year and they go until the year of 2025.

But as we've seen, we can only consider the total number of OTFs as the unit of calculation for the primary packaging equipment. The production and packaging processes are independent, and in the case of the coating process the output is given in square meters. Thereby, we must convert the total number of strips of each product in area of film:

$$A(area) = N(OTFs) * Strip\ Area$$

Eq. 11

$$Total\ \mathrm{A}(area) = \Sigma(N(OTFs) * OTF\ Area) + 20\%$$

Eq. 12

It's easy to understand that multiplying the area of the strip by the number of strips we'll have the area of film they represent. However, and as demonstrated in the last formula, we should consider at least 20% more of area. This is explained by the fact that there is a significant product loss (waste) when it passes from the coating to converting machine. In other words, not all the film that is produced ends inside a pouch ready to use. Due to this reason, we should produce more area of film in order to compensate these losses.

So, following this method we obtained the forecast in the number of strips and also the area of film needed. Therefore, we were able to compare both coating and primary packaging machines capacities with Bluepharma sales expectation and draw a road-map and the corresponding milestones for the next ten years.

CHAPTER 5

Results and Discussion

5 Results and Discussion

In this chapter we will describe and analyze the results of the prospection that was made.

For confidentiality reasons we will not use the names of any of the companies contacted nor the equipment models that we've analyzed. Instead, the following letter system will be used:

- The first letter describes the type of equipment: "M" – for mixing equipment; "C" – for coating equipment; "P"- for primary packaging equipment;
- The second Letter tells the supplier, and can goes from "A" to "B", "C", "D", "E", etc.
- The last letter describe the scale of the equipment: L – for Lab, "P" – for Pilot and "I" – for Industrial scale. If a supplier has more than one equipment for a certain scale then the last letter must have a number next to it (ex: P1 for pilot equipment number one, P2 for pilot equipment number 2)

Let's use an example. "MD-P2": mixing equipment, from supplier D, pilot scale, model 2.

5.1 Identification of CMOs and Possible Suppliers

This first stage comprised the identification of possible equipment suppliers and the Contract Manufacturing Organizations (CMOs) in the market for benchmarking purposes. This is a particularly important step. On one hand suppliers can give us the necessary input on equipment specifications and prices, on the other CMOs are a good barometer not only to classify the possible suppliers, but also to understand how the different market regions are responding to this new kind of dosage form.

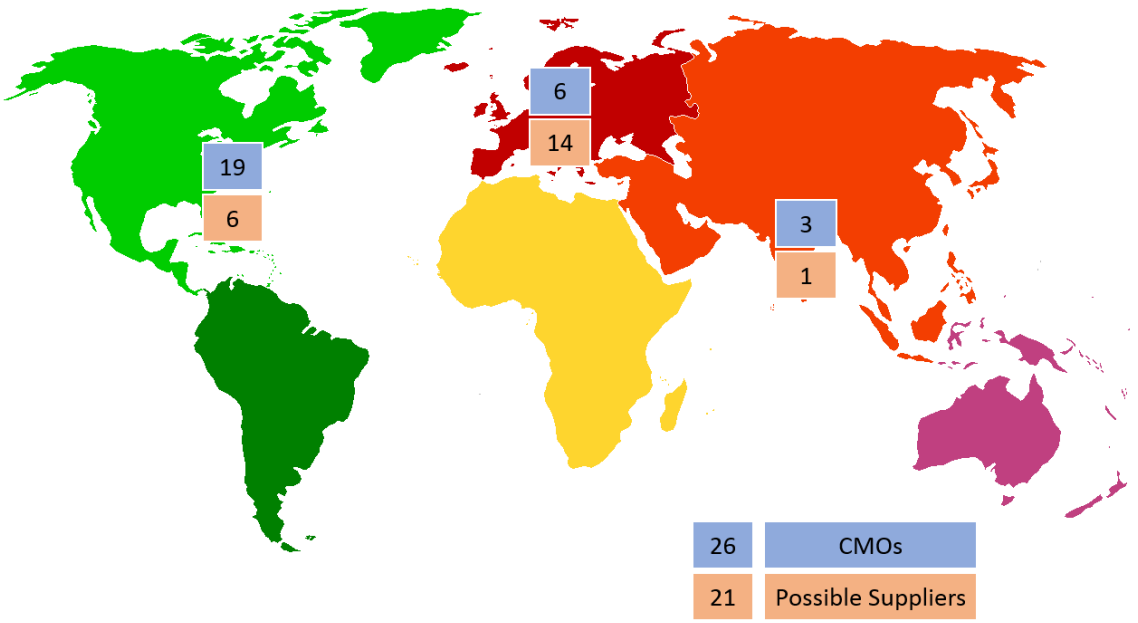


Figure 10 – Geographical distribution of the OTFs contract manufacturers organizations (CMOs) and the identified equipment suppliers.

Figure 10 shows the distribution of Oral Thin Films CMOs and Equipment Suppliers, for Mixing, Coating and Primary Packaging. As we can notice, most of the equipment manufacturers are established in Europe while the majority of CMOs are in the United States of America. In fact, Europe (mainly Germany, as we will see) is the region with the biggest concentration of machinery and equipment companies.

It's almost common sense that Germany is known by their robust machinery, and the pharma equipment is not an exception. It's is estimated that 1 in each 4 pharma machines are made in Germany or by German companies [25]. Also, the basis for innovation in the most prominent players in the pharma packaging equipment is set up in the growing need of solutions for novel drug delivery systems, like OTFs [26].

On the other hand most of the OTF manufacturers are in the USA. The first reason that can explain this is that the USA is where the Headquarters of the major pharma companies are located [27]. The other reasons is due to the fact that OTF products are more accepted by the patients in the USA than in Europe, because this is a technology that was first introduced there and also because both OTC and Rx OTF were first launched in the USA [21], [28].

As we've seen before, from the market search 21 possible equipment suppliers were identified, 7 for each type of equipment: Mixing, Coating and Primary Packaging.

5.2 The Procurement Process

5.2.1 Mixing Equipment

Mixing Supplier	A	B	C	D	E	F	G
Country	Germany	UK	Germany	Switzerland	Germany	USA	USA
Equipment for Pharma Industry	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Possible Matching Equipment	Yes	Not Clear	Yes	Yes	Yes	Not Clear	Not Clear
Selected for First Round	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Contact	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Answer	Positive	Positive	Positive	Positive	Positive	No answer	No answer
Type of Contact	Local Representative	Local Representative	Local Representative	Direct	Direct		
Presentation of Formal Quotations	Yes	Yes	Yes	Yes	Yes		
Lab Scale equipment	3	1	1	2	-		
Pilot Scale equipment	1	1	1	1	1		
Industrial Scale equipment	3	-	3	2	3		
Final Group of Suppliers	Yes	Yes	Yes	Yes	Yes	No	No

Table 8 - Resume of the procurement process for the mixing equipment.

Table 8 resumes the selection of the possible suppliers of the mixing equipment. Five potential suppliers were selected (out of seven) which presented a total of 23 different types of machines.

As we can see, we asked for equipment in each of the three phases (lab, pilot and industrial). This only happens for this type of equipment because Bluepharma already has specific lab scale equipment for coating and primary packaging. .

During the course of this work and in result of the procurement process, a lab mixing equipment with the features identified as critical for OTF manufacturing process was acquired and is operational.

5.2.2 Coating Equipment

Coating Supplier	A	B	C	D	E	F	G
Country	Germany	Germany	Switzerland	Germany	USA	USA	Denmark
Equipment for Pharma Industry	Yes	Yes	Yes	Yes	Not Clear	Yes	Yes
Coating Machines for OTFs	Yes	Yes	Yes	Yes	Not Clear	Not Clear	Not Clear
Selected for First Round	Yes	Yes	Yes	Yes	No	Yes	Yes
Contact	Yes	Yes	Yes	Yes		Yes	Yes
Answer	Positive	Positive	Positive	Positive		Positive	Negative
Type of Contact	Direct	Direct	Local Representative	Direct		Direct	
Presentation of Formal Quotations	Yes	Yes	Yes	Yes		No	
Pilot Scale equipment	2	1	1	1		-	
Industrial Scale equipment	2	1	1	-		-	
Final Group of Suppliers	Yes	Yes	Yes	Yes	No	No	No

Table 9 - Resume of the procurement process for the coating equipment.

In what concerns to coating equipment seven different companies were identified. In the first step we eliminated one of these possible suppliers, due to the fact that we couldn't find enough information about the company and because the only equipment sold by this company is also supplied by another company that was selected for contact. Another company was discarded because they only operate in the Scandinavian region. Finally, the last company excluded from the final list of suppliers never provided an official budget quotation or any technical information although several emails were exchanged.

5.2.3 Primary Packaging Equipment

Primary Packaging Suppliers	A	B	C	D	E	F	G
Country	USA	Italy	Germany	Germany	USA	Germany	Índia
Equipment for Pharma Industry	Yes	Yes	Yes	Yes	Yes	Yes	Not Clear
Primary Packaging Machines for OTFs	Yes	Yes	Yes	Yes	Not Clear	Yes	Not Clear
Selected for First Round	Yes	Yes	Yes	Yes	Yes	Yes	No
Contact	Yes	Yes	Yes	Yes	Yes	Yes	
Answer	Positive	Positive	Positive	Positive	Positive	Positive	
Type of Contact	Direct	Direct	Direct	Direct	Direct	Local Representative	
Presentation of Formal Quotations	Yes	Yes	Yes	Yes	No	No	
Pilot Scale equipment	1	1	1	1	-	-	
Industrial Scale equipment	1	1	1	1	-	-	
Final Group of Suppliers	Yes	Yes	Yes	Yes	No	No	No

Table 10 - Resume of the procurement process for primary packaging equipment.

Finally the web converting and primary packaging equipment, in the Table 10. Only one company was excluded after the preliminary analysis because it was not possible to find any solid information about equipment or guaranties of experience and quality. The contrary happened with another supplier, a well-known company in pharma industry with high experience in the packaging field. We even had a face-to-face meeting with the local representative, but we never received any official proposal. The same occurred with one last company, with the difference that from this company we received some preliminary information and indicative prices, but never an official quotation.

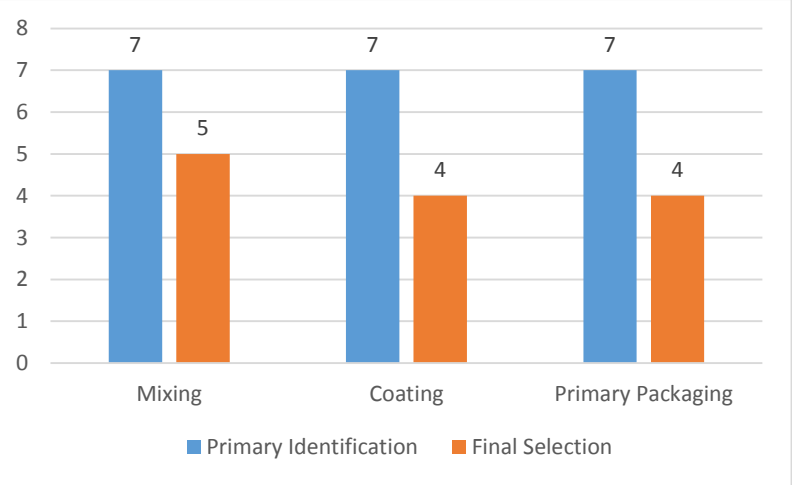
5.2.4 General Analysis

All this process was a very intense and with a lot of exchanged information, as it can be seen in the Table 11.

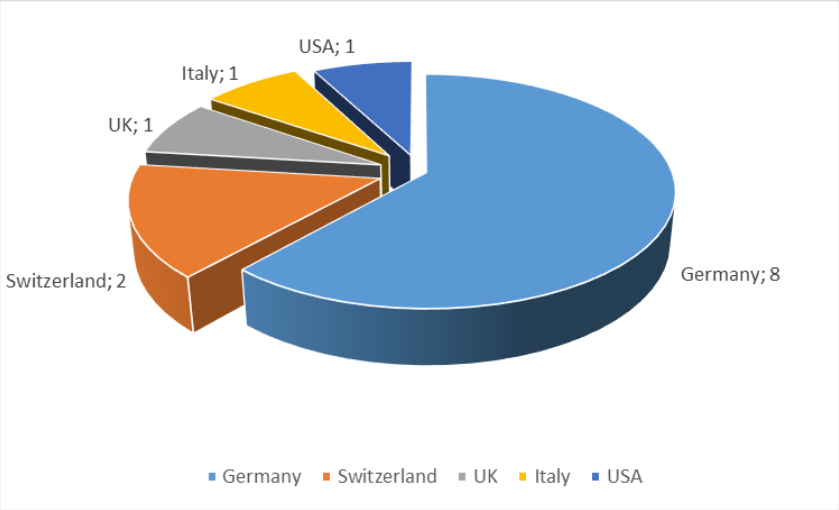
Emails exchanged	Phone calls	Meetings	Equipment models analyzed
> 300	>30	6	39

Table 11- Some numbers that describe the intense contact with equipment suppliers and the number of machines analyzed.

In the next two charts (Graphic 1 and Graphic 2) it is possible to compare the initial number of identified companies and the final selection as well as the geographic distribution of the selected companies by country.

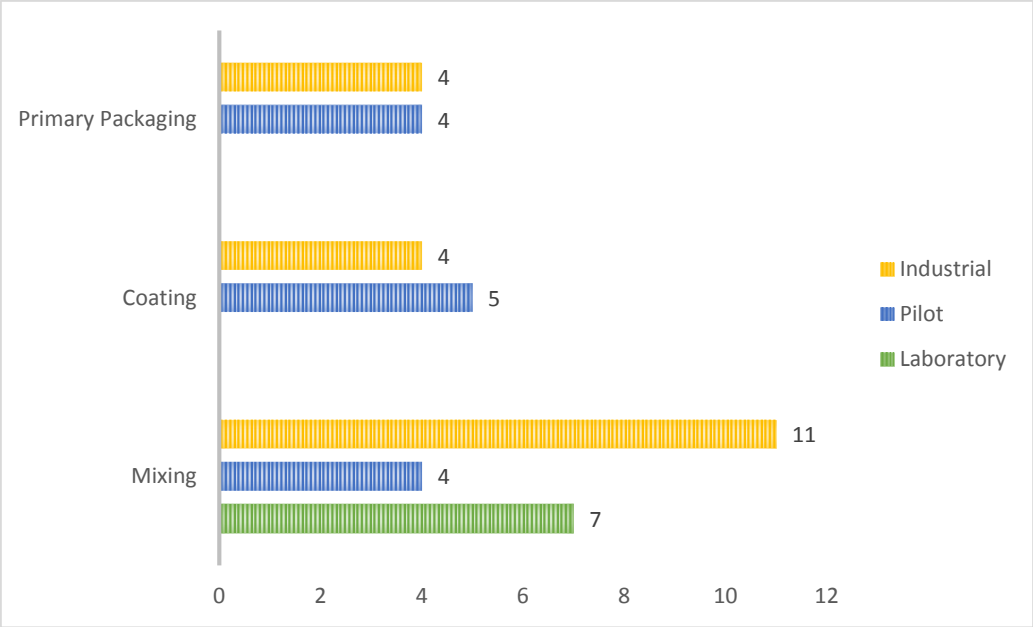


Graphic 1 - Comparison between first identified equipment manufacturers and the selected.



Graphic 2 - Geographical distribution of the selected suppliers, by country.

Graphic 3 shows the number of equipment's analyzed by type and by scale. Analyzing the graph it is possible to observe that there is a higher variety of suppliers of mixing equipment than coating and primary packaging equipment. This is expected considering that this type of equipment can be used in several types of dosage forms, while the coating and primary packaging equipment is limited to the manufacture of OTFs or transdermal patches.



Graphic 3 - Number of different models analyzed by type and by scale.

In conclusion, 62% of the first identified suppliers were selected for the final group of suppliers, 9% were eliminated in the preliminary analysis and 29% were not considered because the response was negative or because proposals were not sent to Bluepharma. Thereby we truly believe this was a task performed successfully.

5.3 Identification of the critical requisites

The machines' specifications were carefully analyzed in order to identify the ones with higher impact on the manufacturing process. It's important to mention that the equipment analyzed is very complex, with hundreds of technical components. The main objective of this project was not to make a complete analysis and comparison but to identify the critical ones.

5.3.1 Mixing Equipment

In the procurement process for the mixing equipment the main objective was to find solutions that could guarantee a proper scale-up (e.g. equipment working with the same process in all scales). Furthermore, there was already an advanced know-how in Bluepharma about the main difficulties of the mixing process which helped the work being performed.

Regardless the formulation composition, it is mandatory to achieve a perfectly homogeneous mixture. This means a mixture without bubbles or lumps and with a homogeneous distribution of the drug(s) substance(s). The existence of any of those problems can seriously compromise the coating process.

The equipment recommended for the mixing process of OTFs corresponds to highly advance processing units, developed for the production of emulsions and suspensions mainly to the pharmaceutical industry. Besides the typical mixing features, like agitation for example, they allow to work with high pressures or vacuum and to regulate the temperature, among several other functions.

In Figure 11 it's possible to see the outlook of a typical processing unit used in the preparation of OTFs.

Figure 11 – Example of a mixing equipment with an anchor agitator. (Image from supplier M.A).

Figure 12 shows a schematic representation of a mixing equipment that will be useful to understand the discussion.

