Formulation and evaluation of fast disintegrating tablets for a pharmaceutical product.

Degree Project in Applied Nutrition and Food Chemistry

KNLM01

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Frequently used terminology

APL blend: The initial pharmaceutical powder blend that has already been developed.
Powder blends: The new formulations that were tested during the main trials of this project.
Composite: the word is used here to describe the two pharmaceutical products Combilac® and Prosolv® that were added in the powder blends.
Tablet press: the machine that was used to make the tablets.
Compression level: refers to the adjustment of the tablet press that regulates the applied pressure of the press during compaction.
Treatments: referring here to the 24 different combinations of composites, disintegrants and compression levels (2x3x4) of the main trials.
Tablet hardness (also seen in the literature as breaking force, crushing strength or tablet strenth): the minimum force that needs to be applied diametrically on a tablet in order to break.
Combinations of disintegrants: the three different selections of disintegrants in this present project; crospovidone 4%, crospovidone 2% and croscaramelose sodium 2%, croscaramelose sodium 4%.
Compression: is used to describe the process of volume reduction of a powder.
Compaction: is used to describe the whole process of powder transformation into a tablet, including the subsequent establishment of bonds.

Abstract

A new pharmaceutical product suitable to act as a negative contrast agent for Computerized Scan (CT-scan) of the abdomen is under development. At the moment the product has the form of a powder, which when dispersed in water and whipped, gives a stable foam. The foam is ingested by individuals who are about to undergo a CT-scan, as a prior preparation step. The powder form has disadvantages such as dosage accuracy and the idea is to develop a tablet that will solve this issue and permit the automatization of foam preparation. At this stage, the aim was to investigate the possibility of making functional tablets of adequate hardness, low friability that will disintegrate rapidly when immersed in water. After whipping the foam should have acceptable properties, in terms of foamability and stability.

The tablets were produced by direct powder compression. Different excipients were added to the initial powder blend to improve disintegration time, hardness, friability and facilitate tableting operations. Two different composites that act as binders were used in an attempt to improve disintegration time and powder compactability. Three different combinations of two disintegrants were tested to investigate which one gives the best disintegration results. A lubricant was also used to reduce adhesion of the powder to the tablet press. Lastly four different compression levels were applied on the powder blends to specify the optimum that gives fast disintegrating tablets of adequate hardness and friability.

The results show that the initial powder blend (mentioned as APL blend) has good flowing properties but poor compactability which gives as a consequence tablets of low hardness and unacceptable friability, that do not disintegrate. The powder blends with the added excipients that were tested show fairly good flowing properties, greatly improved compactability, that resulted in enhanced hardness and friability and vary in time that they need to disintegrate. Optimal levels of compression are indicated for a fast disintegrating, good quality tablet. Foamability remains in acceptable levels even though reduced by the addition of excipients. Foam stability measured three hours after whipping was not significantly influenced.

Popular abstract

A new pharmaceutical product that acts as a contrast agent for examining the small intestine is being developed by an R&D company. Currently the product exists as a powder form which is poured into water and whipped in order to produce a stable drinkable foam as a preparation step before the scanning of the abdomen.

There is a keen interest in developing a tablet from this powder. The reason behind this is that a tablet is more accurate in terms of the dosage and can be used by a dispensing machine, that will automatically produce the final foam, without the need for engaging a nurse.

Some preliminary trials of tablets made with the existing powder showed that the ingredients when compressed in a tablet form do not facilitate the breaking down of the tablet when immersed in water. These ingredients hinder the penetration of water into the core of the tablet, making the whole project not feasible. The same happened after the addition of pharmaceutical ingredients that help the tablets to break down. Thus, there was a need to alter the formulation by adding composites that promote a fast break down.

This project was about comparing different pharmaceutical ingredients (excipients) and compressions to distinguish which combination gives tablets of the best quality, which will be hard enough not to brake during handling but at the same time they will break down as fast as possible when in water. Finally, an important parameter for the functionality of this product was that the foam should be unaffected as much as possible by the addition of these ingredients. The ability to produce a good quality of foam that will be stable long enough was also measured to ensure that the product would not lose its principle purpose.

1. Introduction

A new food-based pharmaceutical product is being developed by Aventure AB. It is a per-oral contrast agent for abdominal Computed Tomography (CT) examination. The product marks off the bowel lumen from all the other inner abdominal tissues and organs making it clearly visible on the CT-images. A phase IIa clinical study of the product was recently finalized.

The product was distributed to the hospital for clinical study in liquid form as a dispersion and a foam was produced out of it by aerating the dispersion, right before the administration to the person who is to be examined. Nevertheless, a liquid form has limited shelf-life, requires chilled storage and includes high transportation costs. Furthermore, preparing the foam occupies the personnel and requires training and equipment. As a first step and in order to surpass these disadvantages, a powder form of the product has been developed and tested. Subsequently, the company is seeking to formulate it into a tablet, which among others has the benefits of accuracy in dosage and suitability for automated preparation of the final foam by a dispensing machine.

1.1. Theoretical background

The product

Product x is a micro-foam, composed of water, phosphate salts as buffer agent (K_2HPO_4:NaH_2PO_4 (75:25), 0.05 M, pH:7.3), Egg Albumen Protein (EAP) or Egg White Protein (EWP) Xanthan Gum (XG) and flavouring. Egg White Protein has excellent foaming properties. Its proteins demonstrate relatively high hyrdophobicity, especially when they are partially denatured, having the ability to diffuse rapidly towards the air-water interface and remain adsorbed (1). Xanthan gum is a polysaccharide soluble in cold water confering high viscosity at low concentrations, due to its very high water binding capacity (10) and in this formulation it plays a role in stabilizing the foam.

Table 1.1 Ingredients of the Product x powder blend.

Ingredient	Amount (g) for 500ml of dispersion	% (w/w) of dry solids
$NaH_2PO_4.2H_2O$ (Dr. Paul Lohmann)	Classified information	
Xanthan gum (XG) (Xantural®11K, Kelco)		
Egg Albumen Protein (EAP-HGI) (Pulviver)		
K_2HPO_4 (Dr. Paul Lohmann)		
Mango flavour (Sensient)		
total		

The first step of the preparation is to disperse the ingredients, which are in dry powder form, in water and as a second step to incorporate air into the system by whipping the

dispersion. The amounts of dry solids in 500 ml of dispersion as well as the relative amounts of the powders are shown in table 1.1.

The purpose of this product is to create a contrast in the gastrointestinal gut owing its attribute to the air content. The differences among positive, neutral and negative contrast agents lay on their radiodensity that is measured in Hounsfield units (HU) as shown in the grey scale in figure 1.1.

Figure 1.1: Haunsfield scale and Product x

According to the Hounsfield scale, air is the optimum negative contrast agent for CT-scan. In this respect Product x is placed around -400 HU giving a very good contrast of the bowl (4). An image of CT-scans taken by using Product x and other contrast agents is given in the appendix.

Product x is aimed to have no or minimum side effects, be non-expensive, acceptable for the patient and have high imaging quality by giving a negative luminal contrast after ingestion (4).

Powder properties

The properties of the powder are important for pharmaceutical applications and apart from proper mixing and compaction, good flowability is necessary as it ensures that the tablet manufacturing operations are not hindered. Moreover, problems in flowability of the powder may cause variations in mass of tablets, leading to non-homogeneous tablets and of uneven mechanical strength and disintegration time (2).

In order to characterize flowability of a powder a number of parameters can be determined such as the angle of repose and Hausner ratio along with the bulk density. Angle of repose is a simple measure of powder flow, but it is based on scientific principles (2). A particle will begin to slide when the angle of inclination is large enough to overcome frictional forces and it will stop its motion when the angle is below that required to overcome cohesion and adhesion to other particles (2). The bulk density of a powder refers to the amount (mass) of a free-flowing powder per occupied volume and depends on particle properties (size, shape, cohesiveness and adhesiveness). Conversely, when a powder is forced to consolidate by tapping, it changes its packing geometry, that is, it packs more tightly reducing the void

space between particles. In figure 1.2 we can see two powders of the same particle size distribution and porosity but different packing properties. The ease with which a powder consolidates can be used as an indirect method of quantifying powder flowability (2). Hausner found that the ratio of tapped density (ρ_{tapped}) to free-flowing density ($\rho_{free\text{-}flowing}$) is related to interparticulate friction (2). Thus, he was able to demonstrate that the following ratio was predictive to powder flowability:

$$Hausner\ ratio = \frac{\rho_{tapped}}{\rho_{freeflowing}}$$

This means that powders with low interparticulate friction have small values, while more cohesive, less free flowing powders have larger values. Table 2.1 below shows the classification that Hausner introduced and the values expected from powder blends with the corresponding flow characteristics.

Table 1.2: Hausner ratio and flow characteristics of powders.

