Universidade de Lisboa
Faculdade de Farmácia

The role of sodium croscarmellose in controlled drug release from oral solid dosage forms

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Trabalho de campo orientado pelo Professor Doutor. João Fernandes Pinto, Professor Associado e coorientado pela Professora Doutora Anna krupa

Mestrado Integrado em Ciências Farmacêuticas

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Resumo

Este projeto tem como objetivo entender três formas diferentes de produzir pellets, duas delas por extrusão e outra usando a técnica de co-extrusão antes da esferonização e secagem dos extrudidos, realizando também uma avaliação do seu potencial de desintegração da croscarmelose sódica presente nos pellets.

Este trabalho de campo foi divido em duas partes. A primeira desenvolvida na Universidade de Lisboa com a produção de pellets por esferonização dos extrudidos e co-extrudidos, obtidos através de uma prensa extrusora, utilizando um esferonizador para posterior esferonização. O rendimento máximo obtido foi de 85.9%. A distribuição por tamanhos foi estreita. O processo de co-extrusão mostrou-se complexo e muito dependente do equipamento. A presença de croscarmelose sódica na estrutura dos pellets diminuiu o tempo de desintegração (<15min) embora a libertação do paracetamol tenha ficado pelos 58%, muito provavelmente pela presença de celulose microcristalina na formulação que atuou como matriz.

Na Jagiellonian University, na segunda fase do projeto, foi possível produzir pellets através de extrusão – esferonização utilizando um extrusor de rolos e um esferonizador antes da secagem. O rendimento deste processo não foi além dos 75.1% e este trabalho de campo mostrou uma forma de produzir pellets com croscarmelose sódica e que esta adição teve um impacto no tempo de desintegração dos pellets.

A circularidade foi de 0.72 e os fatores que se mostraram críticos para a produção destes pellets foram a fração de croscarmelose sódica, o tempo de repouso, a taxa de extrusão e o prato do esferonizador. Estes fatores tiverem um impacto crítico e por isso o seu controlo é importante aquando da formação de pellets.

No geral este projeto provou a possibilidade de produzir pellets por extrusão, co-extrusão e a monitorização do tempo de desintegração por incorporação de croscarmelose sódica na formulação. Mais estudos devem ser conduzidos para desenvolver estas descobertas.

Palavras-chave: co-extrusão, desintegração, extrusão, pellet, croscarmelose sódica

Abstract

This project aims to assess three different ways to manufacture pellets, two of them by extrusion and another one using the process of co-extrusion, prior to the spheronisation of the extrudates and drying and evaluation of their potential disintegration ability of sodium croscarmellose present in the pellets.

This fieldwork is divided in two parts. The first one (University of Lisbon) enabled the manufacture of pellets by spheronisation (radial plate spheronizer) of extrudates and co-extrudates (ram extruder) prior to drying. The maximum yield obtained in this first part was 85.9% and the size distribution was narrow. The process of co-extrusion revealed to be more complex and more dependent of the equipment. The presence of sodium croscarmellose in the structure of the pellets decreased their disintegration time (< 15min) although the maximum release of the active substance (paracetamol) was 58%, likely to due to the presence of microcrystalline cellulose in the formulation acting as a matrix forming agent. In the s part of the project (Jagiellonian University) it was possible to produce pellets by extrusion – spheronization, using a roll extruder and a cross hatched plate spheronizer prior to drying. Pellets were produced with a maximum yield of 75.1% and this research showed a way to produce pellets with sodium croscarmellose with an impact on the disintegration time of the pellets. The circularity was 0.72 and the factors that were considered critical to produce these pellets were the fraction of sodium croscarmellose, the equilibration time, the extrusion rate and the plate type of the spheronizer. This factors had an impact and therefore are critical to control in the production of this pellets.

Overall, the project has proved the possibility of making pellets by extrusion, co-extrusion and the monitoring of the disintegration time by incorporation of sodium croscarmellose in the formulation.

Keywords: co-extrusion, disintegration, extrusion, pellet, sodium croscarmellose

Acknowledgments

Este projeto representa não só o trabalho de dois anos, mas o final de um percurso académico que não poderia ser mais completo.

Agradeço a todos os que fizeram parte desta jornada e que, mesmo sem muitas vezes me verem, contribuíram para que este momento pudesse chegar.

Uma palavra especial para o Professor João F. Pinto (University Lisboa, Lisbon) e para a Professora Anna Kruppa (Jagiellonian University, Krakow). Pelo conhecimento que me passaram, pelo apoio no desconhecido e por me fazerem gostar daquilo que nunca imaginei.

Um projeto, duas cidades, dois países, muitas pessoas.

Ser farmacêutico é mais do que acabar um curso, é garantir que evoluímos em todas as valências que um cidadão tem de ter, porque, no final de contas, **se formos só farmacêuticos nem isso somos.**

A todos,
Obrigado.

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1. Introduction

1.1 Background on pellets

Oral drug administration has been one of the most used routes of delivery for most therapeutic agents. In most cases, oral dosage forms are classified as single unit and multiple unit dosage forms. Multiparticulate dosage forms are receiving an increase attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. Almost 70 % of all ethical pharmaceutical preparations produced include granules, pellets, tablets, and capsules, out of which tablets being the most popular dosage form (1,2).

Many industries use the word pellet to describe different agglomerates produce from raw materials. It's commonly used since the turn of the 20th century, but after the demand of sustained release preparations its utilizations has become more regular particularly since the 1950s. In 1949 a research conducted by Smith Kline and French, regarding the potential of this type of pharmaceutical application (3).

So, the role of pellets became more and more important and there was a grow on the studies performed on this kind of material. More than fifty years later there is still a long path to fully understand all the solutions that this type of technology can bring to the pharmaceutical world.

In the pharmaceutical industry, pellets are simple small free-flowing spherical particles formed by agglomeration of fine powder or granules, which can be given in the form of tablets and capsules for various disease conditions. Usually, the size range of pellet size is of 0.5-2.0 mm (4).

1.2 Advantages and disadvantages of the use of pellets

Dividing the advantages in Technological advantages and Therapeutical advantages we can say that in terms of technological advantages the pellets show excellent flowing properties, due to its form, the efficacy of product is improved due to the safety of the active ingredient also it shows decreased friability, less abrasion and uniform size if done correctly. In terms of therapeutical advantages this new type of pharmaceutical application has brought many new perspectives as pellets prevent from dose dumping and cause lesser side effects when prepared in sustained release form, they disperse freely in gastric intestinal fluids due to small

in size, which gives a larger area for drug absorption and reduces peak plasma fluctuation, also pellets reduce accumulation of drugs which are irritant to gastric mucosa and in a final note they are also used for masking the bitter taste of unpalatable drugs (5).

Although pellets show an evolution in terms or Pharmaceutical Technology, they also have disadvantages comparing with other pharmaceutical dosage forms. Often pellets are too rigid in nature, which is difficult to compress as a tablet, therefore have to be encapsulated into a capsule and the process of pelletization is a highly sophisticated method because specialized equipment is used, with this is also clear to understand that the cost of manufacturing is high and involves a number of formulation and process variables leading to a complex process of manufacture (5).

Several studies show that today there is a partial consensus on the advantages and disadvantages of the use of pellets in pharmaceutical technology. There are different studies throughout the last ten years reviewing this topic (6–8).

1.3 Desirable Properties of Pellets

Regarding coating we can divide pellets in to two different categories:(9)

Uncoated pellets: should have high physical strength (high hardness and low friability) and integrity with uniform shape and smooth surface providing improved flow properties with an optimum size range of 600-1000 µm.

Coated pellets: Along with uncoated properties of pellets, coated pellets maintain the active ingredient to give the uniform size of final dosage form within its standard limits and gives desirable drug release kinetics.

So, when we talked about the desirable properties of pellets, we must consider that they will be different between the ones that are coated from the ones who are not.

For Uncoated pellets: Uniform spherical size; Narrow particle size distribution; Good flow; Low friability; Even surface; Low dust formation; Reproducible packing; Ease of coating.
For Coated pellets: Maintain all above properties plus desirable drug release characteristics.

Other point of interest when we talk about the desirable properties is the fact that the characteristics that we expect of pellets are different considering which method is used to produce pellets. Although there is still a need of further studies in this aspect, there are studies that provide a general approach on this topic (10).

1.4 Applications of Pellets

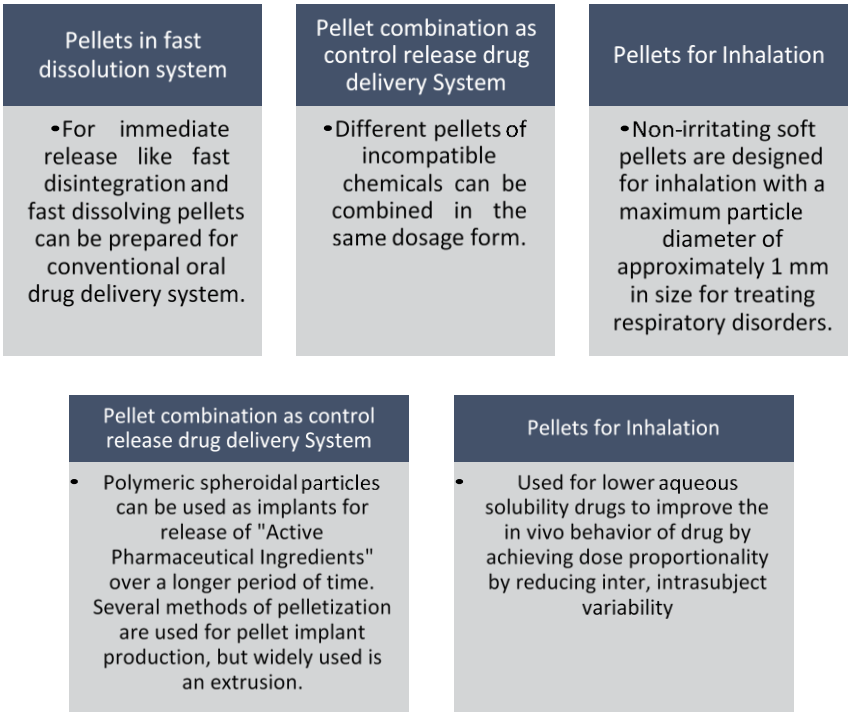


Figure 1. *Different Applications of Pellets with content (adapted from [8,9])*

To study if a substance has the right properties, one must know its characteristics and decide if that drug presents the appropriated properties for the formulation of pellets. Table 1. summarizes the characteristics suitable to produce pellets.

Table 1 *Different Applications of Pellets* (11)

Serial No.	Nature of the properties	
1	Physicochemical properties	Drugs having low molecular weight Drugs with good water solubility pH independent With non-aqueous solubility Unionized (at least 0.1-5%) in GI tract Very weak bases pKa < 5.0 Very weak acids pKa > 8.0 (Pentobarbital pKa = 8.1) Unionized at all pH Moderately weak acids pKa 2.5-5 Moderately weak bases
2	Pharmacokinetic properties	Short half-life Well absorbed from all regions of GI tract
3	Pharmacodynamic property	Therapeutic range of blood concentration - wide enough

Figure 2. summarizes some techniques of pelletization.

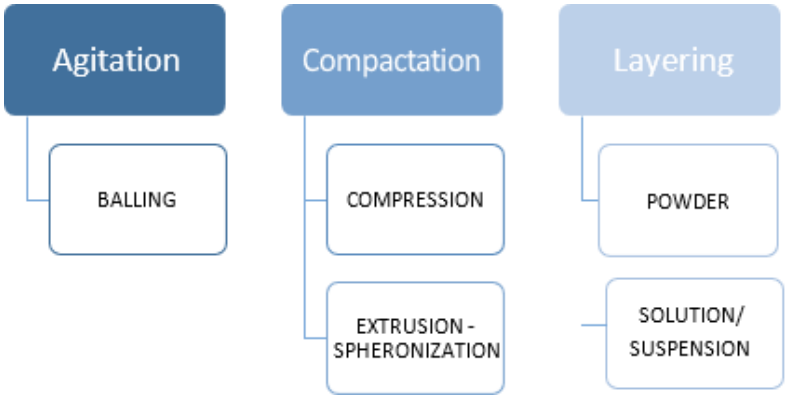


Figure 2 *Some techniques of pelletization (9)*

1.5 Process of extrusion

Pharmaceutical pellets are typically manufactured via extrusion spheronization, that results in spherical granulates roughly 1mm in diameter. Wet mass extrusion spheronization also called cold-mass extrusion spheronization has become the method of choice. When one is desirous of having dense spherical pellets of uniform size and shape. It involves the following steps: **Dry Mixing** (12,13) - Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer; **Wet massing** (12) - is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer. Evaporation of the fluid phase is a major problem with high shear mixers as they introduce a high amount of energy into the wet mass which is partly transformed into heat and induces evaporation of the granulation liquid thus changing the extrusion behavior of the wet mass. Cooling of the granulation bowl may avoid this problem; **Extrusion** (14,15) - This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of the wet mass into long rods, commonly termed ‘extrudate.’ The extrudate particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity to deform but not so much that the extrudate particles adhere to other particles when rolled during spheronization process. Extruders are classified into different categories some of the most used are, Screw feed extruder (axial or end plate, dome and radial), the screw extruder consists of one or two (twin -screw) feeding the wet mass to an axial or radial extrusion. In the axial type, (Figure 3, left) the screen is placed at the end of the

screw, while in radial type the screen is placed around the screw (Figure 3 right), discharging the extrudate perpendicularly to the axis of the screw.