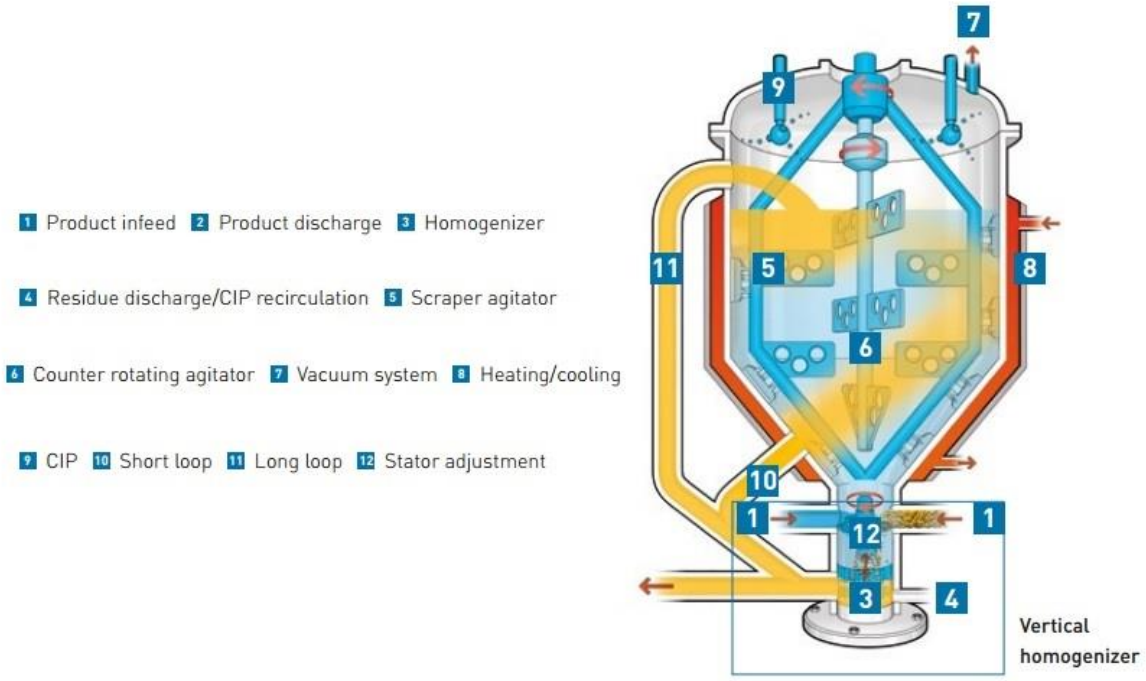


Figure 12 - Schematic representation of a mixing equipment used for the production of OTFs. Legend on the left side. (Image from supplier M.B)

The different models analyzed have a very large range of volumes, from dozens of liters to thousands. The choice of the right volume and the number of equipment and vessels to acquire, depend on the volumes of OTFs that are projected to be produced and also on the number of different products.

Each company contacted offer equipment for both pilot and industrial scale. We have requested the following volumes to the suppliers according with the scale:

- Pilot Scale: 50 Liters.
- Industrial Scale: 500, 1000 and 2000L.

Regarding the lab scale the major concern was the minimum volume because in the beginning of the R&D of new formulations it is very important to work with very small volumes to be as cost-effective as possible.

Agitation

There are various types of agitators in the market, such as propeller, anchor or magnetic agitators. Our demand focus was on the anchor agitators (Figure 13) that are anchor shaped and their blades are very close to the walls and to the bottom of the vessel. They work in low to medium velocities and are recommended for medium to high viscosity solutions or emulsions and for laminar fluids. This can be explained looking to the Reynold's Number:

$$Re = \frac{inertial forces}{viscous forces}$$

Eq. 13

The number of Reynolds is lower when the viscosity is higher, and in this case near-walls agitators are recommended to shear the mixture [29].

Figure 13 -Example of an anchor agitator for laboratory scale. It is also visible the wall scrapers in white. (Image from supplier M.A).

However, for higher volumes the anchor agitators do not show a high performance, because the center zone experience little movement resulting in a non-efficient mixing [29]. Thereby, pilot and industrial equipment present more complex agitators in order to surpass this limitation, like agitators with both internal and external agitation and temperature controlled systems.

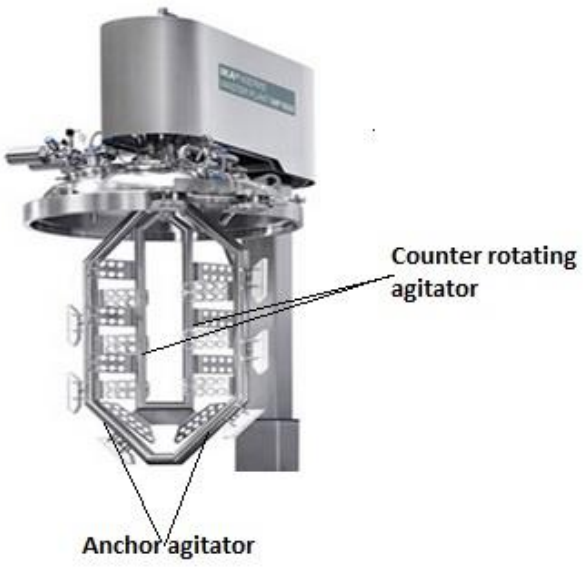


Figure 14 - Detail of an anchor agitator for pilot scale mixing. Besides the external anchor, it's possible to notice the internal counter rotating agitator. (Image from supplier M.A).

As the Figure 14 shows, the anchor works as an external agitator that moves close to the walls and the bottom of the vessel, while the counter rotation agitator (or blade) is placed in the center of the vessel and rotates in the opposite direction of the anchor. The counter rotating is normally vertical and has several paddles along it. This technology is used due to the high vessel volumes, to ensure a constant and uniform agitation not only in the borders but also in the center of the vessel.

Another important feature to mention are the wall scrappers (indicated in the Figure 13). These pieces, normally made of PTFE, scrap the walls and the bottom of the vessel, what ensure that no agglomerates stay glued to the borders of the vessel.

Homogenization

As referred before, one of the most important goal to achieve in the formulation of OTFs is a truly homogeneous mixture. The production step (coating) comprehends the spreading of the solution on a substrate. If the solution has solid agglomerates or air bubbles, for example, an entire batch can be compromised because the resulting film will not comply with the specifications. To achieve perfect homogenization, dispersion equipment (or homogenizers) are commonly used. The dispersion process can be defined as the mixing of at least two substances that don't dissolve in each other, hardly react with each other or don't chemically react with each other [30].

However, and as all the suppliers have explained, these tools are able to mix any mixture and with better results than a simple agitator, because the mixture it's dispersed at very high velocities. Nevertheless it's important to say that it doesn't make the agitator dispensable. The agitator guarantees the uniformity of the mixture inside the vessel and pushes it in the direction of the homogenizer, mainly in bigger vessels.

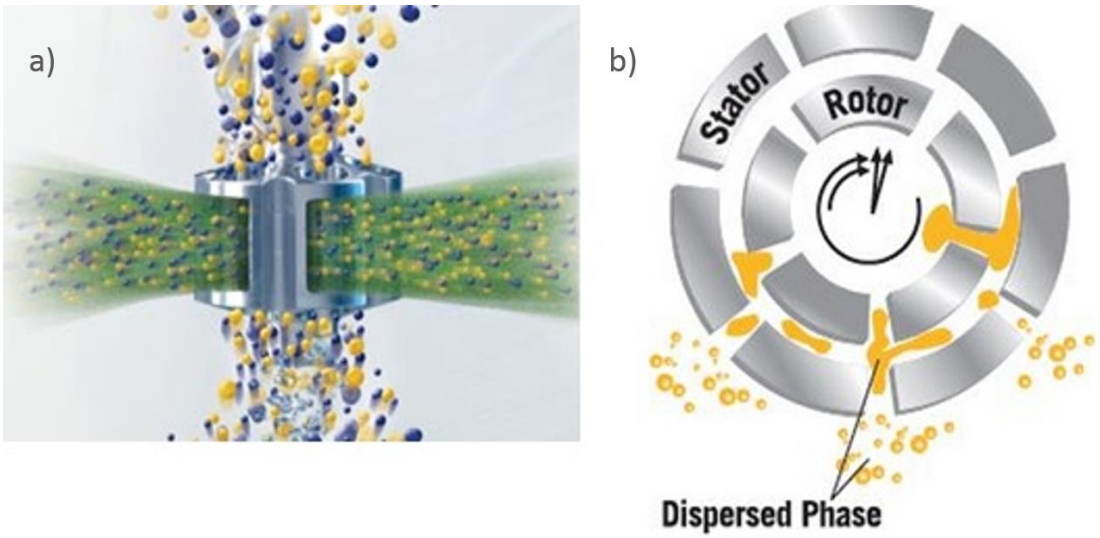


Figure 15 – Dispersion head. a) Representation of what happens in the dispersion head, showing the smaller particles being expelled at high velocity. b) Representation of the rotor stator system. The rotor moves at high velocity sucking the mixture and then expelling it through the slots in in an in the stator, making the mixture to spilt into disperse phase.

These homogenizers have a principal component that is the dispersion head, which works according to the rotor-stator principle, as demonstrated in the Figure 15. The rotor operates at very high velocities creating a very powerful axial suction force that sucks the mixture into the dispersion head, where the rotor rotates at very high velocity forcing the mixture through the stator slots. The mixture is submitted to very high shear forces through those slots being spliced. There are three main factors that characterize these instruments:

- **Range of Velocities**: to create the necessary high shear forces, the rotor has to reach very high velocities, in the order of thousands revolutions per minute (RPM). Nevertheless, very high velocities can damage more sensitive mixtures, for example, mixtures containing some kinds of polymers [31]. In this case, it's important to have special attention to the minimum velocities of the homogenizers.

- **Dispersion head**: for each equipment there are several different heads available, with different shapes and different slot sizes. The selection of a suitable dispersion head should take into account the type of the formulation in order to achieve maximum homogenization.
- **Mode of operation**: there are two different types of homogenizers, the batch and the in-line homogenizers. The first ones are individual tools, normally with the format of a magic wand for kitchen and are placed in an overhead position on the top of the vessel. In the Figure 16 these two operation modes are represented.

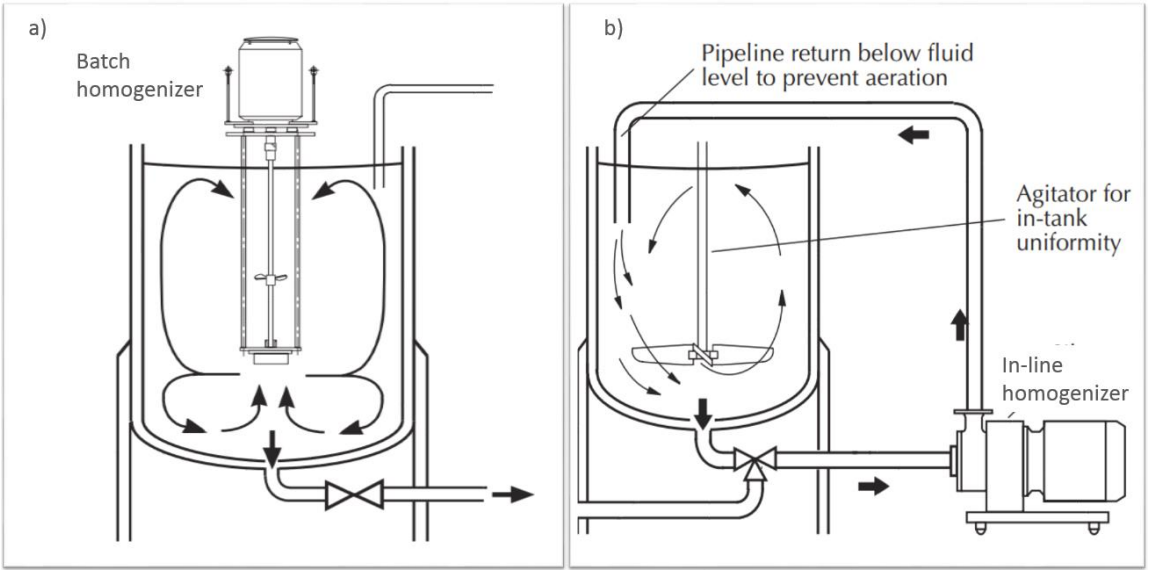


Figure 16 - Different operation modes of homogenizers. a) Shows a batch disperser placed on top of the vessel. b) In-line homogenizer, connected to the bottom of the vessel. It creates an external circulation of the mixture.

While in the batch homogenizer the disperser head is inside of the vessel and the dispersion happens locally, in the case of the in-line dispersers the disperser heads are located outside the vessel (normally on the bottom or connected to it) and create a circulation circuit (Figure 16). These last ones are more effective, once they ensure that all the mixture passes by the circuit of dispersion several times. This is particularly relevant for higher volumes (e.g. pilot scale and industrial scale). For our project, we considered the batch dispersers only for laboratory equipment due to the higher volumes of pilot and commercial scale. However, some laboratory solutions present also in-line homogenizers, what is an advantage in terms of scale-up. Although, to use this

type of homogenizer higher volumes are needed when compared with the batch laboratory homogenizers, which is a disadvantage once we seek the minimum volume possible for this scale.

Vacuum

Another critical aspect of the formulation process is to avoid aeration, i.e. formation of air bubbles inside the mixture. During a mixing process it is frequent the formation of bubbles or foam.

To avoid this, manufacturers of mixing equipment offer optional accessories that ensure that the mixing process is made under vacuum conditions. These accessories are normally vacuum pumps, which are connected to the vessel through an inlet that is sealed and when operating can create vacuum inside by sucking the air inside of the vessel.

Nevertheless, other factors can help to avoid aeration. For example, if a batch disperser is used, the dispersion head should not be placed closed to the surface of the mixture in order to avoid turbulence, which can promote the formation of bubbles or foam. In any case, an in-line disperser is always a better option, because the recirculation system created also helps to eliminate the air entrapped in the mixture. Also it is possible to add the solid ingredients (like powders) directly in the in-line homogenizer so it passes in the rotor-stator before it enters in the mixing vessel, which avoid the formation of lumps and air bubbles.

Temperature Control

The control of the temperature in a mixing process is very important. Depending on the formulation, heat may be necessary. The agitation and homogenizing tools, for example, can create heat that affect the stability of the mixture. The necessity to keep the mixture at high or low temperatures depends on the composition of the formulation. However it is crucial to have the temperature controlled at all time. The presence of unwanted moisture can compromise the OTF mechanical properties, plus it can be necessary to change process temperature to improve or reduce the viscosity of the mixture [15]. Also, drug substances are often very sensitive to temperature, being necessary to control this parameter in order to not affect it [18].

In the pilot and industrial scale equipment analyzed, the vessels have a double wall jacket and for heating the mixture, compressed air and steam are introduced in the wall jacket. On the other side, to cool down the mixture, cold water is introduced in the wall jacket.

Specifications of the Quoted Equipment

The Table 12 and Table 13 resume the specifications of the different quoted equipment.

Type	Mixing Equipment (M)						
Supplier	A			B	C	D	
Model	L1	L2	L3	L1	L1	L1	L2
Code	M.A-L1	M.A-L2	M.A-L3	M.B-L1	M.C-L1	M.D-L1	M.D-L2
Maximum Volume (L)	1	2	2	-	3	1	2
Minimum Volume (L)	0,5	0,8	0,8	-	0,75	0,45	1,1
Máx. Viscosity (mPas)	100.000	150.000	150.000	-	50.000	50.000	50.000
Agitator	Anchor	Anchor	Anchor	-	Other*	Anchor	Anchor
Wall Scrapers	Yes	Yes	Yes	-	Yes	Yes	Yes
Agitator Speed (rpm)	10 - 150	8 - 290	*ndi*	-	30 - 150	10 - 400	10 - 400
Homogenizer	Batch	Batch	Batch/In-line	Batch/In-line	In-line	Batch	Batch
Homogenizer Speed (rpm)	3.000 - 25.000	3.000 - 25.000	3.000 - 25.000 / 3.000 - 26.000	0 - 6.000	3.000 - 12.000	500 - 30.000	500 - 30.000
Vacuum Pump	Yes	Yes	Yes	-	Yes	Yes	Yes
Temperature Control	Yes	Yes	Yes	-	Yes	Yes	Yes

ndi: not delivered information

** patented and registered technology of the supplier that cannot be revealed due to confidential reasons*

Table 12 - Specifications of the quoted mixing laboratory equipment.

On Table 13 it is possible to find the specification of the laboratory equipment. In what concerns the volume, our major concern was the minimum working volume, because the in the R&D phase of new OTFs formulations it is normal to work with very small volumes in order to reduce costs. Only two can of the models work with 0,5 Liters or less, and these volumes are closer to Bluepharma's needs for this scale.

The supplier of equipment M.B-L1 just sent data regarding the homogenizer specifications. This happened because this equipment corresponds to a homogenizer only. Supplier B is known for its homogenizers and claims that, in certain cases, they can exclude the necessity of the agitator and that they can work with volumes in the order of 1 mL. Thereby we decided to consider this supplier just for laboratory equipment, even though it does not present any of the other features.

Besides the M.B-L1 and M.C-L1 models, all the other options present an anchor agitator. This information agrees with what was referred before, that this type of agitators are recommended for medium to high viscosities, which is the case of OTFs formulations [29]. Nevertheless, the M.C-L1 has a patented technology that was designed for working with high viscosities and the supplier "C" claims that it ensures far better results than a typical anchor agitator.

Looking to the type of homogenizer we can see that there are models with in-line homogenizers for lab scale. This is an important thing to consider, because at pilot and industrial scale, most of the equipment uses this technology. In addition to ensure a better homogenization, if we use the same process in all scales, the scale up process will have a higher probability to have success.

Type	Mixing Equipment (M)			
Supplier	A	C	D	E
Equipment	P1	P1	P1	P1
Code	M.A-P1	M.C-P1	M.D-P1	M.E-P1
Maximum Volume (L)	50	50	50	60
Minimum Volume (L)	*ndi*	13	*ndi*	8
Max. Viscosity (mPas)	100.000	50.000	50.000	*ndi*
Agitator	Anchor + Counter rotating blade	Other*	Anchor	Anchor + Counter rotating blade
Wall Scrapers	Yes	yes	Yes	Yes
Agitator Speed (rpm)	22 - 66	24 to 120	*ndi*	*ndi*
Homogenizer	In-line	In-line	Batch/In-line	In-line
Homogenizer Speed (rpm)	3.000	600 - 4.800	Max. 3.000/ 10.000	600 -3000
Homogenizer Recirculation	External	Internal / External	*ndi*	Internal / External
Vacuum Pump	Yes	Yes	Yes	Yes
Temperature Control	Double jacket System	Double Jacket System	Double Jacket System	Double Jacket System
CIP	Yes	Yes	Yes	Yes
ATEX (option)	Yes	Yes	Yes	Yes

ndi: not delivered information

** patented and registered technology of the supplier that cannot be revealed due to confidential reasons*

Table 13 - Specifications of the quoted mixing pilot equipment.

