Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Technology

THE INFLUENCE OF MICRONIZED POLOXAMER ON THE FLOW AND COMPACTION OF A MODEL TABLETING MIXTURE

Diploma Thesis

Brooke Alexandra Dunlap

Supervisor: Assoc. Prof. Šklubalová Zdenka, Ph.D.

Statement of originality

I declare that the content of this thesis is original work. All literature, data, and resources used are cited and found in the references section.

Brooke Alexandra Dunlap

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1 Abstract

Charles University, Faculty of Pharmacy in Hradci Králové

Department of:	Pharmaceutical Technology
Supervisor:	Assoc. Prof. Zdenka Šklubalová, Ph.D.
Consultant:	Sebastien Bailey
Student:	Brooke Dunlap
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Lubricants are an important excipient used in the production of tablets, they facilitate powder flow during manipulation, prevent powder sticking to the press during compression, and aid in tablet ejection. In this thesis the effect of four different concentrations 0.5, 1.0, 1.5, and 2.0 % w/w of micronized Poloxamer 188 on a model tableting mixture consisting of a 1:1 ratio of Microcrystalline Cellulose (MCC) and Lactose (L) was tested to determine its effectiveness as a lubricant for tablet manufacturing. Flow through an orifice, angle of repose, Hausner ratio, compressibility index, dynamics of consolidation, and powder bed porosity were tested. There was no increase in flowability of the powder at any concentration of P188 in any test used, all mixtures showed poor or very poor flow behaviour. Compression process was evaluated according to the force displacement method at three different compression forces (5 kN, 7 kN, 10 kN) and special attention was paid to ejection force. P188 is an effective lubricant during tablet ejection even at low concentrations decreasing the ejection force by at least a factor of 3, with minimal effect on energies of compression. Finally, tablets were tested for tensile strength, friability, and disintegration time. There was no visible negative effect on tablet properties at any concentration tested in comparison to the binary mixture of fillers. In conclusion, P188 showed no effect as a glidant, however was an effective press lubricant with no adverse effects on tablet properties.

2 The Aim of Study

The aim of the theoretical part is to bring information about flowability and compression of powders and to introduce the recent knowledge in microcrystalline cellulose and lactose fillers as well as lubricants in a tableting mixture, their role and mechanisms of action, with a particular focus on the micronized poloxamers.

In the experimental part, the influence of a lubricant, micronized Poloxamer 188 (P188), in a concentration range of 0.5 – 2.0 % w/w on the flow and consolidation properties of a binary model filler mixture will be investigated by the bulk and tapped density, flow through orifice, and angle of repose methods. Specifically, the dynamics of consolidation by gravity will be studied. Tablets will be compressed at three compression forces and the lubricant effect on the compression of a model mixture will by described by the changes in compression energies and in the ejection force. Finally, the effect of P188 on the properties of produced tablets will be evaluated.

3 List of Abbreviations

Abbreviation	Unit	Explanation
AOR	(°)	angle of repose
API		active pharmaceutical ingredient
CF	(N)	crushing force (for breaking the tablet)
CI	(%)	compressibility index
d_0	(g/mL)	tablet density at h0 in a die
d_{24}	(mm)	tablet diameter 24 hours after compaction
d_b	(g/mL)	bulk density
d_c	(g/mL)	cylinder bulk density
d_p	(g/mL)	pile density
d_s	(g/mL)	true density (density of solids)
d_t	(g/mL)	tapped density
DT	(s)	disintegration time
d_{tbl}	(g/mL)	tablet density out of a die after 24 hours
E_1	(Nm)	precompression energy, powder particles are getting closer
E_2	(Nm)	compaction energy, illustrates amount of energy consumed for the tablet creation
E_3	(Nm)	elastic energy, tablet is relaxing
EF	(N)	ejection force
E_{lis}	(Nm)	**Elis=E2+E3**
E_{max}	(Nm)	**Emax=E1+E2+E3**
F-D		Force displacement
F_{max}	(N)	compression force
h_0	(mm)	tablet height immediately after compaction
h_{24}	(mm)	tablet height 24 hours after compaction
h_d	(mm)	initial powder height in a die **hd=Vd/r*r*π**
h_{max}	(mm)	tablet height at the maximal compaction force
HR		Hausner ratio
JKL		Johnson-Kendall-Roberts theory

L		lactose
LOD	(%)	loss on drying
m	(g)	material weight
MCC		microcrystalline cellulose
MCC/L		microcrystalline cellulose and lactose in a 1:1 ratio
P	(%)	porosity of powder bed
PL	(%)	plasticity, describes the easiness of a material to be plastically deformed **PL=100*(E2/(E2+E3))**
Ptbl	(%)	porosity of tablet
Q	(g/s)	the mass flow rate through an orifice
RSD	(%)	relative standard deviation
SEM		scanning electron microscope
span		width of the particle size distribution
TS	(MPa)	tablet tensile strength TS = 2*F/PI*D*H
V_0	(mL)	initial bulk volume of powder bed in a graduated cylinder
Vd	(mL)	initial powder volume in a die Vd=m/dc
Vt	(mL)	final tapped volume
X_{10}	(µm)	mean particle size illustrating 10 % of the cumulative frequency
X_{50}	(µm)	mean particle size illustrating 50 % of the cumulative frequency
X_{90}	(µm)	mean particle size, illustrating 90 % of the cumulative frequency

4 Introduction

Oral tablets are the most widely used dosage form today, as they are cost effective, produced quickly, have the ability to take on a variety of shapes, colours, and strengths, and are well tolerated by patients. Tablets are generally produced by either direct compression, where the powder mixture is poured into the die and compacted, or through granulation where the powder is formed into larger agglomerates that are then pressed into tablets (Shanmugam, 2015; Amidon, 2011). Direct compression requires no wetting of the powder material or extra steps for compression into tablets, this decreases cost and increases the speed at which tablets are produced (Medarević et al, 2021). However, the powder must display sufficient flow and compression properties (Carlin, 2008). On the other hand, granulation produces larger grains of material that display better flow and less sticking due to the reduction of dust (Shanmugam, 2015). The production capacity and rate are controlled by the flow properties of the powder (Janssen et al, 2021). Flow and compressibility of the tableting mixture is therefore a vital factor in the production of oral solid dosage forms, many pharmaceutical preparations rely on dry powder for use as both active pharmaceutical ingredients and excipients (Carlin, 2008). During the tableting process the powder must be of equal volume and weight in the die, have a good compression profile, and the final tablets must avoid capping, sticking, lamination, and breaking. Particularly rotary tablet presses, commonly used in production, are extremely fast and must therefore be a frictionless as possible to cope with the high speeds (Sajdady et al, 1993). Therefore, nearly all industrially produced tablets include lubricants, either as a component for the powder mixture or sprayed directly onto the die. The aim of this thesis was to investigate the efficiency of a new modern hydrophilic lubricant substance, micronized Poloxamer 188 for internal lubrication.

5 Theoretical Section

As mentioned above, tablets are compressed from tableting mixtures which consist of many excipients each having a specific function within the tablet.

A common method of tablet production is direct compression, where the tableting mixture is poured directly into the die and pressed without additional steps, such as granulation; this is nowadays the first choice in industry provided the materials are suitable, due to the low cost, speed, and lack of additional processing. Individual components, e.g., fillers, dry binders, lubricants, and colourants, including the active pharmaceutical ingredient (API), are mixed.

After the tableting mixture is mixed it is often stored for some time depending on the production parameters of the facility in which the tablets are manufactured. Problems with production may include powder segregation, sticking, poor flow, and caking during the phases in which the raw powder is being manipulated (Carlin, 2008). A key limiting step of the process is the filling of the die. This is also a crucial step in the determination of the final properties of the tablet (Puckhaber et al, 2020). It is therefore of the utmost importance that the flow of the material is sufficient to prevent problems both in the mixing and storage of the powder and the compression itself. Powder that is not freely flowing will not result in uniform tablets or will facilitate delays in production (Baxter et al, 2008). Excipients, such as glidants, may be used to enhance the flow of the powder mixture before compression (Janssen et al, 2021).

Alternatively, adding extra processing steps such as granulation may also improve flow. This may be solved through either dry granulation where the powder is compacted into large bricks then broken into granules of suitable size, or wet granulation, wherein the powder is wetted and agglomerates are formed before being dried (Shanmugam, 2015; Amidon 2011). Due to the larger size and less contact area between agglomerates, granulation facilitates better flow than raw powder, and is not at serious risk of sedimentation and segregation of components (Lister et al, 2004).

Generally, the powder or granule mixture is loaded into a hopper and is gravity fed by the feeder into the dies which are mounted in series (Baxter et al, 2008; Amidon 2011). The weight may be controlled, and the lower punch may be moved to adjust the mass

by allowing more material into the die or raising to eject a portion of the tableting mixture. The dies proceed to a smaller roller where there is a small force for precompression to settle to tableting mixture and remove the larger gaps. The dies then proceed to the main compaction which depends on the type of press used. There is either a single upper punch or an upper and lower punch compressing the tablet from both sides.

Once the tablet is compressed the upper punch is removed and the lower punch raised via cam to eject the newly formed tablet (Bourland and Mullarney, 2008; Amidon 2011). Then, the tablet may be directly packaged or go on to further processing like coating or as a component of another dosage form such as a multi-layer tablet.

Manufacturers use the pharmacopeial parameters as well as non-mandatory tests to predict and measure how a tablet may withstand handling during packing and transport, and to check the uniformity of tablets and calibration of machines (Ausburger and Hoag, 2008; Sharma et al, 2017). This means that once the tablet is produced it must meet specific standards, including the mechanical resistance (estimated as the mass loss – friability, or hardness), disintegration time, and dissolution profile of a drug.

5.1 Excipients Used in Tableting Mixtures

An excipient, any ingredient that is not the active pharmaceutical ingredient, is used to produce a medicinal product and contributes to its processing, appearance, and performance (Sharma et al, 2017; Moreton, 2017). It is important for an excipient to be chemically inert as they may react with the API or other excipients in the mixture and change the formulation of the final dose (Good and Wu, 2017). The functionality depends on the chemical and physical properties, amounts present, processing methods, and the target drug product (Sharma et al, 2017).

The exact sourcing and processing of pharmaceutical excipients varies between manufacturers and therefore excipients introduced to the market must undergo pharmacopeial and industry tests to ensure the quality as well as the workability of a product (Good and Wu, 2017; Kestur and Desai, 2017). Monographs are mainly

concerned with the purity and safety of a compound rather than the performance during manufacture, i.e., the same excipient may be approved for use in different dosage forms but may not display suitable behaviour for a given process (Kestur and Desai, 2017).

The simplest forms of tablets contain only the API, however most tablets also include the excipients. Excipients used in the tablet production depend on method of tableting mixture production (either a direct compression or granulation) and generally may include fillers, disintegrants, lubricants, surfactants, and colourants.

5.1.1 Bulking Agents

Bulking agents, also referred to as diluents or fillers, are used in nearly all tablets produced, as a tablet is rarely made entirely of the active pharmaceutical ingredient, due to either poor compressibility or the amount of API not being sufficient for produce an adequately sized tablet (Carlin, 2008). Out of common inorganic, small molecule, and polymer filler excipients used in tablets, microcrystalline cellulose, MCC, and lactose (L) are frequently used (Good and Wu, 2017) to which the only attention is paid in this thesis.

Fillers also increase the flowability, compressibility, and homogeneity of a mixture during production, as well as improve characteristics of the final tablets such as strength, friability, dissolution, and stability (Kestur and Desai, 2017). Several characteristics are important to the functionality of an excipient such as the moisture content, particle size and size distribution, particle shape, degree of polymerization, crystallinity, and solubility (Kestur and Desai, 2017), as well as the bulk and tapped density and compaction properties. Regarding the latter, fragmentation occurs in brittle materials where the breaking of particles exposes new surface area available for bonding (Shubhajit and Changquin, 2018). As MCC and lactose display both plastic deformation and fragmentation, they are commonly used together due to different bonding mechanisms (Kestur and Desai, 2017).

Micro Crystalline Cellulose

Microcrystalline Cellulose (MCC) is a common filler for direct compression as it compacts well without the need for high compression forces (Tobyn et. al., 1998). MCC is produced first by hydrolyzing cellulose to remove amorphous particles and then, by the reaction with a strong mineral acid at high temperatures that produces a crystalline structure. It is then washed and filtered to remove residue (Kumar et. al., 2002, Battista et al, 1961), and spray dried to form porous particles (Guy, 2009). MCC is a slightly acidic compound displaying pH between 5.0 and 7.5; and Avicel PH-102 has a moisture content of less than 5.0% (Guy, 2009), although it is hygroscopic (Good and Wu, 2017).