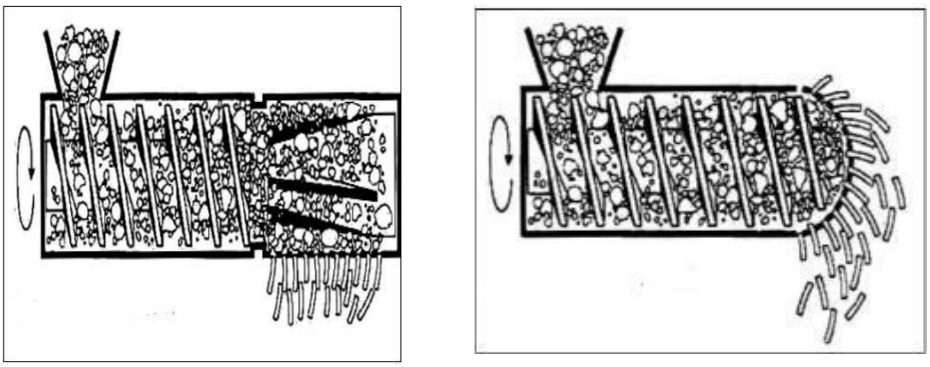


Figure 3 *Screw Feed Extruder, radial (left) and axial (right)*

Gravity feed extruder (cylinder roll or gear roll) and gravity feed extruders include rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes. Piston feed extruders (ram) which are probably the oldest type of extruders (Figure 4); a ram displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations (12).

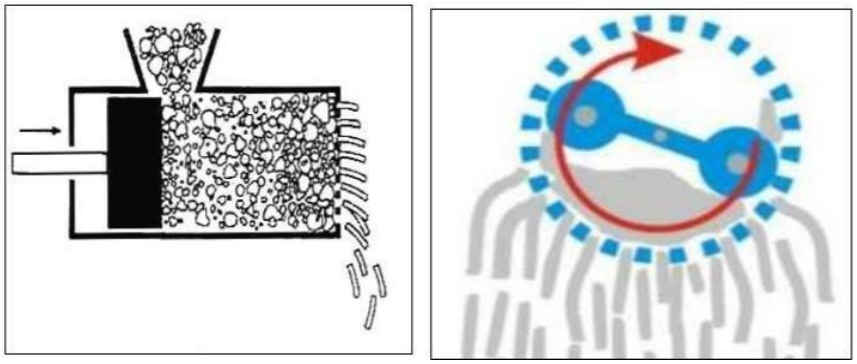


Figure 4 *Ram extruder, axial (left) and radial (right)*

1.5.1 Process parameters for extrusion

Starting Material: The nature of the starting material influences the size, hardness and sphericity of the particle, as well as the release rate of the loaded drug. (11)

Extruders: An axial screw extruder produces a denser material than a radial screw extruder. The latter has a higher output but also produces but shows greater heat production during the

processing. Pellet quality is dependent on the thickness of the screen and the diameter of the perforations. A thinner screen produced a rough and loosely bound extrudate, whereas a thicker screen forms smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of pellets- a larger diameter in the perforations will produce pellets with a larger diameter under similar processing conditions. (11)

Extrusion Rate: The output from the extruder depends on the extruder speed. (11)

Extrusion Temperature: The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug. (11)

1.5.2 Spheronization

The spheronization technology was first introduced by Nakahara in 1964. A spheronizer also known as marumerizer consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. (16,17)

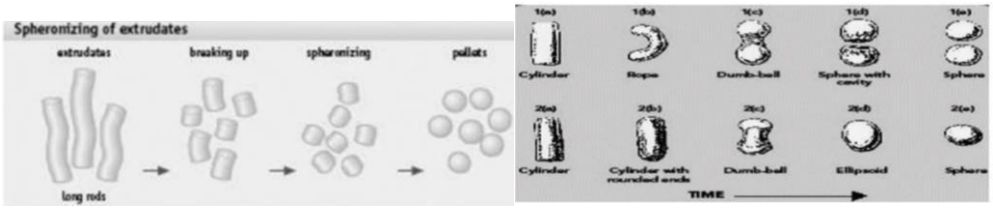


Figure 5 *Mechanisms of spheronisation*

During spheronization process different stages can be distinguished depending upon the shape. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most important component of the equipment.

Two geometric patterns are generally used. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc. The rotational speed of the friction plate varies from 100- 2000 rpm.

Spheronization process involves transition from rods to spheres that might occur in various stages which usually take 5 to 30 min provided mass should not be too dry wherein no more spheres are formed, and the rods will transform as far as dumbbells only (Figure 5). (16,17)

1.5.2.1 Spheronizer specifications

Pellet quality is also dependent on spheronizer load which affects the particle-size distribution, bulk and tap density of the final pellets. There were studies conducted in order to look at the optimum pay load required for the preparation of the best-quality and found that extremely small quantities provided insufficient plate-particle interactions. Also, there was a study that illustrated the effects of spheronization load and spheronization rate on mean pellet size and micropore volume using response surface methodology and concluded that the pellet size and porosity can be controlled by modifying the spheronization rate and spheronization load. For both Avicel grades (PH 101 and PH 102) used in this study, an increase in the spheronization load at a constant spheronization rate resulted in a decrease in both mean pellet size and micropore volume. The shape was characterized by the circularity parameter which was found to increase with an increase in both spheronization rate and load. (16–18)

Other experiments have evaluated the effect of spheronisation load and time on pellet qualities. The yields of pellets obtained at a shorter spheronisation time of 5 min were larger than those obtained when the extrudates were spheronized for 10 min. There was also a number of significant interactions between these variables. With small spheronisation loads, the yield of large pellets increased with longer spheronisation times, which was exacerbated by faster spheronisation speeds. When larger spheroniser loads were used, the production of large pellets was increased by increasing spheronisation time when spheronized at 600 rpm. At 800 rpm, the production of large pellets was high, regardless of spheronisation time. With increasing spheronisation time, the yield of fines reduced significantly. An increase in spheronisation speed and spheronisation load also resulted in an increase in the sphericity of the pellets. The most spherical pellets were obtained when both factors were held at high levels (18).

Pellet size and shape are highly influenced by the surface roughness of the spheroniser plate. There is considerable interaction between spheronization time and spheronization. Both the mean pellet size and micropore volume change in spheronization rate and spheronizaton load. Similarly, pellet size, circularity, and yield change with the change of spheronization time and load. With small loads, the yield of large pellets increases with longer times, and this can be exacerbated by faster speed (18).

1.5.3 Drying

A drying stage is required to achieve the desired moisture content. Drying rate also important an increase drying rate gave more porous pellets due to decrease pellet densification during that drying process. The pellets can be dried at room temperature or at elevated temperature in a tray drier/ oven or in a fluidized bed drier. This process is performed to achieve required level of moisture contents in the formulations. Pellets can be dried at room temperature and even at higher temperature if required. Freeze drying technique, tray drying, and fluidized bed drying techniques are available for drying of pellets. Freeze drying technique has the advantage over other techniques that it not only maintains the shape of the pellets but also retains the size (19).

1.6 Other technologies associated to the manufacture of pellets

1.6.1 Layering

Pellet formation by layering involves the deposition of successive layers of drug molecules from dry powder or granules, suspension, a solution of drug particles. Drug layering is the technique of pelletization which is used to coat or layer the seed material in powder, solution, or suspension form. Initially, drug solution or suspension is prepared by using a suitable solvent. Prepared solution or suspension of the drug is then sprayed over the inert spherical core, usually prepared by using microcrystalline cellulose or sugar. This process results in the formulation of varying sized pellets with inner core and outer shell having different composition. This technique has different types including dry powder layering, solution and suspension layering (17).

1.6.1.1 Dry powder layering

This is the process in which consecutive layers of dry powder of the drug or/and excipients are deposited on preformed core. First, a binding solution is prepared having a suitable binder. The prepared binding solution is sprayed over the inert core of microcrystalline cellulose or sugar to prepare a sticky core with the ability to bind the drug powder over it. The drug, which is to be layered over prepared core, is grinded or micronized, if required, to prepared fine powder and then the finally divided powder is sprinkled over the inert spherical core in controlled manner to achieve uniform sized circular pallets (20,21). Conventional coating pan is usually used for this purpose, but it has few drawbacks like poor mixing and poor drying. The substrate particles are fluidized and suspended by heated and conditioned air. One or several nozzles atomize and spray the drug powder onto the substrate. (22)

1.6.1.2 Suspension/solution layering

In this process, successive layering of solution/suspension of ingredient including binder on starter seeds is done. Starter seeds are usually of inert material or may be of the same drug. In this method, solution or suspension of active ingredients along with other excipients is prepared. This solution/suspension is sprayed over the core material. Fluid-bed apparatus, traditionally a Wurster column (Wurster HS, Glatt). In the Wurster column, the substrate particles are fluidized and suspended by heated and conditioned air. One or several nozzles atomize and spray the drug dispersion onto the substrate. The heated and conditioned air then evaporates the liquid carrier, leaving the drug deposited on the substrate. Drying process is very important as it crystallizes the dissolved material that link the core with consecutive layers of the drug or other polymers. This process is continued until the required drug or polymers layer is achieved. It is also an effective technique but there are few drawbacks of this and one of them is difficulty in achieving evenness in the drug distribution and uniformity in the size of the pellets (22).

1.6.2 Cryopelletization

It is a unique process as it requires a fixing medium. Usually, liquid nitrogen is used as fixing medium which is applied on the droplets of liquid formulation to convert them into solid pellets. This technique is like the one which is used for the lyophilization of viscous bacterial suspension. Liquid nitrogen prepares pellets at the temperature of 160ºC which causes vigorous transformation of heat between drugs loaded droplets and fixing medium. Amount of solid and temperature of the solution or suspension describe how much nitrogen should be used in this process. Apparatus for this process consists of a perforated plate, a conveyor belt which acts as a reservoir, transport baffles storage container. Droplets are generated through perforated plates and freeze when exposed to liquid nitrogen and finally extracted out from the medium and stored at -160ºC. It is a unique method for the preparation which is an expensive one and required expertise for the preparation of pellets by using this technique (21).

1.6.3 Hot melt extrusion

Hot-melt extrusion is one of the most extensively used techniques in different industries. Nowadays, this technique is succeeded in entering the pharmaceutical industry. In pharmaceutical industry, this technique is valuable in formulating different dosage forms including pellets, granules, and transdermal drug delivery systems. In this method, drugs and other excipients are mixed evenly and then melted on a temperature which is high enough to convert the ingredients in molten state. Usually, a spheronizer is used to convert the pellets into spherical form. (21)

1.6.4 Agitation

Agitation involves the conversion of finely divided particles into spheroidal particles by the addition of required liquid by a continuous rolling or tumbling motion. The liquid can be added at the beginning of the process, or during the agitation process. Pans, discs, drums, or mixers may be used to produce pellets by the balling process. It is the oldest and less efficient technique for production of pellets. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid (19).

1.6.5 Compression

Compression is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing (19).

1.7 Formulation

There are different substances with different roles in the formulation of pellets, in the next figure it's possible to see the different possibilities of agents in pellets formulation.