For the pilot equipment the target volume was 50 liters but the information regarding the minimum working volume is also important. However only two suppliers provided that information and as it can be seen in the Table 13, the M.E-P1 presents the lowest useful volume, 8 liters.

Finally, all the models allow the regulation of temperature, vacuum, clean-in-place (CIP) and ATEX configuration. ATEX are the European guidelines and directives to work with Explosive Atmospheres [32]. In many industries, like pharma, there are processes were, for example, inflammable or explosive materials are handled. In this case the equipment must be configured in order to meet those guidelines.

For industrial scale the models are exactly the same presented for pilot scale, the specifications are practically the same and the only major difference is the higher working volume. Using the same models will reduce the probability to have problems in the scale-up of the production.

Thereby, the suppliers “A”, “C” and “E” presented proposals for 500L, 1000L and 2000L capacities, while the supplier “D” only sent us quotes for 500L and 1000L.

5.3.2 Coating Equipment

As referred in the introduction part, coating machines are responsible for transforming the liquid mixture into a solid thin film. The process consists in applying one or more coverings (laminates) in a substrate (release liner). In the Figure 17 it’s possible to see an industrial coating machine for the production of OTFs. These machines are normally very long due to the dryer’s big length.

Figure 17- Example of an industrial scale coating machine.

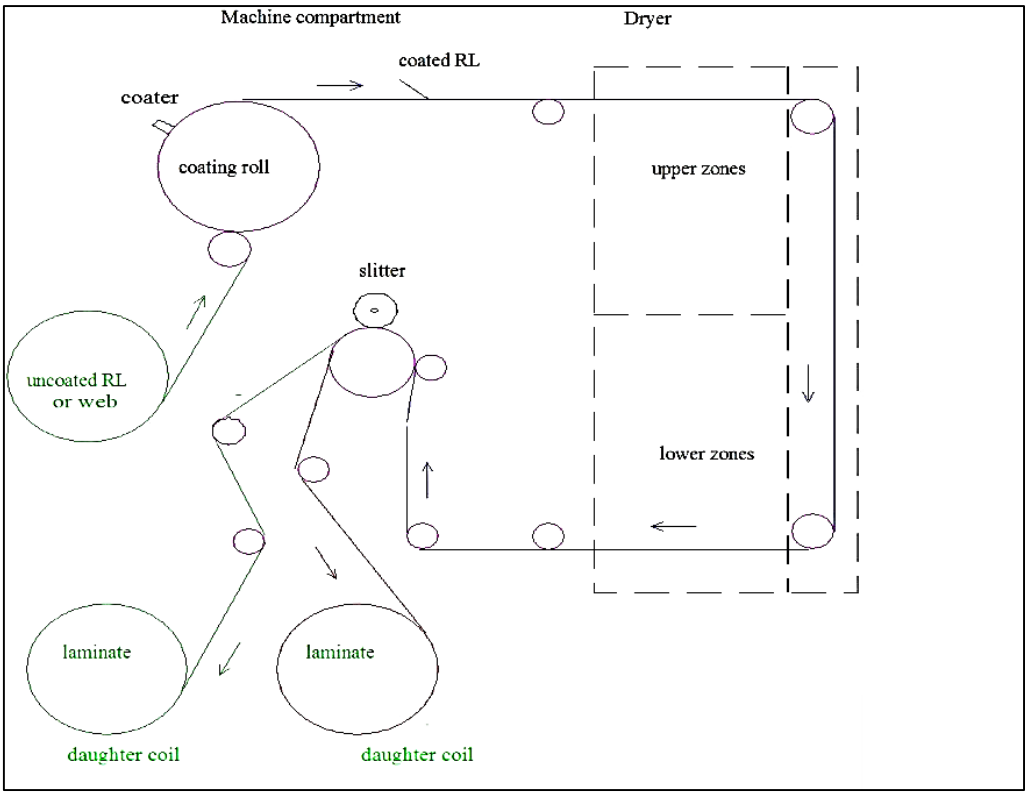


Figure 18 - Scheme of the coating machine path since the uncoated web to the final coated film.

The Figure 18 shows a scheme of the coating process for OTFs, as explained before. In the end the coated films instead of being winded in one roll, it's is first cut in two and winded into two smaller rolls. As we'll see further this due to an optional feature called slitting station that allow us to have two independent coated rolls with a smaller web width.

Web Width

The web width can be defined as the maximum release liner (web) width that is accepted by the coating machine. Normally the machines don't have a fixed width, instead they have defined a maximum value. Pilot scale machines have normally a shorter web width than the industrial ones, the main difference is in the length. It is easy to understand that the web width as well as the web length are directly related with the machine output.

Dryer

The dryer plays a very important role in the coating process. These dryers are very complex systems and the process has to be perfectly adjusted to the mixture

composition in order to ensure a final OTF with the desired properties (plasticity, elasticity). The film has to be dried at a constant velocity and the film cannot be inside of it more than the calculated time, otherwise it may become brittle.

It's also important to refer that the dryers normally come in modules, this means that it is possible to add more modules depending on the capacity that we will need (each module increases the dryer length). This concept is present in the industrial scale machines, but not at pilot scale.

The length of the dryer is probably the most critical aspect of these machines since a dryer with a higher length is synonymous of a higher output of the machine. It's easier to understand if we look to what happens in the machine: the web (release liner) moves slowly in the dryer direction, before it enters the dryer, the mixture is spread in the release liner a fixed thickness and after that, it enters into the dryer. The velocity which the web moves it's determined by the time that the mixture has to stay inside the dryer in order to turn to the solid state. So, if we have a small dryer, the web will move very slowly and on the contrary if we have a longer dryer the web can run at a higher velocity. In any of those cases, the web will be the exactly same time inside the dryer, but the velocity it runs will be different.

There are several drying techniques, like infrared, UV or microwave radiation, by contact eating or by natural air contact, for example. But in case of OTFs manufacturing, the method used by all the suppliers selected and their equipment is drying by hot air. This technique is used because it does not have some of the problems of other techniques:

a) radiation techniques may modify the OTF properties;
b) heating by contact can damage the structure of the coated film due to the very small thickness it presents.

Thereby, drying by hot air allows a uniform distribution of the heat around the film carrier at all moments, due to the convection current originated. Plus, it enables a slow and steady drying, which is the recommended procedure. If the drying process is too fast, the surface and bottom of the film will dry much before the middle part and the solvents can become cloistered inside, creating crusts in the film.

Dimensions

The dimensions of the equipment (length, height and width) are important to make an estimation of the area required for the manufacturing facility.

Application System

The Application System (or coating heads) can be described as the machine feature responsible to coat the release liner with the mixture. These components are very precise and can ensure a wet thickness of micrometers. There are several types of coating heads and they are related with the material that is being produced. In the case of OTFs, the most common systems are the Knife Coater, the Slot Die and the Reverse Roll, however other possibilities may be considered.

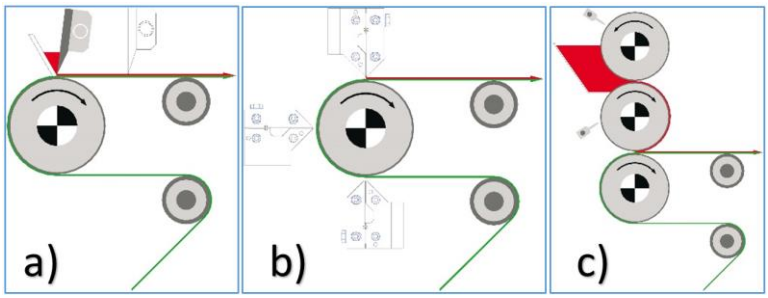


Figure 19 - Representation of three different coating systems: a) Knife Coater, b) Slot Die and c) Reverse Roll.

In the Figure 19, the green layer represents the liner and the mixture is represented in red. The different systems all release the mixture at a constant rate and with a very precise thickness. The selection of the best options depends on the mixture properties, mainly its density, viscosity and composition. All suppliers selected equipment models appropriate for the production of OTFs

Release Liner

There are several options on the market of release liners. In the OTF manufacturing process, it is mandatory that this product fill all the quality requisites required by the authorities, namely the FDA (for the US market) and the EMA (for the European market). Release liners for OTFs production are normally made of a polymeric film or paper substrate that may be coated with silicone.

The release liners play a crucial role in the manufacturing process of OTFs besides being the substrate where the mixture is spread. These liners provide extra strength to the

film, helping to maintain its integrity and surpass all the stresses during the manufacturing process [33]. Before the packaging of the OTFs into individual pouches the release liner is peeled off releasing the film without damaging it.

One of the tasks of this work was to find a suitable release liner fulfilling the US and European regulatory requirements and non-siliconized. Most of the release liners for pharma are siliconized in one or both sides but considering the BlueOS technology composition these release liners are not compatible. Nevertheless, it was possible to find a non-siliconized release liner, compliant with all the necessary requirements.

Specifications of the Quoted Equipment

We will now compare the different equipment models that we've received proposals. The specifications for each equipment received are displayed in Table 14 (pilot scale) and Table 15 (industrial scale).

Type	Coating Equipment (C)				
Supplier	A		B	C	D
Equipment	P1	P2	P1	P1	P1
Code	C.A-P1	C.A-P2	C.B-P1	C.C-P1	C.D-P1
Length (mm)	2216	2200	3000	4121	3200
Width (mm)	646	1000	1250	1500	1000
Height (mm)	600	1100	1850	1600	1900
Area (m^2)	1,4	2,2	3,8	6,2	3,2
Weight	190	1100	*ndi*	*ndi*	6000
Max. Web Width (mm)	155	250	400	350	130
Useable Coating Width (mm)	120	200	250	200	100
Coating System	Coating Knife	Coating Knife	Roll Coater	Knife/Slot die	Knife over roll/Slot Die
Dryer Sections	2	3	3	2	3
Dryer Length (mm)	1600	3400	1660	1876	1500
Dryer Technology	Hot Air	Hot Air	Hot Air	Hot Air	Hot Air
Slitting Station (option)	No	Yes	*ndi*	Yes	*ndi*
Adaptable for TDDS	Yes	Yes	Yes	Yes	*ndi*

ndi: not delivered information

Table 14 - Specifications of the coating equipment for pilot scale.

As we can see, all the models have a small dimension (between 1,4 m^2 and 6,2 m^2) and have a small web width. Also, the dryer lengths are between 1,5m and 2m for four of the five models. Just the equipment C.A-P2 has a higher dryer length. This happens because this is the only machine where the dryer makes a U pathway, almost duplicating the length of the dryer path.

Type	Coating Equipment (C)			
Supplier	A		B	C
Equipment	I1	I2	I1	I1
Code	C.A-I1	C.A-I2	C.B-I1	C.C-I1
Length (mm)	4700	6300	14180	9700
Width (mm)	2100	2600	5200	1500
Height (mm)	2100	2100	6362	2300
Area (m^2)	9,9	16,4	73,7	14,6
Weight	7000	8000	*ndi*	7000
Max. Web Width (mm)	460	460	600	480
Useable Coating Width (mm)	440	440	500	460
Coating System	Coating Knife	Coating Knife	Roll Coater	Knife/Slot die
Dryer Sections	2	4	3	4
Dryer Length (mm)	4700	8500	9000	3810
Dryer Technology	Hot Air	Hot Air	Hot Air	Hot Air
Slitting Station (option)	Yes	Yes	*ndi*	Yes
Adaptable for TDDS	Yes	Yes	No	Yes

ndi: not delivered information

Table 15 - Specifications of the coating equipment for commercial scale manufacturing.

As expected, the commercial scale machines have a significant higher dimensions when compared with pilot equipment (ranging from 9,9 m^2 to 73,7m^2). However, just the equipment P.B-I1 presents a significantly higher area value. This is explained by the fact that this equipment is a two store complex-like unit, what makes the occupied area higher than if we just considered the machinery parts. But once we considered the layouts given by the suppliers for these calculations, we decided to consider the equipment as a whole. Looking to the Figure 20 it's easier to understand this concept.

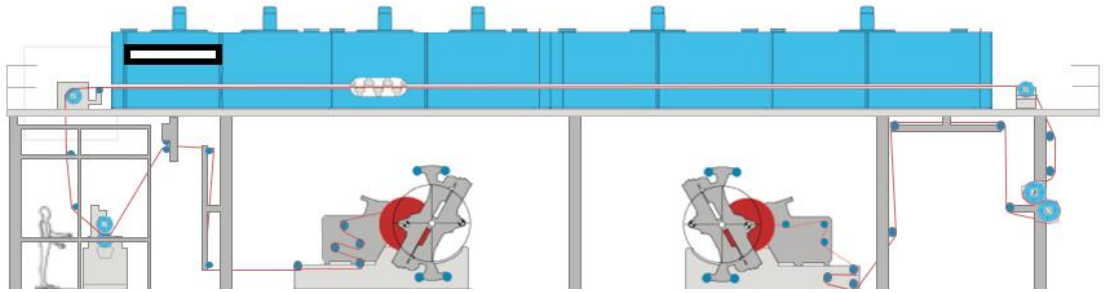


Figure 20 - A scheme of a coating equipment similar to the P.B-I1, a two store complex where the machine parts are inserted.

In what concerns the web width, all the models present the same range of maximum accepted values – around 0,5m. The dryer lengths are considerable different, with two models presenting values above the 5m and the other two presenting almost the double. Nevertheless, it's is important to say that all the suppliers informed us that it is possible to add more dryer modules, although we just considered the parameters of the proposal that were sent.

5.3.3 Primary Packaging Equipment

Web converting and Packaging machines convert the coated film into small individual strips (production process) and after that they ensure the packaging of the final films into individual pouches (packaging process). Like the coating machines we've seen before, this type of equipment is very complex.

Figure 21 - Outlook of a pilot scale web converting and primary packaging machine (eq. P.D-P1).

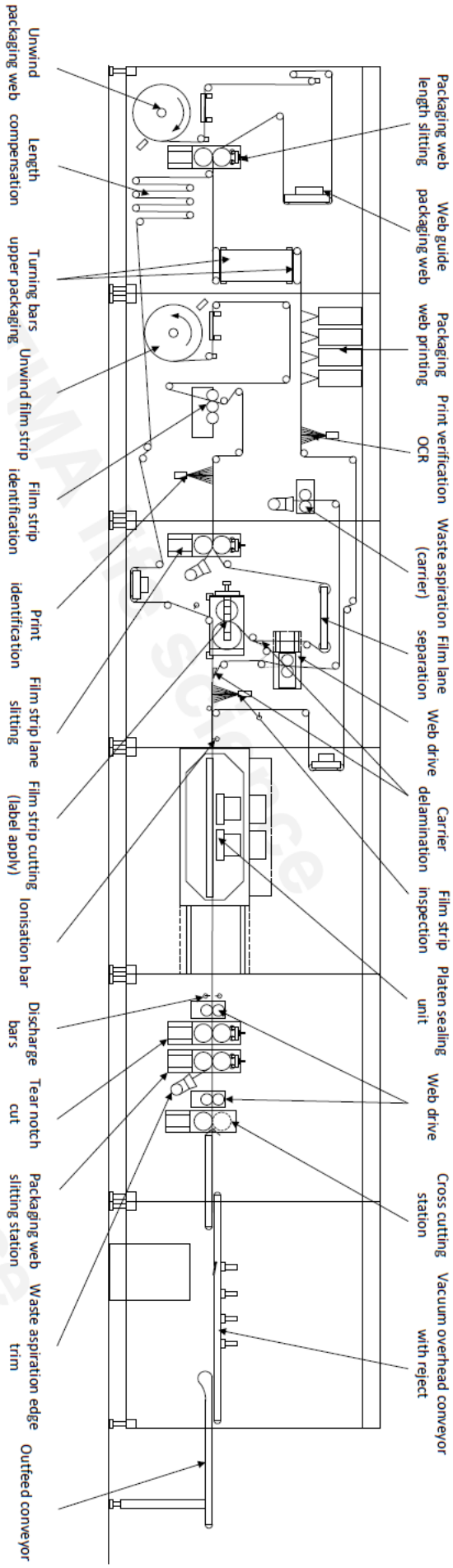


Figure 22 - Layout of an industrial equipment of primary packaging OTFs with the respective legend. (courtesy of supplier P.C)

Looking to the Figure 22 we can describe the web converting and primary packing processes by the following steps:

- From the left to the right, the film roll is inserted in a coil of the machine and starts to be unwinded. Also, the packaging material roll is inserted in the machine.
- The packaging material is dived in two lanes (one for the upper packaging material and other for the bottom packaging material) and then it passes through a web printing station and verification, where the batch number and shelf life is printed.
- The OTF film enters in a slitting station where the film can be divided in several lanes of an appropriate width. See Figure 23.