Flow characteristics	Hausner Ratio
Excellent	1.00 - 1.11
Good	1.12 - 1.18
Fair	1.19 - 1.25
Passable	1.26 - 1.34
Poor	1.35 - 1.45

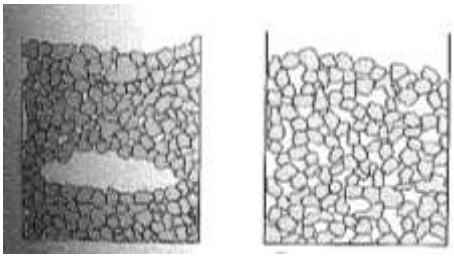


Figure 1.2: two powders with equidimensional powders having the same porosity but different packing properties. (taken from Aulton's Pharmaceutics 2007, Chapter 12)

Tablet compaction and properties

Tablets are normally manufactured by powder compression. In the literature, the term compression is often used to describe the process of volume reduction and the term compaction is used to describe the whole process, including the subsequent establishment of bonds **(Mattson).** The forced particles come into close proximity forming interparticulate bonds which provide coherence to the powder. This process enables the formation of a porous specimen of defined geometry, the tablet.

The main techniques that are used in making tablets are direct compaction and granulation. Different methods of granulation also exist and generally aim at improving flowability and bulk density of a poor flowing powder, improving mixing homogeneity and reducing segregation of a powder and increasing compactability. Although all these are desirable in tableting applications, granulation is often not chosen in order to simplify the operations and reduce manufacturing costs (2).

The compaction of the tablets is made by using a tableting press (figure 1.3). This comprises of the die and the two punches, the lower and the upper, by which the compressive force is applied. The hopper is filled with powder and a cycle begins when the lower punch is immersed into the die, the hopper moves above the die and the powder flows into the die as a result of gravity. At this stage the lower punch is at its lowest point. The compression begins when the upper punch immerses into the die compressing the powder into a tablet. Then both lower and upper punch are moving upwards releasing the newly formed tablet from the die which is ejected by the hopper and a new cycle begins.

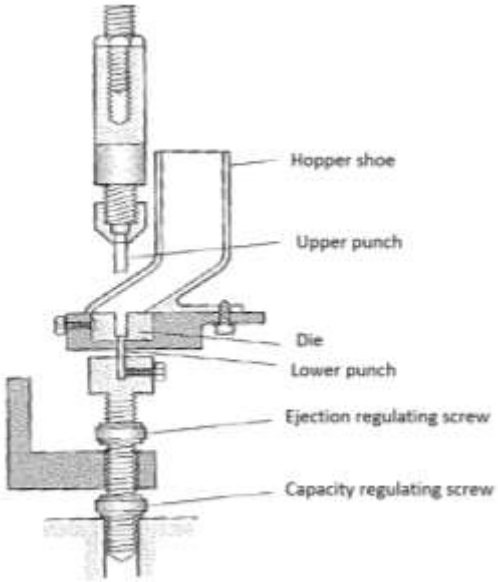


Figure 1.3: Single punch direct press (taken from Aulton's Pharmaceutics 2007, Chapter 30)

The hardness of a tablet (breaking strength) composed of a certain material can be used as a measure of the compactability of that material (2). A powder with a high compactability forms tablets with a high resistance towards fracturing and without tendencies to cap or laminate (figure 1.4). In practice the most common way to assess powder compactability is to study the effect of compaction pressure on the hardness of the resulting tablet, as assessed by the force needed to fracture the formed tablet. Volume reduction takes place by various mechanisms and different types of bonds, like solid bridges, intermolecular and electrostatic forces and mechanical interlocking may be established between the particles depending on the pressure applied and the properties of the powder (2). The durability of the tablets is also tested by using the friability test, which is described in section 2.4. During tableting operations such as transport and packaging the tablets experience friction which may result in reduced quality. The friability test measures the loss of mass after the spinning of the tablets in a drum with specific conditions of rotation speed and time, and an acceptable level by the pharmaceutical industries is below 1% of mass loss. The tendency for friability can be reduced by a better design of the shape of the tablet or improved binding capacity of the powder blend.

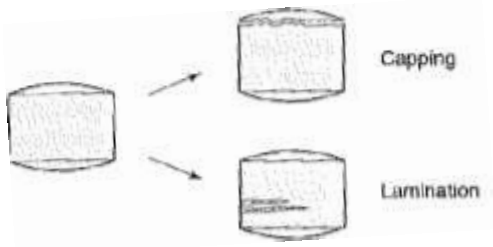


Figure 1.4: Tablet flaws of capping and lamination due to poor compactability or flowability of the powder. (taken from Aulton's Pharmaceutics 2007, Chapter 30)

Disintegration of the tablet is an important property, especially for the case of Product x, as the intended use is to dispense the tablet into the water, the tablet should rapidly disintegrate to create a dispersion, which will be whipped to produce the final foam. In order to assess this property, disintegration tests have been developed and are used in the pharmaceutical industry, which give reproducibility and comparable results between different formulations and they are described in the European Pharmacopeia (3).

Excipients used in tableting

Excipients are added in the powder blends that are intended for tableting, in order to improve the properties of the blends and the tablets and facilitate tableting operations. In the case of Product x four categories of excipients were deemed to be essential, the disintegrants, binders, glidants and lubricants. A disintegrant is used to ensure the breakage of the tablet into small particles when in contact with a liquid, thus increase surface area facilitate dissolution of soluble substances and dispersibility of the other ingredients in the dispersion (8). A binder acts as an adhesive in powders that are intended for tableting and ensures that the tablet has the mechanical strength that is required, improving compactability (2). A glidant is added to improve flowability of a powder, ensuring proper mixing and high production speed (2). Lubricants are also added in almost all tablet formulations, since they provide low friction between the tablet and the parts of the tableting press that come into contact with, like the die wall and the punches and it is necessary for a smooth operation (2). In each of these categories there is a number of commercial substances available with different characteristics. One of the challenges in developing the new formulation of the product is not to hinder foamability and foam stability of the dispersion due to the introduction of excipients into the system, which depends on the powder blend. Thus, foamability but also foam stability are factors that need to be investigated as they will probably influence the imaging capacity of the CT-scan.

1.2. Aim of the thesis

The aim of this master thesis was to assess in total the feasibility of formulating a functional tablet out of the already developed Product x powder. The parameters that were important at this preliminary stage and need to be analysed and reported are listed below:

- the flowability of different powder blends, to ensure a smooth tableting operation.
- the tablet properties of weight, hardness, friability and disintegration time.
- the addition of excipients should not hinder the foamability and stability of the foam which has specific properties (air percentage, overrun, bubble size etc.) for a successful examination.

2. Materials and methods

2.1. Powder blends

As a preliminary work, tablets were made (as described later in the section 2.3) by using the powder blend of Product x (table 1.1) without the addition of any excipients, which was produced by the company APL (Sweden) and in this report it will be referred to as APL blend. The tablets were evaluated in terms of their tablet hardness, friability and disintegration time and they are presented in the results section. As a second step and in order to overcome problems that occurred in the disintegration time and poor compactability of the APL blend tablets, different powder blends were made with the addition of excipients. In this respect, different blends with sugars (maltose monohydrate, Sigma Aldrich, USA), (lactose monohydrate, Sigma Aldrich, USA), (fructose, Sigma Aldrich, USA) and highly specialized composites of different concentrations were tested. The composites that were tested were Combilac® (Meggle, Germany) and Prosolv® (JRS, USA). The disintegrants used were crospovidone (Kollidon®, Basf, Germany) and croscaramelose sodium (Vivasol®, JRS, USA), and as lubricant sodium stearyl fumarate (Pruv®, JRS, USA). The different powder blends that were tested in the main trials of this project are shown in table 2.1.

Table 2.1: Powder blends that were tested in the main trials.

Abbreviation	**Composite** (w/w)	**APL blend** (w/w)	**Disintegrant(s)** (w/w)	**Lubricant** (w/w)
C1, CP	50% **Combilac®**	45%	4% Crospovidone	1% sodium stearyl fumarate
C1, CP & CCS	50% **Combilac®**	45%	2% Crospovidone & 2% Croscarmelose sodium	1% sodium stearyl fumarate
C1, CCS	50% **Combilac®**	45%	4% Croscaramelose sodium	1% sodium stearyl fumarate
C2, CP	50% **Prosolv® EASYtab SP**	45%	4% Crospovidone	1% sodium stearyl fumarate
C2, CP & CCS	50% **Prosolv® EASYtab SP**	45%	2% Crospovidone & 2% Croscarmelose sodium	1% sodium stearyl fumarate
C2, CCS	50% **Prosolv® EASYtab SP**	45%	4% Croscaramelose sodium	1% sodium stearyl fumarate

Prosolv® EASYtab SP* (JRS, USA): Microcrystalline cellulose, Coloidal sillicon dioxide, Sodium starch glycolate, Sodium stearyl fumarate.