MCC is a popular filler as it is chemically inert and non-toxic (Guy, 2009). It also displays properties of a lubricant and disintegrant when used in low concentrations in tablet formulations (Guy, 2009). It plastically deforms under pressure and shows a binding effect due to H-bonding. This arises from the proximity of hydrogen atoms and results in a high degree of interparticle bonding (Thoorens et al, 2014). This leads to stable bonds and a well-formed tablet once it has been compacted. However, due to the plastic deformation rather than fragmentation and lack of new un-lubricated surfaces forming during compaction, MCC is highly sensitive to lubricants which may interfere with tablet strength and friability (Carlin, 2008).

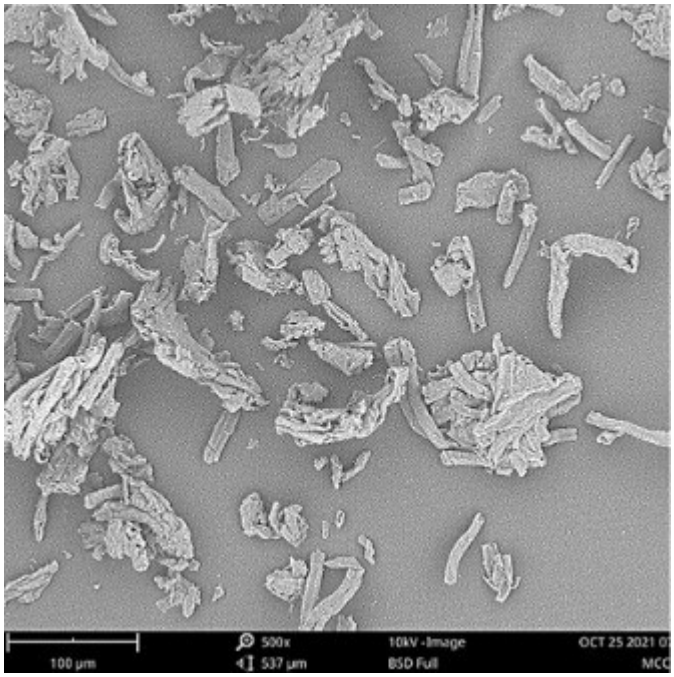


Fig. 1: MCC crystals at 500m magnification (Paredes I Pelejá, 2022)

Lactose

Lactose is a disaccharide molecule found in milk made up of a single unit of each glucose and galactose (Schaafsma, 2008). The glycosidic bond may result in α or β forms; α-lactose monohydrate is most commonly present in a crystal form (Wong and Hartel, 2013). Lactose is industrially produced first by evaporating all water from milk whey, after which it is crystallized before being washed and purified (McSweeney and Fox, 2009). The shape of the crystal depends on the method of precipitation and crystallization, various shapes produced include pyramidal, prism, and tomahawk (Edge et al, 2009).

Lactose is a common filler used in pharmaceutical preparations due to predictability of properties and high stability, and cost effectiveness (Guo, 2004). Lactose monohydrate may be used as a tablet and capsule filler and diluent, a tablet binder, and to a lesser extent lyophilization aid, and a carrier in dry powder inhalants (Edge et al, 2009). The substance contains roughly 5% w/w moisture content however this water is not available for bonding and does not react with the API, lending to a very chemically stable tablet (Kestur and Desai, 2017). Finer grades of lactose are typically

used for wet granulation before compression while larger grades, which are either spray dried or processed to form agglomerates, are more suited to direct compression (Edge et al, 2009). Lactose exhibits brittle fracture during compaction, exposing new particle faces available for bonding and is therefore less lubricant sensitive than MCC, however still exhibits partial plastic deformation and is susceptible to adverse effects of lubrication (Carlin, 2008). This effect is particle size dependent, above 45 µm lactose will display brittle fracture, whereas under 45 µm it will plastically deform or display smoother edges along the fractures (Carlin, 2008; Persson et al, 2022)

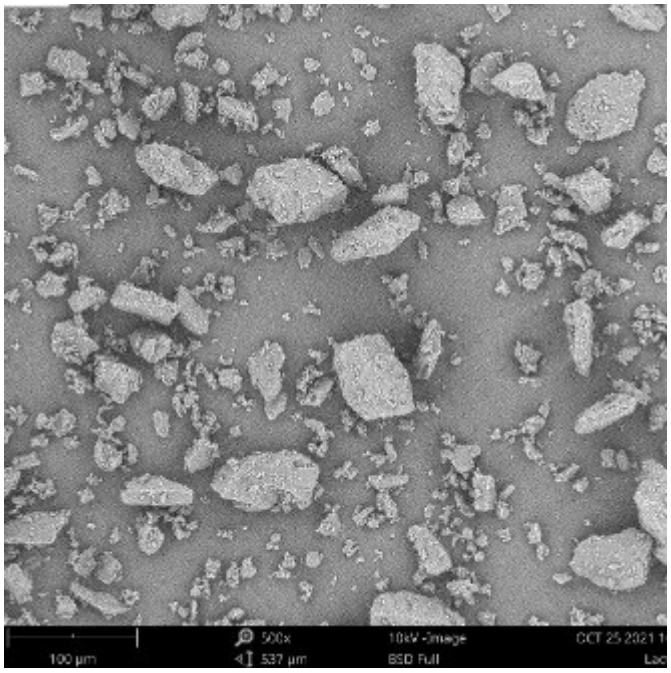


Fig. 2: Lactose monohydrate crystals 500x magnification (Paredes I Pelejá, 2022)

5.1.2 Lubricants and Glidants

Although both lubricants and glidants prevent sticking of the powder by reducing the friction in the powder mixture they refer to slightly different steps of the tableting process (Armstrong, 2008). Glidants refer to substances used to improve the flow of a powder in the die matrix, or to prevent raw powder from sticking at any point before it is compressed into a tablet (Armstrong, 2008).

A lubricant generally decreases the friction between the tablet and the die matrix. To achieve this, a lubricant must form a continuous layer between particles as well as the

die matrix (Li and Wu, 2014). The Johnson-Kendall-Roberts (JKR) theory describes the main methods of reducing adhesion, a reduction in the adhesive forces between particles and matrix and the reduction of area of contact (Johnson, 1985). This is done by a thin film with a low friction coefficient applied as a continuous fluid (Wang et. al., 2010), or by allowing the lubricant to form a continuous or non-continuous physical barrier between the particles and matrix, known as a boundary lubricant (Wang et. al., 2010). In this way it aids the ejection of the tablet from the punch and die matrix (Armstrong, 2008). The most common lubricants used are fatty acids, metallic salts of fatty acids, fatty acid esters, and inorganic materials (Kestur and Desai, 2017).

Lubricants are used in very low concentrations compared to other excipients in the tableting process (Kestur and Desai, 2017) and are selected based on function and compatibility with the formulation. They should be chemically inert with no interaction with either API or excipients and should not negatively impact the final tablet properties. Processing also plays a role in the efficacy of the lubrication. Generally, the lubricant is added into the mixture as the last step before the powder is compressed into tablets, which is referred to as internal lubrication (Wang et. al., 2010). A longer blending time may lead to a decrease in the adhesion forces, and a softer tablet (Carlin, 2008; Kestur and Desai, 2017). As mentioned, brittle materials, such as lactose, are less sensitive to lubricant interference of the bonding process due to new surfaces being exposed during tablet compression (Kestur and Desai, 2017).

An external lubricant is not included into the powder mixture and is placed directly on the surface of the die matrix or punches by fumes. This has less effect on the final tablet properties and is highly effective to prevent sticking (Wang et. al., 2010). Micronized Poloxamer 188 was studied as an internal lubricant for this thesis.

Poloxamer 188

Poloxamer 188 is a water-soluble, non-ionic linear copolymer made up of polyoxyethelene and poloxypropylene units (polyoxyethylene-polyoxypropylene-block-copolymer), with the poloxyethylene units making up approximately 80 % of

the molecular weight (Quadir, 2005). Poloxamers are amphiphilic compounds, most often used as surfactants, emulsifying agents, or aids for gelling (Caffagi et al, 2008). Micronized poloxamer has been milled to approximately 50 µm at low temperature or by fluid atomization to prevent melting (Lisa et al, 2005). Poloxamer as a lubricant has a lesser effect on the final tablet hardness when mixed for a longer period than many traditional lubricants, such as magnesium stearate (Desai et al, 2007).

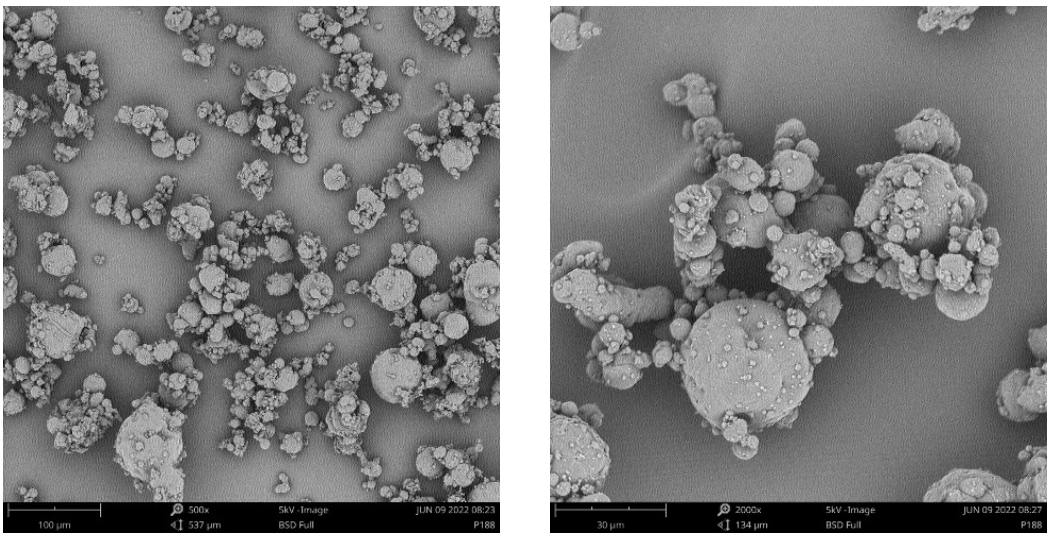


Fig. 3: Poloxamer 188 at 500 (left) and 2000x (right) magnification (SEM figures obtained with help of consultant Bailey, 2022)

5.2 Flow Properties of Powders

Flow properties of a powder are vital to industry, as the vast majority of pharmaceutical excipients in tablets are dry solids. Flow properties are dictated by the excipients used, as there is a low percentage of API present in a mixture (Knowlton et. al., 1994; Medarević et al, 2021), therefore it is important to understand the intrinsic properties and changes to the flow behaviour of a powder used in a pharmaceutical blend before production of dosage forms may begin. Flow of a powder is not a single characteristic; it is instead determined by many factors which may be measured (Hoag and Lim 2008). Factors affecting the flowability of a powder may include changes in moisture content, particle size, particle shape, temperature, density, and the design of containers used for storage and transport (Knowlton et. al., 1994). Based on the powder

behaviour during testing of flow it may be considered free-flowing or cohesive (Sinko, 2011).

Flow behaviour is particularly influenced due to the size and shape of the individual particles. Particle size, and more importantly shape dictate the packing behaviour of a powder bed during stationary phases as the particles will mechanically interlock preventing further movement. Fine particles may remain loosely packed in a container due to the low weight being unable to counteract the other forces acting upon the particle to suspend it, such as van der Waals forces (de Ryck and Hare, 2019; Sinko, 2011). If the mass of the particle is not enough to overcome the van der Waals or capillary forces, the particulate is referred to as a cohesive, poorly flowable (de Ryck and Hare, 2019). On the other hand, finer particles may be added to increase distance between the particles of the powder and decrease van der Waals forces, however an excess of dust may reduce the flow (de Ryck and Hare, 2019).

Friction describes the cohesive forces preventing the particles from sliding past each other freely. The relationship between the normal force pushing the particles together, acting perpendicular to the plane of interface between the moving surfaces, and the force needed to initiate and maintain motion is described by the coefficient of friction (Blau, 2013). The force needed to initiate the movement is the starting friction coefficient, and the force needed to maintain movement is the sliding friction coefficient (Blau, 2013). To initiate sliding, the cohesive forces must be broken, and during sliding the dynamic friction coefficient is generally lower than the static friction coefficient (de Ryck and Hare, 2019); this is important to understand mass flow and fluidization of the powder bed. Cohesion forces, which inhibit the gravitational flow of the powder, are lower during steady flow (de Ryck and Hare, 2019).