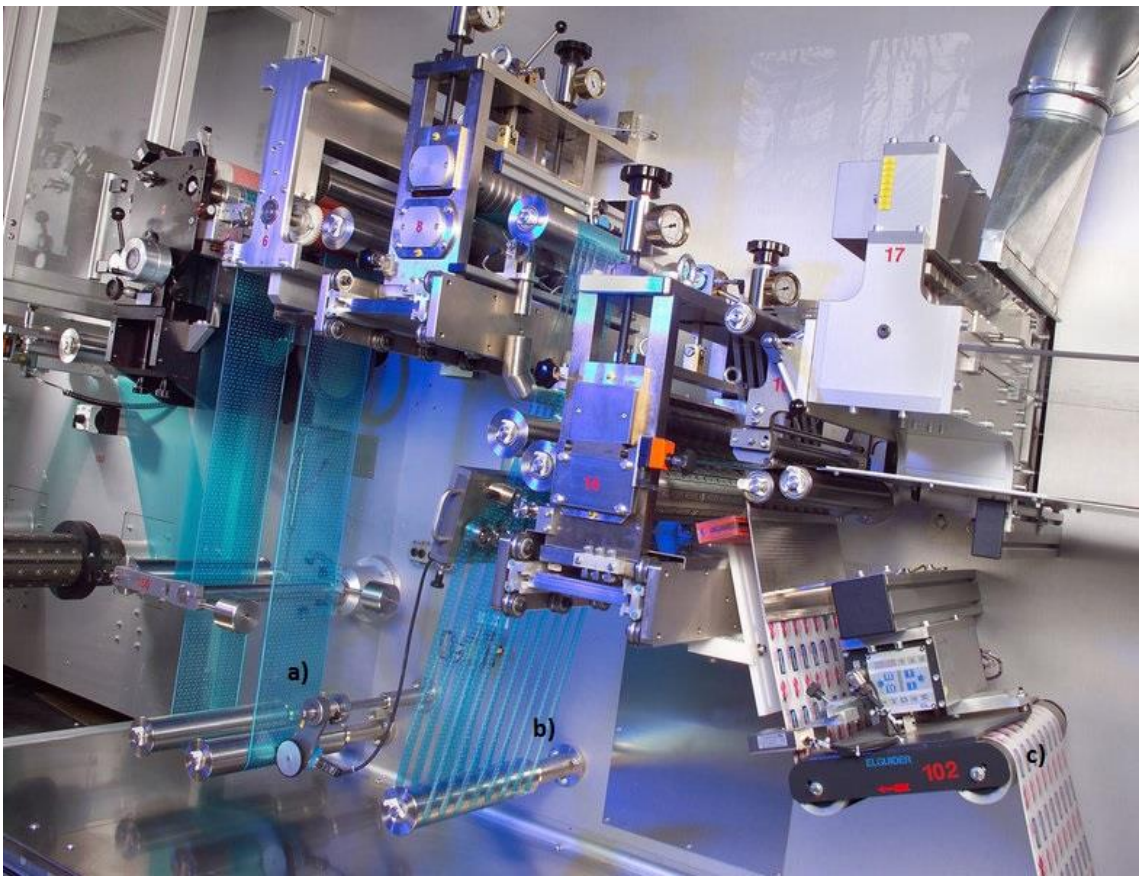


Figure 23 - Detail of a primary packaging machine. a) Initial coated film; b) the film divided in several lanes; c) packaging material. (image from supplier P.D).

- After that, a cutting station cuts the film (already divided in lanes) into small strips with the desired size to ensure the appropriate DS strength in the final dosage form. In parallel, the release liner is peeled off and rewinded.
- At the same time the strips are dropped in the bottom packaging material web and the upper packaging material is immediately placed on top.

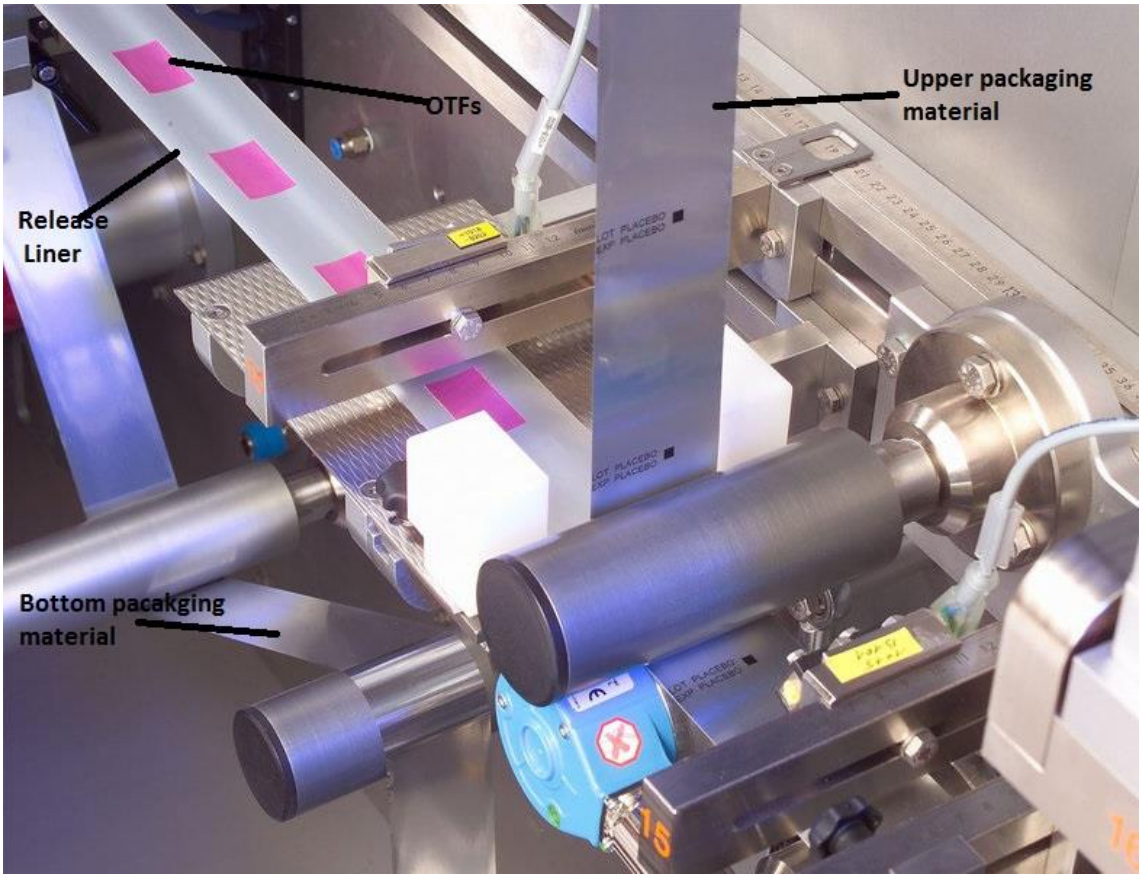


Figure 24 - Detail of a primary packaging machine. The OTFs strips already cut on the top of the release liner are then trasfered to the bottom packaging material and closed with the upper packaging material. (image from supplier P.D).

- These three layers (bottom packaging material, film strips and upper packaging material) go into the sealing station.
- In this station, the pouches are created by a four side hot sealing. The number of pouches made in each sealing cycle depends on the pouch size. At this point the strips are closed in a four sealed pouch but the pouches are still connected to each other.
- The web keeps moving until a cross cut station where they are cut into individual pouches.

- Finally, the products follow through a conveyor and pass by a reject station where the bad parts produced are removed aside.
- It's possible to see a machine working in the following link: https://www.youtube.com/watch?v=jHCu99ZXBxo

Principle of Operation

Primary Packaging equipment can work intermittently or continuously. In the continuous mode the system is already running, non-stop, while in the intermittent mode the system runs by constant cycles. Most of the machines run continuously, but there are some pilot scale machines that run intermittently.

The main difference is that the intermittent machines are used for smaller scale productions, while in the continuous mode the aim is the manufacture of batches with higher number of OTFs [34].

Slitting Station

When it comes to pilot scale manufacturing, normally the web width of the coating machines fits directly into the primary packaging machines. At industrial scale, the web width is higher and the web converting and primary packaging machines are not directly compatible. Thereby, the coated rolls have to be slit in smaller ones before. To do this there are normally three ways:

- The coating machines have a slitting station at the end that divides the film into two rolls instead of one.
- The web converting and packaging machines have a slitting station in the beginning, which divides the coated roll in two rolls.
- By using an individual slitting equipment that only slits the rolls produced by the coating equipment.

The slitting equipment it the most preferred one because it allows to divide a roll in more than two rolls with the desired size. Plus, it does not interfere with any of the manufacturing processes. The search for these type of equipment was not one of the objectives of this work.

Cutting System

The cutting technique used for OTF production is the kiss cut. It consists on making an unique cut with the desired shape and size that only cuts the thin film but not the release liner. In this way, the film waste (i.e. the surrounding edges) it's peeled off and the individual strips, with the defined size and shape, stay on the top of the release liner until it is also peeled off and the strips transferred to the bottom packaging web material.

Number of Lanes

Pilot scale machines normally have one operating lane. As for the commercial scale equipment it is possible to work with more than one lane when they have a slitting statin in their beginning. Thus, the process can be optimized which results in a higher output. The different lanes run alongside at the same process velocity and the capacity of the machine is calculated multiplying one lane output by the number of working lanes.

Printing and inspection features

Web converting and packaging machines for OTFs offer various options for printing. It is possible to print not only the expiration date and the batch number, but also the description of the content. Also it is possible to print directly in the OTF strip.

The inspection features assures that all the process is going well in real time, by examining, for example, if the strip is correctly placed in the middle of the pouch, if the sealing was correctly done or if there is any empty pouch. In case of any error the machine gives an alert and the product is automatically rejected.

These features are chosen according to the production needs and although they do not slow down the machines' output, they can increase the machine cost significantly. The Figure 25 shows a detail of an inspection toll inspecting the size of each OTF strip.

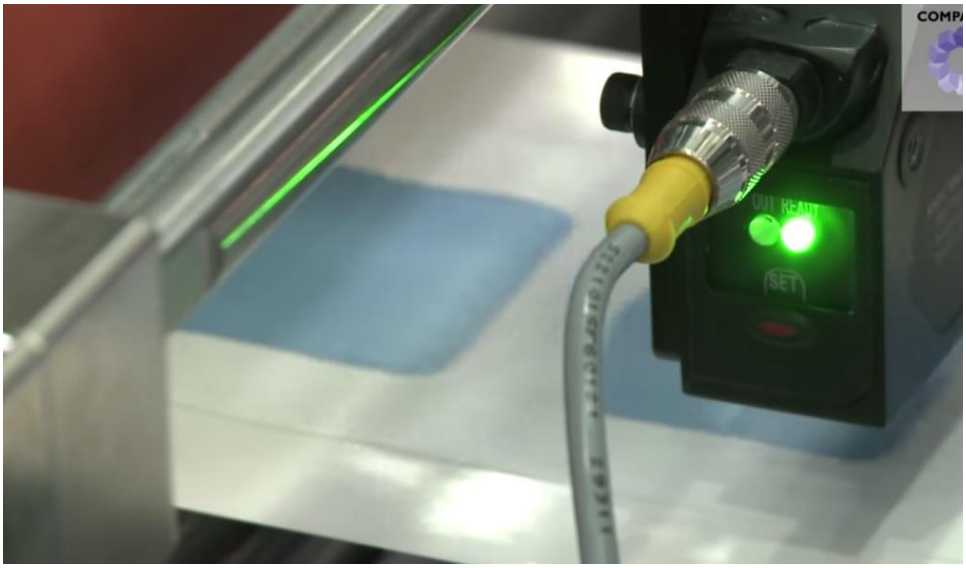


Figure 25 - Detail of an in real time inspection tool. In this case it measures the size of the strips in order to know if it was cut correctly (equipment from supplier P.A).

Pouch size, pouch material and sealing time

These three aspects are the most relevant to determine the output of these machines. As referred before, there are two principal processes that occurs in these machines. The conversion of the inserted film roll into individual OTFs and then the primary packaging of those strips inside a pouch. These processes have to be synchronized so the machine works properly. The actions that affect the process velocity in each part of the process are: the cutting of the strips, for the conversion process, and the sealing of the packaging material to form the pouch, for the primary packaging process.

According to the information collected form the suppliers, sealing the pouch is the process that has more impact on the output of the machines because it takes more time than the cutting of the strip that is very quick (kiss cut). Additionally, the sealing stations have limited space for sealing so, if the pouch size increases, the number of pouch produced in every sealing cycle decreases. Very important is also the type of packaging material: different materials take different times to seal, higher sealing times reduce the machine output. In addition to all this, for changing the pouch format new spare parts may be needed and this means additional costs. In the Figure 26 it's possible to see a schematic representation of a layout of an OTF inside of a pouch.

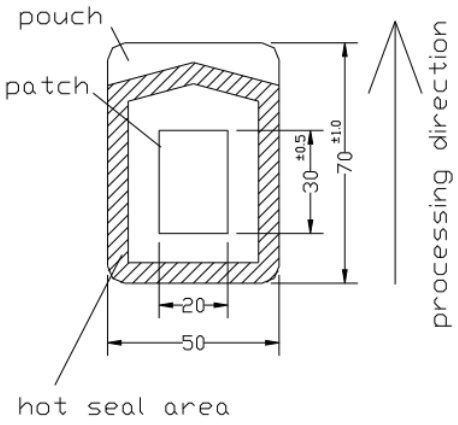


Figure 26 - Layout of a pouch with an OTF strip inside. Both dimensions represent the standard for this particular product (courtesy of supplier P.B).

Thereby, it is important to have in mind that:

- The selected packaging material must be resistant enough to protect the OTF, mainly when the pouch is handled and easy to seal (small temperature and quickly).
- The size of the pouch must take into account the specifications of the sealing station to optimize the project by trying to fit in every sealing cycle the maximum number of pouches possible.
- If possible, the size of the pouches should be maintained in order to maintain the investment in spare parts at a minimum. With the right planning this can be achievable because the size variation of the strips are not very significant.
- The cost of the material is also a very important question. In some cases, the packaging material contributes with the higher percentage of the costs. So, it is very important to negotiate higher quantities in order to decrease the material costs and to improve the cost-effectiveness of the manufacturing process.

Specifications of the Quoted Equipment

The four suppliers selected for web converting and packaging equipment delivered quotations on both pilot (Table 16) and commercial scale equipment (Table 17).

Type	Primary Packaging Equipment (P)			
Supplier	A	B	C	D
Equipment	P1	P1	P1	P1
Code	P.A-P1	P.B-P1	P.C-P1	P.D-P1
Length (mm)	6770	4520	4000	3060
Width (mm)	1500	1700	1600	1376
Height (mm)	1700	1850	2000	2006
Area (m^2)	10,2	7,7	6,4	4,2
Approx. Weight (kg)	7000	3000	4000	3000
Accepted Web Width (mm)	250	200	150	150
N.º of Lanes	1	1	1	1
Principle of Operation	Continuous	Continuous	Intermittent	Intermittent
Slitting Station (option)	No	?	*Yes*	Yes
Adaptable for TDDS	Yes	No	Yes	Yes

ndi: not delivered information

Table 16 - Specifications of the pilot web converting and packaging equipments.

The first two models (P.A-P1 and P.B-P1) work continuously while the last ones work intermittently. By the definitions we've seen before, this should mean that the ones that have an intermittent operation should have a lower capacity of production as we will see later on.

All the models have just one lane of operation and a small web width. Although, this is still a considerable width if we take into account that OTFs are significantly smaller, normally not bigger with an area of 5 to 20cm^2 [35].

Type	Primary Packaging Equipment (P)			
Supplier	A	B	C	D
Equipment	I1	I1	I1	I1
Code	P.A-I1	P.B-I1	P.C-I1	P.D-I1
Length (mm)	10000	10000	12000	7150
Width (mm)	1870	2500	1600	3930
Height (mm)	2400	2000	2000	2320
Area (m^2)	18,7	25,0	19,2	28,1
Approx. Weight (kg)	*ndi*	6000	10000	*ndi*
Accepted Web Width (mm)	330	300	150	150
N.º of Lanes (Maximum)	4	3	4	3
Principle of Operation	Continuous	Continuous	Continuous	Continuous
Slitting Station (option)	No	Yes	*No*	Yes
Adaptable for TDDS	Yes	No	No	Yes

ndi: not delivered information

Table 17 - Specifications of the commercial scale web converting and packaging equipment.

Regarding the commercial scale models we see that the higher differences are in the number of lanes and in the dimensions. All 4 models work continuously. As we will see, the output of these machines are significantly higher, mainly because it's possible to operate more than one lane at the same time. In this cases, a slitting unit in the primary packaging machine may not be needed because the web is already divided by the number of working lanes.

It is also important to make a reference to the printing an inspection features, which are not specified because it exists numerous options for each one of the pilot and industrial machines machine and the chosen features depend on what kind of information must be printed.

5.3.4 Final Remarks

We now know how these different types of equipment work and the critical parameters that influence their performance. The collection of this information is very important because it is not readily available in any source (books, papers, internet, etc.) and

because it will contribute for the understanding of this non-conventional manufacturing process. Furthermore, it will give a very important contribution for the design of a new manufacturing facility dedicated to the manufacture of this novel dosage form, the first of its kind in Portugal.

In a more detailed way it was possible to understand the manufacturing process and identify the principal requisites.

In order to deepen even more the knowledge regarding these machines and the critical quality and process attributes, it is necessary to continue the contact with the suppliers, through more face-to-face meetings, visits to the machines manufacturing sites and ultimately experiment these machines.

All the suppliers, mainly of mixing and coating equipment, offer trial services where a team can go to a test facility not only to try the equipment but also to adapt the parameters of the equipment to the desired formulation. In the case of the mixing equipment it's even possible to experiment an equipment in our own facilities.

5.4 Capacities Estimation

One of the main goals of this project was to determine the necessary production capacity of the new manufacturing facility to meet OTFs' forecasts.

In order to do it, we must first estimate the annual capacity of the coating and the web converting and packaging equipment and then to confront it with Bluepharma's forecasts until 2025.

The calculations were made for both pilot and industrial scale.

The methods used for these calculations were are explained in the Methodology chapter.

