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INVESTIGATION OF TABLETING PROPERTIES OF EXCIPIENTS AND THEIR BINARY MIXTURES WITH TWO DIFFERENT TABLETING DEVICES

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ABSTRACT
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Abstract:
Tablet is the most common pharmaceutical dosage form due to ease of administration, chemical and physical stability, and relatively low manufacturing cost. Direct compression is the preferred method for tablet production. Direct compression formulations typically contain a considerable amount of excipients. Therefore, excipients can have a significant effect on the tableting properties of formulations. More research is needed for better comprehension of the compression behaviour of different materials.
The objective of this work was to investigate tableting properties of different excipients and their binary mixtures with two different laboratory scale tableting devices; the Gamlen® D1000 Powder Compaction Analyzer and the FlexiTab®. The excipients used were microcrystalline cellulose (MCC), lactose, mannitol, starch, and dicalcium phosphate (DCP). Different compression pressures were used to survey the compression behaviour of the excipients at a wide pressure range. In addition, potential effects of compression speed, dwell time, and lubrication method were considered. The excipients and their binary mixtures were characterised based on compressibility (solid fraction vs. compression pressure) and tabletability (tensile strength vs. compression pressure). The results obtained with the devices were compared to enhance process understanding.
Based on the compressibility curves, it appeared that plastic deformation was the main compression mechanism of MCC and starch and fragmentation the main compression mechanism of lactose, mannitol, and DCP. The tabletability of MCC was excellent, and also the tabletability of mannitol was good. The tabletability of DCP was intermediate, whereas lactose and starch had inferior tabletabilities. In general, the tabletabilities and compressibilities of the binary mixtures were more or less what was expected based on the results of the individual materials. The results obtained with the different speed parameters and lubrication methods were mainly in line with the perceptions of the compression mechanisms of different materials. In overall, the results obtained in the Gamlen and FlexiTab experiments were quite similar. However, tensile strengths appeared generally slightly lower in the FlexiTab experiments. Probable explanations are the higher compression speed of the FlexiTab and differences in hardness measurements.
This study indicated that the FlexiTab and Gamlen devices have different benefits. The Gamlen device is clearly very suitable for investigating tableting properties during formulation development, but the FlexiTab device has the advantages of higher compression speed and automatic powder feeding mechanism. Tabletability results were slightly better with the Gamlen, but more experiments are needed for solving the reasons (e.g. compression speed and hardness measurements). More information of the compression behaviour of different materials could be obtained by analyzing punch displacement data and by using different compression equations.

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Tiivistelmä:

Tabletti on yleisin lääkkeen annosmuoto annostelun helppouden, kemiallisen ja fysikaalisen stabiilisuuden ja suhteellisen alhaisten valmistuskustannusten vuoksi. Suorapuristus on tablettituotannon suosituin menetelmä. Suorapuristusformulaatioissa on tyypillisesti huomattava määrä apuaineita. Täten apuaineilla voi olla merkittävä vaikutus formulaatioiden tabletointiominaisuuksiin. Tarvitaan lisää tutkimusta, jotta erilaisten materiaalien puristuskäyttäytymistä ymmärrettäisiin entistä paremmin.

Tämän työn tarkoituksena oli tutkia erilaisten apuaineiden ja niiden binääriseosten tabletointiominaisuuksia kahdella erilaisella laboratoriomittakaavan tabletointilaitteella; Gamlen® D1000 Powder Compaction Analyzer - ja FlexiTab®-laitteella. Käytetyt apuaineet olivat mikrokiteinen selluloosa (MCC), laktoosi, mannitoli, tärkkelys ja dikalsiumfosfaatti (DCP). Työssä käytettiin erilaisia puristuspaineita puristuskäyttäytymisen tutkimiseksi laajalla paineskaalalla. Lisäksi tarkasteltiin puristusnopeuden, puristuksen viipymäajan ja liukuaineen lisäysmenetelmän mahdollisia vaikutuksia. Apuaineet ja niiden binääriseokset karakterisoitiin puristuvuuden (kiinteä fraktio vs. puristuspaine) ja tabletoitavuuden (vetomurtolujuus vs. puristuspaine) perusteella. Laitteilla saatuja tuloksia verrattiin keskenään prosessiymmärryksen parantamiseksi.

Puristuvuuskäyrien perusteella vaikutti siltä, että plastinen muodonmuutos oli MCC:n ja tärkkelyksen ja fragmentoituminen laktoosin, mannitolin ja DCP:n pääasiallinen puristumismekanismi. MCC:n tabletoitavuus oli erinomainen ja myös mannitolin tabletoitavuus oli hyvä. DCP:n tabletoitavuus oli keskinkertainen, laktoosin ja tärkkelyksen tabletoitavuudet puolestaan olivat heikompia. Yleisesti ottaen binääriseosten puristuvuudet ja tabletoitavuudet olivat suurin piirtein yksittäisten apuaineiden tulosten perusteella odotettua tasoa. Erilaisilla nopeusparametreilla ja liukuaineen lisäysmenetelmillä saadut tulokset olivat pääosin linjassa eri materiaalien puristumismekanismeista saatujen käsitysten kanssa. Kaiken kaikkiaan Gamlen- ja FlexiTab-kokeissa saadut tulokset olivat melko samankaltaisia. Vetomurtolujuudet olivat kuitenkin yleisesti ottaen hieman alhaisempia FlexiTab-kokeissa. Todennäköisiä selityksiä ovat FlexiTab-laitteen suurempi puristusnopeus ja erot lujuusmittauksissa.

Tämä tutkimus osoitti, että FlexiTab- ja Gamlen-laitteella on erilaisia etuja. Gamlen-laite on selvästi erittäin soveltuva tabletointiominaisuuksien tutkimiseen formulaatiokehityksen aikana, mutta FlexiTab-laitteella on etuinaan suurempi puristusnopeus ja automaattinen jauheen syöttömekanismi. Tabletoitavuustulokset olivat hieman parempia Gamlen-laitteella, mutta lisää tutkimuksia tarvitaan syyn selvittämiseksi (esim. puristusnopeus ja lujuusmittaukset). Erilaisten materiaalien puristuskäyttäytymisestä voitaisiin saada lisää tietoa analysoimalla paininten matkanmittausdataa ja käyttämällä erilaisia puristusyhtälöitä.

ABBREVIATIONS

API	active pharmaceutical ingredient
DC	direct compression
DCP	dicalcium phosphate
MCC	microcrystalline cellulose
MPa	megapascal
kN	kilonewton
TTA	Tablet Tensile Analyzer
RSD	relative standard deviation

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1. INTRODUCTION

Tablet is the most common dosage form for administering a drug, some of its advantages being ease of administration, chemical and physical stability, and relatively low cost. Direct compression is the simplest method for tablet production, in which pressure is applied to compress a powder blend consisting of the active pharmaceutical ingredient and various excipients. However, a complex formulation is usually required to produce tablets that fulfill quality requirements, such as adequate mechanical strength. It is essential to understand the compression behaviour of each material to design formulations that produce tablets of good quality.

The compression behaviour of pharmaceutical powders is commonly described by terms like compressibility and tabletability (Pitt et al. 2015). Materials can be classified as plastic or brittle based on their principal compression mechanism, i.e. plastic deformation versus fragmentation (Denny 2002). Despite the importance of material behaviour, there are no set analytical testing standards or guidelines for the classification of materials. Various compression equations are commonly utilized in the interpretation of compression results, but they are associated with limitations and may give conflicting results. Moreover, various experimental factors, such as experiment type, compression pressure range, and compression speed, can affect compression results (Sinka et al. 2009). Therefore, it is important to establish experimental methods for distinct tableting devices and to compare compression results obtained with different devices and methods.

The objective of this work was to investigate tableting properties of different excipients and their binary mixtures with two distinct laboratory scale tableting devices; the Gamlen® D1000 Powder Compaction Analyzer and the FlexiTab®. Previous studies have demonstrated the suitability of Gamlen devices for compression experiments, and one goal of this study was to evaluate the suitability of the FlexiTab for similar purposes in comparison to the Gamlen. The compression results were used to characterise excipients and their binary mixtures based on compressibility and tabletability. The results obtained with the distinct devices were compared to enhance understanding of these devices and process parameters affecting compression results.

2. TABLET MANUFACTURE BY DIRECT COMPRESSION

Tablet is the most common dosage form for drug administration. Advantages of the tablet include ease of administration, chemical and physical stability of drug components, and relatively low manufacturing cost (Paul and Sun 2017). Tablets are commonly manufactured by confined compression of powders, i.e. direct compression (Chowdary and Ramya 2013). Other common techniques include dry granulation and wet granulation. In this chapter, some of the essential advantages and challenges of the direct compression method are considered.

2.1. Advantages of direct compression

Direct compression (DC) is a method in which the powder blend consisting of the active pharmaceutical ingredient (API) and different excipients is compressed without a preliminary granulation or aggregation process (Chowdary and Ramya 2013). DC is a relatively simple method for tablet production. Therefore, it is generally used whenever possible.

The simplicity of DC arises from the fact that it encompasses fewer unit operations. Less equipment is needed, processing times are shorter, and energy consumption is lower, therefore, production costs are reduced (Chowdary and Ramya 2013). In addition, DC is more suitable for moisture and heat sensitive APIs, since wetting and drying steps are eliminated. Faster dissolution rates may be achieved, as the tablets disintegrate into API particles instead of granules and the particles come directly into contact with dissolution fluid.

2.2. Challenges of direct compression

Though DC is generally the most preferred method for tablet production due to the simplicity of the process, the method is associated with several challenges related to powder characteristics. Segregation, poor flowability, and poor compression behaviour are commonly encountered challenges (Chowdary and Ramya 2013).

Segregation is the phenomenon in which the components of a powder mixture get separated from each other (Tang and Puri 2004). For example, physical properties such as particle size, size distribution, particle shape, and particle density commonly cause segregation when the powder mixture is exposed to vibration during processing. If segregation occurs, the powder mixture will become unhomogenous, which can interfere with content uniformity. In addition, more variation can be observed in compression results.

Powder flowability can affect blending and die filling (Capece et al. 2016). The success of blending and die filling, in turn, is critical for producing tablets with uniform weight and content. The flow behaviour of powders is dependent on many factors, such as particle size, particle shape, surface texture, surface energy, and moisture content.

Compression behaviour is essential for producing tablets with good quality properties, such as good mechanical strength (Pitt et al. 2015). Compressibility and tabletability are concepts that are commonly used to describe how materials behave in the compression process (see Chapter 4.4.). The pressure applied during compression results in particle deformation and formation of interparticle bonds that hold the resulting tablet together when the pressure is removed. It is essential to understand the compression behaviour of distinct materials to design optimal tablet formulations and compression processes.

3. FORMULATION DESIGN

Formulation design and product development involves choosing the types, grades, and amounts of excipients to be used in combination with the specific API. This is challenging because tablet properties can differ significantly due to variation in the material set or the relative amounts of the components. Consequently, the decisions are often based on certain rules of thumb without a deep understanding of the properties that affect tablet quality in terms of compressibility and tabletability (Osamura et al. 2016). This may lead to production problems or defects in the products

after distribution. In this chapter, important factors for API and excipient selection are considered. In addition, a range of fillers suitable for DC (microcrystalline cellulose, lactose, mannitol, starch, dicalcium phosphate) are examined in detail.

3.1. API selection

Different drugs have distinct molecular structures. Therefore, each compound has unique physicochemical properties. In addition, a drug molecule can exist in different solid forms, such as polymorphs, hydrates, salts, cocrystals, and amorphous state, which can influence its physicochemical properties (Sun 2017). The processability of tablet formulations, i.e. powder flow and compression behaviour, also depends on particle properties, such as particle size, shape, and surface roughness.

A successful tablet product must also exhibit a desired drug release profile. Drug release is affected by drug solubility, drug particle size, and tablet porosity (Sun 2017). These properties are determined by molecular structure, crystal structure, and tablet structure. Therefore, it is important to understand structure-property relationships at different length scales, ranging from molecular level to the finished tablet. Drug release is also dependent on the composition of the formulation. It is even possible to control drug release by different kinds of controlled release systems, which release the drug at a predetermined rate for a specific period of time (Nokhodchi et al. 2012).

3.2. Excipient selection

Manufacturing tablets of good quality usually requires a complex formulation that contains several excipients in the formulation along with the API. These excipients function as fillers, binders, lubricants, disintegrating agents, etc. (Chaudhari and Patil 2012). In many formulations, particularly fillers are present in greater proportions with regard to the API. Consequently, the mechanical properties of these excipients can significantly influence the compression process and the quality of the final products.

Therefore, it is important to choose excipients that have ideal functionality, including good flowability and compressibility (Chowdary and Ramya 2013). Furthermore, it is

important to maintain balance between plasticity and brittleness in the final formulation (see Chapter 4.1.). Excipients with appropriate mechanical properties should be selected considering the properties of the API (Paul et al. 2018). In general, exclusive use of plastic or brittle excipients should be avoided, because it can lead to problems in product quality. For example, brittle tablets are associated with low mechanical strength and high friability. On the other hand, many highly plastic excipients are hygroscopic, which could lead to problems related to moisture sensitivity. Plastic materials generally have high strain rate sensitivity, i.e. compression results are dependent on compression speed (Sinka et al. 2009). This may cause problems in production scale when compression speed is adjusted as high as possible. In addition, several other characteristics need to be considered in excipient selection, including stability, safety, regulatory acceptance, cost, and availability (Chaudhari and Patil 2012).

Many excipients do not meet all the functional requirements for DC. Examples of commonly used fillers/binders that fulfill the requirements for DC include microcrystalline cellulose, lactose, mannitol, starch, and dicalcium phosphate (Jivraj et al. 2000). All of them are available in many different grades. In addition, a variety of co-processed materials have been developed, which include two or more distinct excipients (Chowdary and Ramya 2013). The objective of co-processing is to develop materials with synergistic functionalities and less disadvantages (e.g. improved flow and compression characteristics). However, in this work, the focus is on traditional and commonly used excipients.