This is most evident in the angle of repose when the powder pile is formed with occasional avalanches when particles overcome the static friction force and begin to move. To continue to slide down the sides of the pile, it must be larger and maintain greater energy than the kinetic friction force (Blau, 2013).

Based on the static angle of repose (AOR) value, the following scale of flowability is generally accepted.

Table 1: Flow properties based on Angle of Repose (PhEur 11.0, 2.9.36)

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	> 66

Apart from the static AOR, the dynamic angle is also important to observe. As recently demonstrated for pharmaceutical excipients and binary mixtures, cohesive properties relate closely to avalanching behaviour of a powder bed (Trpělková et al, 2020) in which the surface energetics of particles play an important role (Brokešová et al, 2022). This directly affects powder mixing and dry coating, having a great effect on preparation of the interactive mixtures, in which the drug is adhered to a carrier particle.

Particle flow and avalanching of the powder bed relate to the cohesive forces within this bed. Only a fraction of the powder bed volume is made up of the solid particles; the voids between them are filled with air determining its porosity. This is why a powder is classified as a fluid solid where either the particles or the air makes up the continuous phase (de Ryck and Hare, 2019, Nyström and Per-Gunnar, 1996) and its density is an apparent density.

Bulk density refers to the entire powder bed with air pockets included and is often measured via graduated cylinder or other manual methods (Sinko, 2011; PhEur. 11.0, 2.9.34). It includes gaps between particles as well as pores on the surface of the solid particles. In opposite, true density or density of solids, is measured by excluding the air between particles (Paronen and Ilkka, 1995) by a gas pycnometer. True particle

density only includes the solid portion of a particle and true density includes the pores trapped inside the particle (de Ryck and Hare, 2019).

As a powder is handled, the bulk density will change without a change in the true particle density. A powder bed may undergo many changes in density and different densities are present in the material. The Hausner Ratio and Compressibility Index are two simple parameters to classify the flow properties of a powder (Table 2). They are based on the change in bulk density as a powder is tapped, in order to predict the behaviour of a powder during handling. As the powder is consolidated the packing sequences change and prevent further interparticle movement as the voids between particles are filled and eliminated (Nyström and Per-Gunnar, 1995), this is important for understanding the dynamics of consolidation and how a powder reacts to continuous handling.

Table 2: The scale of flowability by Hausner Ratio and Carr's Compressibility Index (PhEur 11.0, 2.9.36)

Carr's index	Flowability	Hausner ratio
≤10	Excellent	1.00–1.11
11.0–15.0	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Awful	>1.60

Early stages of powder handling may have broad impacts on the finished product, so it is important to investigate how the powder is affected during e.g., vibrations or gravity (Svačinová et al, 2022). At the first 30 taps the consolidation behaviour of different powder materials shows the greatest change in volume and density as well as porosity of the powder bed. This is important to predict the changes in density and the packing behaviour of a powder during handling, and the disposition of a powder bed to packing (Svačinová et al, 2022).

The changes in bulk density and porosity are not only important for the flow of the powder but also for the lubricant effectiveness. The porosity and bulk density changes may decrease the effectiveness of the lubricant. The first reason is that there are more free surfaces to coat as well as pockets in which the lubricant may pack into. As a result, it does not come in to contact with all particle surfaces, and second, an increase in particle rearrangement during compression will disrupt its efficient coating (Bos et al, 1991).

The glidant is important for the movement of the powder between hoppers, into the die, and between machinery components. Mass flow through a hopper orifice is the generally preferred type of flow during powder handling. Such flow is characterised as all material is in motion and this prevents segregation and stagnation of material (Carson and Pittenger, 1998). In addition to a hopper design, sufficient flowability of a powder mixture is needed to achieve mass flow. Contrary, if the material is unable to achieve mass flow it will instead undergo a funnel flow, in which only the centre of the material flows toward to orifice creating gaps and ratholes (Fitzpatrick, 2014). Such flow design is often source of manufacturing troubles.

In conclusion, the material density and flow will have a large impact on the compression process of a powder and the uniformity of tablets. Density is important for the correct filling of a die as most dies are filled volumetrically and the press is either set to a specific compression force or a specific position (Carson and Pittenger, 1998). If the press is set to a predetermined position the bulk density must be consistent to ensure the pressure exerted on the tablets is consistent, and if the pressure is constant the die must be filled uniformly to produce tablets of the same height (Carson and Pittenger, 1998).

5.3 Compression Process

Compression is the rearrangement of particles within the powder bed and the formation of new bonds between the particles under force. Powders intended for solid dosage forms, especially tablets, must go through some compression process. Successful production of tablets can be categorized into three main components, the

compressibility, compatibility, and manufacturability of the powder (Osamura et al., 2016). Compressibility refers to decrease of space between the particle and increase in density during compression within the die; compaction is the process in which particles take new shapes and contributes to the mechanical strength of the tablets. Manufacturability more generally refers to the ease in which a powder is able to be processed in industry, this may include even flow, lack of sticking, or low hygroscopicity of a powder, the factors commented also in the previous chapters. The lesser compressible material generally dictates the behaviour and the final properties of the tablet (Reynolds et al, 2017). Therefore, a good compressibility, compatibility, and manufacturability of a powder results in consistent tablets and a reduction in tablet failures, such as capping, lamination, or pitting (Osamura et al., 2016). Lower bulk density leads to better compressibility (Kestur and Desai, 2017).

Tablet compression is the rearrangement of powder particles into a compact shape that remains once the compression forces have been removed. During compression the material undergoes transitional restacking where the gaps between particles are eliminated, as force is continued to be applied the contact points between particles form bridges that will be permanent after the force is removed (Young 1996). The traditional graphical representation of the compression process is described by the force-displacement record (F-D) (Fig. 4).

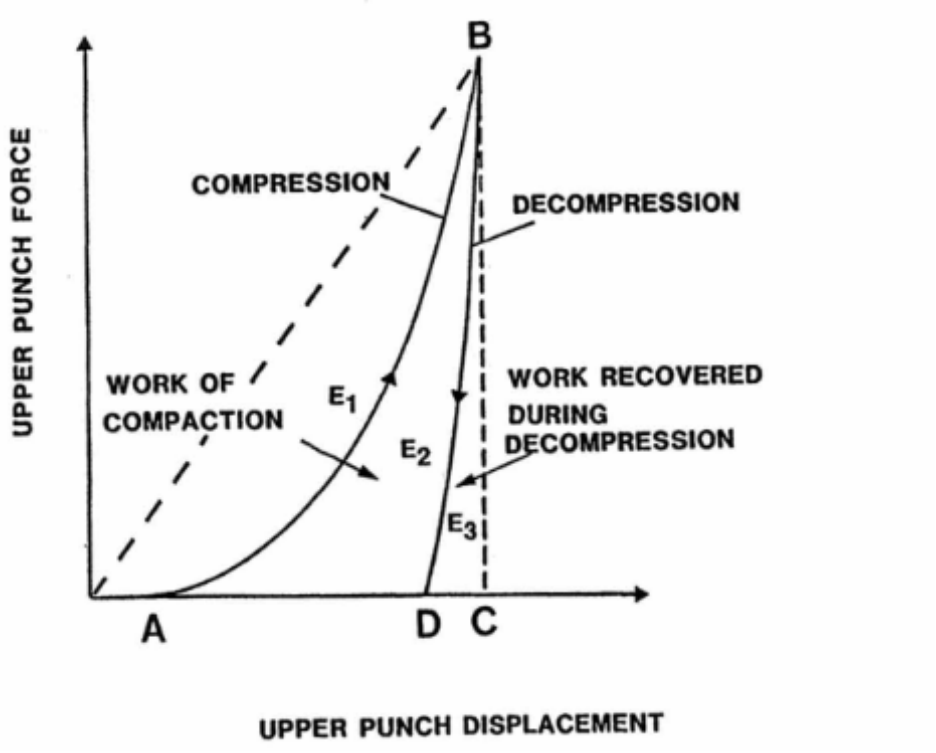


Fig. 4: Force-Displacement graph demonstrating the energies consumed in compression steps (Ragnarsson, 1996)

The F-D record is the area under the curve, ABC, and shows the total work performed on the powder bed by the punch coming into contact with the powder bed inside the die (Ragnarsson, 1996). A stress gradient is present in the powder column and the force of the press is transferred throughout the powder bed (Kervinen et al, 1993). The powder particles first go through elastic, then plastic deformation, finally the particle breaks, and the newly formed fragments fill the voids and decrease the volume of the compact.

Work performed by the press does not entirely go into creating bonds between particles, energy is consumed to rearrange the particles, by friction between particles and the die wall, between particles and each other, and elastic and plastic deformation (Ragnarsson, 1996). Energy is also lost towards heat as compression is an exothermic process; therefore the force displacement profile does not account for the entire energy of the press (Coffin-Beach and Hollenbeck, 1983). As illustrated, it is further divided into three different energy profiles of compression referring to different steps during

tableting (Ragnarsson, 1996). The energy spent on removing the gaps between particles, E_1, is the *energy of precompression*, which is reliant on the friction between both particles and the surface of the matrix, there is an increase in friction and contact between the powder and wall of the die (Armstrong, 2008).

The energy remaining in the tablet, responsible for forming the irreversible bonds and final shape is called the *energy of plastic deformation,* E_2. The yield point is the force applied at which the material undergoes plastic deformation and permanent bonds are formed. Under this threshold the material exhibits elastic deformation and will not retain its shape once the force is removed (Cocks, 2008).

Elastic deformation is not permanent and E_3 is therefore the energy lost, or work recovered, once the tablet has finished compression and the force is removed (Ragnarsson, 1996). E_{lis} the *total energy* remaining inside the tablet that is not released once the tablet is no longer under force, and contributes to the final shape (Ragnarsson, 1996).

Plasticity refers to the amount of energy that contributes to the irreversible deformation of the tablet. The higher percentage of compression energy that allows for plastic deformation rather than elastic deformation the stronger the tablet will be, and the ratio between E_1 and E_{lis} should be a large as possible, ideally a large proportion of the work put into the powder bed will be used to form bonds and maintain the compact (Ragnarsson, 1996).

Plastic deformation takes place along the slip planes of the particles (Ragnarsson, 1996). This process can happen several times to the same particle as it is compacted (Nyström and Per-Gunnar, 1996). Smaller particles display more plastic and less brittle behaviour, as particles undergo fragmentation, they are less likely to fracture continuously and instead are more inclined to undergo plastic deformation (Alderborn, 1995). MCC is prone to plastic deformation while lactose mainly undergoes fragmentation, leading to new bonding surfaces (Nyström and Per-Gunnar, 1996).

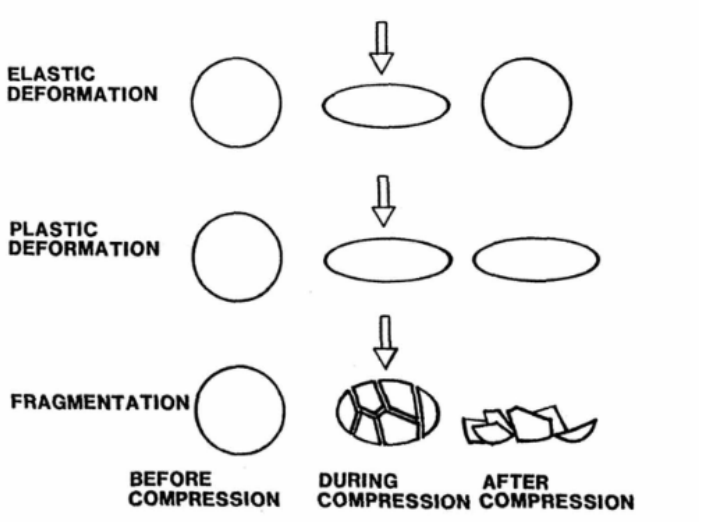


Fig. 5: Types of deformation present in the compression process (Ragnarsson, 1996)

There are several types of bonds able to be formed between particles; solid bridges, moveable bridges, mechanical interlocking, and attraction between particles. Dry powders mainly form solid bridges accounting for most of the tablet strength before intermolecular forces of interlocking particles (Nyström and Per-Gunnar, 1995). This shape is held by the rearrangement of particles, new bonds being formed between the particles, and plastic deformation, whereas the elastic deformation is the energy recovered once the forces have been removed from the tablet (Wang et. al., 2010).

The end product of compression is a tablet with 0 percent porosity, if force is continuously applied the voids will be completely eliminated (Mahmoodi, 2013). However, this is not realistic and the material is still somewhat porous. The exact porosity will depend on the desired outcome of the tablet, fast dissolving or soluble tablets for instance must be more porous. Typically, a compaction pressure of 300-500 kPa will result in a tablet with 1-25 percent porosity (Nyström and Per-Gunnar, 1996), and most pharmaceutical tablets display between 10 and 30 percent porosity (Amidon, 2011).