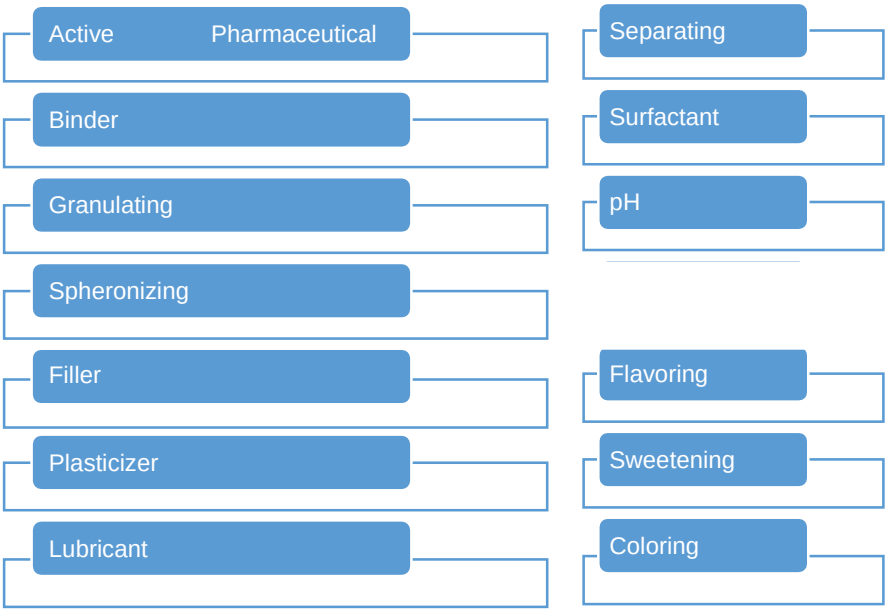


Figure 6 *Different types of roles of substances in pelletization*

1.8 Characterization of Pellets

There is a lot of information on the characterization of pellets, this information bellow contains a summary based on review articles (23–25).

Size and size distribution: The sizing of pellets is necessary because it has significant influence on the release kinetics. In most of the cases particle size determination is carried out by using a sleeve shaker. (23–25)

Shape: Visual inspection of pellets by microscope and stereomicroscope are a method to determine shape of pellets. An angle at which a plane must be tilted before a particle begins to roll is called to be One plane critical stability, is one of the important methods used for determining shape. The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain number of pellets are allowed to flow through a specific orifice from a given height.

Surface morphology: Scanning electron microscopy is used to examine the surface morphology and cross section of pellets

Specific surface area: Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area. Specific surface area of pellets is determined by gas adsorption

Hardness and Friability: The mechanical properties of pellets are important for processing. Pellets flake off during handling, shipping, storage coating process and other unit operations thereby resulting in formation of dust. Variations in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations with hardness and/or friability of pellets. Hardness of pellets can be determined using Kahl pellet-hardness tester but might not be accurate. Friability of pellets are determined by using Erkewa type tablet friabiliator or turbula mixer for a fixed period combined with glass beads of certain diameter to generate abrasion and to generate friability index. Friability can also be determined using fluidized bed with Wurster insert by using stream of air

Tensile Strength: The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded, and the tensile strength is calculated applying the value for the failure load and the radius of the pellets

Density: Density of pellets (bulk and tapped) can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression and is determined simply by USP density apparatus. The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be determined by an air-comparison pycnometer or by solvent displacement method.

Pellet surface roughness: The surface roughness measurements can be carried out on the same samples of pellets as those used to measure the diameter

Porosity: The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry

In vitro dissolution studies: In vitro dissolution studies are predominantly recognized as an important element both in drug development and quality assessment over the past four decades. These tests were performed for studying the release behavior of different formulations in different dissolution media and to establish a corelation between in vitro release and in vivo absorption for the modified-release pellets. Release of drug from solid dosage form often constitute a determining step in the in vivo absorption process and used in conjunction with in vivo/in vitro correlation to establish quality control parameter.

1.9 Co-extrusion

The process came about because some service demands, particularly from the packaging industry, could not be satisfied by a single polymer although they could be met by a combination of polymers. Coextrusion was first practiced in the production of cast film and is now also used in blown film and sheet extrusion. The intention is normally to produce a laminar structure in which each layer contributes a key property to the overall product performance (26,27).

Co-extrusion is the simultaneous extrusion of two or more materials, this approach will form a multi-layered extrudate that can be more complex or easy depending on the number of layers. Probably, the easiest co-extrudate to produce is that consisting of two or more layers forming a lamella. Even though this fact, it would be difficult to spheronize these extruders to. As an alternative, the production of concentric cylindrical co-extrudates will easily provide spherical pellets (26,27).

1.9.1 Advantages of co-extrusion

The process of co-extrusion represents a new and exciting way of producing pellets. Although all the potential of this technique is still to be explored, it is easy to identify major advantages regarding the traditional technique of extrusion (20).

- Simultaneous administration of non-compatible drugs, each presented in a different layer.
- The external layer may function as a coat to the inner layer, either protecting the active ingredient or tailoring its release.
- Modulation of the release of the drug either by loading the different layers with different amounts of drug or by incorporating the drug in different matrices (e.g., a prolonged release core and an external layer of rapid drug release).
- The ability of having different layers with different roles in the formulation, allows this type of technology to gain more and more importance in the pharmaceutical field.

1.10 Sodium Croscarmellose

The slow dissolution of poorly hydrosoluble drugs from microcrystalline cellulose pellets prepared by extrusion– spheronization has been widely documented (28). This slow dissolution rate derives from the pronounced contraction of the pellet during the drying phase, leading to reduced porosity which hinders entry of the dissolution medium into the pellet. Of the approaches that have been proposed for overcoming this limitation of microcrystalline cellulose.

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct- compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant,

although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table 2 *Use of croscarmellose sodium (Handbook of pharmaceutical excipients* (29)

Use	Fraction (%)
Disintegrant in Capsules	10-25
Disintegrant in Tablets	0.5-5.0

In this research project the effect of adding sodium croscarmellose as a superdisintegrant in the expectation of improving the release of the active substance and make the dissolutions tests to see the role and importance of this substance, is also studied.

2. Objective

The purpose of this project is:

(a) To understand and execute the process of extrusion, co-extrusion and spheronization.

(b) To understand the possible role of a super disintegrant, sodium croscarmellose on pellets formulations, in order to understand if it allows the production of pellets of good quality and if the disintegrant profile changes.

3. Material and Methods

3.1 Materials

Lactose monohydrate EP (Granulac 230, Meggle), microcrystalline cellulose (Avicel PH 101, FMC Corp.) Paracetamol (Lusifarma), sodium croscarmellose (FMC BioPolymer, AC-DI-SOL), Sudan III, a red dye (Merck, median particle size 19 µm, by laser diffractometry) and de-mineralised water were used in the different formulations.

3.2 Methods

3.2.1 Data record

All the data of this research project was recorded in an online platform, this way every person that was part of the project could have live access of the results in each day of research. The online Platform was divided in different sections as General Resume of Formulations,

Process, Comments, and a folder for each formulation with the process and graphic of the process of extrusion.

3.2.2 First part of the project

3.2.2.1 Extrusion – Spheronization

For better understanding of the two different phases of the project, several methods and results will be divided between the first phase in the University of Lisbon and the s one at the Jagiellonian University.

The powders considered in the different mixtures (Table 3) were dry-mixed in a planetary mixer (Kenwood Chef, UK) for 10 min.

Table 3 *Formulations (g) considered for the production of the extrudates*

FORMULATION	MICROCRYSTALLINE CELLULOSE	LACTOSE	PARACETAMOL	WATER	CROSCARMELLOSE SODIUM
1	40	40	20	55	-
2	40	40	20	52	-
3	40	40	20	52	-
4	30	40	20	52	10
5	30	40	20	52	10
6	30	40	20	52	10
7	30	40	20	55	10
8	35	40	20	55	5
9	35	40	20	52	5
10	35	40	20	55	5
11	35	40	20	55	5
12	35	40	20	55	5

The wetting of the powder blend was done by the slow addition of de-mineralized water for 10 min. The wet mass was placed in a sealed polyethylene bag and left to rest at room temperature for 24 h prior to extrusion. This period of rest of the mass was variable but the average was 24 h.

The extrusion was carried out with a ram co-extruder fitted to a mechanical press (Lloyd Instruments LR 50K, UK) with a 45 kN load cell that allowed the collection of data for the representation of the extrusion profiles. The extrusion rate was set for formulations 1 to 6 at 100 mm/min, for formulations 7 to 12 at 250 mm/min, for a maximum force applied of 45 kN on the wet mass.

The extrudates (single, tubular, and co-extrudates) were spheronized in a radial plate spheronizer (GB Caleva, model 230, UK) at 1000 rpm, for different periods of time. Drying of either extrudates or spheroids was carried out in an oven overnight, at 105 °C.

Pellets were characterized for size (sieves with 500, 710 and 1000 μm) for disintegration time.

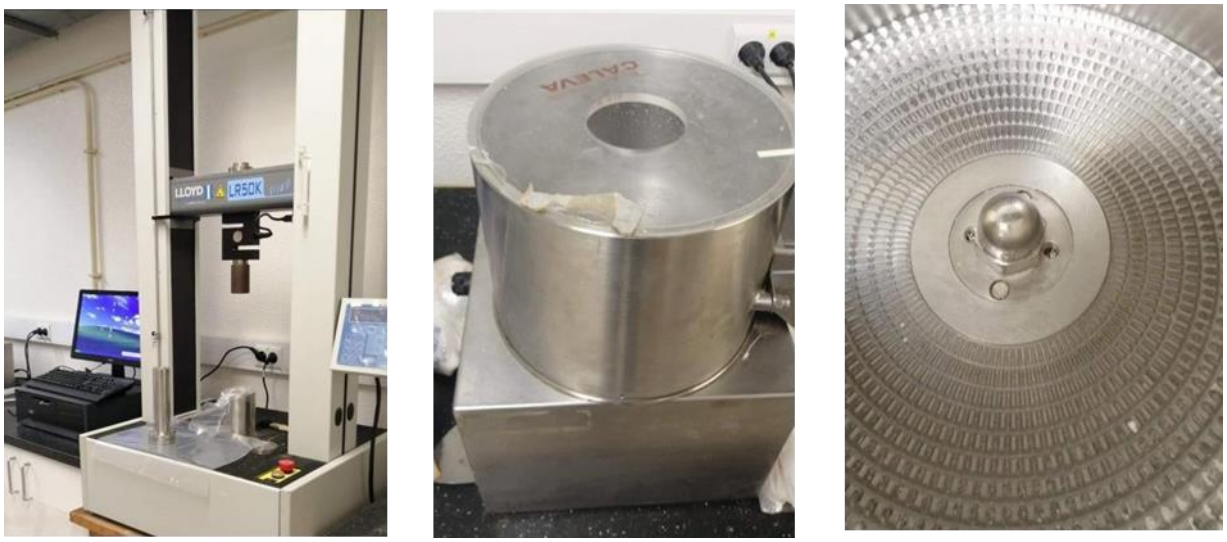


Figure 7 *Ram extruder (left), spheronizer (center) and sheronizer's cross hatched plate (right)*

3.2.2.2 Co-extrusion

Table 4 summarizes the formulations considered in the different mixtures. Powders were dry- mixed in a planetary mixer (Kenwood Chef, UK) for 10 min. The formulation for the outer layer incorporated Sudan III.

The wetting of the powder blend was done by the slow addition of de-mineralised water for 10 min. The wet mass was placed in a sealed polyethylene bag and left to rest at room temperature for about 24 h prior to extrusion.

Table 4 *. Formulations considered to produce the co-extrudates (in %)*

MIXTURE	MICROCRYSTALLINE CELLULOSE	LACTOSE	WATER
1	30	30	40
2	30	30	40
3	32	30	38
4	38	28	34
5	37	28	35

The extrusion was carried out with a ram co-extruder fitted to a mechanical press (Lloyd Instruments LR 50K, UK) with a 50 kN load cell that allowed the collection of data for the representation of the extrusion profiles. The co-extruder built in-house was designed with two concentric chambers, one internal and the other external.

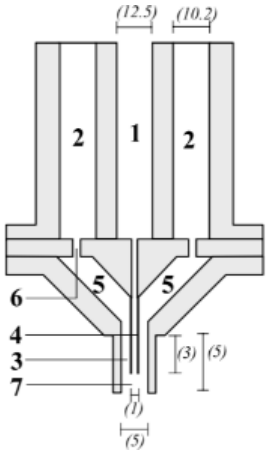


Figure 8 *Schematic representation of a ram co-extruder (side view). (1) Internal chamber with internal ram; (2) external chamber with external ram; (3) external die; (4) internal die; (5) external die feeding area; (6) connecting orifices to the external feeding*

The extrusion rate for formulations 1 to 3 was set at 100 mm/min whereas for formulations 4 to 5 was set at 250 mm/min, for a maximum force of 45 kN applied to the wet masses.

The extrudates (single and co-extrudates) were spheronized in a radial plate spheronizer (GB Caleva, model 230, UK) at 1000 rpm, for different periods of time. Drying of either extrudates or spheroids was carried out in an oven overnight, at 105 °C.

3.2.2.3 Release of paracetamol (test of dissolution)

The dissolution test was performed in an automatic dissolution equipment (Sotax AT, paddle method, 100rpm, in water).

The paracetamol released from the pellets was quantified by spectrophotometry (UV-visible spectrophotometer, Hitachi U-200). With a dissolution factor of 20, the samples were prepared, and the wavelength was discovered by tracing the different variations of the absorbance and the peeks where we could find the maximum absorbance for paracetamol.