3.2.1. Microcrystalline cellulose

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose prepared by treating pulp-derived alpha cellulose with mineral acids (Thoorens et al. 2015). It is generally manufactured by spray-drying the neutralized aqueous slurry obtained by the hydrolysis of cellulose. MCC is one of the most preferred fillers/binders for DC formulations due to excellent tableting properties. Different grades of MCC are formed by varying spray-drying conditions, the products having

differences in particle size distribution and moisture content. Particle size and moisture content of MCC are considered as critical material attributes for tableting performance.

MCC is classified as a plastic material, i.e. plastic deformation contributes significantly to powder volume reduction during compression (Zhang et al. 2017). Due to plastic deformation, an extremely large surface area comes into close contact and facilitates hydrogen bonding between adjacent cellulose particles. MCC exhibits great performance in terms of compressibility and tabletability (Pitt et al. 2015). A disadvantage of MCC is poor flow, but this can be compensated by mixing it with another filler with good flowability (Jivraj et al. 2000). MCC is insoluble and swells in water, therefore, it acts as a disintegrant.

3.2.2. Lactose

Lactose is a milk-derived disaccharide that exists in different solid forms, including α-lactose monohydrate, anhydrous α-lactose, anhydrous β-lactose, and amorphous lactose (Ruangchayajatuporn et al. 2011). Lactose is commonly used as a filler in tablet formulations, its use being driven by long traditions and low cost. Various methods, including spray-drying and granulation, are used to produce lactose grades specifically for DC formulations (Paul et al. 2018). Depending on the processing method, a range of lactose types with different properties (e.g. particle size, particle shape, amorphous content) can be produced (Ruangchayajatuporn et al. 2011).

Lactose is generally considered as a brittle material, i.e. particle fragmentation is the main compression mechanism (Zhang et al. 2017). Fragmentation creates a large amount of small particles, which results in a large number of interparticle contact points. However, spray-dried lactose types that are commonly used for DC show also some extent of plasticity. This is due to the fact that spray-dried lactose types contain a small amount of amorphous material on particle surfaces and amorphous lactose displays plastic deformation (Ruangchayajatuporn et al. 2011). Advantages of lactose include good flowability and good water solubility (Jivraj et al. 2000).

3.2.3. Mannitol

Mannitol is a sugar alcohol commonly found in plants that is produced industrially via the hydrogenation of fructose (Ohrem et al. 2014). It exists in different polymorphic forms, including the α, β, γ, and δ forms. β-mannitol is the stable polymorph and therefore commonly used. Mannitol is used in tablet formulations as a filler in increasing frequency due to its many advantageous properties. Specific grades are available for DC, produced by granulation and spray-drying methods (Paul et al. 2018).

Mannitol is often described as a brittle material, but obviously distinct mannitol grades may differ considerably in their compression behaviour. Crystalline, unprocessed or granulated grades can show a remarkable extent of plastic deformation, whereas spray-dried grades are more inclined to fragmentation (Paul et al. 2019). Mannitol is often compared to lactose, as there are similarities in the compression behaviour of specific types of mannitol and lactose (Paul et al. 2018). In many cases, they can be used for similar purposes. Mannitol has attracted increasing attention in recent years due to several advantages compared to lactose, including non-hygroscopicity and high physiological tolerability (Ohrem et al. 2014). Mannitol is especially suitable for orally disintegrating tablets because it has good water solubility along with a pleasant mouthfeel.

3.2.4. Starches

Starches are plant-derived polysaccharides that consist of glucose units forming amylose (linear chains) and amylopectin (branched chains). Starches from different origins may have different physicochemical properties, which can be attributed to variation in amylose content (Adedokun and Itiola 2010). Furthermore, the properties of starches can be modified by various treatments, including pregelatinization and chemical modifications. Starches are widely used in tablet formulations as excipients with multiple purposes and low cost. Their physicochemical properties make them suitable as fillers, binders, and disintegrants.

Starches are generally classified as plastic materials (Adedokun and Itiola 2010). Compared to MCC, which is also a plastic material, using large amounts of starch leads to low mechanical strength of tablets. A contributing factor to low mechanical strength is high elasticity (Jivraj et al. 2000). Natural starches generally exhibit poor flowability, which may be attributed to high moisture content. However, flowability can be improved by pregelatinization (Adedokun and Itiola 2010). In addition, pregelatinization can improve compressibility. Native starches are insoluble in water, whereas pregelatinized starches show variable extent of solubility and higher swelling ability.

3.2.5. Dicalcium phosphate

Dicalcium phosphate (DCP) is produced by a complicated process using phosphoric acid and slaked lime (Jivraj et al. 2000). It has been predominantly used in vitamin and mineral supplements, but its low cost and good flow characteristic has increased its use in pharmaceutical preparations. Presently, DCP is commonly used as a filler in DC formulations.

DCP is classified as a brittle material, as it undergoes considerable fragmentation during compression (Zhang et al. 2003). An advantage of DCP is superior flowability compared to other common excipients. Important factors affecting flowability are large particle size and high density. In addition, tablets containing DCP are rapidly penetrated by dissolution media due to the hydrophilic nature of the compound and high porosity of the tablets (Jivraj et al. 2000). However, DCP is insoluble in water and use of a disintegrant in the formulation is therefore needed.

4. COMPRESSION PROCESS OF PHARMACEUTICAL POWDERS

Development of formulations that produce tablets of good quality requires understanding of the compression behaviour of each individual component. Despite the importance of material behaviour, there are no set analytical testing standards or guidelines for the classification of materials (Hooper et al. 2016). Therefore, it is often

difficult to evaluate tableting properties quantitatively. Compressibility and tabletability are concepts that are commonly used to describe the compression behaviour of pharmaceutical powders (Pitt et al. 2015). In this chapter, the basic mechanisms of compression are introduced on a general level. Relevant process parameters are presented and their influences on compression results are considered.

4.1. Compression mechanisms

Despite the large amount of literature on powder compression, there is still some degree of confusion and disagreement about the possible mechanisms by which compression may occur (Denny 2002). In general, the following mechanisms are usually considered. During the initial stage when low pressure is applied onto the powder bed, it is considered that some rearrangement, sliding, or deformationless restacking of particles is occurring. When rearrangement is no more possible, particles first compress by elastic deformation, which is a reversible process (Fig. 1). After reaching a material specific yield point, compression occurs by plastic deformation or fragmentation, which are irreversible processes. Plastic deformation enables denser packing of primary particles. Fragmentation, in turn, causes breakage of the primary particles into smaller particles that can arrange in a more compact state. Both plastic deformation and fragmentation result in increased particle surface area, which enables increased bonding between particles. Finally, when the compression pressure is removed, elastic recovery may occur. For soft materials, such as pharmaceuticals, elasticity may be significant at higher pressures.

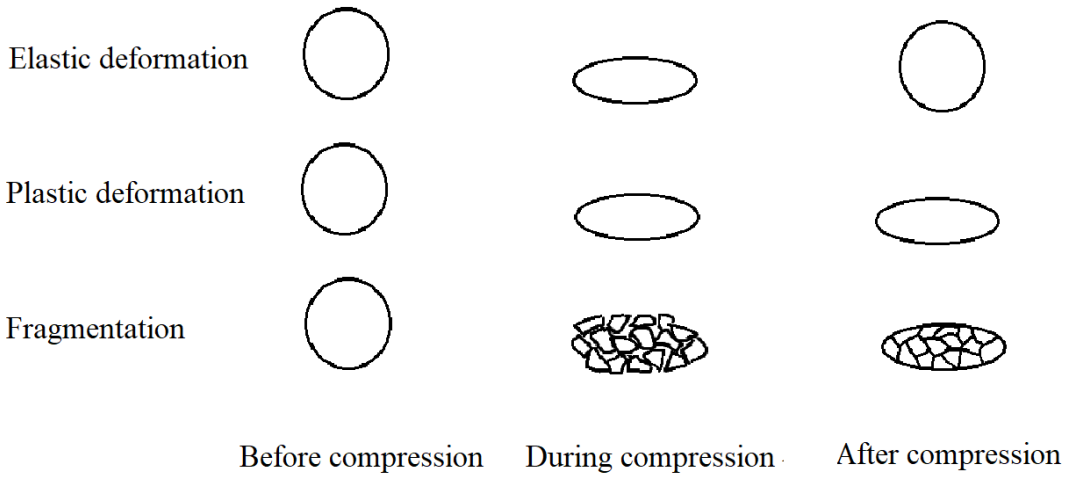

Figure 1. Different compression mechanisms.

Tableting devices are commonly equipped with different force sensors, which allow measurement of the compression force, from which compression pressure can be calculated. Tablet properties (weight, diameter, thickness, hardness) can be measured with appropriate devices. This data can be used to evaluate compression behaviour, for example, in terms of compressibility and tabletability (Pitt et al. 2015). When interpreting compression data, it should be acknowledged that different compression mechanisms may occur over different regions of pressure (Denny 2002). Furthermore, it is essential to acknowledge the importance of the experimental methods used, as there are no generally agreed methods.

4.2. Compression parameters

4.2.1. Compression pressure

Compression pressure is considered the most essential process parameter influencing the mechanical strength of tablet products (Sinka et al. 2009). Compression pressure is obtained by dividing compression force with the surface area onto which the force is exerted to. In general, pressure increase results in powder volume reduction. Powder porosity is decreased, i.e. solid fraction is increased. At some point, densification decelerates and reaches a plateau. The extent of volume reduction is generally described by compressibility. Densification typically results in increased mechanical

strength of the resulting tablets. Mechanical strength is commonly evaluated based on tensile strength. In addition, friability is another indicator of mechanical strength.

Production of tablets with good mechanical strength requires evaluation of the relationship between compression pressure and mechanical properties. Ideally, compression pressure should be sufficient for producing tablets with tensile strengths greater than 2 MPa (Pitt et al. 2015).

4.2.2. Compression speed

Compression speed is considered one of the most important process parameters after compression pressure (Sinka et al. 2009). Press speed and dwell time may have a significant impact on tablet properties. Dwell time refers to the time interval that the punch remains stationary with respect to the die at maximum displacement of the punch. For example, tensile strength may decrease when compression speed is increased and dwell time is decreased. However, the effects differ between distinct materials. Strain rate sensitivity is a concept that is used to describe the dependency of compression behaviour on press speed and dwell time (Roberts and Rowe 1985). In general, strain rate sensitivity is more evident in plastic materials. Plastic deformation is a time dependent phenomenon, therefore, compression speed generally influences the extent of deformation. On the other hand, fragmentation typically occurs very rapidly, and compression speed has little or no effect on the deformation of brittle materials.

4.3. Compression studies

When developing tablet formulations, it is essential to understand the compression behaviour of each excipient as well as that of the API. Small scale compression studies are commonly used to develop process understanding of tablet formulations (Pitt et al. 2015). It is important that the equipment used in small scale are representative of the large scale devices used for commercial manufacture. Process differences, such as compression speed and dwell time, may affect compression results.

In recent years, computerized tablet presses have been developed that are equipped with software for the evaluation of compression data. For example, data produced by the Gamlen Tablet Press (GTP-1) has been successfully utilized for evaluating various tableting properties (e.g. compressibility and tabletability) of tablet formulations (Pitt et al. 2015). The study demonstrated that the results predicted well the performance of the formulations in large scale manufacture. However, it is always important to compare results obtained with different devices and different process parameters to identify factors that could affect compression results. For example, differences in compression speed might affect the compression behaviour of plastic materials.

4.4. Interpretation of compression results

4.4.1. Compressibility

Compressibility describes the volume reduction of pharmaceutical powders under applied pressure. Compressibility is typically expressed by plotting solid fraction against compression pressure. Solid fraction, in turn, is obtained from the ratio of tablet density and true density. It has been frequently stated that a solid fraction value of 0.85±0.05 is ideal for good tablet quality (Pitt et al. 2015). Excessive compression, i.e. overcompression, might lead to tablet defects, such as capping, laminating and fracturing. Insufficient compression, in turn, is associated with low mechanical strength.

Furthermore, different compression equations, such as the Heckel analysis (Heckel 1961) and the Kawakita analysis (Kawakita and Lüdde 1969) are commonly used to interpret compression data. However, the applicability of these equations has been frequently questioned. For example, nonlinearity of the plots can make it hard to determine the appropriate pressure region used for the analyses.

4.4.2. Tabletability

Tabletability describes the development of mechanical strength under applied pressure. It is typically expressed by plotting tensile strength against compression

pressure. Tensile strength describes the maximum amount of tensile stress that a tablet can withstand before breaking. It is calculated from tablet hardness and tablet dimensions. Ideally, tensile strengths greater than 2 MPa should be targeted to ensure good mechanical strength of tablets (Pitt et al. 2015). However, tensile strengths of 1.7 MPa are often sufficient for ensuring tablets are strong enough to withstand typical processing steps.

5. COMPUTERIZED TABLET PRESSES

Modern, computerized tablet presses produce a wide range of data of the compression process. The data can be utilized for evaluating and comparing the compression behaviour of different materials. This information might accelerate product development processes and better product quality might be achieved. In this study, compression studies were performed with two different computerized tablet presses; the Gamlen® D1000 Powder Compaction Analyzer and the FlexiTab®. In this chapter, these devices are introduced and their features are considered in detail.

5.1. The Gamlen D1000 Powder Compaction Analyzer

The Gamlen® D1000 Powder Compaction Analyzer (Gamlen Instruments Ltd., London, UK) is a benchtop single-punch tablet press for the compression of pharmaceutical powders (Fig. 2). It is a force-controlled compression analyzer that operates under full computer control with real time display of punch position and force. The instrument carries out compression, detachment, and ejection operations and generates force/displacement curves for each operation. The data is captured by the Gamlen® Dashboard (Gamlen Instruments Ltd., London, UK), which is a data analysis software.

Figure 2. The Gamlen D1000 Powder Compaction Analyzer.