Combilac® (Meggle, Germany): 70% alpha-lactose monohydrate, 20% microcrystalline cellulose (MCC), 10% white native corn starch.

***** relative proportions are not given by the company

The selection of compositions of the six powder blends (types of excipients and concentrations in the blend) were based on the results of preliminary trials. As mentioned before, the disintegration time is considered to be crucial for the development of the Product x tablet and in this respect, Combilac® and Prosolv® gave the best overall results in disintegration time, powder flowability and compactability.

2.2. Preparation and characterization of powder blends

Preparation of blends

The powder blends were made by mixing the different ingredients in a 1.5 L PET jar. The jar was manually shaken to random directions for 6 cycles of 30 seconds shaking and 4:30 minutes of rest. Each powder blend was then stored in a PET container under airtight conditions to avoid absorption of ambient moisture.

Angle of repose

The angle of repose was measured by using the set up shown in figure 2.1.

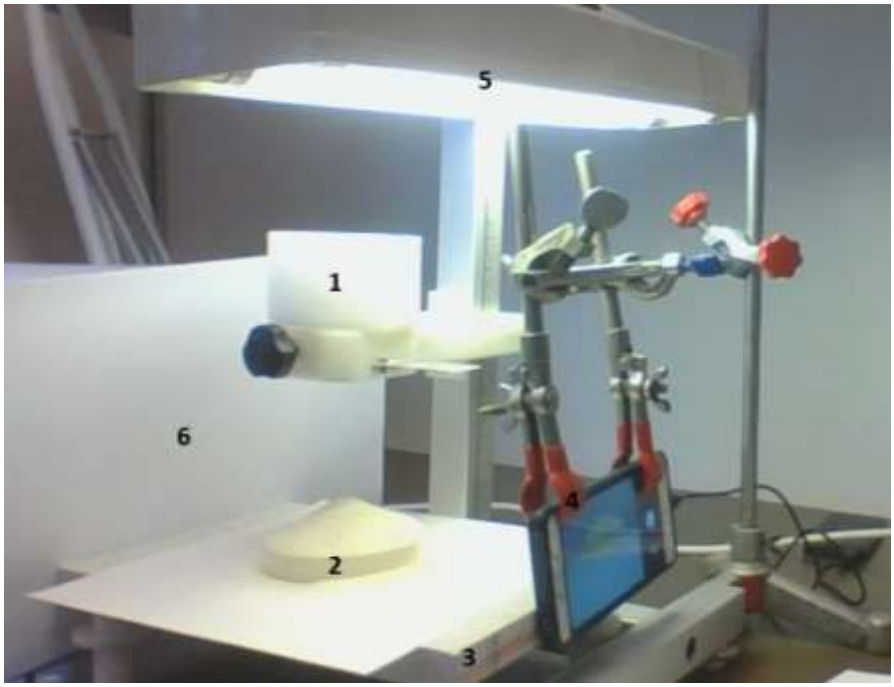


Figure 2.1: The set-up that was used to measure the angle of repose. 1) funnel 2) petri dish 3) marble bench 4) stand with fixed camera 5) light 6) white background.

The powder blend was poured through a funnel into a round petri dish (100 mm × 15 mm). The height of the funnel was fixed at 10 cm from the marble bench. The amount of powder that was poured into the funnel was 70 g. The petri dish was centred right below the center of the funnel hole, by measuring the distance from the edges of the marble bench (13.2cm x 4.5cm) to make sure that the position of the dish would not affect the angle of repose. The camera was fixed on the stand so that it was straightened to the upper level of the dish. The photos taken from this set up can be seen in the figure 2.2.

Figure 2.2: An example of a picture taken by the set-up of figure 2.1. The angle of repose was measured by using the software ImageJ.

Each powder blend creates a pile with a specific angle that is related with the flowability, in a way that the smaller the angle, the better the flowability of the powder. Each blend was poured three times and a photo was taken from each time. The angle of both sides of the pile was measured by using the software *ImageJ* and the average of the two sides was taken as the measurement. In order to minimize the impact of the falling powder on the tip of the cone, the angle was measured at the base of the pile and the tip was not considered, as it is shown in the figure 2.2.

Bulk density and Hausner ratio

The bulk density of the powders was measured by using a 100 ml volumetric cylinder. Each powder blend was poured into the cylinder and it was levelled at 100 ml. The powder was weighed to calculate the bulk density (or free-flowing density) and as a next step the cylinder was tapped manually 200 times on the surface of a wooden bench. The volume that the powder occupied after tapping was determined to calculate the tapped density. The experiment was repeated 4 times for each powder blend.

$$Hausner\ ratio = \frac{\rho_{tapped}}{\rho_{freeflowing}} = \frac{\frac{powder\ mass\ (g)}{tapped\ volume\ (ml)}}{\frac{powder\ mass\ (g)}{100\ ml}}$$

Figure 2.3 shows a volumetric cylinder with powder which was tapped, resulting in a reduced occupying volume of 87 ml, from the initial of 100 ml.

Figure 2.3 A volumetric cylinder with powder after tapping (initial volume or free flowing volume was 100 ml).

2.3. Tableting operation: preliminary and main trials

The tableting machine used in this project was a single punch direct press of the Department of Food Technology, LTH, Lund University made by the company Diaf, Denmark (figure 2.4). The shape of the tablets was circular flat-faced. The compression in this tableting press is adjusted by a rotor at the head of the upper punch, which is shown in figure 2.5. The numbers of the rotor do not correspond at a specific unit of applying pressure and they range from 1 to 9 with two intermediate levels between each number (e.g. 7, 7.33, 7.67, 8 etc.) and they will be referred to as compression levels. This scale of numbers is proportional to the pressure that the upper punch applies.

Figure 2.4: Tableting press at the Department of Food Technology.

Figure 2.5: The rotor adjusts the pressure of the press.

In the preliminary trials, the first tablets were made by using the APL blend (Product x powder) without the addition of excipients, to see the quality of manufactured tablets and

then improve powder blends and tablet properties. Tablets were made for 6 compression levels (7, 7.33, 7.67, 8, 8.33 and 8.67) to assess the compactability of the powder by measuring the hardness and friability of the tablet at each compression level. 6 tablets per compression level were measured to determine hardness, 20 tablets to determine friability (2 friability tests x 10 tablets each test) and 6 tablets to test disintegration time.

In the main trials, tablets were manufactured at four compression levels and this was determined after initial tableting trials with the powder blends of table 2.1. These compression levels were 7.33, 7.67, 8 and 8.33 and they were applied in each powder blend. This gives a total of 24 treatments or sets of tablets (6 powder blends x 4 compression levels) that were characterized in terms of their weight, hardness, friability and disintegration time. Details on characterization of tablets for the main trials are given below.

2.4. Characterization of tablets

Weight

In total 50 tablets were produced per treatment and their weight was determined by using a scale of 4 decimals of the gram accuracy. The number of the tablets was high in order to have a view of the weight distribution of the tablets and how the press was performing in terms of reproducibility.

Tablet hardness

The tablets were tested in terms of their hardness by using a Tablet Hardness Tester (Dr Schleuniger 4M, figure 2.6). The tablet is diametrically placed between two horizontal plates, one that is moving by a motor and presses the tablet against the other which is stable and measures the maximum force applied at the breaking point. This instrument can measure breaking forces above 5 kPonds and for this reason tablets of lower hardness were measured by the texture analyser TA.XTplusC (Stable Micro Systems, figure 2.7), which runs on a similar

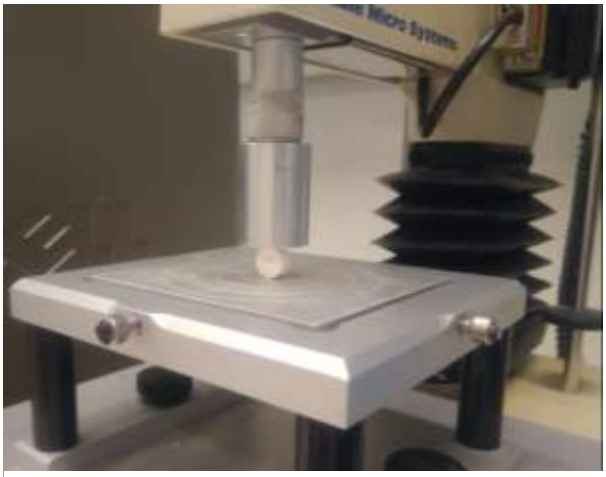


Figure 2.6: Texture analyzer. The tablets with hardness below 5 kPonds were measured with this instrument.

Figure 2.7: Tablet hardness tester. For measuring hardness over 5 kPonds.

way but on a vertical direction of compression. In total 6 tablets were measured per treatment and the maximum breaking force was determined.