Once the compact has been formed it must then be removed from the die in a step known as ejection. Elastic rebound is important during ejection, as the tablet will

slightly expand exerting force on the die that must be overcome to ejected, this is more pronounced in fragmenting materials as the elastic forces are not recovered like those of more plastically deforming materials (Delacourte et al, 1993; Imayoshi et al, 2022; Uzondu et al, 2018). The resistance exerted by the tablet on the die walls does not change during ejection (Delacourte et al, 1993). It is important for the tablet to overcome adhesive forces to be released easily from the die and to prevent wear on the tooling of the machinery. The cohesive forces of the newly formed tablet must be higher than the adhesion between the powder and the walls of the die, elsewise the tablet will stick (Al-Karawi and Leopold, 2018; Paul et al, 2017).

Too high **ejection force** due to tablet friction may damage the tablet (Sun, 2015). The adhesive forces between the tablet and die wall (the initial friction) form during the static phase; contrary, sliding friction is the main force acting against tablet ejection in the kinematic phase (de Backere et al, 2023; Uzondu et al, 2018). Ejection is much faster than compression and as a result will have higher friction, despite the pressure on the die wall sharply decreasing once compression force is removed (Sajdadz et al, 1993; Imayoshi et al, 2022). Contrary, a higher speed of compression increases friction.

Lubricants reduce the shear stress between the compact and the die matrix during compaction but especially during ejection, the higher friction process (Li and Wu, 2014). Having good lubrication will reduce material build up on the die during compression and ejection (Sun, 2015). Lubrication effect is therefore most noticeable with the sharp decrease in ejection force (Wang et. al., 2010). This may be achieved by external lubrication, however in order to reduce internal friction and powder cohesion, internal lubrication is needed. For an effective internal lubrication, the lubricant should be able to adhere to the other excipient particles and retain its dispersion throughout the mixture as described above in Chapter 5.1.2 (Li and Wu, 2014). The lubricant film on the die wall can be unfortunately disrupted by the high speed of compression, leading to a decrease in lubricant effectiveness (Imayoshi et al, 2022).

5.4 Tablet Properties

After compression tablets may go to further production such as coating, and must retain suitable strength to withstand the processing, once the tablet has been completed it must be robust in order to be packaged, transported, and handled (Amidon, 2011), while also maintaining bioavailability in line with pharmacopeial specifications (Davies and Newton, 1995). Powder compacts may be brittle and tend to fracture before there is visible damage or deformation (Davies and Newton, 1995), therefore it is important to determine the mechanical strength of a tablet before handling because a weak tablet or damage may not be visible. For instance, capping and lamination are most commonly seen as a function of elastic relaxation of the tablet and may not be apparent immediately after compression (Lum, 2011).

Crushing strength increases with increasing compression load while porosity of the tablet decreases (Armstrong, 1995). A decrease in particle size of raw substances leads to an increase in the tablet strength, due to the increased surface area available for bonding (Alderborn, 1995). However, the strength of the tablet finally depends on the combination of material properties (particle size, distribution, density, and surface area), bonding mechanism (Nyström and Per-Gunnar, 1996), and manufacturing and compression process (Egart et al, 2014; Peddapatla et al, 2022; Marshall, 2020). Crushing force/ tensile strength is therefore an important in process control to ensure the proper settings of the machines and consistent results (Amidon, 2011).

Lubrication generally has a negative effect on tablet strength, as the lubricant interferes with the bonds between particles by forming a physical barrier (Bolhuis and Hölzer, 1996). This is less pronounced in materials that undergo fragmentation, as this exposes new, clean bonding surfaces (Nyström and Per-Gunnar, 1995). Brittle excipients, such as lactose, display higher tensile strength and less sensitivity to lubricants than plastic or elastically deforming excipients (Peddapatla et al, 2022; Morin and Briens, 2013). Friability of tablets however, decreases with higher compaction pressure regardless of lubricant concentration (Plaizier-Vercammen and van den Bossche, 1993). External lubricants, applied directly to the die matrix, have a lesser effect on the bonding and tensile strength than internal lubricants (De Backere et al, 2021).

Although friability decreases with an increase in compaction pressure there is a risk of prolonging the tablet disintegration, as porosity also decreases. A balance must be struck between tablet strength and disintegration. There is a linear relationship between the compaction load and the surface area of a tablet. The higher the compaction pressure the smoother a tablets surface will be, with less pores and imperfections (Armstrong, 1995). The porous structure of the tablet depends on many factors such as granulometric characteristics, compression characteristics, bond strength, interactions between the excipients (Jange et al, 2023).

The porosity of the tablet also dictates the disintegration of the compact. Disintegration is breaking of interparticle bonds formed during the compression process (Jange et al, 2023). Tablet disintegration is an important first step for the dissolution, release and in vivo behaviour of the drug (Juppo et al, 1993). The speed of disintegration is dependent on liquid penetration through the porous structure as liquid enters the tablet through the capillary stage, leading to the swelling and then the breaking a part of the tablet as cohesive forces are overcome (Jange et al, 2023). Microcrystalline cellulose is a well disintegrating excipient even when the porosity is low, as it has a high portion of hydrogen bonds, and serves to make the capillaries larger during water uptake (Lerk et al, 1979). Many lubricants, which cover the surface of the particles, are hydrophobic (Bolhuis and Hölzer, 1996) and can therefore increase tablet disintegration time by creating a film between the disintegration medium and the tablet (Morin and Briens, 2013; Li and Wu, 2014; Kuck and Breitkreutz, 2022). However hydrophilic substances, such as poloxamers, may also increase the disintegration time by competing for water instead of having all water available for interactions with the other excipients (de Backere et al, 2023).

6 Experimental Section

6.1 Materials

Microcrystalline cellulose (AVICEL PH102, MCC102) Mingtai Chemical Co. Ltd. (Ph.Eur.)

Lactose monohydrate (L) Lactochem® (Ph. Eur.)

Kollipohor® P188, micro (Luptro micro 68, Poloxamer 188) Sigma-Aldrich, Germany

6.2 Equipment

Density tester SVM 102 (Erweka®, Germany)

Helium pycnometer AccuPyc II 1340 (Micromeritics Inc., USA)

Tablet tester 8M Pharmatron (Dr. Schleuniger®, Germany)

FT 2 Tablet Friability Tester (SOTAX, Czech Republic)

ZT301 Disintegration Tester (Erweka®, Germany)

3 Dimensional shaker T2F, (Turbula®, Switzerland)

Granulate flow tester GTB (Erweka®, Germany)

GX-124A Analytical Scale (Helago, Czech Republic)

T1-FRO 50 TH. AIK Tabletle Press (Zwick-Roell, Switzerland)

Vacuum Drying Oven VD 23 (Binder GmbH, Germany)

Malvern Mastersizer 3000 (Malvern Instruments Ltd., UK)

6.3 Methods

Bulk properties of powders were measured under standard laboratory conditions of relative humidity 30 ± 5 % and temperature 24 ± 3 °C.

6.3.1 Preparation of Mixtures

Firstly, the powder mixture consisting of raw materials Microcrystalline Cellulose and Lactose in a 1:1 ratio was prepared (MCC/L). The sandwich method was used to ensure even distribution and homogeneity, 40 grams of each powder was added to a 1.5 litre plastic jar, alternating between the two until a total of 400 grams is reached.

The container is then closed and put into a 3D-mixer for seven minutes at a speed of 34 rotations per minute.

Once the powder mixture MCC/L is made the lubricant is added using the same mixing conditions and layering method. Poloxamer 188 (P188) was added in concentrations of 0.5, 1.0, 1.5, and 2.0 percent to 300 grams of MCC/L powder mixture.

6.3.2 Loss on Drying

To determine the loss on drying (LOD) and moisture content of the P188 five samples of approximately 3.000 g were placed on the aluminium tray and the dryer was set to 45 °C to accommodate the low melting temperature of poloxamer. The apparatus was set to a maximum of 15 minutes drying time or until the moisture level was stabilized. The LOD was then recorded, and the powder was immediately placed in a sealed container to be used for true density measurement.

For pure poloxamer drying, the poloxamer was placed in the vacuum dryer and dried for 1 hour at 40°C in order to prevent melting of the sample.

6.3.3 Pycnometric Density

The true density d_s (g/mL) of both powder mixtures and tablets were measured using a Helium pycnometer. 24 hours before use the pycnometer was switched on and calibrated according to manufacturer instructions. During all handling of the pycnometer, gloves were worn to keep the measuring cell free of dirt and oils.

When testing the powder mixtures, the measuring cup was filled to approximately 80 percent of the total capacity with dried powders (see previous section). The powder was sieved through a 0.5mm mesh before loading into the cup. Once the cup was filled with powder and the weight recorded on an analytical balance, and the cup was placed in the pycnometer chamber, the weight of the sample was entered into the machine, and five readings were selected. The measurement was repeated twice with a new powder portion each time.

Finally, porosity of powder bed P (%) was calculated using formula:

$$P = (1 - \frac{\mathrm{d}b}{\mathrm{d}s})100 \qquad (1)$$

When measuring tablets, six tablets were placed in the cup and measured as above.
Porosity of tablet P_{tbl} (%) was calculated using the measured tablet true density of 6 tablets and the theoretical bulk density estimated from the geometry of cylindrical compact (i.e., tablet).

6.3.4 Particle Size

Particle size was measured according to the European Pharmacopoeia 11.0. A small amount of powder was placed in the Mastersizer 3000 analyser and measured according to manufacturer instructions for dry cell measurement. Data was recorded for X_{10}, X_{50}, and X_{90} and of poloxamer.
Data for lactose and MCC were received from consultant for comparison reason (Bailey, 2022).

6.3.5 Bulk and Tapped Density

The bulk and tapped density were determined using an Erweka tapping machine according to the European Pharmacopoeia 11.0 (2.9.34). Freshly mixed MCC/L powder with lubricant P188 in different concentrations was used and handled carefully to avoid altering the density and prevent the powder settling before the test was carried out.
A 100mL graduated cylinder was cleaned and dried before adding 35.00 g of powder using a paper funnel. After filling the cylinder, the bulk volume V_0 (mL) was recorded prior to tapping. The bulk density d_c (g/mL) was calculated as a ratio of the known mass and volume.
The tapped volume of the MCC/L with lubricant was recorded after 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 100, 250, 500, and 1250 taps (final tapped volume V_t (mL)). The tapped density d_t (g/mL) at each consolidation step was expressed and followed with calculation of Hausner ratio (HR) and compressibility index (CI) using the following formulas:

$$HR = \frac{db}{dt} \qquad (2)$$

$$CI = \frac{dt-db}{dt} \quad (3)$$

Five measurements of each lubricant concentration in the mixture tested were carried out.

6.3.6 Angle of Repose

The test for **angle of repose** (AOR) was carried out according to the monograph in the European Pharmacopoeia 11.0 (PhEur. 11.0, 2.9.36). To determine the angle of repose approximately 50.00 g of powder was loaded into a 200mL stainless steel conical funnel with an orifice above a levelled bed of the same powder on a rimmed plate with a 10.0cm diameter. A 15mm orifice was used for P188 concentrations of 1.5 and 2.0 percent, however 25mm orifice was used for P188 concentrations of 0.5 and 1.0 percent.

Initially the bottom of the funnel was in contact with the powder bed and the funnel was slowly raised as the MCC/L flowed out of the orifice. The bottom of the funnel was kept as close to the top of the emerging cone as possible and raised slowly to avoid dropping the material from a height and impacting the cone. Due to the extremely poor flow of the material, slight tapping on the funnel was required in order to dislodge the powder continuously.

A minimum of five measurements of each P188 concentration were taken by carefully building a powder cone until the mixture flowed over all sides of the plate. Once the cone was complete the height h (mm) was noted using a micrometer. The cone was carefully scraped off the plate using a paper card and weighed.

The height and weight of the cone (m (g)) were used to calculate volume (V (mL)) of the cone and pile density d_p (g/mL) of the sample, and to express the angle of repose AOR (°) using the following formulas where *r* is the radius of a base (mm).

$$V = \frac{1}{3}\pi r^2 h \quad (4)$$

$$d_p = m/v \quad (5)$$

$$AoR = tan^{-1}\left(\frac{h}{r}\right) \quad (6)$$

6.3.7 Flow Rate

Flow rate of the powder mixtures was tested using an Erweka tester in agreement with (PhEur 11.0, 2.9.36) Approximately 50.00 g of sample was loaded into the above-mentioned stainless steel conical funnel with a 25mm orifice.