3.2.3 Second part of the project

3.2.3.1 Extrusion

The powders considered in the different mixtures were dry-mixed in a bowl for 10 min with the help of a spatula. The wetting of the powder blend was done by the slow addition of demineralized water for 10 min by a peristaltic pump at a variable rate between 2.7 ml/min and 3.5 ml/min. the wet mixture was left for equilibrium for 0-24 h to understand the differences and impact of this factor on the processability of the wet mixtures.

Figure 9 *Preparation of powder blends (left) and evaluation analysis of the water content in the mixtures (right)*

The extrusion of the wet masses was carried out in a cylindrical extruder (Alexanderwerk) with two counter-rotating rollers set at two different extrusion rates (120 mm/min and 360 mm/min). The spheronization of the extrudates (was performed with different rates (1000-1400 rpm).

Table 5 *Different formulations of pellets produced in the s part of the project*

Formulation	MCC	Lactose	Paracetamol	Sodium Croscarmellose	Water
A - 18-02	20	20	10	-	30
B - 18-02	20	20	10	-	27.5
C - 19-02	17.5	20	10	2.5	27.5
D - 19.02	17.5	20	10	2.5	27.5
E - 19.02	17.5	20	10	2.5	27.5
F - 20.02	17.5	20	10	2.5	27.5
G - 20.02	17.5	20	10	2.5	35
H - 21-02	17.5	20	10	2.5	35
I - 24-02	18.25	20	10	1.25	27.5
J - 24-02	17.5	20	10	2.5	35
K1 25-02	18.25	20	10	1.25	27.5
K2 - 25-02	18.25	20	10	1.25	27.5
L - 02-03	18.25	20	10	1.25	27.5
M - 02 -03	17.5	20	10	2.5	27.5

Table 6 *Process parameters considered for the manufacture of pellets from individual formulations*

Formulation	Extrusion rate (mm/min)	Spheronization time (s)	Spheronization rate (rpm)
A	120/160	60	1400
B	120/160	120	1400
C	120/160	10	1400
D	120/160	10	1003
E	240/360	10	1003
F	240/361	20	1003
G	240/362	20	1003
H	240/363	20	1003
I	240/364	120	1003
J	240/365	120	1003
K1	240/366	120	1003
K2	240/367	120	1003
L	240/368	120	1003
M	240/369	240	1003

The spheronization rate was modify from the third formulation on in order to produce less friable pellets. The formulations A,B,C had shown a low yield and, therefore, that parameter was changed in the following experiments.

Figure 10 *Roll extruder Alexanderwerk Gun with two counter-rotating rollers. Chamber (left), Rollers (Center and right)*

The pellets were dried in the oven overnight at a temperature of 60 ºC.

3.2.3.1 Settling volume of sodium croscarmellose

To 75 mL of water in a 100mL graduated cylinder add 1.5 g of it in 0.5g portions, shaking vigorously after each addition. Add water to make 100 mL, shake again until all of the powder is homogeneously distributed, and allow to stand for 4 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL.

3.2.3.2 Characterization of products

Water content - The quantities of water in the raw material and in each intermediate product of the production of pellets (dry-mix, wet-mix, extrudates, pellets) were determined. The contents were found by drying samples of the products until constant weight in an oven at 120ºC. This is particularly important in sodium croscarmellose (30).

Size and size distribution - Pellets were characterized for size and size distribution by sieve analysis (sieves with 500, 800, 1000 and 1400 µm)

Circularity - The circularity of pellets was calculated from pictures captured by a camera and then analysed in ImageJ to calculate the values.

Dosing of paracetamol - The paracetamol released from the pellets was quantified by spectrophotometry. 200 mg of pellets were added to 50 mL of the buffer, and it was then put in an agitator with a speed of x rpm. Then the three samples of each formulation were measure and then the absorbance was measured to calculate the quantity of paracetamol in the pellets.

4. Results

4.1 First part of the project

4.1.1 Extrusion – Spheronization

Extrusion of the formulations through the internal die was possible, providing extrudates with smooth surfaces for extrusion rates ranging from 100 up to 250 mm/min.

The number of different formulations of this project is very high due to the need of achieving the right formulation, and the right balanced between active substance, excipients, and content of water. The formulation 1 proved to have too much water this way the extruder did not have the properties needed to be part of a process of spheronization. Figure 9 presents a poor graph of “force versus displacement” since the output was far from appropriated for a good extrudate, ie., a long steady state followed by a sudden increase on the extrusion force at the end of the extrusion. We were able to compare this type of images with others that were conducted with the same equipment (20,31)

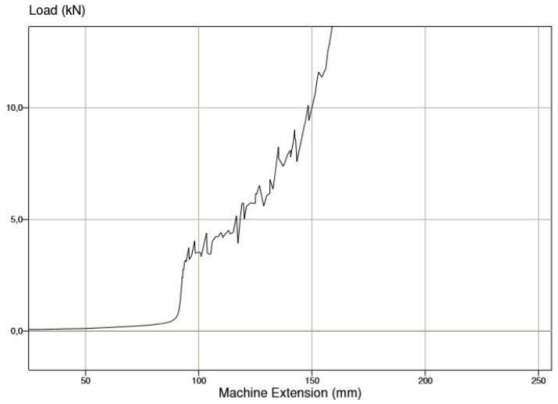


Figure 11 *Force versus displacement curve for a wet mass (Formulation 1)*

In formulations 2 and 3 the fraction of water in the mixture was changed and that had a positive impact on the characteristics of the pellets (Figure 12, left to right). The extrudate was spheronized prior to collection for characterization. The curve 'force/displacement' presents a clear steady state followed by a sudden increase on the extrusion force at the end of the extrusion.

Figure 12 *Images related to the production of good quality pellets – curve 'force/displacement' (left), extrudates produced (center) and pellets collected after spheronisation (right), for formulation 3.*

The homogeneous extrudates were spheronized for 5 min and then dried in the oven overnight (Figure 13). There was also done test to characterize the pellets produced with the calculation of the yield for some formulations and the size distribution.

After achieving the correct formulation that was represented for the right amount of water in the mixture, the main goal of this research project was to be able to understand the role of the Croscarmellose sodium in the release of the active substance (Paracetamol). With the addiction of the Croscarmellose sodium there was a need to test the formulation. The formulation 4,5,6,7 shown that the addiction of 10% of the supper disintegrant lead to the

incapability of spheronize the extruder that were turn to powder in the first 30 s of the spheronization. The decrease of the percentage used of Croscarmellose sodium to 5% shown an improvement of the capacity of producing more uniform pellets even though that the spheronization time had to be reduced to 1 min because of the lack of consistence of the pellets. With the use of the formulation 10, 11, 12 was possible to produce smooth surface pellets with uniform size and characteristics. As seen in the formulation 3, the steady state is also recognizable with the addiction of the Croscarmellose sodium.

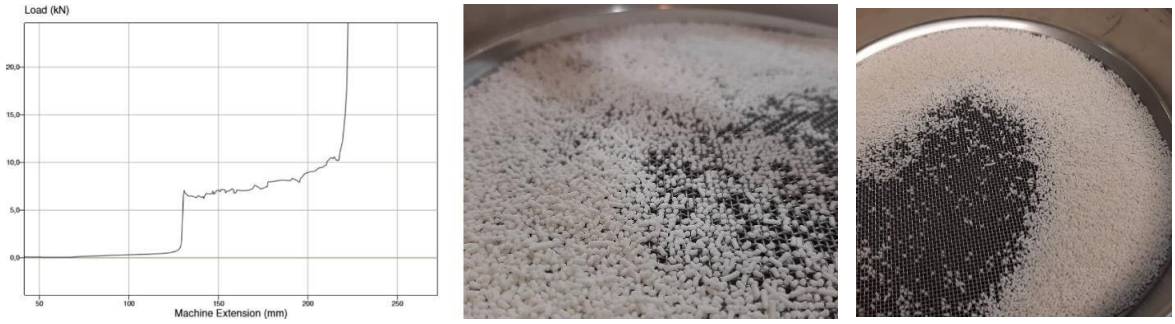


Figure 13 *Images related to the production of acceptable quality pellets - curve 'force/displacement' (left), extrudates produced (center) and pellets collected after spheronisation (right), for formulation 12.*

The pellets have shown good characteristics at the human touch, and where not easily broken down into powder, like the ones with 10% of Croscarmellose sodium (Figure 14.) These results are aligned with the studies that were able to produce these kind of pellets, with similar yields in some cases (28).

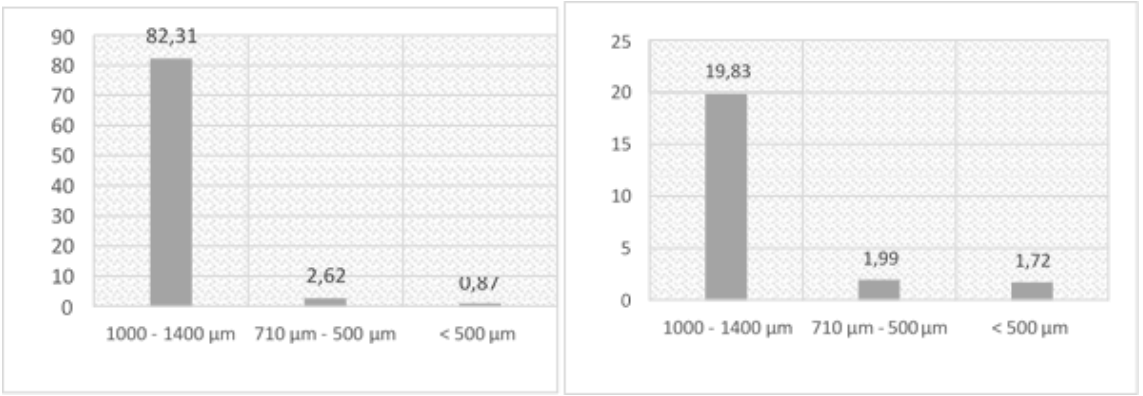


Figure 14 *Size distribution (in percentage) of pellets based on formulations 3 (left) and 12 (right)*

The choice of the formulation 3 and 12 as examples was based in the consistence and differences in the formulation. The size distribution was done with the agitation of an automatic shaker to guarantee the correct dispersion within the sieves. Figure 15 (left and right) presents the differences in the sizes of the pellets (in %).

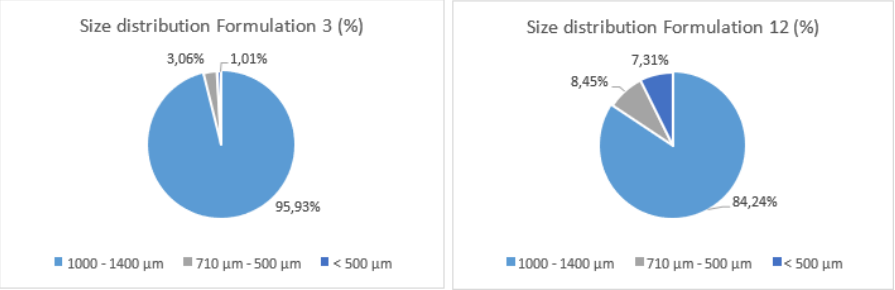


Figure 15 *Size distribution of pellets based on formulations 3 (left) and 12 (right)*

Yield determination (%) is carried out to know the preparation procedure chosen for pellet formation is effective or not, and to know the importance of the procedure used regarding safety and efficacy with lesser effort and greater benefit. Hence the quantity or the amount of active pharmaceutical ingredients, polymers, binding agent, anti-frictional agents, starch paste, and other process parameters are the factors which play a major role in deciding the yield of the pellets during pelletization process. The equation for calculation of % yield of a pellet is as follows:

Yield (%) = Weight of pellets/ (Weight of drug + Weight of polymers) × 100

To now the efficiency of the process the yield was calculated to the successful formulations, though this never was a priority for the research project. The main goal was to achieve and explore the right characteristics of the pellets and not the maximum yield of the extrusion – spheronization process. The yield of formulation 3 is consider to be normal on the criteria of some studies (32), the rest is off limits.