Friability

The friability apparatus (Friability Tester ERWEKA TA) is composed of a drum of specific dimensions that spins at a rotational speed of 25 rpm for 4 minutes (3). The total mass of 10 tablets is determined before and after the test and the loss of mass is calculated. If during the test any of the tablets are either broken, cracked or cleaved the tablets are considered to fail the test. The test was performed twice for each set of tablets.

Figure 2.8 tablet: friability apparatus.

Figure 2.9: . Tablets in the drum after the end of the friability test.

Disintegration time

The disintegration time was measured by the Disintegration tester (Pharma test) shown in figure 2.10 and it is a standardized method described in the Pharmacopoeia (3) to give reproducible results. The instrument comprises of a tank with distilled water which is kept at a constant temperature of 37 $\pm$ 2 ^{o}C, and a basket with 6 tubes of inner dimensions 77.5 mm long x 21 mm diameter. The lower end of the tubes is covered with a metal 2mm mesh holding the tablets. The basket is lowered and raised at a constant frequency of 30 cycles per minute in the water tank. In the pharmacopoeia the test ends when all tablets have fully disintegrated with no particles visible on the mesh and the test fails when the tablets do not disintegrate within 30 minutes for uncoated tablets.

Figure 2.10: Disintegration tester.

The tablets are not intended for the typical uses of a pharmaceutical tablet but need to disintegrate as quickly as possible when in contact with water. This demanded a modification of the method described in the pharmacopoeia, in the sense that the

disintegration time of each tablet was noted seperately to provide an average and the test was ended at 60 minutes. One test was performed for each treatment with a set of 6 tablets. If even one tablet failed to disintegrate within this time the treatment was considered to fail the test.

2.5. Dispersion and foam preparation

In order to assess if the excipients that were added in the powder blend for the tablet formulation affect the foamability of the dispersion, the powder blends of table 2.2 were tested. As shown, in all three treatments the same amount of APL blend (Product x powder) was added and the first treatment did not contain any excipients.

Figure 2.11 shows the equipment used in dispersion and foam preparation. An orbital shaker was used to help the powder disperse into the water. 500 ml of distilled water (of temperature 11.5 $\pm$ 0.5 ^{o}C) were poured into a 1.5 litre PET jar, which was placed onto the platform of the orbital shaker, that moves in a circular way and was initially adjusted at 240 motions/minute. The powder blend was poured gradually into the water. When all the powder was transferred into the jar, the speed of the orbital shaker was increased at 400 motions/minute for 15 minutes. Then the dispersion was whipped for 5 minutes by using a blender (Bamix Gastro® 350) at 18000 rpm. In total 2 foams per treatment were prepared and characterized.

Table 2.2: Treatments tested for foamability and foam stability.

Treatment	**Ingredients**				
Abbreviation	**Composite**	**Product x**	**Disintegrant**	**Lubricant**	**Total amount per 500 ml of water**
APL blend	-	APL blend 17.36g (100% w/w)	-	-	17.36g (100% w/w)
C1, CP	Combilac® 19.29g (50% w/w)	APL blend 17.36g (45% w/w)	Crospovidone 1.54g (4% w/w)	Sodium stearyl fumarate 0.39g (1% w/w)	38.58g (100% w/w)
C2, CP	Prosolv® 19.29g (50% w/w)	APL blend 17.36g (45% w/w)	Crospovidone 1.54g (4% w/w)	Sodium stearyl fumarate 0.39g (1% w/w)	38.58g (100% w/w)

2.6. Foam characterization and stability

The foams were characterized by measuring three different parameters: the consistency, the overrun of the foam and the average bubble size right after whipping. The consistency was measured once per foam by using a consistometer (Bostwick Consistometer) and the average of the longest and shortest distance travelled in 30 seconds was determined. The overrun was determined by measuring the net weight of the foam in a levelled plastic cup of 46 ml, knowing the weight of the dispersion in the same cup according to the formula (5):

$$overrun\ (\%) = \frac{wt\ of\ dispersion - wt\ of\ foam}{wt\ of\ foam} \times 100\% \quad (5)$$

The average bubble size was determined by using an optical microscope (ref Olympus CX41RF at x 40 magnification) with a camera (Infinity 1 LUMENERA) and the software *Infinity Analyse.* The diameter of the third largest bubble was taken as the average diameter. 3 different positions of the microscope slide were checked for their bubble size (three replicates per foam).

In order to measure the stability of the foam over time, the measurements of overrun and average bubble size were repeated three hours after whipping for the same foams and repetitions. The foams for this time were stored in room temperature with the jar firmly closed with a lid and without shaking.

Figure 2.11: Procedures and equipment used in dispersion and foam preparation and characterization. a) orbital shaker, b) dispersion, c) set up of the blender, d) foam, e) weighing the foam in a plastic cup of 46 dL f) consistometer g) bubble diameter measurement using optical microscopy.

2.7. Data analysis and interpretation

All data was collected and analysed by using MS Excel. The graphs and their interpretations are based on the assumption that all the data collected follow the normal distribution. The error bars that are used represent two times the Standard Error of the Mean (2 x SEM above and 2 x SEM below the mean value) for a reliable demonstration of the differences between the samples which reflect to the populations. In the cases where the error bars do not overlap it can be inferred that there is a statistically significant difference between the samples. Whenever the error bars overlap there is not enough evidence to support that the samples belong to different populations.

3. Results and Discussion

3.1. Preliminary trials

As mentioned in materials and methods, in the preliminary trials, tablets were produced by using the APL blend (Product x powder) without the addition of any excipients. The results of hardness and friability are shown in figures 3.1 and 3.2 respectively. We can see that the tablet hardness increases in an exponential way as the compression applied by the press increases. When tested for their friability, the tablets of compression level less than 8.33 failed the test, as some or all of them cracked or cleaved. For this reason, in figure 3.2, only friability of tablets of compression levels 8.33 and 8.67 are presented.

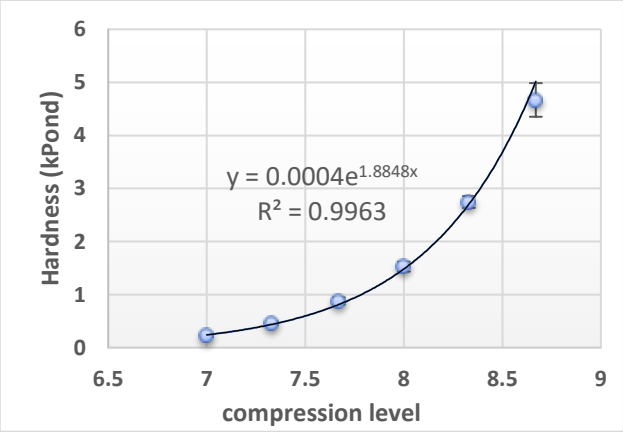


Figure 3.1: Hardness of the tablets made by using the APL blend.

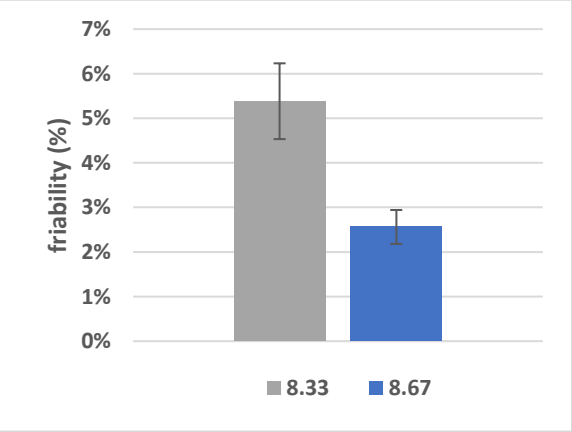


Figure 3.2: Friability of the tablets made by using the APL blend.

Generally for tablets a minimum acceptable hardness is at least 3 to 4 kPond (usually it is much higher), and depends on the intended use in order to have adequate mechanical strength during production, ejection from the blister etc. (5). Nevertheless, what is also important for a tablet is not to be too hard, so that it compromises the time that it needs to disintegrate, given that generally the higher the hardness of a tablet is, the longer the disintegration time gets. The friability is more than is usually accepted by the pharmaceutical industry (usually less than 1% is accepted). Although for this property the shape of the tablet

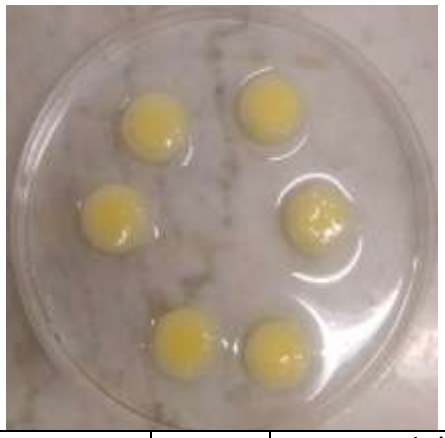
plays an important role, as shapes with sharp edges exhibit higher friability. It is reminded that, the shape in this project was cylindrical, so an oval shape is expected to give lower friability.