5.4.1 Coating Equipment Capacities

As seen before, the velocity of the coating machines depend on the dryer length. The higher it is, the higher the velocity will be. As we know the Velocity of the process it's given by Eq. 2,

$$Velocity = \frac{Dryer\ lenght}{Drying\ time}$$

So considering that the Drying Time of the Bluepharma's formulation in a coating machine is 10 minutes, the annual capacity of the coating equipment is given by using Eq. 9

$$C(m2) = Time\ (min) * OEE * Velocity(m/min) * Web\ Width(m)$$

Additionally, and as we've seen, it was considered 250 days of work per year, divided by weeks of 5 days. We also considered 2 and 3 shifts of 8 hours per day to have two scenarios.

Table 18 gathers all the necessary data for this estimation and has the results for the annual capacities (in square meters of film) for each equipment model when working in 2 shifts and in 3 shifts.

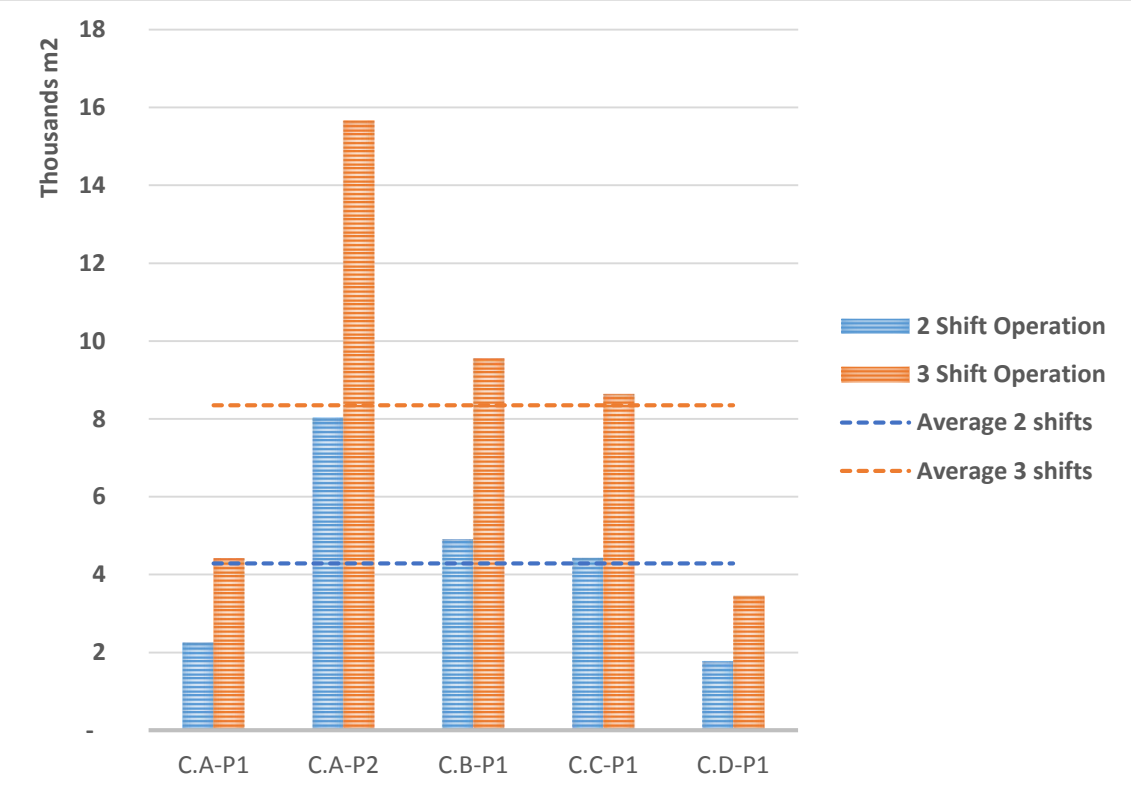
Type	Coating Equipment (C)				
Supplier	A		B	C	D
Equipment	P1	P2	P1	P1	P1
Code	C.A-P1	C.A-P2	C.B-P1	C.C-P1	C.D-P1
Drying Time BLPH formulation (min)	10				
Useable Coating Width (mm)	120	200	250	200	100
Dryer Length(mm)	1600	3400	1660	1876	1500
Velocity (m/min)	0,16	0,34	0,17	0,19	0,15
2 Shift Operation					
OEE	49,24%				
Annual Capacity (m^2)	2.269	8.036	4.905	4.434	1.773
Average	4.283				
3 Shift Operation					
OEE	64,00%				
Annual Capacity (m^2)	4.424	15.667	9.562	8.645	3.456
Average	8.351				

Table 18 - Annual capacity of each pilot coating equipment considering 2 shifts and 3 shifts.

Looking to Table 18, Models C.A-P1 and C.D-P1 present the lowest capacities, while models C.B-P1 and C.C-P1 present similar capacities. The machine C.A-P2 presents by

far the higher capacity when compared with all the other options – 8.036m^2 and 15.667m^2. Another important thing to notice is the enormous difference between a production with 2 shifts and with 3 shifts. This due to the higher time of production, and also because of the OEE that is also significantly different by the reasons explained in the Methodology: the equipment has to stop more times what increases its downtimes.

To facilitate the comparison between each machine, results are also displayed in Graphic 4



Graphic 4 - Calculated annual capacity for each pilot coating equipment, considering 2 or 3 shifts and respective averages.

Concluding, we can say that C.A-P2 model is by far the option with the highest capacity, and that the average capacity for a 2 shift operation is 4.283m^2 and 8.351 m^2 for 3 shifts. We can say, that in average these models produce 94% more when running in 3 shifts than when just work 2 shifts per day. Almost the double.

The Next table, Table 19, displays the estimations for the annual capacity of each industrial scale model working in 2 or 3 shifts.

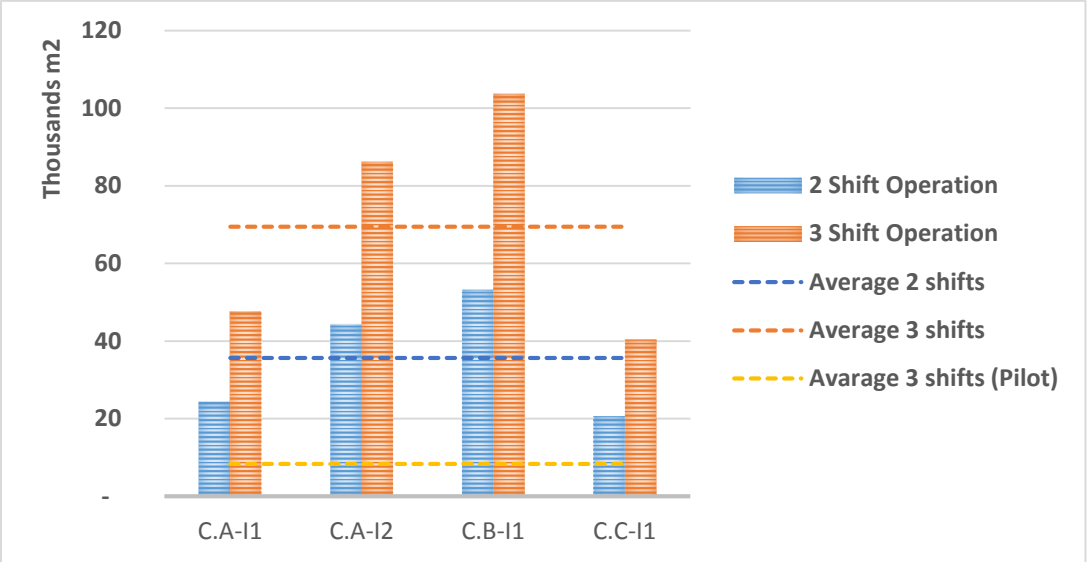
Type	Coating Equipment (C)			
Supplier	A		B	C
Equipment	I1	I2	I1	I1
Code	C.A-I1	C.A-I2	C.B-I1	C.C-I1
Drying Time BLPH formulation (min)	10			
Useable Coating Width (mm)	440	440	500	460
Dryer Length (mm)	4700	8500	9000	3810
Velocity (m/min)	0,47	0,85	0,90	0,38
2 Shift Operation				
OEE	49,24%			
Annual Capacity (m^2)	24.440	44.200	53.182	20.713
Average	35.634			
3 Shift Operation				
OEE	64,00%			
Annual Capacity (m^2)	47.647	86.170	103.681	40.380
Average	69.469			

Table 19 - Annual capacity of each pilot coating equipment considering 2 shifts and 3 shifts.

From the four models analyzed, we can notice that the capacities calculated are very heterogeneous. However, model C.B-I1 is clearly the one that ensures the highest annual capacity, followed by the C.A-I2. Like in the pilot equipment, the difference between 2 and 3 shifts of operation is enormous.

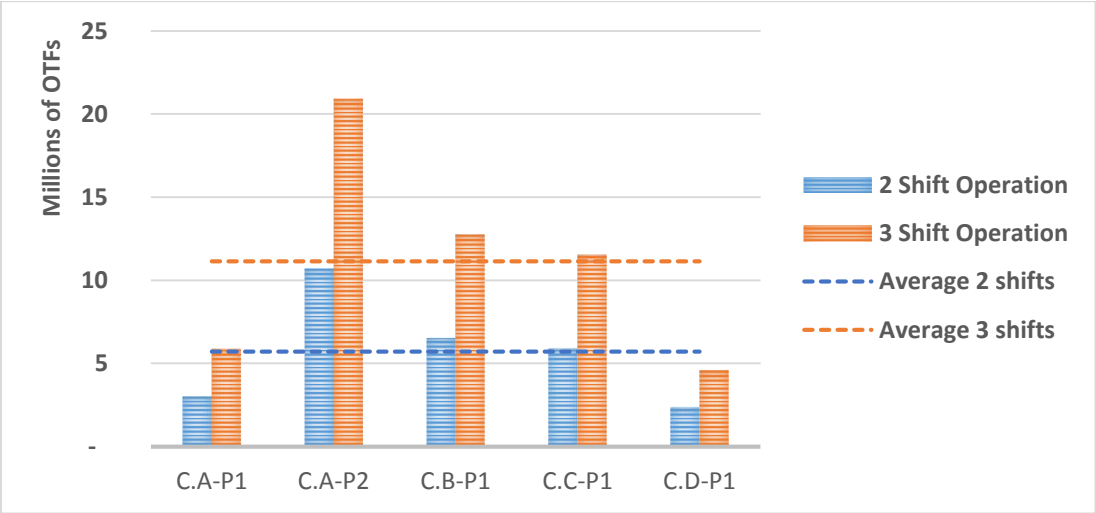
Analyzing this table we can notice that the coating width, the dryer length and the velocity are significantly higher than the values of Table 18, for pilot equipment.

In fact, looking to the Graphic 5, we realize that the industrial equipment can produce, in average, ca. 8 times more area of film than the pilot equipment (if we compare the 3 shift operation capacities).

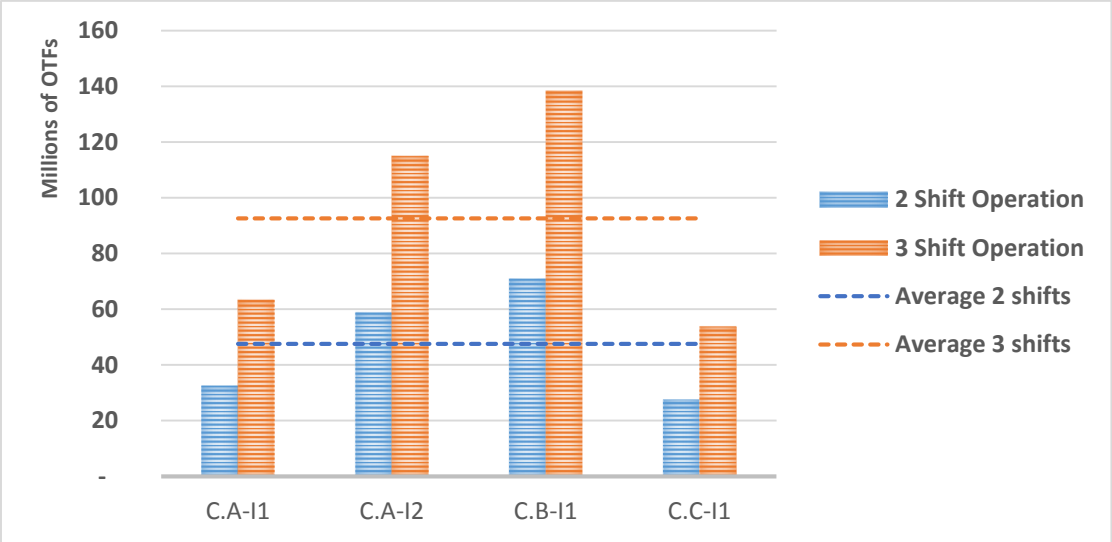


Graphic 5 - The annual capacities of each industrial coating equipment, working in 2 or 3 shifts and respective averages. Also it's represented the average of the 3 shifts operation of pilot equipment.

In the coating process, the size of the film for each product may vary and so it is best to estimate the annual capacity in area than in number of films. Nevertheless it may be important to have a notion of how many strips those capacities represent. Graphic 6 and Graphic 7 show the conversion of the area to the corresponding number of OTF of a standard size of 20x30 millimeters and a wasted area of 20%, as explained in chapter 4.



Graphic 6 - Number of OTFs that correspond to the produced area of each pilot coating equipment. A standard size of 20x30mm per OTF was considered as well as a film waste of 20%.



Graphic 7 - Number of OTFs that correspond to the produced area of each industrial coating equipment. Was considered a 20x30mm OTF and a film waste of 20%.

There is an enormous difference separating the two scales. The best pilot option (C.A-P2) can produce enough area for more than 20 million OTFs, while the best industrial solution (C.B-I1) can produce an annual area of film for more than 160 million OTFs. Another important thing to take from this charts, is that the pilot equipment can produce, during the year, several pilot batches. The pilot batches are an important requirement, because they are necessary to validate the manufacturing process. Normally, a pilot batch need to have at least 100.000 product units [36]. In addition, the high capacities of the pilot equipment makes it a good option for low productions and niche products.

5.4.2 Packaging Equipment Capacities

As referred in the methodology chapter, the capacity of this type of equipment (number of OTFs delivered by each machine inside a pouch) is given by the Eq. 10:

$$C(number\ of\ OTFs) = T(\min) * OEE * Notf(\frac{OTF}{min}) * Nl$$

Ns is the number of strips delivered in a certain range of time and the NL it's the maximum number of lanes which the machine can run.

For these calculations we've assumed again the standard strip size of 20x30 millimeters.

We already seen the meaning and advantages of the Overall Equipment Effectiveness indicator. Although, we choose to use in this estimation the OEE of Bluepharma.

$$OEE\ Bluepharma = 35\%$$

Bluepharma only measures the OEE for packaging. The value is significantly lower than the one we estimated for the production. However, this is an acceptable value for the packaging phase in the pharmaceutical industry. In fact, reports say that generally packaging OEE in pharma goes from 15% to 45% [37]. Also the suppliers confirmed this information and explained us that this low OEE it's due to the fact that there is a lot of unexpected stops because of the complexity of these machines and also because the packaging is always dependent on the production.

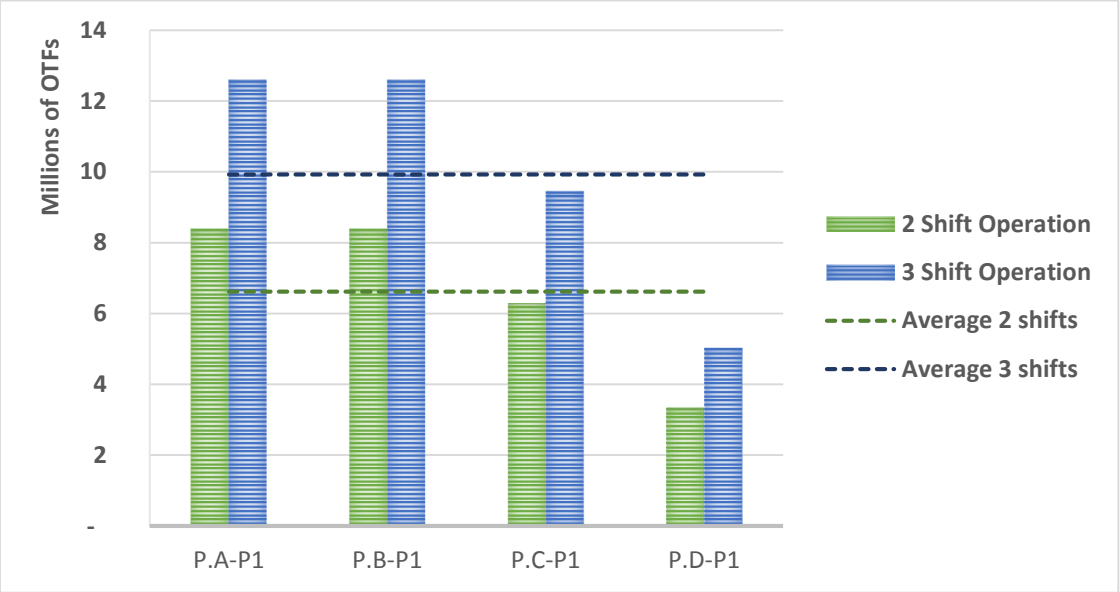
Table 20 gathers all the necessary data for the capacity estimation of the pilot primary packaging equipment. In the same table are presented the results for the annual capacities (in number of OTFs) for each equipment when working in 2 shifts and in 3 shifts.

Type	Primary Packaging Equipment (P)			
Supplier	A	B	C	D
Equipment	P1	P1	P1	P1
Code	P.A-P1	P.B-P1	P.C-P1	P.D-P1
Pouches per Minute	100	100	75	40
N.º of Lanes	1	1	1	1
Pouches per Hour	6.000	6.000	4.500	2.400
2 Shift Operation				
OEE	35%			
Annual Capacity (OTFs)	8.400.000	8.400.000	6.300.000	3.360.000
Average	6.615.000			
3 Shift Operation				
OEE	35%			
Annual Capacity (OTFs)	12.600.000	12.600.000	9.450.000	5.040.000
Average	9.922.500			

Table 20 - Annual capacities of the pilot primary packaging machine, in number of OTFs.