Before performing the experiments, experiment details (compression forces, number of tablets) and batch details (tablet diameter, true density) are set by the user (Gamlen D1000 Powder Compaction Analyzer Manual). A typical compression study includes analyzing three tablets per force with five different forces. After all settings are clear, the powder samples are applied into the die manually each in turn. When the powder is compressed, the force/displacement curve is displayed. On completion of compression, the peak load and peak punch position are displayed. Similarly, during detachment and ejection, the corresponding force/displacement profiles are displayed. After each compression event, tablet weight, thickness, diameter, and hardness are measured with appropriate devices (e.g. equipment package provided by Gamlen Instruments Ltd.). Tablet measurement data can be captured automatically by the Gamlen Dashboard when the measurement devices are connected to the computer. Alternatively, manual data entry can be used. After completing the experiment, the software produces an assessment report that describes various tableting properties of the formulation (e.g. compressibility, tabletability, elastic recovery).

5.2. The FlexiTab

The FlexiTab® (Röltgen GmbH & Co. KG, Solingen, Germany) is a single-punch tablet press for compressing powdered pharmaceutical substances to tablets for research purposes (Fig. 3). The machine is controlled by a computer and a programmable logic controller. The process parameters are adjusted by the operator by touch functions at the screen or by the integrated mouse. In addition, all operating steps of the compression process can be executed by touch functions or by using the mouse.

Figure 3. The FlexiTab.

The compression process includes the following steps (FlexiTab Operating Manual). First, the lower punch moves by a servo drive to the set fill height. The feeding shoe then transports the powder to be compressed from the filling reservoir to the die. The retreatment of the feeding shoe aligns the powder at the upper side. Next, the powder is compressed by a pneumatic / hydraulic compression force system. This system enables adjustment of compression profiles, i.e. different compression speeds can be used. After the compression, the ready tablet is pneumatically lifted out by the lower

punch and pushed by the feeding shoe into the ejecting shaft during the next filling sequence of the die. Compression data is collected by DAQ4 (Hucke Software, Solingen, Germany), which is an optional, machine type independent software package for data acquisition and analysis on tablet presses. After the compression process, tablet properties have to be measured with separate devices. For example, combination testers that measure weight, diameter, thickness, and hardness are fast and convenient.

6. OBJECTIVE OF THE STUDY

The objective of the study was to investigate tableting properties of commonly used direct compression excipients and their binary mixtures with two different laboratory scale tableting devices; the Gamlen® D1000 Powder Compaction Analyzer and the FlexiTab®. Whereas the suitability of Gamlen tablet presses for compression experiments has been demonstrated in previous studies (Pitt et al. 2015, Osamura et al. 2016), in this study, the suitability of the FlexiTab for similar purposes was evaluated in comparison to the Gamlen.

Microcrystalline cellulose, lactose, mannitol, starch, and dicalcium phosphate were chosen as materials for the compression studies, as they are the most common fillers used in DC formulations. Compression behaviour was evaluated in terms of compressibility (solid fraction vs. compression pressure) and tabletability (tensile strength vs. compression pressure). The results obtained with the two tableting devices were compared to identify any differences that could be dependent on the device and process parameters. Sample amount per each measurement point was rather small (n=3 in the Gamlen experiments, n=10 in the FlexiTab experiments), therefore, statistical methods were not used to analyse the results. The results are intended to be indicative and any results of specific interest could be further investigated by performing more comprehensive experiments.

Analyzing punch displacement data was included in the initial plan, however, the displacement sensors of the FlexiTab did not function properly despite several installation efforts. Therefore, displacement data is not addressed further in this work.

7. MATERIALS AND METHODS

7.1. Materials

Tablets were produced by using five different excipients and their binary mixtures. They included microcrystalline cellulose (Avicel® PH-102, FMC International Ltd., Cork, Ireland), spray-dried lactose (SuperTab® 11SD, DMV-Fonterra Excipients GmbH & Co. KG, Goch, Germany), spray-dried mannitol (PEARLITOL® 200 SD, Roquette, Lestrem, France), pregelatinized starch (LYCATAB® C, Roquette, Lestrem, France), and dicalcium phosphate dihydrate (DI-CAFOS® D14, Chemische Fabrik Budenheim KG, Budenheim, Germany). In addition, magnesium stearate (LIGAMED® MF-2-V, Peter Greven Nederland C.V., Venlo, The Netherlands) was used as a lubricant.

MCC, lactose, mannitol, starch, and DCP were chosen because they represent materials with different compression behaviour and they are the most common fillers/binders used in DC formulations. When selecting the specific grades, suitability for DC was considered, but otherwise the grades were chosen more or less arbitrarily, the main goal being representation of materials with different compression behaviour.

7.2. Methods

7.2.1. Blend preparation

Prior to other procedures, all of the materials were sieved to remove any aggregates present. The sieve size was 1 mm.

Each material was first studied individually. Internal and external lubrication were investigated as alternative lubrication methods in the Gamlen experiments, whereas only internal lubrication was used in the FlexiTab experiments. Internal lubrication was carried out by adding 1 % (w/w) magnesium stearate among the excipient and subsequently mixing the powder for 2 min with TURBULA® T 2 C mixer (Willy A. Bachofen AG, Muttenz, Swizerland). External lubrication was carried out by dipping the punch and the die in 5 % (w/w) suspension of magnesium stearate in ethanol.

Binary mixtures were prepared in three different weight ratios for every pair of materials. The ratios were 1:3, 1:1, and 3:1. The pair of excipients were first mixed for 5 min with TURBULA T 2 C mixer. Subsequently 1 % (w/w) magnesium stearate was added and mixing was continued for 2 min.

Before tableting, the moisture contents of the powders were analyzed with the Sartorius™ Moisture Analyzer MA100 (Sartorius AG, Göttingen, Germany). LYCATAB C had the highest moisture content, followed by Avicel PH-102 (APPENDIX 1). Moisture contents of DI-CAFOS D14, PEARLITOL 200 SD, and SuperTab 11SD were low. The values appeared similar in the Gamlen and FlexiTab experiments. Water activities were measured with AquaLab™ Series 3 (Decagon Devices, Inc., Pullman, WA, US), but they were not examined thoroughly. It is not ruled out that moisture conditions could have affected the compression results, but it is considered that they probably do not have a significant effect on the general view.

7.2.2. Tablet compression with the Gamlen

Five different compression loads were used in the tableting experiments with the Gamlen® D1000 Powder Compaction Analyzer (Table 1). The corresponding compression pressures were between 69 and 347 MPa. The punch was round and flat. Nominal tablet diameter was 6 mm and nominal tablet weight 100 mg (range 85−115 mg). Three tablets were compressed with each load. Compression speed was 120 mm/min. No dwell was used (dwell time 0 ms).

Table 1. Compression loads and corresponding compression pressures used in the Gamlen experiments.

Compression load (kg)	Compression pressure (MPa)
200	69
400	139
600	208
800	277
1000	347

After each compression event, tablet weight was measured with an analytical balance (Mettler-Toledo Inc., Columbus, OH, US), tablet thickness was measured with an electronic micrometer (Mitutoyo America Corporation, Aurora, IL, US), and tablet diameter and hardness were measured with the Gamlen® Tablet Tensile Analyzer (TTA) (Gamlen Instruments Ltd., London, UK). Tablet measurement data was gathered with the Gamlen® Dashboard software (Gamlen Instruments Ltd., London, UK).

7.2.3. Tablet compression with the FlexiTab

Before the actual compression experiments with the FlexiTab® were performed, test compressions were performed to adjust die filling depth so that tablet weight was approximately 100 mg (range 85−115 mg). In addition, parameters affecting the success of die filling (the number of filling times, delay time of feeding, shaker speed) were adjusted if insufficient die filling was observed. Compression speed was adjusted to 30 % (percentage of valve opening), because the actual forces were then closest to the set values. Higher compression speeds led to overshooting issues (i.e. the actual force exceeded the set force to a remarkable extent).

Five different compression forces were used in the FlexiTab experiments (Table 2). The corresponding compression pressures were between 99 and 495 MPa. The punches were round and flat. Nominal tablet diameter was 6 mm. Ten tablets were compressed with each force. All the materials and mixtures were tableted by using a dwell time of 50 ms. In addition, the individual materials and the mixtures with weight ratios 1:1 were tableted by using a dwell time of 1000 ms.

Table 2. Compression forces and corresponding compression pressures used in the FlexiTab experiments.

Compression force (kN)	Compression pressure (MPa)
2.8	99
5.6	198
8.4	297
11.2	396
14.0	495

After the compression events, tablet weight, thickness, diameter, and hardness were measured with the EasyCheck tablet combination tester (ERWEKA GmbH, Langen, Germany).

7.2.4. Analysis of the compression data

7.2.4.1. Compressibility

Compressibility was expressed by plotting solid fraction against compression pressure. Solid fractions were calculated from the ratio of tablet density and true density of the material or binary mixture:

$$Solid\ fraction = \frac{\rho_{tablet}}{\rho_{true}} \quad (1)$$

where ρ_{tablet} is the tablet density calculated from tablet weight and tablet dimensions and ρ_{true} is the true density. The true density values of the individual materials were obtained from literature (APPENDIX 2). It is acknowledged that slightly different true density values might be obtained for the same material depending on the analysis method and material batch, but it was considered that a small deviation would not affect solid fraction significantly. The true densities of the binary mixtures were calculated from true densities of the individual materials:

$$\rho_m = \frac{1}{\frac{n_1}{\rho_1}+\frac{n_2}{\rho_2}} \quad (2)$$

where ρ_m is the true density of the binary mixture, ρ_1 and ρ_2 are the true densities of the components, and n_1 and n_2 are the weight fractions of the components.

It has been frequently stated in literature that the optimal range for solid fraction is 0.85±0.05 (Pitt et al. 2015). Therefore, this was considered the target range in this study as well.

7.2.4.2. Tabletability

Tabletability was expressed by plotting tensile strength against compression pressure. Tensile strengths were calculated from tablet hardness and tablet dimensions:

$$Tensile\ strength\ (MPa) = \frac{2P}{\pi Dt} \quad (3)$$

where P is tablet hardness, D is tablet diameter, and t is tablet thickness (Fell and Newton 1970). This equation holds for round, flat-faced tablets. There are distinct equations for tablets of different shape.

It has been commonly recommended in literature that tensile strengths greater than 2 MPa should be targeted to ensure good mechanical strength of tablets (Pitt et al. 2015). Therefore, this was considered a target value in this study as well. In addition, attention was paid to the required compression pressure for achieving this value and to tensile strength increase at higher pressures.

7.2.4.3. Comparison of hardness measurements

After the compression results of the Gamlen and FlexiTab experiments had been analyzed, it seemed that tensile strengths were generally somewhat higher in the Gamlen experiments. Therefore, an experiment was performed to compare the hardness values obtained from the Gamlen TTA and the EasyCheck tablet combination tester. Avicel PH-102 containing 1 % (w/w) magnesium stearate was used as a test material. All the compressions were performed with the Gamlen during the same day. Ten tablets were measured with the analytical balance, micrometer, and the Gamlen

TTA, which were used in the former Gamlen experiments. In this case, the tablets were measured immediately after compression (within 1–2 min). Likewise, ten tablets were measured with the EasyCheck, which was used in the former FlexiTab experiments. In this case, however, tablet properties were measured after all compressions had been performed, which means that there was a short delay (≤30 min) between the compressions and the measurements.

Tablet measurement data was analyzed by calculating solid fractions and tensile strengths. The results obtained with the different measurement devices were then compared to detect possible differences.

8. RESULTS AND DISCUSSION

Compression results are presented in terms of compressibility and tabletability. Each material is first addressed individually, and binary mixtures are addressed subsequently. The results of the Gamlen and FlexiTab experiments are compared in each case.

8.1. Compressibility

8.1.1. Avicel PH-102

The compressibility curves of Avicel PH-102 appeared to be of a shape typical to plastic materials. In the Gamlen experiments, solid fractions increased steeply at lower compression pressures, whereas they remained rather constant at higher pressures (Fig. 4, APPENDIX 3). This indicates to plasticity, as plastic deformation generally occurs at lower pressures than fragmentation (Katz and Buckner 2013). Solid fractions were in the ideal range of 0.85±0.05 when the compression pressure was over 100 MPa. Lubrication method had no apparent effect on solid fraction. RSD values were low in all experiments (≤1 %).

Compressibility appeared very similar in the FlexiTab experiments (Fig. 4, APPENDIX 4). It seemed that the longer dwell time might have resulted in slightly higher solid fractions at low pressures, but the differences were inconspicuous. However, this conclusion would be in line with the observation that dwell time probably had a subtle effect on tensile strengths in the same pressure range. In addition, plastic materials typically are sensitive to dwell time (Katz and Buckner 2013). RSD values were low and quite similar to those in the Gamlen experiments (typically ≤1 %).

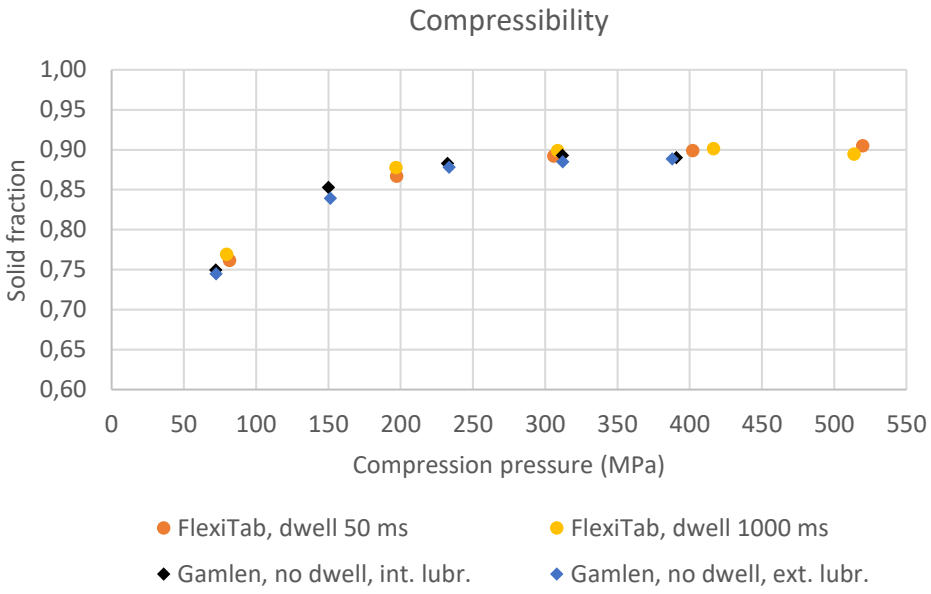

Figure 4. Compressibility of Avicel PH-102 based on the Gamlen (n=3) and FlexiTab results (n=10).