These results indicate that the APL blend has poor compactability. The tablets were made by applying relatively high compression level, given that the maximum of the scale of the specific tablet press is 9.67. Eventhough the achieved hardness is low and the friability is exceeding what is generally acceptable. Additionally the tablets failed the disintegration test. After 60 minutes in the test the tablets had a soft surface but the core was very hard, they did not appear to have lost any of their mass and the water of the tank was almost clear with no powder precipitates at the bottom.

During preliminary trials, several attempts were made with different ratios of egg albumen protein and xanthan gum and with the addition of disintegrants in the powder blend. The puprose was to investigate which of these two ingredients inhibits tablet disintegration. Table 3.1 shows four different series of tablets after 30 minutes in the disintegration test. It is important to mention that the four different treatments are not comparable to each other but they show that both Egg Albumen Protein and Xanthan gum do not favour fast disintegration of the tablets.

Figure 3.1: Preliminary trials with different ratios of Egg Albumen Protein and Xanthan gum with the addition of disintegrants. Testing disintegration time: 30 minutes test.

APL blend with 6% disintegrant compression level 8.3



Ingredient	Amount	Percentage (w/w) of solids
$NaH_2PO_4.2H_2O$	Classified information	
Xanthan gum		
Egg Albumen Protein		
K_2HPO_4		
Mango flavour		
Crospovidone	1.10	6.0%
Croscaramelose sodium	0.00	0.0%
total	18.47	100.0%

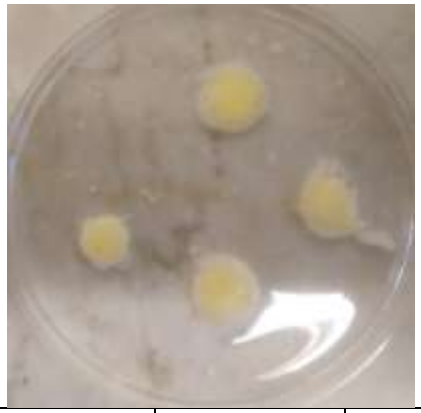
No xanthan gum with 2% disintegrants compression level 8.3

Ingredient	Amount	Percentage (w/w) of solids
$NaH_2PO_4.2H_2O$	1.02	5.7%
Xanthan gum	0.00	0.0%
Egg Albumen Protein	12.48	70.5%
K_2HPO_4	3.38	19.1%
Mango flavour	0.48	2.7%
Crospovidone	0.17	1.0%
Croscaramelose sodium	0.17	1.0%
total	17.71	100.0%

No egg albumen protein with 2% disintegrants compression level 8.3

Ingredient	Amount	Percentage (w/w) of solids
$NaH_2PO_4.2H_2O$	1.02	5.7%
Xanthan gum	12.48	70.5%
Egg Albumen Protein	0.00	0.0%
K_2HPO_4	3.38	19.1%
Mango flavour	0.48	2.7%
Crospovidone	0.17	1.0%
Croscaramelose sodium	0.17	1.0%
total	17.71	100.0%

Less xanthan gum (4.9%) than in APL blend with 2% disintegrants compression level 8.3



Ingredient	Amount	Percentage (w/w) of solids
$NaH_2PO_4.2H_2O$	1.02	5.7%
Xanthan gum	0.87	4.9%
Egg Albumen Protein	11.62	65.6%
K_2HPO_4	3.38	19.1%
Mango flavour	0.48	2.7%
Crospovidone	0.17	1.0%
Croscaramelose sodium	0.17	1.0%
total	17.71	100.0%

In the first treatment, a high amount of crospovidone (6%) was added into the APL blend, gave tablets that resisted disintegration, with a soft gel at their surface but the core remained hard. The second one, comprised of a blend with no xanthan gum and a combination of 2 disintegrands (1% crospovidone and 1% of croscaramelose sodium), with tablets of better disintegration. The third was a blend with no egg albumen protein, produced tablets that at the end of the test had a thick gellous outer layer and a soft core. The last treatment produced tablets that had improved disintegration time (2 tablets of the 6 disintegrated completely) with a soft core.

The combination of xanthan gum and egg albumen protein at the ratios of the APL blend gave the longest disintegration time as the tablets were intact even with significantly higher amount of disintegrant. These two ingredients in the tablet had an inhibiting effect in water penetration which prevented disintegration.

Although water soluble in cold water, xanthan gum particles need to be well dispersed in a solution in order to hydrate. If not properly dispersed, the gum can easily produce partially swollen lumps during mixing, sometimes referred to as 'fish eyes' (10). For this reason in most industrial applications the gum is mixed with other solid ingredients like sugar starch or salt, in ratios 1:5 or 1:10 before it is incorporated in liquids. A similar phenomenon to the 'fish eyes' occurred when the tablets which are highly compacted and contain a high percentage of the gum, were immersed into the water. Xanthan gum is important in this blend as it delays drainage of water (one of the destabilizing mechanisms in foams) which is present as the continuous phase of the foam.

A strategy to overcome the problems of low compactability and slow disintegration was to mix the APL blend with binders/composites that are used in the pharmaceutical industry. The results of the main trials are presented below.

3.2. Flowability of the powder blends

The flowability of the powder blends is presented in figures 3.3 and 3.4. The first one shows the angle of repose of the six different blends as well as the APL blend. On the right hand, a scale of the angle of repose characterizing the flowing properties is shown. It is concluded that the APL blend has the best flowability of all the treatments, although the measurements were very close to those of Combilac 4% CP and Combilac 4% CCS. It is also apparent that the blends with Prosolv have generally worse flowing properties than Combilac blends. All the blends generally have fair flowing properties and the addition of a glidant, which would improve flowability, is not usually necessary for normal tableting conditions (2).

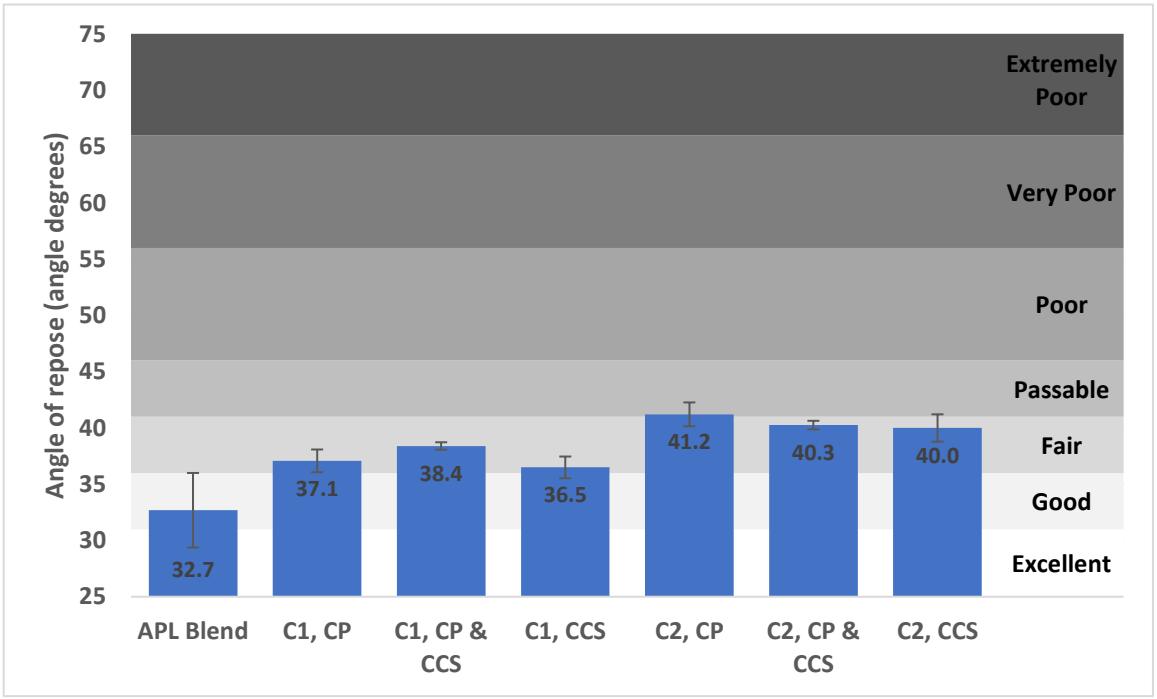


Figure 3.3: Flowability of powder blends: Angle of repose. C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium.

The flowability determined by Hausner ratio gave slightly different results, as the powder blends with Prosolv are falling in the category of 'passable' flowing properties, while the Combilac blends have 'good' ones, and the difference between the two is bigger. Although the analogies are similar, with the APL blend having the best flowing properties and blends with Combilac being significantly better than the one with Prosolv.