All the models analyzed have only one lane, and the maximum output claimed by the suppliers don't surpass the 100 pouches per minute. Models P.A-P1 and P.B-P1 present

the same capacity. In the next chart it's easy to compare all the different equipment capacities.



Graphic 8 - The annual capacities of the pilot equipment for primary packaging and the respective averages, in number of OTFs and considering a standard strip of 20x30 mm.

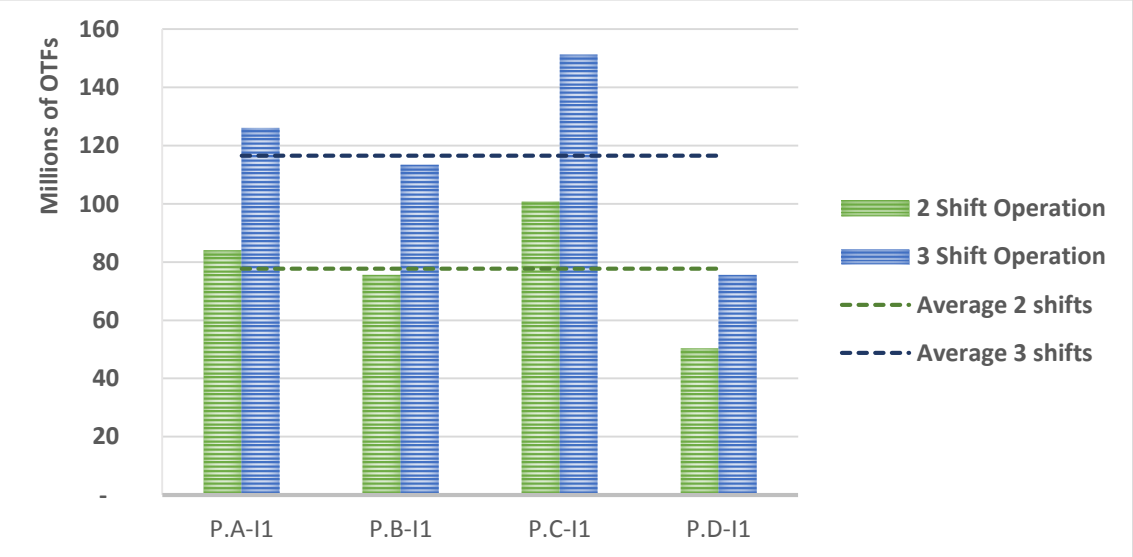
None of the machines, when working in two shifts can reach the 10 million of OTFs/year, while the two first models can surpass the 12 million OTFs /per year if a 3 shift operation is considered. We can conclude that those two machines would be able to convert and pack the average area of film produced by the pilot coating machines in one year, as showed in the Graphic 6. However, none of the options can assure the packaging of the films manufactured during one year with coating equipment C.A-P2 in 3 shifts.

The next table (Table 21) displays all the needed information to calculate the capacities of each industrial equipment.

Type	Primary Packaging Equipment (P)			
Supplier	A	B	C	D
Equipment	I1	I1	I1	I1
Code	P.A-I1	P.B-I1	P.C-I1	P.D-I1
Pouches per Minute	250	300	300	200
N.º of Lanes	4	3	4	3
Pouches per Hour	60.000	54.000	72.000	36.000
2 Shift Operation				
OEE	35%			
Annual Capacity (OTFs)	84.000.000	75.600.000	100.800.000	50.400.000
Average	77.700.000			
3 Shift Operation				
OEE	35%			
Annual Capacity (OTFs)	126.000.000	113.400.000	151.200.000	75.600.000
Average	116.550.000			

Table 21 - Annual capacities of the industrial primary packaging machine, in number of OTFs.

The industrial scale packaging equipment has, in average, an output ca. 12 times higher than the pilot scale equipment, with 3 of the models analyzed exceeding the 100 million of OTFs.



Graphic 9 - The annual capacities of the industrial equipment for primary packaging in number of OTFs and the respective averages. It was considered a standard size of 20x30 millimeters.

The model P.C-I1 is the one with the highest capacity, ca. 150 million OTFs per year, at full capacity (3 shifts). The model P.D-I1 from supplier "D" is the one with the lowest capacity. The same happened in the pilot scale.

Only equipment P.C-I1 will be able to convert the area produced during one year and working in 3 shifts by the most powerful coating equipment, the C.B-1.

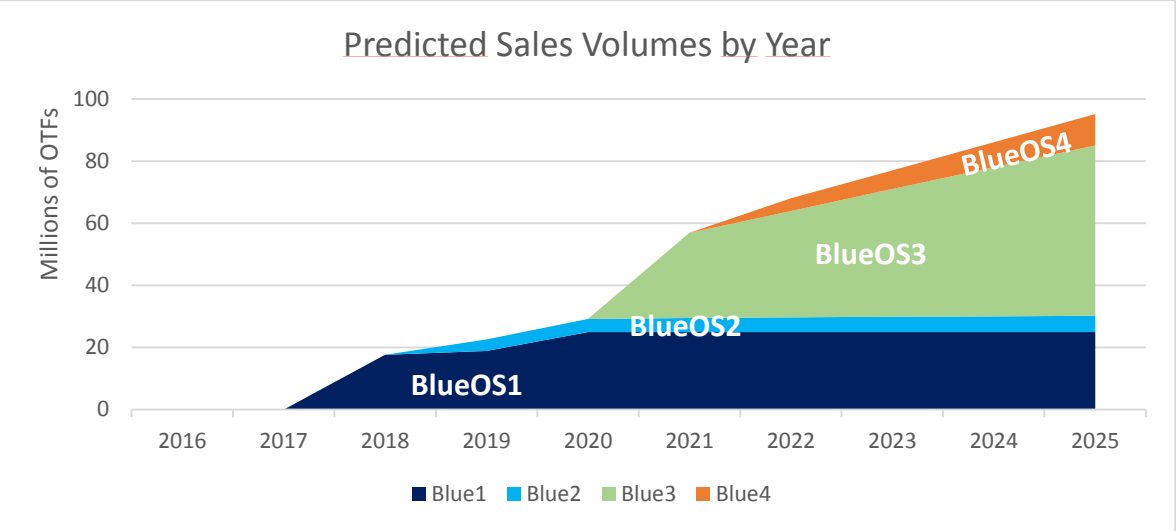
5.4.3 Final Remarks

From the analysis of these results it is possible to conclude that the limiting step of OTFs production is the web conversion and the primary packaging. This means that what will define the number of products produced in one year is the capacity of the web converting and packaging equipment. It's also important to refer that these estimations have some limitations:

- The drying time considered for the coating process (T=10min) is significantly higher than the normal values for OTFs. This assumption was made due to composition of Bluepharma's technology and considering a worst case scenario.
- If it is possible to reduce the drying time for example to T=5min, the velocity of the process in each machine would duplicate and the annual capacity too.
- On the contrary, it is not possible to significantly increase the capacity of the primary packaging equipment. Depending on the pouch size and material better outputs can be achieved, but those variations are not in the same order of magnitude as in the case of the coating machines.

In a normal scenario of an industrial production of OTFs, with one coating machine and one primary packaging machine, it is this second equipment performance that will determinate the annual capacity of the production process.

5.5 Bluepharma Forecasts



Graphic 10- Bluepharma's Forecasts from 2018 to 2025.

Currently, the company has four products in pipeline, which will be referred by their code names BlueOS1, BlueOS2, BlueOS3 and BlueOS4, due to confidential reasons.

Looking to the Graphic 10 we can have an idea concerning the expected sales evolution of OTFs until 2025. This prediction points to the launch of BlueOS1 in 2018, BlueOS2 in 2019, BlueOS3 in 2021 and BlueOS4 in 2022. It's also easily spotted that BlueOS03 is by the best-selling product, followed by BlueOS01. Another important point is the total number of OTFs predicted for 2025 – near 100 millions of strips. Further we will see the concrete numbers for each year and each product (Table 23)

At this point it's important to remember that the method of calculation of the capacities, as we've seen before, is different from coating to web converting and primary packaging. In the first case the unit used is square meters of film (m^2) and in the second case the unit is the number of OTFs.

Once the forecasts provided by Bluepharma are represented in number of OTF, they can just be directly compared with the primary packaging capacities. In order to use this forecasts for a comparison with the coating capacities estimated, we must convert it into area of film.

To do this we must follow the procedure explained in the Methodology chapter and apply the Eq. 12:

$$Total\ (area) = \Sigma(N(OTFs) * OTF\ Area) + 20\%$$

The Table 22 - Bluepharma OTFs sizes and areas.

Table 22 shows the different sizes and areas of the different BlueOS. As it possible to see, not all of them have the final size approved, so we considered for those cases (BlueOS3 and BlueOS4) a standard strip size of 20x30mm.

	BlueOS1	BlueOS2	BlueOS3	BlueOS4
Strip Size (mm)	12,8x22	15x20	20x30*	20x30*
	19,2x22			
	25,6x22			
Strip Area (m^2)	2,82E-04	3,00E-04	6,00E-04	6,00E-04
	4,22E-04			
	5,63E-04			

*standard strip

Table 22 - Bluepharma OTFs sizes and areas.

With the information of Table 22 we can now apply the Eq. 12 and convert Bluepharma's forecasts to area of film. The fact that the BlueOS1 presents 3 different sizes, it's because this product will be marketed in different doses and each size means a different dose of the product.

Thereby, in the next two tables (Table 23 and Table 24) it's shown the company forecasts in number of OTFs and area of film, respectively.

Year	2018	2019	2020	2021	2022	2023	2024	2025
BlueOS1	17.580.000	18.810.000	24.960.000	24.960.000	24.960.000	24.960.000	24.960.000	24.960.000
BlueOS2		3.782.352	4.181.968	4.571.476	4.749.556	4.917.556	5.085.556	5.253.556
BlueOS3				27.417.840	34.272.300	41.126.760	47.981.220	54.835.680
BlueOS4					4.048.400	6.072.600	8.069.700	10.120.900
TOTAL (OTFs)	17.580.000	22.592.352	29.141.968	56.949.316	68.030.256	77.076.916	86.096.476	95.170.136

Table 23 - Bluepharma's forecasts for each product.

Year	2018	2019	2020	2021	2022	2023	2024	2025
BlueOS1	6.559	7.010	9.306	9.306	9.306	9.306	9.306	9.306
BlueOS2		1.362	1.506	1.646	1.710	1.770	1.831	1.891
BlueOS3				19.741	24.676	29.611	34.546	39.482
BlueOS4					2.915	4.372	5.810	7.287
TOTAL (m^2)	6.559	8.372	10.812	30.693	38.607	45.060	51.494	57.966

Table 24 - Bluepharma's sales forecast converted to area of film.

The areas calculated (Table 24) will be used to analyze the capacities of the different coating models while the values of Table 23 will be used to do the same exercise but with the primary packaging equipment.

5.6 Equipment Capacity V.S. Bluepharma Forecasts

The purpose of this confrontation it's to determine if the coating and primary packaging equipment models analyzed in this project can guarantee, or not, the predicted production of Bluepharma. For that, a series of timeline tables that display if a determined machine can ensure the company's forecast in each of the years, will be presented.

5.6.1 Coating Equipment

Table 25 shows the forecast for the area of film that is necessary to be manufactured in each year. Then, the models of the pilot coating equipment are considered at the left side of the table, for 2 shift and 3 shift operations.

	Year	2018	2019	2020	2021	2022	2023	2024	2025
	TOTAL (m2)	6.559	8.372	10.812	30.693	38.607	45.060	51.494	57.966
Pilot scale	2 Shift Operation								
	C.A-P1	n	n	n	n	n	n	n	n
	C.A-P2	y	n	n	n	n	n	n	n
	C.B-P1	n	n	n	n	n	n	n	n
	C.C-P1	n	n	n	n	n	n	n	n
	C.D-P1	n	n	n	n	n	n	n	n
	3 Shift Operation								
	C.A-P1	n	n	n	n	n	n	n	n
	C.A-P2	y	y	y	n	n	n	n	n
	C.B-P1	y	y	n	n	n	n	n	n
	C.C-P1	y	y	n	n	n	n	n	n
	C.D-P1	n	n	n	n	n	n	n	n

Table 25 - Confrontation between the pilot coating equipment capacities and the company's forecasts.

The green cells with a "y" means that the equipment in that line can ensure the necessary production for that year. On the contrary, the red cells with an "n" means that the equipment alone does not have the necessary capacity for the projected production for that year. For example, the model C.A-P2 when working 2 shifts per day, can ensure the full production of the year 2018, but not in any of the other years.

Looking again to Table 25, we conclude that with a 2 shift operation, only model C.A-P2 is able to produce the required quantity, but only in the first year (2018). Considering a 3 shift operation, this machine is able to assure the production of OTF until 2020, and models C.B-P1 and C.C-P1 can assure it until 2019.

In conclusion we can say that pilot coating equipment is not a suitable option in the long term, but it can be a possibility for the first years of production. Plus, it can be used to produce pilot batches and niche products.

Year		2018	2019	2020	2021	2022	2023	2024	2025
TOTAL		6.559	8.372	10.812	30.693	38.607	45.060	51.494	57.966
Commercial scale Equipment	2 Shift Operation								
	C.A-I1	y	y	y	n	n	n	n	n
	C.A-I2	y	y	y	y	y	n	n	n
	C.B-I1	y	y	y	y	y	y	y	n
	C.C-I1	y	y	y	n	n	n	n	n
	3 Shift Operation								
	C.A-I1	y	y	y	y	y	y	n	n
	C.A-I2	y	y	y	y	y	y	y	y
	C.B-I1	y	y	y	y	y	y	y	y
	C.C-I1	y	y	y	y	y	n	n	n

Table 26 - Confrontation between the industrial coating equipment capacities and the company's forecast.

When considering the industrial coating equipment, the results are totally different, as showed in the Table 26. All the models have the necessary capacity for the full industrial production of the projected amounts of OTFs until 2020, for a 2 shift operation, and until 2022, if 3 shits per day are considered. Nevertheless, it's important to refer that in the first case, none of the options can guarantee the production in all of the years, while in the 3 shift operation, only two models (C.A-I2 and C.B-I1) can satisfy the full production

until 2025. This evaluation is important not only to have an estimation of the overall budget for the project but also for dividing the budget per year.

5.6.2 Primary Packaging Equipment

Table 27 displays if the different pilot scale models can or cannot support the predicted full production for each year. As we know at this point, this analysis is made in number of OTFs and not in area of film.

	Year	2018	2019	2020	2021	2022	2023	2024	2025
	TOTAL	17.580.000	22.592.352	29.141.968	56.949.316	68.030.256	77.076.916	86.096.476	95.170.136
Pilot Equipment	2 Shift Operation								
	P.A-P1	n	n	n	n	n	n	n	n
	P.B-P1	n	n	n	n	n	n	n	n
	P.C-P1	n	n	n	n	n	n	n	n
	P.D-P1	n	n	n	n	n	n	n	n
	3 Shift Operation								
	P.A-P1	n	n	n	n	n	n	n	n
	P.B-P1	n	n	n	n	n	n	n	n
	P.C-P1	n	n	n	n	n	n	n	n
	P.D-P1	n	n	n	n	n	n	n	n

Table 27 - Confrontation between the pilot primary packaging equipment capacities and the company's forecast.

None of the pilot scale equipment is able to ensure complete production in any year. This tells already that the investment in an equipment like this is not enough even in the short term for the packaging of the commercial scale production.

	Year	2018	2019	2020	2021	2022	2023	2024	2025
	TOTAL	17.580.000	22.592.352	29.141.968	56.949.316	68.030.256	77.076.916	86.096.476	95.170.136
Industrial scale Equipment	2 Shift Operation								
	P.A-I1	y	y	y	y	y	y	n	n
	P.B-I1	y	y	y	y	y	n	n	n
	P.C-I1	y	y	y	y	y	y	y	y
	P.D-I1	y	y	y	n	n	n	n	n
	3 Shift Operation								
	P.A-I1	y	y	y	y	y	y	y	y
	P.B-I1	y	y	y	y	y	y	y	y
	P.C-I1	y	y	y	y	y	y	y	y
	P.D-I1	y	y	y	y	y	n	n	n

Table 28 - Confrontation between the industrial primary packaging equipment capacities and the company's forecast.

Table 28 shows the results for the industrial scale primary packaging machines. In a 2 shift operation, just the model P.C-I can assure full production in all the years of the forecast. But if we operate with 3 shifts per day, three of the four machines have the necessary capacity to ensure the production forecasts. Only the machine P.D-I1 can't produce all the OTFs in all the considered years.

5.6.3 Final Remarks

It is clear the need of an investment in an industrial scale equipment since the early years. Some of the models analyzed still have some capacity remaining that can also support a significant increase in the production when compared to the forecasts.

Considering all these we can conclude that the following models fulfill all the requirements for Bluepharma's new manufacturing facility:

- Coating Equipment: C.A-I2 and C.B-I1;
- Primary Packaging Equipment: C.A-I1, C.B-I1, C.C-I1.

Nevertheless, the acquisition of pilot scale equipment for the coating, web converting and packaging will be necessary to perform the scale up of the manufacturing process of all new products.

5.7 Road-Map

With the equipment's capacities estimated and crossed with the sales forecasts of the company, it's now possible to trace a road-map. By road-map we mean a timeline map with the equipment acquisition milestones identified. In this map are presented the needed scales and not the individual equipment.

The Figure 27 illustrates the resulting road-map of the project.