8.1.2. DI-CAFOS D14

The compressibility curves of DI-CAFOS D14 indicated to brittleness. In the Gamlen experiments, solid fractions increased slowly but steadily over the whole pressure range (Fig. 5, APPENDIX 3). This is a sign of fragmentation, which typically occurs at higher pressures than plastic deformation (Katz and Buckner 2013). It is noteworthy that DI-CAFOS D14 had very low solid fractions compared to the other materials. Poor compression behaviour is probably attributed to hardness of the material, but it could be also linked to small particle size (Alshafiee et al. 2019). Solid fractions

remained under the ideal range of 0.85±0.05 over the whole pressure range. Low solid fraction might be associated with low mechanical strength and high friability (Sun 2017). However, mechanical strength appeared acceptable based on tensile strength. Lubrication method had no obvious effect on solid fraction. RSD values were low in all experiments (≤1 %).

Compressibility appeared very similar in the FlexiTab experiments (Fig. 5, APPENDIX 4). The longer dwell time resulted in slightly higher solid fractions at several measurement points, but it is assumed that the differences were insignificant. Dwell time generally has no effect on the compression behaviour of brittle materials (Katz and Buckner 2013). RSD values were higher than in the Gamlen experiments (≤3 %), which might be linked to uneven die filling.

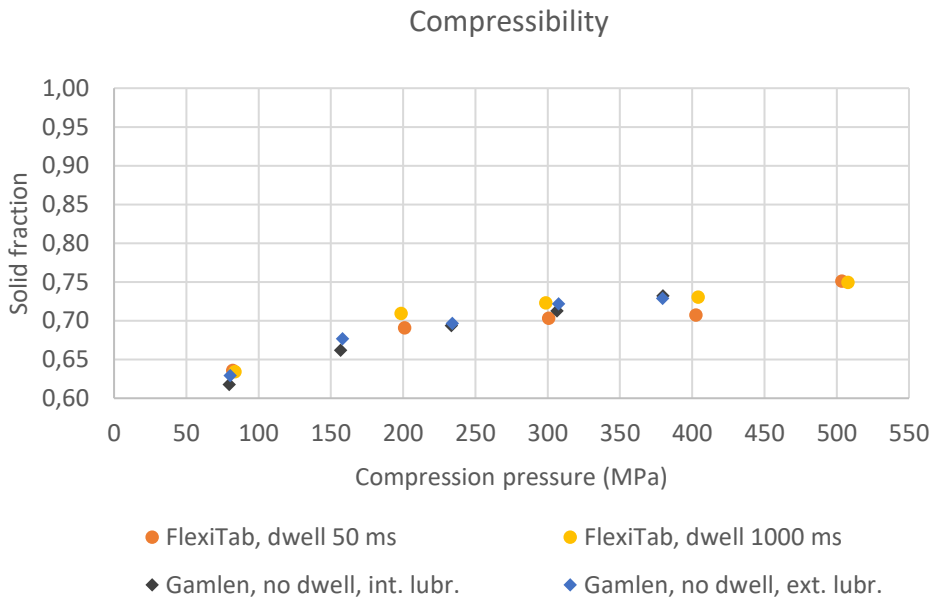

Figure 5. Compressibility of DI-CAFOS D14 based on the Gamlen (n=3) and FlexiTab results (n=10).

8.1.3. LYCATAB C

The compressibility curves of LYCATAB C had a shape typical to plastic materials. In the Gamlen experiments, solid fractions increased steeply at low compression pressures, after which they remained rather constant (Fig. 6, APPENDIX 3). This is

typical of plastic materials, as plastic deformation generally occurs at a lower pressure range than fragmentation (Katz and Buckner 2013). The shapes of the curves were reminiscent to those of Avicel PH-102, but LYCATAB C had somewhat lower solid fraction values over the whole pressure range. Solid fractions were in the ideal range of 0.85±0.05 when the compression pressure was over 150 MPa. Lubrication method had no apparent effect on solid fraction. RSD values were low in all experiments (typically ≤1 %).

Compressibility appeared very similar in the FlexiTab experiments when the shorter dwell time was used (Fig. 6, APPENDIX 4). The longer dwell time resulted in somewhat higher solid fractions, especially at low pressures. This could be expected, as plastic materials typically are sensitive to dwell time (Katz and Buckner 2013). RSD values were low and quite similar to those in the Gamlen experiments (typically ≤1 %).

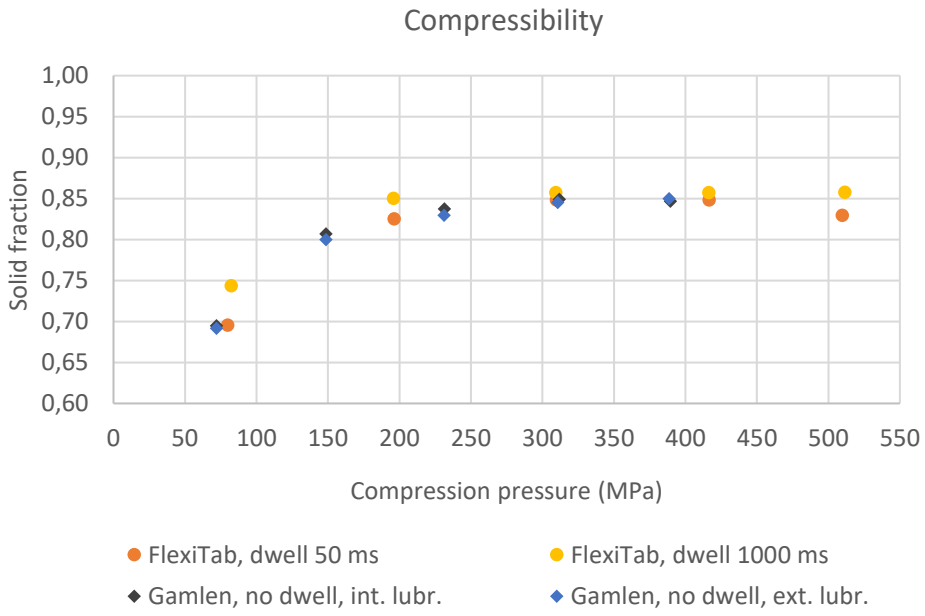

Figure 6. Compressibility of LYCATAB C based on the Gamlen (n=3) and FlexiTab results (n=10).

8.1.4. PEARLITOL 200 SD

The compressibility curves of PEARLITOL 200 SD referred to brittleness. In the Gamlen experiments, solid fractions increased gradually over the whole pressure range (Fig. 7, APPENDIX 3). This indicates to fragmentation, which generally occurs at higher pressures than plastic deformation (Katz and Buckner 2013). Solid fractions were in the ideal range of 0.85±0.05 when the compression pressure was between 100 and 300 MPa. Higher pressures might be a risk for problems associated with overcompression (Sun 2017). Lubrication method had no clear effect on solid fraction. RSD values were low in all experiments (typically ≤1 %).

Compressibility appeared slightly different in the FlexiTab experiments depending on the dwell time used (Fig. 7, APPENDIX 4). The longer dwell time resulted in higher solid fractions at lower pressures. This might indicate that some plastic deformation occurred, even though it is considered that spray-dried mannitol grades are rather brittle materials. Brittle materials are typically insensitive to dwell time (Katz and Buckner 2013). However, spray-dried mannitol grades may show some extent of plastic deformability (Paul et al. 2019). When the longer dwell time was used, solid fraction exceeded 0.90 already at a compression pressure of 200 MPa. RSD values appeared slightly higher than in the Gamlen experiments but still reasonably low (typically ≤2 %).

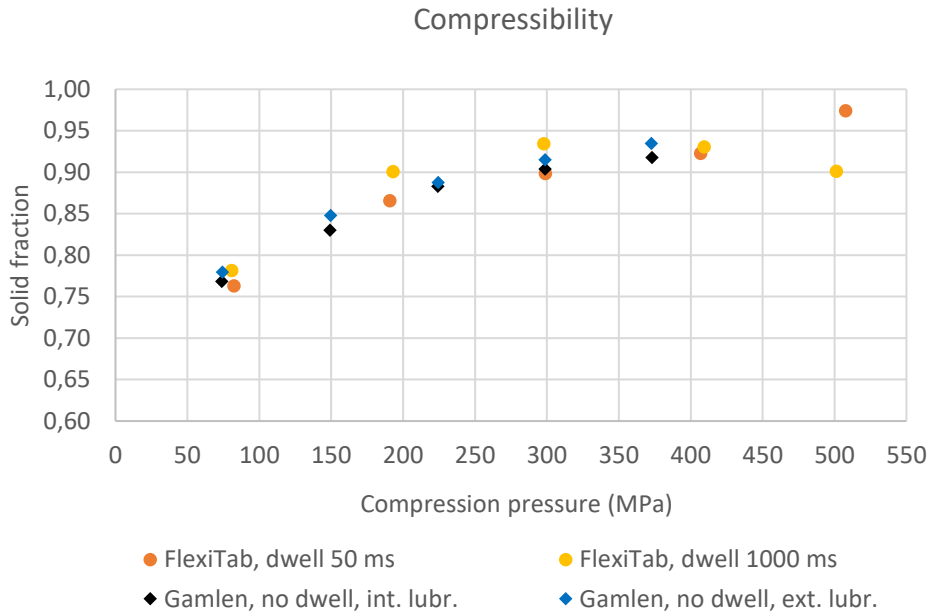

Figure 7. Compressibility of PEARLITOL 200 SD based on the Gamlen (n=3) and FlexiTab results (n=10).

8.1.5. SuperTab 11SD

The compressibility curves of SuperTab 11SD had a shape typical to brittle materials. In the Gamlen experiments, solid fractions increased gradually over the whole pressure range (Fig. 8, APPENDIX 3). This is typical of brittle materials (Katz and Buckner 2013). Solid fractions were in the ideal range of 0.85±0.05 up to a compression pressure of about 250 MPa. Higher pressures resulted in solid fractions over 0.90, which might be a risk for problems associated with overcompression (Sun 2017). Lubrication method had no apparent effect on solid fraction. RSD values were low (typically ≤1 %).

Compressibility appeared quite similar in the FlexiTab experiments (Fig. 8, APPENDIX 4). However, solid fractions were slightly higher with the FlexiTab, especially when the shorter dwell time was used. According to the FlexiTab results, solid fractions exceeded 0.90 already at a compression pressure of about 200 MPa. The difference between the distinct dwell times might be insignificant, and no reasons have been figured out that would explain it. Brittle materials are typically insensitive to dwell time (Katz and Buckner 2013). However, spray-dried lactose grades generally

contain a small amount of amorphous material that shows plastic compression behaviour (Ruangchayajatuporn et al. 2011). Yet this seems an unlikely explanation, as the compressibility curve with the longer dwell time does not indicate to plastic deformation. RSD values were mainly low, but relatively high values (up to 4 %) were observed in the case where the results with the shorter dwell time appeared to diverge.

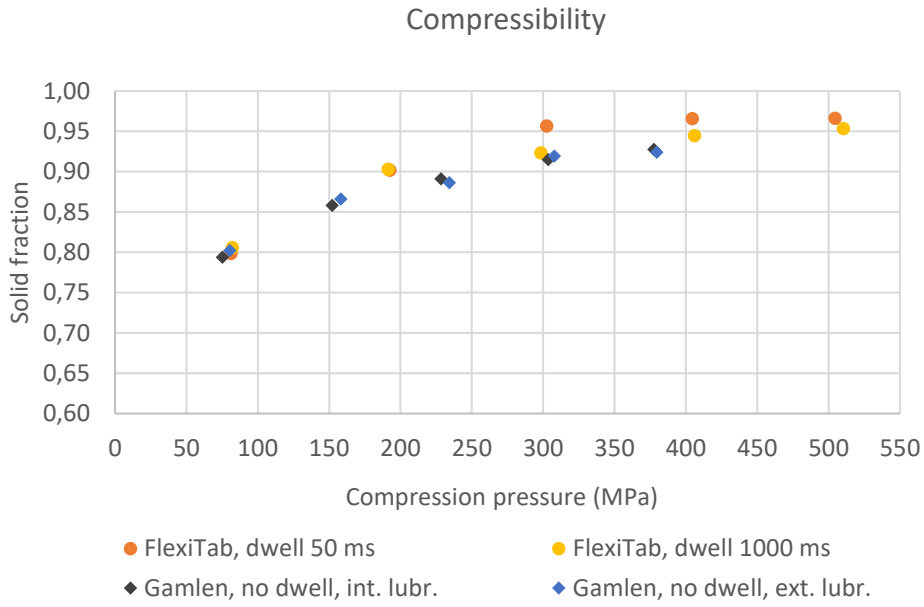

Figure 8. Compressibility of SuperTab 11SD based on the Gamlen (n=3) and FlexiTab results (n=10).

8.1.6. Binary mixtures

The compressibilities of the binary mixtures were generally more or less what might be expected based on the compressibilities of the individual materials and their proportions in the mixture. On the other hand, compression curves were in many cases very similar or overlapping, and it was hard to make any definite conclusions. The equation used for the calculation of the true densities of the binary mixtures (Eq. 2) takes into account that the materials have different volumes based on their true densities.

The compressibility curves obtained in the Gamlen experiments (APPENDIX 5) were generally similar to those obtained in the FlexiTab experiments (APPENDIX 6). The

combination of PEARLITOL 200 SD and DI-CAFOS D14 is given as an example, where the compressibility curves of the different mixtures could be distinguished very well (Fig. 9). Based on the experiments performed with the individual materials, PEARLITOL 200 SD had very high solid fractions compared to DI-CAFOS D14 (APPENDIX 3, APPENDIX 4). Therefore, it was logical that solid fractions increased when the amount of PEARLITOL 200 SD in the mixture was increased.