A minimum of 5 measurements of each P188 concentration, 0.5, 1.0, 1.5, and 2.0 percent, were preformed and time was measured to the hundredth of a second and recorded. The mass flow rate of the powders, Q (g/s), was calculated.

6.3.8 Compression of Tablets

After preparing the powder mixtures, 30 samples of approximately 0.5000 g were weighed on an analytical balance on paper cards (precision 0.1 mg) and powder weight was recorded, all samples were between 0.5085 g and 0.5015 g.

The powders were then loaded one at a time into a 13mm die matrix with care taken to brush all the powder from the card into the powder bed, and the upper punch was placed on top without shaking the die or pressing the punch down to avoid disturbing the powder bed. The die was then placed in a Zwick-Roell hydraulic press, and the initial height of the powder bed was registered (h_d).

Each lubricant concentration batch was compressed with 30 tablets each at three different forces of 5 kN, 7 kN, and 10 kN, with a pre-compression force of 2 kN and a punch speed of 20 mm/min. The energies of compression (*force-displacement* method), plasticity, tablet height both at (h_{max}) and after (h_0) maximum compression force, and tablet diameter (d_0) were measured using the press software. Following compression, the cross bar of the die was removed to allow tablet removal and ejection force was measured and recorded on the same press, generally for the first 10 tablets of each batch.

The die was then removed from the press and the tablet removed, labelled, and placed in a closed glass or plastic jar.

Between each ejection force and new compression, the punch and die were cleaned by dry cloth or using purified water and ethanol when required to prevent sticking of the tablets. The punch was dried before the next powder was loaded.

The tablets were allowed to rest for a minimum of 24 hours after compression to allow relaxation and to measure the dimensions and to continue with tablet testing.

6.3.9 Friability

Friability of tablets was tested according to the European Pharmacopoeia 11.0 monograph for uncoated tablets (2.9.7). 13 tablets were selected at random from each batch of compression totalling a weight of approximately 6.5000 g. Tablets were carefully dedusted and weighed before being placed in a clean drum with a speed of 25 revolutions per minute for four minutes (a total of 100 revolutions). Once the tablets were finished tumbling they were again dedusted using a soft brush and weighed. After weighing the loss of the tablet mass (%) was calculated.

6.3.10 Tensile Strength of Tablets

Five tablets were selected to test crushing force using a tablet crusher. The tablets were placed horizontally in the apparatus to measure the exact tablet diameter after relaxation, followed by placing them vertically to measure tablet height (h_{24}). Following measurement of dimension, the tablets were crushed in the same machine horizontally. After each tablet the apparatus was cleaned with a dry brush.

Once the crushing force CF (N) was registered it was used to calculate the tensile strength TS (MPa) of the tablets, using the following formula.

$$TS = \frac{2\,CF}{\pi\,D\,h_{24}} \tag{7}$$

Where

CF = crushing force (N)

D = diameter of tablet (mm)

h_{24} = height of tablet (mm)

6.3.11 Disintegration time

Disintegration of tablets DT (min) was tested according to the monograph for normal sized tablets and capsules (PhEur11.0, 2.2.32). Six tablets were tested using a basket apparatus. The tablets were placed in the basket and lowered into purified water heated to 37°C ±0.5°C. The apparatus raised and lowered tablets at a speed of 32 cycles per minute. The time of disintegration was recorded when the complete tablet had disappeared from the basket and there were no fragments left on the bottom mesh of the basket. Between each batch of tablets, the apparatus was cleaned, and fresh medium was added and heated.

6.3.12 Data processing

The data were processed using MS Excel. Statistical evaluation was performed using analysis of variance (ANOVA) at $\alpha = 0.05$.

7 Results and Discussion

In this thesis, the influence of Poloxamer 188 micronized (P188) in a concentration range of 0.5 – 2.0 % on the flow, consolidation, and compaction properties of binary filler MCC/L mixture as well as properties of the tablets produced at three compression forces were investigated. Samples are coded regarding the concentration of P188, e.g., P188 2.0 means 2% of P188 by weight added to MCC/L binary mixture.

The results both for bulk and flow properties of MCC/L were obtained from a previous thesis (Paredes I Pelejá, 2022) and the tests were not performed at the same time as the tests of MCC/L containing P188. They have been included here as a comparison of lubricated and unlubricated MCC/L mixtures. The tablet properties for MCC/L mixtures were obtained from consultant experimental data for the same reason (Bailey, 2022).

Optimum water content for powder intended for tablet compression is generally regarded as 5-8 percent (Sheath et al, 1980); with increased water content leading to powder sticking, and lower moisture content lending itself to capping of the tablets (Crouter and Briens, 2014). Powder samples were therefore characterized by the water content using the loss on drying (LOD%) method (PhEur, 11.0, 2.2.32). LOD for both lactose and MCC is generally carried out at a much higher temperature of 105℃ (Paredes I Pelejá, 2022), but due to the low melting temperature of poloxamer of between 52 and 57 °C (Harmely et al, 2020), a low drying temperature of 45℃ was used. Drying of poloxamer itself was carried out in a vacuum dryer.

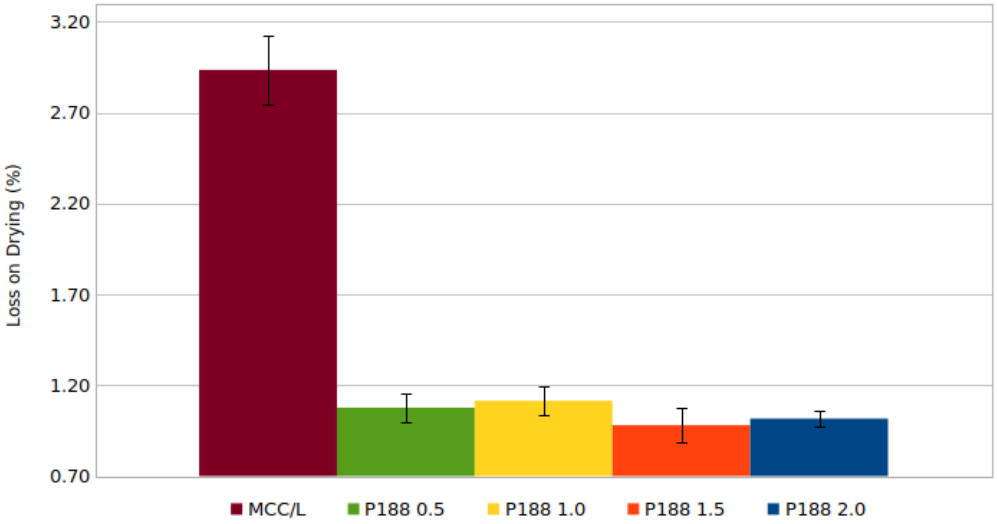


Fig. 6: Effect of lubricant concentration on the moisture content of MCC/L (*Data for MCC/L (Paredes I Pelejá, 2022)

As can be seen in Fig. 6, the samples had a much lower water content of approximately 1 percent, between 0.98% and 1.11%, with no significant difference between concentrations of P188. MCC/L without P188 displayed nearly triple the loss on drying with 2.94% LOD. Lactose typically displays 5% w/w water content (Edge et al, 2009), however has a very low loss on drying around 0.5% (DFE Pharma), where MCC has a loss on drying of maximum 7% (Roquette Pharma). Poloxamers alone display very low water sorption (Burnett et.al., 2015), and due to presence in low concentrations, it did not impact hygroscopicity of the powder mixture. The mixtures containing P188 were also dried at a much lower temperature to account for the low melting point of poloxamer, however the LOD remains within the typical ranges for water content.

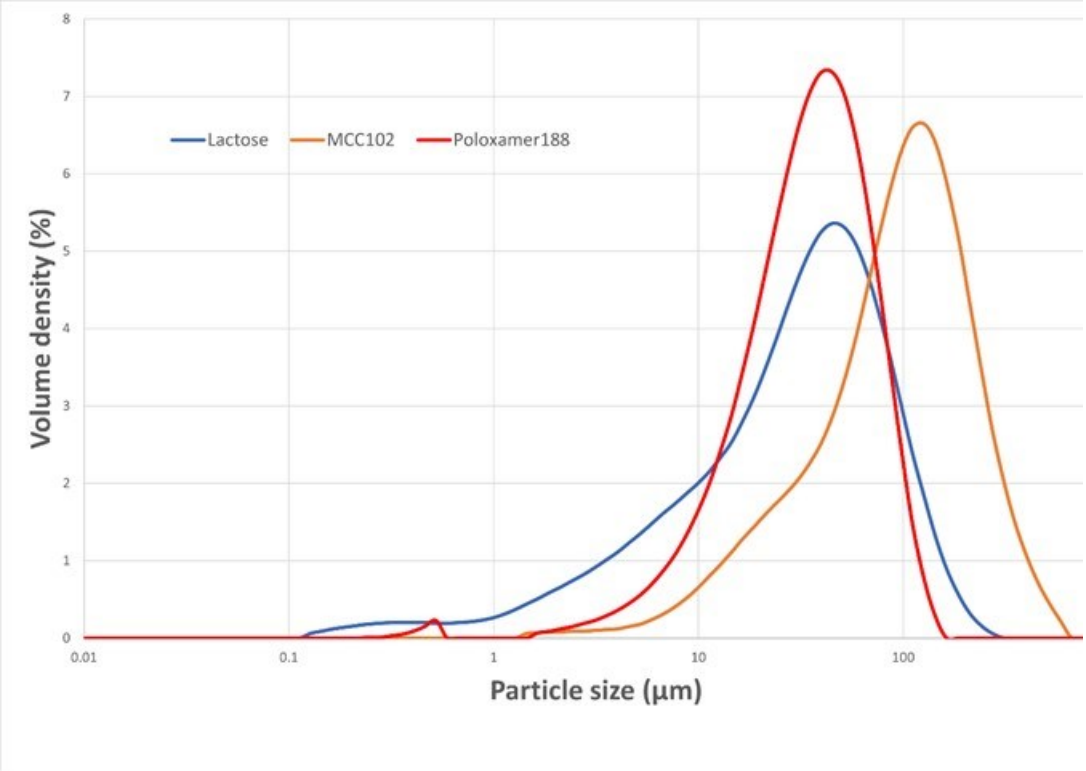


Fig 7: Distribution of particle size for Lactose*, MCC*, and Poloxamer (*Data taken from Bailey, 2022)

Table 3: Cumulative Frequencies of Particle size (*Data taken from Bailey, 2022)

	Span	**X_{10} (µm)**	**X_{50} (µm)**	**X_{90} (µm)**
MCC*	2.241	23.4	105.0	259.0
Lactose*	2.786	4.34	34.3	100.0
Poloxamer*	1.866	12.4	38.0	83.3

Fig. 7 illustrates the distribution of particle size as measured by laser diffraction. Powders made up of homogenously sized particles i.e. those with a smaller span, display better flow, and particles that are too fine are susceptible to Van der Waals forces resulting in sticking (de Ryck and Haare, 2019; Sinko, 2011). Lactose displayed the larger span than MCC; Poloxamer had a lower span than both MCC and lactose, although the mean size X_{50} was similar to lactose. This resulted from a much lower X_{90} than the fillers.

7.1 Bulk and Flow Properties of Powder Mixtures

Fig. 8 illustrates the results of **bulk density** d_c (g/mL), which is generally used to characterize the flow properties of a powder. MCC/L has a much lower bulk density and therefore less settling than powders containing P188 due to agglomerates of fine, sticky particles filled with air voids. The more P188 added to the mixture, the less friction there was between the particles and the particles more readily fill the gaps between larger agglomerates. Filling the voids with smaller particles instead of air increases the bulk density of the powder bed (Carson and Pittenger, 1998). The highest bulk density was noted for the 1.5% concentration of P188.