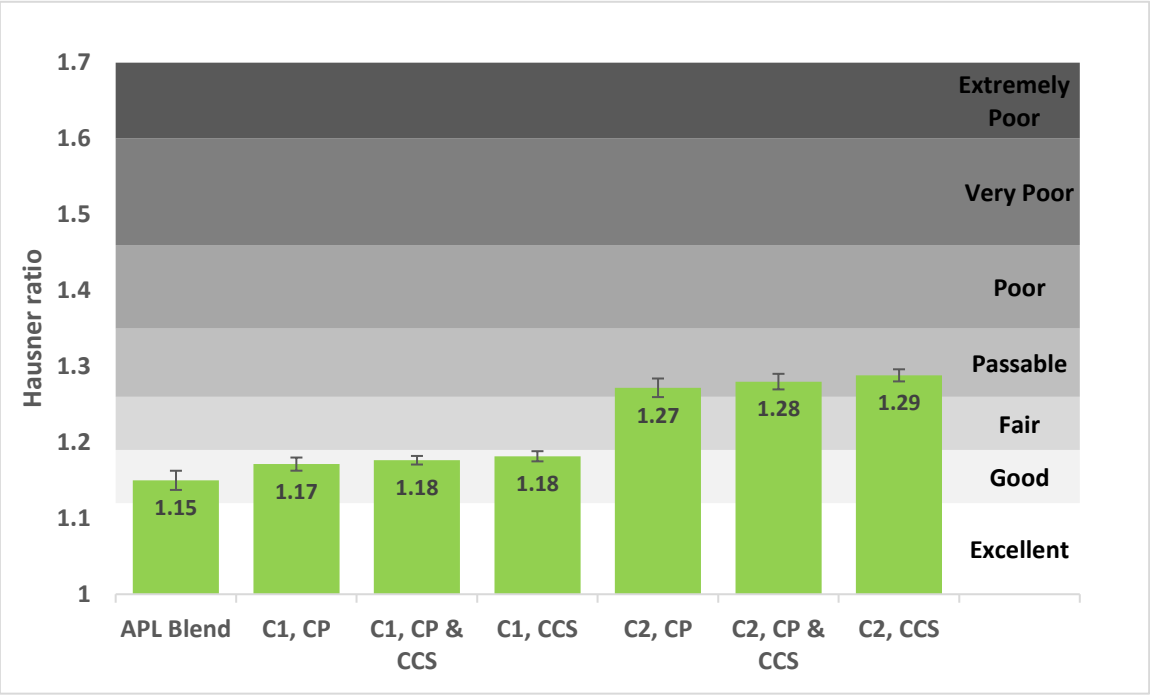


Figure 3.4: Flowability of powder blends: Hausner ratio. C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium.

In both diagrams the differences among blends with the same composite are not statistically significant. Also, there is no specific pattern between the different disintegrant compositions CP, CP&CCS and CCS for the same composite, meaning that with these results it cannot be inferred that one of the three combinations of disintegrants at this low percentage can significantly influence the flowing properties of the blend.

Between the two methods that determine flowability, considering the way that they were set up, the angle of repose was more subjective to user error and not as accurate. As the measurements were taken from pictures, the analysis of the angle can give different results depending on the user. This is not that important in the method measuring Hausner ratio and this can be seen from the generally narrower error bars when the two graphs are compared.

3.3. Characterization of tablets

Weight

Tablet weights of the different treatments are shown in figure 3.5. A first conclusion is that in most of the cases there are not statistically significant differences between the different compression levels for the same powder blend, or the compression level does not influence tablet weight. Although there are differences between each powder blend. Combilac generally produces bigger tablets than Prosolv. Furthermore, the powder blends with Crospovidone tend to produce tablets with lower weights while the combination of the two disintegrants produces the tablets with the highest mass between the three combinations of the same composite.

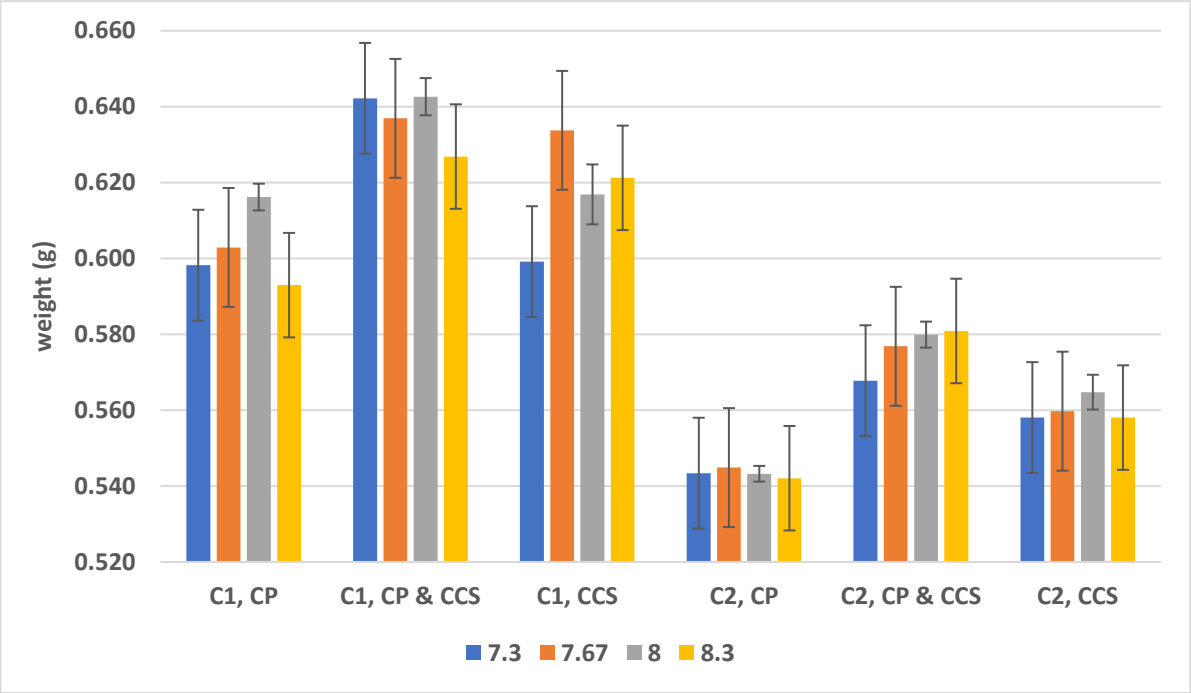


Figure 3.5: Tablet weights. C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium.

These differences in tablet weights are related to the packing properties of each blend. When measuring Hausner ratio, it was clear that blends with Prosolv had different packing geometry as they reduced in volume more after tapping than blends with Combilac. This means that the particles of Prosolv do not pack as efficiently, having lower bulk density than blends with Combilac. In the tablet press the die volume was fixed and could hold a specific amount of powder. If the powder blend has good flowability and packing properties, more powder will flow into the die resulting in increased tablet weight. In conclusion, resulting tablet weight is related to flowability and packing properties of the powder blend.

Tablet hardness

Figure 3.6 shows tablet hardness of the powder blends or the force that needs to be applied on a tablet in order to break. As can be seen and expected, there is a positive relation between compression level and tablet hardness in all powder blends. It is also apparent that

this proportionality approaches a linear correlation which was not observed in the case of the tablets produced by the APL blend (figure 3.1), but in that case the relation was exponential. Another inference is that the powder blends have the capacity when compacted, to produce tablets of much higher hardness. For example, an APL tablet with compression level of 8.3 produced tablets with less than 3 kPonds of hardness, while all the powder blends in figure 3.6 produced tablets with more than 12 kPonds of hardness. The difference is huge and shows that the powder blends have greatly improved compactability, comparing with the initial powder. In addition, powder blends with Prosolv seem to acquire less hardness than Compilac in some cases such as comparing C1, CCS and C2 CCS for compression levels 7.67, 8 and 8.3 although this is not a general rule as the differences between other powder blends are statistically insignificant. Finally, variances between treatments with the same composite but different combination of disintegrants shows the disintegrants can influence tablet hardness in many cases and compression levels.