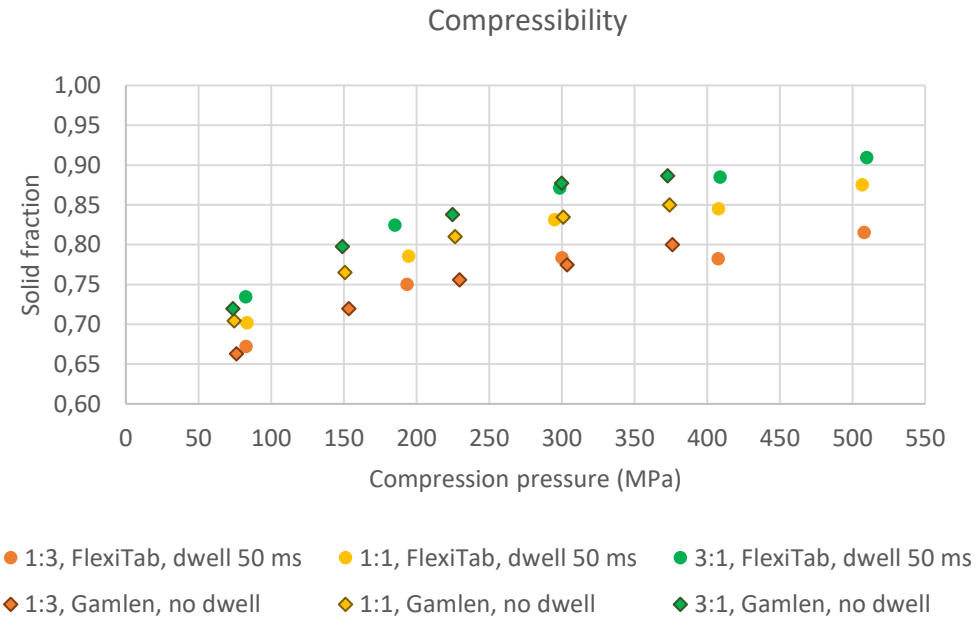

Figure 9. Compressibilities of the binary mixtures of PEARLITOL 200 SD and DI-CAFOS D14 based on the Gamlen (n=3) and FlexiTab results (n=10). Component ratios are expressed as the weight ratio of PEARLITOL 200 SD to DI-CAFOS D14.

In general, solid fractions of the binary mixtures were not affected by dwell time. The combination of Avicel PH-102 and LYCATAB C was the only case in which the longer dwell time resulted in slightly higher solid fractions. This was logical because this was the only combination in which both of the components were plastic materials. Combinations of Avicel PH-102 or LYCATAB C with other materials might have been affected by dwell time too, but no evident effects on solid fraction were observed.

8.2. Tabletability

8.2.1. Avicel PH-102

The tabletability of Avicel PH-102 appeared excellent in the Gamlen experiments with both lubrication methods (Fig. 10, APPENDIX 3). Tensile strengths were very high compared to the rest of the materials. Even the lowest compression pressure of 70 MPa resulted in tablets with tensile strengths over 4 MPa. Furthermore, the values also increased remarkably by following pressure increases, the highest value being 11.6 ± 0.2 MPa with external lubrication and 9.6 ± 0.3 MPa with internal lubrication. Tensile strengths were slightly higher with external lubrication throughout the whole pressure range, although the difference was more pronounced at high pressures. However, also RSD values were higher with external lubrication. The tensile strength difference observed with the distinct lubrication methods could be expected, as plastic materials are generally sensitive to lubricants (Jivraj et al. 2000).

Tabletability appeared excellent in the FlexiTab experiments as well (Fig. 10, APPENDIX 4). Tensile strengths were over 3 MPa already at the lowest compression pressure of 80 MPa. However, somewhat lower tensile strengths were observed compared to the Gamlen experiments. In addition, it appeared that the increase in tensile strength leveled out at high pressures. Tensile strengths were still high over the whole pressure range. It appeared that the longer dwell time might have resulted in slightly higher tensile strengths at low pressures, although the difference was surprisingly inconspicuous. This would be in line with the fact that plastic materials are typically sensitive to compression speed and dwell time (Sinka et al. 2009). The highest tensile strength value was 8.5 ± 0.6 MPa with the shorter dwell time and 7.6 ± 0.4 MPa with the longer dwell time. RSD values were somewhat higher compared to the Gamlen results. It is assumed that the tensile strength difference between the FlexiTab and Gamlen experiments was influenced by the higher compression speed of the FlexiTab. However, it is probable that hardness measurements also contributed to the difference (see Chapter 8.3.).

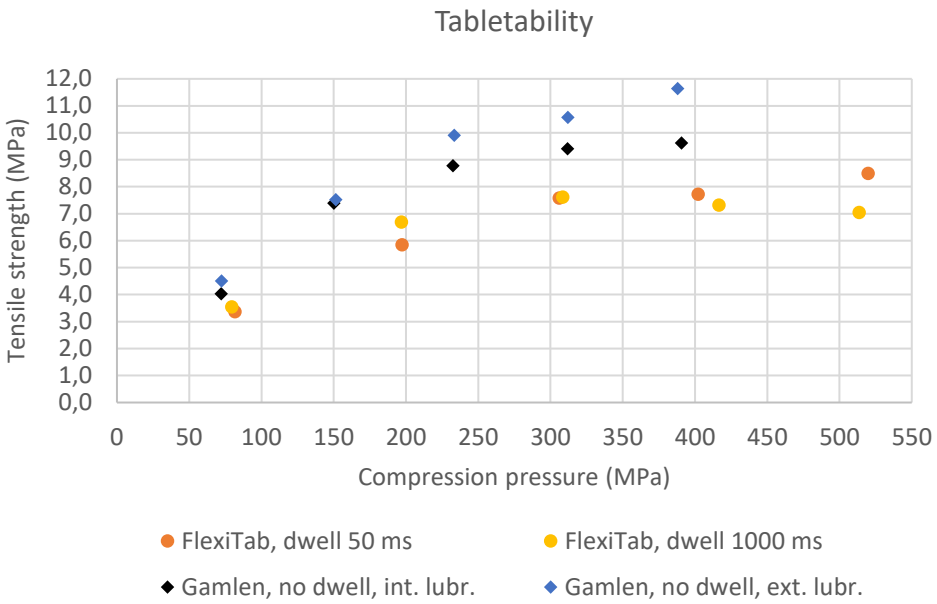

Figure 10. Tabletability of Avicel PH-102 based on the Gamlen (n=3) and FlexiTab results (n=10).

8.2.2. DI-CAFOS D14

The tabletability of DI-CAFOS D14 appeared acceptable in the Gamlen experiments with both lubrication methods (Fig. 11, APPENDIX 3). Tensile strengths of 2 MPa were achieved at compression pressures between 150 MPa and 200 MPa. The highest values were 4.3 ± 0.9 MPa and 3.9 ± 0.7 MPa with external and internal lubrication, respectively. RSD values were high with both methods. When the variation of the values was taken into account, it appeared that tensile strength was not affected by lubrication method. This is in line with the general perception that DCP is a brittle material and lubricants have no effect on its binding properties (Jivraj et al. 2000).

Tabletability appeared acceptable in the FlexiTab experiments as well (Fig. 11, APPENDIX 4). Tensile strengths were quite similar as in the Gamlen experiments, however, tensile strengths increased more steadily throughout the whole pressure range when the FlexiTab was used. Dwell time had no apparent effect on the results, which is typical for brittle materials (Sinka et al. 2009). The highest value with the shorter dwell time was 4.0 ± 0.8 MPa and 4.5 ± 0.7 MPa with the longer dwell time. RSD values were high, like they were in the Gamlen experiments as well.

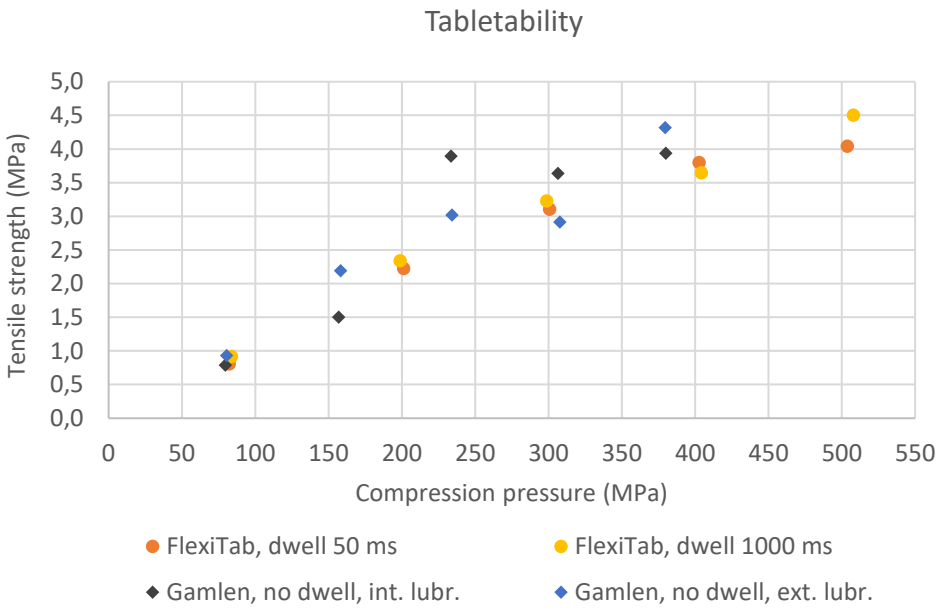

Figure 11. Tabletability of DI-CAFOS D14 based on the Gamlen (n=3) and FlexiTab results (n=10).

8.2.3. LYCATAB C

The tabletability of LYCATAB C was clearly affected by the lubrication method in the Gamlen experiments; tabletability was acceptable with external lubrication but poor with internal lubrication (Fig. 12, APPENDIX 3). A tensile strength of 2 MPa was achieved with a compression pressure under 150 MPa when external lubrication was used, whereas approximately 350 MPa was required to achieve the same strength with internal lubrication. The highest values with the distinct methods were 3.6 ± 0.6 MPa and 2.2 ± 0.3 MPa, respectively. RSD values were quite high with both methods. The tensile strength difference observed between the lubrication methods could be expected, as starches are plastic materials and known to be sensitive to alkalic lubricants, such as magnesium stearate (Jivraj et al. 2000).

Tabletability appeared even poorer in the FlexiTab experiments (Fig. 12, APPENDIX 4). Tensile strengths remained under 1.5 MPa over the whole pressure range. The longer dwell time resulted in higher tensile strengths at low pressures, which could be expected as plastic materials typically are sensitive to compression speed and dwell time (Sinka et al. 2009). In contrast to the Gamlen experiments, tensile strengths did

not increase at high pressures at all. The highest value with the shorter dwell time was 1.2 ± 0.1 MPa and with the longer dwell time 1.4 ± 0.1 MPa. RSD values appeared slightly lower compared to the Gamlen results. The difference in tensile strengths between the FlexiTab and Gamlen experiments was probably influenced by the higher compression speed of the FlexiTab. In addition, hardness measurements may have contributed to the difference (see Chapter 8.3.).

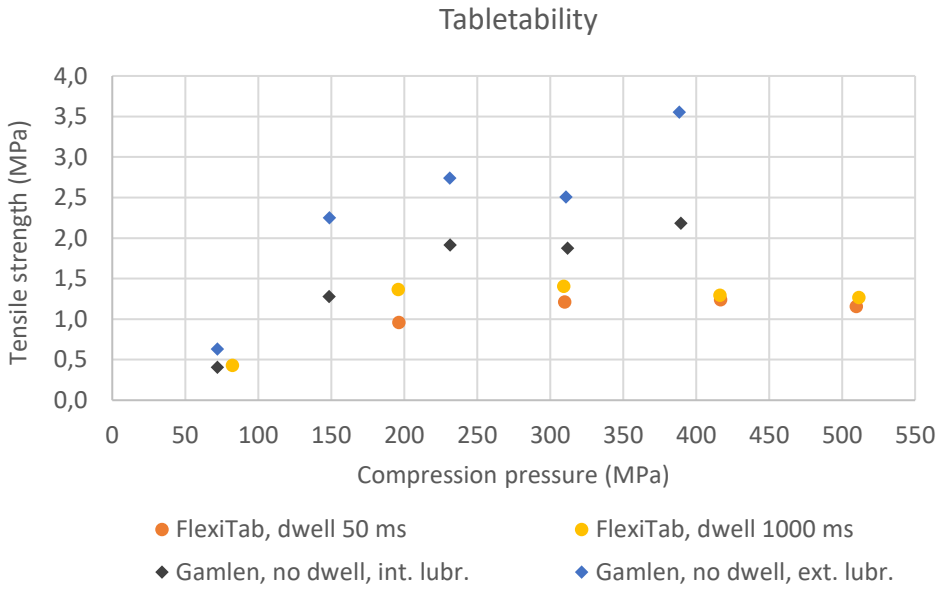

Figure 12. Tabletability of LYCATAB C based on the Gamlen (n=3) and FlexiTab results (n=10).

8.2.4. PEARLITOL 200 SD

The tabletability of PEARLITOL 200 SD appeared good in the Gamlen experiments with internal lubrication and acceptable with external lubrication (Fig. 13, APPENDIX 3). With internal lubrication, a compression pressure of roughly 150 MPa was required to achieve a tensile strength of 2 MPa, whereas about 200 MPa was required to achieve the same strength with external lubrication. Tensile strengths increased quite steadily as the pressure was increased, the highest values being 6.0 ± 0.3 MPa and 4.8 ± 0.9 MPa with internal and external lubrication, respectively. RSD values were remarkably higher with external lubrication. It remains unclear why internal lubrication resulted in higher tensile strengths, but one explanation could be that magnesium stearate might

fill surface cavities of the mannitol particles making them more spherical and smoother, which could reduce interparticle friction. This has been previously reported in the context of flowability studies with spray-dried lactose (Morin and Briens 2013). Another explanation might be that the lubricant suspension on the punch and in the die had not dried completely and that the remaining moisture had a negative effect on tensile strength.