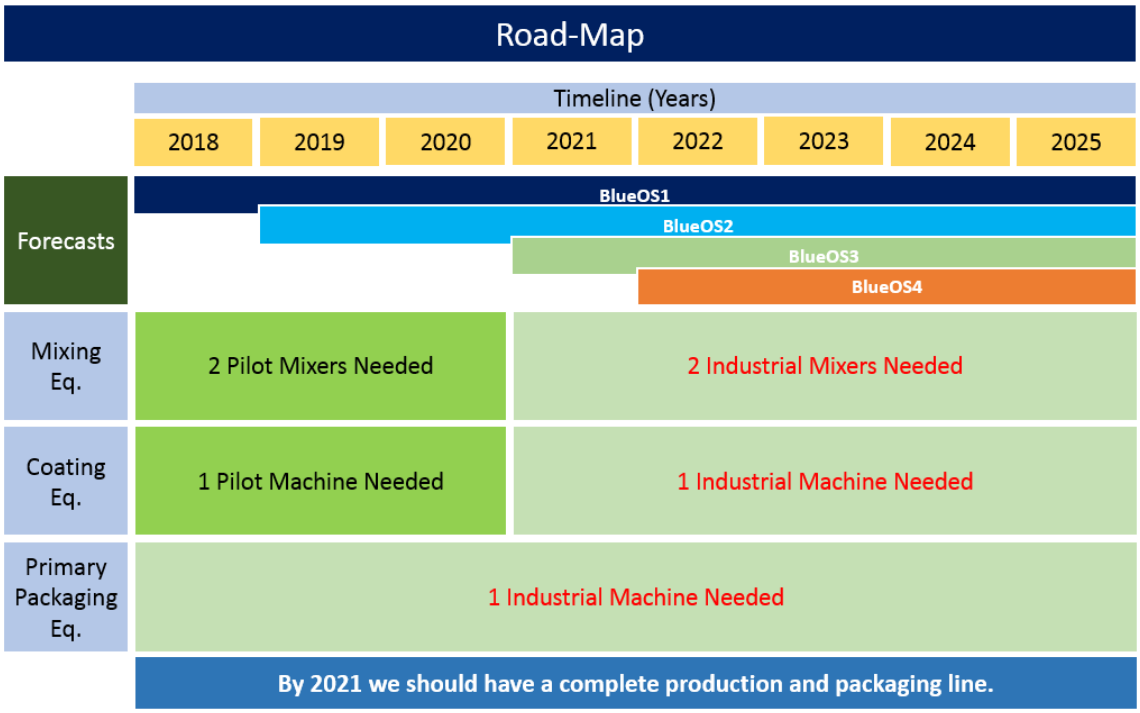


Figure 27 - Project Road-Map until 2025. It's possible to see the products launch and the equipment needs.

Looking to the Figure 27, the most important conclusion we can take is that by 2021, Bluepharma must be fully equipped (industrial scale equipment), in order to produce the expected forecasts of OTFs.

The mixing equipment obviously follow the scale of the coating equipment. It was considered by the company that 2 pilot mixers and 2 industrial mixers (one of 500L and other of 1000L) should be acquired.

One pilot coating machine can guarantee the first three years of industrial production, which minimizes the initial investment. After that, by 2021, industrial scale equipment is necessary to ensure the production.

In what concerns the primary packaging equipment, an industrial machine is needed to ensure the company forecasts since the beginning. Although, it is necessary the acquisition of a pilot scale machine for scale-up purposes.

To conclude, this road-map give us an outlook of the crucial milestones in terms of equipment needs. Future changes in the forecasts or in the estimation of the capacities, can affect, obviously, the planned road-map. For those reasons, this exercise must be a continuous process.

5.8 Investment Analysis

Table 26 shows the range of investment necessary for each type of equipment and according to their scale. Due to confidential reasons it's not possible to present the prices for each one of the models analyzed.

Equipment Investment Range				
	Equipment Scale			
	Pilot Scale	Industrial Scale		
		500 L	1000 L	2000 L
Mixing Eq.	95.000,00 € to 230.700,00 €	145.000,00 € to 325.600,00 €	190.000,00 € to 377.050,00 €	305.800,00 € to 549.700,00 L
Coating Eq.	110.887,00 € to 360.000,00 €	860.000,00 to 1.538.200,00 €		
Primary Packaging Eq.	494.800,00 € to 886.415,00 €	791.800,00 to 1.894.500,00 €		

Figure 28 - Investment range table. Each range displays the lowest and the highest budgetary quotation received for that type of equipment and its respective scale.

Each range displays the lowest and the highest budgetary quotation for that equipment type. All the models analyzed in this project were considered to this investment analysis.

Crossing this information with the road-map, we can get the investment road-map.

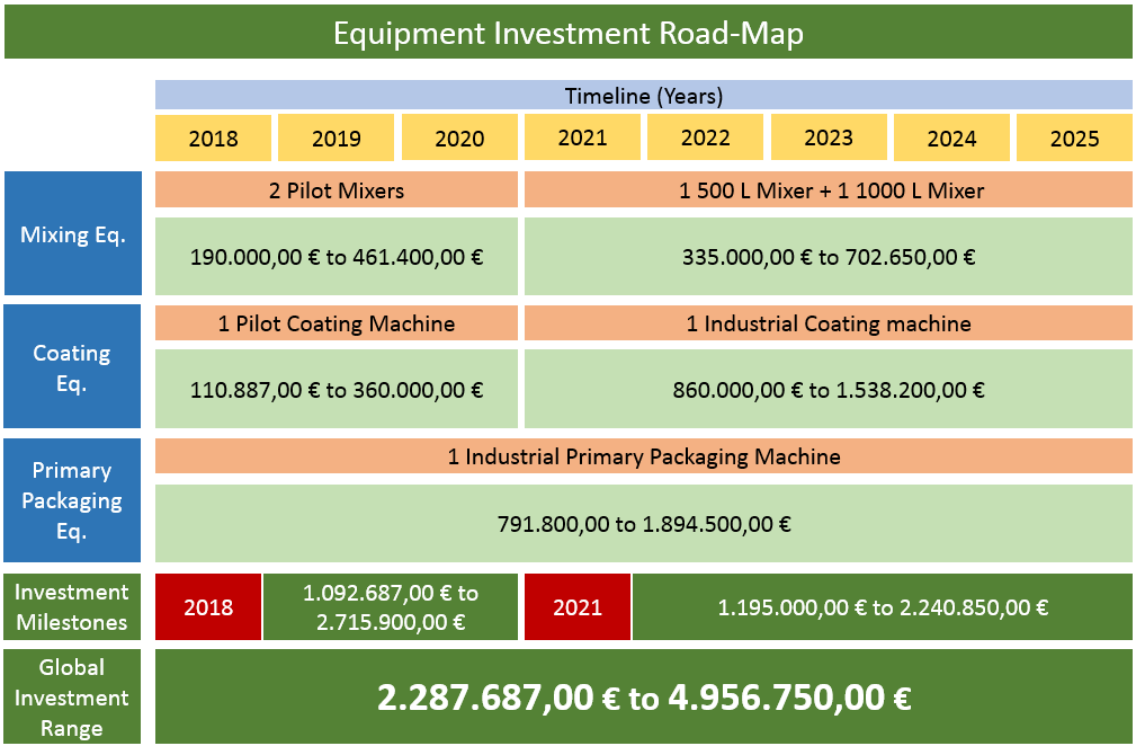


Figure 29 - Road-Map of investment. Shows the necessary investment needed in order to fulfil the sales forecasts. In the bottom it is also possible to see the global investment range (in equipment only).

Figure 29 shows us when and how much the company has to invest in equipment, in order to fulfill the expected production of OTFs.

As described above, there are two main investment milestones, the first is in 2018 and the second is in 2021. The necessary investment in a pilot coating machine, in an industrial primary packaging machine and in 2 pilot mixers of 50L represents an investment ranging from approx. 1 Million Euros to approx. 2.7 Million Euros. Three years from that, an industrial machine for coating is needed. The option for a mixer of 500L and another of 1000L was decided by the company. This investment may reach approx. 2.2 Million Euros in the more expensive solution and around 1.2 Million if all the less expensive equipment is acquired considering today's quotations.

Concluding, the global investment range in equipment can go from 2.287.687,00 € to 4.956.750,00 €.

The investment described before represents only the investment in mixing, coating and primary packaging equipment taking into account the company forecasts. These are not

the only costs for the set-up of the new manufacturing facility. Building a facility involves several other investments (e.g. building, air systems, etc) and other types of equipment not included here such as the secondary packaging machines and the slitting machines. Additionally, and as said before, it is also planned the acquisition of a pilot primary packaging machine for scale-up purposes.

According to Bluepharma's know-how, the additional estimated costs must be considered:

- Facility building costs: approx. 1.500.000,00€;
- Other infrastructures: approx. 500.000,00 €;
- Pilot primary packaging machine: from 494.800,00 € to 886.415,00 €;
- Other equipment (i.e. secondary packaging machine): approx. 500.000,00 €

Adding these costs to the investment already considered, we will get the total investment range necessary to implement a facility for the production of oral thin films (Table 29).

Equipment Investment Range	Pilot Primary Packaging Machine	Facility Building Costs	Other Infrastructures + Other Equipment
2.287.687,00 € to 4.956.750,00 €	494.800,00 € to 886.415,00 €	Approx. 1.500.000,00 €	Approx. 1.000.000,00 €

TOTAL INVESTMENT RANGE
5.282.487,00 € to 8.343.165,00 €

TOTAL INVESTMENT AVERAGE
Approx. 6.812.826,00 €

Table 29 - Total investment range and average value for setting up the new manufacturing facility.

It's important to refer that the facility building costs presented took into account the space needs that resulted of our outline design of the manufacturing facility, which can be seen in the next chapter.

5.9 Outline Design of the Manufacturing Facility

The design of the new manufacturing facility must be an integrated design that satisfies process and equipment layout requirements (already discussed in this thesis), operational access requirements, maintenance access requirements, personnel flows, material flows (product, component and raw materials movements). For the definition of operational access and maintenance requirements as well as personnel and materials flows it was very important the support of experienced professionals from Bluepharma and some examples of layouts for the manufacturing of the same dosage forms.

Figure 30 shows a small lab for development of OTFs. This information was provided by one of the suppliers. It's possible to see, in the left, a laboratory machine for coating and other for web converting and primary packaging (punch and pouching). On the right side is the mixing station.

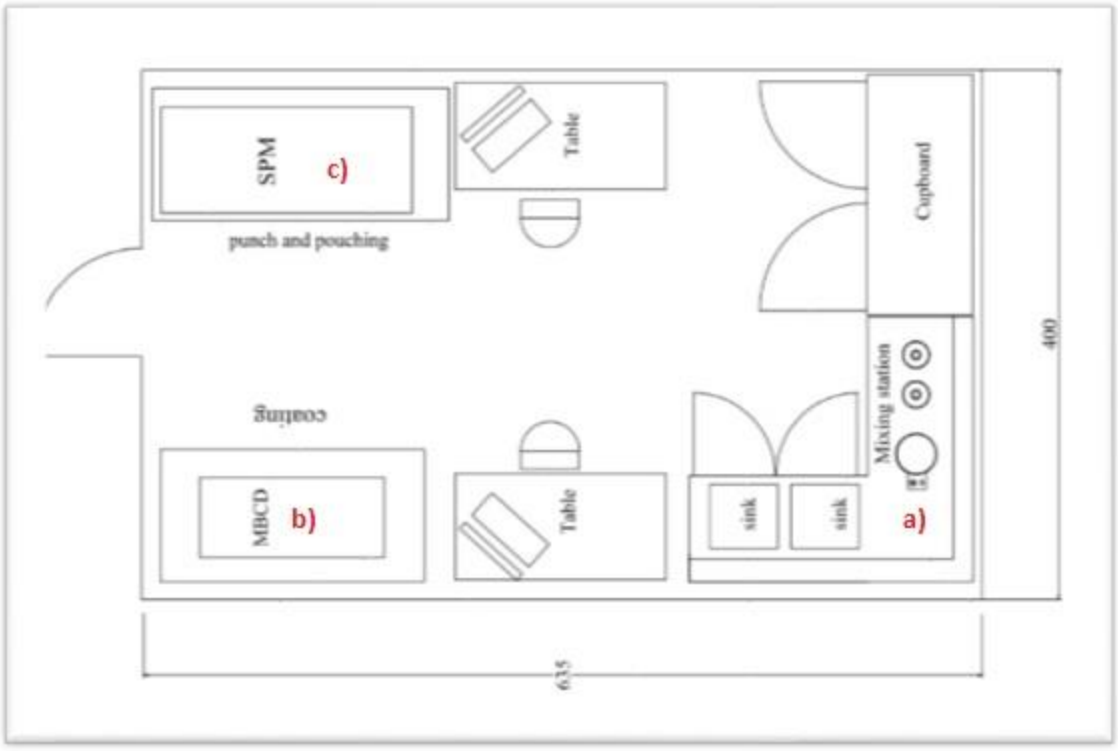


Figure 30 - Design of a laboratory for the development of OTFs with approx. 25m^2 of area. a) mixing equipment. b) lab coating machine. c) lab primary packaging machine (courtesy of supplier C.A).

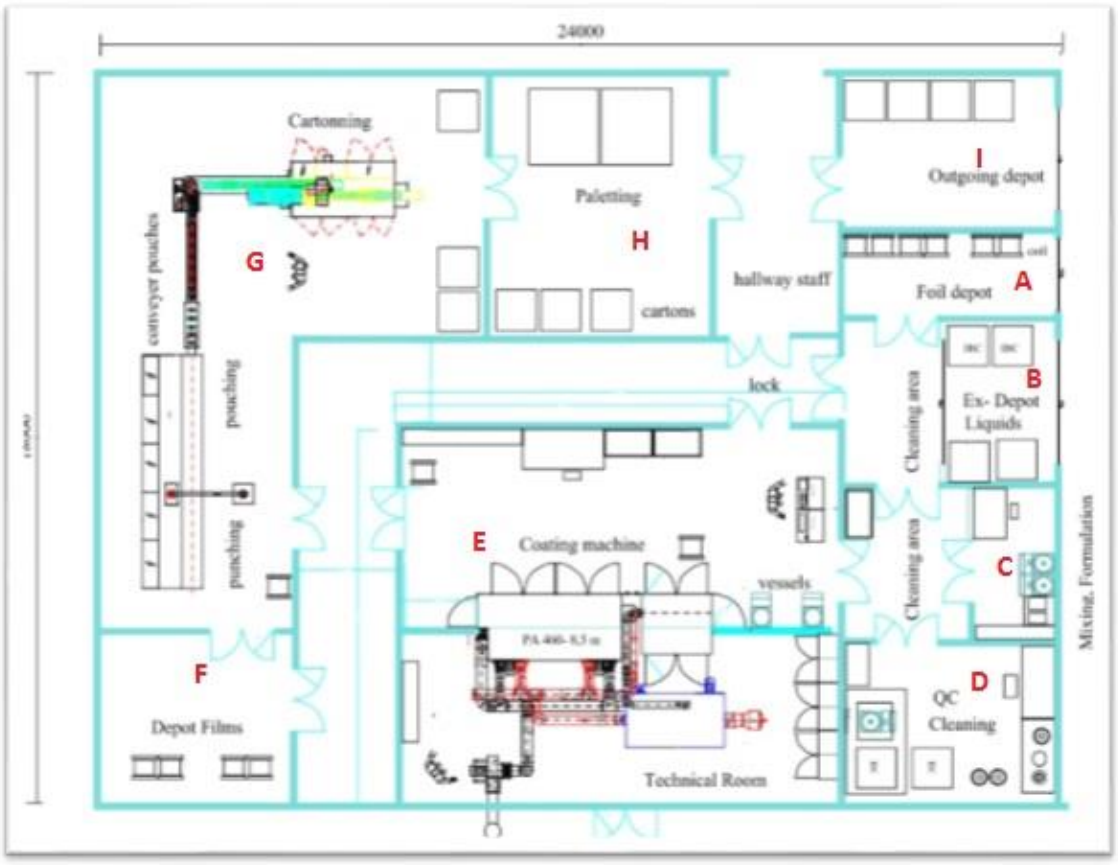


Figure 31 - Draw of a medium industrial installation for the production of OTFs with approx. 432m^2 of area (courtesy of supplier C.A).

Figure 31 shows a medium size (432 m2 of total area) manufacturing facility for the commercial scale of OTFs. The rooms A and B is where the release liner rolls and the mixing ingredients are delivered. It must be separated rooms because each type of product will follow a different flow - the release liner follows to the coating room E and the mixing ingredients go to the mixing room C. The room D is the Quality Control (QC) room. For our project it will not be considered because the QC will be in the actual facility. On the center it's possible to see the coating room (E) with the coating machine. It has a technical room, one of the critical aspects as we will see. The room F is a depot to store the coated film rolls before they go to conversion and packaging. The web converting and primary packaging machine is located on room G and it is also possible to find a cartoning machine for the secondary packaging, where the pouches are putted inside of boxes. The final product (OTF box) it's then put in pallets (room H) and stored in the outgoing depot (I) to be shipped. This plant was also provided by the same supplier that provided the laboratory plant.

For easier understanding of the process flow we should look to Figure 32 where it is possible to have an overview of how the manufacturing process that occurs in that layout.