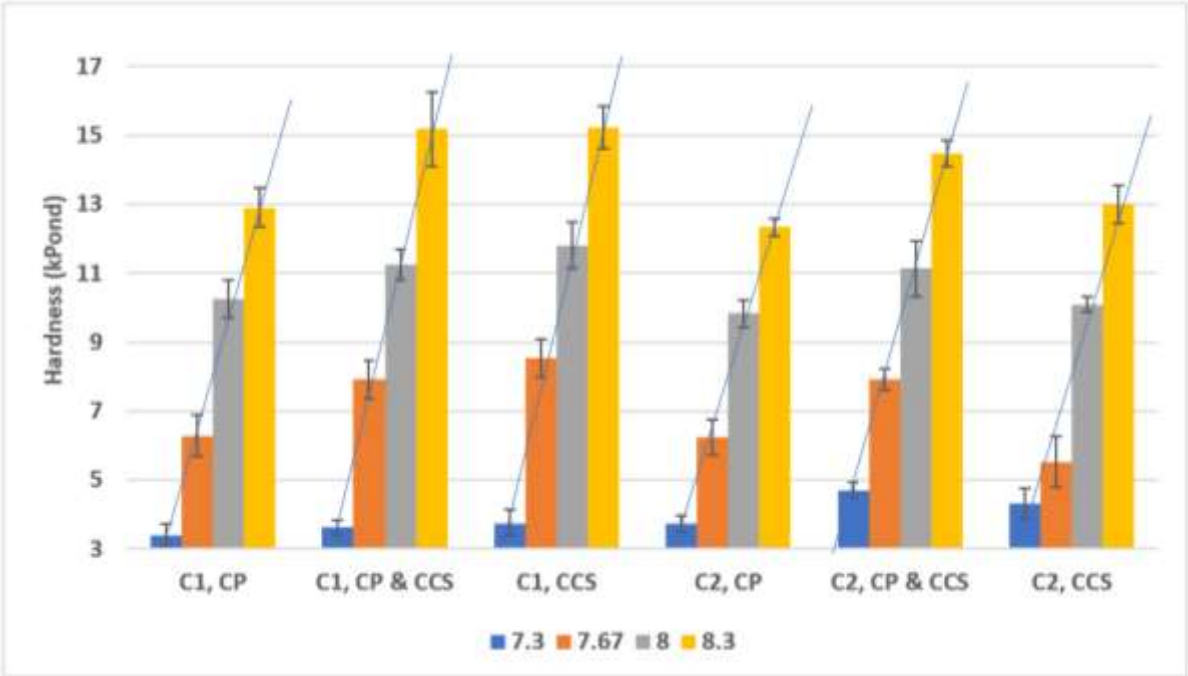


Figure 3.6: tablet hardness (breaking force). C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium.

Friability

The friability of the tablets from the powder blends is presented in figure 3.7. As expected, friability is inversely proportional to the compression level. Comparing it with the tablets produced from the APL blend, friability is much lower here for the same compression level, for example the APL blend tablets at 8.3 have friability over 5% while for all powder blends the corresponding values are below 1% which is considered acceptable for most pharmaceutical products. There is a big difference between 7.3 and 7.67 as friability drops rapidly for all powder blends. Although in highest compression level the average values are the lowest, the differences are not statistically significant when comparing 8 to 8.3.

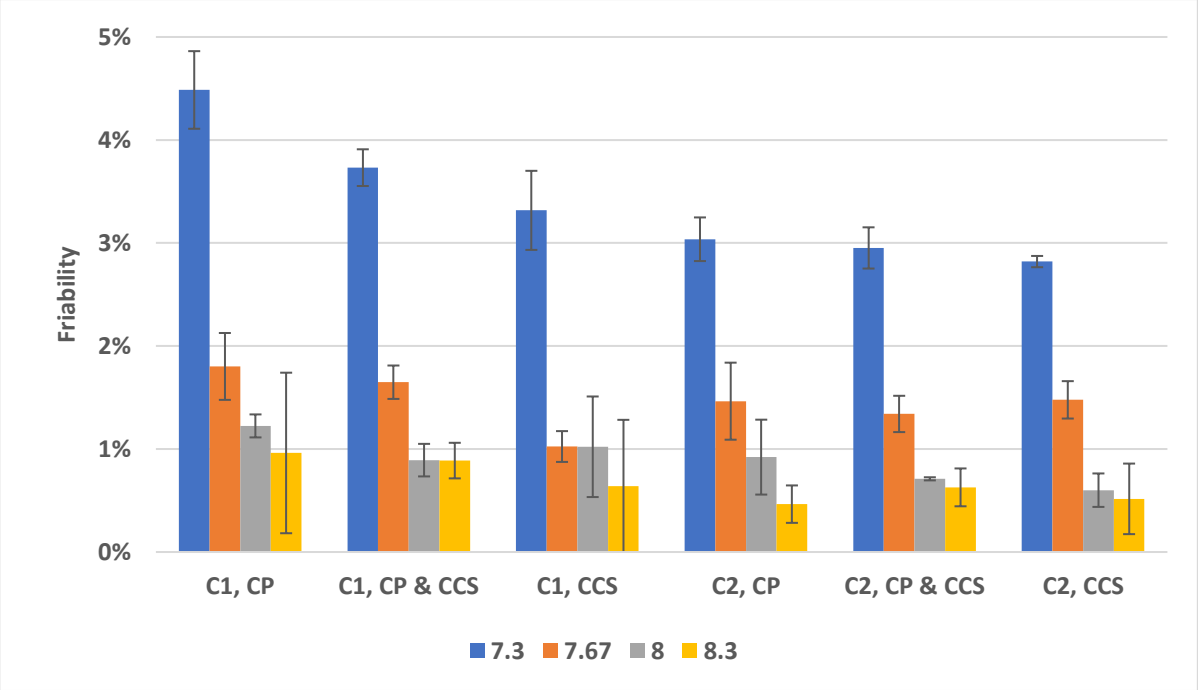


Figure 3.7: friability C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium.

Equally to tablet hardness, the results of friability tests confirm that the powder blends have greatly improved compactability when associated with the results of the preliminary trials concerning the APL blend.

Disintegration time

The final tests performed on tablets and probably the most critical for this project were the disintegration tests and the results are shown in figure 3.8. Because some treatments failed to disintegrate within 60 minutes, striped bars were used to indicate were the tests failed. As expected, tablets with higher compression level had longer disintegration times. Generally, treatments with Combilac used as a composite had eight failed tests out of twelve and did not perform as well as the ones with Prosolv. The fastest disintegration time occurred with tablets of 50% Prosolv and 4% of crospovidone, were the tablets fully disintegrated in an average of one minute. It can be also concluded that the treatment with Prosolv and crospovidone 4% gave better results than the cases of 2% crospovidone & 2% croscaramelose sodium and 4% croscaramelose sodium.

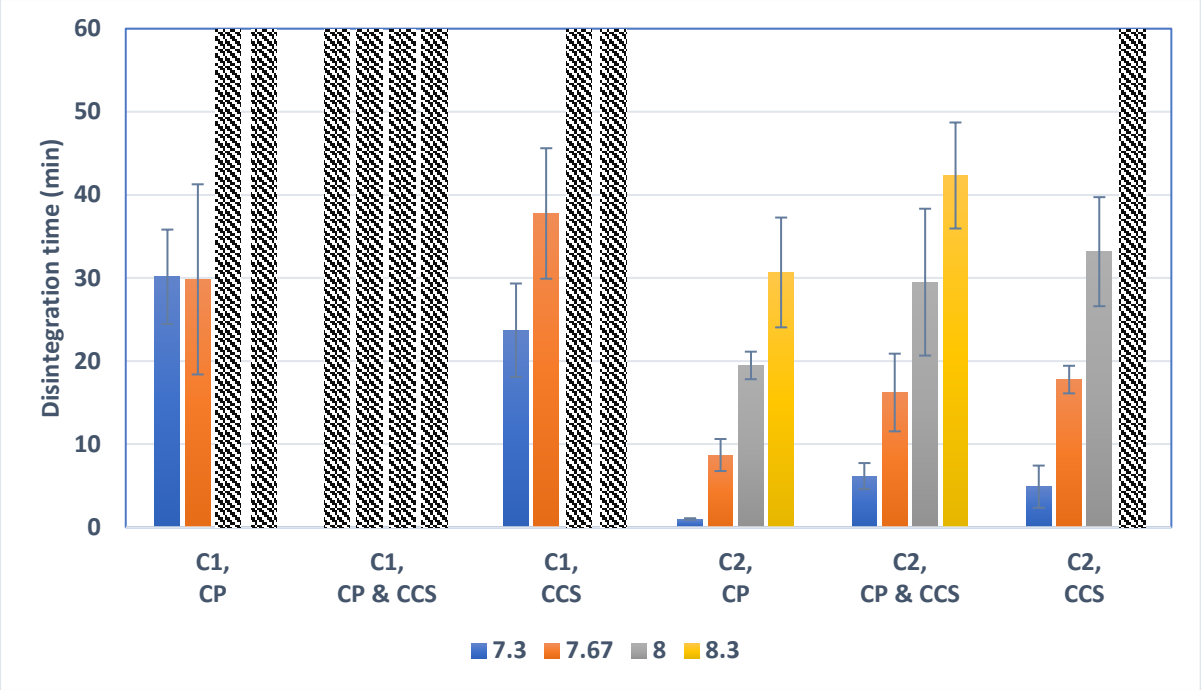


Figure 3.8 : Disintegration time C1: Combilac, C2: Prosolv, CP: Crospovidone, CCS: Croscaramelose sodium. The striped bars show that the corresponding tablets failed to disintegrate within 60 minutes.