Tabletability appeared good in the FlexiTab experiments as well (Fig. 13, APPENDIX 4). At lower pressures, tensile strengths were very similar to the Gamlen results with internal lubrication. However, at higher pressures somewhat lower tensile strengths were observed with the FlexiTab. Dwell time had no apparent effect on tensile strength, which is in line with the conceptions that fragmentation is the main deformation mechanism of spray-dried mannitol grades and that brittle materials are generally insensitive to dwell time (Sinka et al. 2009). The highest value with the shorter dwell time was 4.4 ± 1.1 MPa and with the longer dwell time 4.7 ± 0.9 MPa. RSD values were remarkably higher than in the Gamlen experiments. The explanation for the higher tensile strengths observed in the Gamlen experiments remains unclear, as brittle materials are typically insensitive to compression speed (Sinka et al. 2009). However, spray-dried mannitol grades may also show some extent of plastic deformability (Paul et al. 2019). It might be that some kind of overcompression effect occurred at high pressures, which could have resulted in lower tensile strengths. On the other hand, it is probable that hardness measurements contributed to the difference (see Chapter 8.3.).

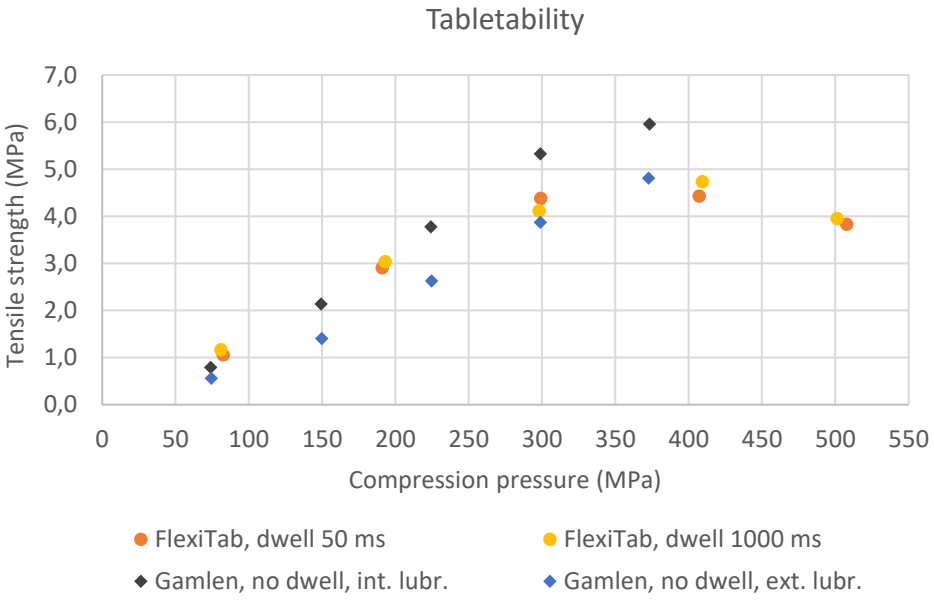

Figure 13. Tabletability of PEARLITOL 200 SD based on the Gamlen (n=3) and FlexiTab results (n=10).

8.2.5. SuperTab 11SD

The tabletability of SuperTab 11SD appeared poor in the Gamlen experiments with internal lubrication and unacceptable with external lubrication (Fig. 14, APPENDIX 3). A tensile strength of 2 MPa required a compression pressure over 250 MPa when internal lubrication was used, and even 300 MPa was required to achieve the same strength with external lubrication. However, tensile strengths increased quite steadily when the pressure was increased. The highest values with internal and external lubrication were 2.9 ± 0.1 MPa and 2.3 ± 0.6 MPa, respectively. RSD values were clearly higher with external lubrication. The effect of the distinct lubrication methods on tabletability was similar to that observed with PEARLITOL 200 SD. Same mechanisms might explain these results, for example, magnesium stearate filling surface cavities of lactose particles, making the particles more spherical and smoother and thus reducing interparticle friction. This has been previously addressed as the cause for improved flowability with spray-dried lactose (Morin and Briens 2013). It is also possible that the lubricant suspension on the punch and in the die had not dried completely and that the remaining moisture deteriorated tabletability results.

Tabletability results obtained in the FlexiTab experiments were very similar to the results of the Gamlen experiment with internal lubrication (Fig. 14, APPENDIX 4). A tensile strength of 2 MPa required a compression pressure about 250 MPa. Dwell time had no apparent effect on tensile strength, which is typical for brittle materials (Sinka et al. 2009). The highest value with the shorter dwell time was 3.6 ± 0.1 MPa and with the longer dwell time 3.6 ± 0.3 MPa. On average, RSD values appeared slightly higher compared to the Gamlen results.

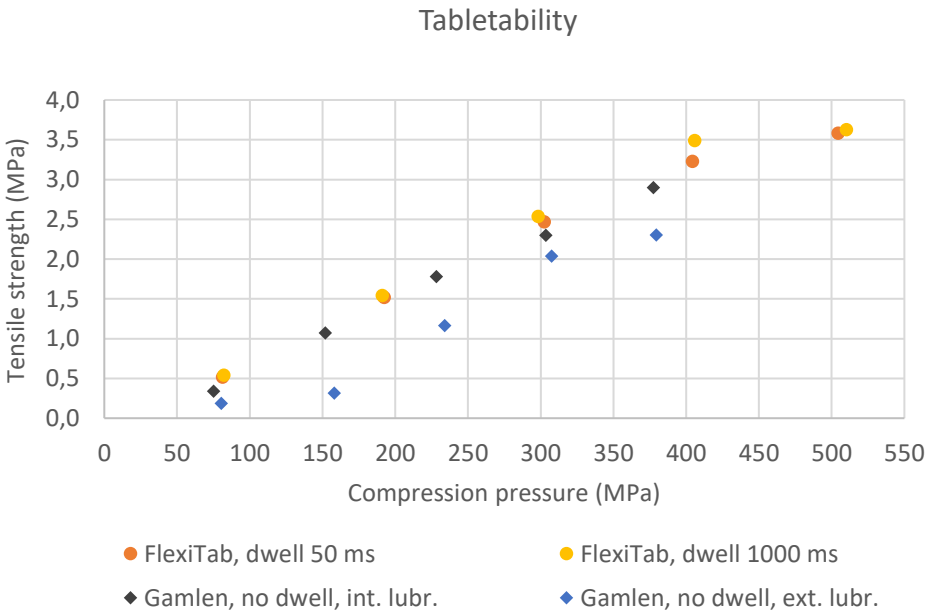

Figure 14. Tabletability of SuperTab 11SD based on the Gamlen (n=3) and FlexiTab results (n=10).

8.2.6. Binary mixtures

The tabletabilities of the different binary mixtures were more or less what might be expected based on the tabletabilities of the individual materials and their proportions in the mixture. Tensile strengths were generally somewhat higher in the Gamlen experiments (APPENDIX 5) compared to the FlexiTab experiments (APPENDIX 6). This was in line with the observations made with the individual materials.

It is noteworthy that considering volume proportions rather than weight proportions might be more appropriate (Wu et al. 2005). In cases where the exact volumes of the

components are not known, they can be estimated based on true density values. Whereas PEARLITOL 200 SD, LYCATAB C, SuperTab 11SD, and Avicel PH-102 have somewhat similar true densities, DI-CAFOS D14 has a remarkably higher true density (APPENDIX 2). Thus, its volume in the mixtures was smaller with respect to weight proportion compared to the rest of the materials. Therefore, it is possible that DI-CAFOS D14 contributed less to tensile strength than what would be expected based on weight proportions. In some instances it appeared that this might indeed be the case, but no analyses were carried out to explore this further.

In overall, Avicel PH-102 had the best impact on tabletability. All of the binary mixtures containing Avicel PH-102 had relatively high tensile strengths. The combinations of Avicel PH-102 with DI-CAFOS D14 are examples of mixtures with good or excellent tabletability (Fig. 15). With each of these mixtures, a tensile strength of 2 MPa was achieved at a compression pressure of 150 MPa or lower, and the values increased remarkably by following pressure increases. Tensile strengths increased logically when the proportion of Avicel PH-102 increased. The Gamlen experiments clearly gave higher values than the FlexiTab experiments, and the differences were even 2 MPa. It was assumed that compression speed might affect the compression behaviour of Avicel PH-102 but probably not the behaviour of DI-CAFOS D14. Therefore, the differences in tensile strength appeared surprisingly outstanding. It seems probable that some extent of the differences was caused by hardness measurements (see Chapter 8.3.).

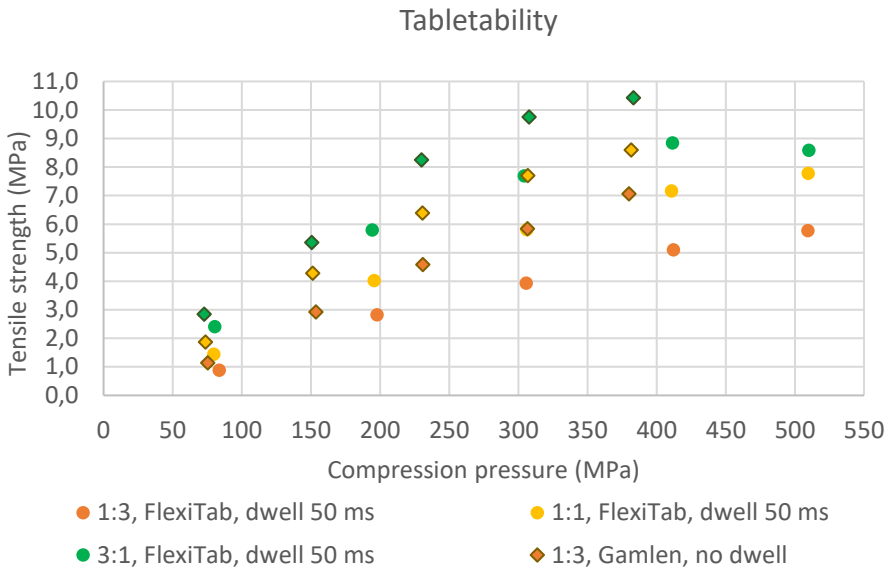

Figure 15. Tabletabilities of the binary mixtures of Avicel PH-102 and DI-CAFOS D14 based on the Gamlen (n=3) and FlexiTab results (n=10). Component ratios are expressed as the weight ratio of Avicel PH-102 to DI-CAFOS D14.

Of the combinations that did not contain Avicel PH-102, the mixtures of PEARLITOL 200 SD with DI-CAFOS D14 stood out with good tabletability (Fig. 16). A tensile strength of 2 MPa was achieved at a compression pressure around 150 MPa or lower. The tabletabilities of other combinations were modest in comparison.

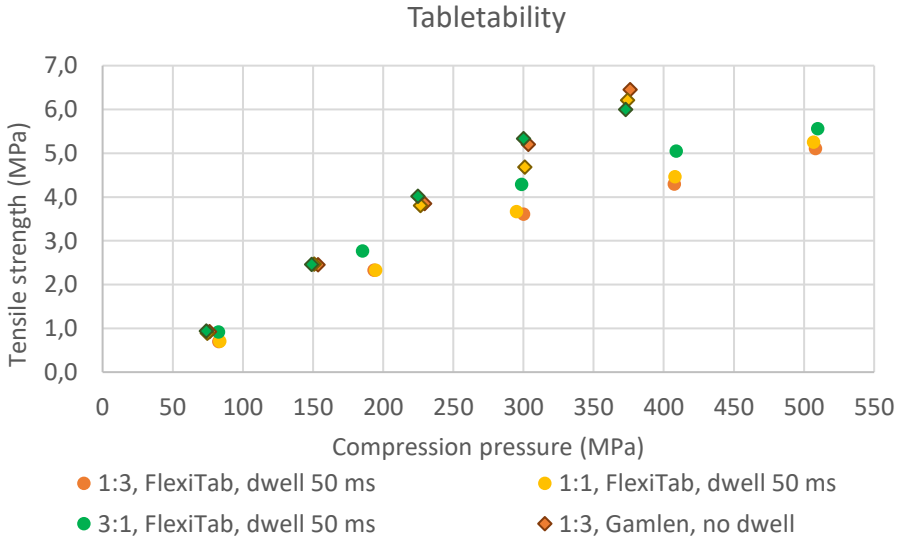

Figure 16. Tabletabilities of the binary mixtures of PEARLITOL 200 SD and DI-CAFOS D14 based on the Gamlen (n=3) and FlexiTab results (n=10). Component ratios are expressed as the weight ratio of PEARLITOL 200 SD to DI-CAFOS D14.

Dwell time apparently had an effect on some of the binary mixtures. It appeared that the combination of Avicel PH-102 and LYCATAB C had slightly higher tensile strengths when the longer dwell time was used, which could be expected based on the compressibility results and the plasticity of the materials. In addition, it appeared that the combinations of LYCATAB C with DI-CAFOS D14 and PEARLITOL 200 SD had slightly higher tensile strengths with the longer dwell time.

8.3. Comparison of hardness measurements

Comparison of the devices used for tablet measurements in the Gamlen and FlexiTab experiments revealed that it is highly probable that there was a difference between the measurement results. The main focus was on comparing tensile strengths of Avicel PH-102 obtained with the Gamlen TTA and the EasyCheck, but also solid fractions were compared (Table 3, APPENDIX 7). It appeared obvious that higher tensile strengths were obtained when the Gamlen TTA was used. In addition, RSD was lower with the Gamlen TTA. However, it appeared also that solid fraction was higher in this case. This might indicate that some elastic recovery had occurred in the case of the EasyCheck, as there was a short delay (≤30 min) between the compressions and tablet measurements. It is not clear if this could have had a significant effect on tensile strength.

Table 3. Solid fraction and tensile strength of Avicel PH-102 based on measurements with different devices.

Measurement device	Solid fraction	Solid fraction, RSD (%)	Tensile strength (MPa)	Tensile strength, RSD (%)
Balance, micrometer, and the Gamlen TTA	0.89	0.5	10.4	1.8
The EasyCheck	0.84	2.0	9.1	5.0

Elastic recovery is typically higher for plastic materials (Zhang et al. 2017). This could be observed also in the Gamlen experiments, where the immediate elastic recovery was high for Avicel PH-102 and LYCATAB C and lower for SuperTab 11SD, PEARLITOL 200 SD, and DI-CAFOS D14. Probably also short-term elastic recovery is higher for Avicel PH-102 and LYCATAB C. In the Gamlen experiments, tablet

properties were measured immediately after compression (within 1–2 min), whereas there was a short delay between the compressions and the measurements in the FlexiTab experiments (≤20 min). However, this delay was rather short and it is unclear if any significant elastic recovery occurred during this short time period and would there be any significant effect on tensile strength values.