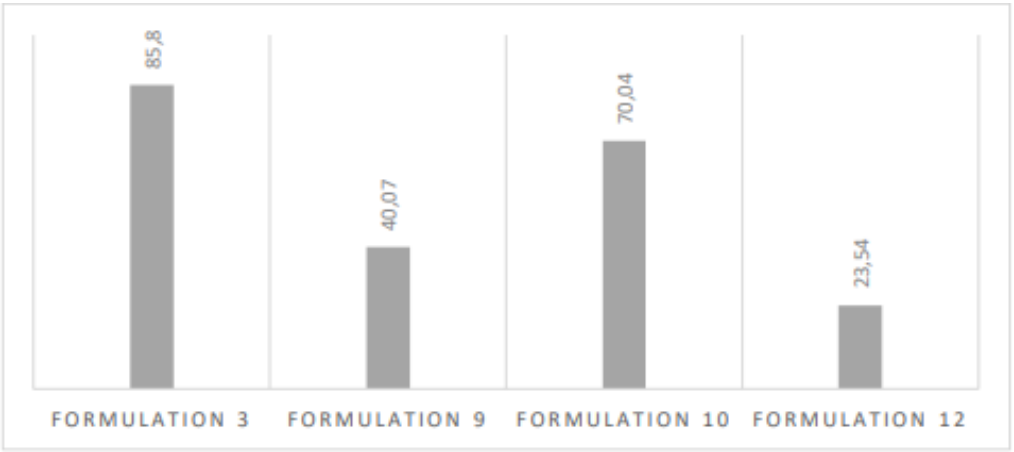


Figure 16 *Yield of the process for different formulation.*

4.1.2 Co-extrusion

The first formulation was designed with the main goal of understanding the assembly of the extruder and the process. Co-extrudates were produced by filling both chambers either with the normal mixture or mixture with (Sudan III). Consequently, co-extrudates with a white or colored external layer were produced and, in either case, some common features were observed. But the results are not similar to other studies that were able to produce this type of pellets (20,26). The force versus displacement curve (not shown) did not have a long steady state followed by a sudden increase on the extrusion force at the end of the extrusion like it was expected. These extrudates (formulations 4 and 5) were spheronized but the results showed a lack of consistency between the layers of the extrudate, although the consistency of the extrudate itself has proved to be good for the process of spheronization.

The co-extruder used to make the pellets began to malfunction with formulation 5, therefore there was a lack of data of the co-extrusion process. After this incident the course of the project has changed from co-extrusion to extrusion and the role of a superdisintegrant in the formation of pellets was studied.

4.1.3 Effect of the sodium croscarmellose in the pellets

To evaluate the properties of disintegration and release of the active substance, after the process of extrusion – spheronization of the pellets (formulation 12), a dissolution test to the pellets (1000 mg) was performed. To quantify the paracetamol released from the pellets dissolution tests were performed and the raw data (absorbance) is present in the supplementary materials sections. Although this analysis does not have so much detail, it was possible to understand the process of analysis of this type of results in other studies (33)

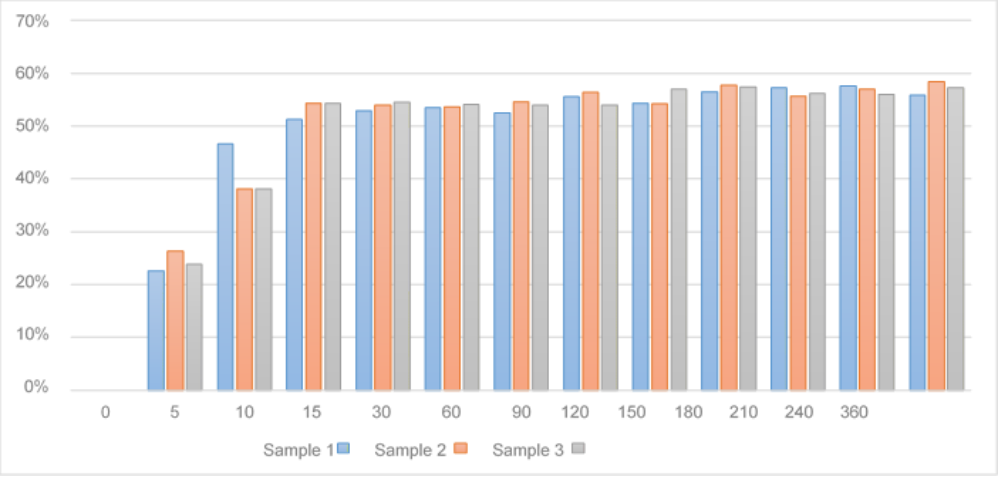


Figure 17 *Release of paracetamol from pellets (formulation 12), expressed as percentage of release vs time (min)*

It can be observed a fast release over the first 60 min until reaching a plateau. Taking advantage of the calibration curve it was possible to convert absorbance into concentrations and then into quantities of paracetamol released. In each sample that we take form the dissolution test, this 5ml have concentration in paracetamol and the equipment replaces it with jut the phosphate buffer, this means that although they are small quantities there is an error associated with this type of process.

4.2 Second part of the project

Extrusion of the formulations through the dies of 1mm was possible, providing extrudates with different characteristics.

The number of different formulations of this project was large due to the need of achieving the right formulation, and the right balanced between active substance, excipients, and content of water.

The evaluation of the formulation was needed to understand how to produce pellets with the addiction of sodium croscarmellose. Since the first formulations it was clear that the extrudates were not stable enough to be able to spheronize, so with the addition of the equilibration time and with the decrease of the percentage of sodium croscarmellose in the formulation, it was possible to achieve pellets with acceptable characteristics to be studied.

To evaluate the ability of producing good pellets with the addiction of the super disintegrant, one parameter that was critical was the size distribution, in most of the formulations with 5% of sodium croscarmellose it was very difficult to spheronize the extrudates without transforming the majority of the extrudates in the powder.

To analyze the differences of the changes mentioned in the figure, regarding the process variables and formulation variables, we decided to compare the different size distributions according to the changes that we made in each parameter. The following images compare the size distribution.

The next image shows the different size distribution of pellets with different contents of water. Formulation F has 27.5 g of water, Formulation G has an increase of 9% on the amount of water comparing with F and has less 15% than formulation A.

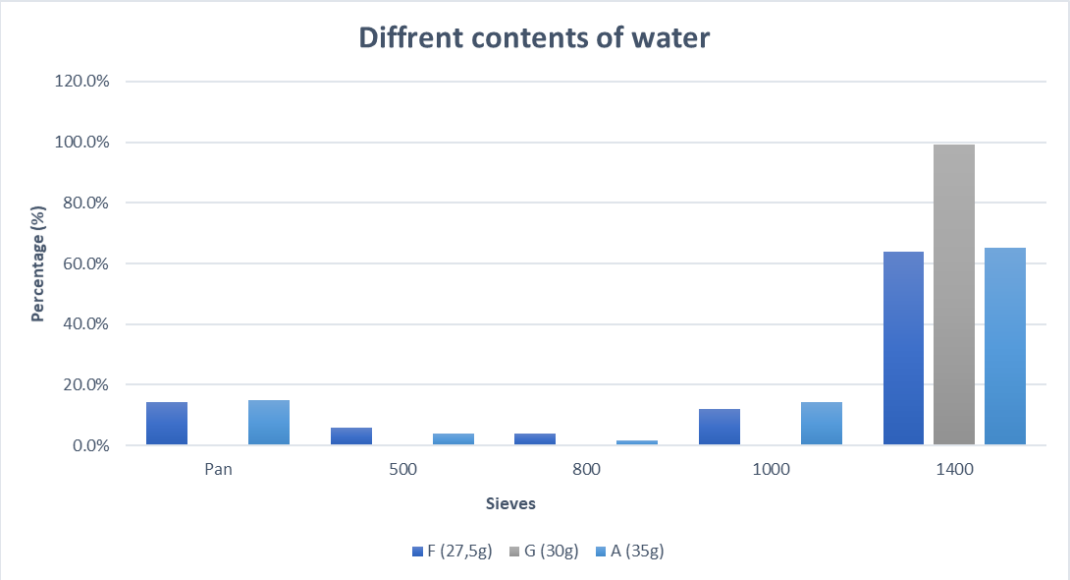


Figure 18 *Size distribution on formulations with different contents of water*

Figure 20 shows the impact of the existence of equilibration time on the size distribution of the pellets produced.

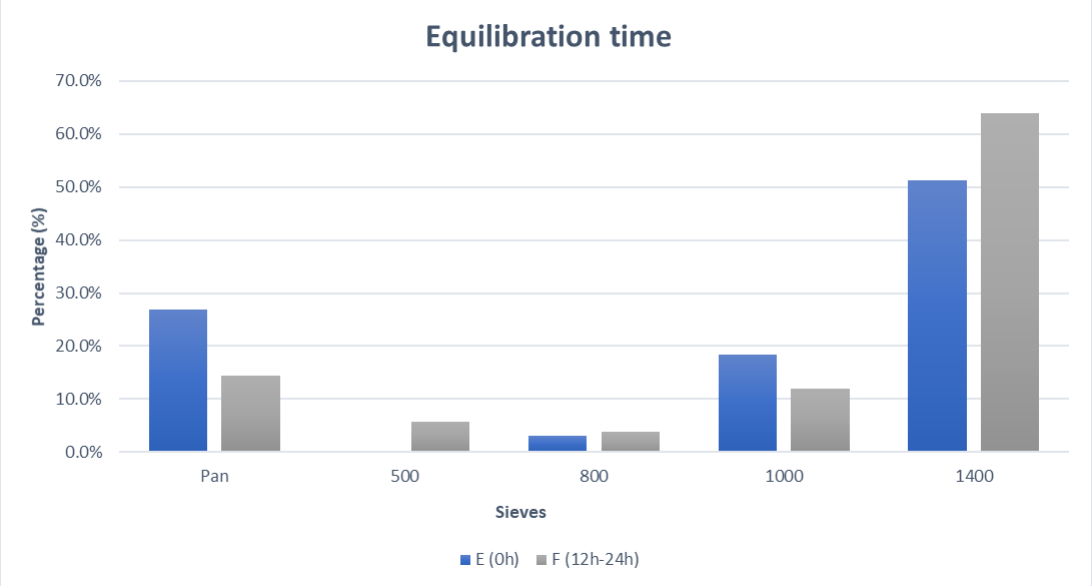


Figure 19 *Size distribution on formulations with different equilibration time*

This study also aims to measure the impact and possibilities that the introduction of a superdisintigrant in the formulation of pellets. Therefore, the next figure shows the impact of increased percentages of sodium croscarmellose in the size of the pellets.

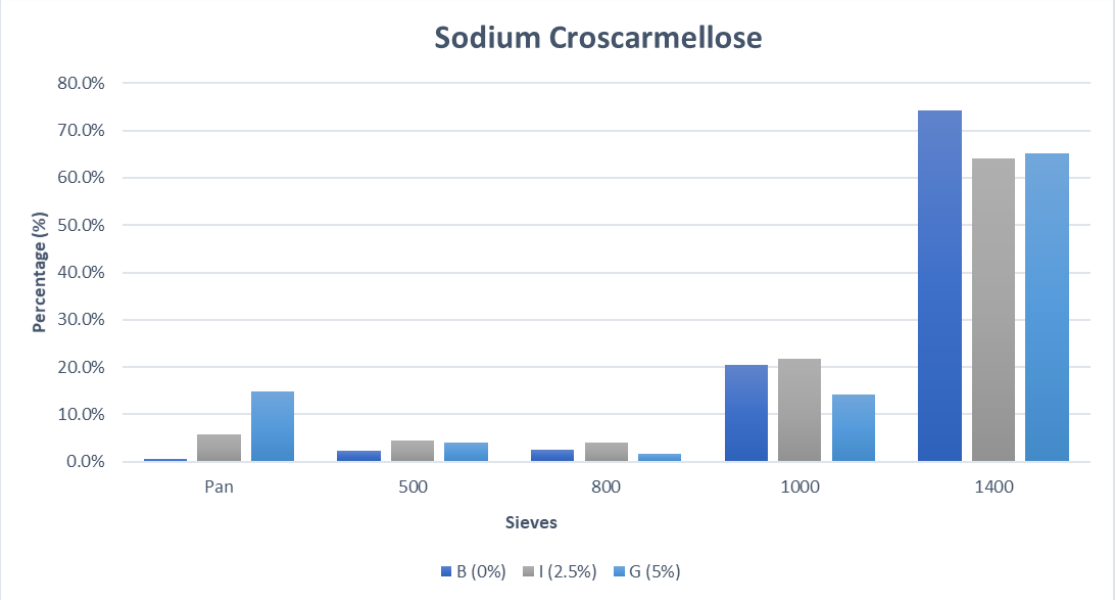


Figure 20 *Size distribution on formulations with different content of sodium croscarmellose*

The extrusion rate was also something that we could vary during the course of this experiment. The results can be found in Figure 22.