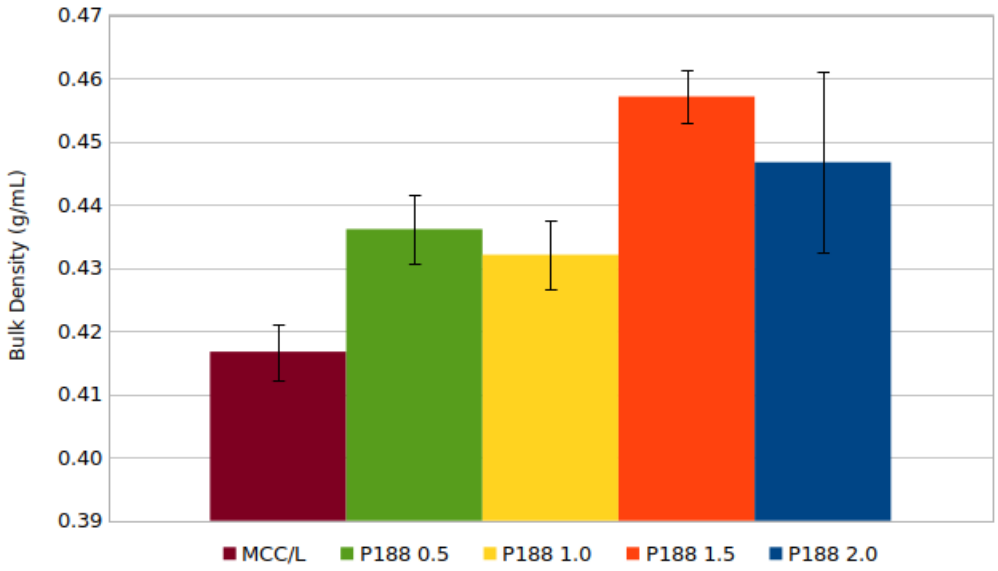


Fig. 8: Influence of lubricant on bulk density d_b (g/mL) (*Data for MCC/L taken from Paredes I Pelejá, 2022)

During pharmaceutical production of tablets, a powder mixture is manipulated many times and moved before being compressed. The effect of tapping and handling of the powder leads to a difference between unsettled and settled volume and density. An ideal powder would display very little consolidation and remain free flowing during all steps of a process or handling. The investigation of consolidation of behaviour of powder and the estimation of tapped density d_t (g/mL) are therefore important in

achieving correct dosing by consistent filling of the die (Zhong et al, 2021; Schomberg et al, 2021).

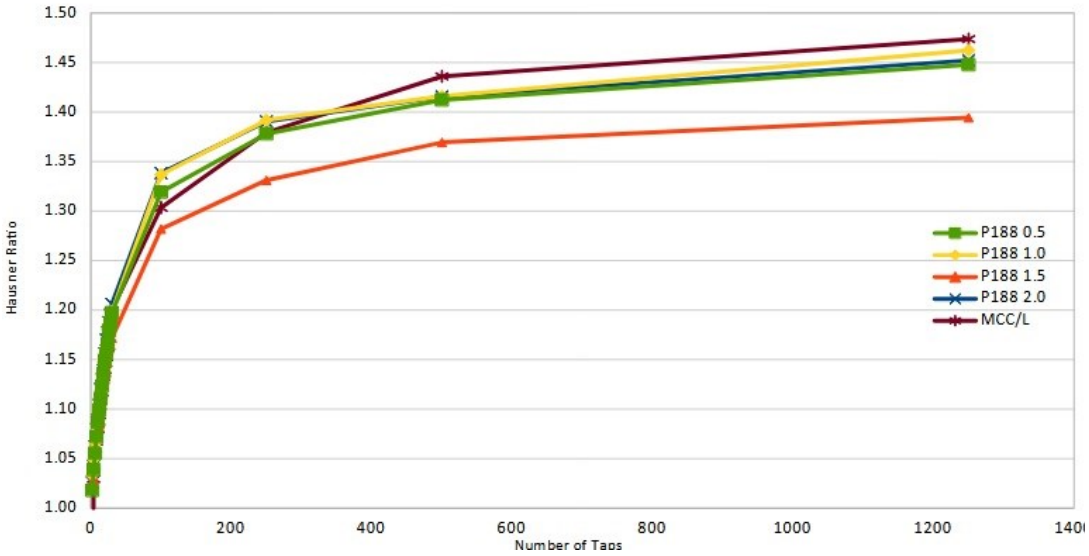


Fig. 9: Hausner ratio as influenced by concentration of P188 and number of taps (*Data for MCC/L taken from Paredes I Pelejá, 2022)

Hausner Ratio (HR) is used to characterize the flow behaviour of a powder by describing the relationship between handling and compression tendencies of a material, the lower the HR is, the less change there is between the bulk and tapped powder volume and density. A powder with good flow will settle without sticking and tapping and handling the powder will have very little influence on the density. This ensures predictability as well as easy handling when working with a raw material (Tangirala, 2014). The changes in HR value during tapping are illustrated in Fig. 9. According to the final HR and CI values at 1250 taps (Table 4) all samples tested displayed either poor or very poor flow properties as found in the European Pharmacopoeia (PhEur 11.0, 2.9.36). However, the addition of P188 improved the flow properties of the filler mixture a small amount, albeit not enough to improve the flow to a more desirable classification and thus better workability and handling.

Table 4: Dependence of Hausner Ratio and Carr Compressibility Index on P188 Concentration (*MCC/L Data taken from Peredes I Pelejá, 2022)

P188 Concentration	Hausner Ratio	Compressibility Index
MCC/L*	1.51 (0.01)	33.93 (0.52)
0.5	1.45 (0.02)	30.91 (1.19)
1.0	1.46 (0.02)	31.60 (1.08)
1.5	1.39 (0.02)	28.28 (0.82)
2.0	1.45 (0.03)	31.11 (1.46)

During the testing of tapped density, over-tapping of the powder should be avoided as it may lead to aeration when the powder again becomes unsettled, and air is trapped in the powder bed (Saker et al, 2019). Aeration of the powder and thus a decrease in tapped densities was not an issue during these tests, as the powder remained settled.

Consolidation of a powder describes the changes in density and is important to understand how the powder answers to handling. Apart from the conventional testing of bulk and final tapped density, the dynamic change in tapped density at early consolidation was recommended to study in order to understand the behaviour of a powder during manipulation and production (Abdullah and Geldart 1999; Lumay et al, 2012). At the first 30 taps, the consolidation behaviour of different powder excipients and binary mixtures was investigated by Trpělková et al. 2020 and Svačinová et al. 2022 and the influence of particle size and shape was clearly demonstrated. Fig. 10 shows the effect of initial consolidation within 30 taps in detail for P188 samples.

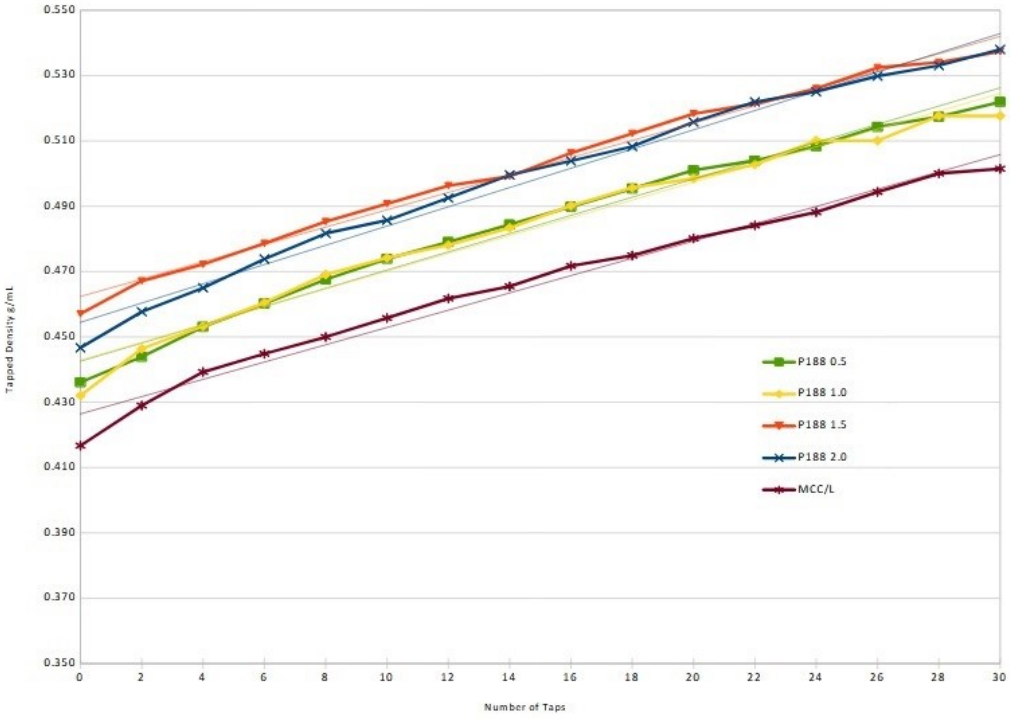


Fig. 10: Influence of lubricant concentration on the tapped density for the first 30 taps (*Data for MCC/L taken from Paredes I Pelejá, 2022)

The change in tapped density seems to depend mainly on the bulk density of the powder rather than a change in behaviour during tapping. All powder samples displayed similar consolidation behaviour during tapping. Although, the densities of the powders reflect the amount of lubricant added. As illustrated in Fig. 10, the change in tapped density by consolidation within 30 taps is roughly linear. This can be described by linear regressions 8-12 with coefficients of determination R^2 in a range of 0.974 to 0.991. This means that d_t would be predictable by both the number of taps and composition of the powder mixture.

d_t (MCC/L) = 0.421 + 0.0052 N (R^2 =0.980) (8)*

d_t (P188 0.5) = 0.437 + 0.0056 N (R^2 = 0.986) (9)

d_t (P188 1.0) = 0.437 + 0.0054 N (R^2 = 0.974) (10)

d_t (P188 1.5) = 0.457 + 0.0053 N (R^2 = 0.991) (11)

d_t (P188 2.0) = 0.449 + 0.0060 N (R^2 = 0.986) (12)

*MCC/L data taken from Paredes I Pelejá, 2022.

The highest slope of 0.0060 was observed for 2 % of P188 addition showing the fastest change in tapped density due to rearrangement of particles. Such consolidation behaviour would be advantageous to prevent the volume reduction during occasional manipulation of the powder mixture.

The **angle of repose** (AoR) is another simple test to determine the flow behaviour of a powder and the interactions between particles. The greater the adhesion forces of the powder the greater the angle of repose. Powders with better flow properties will form low piles and therefore have a smaller AoR (Shah et al, 2008). The circular base and slow formation of a pile was used in the experiment, the diameter of the funnel is not generally defined. As no concentration of P188 would flow through a 15mm orifice, and the 25mm orifice use resulted in large portions of powder dropping, so the decision was made to carry out the test with a 15mm orifice, despite the poorer flow and slight tapping on the funnel wall. All concentrations of P188 were prone to avalanches and large portions of powder dropping irregularly which resulted in some difficulty in achieving a well-shaped pile as illustrated in Fig. 11

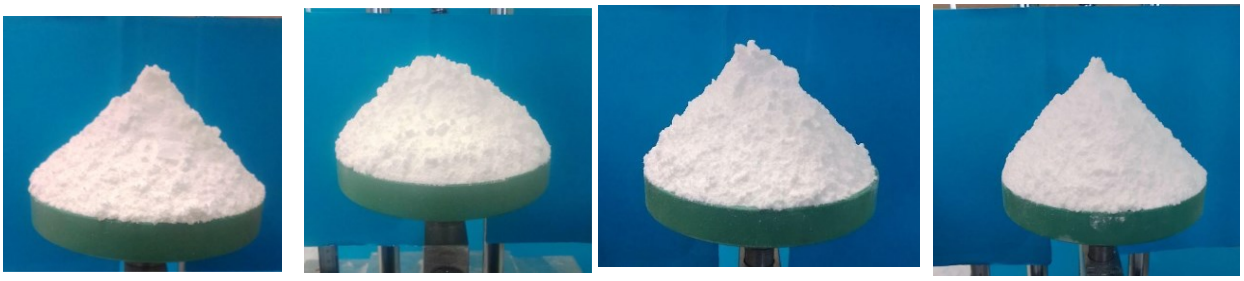


Fig. 11: Representative angle of repose for MCC/L mixture containing P188 0.5, 1.0, 1.5, and 2.0 (from left to right)

All powders displayed very poor flow properties according to generally accepted scale (Ph. Eu. 11.0, 2.9.36), with an AoR between 56° and 65°. There was only small effect on AOR of the filler mixture as well as the difference between concentrations of P188 use (Fig. 12).

Lactose has a larger particle size distribution than both MCC and P188 and has a smaller mean particle size than either. Smaller particles, less than 200 µm (Marushka

et al, 2022) may result in poorer flow behaviour due to the increase in cohesive forces and relative surface area.