It has been previously reported that high compression pressures might cause excessive elastic deformation in plastic materials (Sun et al. 2018). This in turn, might cause defects in the tablets, which could result in lower tensile strength. It has also been reported that elastic recovery of Avicel PH-102 continues for a long time after compression, but elastic changes are most prominent during the first hour after compression (Zhang et al. 2017).

It appears possible that elastic recovery had an effect on tensile strengths in this experiment as well as in the FlexiTab experiments. However, elastic recovery could not be indicated based on solid fractions, which were similar between the Gamlen and FlexiTab experiments. Without further experiments it remains unclear how the tensile strength difference observed between the Gamlen and FlexiTab experiments was dependent on the hardness measurements. There probably was a difference between the measurement results regardless of any elastic recovery events, but the extent of the difference remains indefinite.

It appeared also that RSD values of tensile strengths were usually somewhat higher in the FlexiTab experiments than in the Gamlen experiments. Some extent of the differences observed in RSD values were probably caused by differences in hardness measurements. On the other hand, there were more variation in compression pressure in the FlexiTab experiments, which could explain higher RSD values to some extent.

9. CONCLUSIONS

The objective of this work was to investigate tableting properties of different excipients with two different laboratory scale tableting devices; the Gamlen® D1000

Powder Compaction Analyzer and the FlexiTab®. Whereas the suitability of Gamlen devices for compression experiments has been demonstrated before, in this study, the suitability of the FlexiTab for similar purposes was evaluated in comparison to the Gamlen.

The excipients and their binary mixtures were characterised based on compressibility and tabletability. Based on the compressibility curves, it appeared that plastic deformation was the main compression mechanism of MCC (Avicel PH-102) and starch (LYCATAB C), and fragmentation was the main compression mechanism of lactose (SuperTab 11SD), mannitol (PEARLITOL 200 SD), and DCP (DI-CAFOS D14). The tabletability of MCC was excellent, and also the tabletability of mannitol was good. The tabletability of DCP was intermediate, whereas lactose and starch had inferior tabletabilities. In general, the tabletabilities and compressibilities of the binary mixtures were more or less what was expected based on the results of the individual materials. Comparison of the results obtained with the different speed parameters and lubrication methods were in line with the perceptions of the compression mechanisms of different materials. In overall, quite similar results were obtained in the Gamlen and FlexiTab experiments. However, tensile strengths were generally somewhat lower in the FlexiTab experiments. This is probably explained by differences in compression speed as well as differences in hardness measurements.

Compression experiments with the Gamlen underlined the usefulness of automatic data analysis and the comprehensive assessment report. The report is very informative and easy to interpret. Tableting experiments with the Gamlen require only a small amount of material, as only a few tablets per measurement point is usually enough to obtain a view of the various compression properties. The compression events are very precise, i.e. there is very little deviation in the compression pressure and the compression speed is constant. Because the die is filled manually, it is easy to produce tablets of desired weight. It is convenient that the software is capable of collecting tablet measurement data automatically. However, manual filling of the die and measuring tablet properties with separate devices also consumes time. In addition, a disadvantage of manual filling is that flowability issues might not be noticed. In conclusion, it is considered that compression experiments with the Gamlen is a very

informative and material-sparing method for gathering knowledge during formulation development.

Compression experiments with the FlexiTab showed the utility of controlling various process parameters, such as compression speed. Compression speed is closer to production scale devices than that of the Gamlen. In addition, an essential advantage compared to the Gamlen is also the automatic powder feeding mechanism. It is easy and fast to produce a large number of tablets, once all parameters have been set. In addition, an impression of powder flowability can be obtained and possible flowability issues might be noticed. However, adjusting different parameters might consume time and material. Compared to the Gamlen, data analysis appeared laborious. Although the data report contains a lot of information, interpreting the data was challenging. In addition, tablet properties need to be measured with separate devices, and analyzing tablet measurement data might consume a significant amount of time. In conclusion, it is considered that tablet production with the FlexiTab can be easy and fast. Higher compression speed and the automatic powder feed mechanism might give clues about speed and flow-related issues that could be encountered in production scale. However, more research is needed for better comprehension of the compression data.

The tensile strength difference observed between the Gamlen and FlexiTab experiments was considered thoroughly. It was first concluded that this might be explained by different compression speeds, but it was later found out that apparently the Gamlen TTA gave slightly higher hardness values than the EasyCheck tablet combination tester used with the FlexiTab. Furthermore, it was concluded that elastic recovery might be higher in the FlexiTab experiments, as the delay between the compressions and tablet measurements was slightly longer. More experiments would be needed to find out what extent of difference there actually is between the measurement devices. Consequently, it is hard to determine how much of the difference observed between the tabletability results of the Gamlen and the FlexiTab was actually caused by the compression events. However, it is assumed that the different compression speeds did contribute to the differences in the case of plastic materials.

More information of the compression behaviour of different materials might be obtained by gathering punch displacement data. In addition, different compression equations, such as the Heckel analysis, might be used to interpret compression data. In this case, it is recommended that true density values are measured instead of using literature values. In addition, more measurement points would make it easier to determinate the pressure region used for the analyses.

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APPENDIX 1. Moisture contents of the materials and their binary mixtures.

Table 1a. Moisture contents of the materials.

Material	Moisture content (%)	Moisture content (%)
	Gamlen experiments	FlexiTab experiments
Avicel PH-102	4.3	4.1
DI-CAFOS D14	0.4	0.4
LYCATAB C	7.9	7.7
PEARLITOL 200 SD	0.3	0.2
SuperTab 11SD	0.3	0.3

Table 1b. Moisture contents of the binary mixtures.

Material 1	Material 2	Weight ratio	Moisture content (%)	Moisture content (%)
			Gamlen experiments	FlexiTab experiments
Avicel PH-102	DI-CAFOS D14	1:3	1.2	1.2
Avicel PH-102	DI-CAFOS D14	1:1	2.2	2.4
Avicel PH-102	DI-CAFOS D14	3:1	3.2	3.3
Avicel PH-102	LYCATAB C	1:3	7.0	6.5
Avicel PH-102	LYCATAB C	1:1	5.7	5.5
Avicel PH-102	LYCATAB C	3:1	4.9	5.0
Avicel PH-102	PEARLITOL 200 SD	1:3	1.1	1.2
Avicel PH-102	PEARLITOL 200 SD	1:1	2.0	2.4
Avicel PH-102	PEARLITOL 200 SD	3:1	2.9	3.3
Avicel PH-102	SuperTab 11SD	1:3	1.2	1.2
Avicel PH-102	SuperTab 11SD	1:1	2.0	2.1
Avicel PH-102	SuperTab 11SD	3:1	2.9	2.9
DI-CAFOS D14	LYCATAB C	1:3	6.6	6.4
DI-CAFOS D14	LYCATAB C	1:1	2.9	4.0
DI-CAFOS D14	LYCATAB C	3:1	2.3	1.5
DI-CAFOS D14	PEARLITOL 200 SD	1:3	0.4	0.3
DI-CAFOS D14	PEARLITOL 200 SD	1:1	0.4	0.4
DI-CAFOS D14	PEARLITOL 200 SD	3:1	0.4	0.2
DI-CAFOS D14	SuperTab 11SD	1:3	0.2	0.2
DI-CAFOS D14	SuperTab 11SD	1:1	0.3	0.4
DI-CAFOS D14	SuperTab 11SD	3:1	0.5	0.3
LYCATAB C	PEARLITOL 200 SD	1:3	1.3	1.4
LYCATAB C	PEARLITOL 200 SD	1:1	3.7	3.9
LYCATAB C	PEARLITOL 200 SD	3:1	5.7	5.7
LYCATAB C	SuperTab 11SD	1:3	2.0	2.1
LYCATAB C	SuperTab 11SD	1:1	3.8	3.7
LYCATAB C	SuperTab 11SD	3:1	5.8	5.9
PEARLITOL 200 SD	SuperTab 11SD	1:3	0.2	0.2
PEARLITOL 200 SD	SuperTab 11SD	1:1	0.3	0.3
PEARLITOL 200 SD	SuperTab 11SD	3:1	0.2	0.3

APPENDIX 2. True densities of the materials and their binary mixtures.

Table 1a. True densities of the materials. True densities are presented as an average of two literature values.

Material	True density (g/ml)
Avicel PH-102	1.57[1]
DI-CAFOS D14	2.60[2]
LYCATAB C	1.50[3]
PEARLITOL 200 SD	1.47[4]
SuperTab 11SD	1.54[5]

[1] Kumar et al. 2002, Choi et al. 2010
[2] Alshafiee et al. 2019 (no other values available)
[3] Hagelstein et al. 2018, Desbois et al. 2020
[4] Roopwani and Buckner 2011, Paul et al. 2018
[5] Choi et al. 2010, Paul et al. 2018

Table 1b. True densities of the binary mixtures.

Material 1	Material 2	Weight ratio	True density[1] (g/ml)
Avicel PH-102	DI-CAFOS D14	1:3	2.23
Avicel PH-102	DI-CAFOS D14	1:1	1.96
Avicel PH-102	DI-CAFOS D14	3:1	1.74
Avicel PH-102	LYCATAB C	1:3	1.52
Avicel PH-102	LYCATAB C	1:1	1.53
Avicel PH-102	LYCATAB C	3:1	1.55
Avicel PH-102	PEARLITOL 200 SD	1:3	1.49
Avicel PH-102	PEARLITOL 200 SD	1:1	1.52
Avicel PH-102	PEARLITOL 200 SD	3:1	1.54
Avicel PH-102	SuperTab 11SD	1:3	1.55
Avicel PH-102	SuperTab 11SD	1:1	1.55
Avicel PH-102	SuperTab 11SD	3:1	1.56
DI-CAFOS D14	LYCATAB C	1:3	1.68
DI-CAFOS D14	LYCATAB C	1:1	1.90
DI-CAFOS D14	LYCATAB C	3:1	2.20
DI-CAFOS D14	PEARLITOL 200 SD	1:3	1.65
DI-CAFOS D14	PEARLITOL 200 SD	1:1	1.88
DI-CAFOS D14	PEARLITOL 200 SD	3:1	2.18
DI-CAFOS D14	SuperTab 11SD	1:3	1.71
DI-CAFOS D14	SuperTab 11SD	1:1	1.93
DI-CAFOS D14	SuperTab 11SD	3:1	2.22
LYCATAB C	PEARLITOL 200 SD	1:3	1.48
LYCATAB C	PEARLITOL 200 SD	1:1	1.48
LYCATAB C	PEARLITOL 200 SD	3:1	1.49
LYCATAB C	SuperTab 11SD	1:3	1.53
LYCATAB C	SuperTab 11SD	1:1	1.52
LYCATAB C	SuperTab 11SD	3:1	1.51
PEARLITOL 200 SD	SuperTab 11SD	1:3	1.52
PEARLITOL 200 SD	SuperTab 11SD	1:1	1.50
PEARLITOL 200 SD	SuperTab 11SD	3:1	1.49

[1] True densities of the binary mixtures were calculated with Eq. (2) (p. 20) using true density values presented in Table 1a.

APPENDIX 3. Solid fraction and tensile strength of the individual materials at different compression pressures based on the Gamlen experiments.

Table 1a. Solid fraction and tensile strength of Avicel PH-102 (n=3).

Lubrication method	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
internal	72.2	3.08	1.5	0.75	0.7	4.0	2.4
internal	150.1	2.64	1.5	0.85	0.4	7.4	2.1
internal	232.5	2.56	1.2	0.88	0.2	8.8	1.1
internal	311.9	2.55	1.3	0.89	0.4	9.4	2.3
internal	390.8	2.45	2.3	0.89	0.5	9.6	3.2
external	72.3	2.95	1.0	0.75	0.7	4.5	8.2
external	151.4	2.75	1.2	0.84	0.5	7.5	7.1
external	233.5	2.46	4.7	0.88	0.3	9.9	2.0
external	312.2	2.48	4.6	0.88	0.4	10.6	5.3
external	388.0	2.50	4.9	0.89	0.2	11.6	1.6

Table 1b. Solid fraction and tensile strength of DI-CAFOS D14 (n=3).

Lubrication method	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
internal	79.6	2.20	3.0	0.62	0.6	0.8	23.4
internal	156.7	2.20	2.3	0.66	0.2	1.5	22.6
internal	233.4	2.03	2.0	0.69	0.3	3.9	4.3
internal	306.5	2.02	2.4	0.71	0.6	3.6	10.1
internal	379.8	1.90	1.6	0.73	0.3	3.9	17.4
external	80.5	2.14	2.9	0.63	0.7	0.9	7.9
external	158.2	2.11	1.6	0.68	0.4	2.2	3.4
external	234.2	2.02	5.8	0.70	0.6	3.0	19.8
external	307.7	1.95	1.6	0.72	0.7	2.9	10.6
external	379.6	1.88	3.0	0.73	0.8	4.3	20.1

Table 1c. Solid fraction and tensile strength of LYCATAB C (n=3).

Lubrication method	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
internal	72.0	3.43	1.7	0.69	0.4	0.4	5.2
internal	148.6	2.97	0.9	0.81	0.4	1.3	5.0
internal	231.4	2.84	0.5	0.84	0.1	1.9	10.4
internal	311.8	2.84	1.1	0.85	0.2	1.9	8.9
internal	389.5	2.83	1.5	0.85	0.2	2.2	11.7
external	72.1	3.49	0.9	0.69	0.3	0.6	8.4
external	148.7	3.02	1.8	0.80	0.5	2.2	14.2
external	231.3	2.93	2.8	0.83	1.4	2.7	10.4
external	310.7	2.90	1.1	0.85	0.2	2.5	3.6
external	388.5	2.83	1.8	0.85	0.2	3.6	18.3

Table 1d. Solid fraction and tensile strength of PEARLITOL 200 SD (n=3).