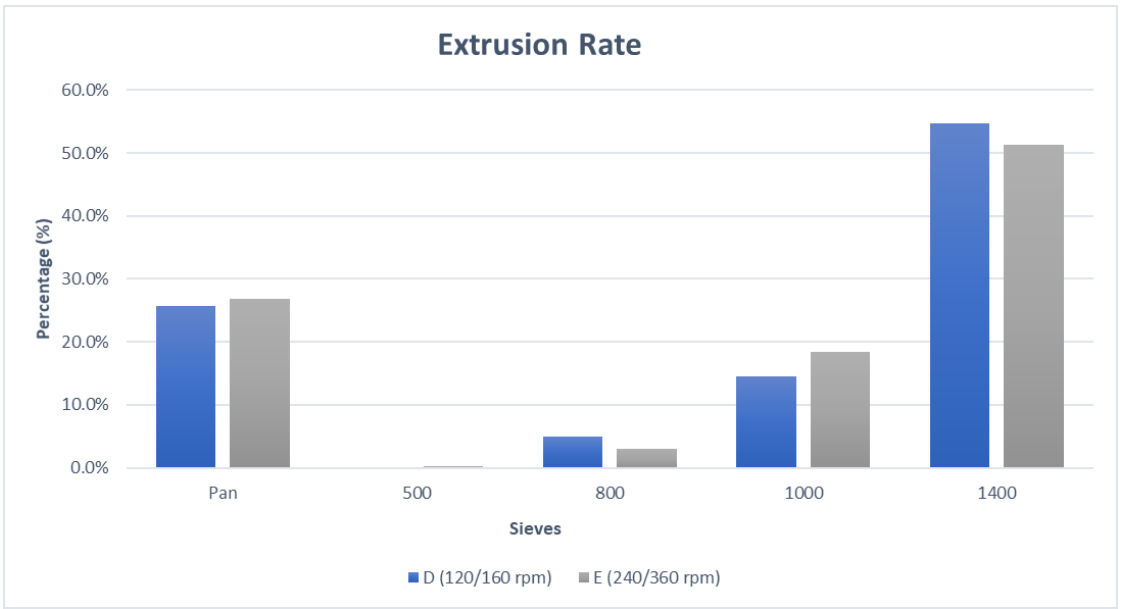


Figure 21 *Size distribution on formulations with different extrusion rates*

As mentioned in the methods chapter, the spheronization rate was also varied in this study. Some of the first formulations did not produce pellets considered to have good quality and, for a number of different factors, including the spheronization rate. Although the size distribution was not that different there were major changes in the consistence of the pellets.

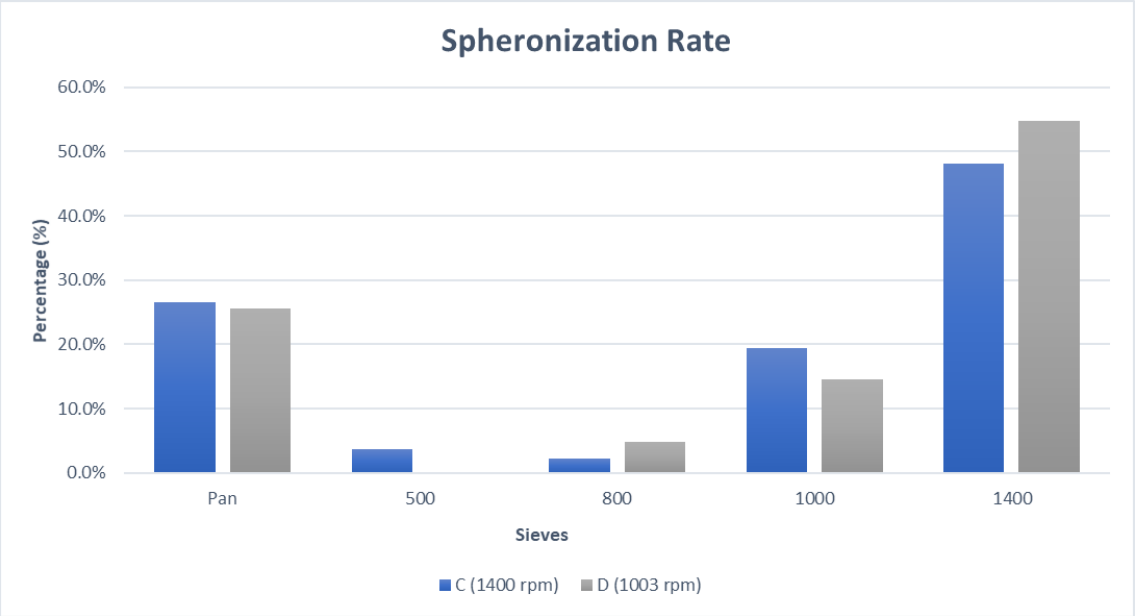
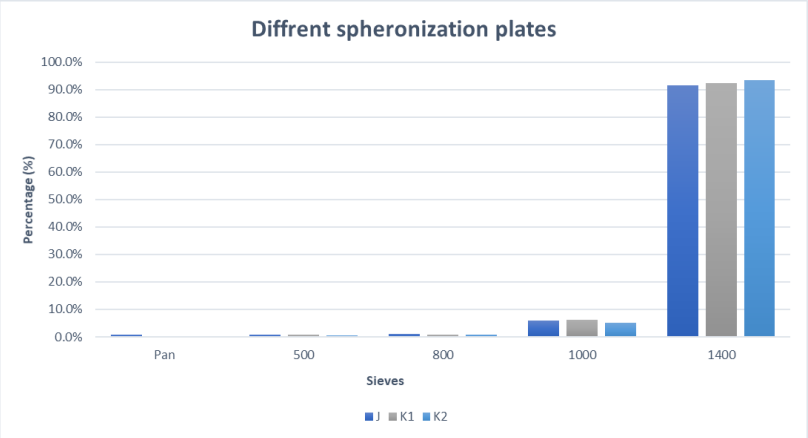


Figure 22 *Size distribution on formulations with different spheronization rates*

There were also different plates available to the spheronizer, so it was also possible to compare the effect of different sized plates in the size distribution.



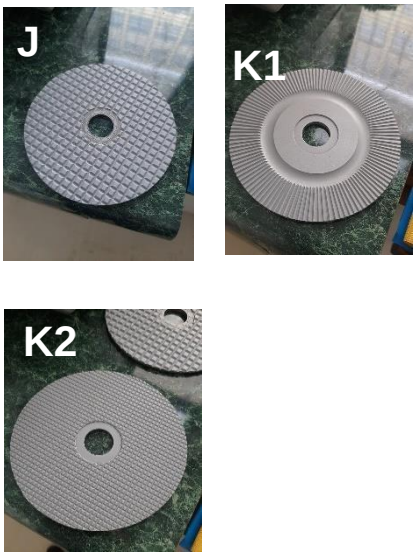


Figure 23 *Differences in the size distribution with the change of the spheronizer plate (J, K1, K2)*

For a general approach, the figure 25. shows the percentage of pellets in the different formulations. We have considered the formulation of pellets to be when they are in the 1000-1400 or higher interval.

The most challenging criteria was the friability of the pellets, as mentioned before most of the times the addition of sodium croscarmellose turn to be a major criterion to increase the proportion of powder in the sieve analysis.

The formulation that produced a higher percentage of pellets was **formulation A (99.7%).** On other hand, **formulation C (67.6%)** has proven to be the one with the lowest yield regarding the formation of pellets. Although formulation A proven to be the one with the higher yield it did not contain sodium croscarmellose, **formulation K2 (98.6%)** was the one that combine the superdisintegrant and a good yield.

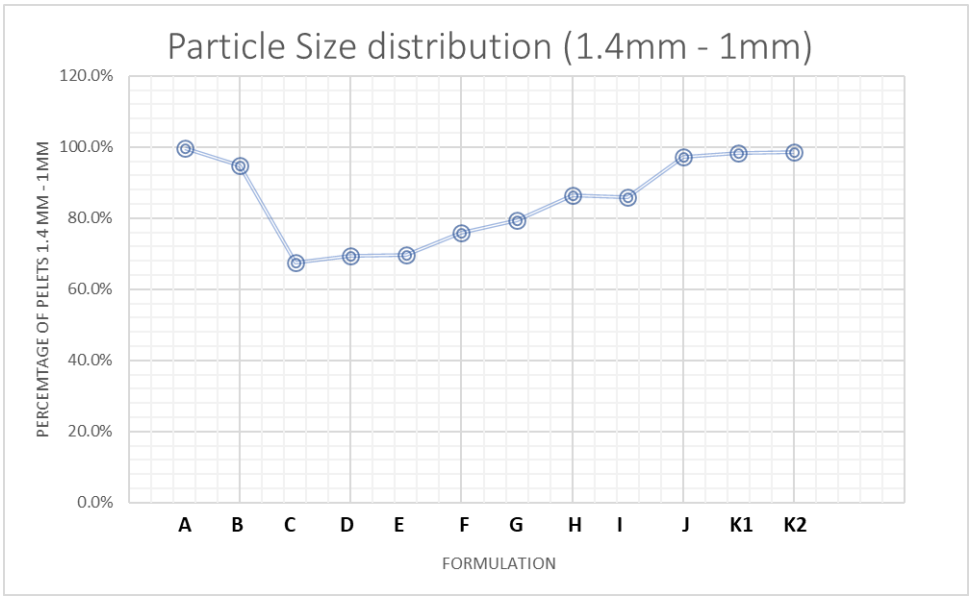


Figure 24 *Different percentage of pellets produced in the formulation produced in the project*

The ability to make pellets is also related with the circularity of the pellets formed, as this is a good way to evaluate if our product is homogeneous. Although the results in general does not show that the pellets were very spherical.

We managed to produce, with formulation K, pellets that have much more sphericity than the ones produced in the beginning this is also linked with the change in the spheronization plate, that allowed a bigger spheronization time with the same load.

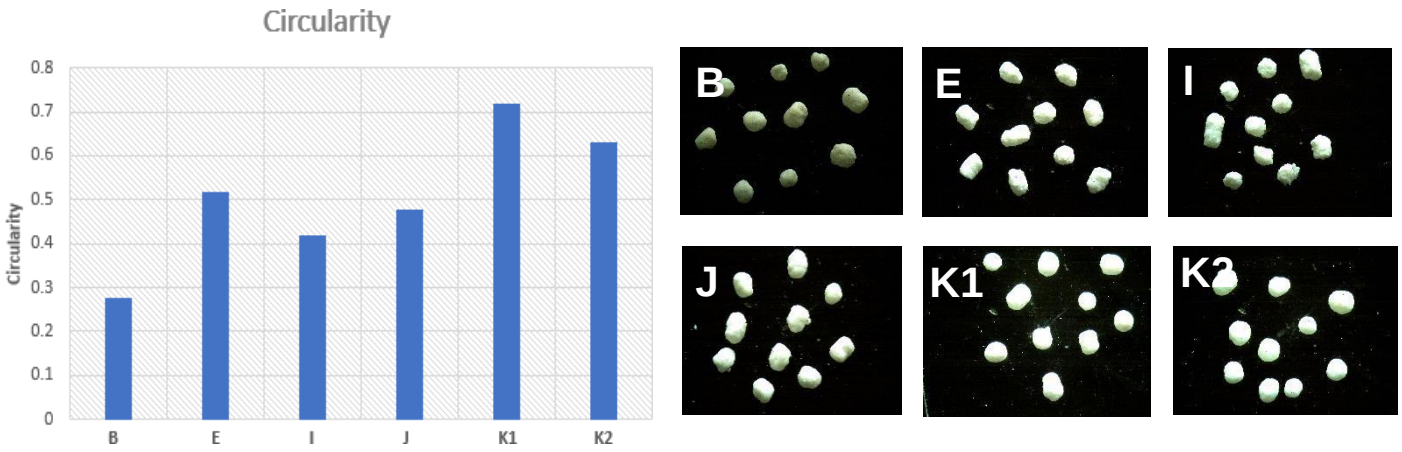


Figure 25 *Analysis on the circularity of the different formulations (left) images collected to calculate the circularity of the pellets (right)*

It was also performed a disintegration test to compare different formulations, the main goal was to choose formulations with no sodium croscarmellose and, if present, different quantities of this compound. For that purpose, we used the formulation B (0% of sodium croscarmellose), formulation F (5% of sodium croscarmellose) and formulation K2 (2.5% of sodium croscarmellose). The results tend to be according to what was expected and were very positive. In the formulation that did not have the super disintegrant after 35 min there was still no change in the structure of the pellets. Increasing the quantity of sodium croscarmellose had a positive effect in the disintegration time, the formulation with 2.5% disintegrate on average (three trials) in 8 min and 30 s and the formulation with 5% disintegrate on average (three trials) in 4 min.

Under a magnifying lent it was also possible to see the differences between the formulations as seen in the figure 26. This disintegration test also showed that the formulation with a bigger content of sodium croscarmellose would disintegrate faster. The test was performed in 60 s, but the formulations with sodium croscarmellose did not show any difference from the 20 s until the end. This test is often use to see the disintegration ability of pellets also (34).