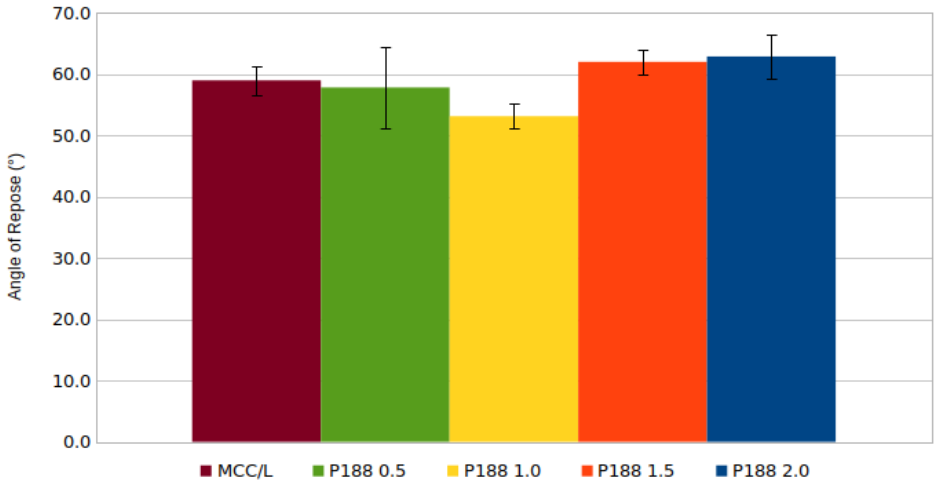


Fig. 12: Effect of lubricant concentration on angle of repose (*Data for MCC/L taken from Paredes I Pelejá, 2022)

Perhaps the most literal and demonstrative test of flow is the rate of flow through an orifice. Flow through an orifice is recommended on powders that are free flowing and have uniform flow with litter disruption. (PhEur 11.0, 2.9.36). To test flow rate a stainless stell conical hopper having a circular opening was used. Testing hopper with a 10mm orifice was previously recommended for easily and quickly distinguishing flowability of pharmaceutical substances (Hurychová et al, 2018). It was unfortunately difficult to carry out due to poor flowability of samples; no powder would flow continuously through the 15mm orifice regardless of lubricant concentration so a 25mm orifice was used.

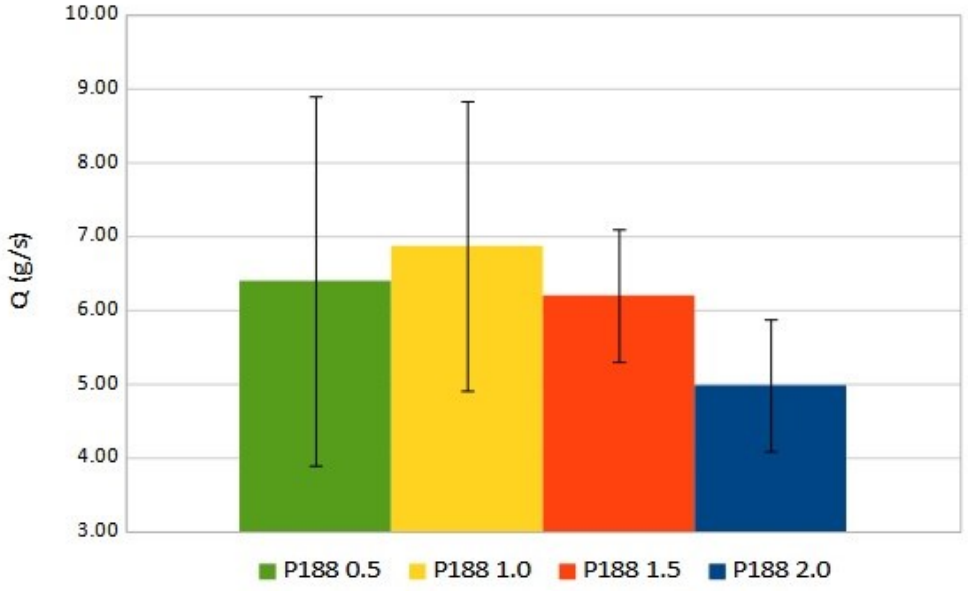


Fig. 13: Effect of lubricant concentration on rate of flow through an orifice of 25 mm. MCC/L without lubricant was omitted due to a complete lack of flow.

Unlubricated MCC/L did not flow at all. Lubricated samples required continuous tapping on the hopper and the large deviations between repetitions were noted (Fig 13). However, P188 0.5% displayed the most reluctant flow and required the most amount of tapping of the hopper to begin and continue to flow; slightly better behaviour was noted with P188 2.0 percent. In agreement with the above-mentioned explanation, the results are considered only as the confirmation of the results obtained by the use of other methods.

True density measures the density of the powder particles, while managing to exclude the gaps between them and any voids that are not a part of the intrinsic structure (Merlin Powder Characterization, 2023). In general, the measurement cannot include the pores sealed within the solid particle (Sinko, 2011), referred to as closed pores. Increasing the concentration of P188 decreases the true density d_s (g/mL) of the powder estimated by helium pycnometry. This may be explained by the less sticking of the particles to each other and exposing a greater surface area, as well as the lesser density of P188 itself.

It is clearly visible from the Table 5 that d_s (g/mL) decreases with the increase in P188 concentration. Using Eq. 1, porosity of the powder bed P (%) was expressed.

Table 5 The influence of P188 on the true density and porosity of powder bed (*Data for MCC/L taken from Paredes I Pelejá, 2022)

P188 Concentration	ds (g/mL)	P (%)
MCC/L*	1.549 (0.002)	73.08 (0.32)
0.5	1.547 (0.001)	71.77 (0.45)
1.0	1.540 (0.001)	71.96 (0.33)
1.5	1.539 (0.001)	70.18 (0.27)
2.0	1.537 (0.001)	70.95 (0.92)

The porosity of the MCC/L decreases slightly with the additional concentrations of P188. Similar to true density, this may because of closer packing of the particles influenced by the lubricant, leaving less gaps between them and increasing the solid fraction. Both results are in a good agreement with the bulk density (Fig. 8) showing that micronized P188 fills the interparticular voids and reduces the amount of the entrapped air.

7.2 Compression Properties of Powder Mixtures

All powder mixtures were compressed using a Zwick-Roell tablet press and the energies of compression were recorded by the press software based on the force displacement method of tablet compression. 30 tablets of each P188 concentration were compressed at 3 different forces, 5 kN, 7 kN, and 10 kN, for a total of 360 tablets. For the majority of batches only the first 10 ejection forces were recorded.

The following Table 6 summarizes the energies of compression; energy of precompression (E_1), energy of plastic deformation (E_2), energy of elastic deformation (E_3), energies of plastic and elastic deformation combined ($E_{lis} = E_2 + E_3$), total energy of compression (E_{max}), and plasticity (PL). All results for MCC/L without lubricant were taken from consultant data (Bailey, 2022).

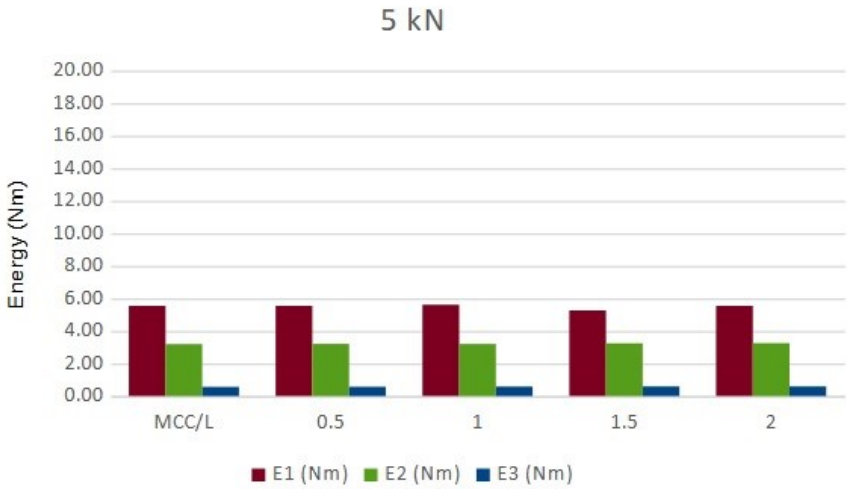
Table 6: Compression energies as influenced by lubricant concentration (standard deviations in brackets). (*Data for MCC/L compression taken from Bailey, 2022)

P188 %	E_1 (N)	E_2 (Nm)	E_3 (Nm)	E_{lis} (Nm)	E_{max} (Nm)	PL (%)
Compression Force 5 kN						
MCC/L*	5.536 (0.297)	3.189 (0.068)	0.559 (0.009)	3.748 (0.070)	9.284 (0.335)	85.077 (0.305)
P188 0.5	5.546 (0.302)	3.203 (0.036)	0.567 (0.007)	3.770 (0.037)	9.316 (0.318)	84.956 (0.206)
P188 1.0	5.611 (0.292)	3.200 (0.044)	0.582 (0.008)	3.781 (0.048)	9.393 (0.303)	84.617 (0.205)
P188 1.5	5.253 (0.177)	3.241 (0.046)	0.591 (0.006)	3.832 (0.048)	9.086 (0.181)	84.576 (0.191)
P188 2.0	5.548 (0.468)	3.250 (0.039)	0.589 (0.006)	3.839 (0.040)	9.387 (0.040)	84.654 (0.210)
Compression Force 7 kN						
MCC/L*	8.176 (0.568)	4.416 (0.111)	0.965 (0.020)	5.381 (0.111)	13.557 (0.597)	82.057 (0.507)
P188 0.5	9.584 (2.507)	4.389 (0.051)	1.011 (0.011)	5.401 (0.054)	14.984 (2.496)	81.273 (0.225)
P188 1.0	10.674 (5.933)	4.384 (0.044)	1.019 (0.017)	5.406 (0.055)	16.120 (6.040)	81.136 (0.228)
P188 1.5	10.203 (7.310)	4.474 (0.031)	1.038 (0.010)	5.512 (0.034)	15.715 (7.303)	81.165 (0.169)
P188 2.0	7.787 (0.288)	4.403 (0.053)	1.028 (0.008)	5.431 (0.052)	13.218 (0.314)	81.065 (0.239)
Compression Force 10 kN						
MCC/L*	13.992 (2.488)	6.022 (0.155)	1.836 (0.030)	7.858 (0.150)	21.850 (2.498)	76.630 (0.623)
P188 0.5	12.872 (0.475)	6.017 (0.080)	1.874 (0.017)	7.891 (0.083)	20.763 (0.533)	76.249 (0.280)
P188 1.0	16.718 (5.868)	6.052 (0.067)	1.878 (0.027)	7.930 (0.060)	24.648 (5.882)	76.316 (0.393)
P188 1.5	12.567 (0.306)	6.079 (0.100)	1.931 (0.020)	8.010 (0.097)	20.577 (0.371)	75.893 (0.395)
P188 2.0	12.220 (0.729)	6.008 (0.072)	1.915 (0.020)	7.923 (0.073)	20.144 (0.740)	75.823 (0.303)

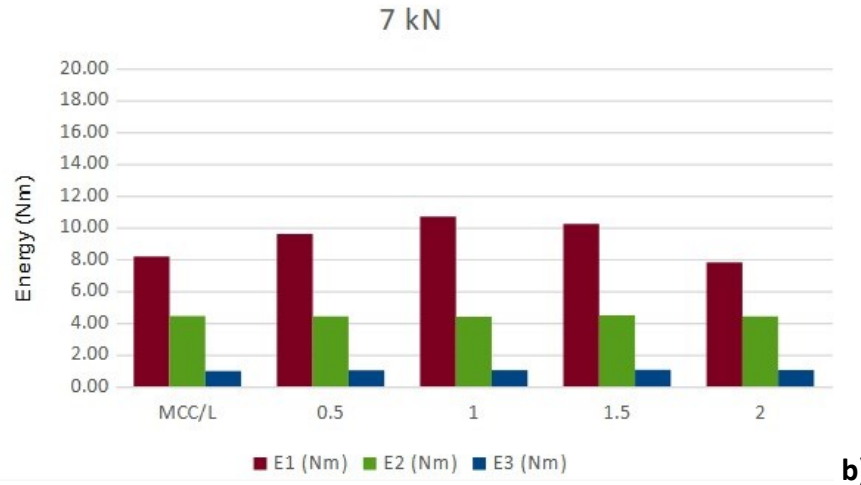
The energy profile in Fig. 14 shows that the energies of compression are influenced by compression force in the range used but were less influenced by the concentration of P188 in a mixture. The only exclusion is the increase in E_1 observed at compression force 7 kN and 10 kN after addition of 1 % of P188. In theory, this should best display the effect of the action of P188 as a glidant. However there is no clear decrease on the energy expended to remove gaps from between the particles.

Energy of elastic deformation, E_3, is the energy lost once the tablet has finished compression (Ragnarsson, 1996), this value relies more on the compression force than the amount of lubricant in the tableting mixture, although it does show a slight increase with the increasing concentration. This may be due to the lubricant preventing internal friction between the tablets and lowering the bonding activity of the MCC/L mixture. The effects of the lubricant P188 on MCC/L mixture was most visible at higher compression forces. E_3 was increased by the presence of P188 and with its concentration.