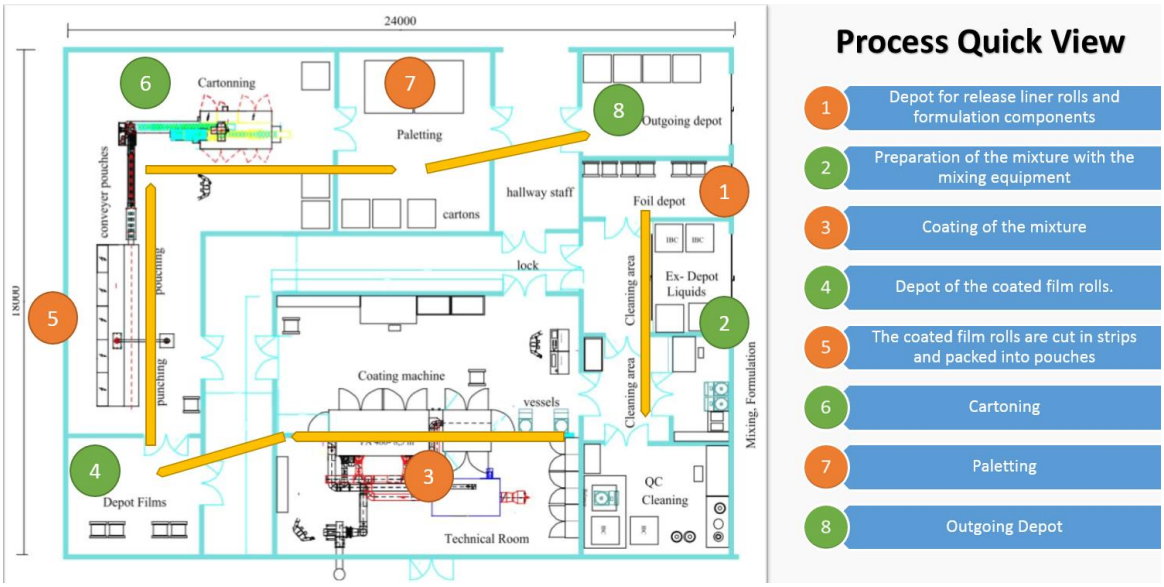


Figure 32 - Quick view of the manufacturing process flow. Each number has the correspondent legend on the right.

This image is important, because it shows that there was a logic in the projection of the facility. It follows a constant and direct path in order to optimize the space available.

Gathering all these information and data it was possible to make an outline concept design of a one floor manufacturing facility for the development, scale up and commercial scale manufacturing of Bluepharma's OTFs with the dimensions appropriate according to the company forecasts.

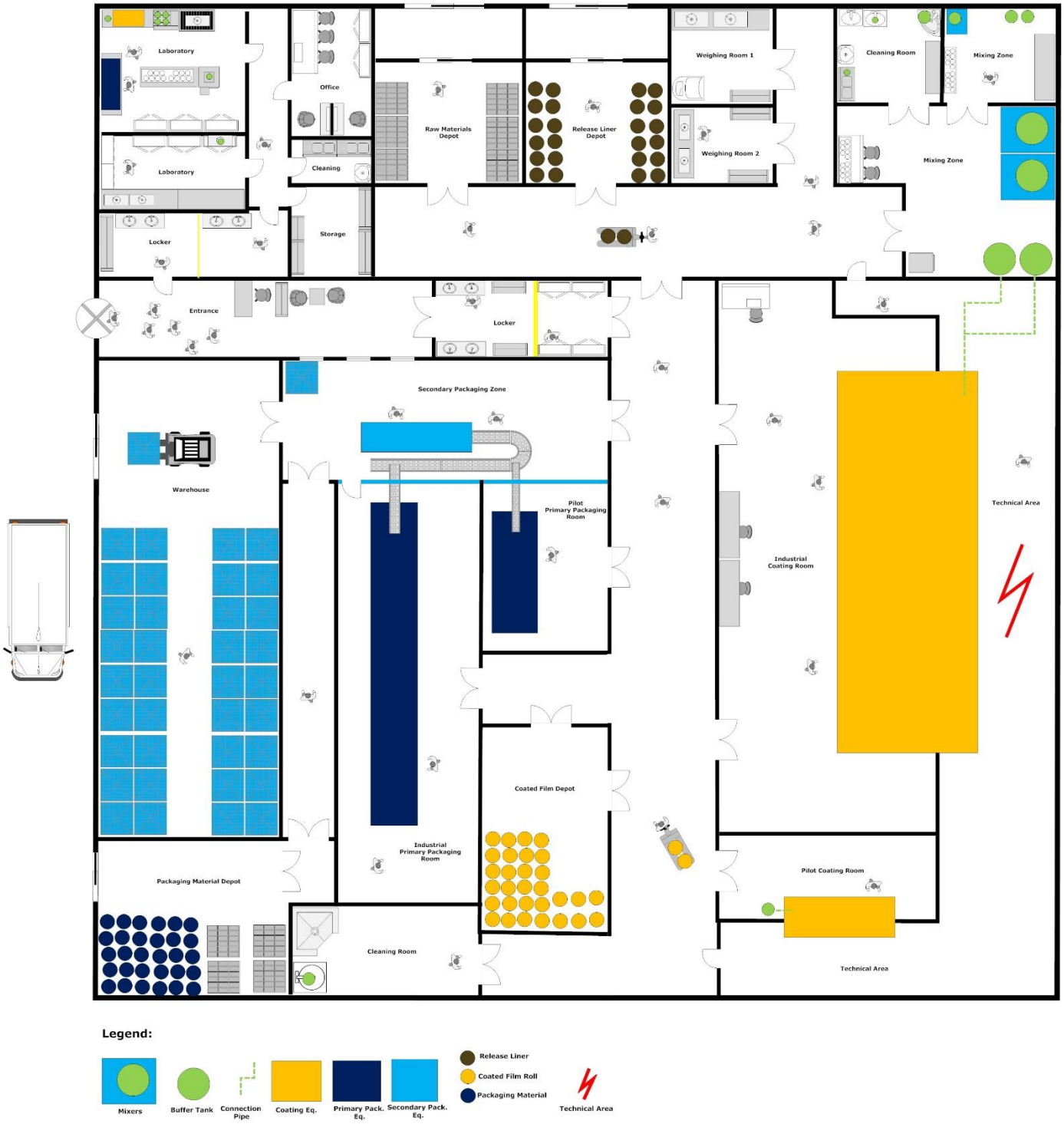


Figure 33 - Outline concept design of a facility for the development and production of OTFs at lab, pilot and industrial scale.

Figure 34 - Outline concept design of a facility for the development and production. The letters and number in this figure help to understand the following text

Figure 33 and Figure 34 show the concept plant of the manufacturing facility designed for this project. The second image has letters that will help to understand the next paragraphs.

The first concern was, of course, the space. As we have seen, machines have very different areas. Thereby, we decides to represent the ones with higher areas and consider the possibility to expand the capacity in the future. The coating machines (pilot and industrial) are represented in orange and the primary packaging equipment in dark blue. Also, a secondary packaging machine it's represented in light blue and the mixers and buffer tanks in green.

Also in this image there are several rolls represented: the ones in brown represent the release liner. The orange ones the coated film rolls, i.e. the release liner already with the film on it. Finally the dark blue rolls represent the packaging material.

We separated the laboratory area from the rest. So it's considered that pilot and industrial scale are both in the production zone of the facility. This must be like this because even though pilot scale represents a lower scale, it must also comply with the GMP.

The staff entry (and exit) is made through Ent1/Exit1. People that work in the laboratory enters to the lab zone (L) through the locker room L1 and the production personnel through L2 locker room. These happens because lab and production have different requirements. Plus, they are two independent activities and it's recommended to have them separated.

As already said before, a Quality Control (QC) room is not necessary in this plant, because it will be located in other adjacent facility.

The second entry of the facility (Ent2) is the door for the entry of the production raw materials and the release liner (for coating and mixing). The release liner is stored in the depot room D1 and the materials for the mixing process are stored in a second depot, D2. They must be separated first because they will follow different paths (the release liner goes directly to the coating room (C) and the mixture ingredients to the mixing

room (M)) and second because the mixing ingredients are often very sensitive and should be stored in more controlled conditions.

The plant presents one more entry (Ent3) that is dedicated exclusively for the packaging material. This happens due to the proximity to the packaging zone (PP and SP) but mainly because this material should be separated from the production raw materials for safety reasons. Much of this material is carton and paper for the secondary packaging and can liberate dust and other particles that could contaminate other products. These materials are stored in the depot D4.

The D3 depot is where the coated film rolls are kept after the coating process. They must be stored in a controlled room in order to preserve the film. According with the contacted suppliers if the film doesn't contain organic components it can be stored for a long period, normally more than six weeks. If there are organic components on the film formulation, the conversion to strips and primary packaging should happen until forty eight hours after end of coating process.

Looking again to the top of the plant, W1 and W2 are two weighing rooms to weigh the different components of the formulation with weighing machines with different sizes and precisions in order to serve the different scales. They are next to the mixing room for convenience.

There are two cleaning rooms (Cl1 and Cl2). The first is located in the top of the plant and serves the mixing area. The second is located near the coating and the packaging areas and it's supposed to be used to clean the mixture tanks after they are used in the coating process and to clean other equipment or tools of the coating and packaging processes.

In what concerns the mixing area (M), it must have the necessary space to accommodate pilot scale and industrial scale mixing equipment. As we have seen industrial mixers can go to thousands of liters. If we have only one pilot mixer it's recommended to have two portable buffer tanks. In this way, after the mixture in the reactor is finished it can be discharged to a tank that will be transported and connected to the coating machine. The reactor can then be cleaned and used again. When finished it can be discharged to the other buffer tank as the first one goes to clean. For industrial mixers transportable buffer

tanks can also be used, however it's recommended that the mixture is discharged to big buffer tanks that are fixed. These last ones in their turn, are directly connected to one (or more) coating machine through a complex system of pipes and pumps that guide the mixture directly from the deposit to the coating head pump. In the Figure the industrial mixers are represented by the letter "m" and the buffer tanks, connected to the coating room, by the letter "b". Also, smaller mixers and buffer tanks (for pilot production) are represented in this floor plan.

The coating rooms (C) are the areas where the coating equipment are placed. Due to the contact with the suppliers we were also able to collect some important information on the requisites of those zones:

- Technical room (T): the coating machines often need small adjustments and have a very complex air ducts. Thus, it's recommended to have a physically separated technical area from the coating room with an independent entrance. The back of the coating machine should fit through the physical barrier so it can be accessed through the technical room.
- The place where the coating machine operates must be a closed cleanroom. A cleanroom is a controlled environment normally used in the most diverse industries, where the level of micro particles (as dust, pollutants, etc.) are maintained at very low levels. To guarantee this, and as the suppliers explained, HEPA (high-efficiency particulate arrestance) air filters systems are placed in the room. In the case of OTF production this rooms must be cleanrooms class 10.000 (by USA regulation) or Class B (by EU GMP guidelines). This means, that an area of one cubic feet can't have more than 10.000 particles equal or superior than 0,5um or, by the European guidelines, on cubic meter can't have more than 350.000 particles of 0,5um when the machine is operating. Due to all this, these rooms should have proper air handler units (AHU) that together with HEPA systems can regulate the quality of air in the room and also its temperature and humidity.
- Despite of the quality of the air in the room, the coating machines' dryers are closed systems with their own AHUs that suck the air from the room, heat it and then the hot air is expelled (together with the solvents) to outside of the

facility. Also inside the coating machine, the air quality should be class 10.000. This means that the air sucked from the room, which in theory is already a "cleaned" air, passes again in the filters of the coating machine air system. This happens because it's crucial that the air is always clean and in circulation, to reach a high quality drying process with hot air. Normally, the volume of air changed every hour is 8 times the volume of the room.

- The room pressure should be normal but the pressure inside the dryer of the coating machine must be negative, this means lower than room pressure. This happens mainly because of safety reasons, preventing contamination. If a door of the dryer opens or there is a fugue, the air inside the dryer (that may contains dangerous components for the health) will not escape to the outside. On the contrary, the air of the room will get inside the dryer so the pressure reaches an equilibrium. This is another reason why the air in the room has the same quality as the air inside the coating machine.
- The recommend temperature for the room is 22ºC and the humidity 55%.

Primary Packaging equipment doesn't have a closed air system, like the coating machines. Nevertheless, the web converting process is still considered part of the production process. Thereby, for the rooms where these machines are placed (PP) all the suppliers recommend to have the same cleanroom conditions as in the coating process. This means that the room where the machines is placed should also be a clean room class 10.000.

Also, there is no need for a technical area, because the adjustments on the machine are made through the front part by opening the machine doors. Nevertheless there are other manufacturing aspects that must be considered:

The secondary packaging room (SP) has the secondary packaging equipment where the pouches are placed into carton boxes. All the suppliers told us that this area must be physically separated from the primary packaging room (PP). This is explained by the fact that the secondary packaging material (normally carton) may release dust and other particles into the air that can contaminate the OTF strips before they're sealed into the pouch. To optimize the process, it's normal that the physical barrier between the two

rooms have a very small opening were the conveyor that comes from the primary packaging machine passes through, connecting the two machines. The air pressure in the primary packaging room should be higher than in the secondary packaging room, so the air from this last one does not get into the primary packaging room though the referred opening.

To conclude, the facility has approx. 35m by 36m, which represents a total area of approx. 1260m^2.

5.9.1 Final Remarks

It is important to refer that there are still many more things to consider. The manufacturing of pharmaceutical products involves a lot of regulations, rules and well defined procedures, like the implementation of the Good Manufacturing Procedures (GMP). It was not an objective to look to all of these requirements and moreover, Bluepharma have a considerable internal know-how in the production of oral dosage forms with the highest standards of quality.

CHAPTER 6

Conclusions

6 Conclusions

6.1 Main Conclusions

The following bullets resume the main conclusions of this dissertation:

- There is a clear geographical division between the OTF manufacturers and the equipment suppliers;
- The models analyzed are comparable to each other and can assure a proper scale-up;
- The critical requisites were identified and will contribute to a deeper understanding of the manufacturing process and to the design of a new facility, the first in Portugal;
- The output of the coating machines depend directly on the drying time and conditions, while in the primary packaging machines the output it's mainly determined by the pouch characteristics. This means that the coating process it's directly related with the type of the formulation;
- The limiting step of the manufacturing process it's the primary packaging. Thereby, the maximum annual capacity it's approx. 150M OTFs;
- The output of the industrial machines, when compared with the pilot equipment, is ca. 8 times higher for the coating equipment and ca. 12 higher for the primary packaging equipment;
- The capacity estimation of the coating machines can be significantly increased, but not for the primary packaging equipment;
- There are equipments that can meet Bluepharma' sales forecasts.
- Pilot equipment it's an option for the coating process but not for the primary packaging process. However, by 2021 a complete industrial line it's needed to fulfill the company forecasts;
- There is no direct relation between the output and the investment of the three types of equipments analyzed;
- The global investment range goes from 5,2M€ to 8,3M€ (approx.).
- Considering the biggest equipment models, the facility must have approx. 1200m^2 of area. The critical process requisites were also identified.

6.2 Personal Considerations

In what concerns the objectives of this project, I would say that the results are positive and surpassed my expectations:

- The major players in this area were identified as well as the principal suppliers of equipment. I believe this information improves understanding that the company has about the this particular environment;
- Thirty nine different equipments were studied during the duration of this project. For each one of those models it was received an official budgetary quotation with very technical information and, of course, the investment involved. Through the analysis of those long documents we were able to understand more and more of each type of equipment and, thereby, identify the most critical aspects and how they determine the output;
- Consequently to the previous point, we were able to understand how to estimate the capacities of the equipment by applying a consistent method. Even though there are many factors that can contribute to the output of each machine, I truly believe that the results we got were extremely accurate if we take into account the internal information available at the time of this project. The company has now the clear notion of what each scale of production represents in terms of capacity.
- It was determined the range of investment in equipment and was also estimated the global investment of the complete facility. Even though that for confidential reasons we can't reveal the prices of each equipment, the results give a clear notion of what the company should expect for this project in terms of investment. I believe this an important legacy of this project that can help the company in future decisions;
- The outline of the new facility was a big challenge. It was not the objective to have a detailed floor plan of it, but the result gives the company already important information, like the space needed and can serve as a good basis for the future. Additionally to the requirements in terms of space, it was possible to identify several manufacturing requisites for this technology. This part was another big challenge for me, which made me go into the field several times, talk

with very expert people in the company and make a lot of experiences until achieving the presented result.

It was the main objective of this project to leave in the company a work that could serve has basis for the future implementation of a new facility. I place my confidence that this goal was accomplished. The results in this thesis were also presented to the company and received very positive feedbacks.

These last nine months were undoubtedly an enormous challenge and one of the most learning experiences I have ever had. I had full support of the company during my trainee and freedom to develop my work. The guidance I had during the project was of extreme quality and availability, which helped me in every step. I was also completely integrated in the company's routine and I was able to learn what means to work in a top level company. For all this reason I'm extremely satisfied with the experience and the resulting work.

6.3 Future Work

There is still a long way to go and more knowledge is still necessary. Thereby, several tasks are suggested for future work in this project:

- To reduce the number of suppliers and consequently the investment range, through face-to-face meetings, visits to the factories and benchmarking;
- To improve the manufacturing facility concept design through trained people in architecture and engineering;
- Start a procurement process for secondary packaging material and slitting stations;
- Gather information about the pouch size and material in order to determine more accurately the sealing time;
- To improve the accuracy of the considered drying time in the coating process. It can be made, for example, in a pilot facility of a supplier.

CHAPTER 7

S.W.O.T. Analysis

7 S.W.O.T. Analysis

To conclude, S.W.O.T. analysis was made, to evaluate the strengths, the weaknesses, the opportunities and threats of the OTFs project in the company.

Clearly the major weaknesses are the lack of know-how in this manufacturing process and the investment that it represents. Also, economic factors should be taken into account both for the opportunities and threats. If it's true that the economy is starting to grow again, uncertainty around the Greek situation and the agitated European political scenario can affect negatively the economic and consequently the investment capacity of the companies.

On the other side, Bluepharma has already a very substantial scientific knowledge concerning this technology. The fact that it's still a recent dosage form and that there are few products on the market it's an opportunity. Plus, Bluepharma it's a company dedicated to the external market, which together with its FDA approved manufacturing facility can be a good advantage. Figure 35, bellow, displays the S.W.O.T. analysis made for this project.

Figure 35 - Bluepharma's OTFs project S.W.O.T. analysis.

Bluepharma is a young and ambitious company, which has already a history of success. The Oral Thin Film technology represents an opportunity which can take the company to play in a completely different level. But like all great opportunities, there is a risk associated. The path made so far resulted in good results and makes the company look to the future with hope and expectation. It's important that the good work can be maintained, and that the market possibilities can be continuously updated and evaluated. Only well based decisions can reduce its inherent risks.

CHAPTER 8

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8 References

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