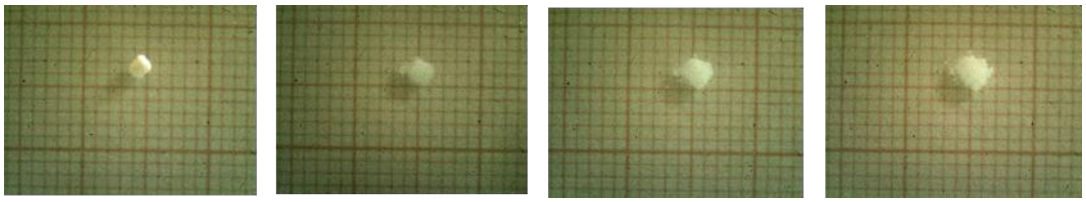


Figure 26 *Disintegration of pellets produced by formulation K2 (2.5% sodium croscarmellose)*

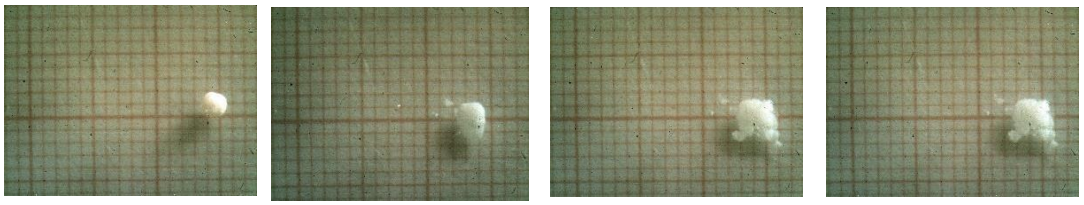


Figure 27 *Disintegration of pellets produced by formulation G (5% sodium croscarmellose)*

The yield of the process was calculated following the same principles indicated in page 33. The formula used was the same in this s part of the project.

Yield (%) = Weight of pellets/ (Weight of drug + Weight of polymers) × 100

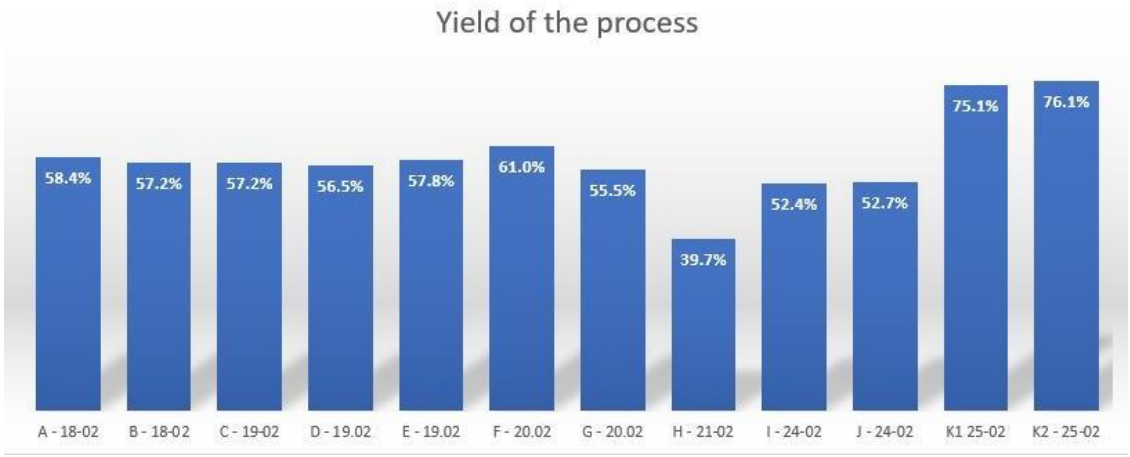


Figure 28 *Yield of the process for different formulations*

It was necessary to know the correct amount of paracetamol on the dry pellets. It is important to fully understand the amount of paracetamol on the final product, although the results that we had were not expected.

It is important also to clarify that there was chosen two different formulations one of them with the addition of sodium croscarmellose. In this table one of the formulations is named as K because the mix of formulation K1 and K2 is the same. They have different spherization plates but the same content in terms of formulation.

Table 7 *Amount of paracetamol in the dried pellets of formulations B and K (K1 and K2)*

Formulation B	Concentration (mg/mL)	Percentage of paracetamol (%)	Average (%)
Sample 1	3927.12	98	99
Sample 2	3888.61	97	
Sample 3	4059.41	101	
Formulation K			
Sample 1	4180.69	105	107
Sample 2	4323.71	108	
Sample 3	4374.31	109	

The formulation B with 5% of sodium croscarmellose, showed a percentage of 99% of paracetamol in proportion with the theorical value, meaning that from the 10 g of paracetamol inserted in the mix, in the end we had 9.9 g.

The formulation K with 2.5% of sodium croscarmellose, showed a percentage of 107% of paracetamol in proportion with the theorical value, meaning that from the 10 g of paracetamol inserted in the mix, in the end we had 10.7 g. This number does not have a significance because it shows impossible data.

There are studies analyzing the release of a substance in this type of matrix but none has percentages above 100% (35).

5. Discussion

Recent studies have tried to show the effect of disintegrants and his role on pellets formulation (36,37). In addition, the studies and articles on co-extrusion do not show an improved knowledge about the technology and are not that numerous in the last few years. A study showed the capability to produce of orodispersible tablets containing ketoprofen with the addition of a superdisintegrant (croscarmellose, crospovidone, or starch glycolate) (38). In this study, although it is described that working with croscarmellose can be difficult due to his hygroscopic characteristics, among the superdisintegrants, croscarmellose contributed most significantly to reduce the disintegration time and to dissolve KTP effectively in 20 min. Other studies have shown the use of sodium croscarmellose for the formulation of pellets (28,39,40).

In the **first part of the project,** it was clear that the assembly of the extruder was one of the hardest processes to learn but with the number of formulations done, the process became to gain consistence and efficiency.

The pellets produced by co-extrusion still did not show the results expected, in terms of formulation and process there is still a need for improvement. The default on the equipment

did not allow the continuation of the research, otherwise the process could have been improved and the results could had shown better date. The properties of the pellets were lacking consistency and the outside layer and inner layer were not separated, this may be due the quantity of water used in the formulation, because there was a mix of content between the two layers. To improve this research project, the number of formulations should be increased to see the effect of changing any material quantity. Although this project does not add on the work made by different studies, there are relevant works showing that it is possible to produce bi-layered self-emulsifying pellets prepared by co-extrusion and spheronization with good properties (41) or to produce pellets by co-extrusion using a hot-melt co-extrusion approach (26).

The pellets obtained by simple extrusion have shown good characteristics - they were uniform and smooth and had a good size distribution. The overall process went according to the expectations and pellets were produced and analyzed.

The use of Croscarmellose sodium had an impact on the fast release and disintegration of the pellets, therefore that is a positive point in this research project, that shown that the addition of Croscarmellose sodium to a formulation of pellets, can improve the release of the active substance like it can be shown in the dissolution test. Even though these facts were observed more work must be put to evaluate the right formulation that can allow more consistent pellets that does not turn to powder with the spheronizer, allowing a longer time of spheronization. The disintegration of pellets was fast even though the percentage of paracetamol released was, in the maximum, 58% more studies must be done to access the consistence of this process, although this research project shows a promising use of Croscarmellose sodium in the formulation of faster releasing pellets as already described in other studies, when it was shown that the addiction of sodium croscarmellose proved to have a positive effect on the release of the active substance (42). A study already mentioned in this work (28) shows data that also finds that although sodium croscarmellose provides a faster disintegration, the amount of substance released is less compared with pellets without this component.

Although these facts, in the future we should compare the dissolution test with pellets without sodium Croscarmellose, to prove the importance of the role of the superdisintegrate in this type of formulation.

At the second part of the project, the process of development of the project was more methodic with more formulations under a different technique with a lot of more data and characterization. This s part developed in Poland was able to show other way to produce pellets with similar conclusions in what's regarding the addition of sodium croscarmellose.

At first there was need to make sure that we adapt the formulation that we used in the

first part of the project to this new reality of a different technique and extruder. After a few days withs a clear that with small changes it was possible to adapt the formulations made in Portugal to fulfill the needs of the new method. In order to help with this transition, it was possible to identify research papers on the differences between extruders that leads to different outcomes (43).

After that, the main goal was to understand the main challenges of the addition of a superdisintegrant in a different technique. Although it is possible to find studies using these types of extruders (44), it is still difficult to find data that can introduce a method to change the formulations according with the type of process. A study showing the outcomes of the same formulation in different extruders could be useful.

Sodium croscarmellose has shown good disintegration ability in the formulation of pellets when used in the right percentage, reflected by a proper balance, due to the small degree of freedom between consistency and disintegration. In our case, the percentage of sodium croscarmellose that we found to be optimal with our conditions was 5%. Bearing in mind that studies showed that it is possible to produce pellets with good properties with 22% of sodium croscarmellose (45), this means that we should look for measures that can improve the stability of pellets while increasing the amount of sodium croscarmellose, in order to understand if that has a positive aspect in the ratio release/stability.

We can assume that the critical factor to produce pellets was the fraction of sodium croscarmellose. It was clear that with this type of extruder, it was required to decrease the fraction of sodium croscarmellose to prevent the production of a considerable quantity of powder, as observed on sieving.

Data suggest that water fraction is something to take in consideration in the development of a pellets formulation (46,47). In our case, the different fractions of water did not have a significant effect on the result. This was unexpected due to the sensitivity of the formulations to the content of water. It also showed that it’s possible to produce pellets with different kinds of water contents, but, with differences on the friability of the final product. Further studies should also focus on more characterization as it may prove that although the yield and size distribution is similar, the final characteristics may vary. A possible explanation is due to the fact that although we have made formulations with different water content, the changes were not relevant enough in order to have an impact in the final result.

The equilibration time for powder blends proved to be an important factor of the process, as observed in the output of sieving, underpinning the relevant role in the process of extrusion-spheronization with a large effect on the quality of the pellets containing sodium croscarmellose in the formulation. This factor has proven to be an important discovery in this project has there is very low research on this indicator especially his connection regarding the production of pellets. Although this factor showed to be an important one in our research, there

are not major studies on the effect of equilibration time on the production of pellets.

As it was mentioned before, even though there was not concrete data to substance this affirmation, the higher the extrusion rate the more compacted the extrudates obtained. This has shown to be an important factor to decide the extrusion rate that we were going to use in this project. This factor was already described in the literature under a Quality By Design approach (48).

The spheronization rate did not impact on the pellets quality. However, more detailed studies should be carried on. The spheronization plate however has shown a big impact in the ability of spheronizing the extrudates with impact on the fraction of good quality pellets manufactured. Data of recent studies shows that higher rates of spheronization can be critical for the physical stability of the pellets (49).

The circularity has varied between 0.25 to 0.75, reflecting the evolution in the process for a limit of 5% sodium croscarmellose in formulations, above which pellets became non homogenous. Even though a circularity of 0.75 is not ideal, this was the last formulation to be made in this project. Which gives a hope that if the work had continued with more formulations and a better understanding of the technique, the circularity of the pellets could be improved. But considering the first results there was a big change and better results throughout the course of the project. These best values are above the ones that are mentioned in the literature as acceptable, defining an lower value in the 0.6 (50).

The disintegration time of pellets decreased with increased fraction of sodium croscarmellose. Without the disintegrant pellets failed to disintegrate. This is a key finding to proof, like in other studies performed (28,51), that the addition of a super disintegrant can play a role on the fast release of some medicines like paracetamol.

Studies show the importance of permeating tests related with the settling volume of sodium croscarmellose (52). The test proved that sodium croscarmellose still pass the pharmacopoeia test for settling after drying, emphasizing the ability of this disintegrant to be used in wet masses prepared for extrusion and spheronisation.

Even though the project has proven to build up on other different studies, more work is needed to confirm these findings.

Small changes in this process could have a huge impact on the result, so a Quality by Design approach could be a good strategy to have full knowledge of the process and his vulnerabilities and opportunities. The full knowledge of this process would give us the capability to change different details in the project to improve the final characteristic of this pellets. This is something that its already described in the literature (48) and can improve a future work by creating a closed and control environment that can provide better outcomes.

6. Conclusions

It was possible to understand and perform two different techniques of extrusion and spheronization and to briefly understand the key principles of co-extrusion. In both phases of the project, it was possible to produce pellets with good characteristics and with the addition of sodium croscarmellose.

The production of pellets in the first part was the beginning to understand the role of sodium croscarmellose in the formulations.

In both phases we achieved formulations that suit our expectations and produce pellets with good characteristics to perform dissolution studies. In the first phase the weakest point was the lack of comparison, in dissolution studies, of pellets with or without sodium croscarmellose has the studies were only performed in pellets with the super disintegrant.

Even though the production of pellets made by co-extrusion was not entirely a success, the process was understood, and it was also possible to produce extrudates that had similar characteristics with the main goal of co-extrusion.

The 2nd part has shown to be more developed and therefore there are more conclusions regarding the different factors there were in study.