There was a decrease in plasticity and slight decrease in the true density of the tablets. MCC/L without lubricant had a higher plasticity than mixtures containing P188, although there was no significant difference between concentrations of lubricant. The largest differences in plasticity came from the compression force itself, with larger compression forces having lower plasticity and losing more energy to elastic deformation of the material.



a)



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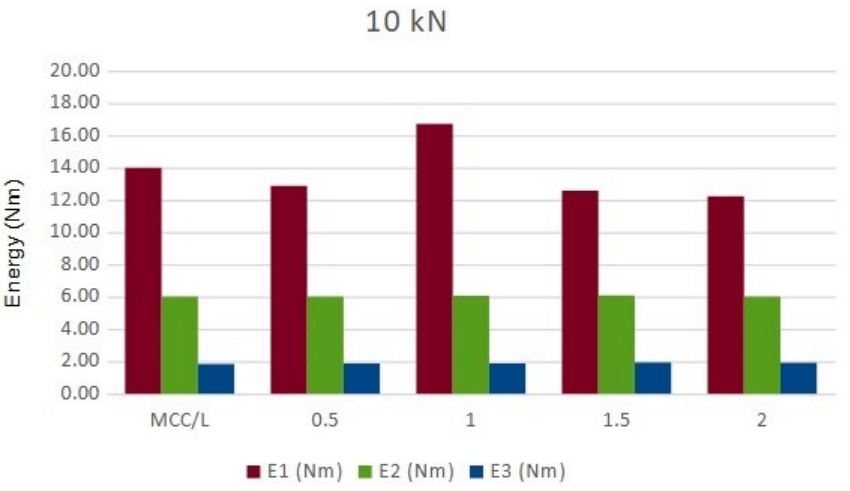

c)

Fig. 14: The influence of F_{max} and concentration of P188 on energy profile of compression a) E_1, b) E_2, c) E_3 (*Data for MCC/L taken from Bailey, 2022)

Ejection of the tablet is a high speed and high friction process and represents the step during compression when the tablet is most likely to be damaged. In Fig.. 15, the ejection force EF is illustrated for the filler mixture and lubricated mixtures. EF was greatly reduced by using P188 as a lubricant, although there was not a significant decrease in EF with an increase in concentration, apart from the compression force 10 kN. As can be seen from the Fig. 15, the effect was lower under 10 kN when higher concentration was used. The best effect was observed, surprisingly, at the lowest concentration 0.5 %.

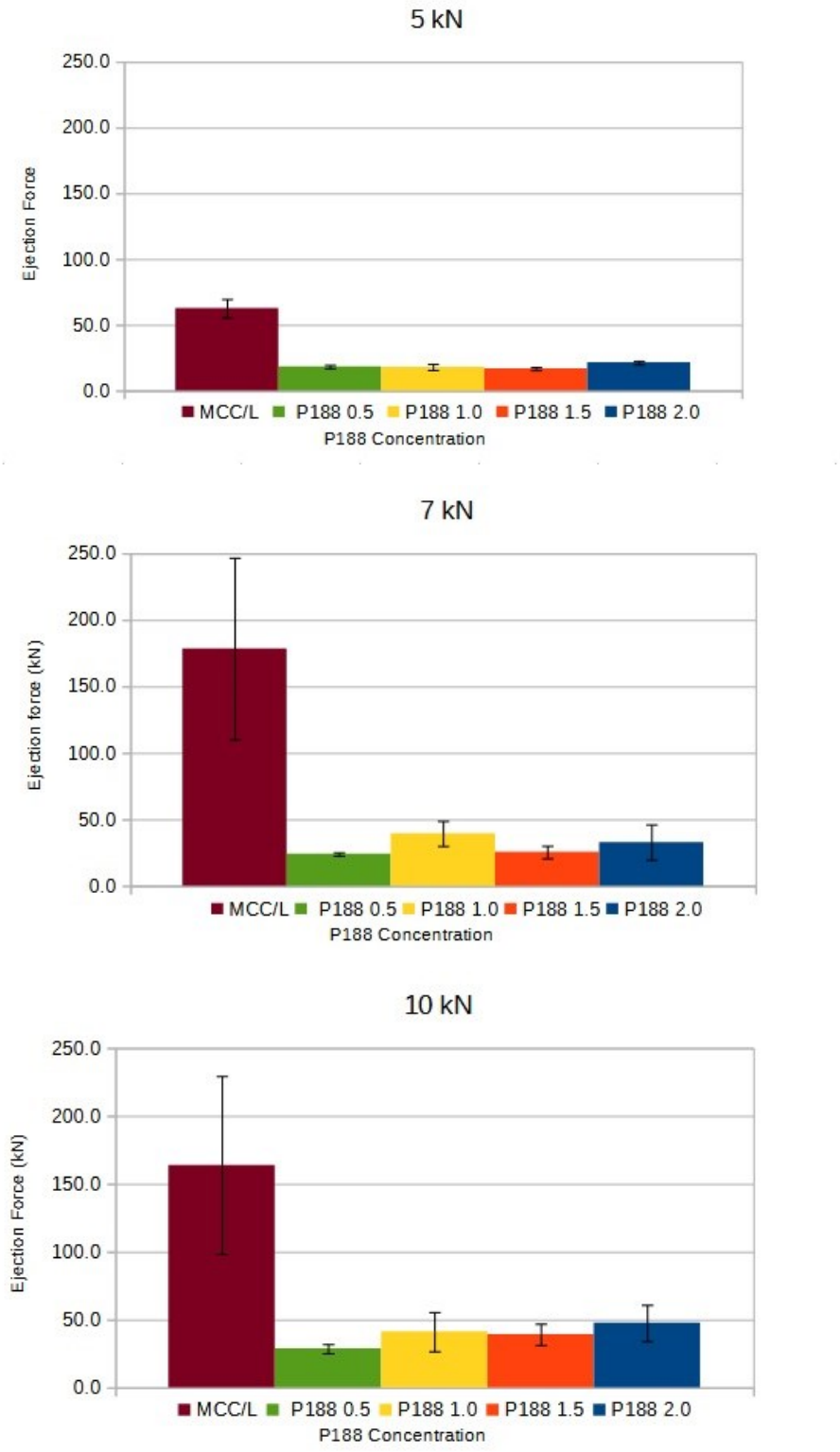

Fig. 15: The influence of F_{max} and concentration of P188 on ejection force of tablets (*Data for MCC/L taken from Bailey, 2022)

7.3 Tablet Properties

Tablet properties are important to understand in order to predict tablet behaviour during processing, handling, shipping, and dispensation. They are also crucial in process tests to assure the quality of the product and the correct manufacturing process. In this thesis the mechanical strength was tested using friability, the tensile strength, and the disintegration time. Friability and disintegration time are pharmacopeial tests. Tensile strength is not defined, however it is used as a guideline and a quality control test during manufacture. The results obtained 24 hours after compression are summarized in Table 7.

Table 7: Influence of compression force and P188 concentration on properties of tablets (standard deviations in brackets). (*Data for MCC/L taken from Bailey, 2022)

P188 %	TS (MPa)	DT (s)	Fr (%)
Compression Force 5 kN			
MCC/L*	0.603 (0.039)	9.0 (1.673)	1.5871 (N/A)
0.5	0.746 (0.001)	11.7 (1.506)	1.889 (N/A)
1.0	0.679 (0.058)	11.5 (0.548)	2.35 (N/A)
1.5	0.688 (0.025)	12.5 (1.049)	2.082 (N/A)
2.0	0.622 (0.021)	14.7 (1.366)	2.246 (N/A)
Compression Force 7 kN			
MCC/L*	0.979 (0.081)	13.6 (0.817)	1.038 (N/A)
0.5	1.21 (0.032)	13.7 (0.816)	1.066 (N/A)
1.0	1.095 (0.037)	19.2 (7.441)	1.367 (N/A)
1.5	1.064 (0.032)	19.5 (10.095)	1.182 (N/A)
2.0	0.988 (0.050)	15.3 (0.817)	1.265 (N/A)
Compression Force 10 kN			
MCC/L*	1.462 (0.143)	12.8 (0.632)	0.564 (N/A)
0.5	1.814 (0.073)	18.7 (12.011)	0.533 (N/A)
1.0	1.737 (0.170)	19.3 (5.750)	0.644 (N/A)
1.5	1.677 (0.060)	21.8 (5.672)	0.681 (N/A)
2.0	1.561 (0.035)	16.8 (0.753)	0.569 (N/A)

Friability is used to determine if the strength of tablets is suitable for handling and packaging without a loss of mass and therefore dose of the active ingredient. The pharmacopeial limit for tablet friability is 1 percent of the mass lost during the test and no tablets breaking. Over all of the tests no tablets were broken, however only tablets compressed at 10 kN displayed a loss of less than 1 percent; all tablets compressed at 5 kN and 7 kN did not meet the requirements, including MCC/L mixture (Table 7).

There is still a relationship between the amount of lubricant added and the friability of the tablet, with increasing concentration of lubricant the friability increases but not linearly; there was no visible effect of lubricant concentration on the tablets.

Mechanical resistance of tablets can be also expressed by the force necessary for crushing of a tablet. **Crushing force** (**CR)** is used mainly as quality control during production and can be further used to calculate the tensile strength. Depending on tablet diameter, the **tensile strength** TS (MPa) was calculated. As seen in the Table 7 adding lubricant initially increases the crushing force across all compression forces compared to pure MCC/L, before decreasing the force once 1.5 percent of P188 was added to the mixture. With the addition of poloxamer, in general, TS of tablets was not largely increased when compared with the filler mixture MCC/L itself; the effect was dependent on the compression force used. The higher jump from 0.603 MPa to 0.746 MPa and 0.979 MPa to 1.216 MPa was only observable with the addition of 0.5 percent of P188 at 5 kN and 7 kN, respectively. TS then decreased as greater amounts of poloxamer were added, finally reaching that of MCC/L tablets without the lubricant at a 2% concentration of P188. The higher influence was only visible when tablets were compressed under 10 kN pressure.

Poloxamers binding properties were also visible with **disintegration times**, slightly increasing the time compared to MCC/L without the lubricant. However, there was no large influence on disintegration time by the compression force or the poloxamer concentration as nearly all tablets were dissolved in 20 seconds or less. This is probably due to the high concentration of soluble lactose in the mixture. The Pharmacopoeia outlines a disintegration time of 15 minutes (PhEur 11.0, 2.9.1), so any

difference in time as shown in the chart is negligible. However, higher compression force led to longer DT.

8 Conclusions

Based on the experimental results achieved in the diploma thesis, the conclusions about the micronized poloxamer 188 (P188) in a concentration range of 0.5 – 2.0 % can be summarized as follows:

1. P188 displayed the mean particle size X_{50} 38.0 μm with a narrower span 1.866.
2. The bulk density of the MCC/L mixture increased with the addition of the P188 lubricant; this corresponded with the reduction in porosity of a powder bed. The highest bulk density, the lowest porosity as well as the greatest influence of tapping on the tapped density was observed for 1.5 % of the P188. This mixture showed the lowest Hausner ratio 1.39.
3. The linear relationship between the tapped density and number of taps was observed by dynamics of gravitational tapping for all concentrations of P188 used within first 30 taps. The relationships were characterized by the coefficients of determination R^2 in a range of 0.974 to 0.991.
4. The MCC/L mixtures with P188 displayed either poor or very poor flow behaviour based on Hausner Ratio, Compressibility Index, flow through an orifice, and Angle of Repose results. Mixtures were impacted a negligible amount by the added concentration of P188 in a range of 0.5 – 2.0 %. Poloxamer 188 was not an effective glidant.
5. The addition of micronized poloxamer 188 did not visibly affect the energies of the compression process evaluated by force-displacement method when compared to MCC/L at any compression force. The only exclusion is E_1 increased by 1 % of P188 at compression force 7 kN and 10 kN.
6. P188 showed an effective die lubrication efficiency during ejection of the tablet in all concentrations used and all compression forced tested. The best results were in general noted at the lowest concentration of 0.5 %.
7. There were no large negative effects of P188 on the final tablets in regard to friability, tensile strength, or disintegration time. However, compared to MCC/L, the effect of poloxamer P188 can be described as follows:

a. Even though no tablets were broken, only tablets compressed at 10 kN displayed a loss of mass less than 1 percent; all tablets compressed at 5 kN and 7 kN did not meet the Pharmacopeial requirements. With increasing concentration of P188 the friability generally increases.
b. TS was directly influenced by compression force used; the higher pressure the higher tensile strength. Opposite was true for concentration effect; at the higher concentration of P188, tensile strength decreased.
c. The addition of P188 slightly increased the disintegration time but all tablets disintegrated within 22 seconds regardless of the compression force or the concentration used.

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