It is important to note that Prosolv contains sodium starch glycolate that acts as a disintegrant which probably played a role in improved disintegration time.

Foamability and foam stability

The results of the overrun of the foams produced with the APL blend and the powder blends with 4% of crospovidone in 0 hours (right after whipping) and 3 hours are shown in figure 3.9. It is clear that the APL dispersions when whipped, acquired more overrun than the 2 other dispersions. Nevertheless, the differences between two composites are not statistically significant in 0 hours. The increased values at 3 hours of the overrun are not expected and the reason behind this is probably the sampling method. An explanation could be that the foam is not homogeneous at all layers and some drainage of water had occurred in 3 hours. The upper layer of the foam contains more air and the layer at the bottom of the jar more water which is heavier than air. Thus, the sampling method of tilting the jar to pour the foam into the plastic cup and weighing the cup

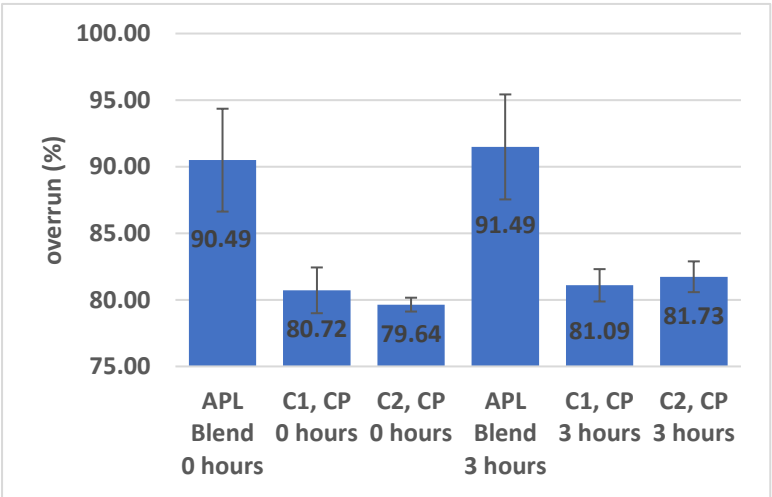


Figure 3.9 : Overrun of the foam C1: Combilac, C2: Prosolv, CP: Crospovidone. 0 and 3 hours denotes that the measurements were made right after whipping of the foam and 3 hours later.

produced an important error which is depicted in the graph. That is to say, the sample was not representative of the whole foam. Although there is a strong indication that the foams are very stable as the differences are very small between 0 and 3 hours.

The decrease in overrun is obviously due to the incorporation into the system of the excipients. The excipients remained in the system either as dispersed polymers in the aqueous phase (microcrystalline cellulose, sodium starch glycolate), suspended (colloidal silica), precipitated (native corn starch) or solubilized in the aqueous phase (lactose) and reduced the amount of air that was incorporated into the system. This can be attributed to the fact that sugars and polymers increase the viscosity of the dispersion and as a result it is harder to incorporate air into the system with a more viscous continuous phase. Lau et al. examined systems with 2-6% egg albumen and 60-82% invert sugar and concluded that reducing the invert sugar concentration in the serum phase (from 82% total solids) produced a foam of much higher overrun, but it led to an increased rate of destabilization (6).

The average bubble size is presented in figure 3.10. For the values of 0 hours there is a statistically significant difference between the treatments. The foams produced using the powder blends with Combilac and Prosolv have both significantly smaller bubble sizes than the APL blend.

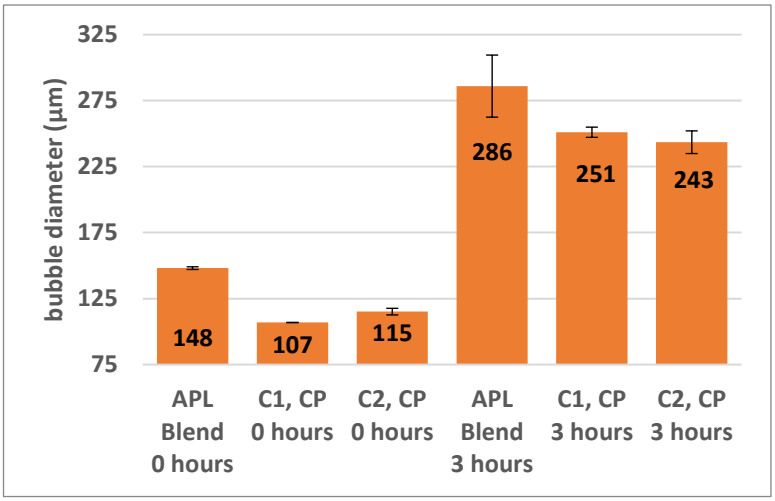


Figure 3.10 : Bubble size. C1: Combilac, C2: Prosolv, CP: Crospovidone. 0 and 3 hours denotes that the measurements were made right after whipping of the foam and 3 hours later.

Three hours after the production of the foam, the size of the bubbles had increased due to disproportionation. The bubble sizes of the powder blends remain smaller than the APL blend. This result along with the subtle change in the overrun of the foams indicate that the systems are fairly stable.

The main instability mechanisms in foams are dispoportionation (Ostwalt ripening), coalescence and drainage. Coalescence happens when two bubbles approach each other, separated by a thin film which ruptures. In the examined types of foams in this project, coalescence is not expected to be a main instability mechanism at this stage, because the foam is highly stabilised and the film between the bubbles is thick (11). On the other hand, dispoportionation is a phenomenon that occurs due to difference in Laplace pressure between the bubbles. Air has increased solubility in water under these conditions and molecules from the air bubbles can diffuse, from smaller to bigger, through the aqueous phase (11). Drainage of water happens due to gravity and can be hindered by increasing the viscosity of the continuous phase. The concentration of xanthan gum in the dispersion is approximately 0.5% (table 1.1) which is adequate to greatly increase viscosity and foam stability. Furthermore, Combilac and Prosolv both contain microcrystalline cellulose, which is

used as a stabilizer, it has the ability to control the viscosity of a solution or dispersion by creating interactions and networks with other hydrocolloids and it provides effective foam stabilization in a variety of whipped food systems (**Philips**).

4. Conclusions

As it was shown, the APL blend has good flowing properties but poor compactability, producing tablets of low hardness and high friability, that do not disintegrate by using the described disintegration method. This is due to the nature of the ingredients, mainly xanthan gum and egg albumen protein and the compaction effect. These ingredients both inhibit water penetration into the tablet and do not easily dissolve in water as salts or sugars would do. The powder blends which were produced to overcome these difficulties and to improve tablet quality showed fairly good flowing properties, with Combilac having better results than Prosolv. Although it is not clear if the different combinations of disintegrants influenced flowability. All powder blends had greatly improved compactability in comparison to the APL blend, that resulted in tablets of good hardness and friability at lower compression levels and disintegrate significantly faster, making the whole project feasible. It is important to note that different powder blends produced different tablet weights although the compression did not affect this parameter as expected. Foamability was negatively affected by the added excipients and this is shown by the reduced percentage of overrun. Although foam stability that was measured three hours after whipping was similar in the powder blends and APL blend as the overrun and bubble size show.

References

1. ANTON, M.; NAU, Françoise; LECHEVALIER, V. Egg proteins. In: *Handbook of hydrocolloids*. Woodhead Publishing, 2009. p. 359-382.

2. AULTON, Michael E. Aulton's Pharmaceutics. Chapters 12 and 30 ed. 2007.

3. EUROPEAN PHARMACOPOEIA COMMISSION; EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE. *European pharmacopoeia*. Council of Europe, 2010.

4. GIRARD, Flora. *Studies to overcome current limitations of a micro-foam negative contrast agent used for abdominal CT-scan. Internship report.* Rouen : ESITech - Université de Rouen Normandie, 2018.

5. HUI, Yiu H.; SHERKAT, Frank. *Handbook of food science, technology, and engineering-4 volume Set*. CRC press, 2005.

6. LAU, Cathy Ka; DICKINSON, Eric. Instability and structural change in an aerated system containing egg albumen and invert sugar. *Food Hydrocolloids*, 2005, 19.1: 111-121.

7. LUMAY, Geoffroy, et al. Measuring the flowing properties of powders and grains. *Powder Technology*, 2012, 224: 19-27.

8. QUODBACH, Julian; KLEINEBUDDE, Peter. A critical review on tablet disintegration. *Pharmaceutical Development and Technology*, 2016, 21.6: 763-774.

9. RAIKOS, Vassilios; CAMPBELL, Lydia; EUSTON, Stephen R. Effects of sucrose and sodium chloride on foaming properties of egg white proteins. *Food Research International*, 2007, 40.3: 347-355.

10. SWORN, Graham. Xanthan gum. In: *Handbook of hydrocolloids*. Woodhead Publishing, 2009. p. 186-203.

11. WALSTRA, Pieter. *Physical chemistry of foods*. CRC Press, 2002.