Pellets with sodium croscarmellose proof to have a more disintegrant behavior and, at the same time, showed a good stability after drying. There were some key findings of changes that had an impact on the size distribution of the pellets. The fraction of sodium croscarmellose (in the first assay), the equilibration time, the extrusion rate, and the plate of the spheronizer had an impact a therefore are critical to control in the production of this pellets. It could not be proven that changes in the water content and the extrusion rate and spherization rate had an impact on the result.

At the end we were able to produce pellets with yields going as much as 85.9% and 75.1% in the s part, and that showed circularity of 0.72. In some formulations the yield of pellets achieved rise to 98.6% if we take out the losses and exclude the powder and fractions that do not match the characteristics needed to be considered a pellet.

It was possible to see that the disintegration time was very different in the pellets with sodium croscarmellose which proof the critical role of adding a super disintegrant in a formulation like these. Further studies should continue this work to study other characteristics of this kind of pellets and to perform dissolution broader tests that can proof the controlled release of medicines like paracetamol with the use of pellets containing sodium croscarmellose.

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8. Annex

First part of the project

A1. Calibration curve

It was prepared a mother solution with 15.2 mg of paracetamol for 1 L of phosphate buffer, then there were made five dilutions to build the calibration curve. To volumetric flasks of 25 mL were prepared the solutions for the curve (Table A1).

Table A 1 *Concentrations of the different solutions of paracetamol of the calibration curve*

Solution	*Volume of the mother solution (mL)*	*Concentration (mg/mL)*
1	5	3.04
2	10	6.08
3	15	9.12
4	20	12.16
5	25	15.20

The calibration curve was obtained according to the following equation:

$$Y = 0.0612X + 0.0452$$

Where X was paracetamol concentration and Y the absorbance ($R^2 = 0,9892$)

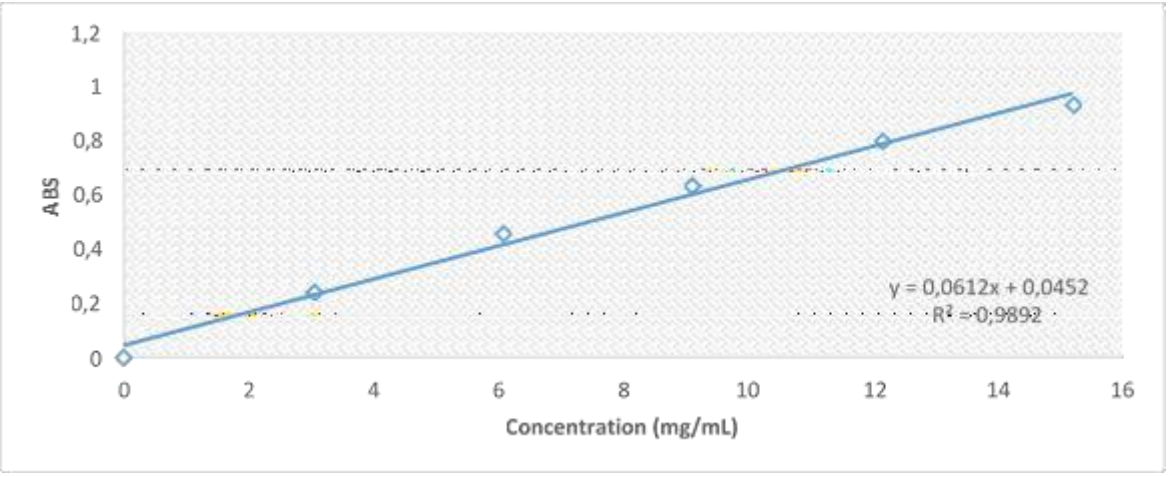

Figure A 1 *Calibration Curve of the paracetamol solution.*

The calibration curve to convert the absorbance in the samples taken from the dissolution test into concentrations and then into paracetamol mass.

Three samples were diluted to enable reading in UV-Spectrophotometer, each one read 3 times.

After testing different dilutions, the method was set as a solution made of 1mL of the sample + 19 mL of phosphate buffer (Dilution 1/20).

A.2 Raw dissolution test data

Table A2 summarizes the data of the absorbance of every sample at different time points.

Table A 2 *Absorbance of each sample of the dissolution test by time that the samples were collected.*

	Sample 1				Sample 2				Sample 3			
Time (min)	Abs 1	Abs2	Abs3	Average	Abs 1	Abs2	Abs3	Average	Abs 1	Abs2	Abs3	Average
0	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
5	0,594	0,587	0,590	0,590	0,602	0,617	0,620	0,613	0,589	0,601	0,604	0,598
10	0,745	0,732	0,735	0,737	0,690	0,684	0,682	0,685	0,685	0,689	0,681	0,685
15	0,773	0,760	0,764	0,766	0,780	0,788	0,785	0,784	0,783	0,785	0,785	0,784
30	0,780	0,773	0,774	0,776	0,785	0,783	0,779	0,782	0,784	0,789	0,783	0,785
60	0,780	0,782	0,776	0,779	0,782	0,781	0,778	0,780	0,783	0,785	0,781	0,783
90	0,774	0,775	0,770	0,773	0,785	0,784	0,789	0,786	0,787	0,781	0,779	0,782
120	0,794	0,790	0,792	0,792	0,788	0,801	0,803	0,797	0,785	0,780	0,782	0,782
150	0,778	0,790	0,785	0,784	0,780	0,785	0,787	0,784	0,800	0,803	0,799	0,801
180	0,801	0,795	0,797	0,798	0,807	0,803	0,806	0,805	0,802	0,803	0,805	0,803
210	0,804	0,803	0,800	0,802	0,792	0,794	0,791	0,792	0,795	0,797	0,794	0,795
240	0,802	0,801	0,809	0,804	0,795	0,800	0,807	0,801	0,793	0,794	0,796	0,794
360	0,790	0,801	0,790	0,794	0,811	0,813	0,804	0,809	0,802	0,803	0,802	0,802

With the data of the average of each simple it was calculated the standard deviation between the averages in each time and also the medium deviation. The color scale shows the difference between the different deviations (Table A3).

Table A 3 *Standard deviation and medium deviation between the averages of absorbance of the 3 samples over time*

Time (min)	Average (ABS)	Average (ABS)	Average (ABS)	Standard Deviation	Medium Deviation
0	0,000	0,000	0,000	0,0000	0,0000
5	0,590	0,613	0,598	0,0115	0,0084
10	0,737	0,685	0,685	0,0301	0,0232
15	0,766	0,784	0,784	0,0108	0,0083
30	0,776	0,782	0,785	0,0049	0,0036
60	0,779	0,780	0,783	0,0019	0,0014
90	0,773	0,786	0,782	0,0067	0,0050
120	0,792	0,797	0,782	0,0076	0,0055
150	0,784	0,784	0,801	0,0095	0,0073
180	0,798	0,805	0,803	0,0040	0,0030
210	0,802	0,792	0,795	0,0051	0,0038
240	0,804	0,801	0,794	0,0049	0,0036
360	0,794	0,809	0,802	0,0078	0,0054

The graphic of the variation of the standard deviation over time presents the higher deviation at 10 min (Figure A2). In general, the deviations are acceptable due to the characteristics of this experiments and different sizes of pellets.

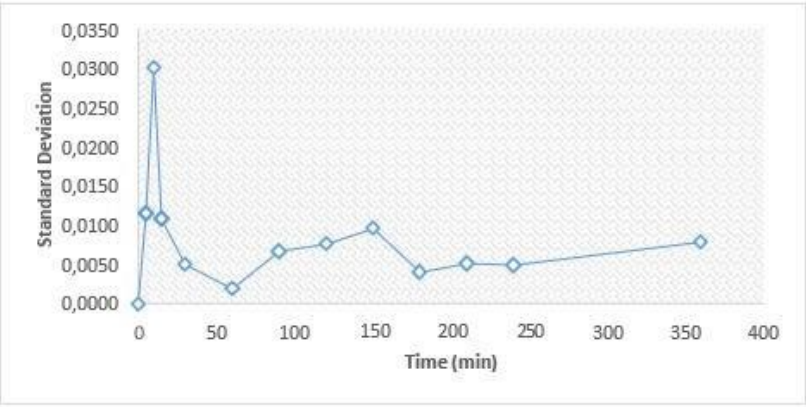

Figure A 2 *Standard deviation over time*

Second part of the project

A3. Water content on the raw materials

The samples were dried until constant weight, and the water content was calculated by the difference of the masses.

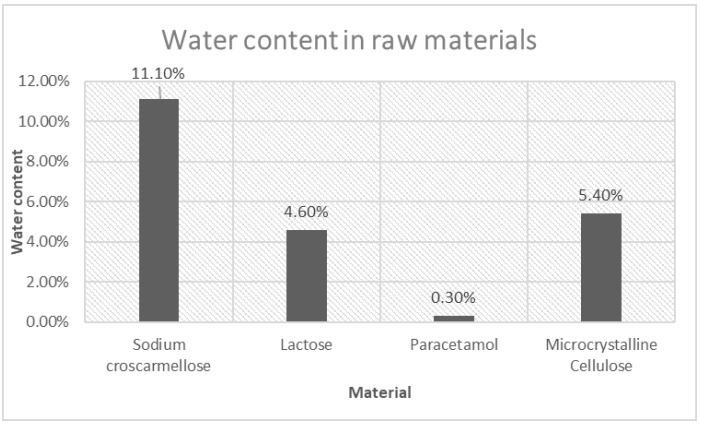

Figure A 3 *Water content in raw materials.*

The values of water content proof to be in the range required.

A4. Settling volume

The results shown that the average settling volume of raw sodium croscarmellose was 25 cm3 which agrees with the value described in the literature.

It was also performed a test on pellets, but it was not successful due to the interference of lactose in the fluid, It was not possible to see the final settling volume, therefore we can confirm that this test is only able to be used in raw material.

A5. Calibration curve

A stock solution was prepared (1.52 mg of paracetamol / 100 mL of phosphate buffer) enabling the production of 5 diluted standards enabling the construction of the calibration curve (Table A4).

Table A 4 *Concentrations of the different solutions of paracetamol of the calibration curve*

Sample	*Volume of the mother solution (mL)*	*Concentration (mg/mL)*
1	5	3.04
2	10	6.08
3	15	9.12
4	20	12.16
5	25	15.20

From the calibration curve the following equation was obtained:
$Y = 0.0606\ X + 0.0058$

Where, X was the paracetamol concentration in the standard solution and Y the absorbance ($R^2 = 0,9986$).

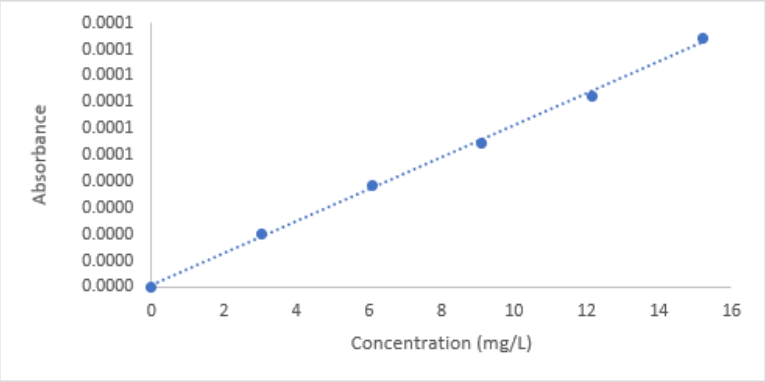

Figure A 4 *Calibration Curve of the paracetamol solution.*

A6. Quantification of paracetamol

The expected mass of paracetamol in the pellets was 10 g in 50 g (20%).

In a flask a solution containing 200 mg of paracetamol in 50 mL of the buffer was prepared and then diluted (1:500).

Table A 5 *Quantification of paracetamol solution*

Formulation B						Multiply by the dilution factor	
Sample	Absorbance	Average	Deviation	Total Deviation	Concentration (mg/L)	Dilution (mg/L)	Percentage
A1	0.4861						
A2	0.478	0.4818	0.0041		7.8542	3927.1177	
A3	0.4812						98%
B1	0.4793						
B2	0.4756	0.4771	0.0019	0.0097	7.7772	3888.6139	
B3	0.4764						97%
C1	0.4997						
C2	0.4973	0.4978	0.0017		8.1188	4059.4059	
C3	0.4964						101%

Formulation K						Multiply by the dilution factor	
Sample	Absorbance	Average	Deviation	Total Deviation	Concentration (mg/L)	Dilution (mg/L)	Percentage
A1	0.5184						
A2	0.5108	0.5125	0.0053		8.3614	4180.6931	
A3	0.5083						105%
B1	0.5322						
B2	0.5283	0.5298	0.0021	0.0111	8.6474	4323.7074	
B3	0.529						108%
C1	0.5381						
C2	0.5319	0.5360	0.0035		8.7486	4374.3124	
C3	0.5379						109%