Lubrication method	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
internal	74.1	3.11	2.5	0.77	1.4	0.8	3.9
internal	149.3	2.88	2.3	0.83	1.1	2.1	2.8
internal	224.2	2.71	1.7	0.88	0.5	3.8	1.5
internal	298.8	2.64	0.7	0.90	0.6	5.3	2.3
internal	373.2	2.62	1.7	0.92	0.4	6.0	4.8
external	74.4	3.08	3.8	0.78	0.7	0.6	12.7
external	149.8	2.83	1.0	0.85	0.2	1.4	6.8
external	224.6	2.69	1.2	0.89	0.2	2.6	9.6
external	298.8	2.65	0.6	0.92	0.2	3.9	22.3
external	372.7	2.61	1.2	0.93	0.2	4.8	19.3

Table 1e. Solid fraction and tensile strength of SuperTab 11SD (n=3).

Lubrication method	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
internal	75.2	2.88	3.0	0.79	0.2	0.3	31.5
internal	152.0	2.65	1.5	0.86	0.5	1.1	5.8
internal	228.4	2.52	1.6	0.89	1.0	1.8	2.8
internal	303.5	2.49	2.9	0.92	0.3	2.3	4.3
internal	377.5	2.54	2.4	0.93	0.2	2.9	4.6
external	80.5	2.70	2.9	0.80	1.9	0.2	27.9
external	158.2	2.39	6.7	0.87	1.0	0.3	31.7
external	234.2	2.62	1.6	0.89	1.3	1.2	12.2
external	307.7	2.47	2.4	0.92	0.3	2.0	14.4
external	379.6	2.50	1.5	0.92	0.4	2.3	26.4

APPENDIX 4. Solid fraction and tensile strength of the individual materials at different compression pressures based on the FlexiTab experiments.

Table 1a. Solid fraction and tensile strength of Avicel PH-102 (n=10).

Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
50	81.7	2.93	2.5	0.76	0.7	3.4	4.5
50	197.3	2.50	2.0	0.87	0.7	5.8	6.4
50	306.1	2.50	3.9	0.89	0.6	7.6	7.6
50	402.2	2.46	2.4	0.90	0.5	7.7	5.5
50	519.8	2.47	2.1	0.91	0.9	8.5	6.9
1000	79.5	2.99	1.8	0.77	0.4	3.5	11.8
1000	196.9	2.58	1.8	0.88	0.6	6.7	6.2
1000	308.6	2.56	2.5	0.90	0.6	7.6	5.6
1000	416.6	2.46	3.6	0.90	0.6	7.3	13.4
1000	513.8	2.55	3.0	0.89	1.7	7.0	14.7

Table 1b. Solid fraction and tensile strength of DI-CAFOS D14 (n=10).

Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
50	82.2	2.33	5.4	0.64	1.2	0.8	6.1
50	201.1	2.10	4.1	0.69	2.0	2.2	9.3
50	300.7	2.08	5.7	0.70	3.1	3.1	10.4
50	402.5	1.98	4.8	0.71	1.1	3.8	11.8
50	503.6	1.97	4.6	0.75	2.8	4.0	20.5
1000	83.7	2.26	5.4	0.63	1.3	0.9	19.7
1000	198.7	2.13	3.8	0.71	0.7	2.3	9.4
1000	298.7	2.08	3.9	0.72	2.7	3.2	12.4
1000	404.1	1.96	8.3	0.73	2.3	3.6	21.3
1000	507.9	1.92	6.3	0.75	3.0	4.5	16.3

Table 1c. Solid fraction and tensile strength of LYCATAB C (n=10).

Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
50	79.9	3.54	1.0	0.70	1.1	*	*
50	196.3	2.98	0.9	0.83	1.0	1.0	6.8
50	309.9	2.87	0.4	0.85	0.3	1.2	3.9
50	416.6	2.88	1.1	0.85	0.5	1.2	8.5
50	509.7	2.78	2.0	0.83	0.4	1.2	7.7
1000	82.4	3.24	1.3	0.74	0.4	0.4	5.3
1000	195.8	2.81	3.6	0.85	0.6	1.4	3.8
1000	309.3	2.76	1.5	0.86	0.6	1.4	4.5
1000	416.3	2.93	0.8	0.86	0.4	1.3	3.3
1000	511.4	2.92	0.5	0.86	0.3	1.3	4.6

* EasyCheck crushed the tablets without obtaining hardness values.

Table 1d. Solid fraction and tensile strength of PEARLITOL 200 SD (n=10).

Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
50	82.4	3.33	0.7	0.76	0.5	1.1	9.5
50	191.0	2.95	1.3	0.87	1.2	2.9	9.1
50	299.0	2.83	0.9	0.90	1.8	4.4	13.1
50	407.0	2.71	0.7	0.92	1.0	4.4	24.5
50	507.8	2.65	0.5	0.97	1.9	3.8	33.5
1000	80.9	3.26	0.6	0.78	0.8	1.2	9.2
1000	193.0	2.88	0.6	0.90	0.5	3.0	4.9
1000	298.0	2.74	1.0	0.93	0.8	4.1	24.0
1000	409.4	2.64	0.4	0.93	2.8	4.7	18.5
1000	501.3	2.64	0.5	0.90	1.7	4.0	25.4

Table 1e. Solid fraction and tensile strength of SuperTab 11SD (n=10).

Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
50	81.3	2.92	1.0	0.80	0.7	0.5	4.0
50	192.5	2.63	1.2	0.90	1.8	1.5	4.5
50	302.4	2.52	1.5	0.96	2.7	2.5	6.1
50	404.5	2.44	1.2	0.97	4.1	3.2	3.2
50	504.5	2.41	0.8	0.97	1.5	3.6	2.7
1000	82.2	2.89	1.2	0.81	0.6	0.5	10.0
1000	191.3	2.62	1.3	0.90	1.2	1.5	4.0
1000	298.4	2.49	1.4	0.92	0.7	2.5	5.8
1000	406.0	2.48	1.8	0.94	0.6	3.5	10.1
1000	510.3	2.42	1.3	0.95	0.4	3.6	9.5

APPENDIX 5. Solid fraction and tensile strength of the binary mixtures at different compression pressures based on the Gamlen experiments.

Table 1a. Solid fraction and tensile strength of Avicel PH-102 and DI-CAFOS D14 (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	75.4	2.47	1.2	0.66	0.3	1.1	0.7
1:3	153.5	2.28	1.2	0.73	0.2	2.9	1.7
1:3	231.0	2.21	6.0	0.76	0.2	4.6	2.3
1:3	306.5	2.11	1.3	0.78	0.1	5.8	2.4
1:3	380.0	2.05	1.2	0.79	0.3	7.1	2.5
1:1	73.7	2.71	0.4	0.69	0.4	1.9	1.9
1:1	151.1	2.46	0.4	0.77	0.8	4.3	2.7
1:1	230.7	2.27	1.4	0.81	0.7	6.4	3.7
1:1	306.9	2.28	1.6	0.82	0.2	7.7	1.2
1:1	381.5	2.23	2.8	0.83	0.2	8.6	1.2
3:1	72.7	2.93	1.4	0.71	0.4	2.8	1.2
3:1	150.4	2.52	2.2	0.81	0.9	5.4	19.9
3:1	229.9	2.44	1.1	0.85	0.6	8.3	1.9
3:1	307.7	2.40	1.0	0.86	0.2	9.8	1.0
3:1	383.1	2.44	3.0	0.86	0.4	10.4	0.3

Table 1b. Solid fraction and tensile strength of Avicel PH-102 and LYCATAB C (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	72.1	3.42	3.9	0.68	0.6	0.6	4.0
1:3	148.5	2.99	2.2	0.80	0.2	2.0	4.1
1:3	229.8	2.87	1.5	0.83	0.3	2.7	0.9
1:3	308.5	2.91	5.1	0.84	0.6	3.0	9.1
1:3	386.4	2.82	5.7	0.84	0.5	3.0	2.6
1:1	72.2	3.16	5.8	0.71	0.2	1.4	2.5
1:1	149.3	2.78	1.6	0.82	0.3	3.2	0.4
1:1	229.8	2.78	1.1	0.85	0.5	4.1	5.3
1:1	310.1	2.72	5.6	0.86	0.4	4.4	1.2
1:1	387.9	2.66	0.7	0.86	0.7	4.6	1.2
3:1	72.4	3.00	3.9	0.73	0.2	2.6	2.0
3:1	148.2	2.93	1.2	0.83	0.2	5.4	2.2
3:1	229.4	2.76	2.8	0.87	0.2	6.7	1.7
3:1	309.1	2.70	0.8	0.87	0.2	7.1	1.0
3:1	386.7	2.69	0.5	0.88	0.2	7.7	1.2

Table 1c. Solid fraction and tensile strength of Avicel PH-102 and PEARLITOL 200 SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	72.8	3.27	3.2	0.75	0.4	1.1	3.7
1:3	148.7	2.86	3.2	0.83	1.0	2.8	3.3
1:3	225.4	2.69	4.3	0.87	1.0	4.4	2.3
1:3	299.5	2.74	3.1	0.89	0.5	5.8	2.5
1:3	375.1	2.56	2.9	0.91	0.3	6.7	2.2
1:1	72.4	3.24	2.1	0.75	0.9	1.6	0.4
1:1	149.3	2.63	2.0	0.84	0.3	3.5	4.9
1:1	226.3	2.72	1.0	0.88	0.7	5.5	0.9
1:1	303.2	2.56	4.7	0.90	0.8	6.5	0.8
1:1	377.2	2.59	3.4	0.91	0.6	7.6	2.6
3:1	72.4	3.04	1.6	0.74	0.7	2.4	2.1
3:1	149.5	2.66	5.6	0.84	0.2	5.2	1.5
3:1	228.3	2.60	4.8	0.88	0.4	7.1	4.0
3:1	306.2	2.55	0.8	0.89	0.2	8.3	0.9
3:1	381.6	2.61	2.2	0.90	0.1	8.9	2.2

Table 1d. Solid fraction and tensile strength of Avicel PH-102 and SuperTab 11SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	74.3	2.73	3.9	0.77	0.3	0.7	4.5
1:3	150.0	2.74	4.5	0.84	0.2	1.8	3.5
1:3	228.4	2.48	9.0	0.88	0.8	2.8	2.6
1:3	302.4	2.59	2.8	0.91	0.4	3.6	2.5
1:3	377.4	2.64	4.6	0.92	0.3	4.3	5.5
1:1	73.1	2.93	0.9	0.75	0.2	1.3	4.1
1:1	149.4	2.73	1.0	0.85	0.5	3.1	1.5
1:1	227.3	2.62	0.8	0.89	0.5	4.4	2.5
1:1	305.2	2.52	2.0	0.91	0.0	5.5	0.2
1:1	380.9	2.50	1.8	0.91	1.2	5.7	2.0
3:1	72.6	3.03	3.3	0.74	0.6	2.4	3.0
3:1	149.2	2.59	2.6	0.84	0.1	5.0	4.3
3:1	228.8	2.54	2.1	0.88	0.7	6.6	1.9
3:1	306.7	2.50	2.3	0.90	0.1	7.5	2.7
3:1	384.0	2.42	5.6	0.90	0.9	7.9	1.6

Table 1e. Solid fraction and tensile strength of DI-CAFOS D14 and LYCATAB C (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	73.5	3.11	3.0	0.70	0.4	0.4	3.9
1:3	151.3	2.86	2.7	0.79	0.3	1.3	1.9
1:3	232.2	2.64	1.8	0.82	0.8	2.1	2.5
1:3	309.5	2.59	0.7	0.83	0.1	2.7	3.5
1:3	384.8	2.57	0.4	0.83	0.5	3.0	2.7
1:1	75.2	2.99	4.6	0.68	0.9	0.3	6.5
1:1	153.8	2.49	3.6	0.75	0.2	1.0	3.0
1:1	230.5	2.57	5.6	0.78	0.8	1.8	2.8
1:1	307.0	2.41	4.2	0.81	1.9	2.5	2.4
1:1	381.4	2.39	3.1	0.81	0.5	3.0	2.5
3:1	76.9	2.72	3.0	0.65	0.7	0.3	1.6
3:1	155.1	2.41	2.5	0.70	1.6	1.0	2.5
3:1	231.7	2.28	3.1	0.74	0.6	1.8	1.9
3:1	305.6	2.25	5.1	0.77	0.2	2.6	2.1
3:1	379.9	2.15	0.7	0.76	3.2	3.7	1.7

Table 1f. Solid fraction and tensile strength of DI-CAFOS D14 and PEARLITOL 200 SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	73.7	3.02	1.2	0.72	0.7	0.9	2.1
1:3	149.0	2.73	0.9	0.80	0.8	2.5	2.6
1:3	224.6	2.56	1.0	0.84	0.3	4.0	1.3
1:3	299.8	2.41	4.0	0.88	0.4	5.3	2.3
1:3	372.8	2.42	2.1	0.89	0.4	6.0	13.4
1:1	74.5	2.83	1.4	0.70	0.8	0.9	1.0
1:1	150.7	2.51	2.1	0.77	0.3	2.5	1.2
1:1	226.5	2.39	0.7	0.81	0.3	3.8	2.9
1:1	300.8	2.31	1.7	0.83	0.2	4.7	8.0
1:1	374.0	2.25	2.3	0.85	0.5	6.2	1.4
3:1	76.1	2.52	4.3	0.66	0.3	0.9	0.4
3:1	153.4	2.30	2.6	0.72	0.3	2.5	2.7
3:1	229.5	2.21	4.0	0.76	0.4	3.8	2.8
3:1	303.5	2.13	2.1	0.77	1.1	5.2	2.8
3:1	375.9	2.11	0.2	0.80	0.6	6.5	4.4

Table 1g. Solid fraction and tensile strength of DI-CAFOS D14 and SuperTab 11SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	77.1	2.76	2.0	0.76	0.2	0.3	44.0
1:3	153.0	2.64	2.9	0.82	0.4	1.3	3.4
1:3	228.4	2.58	3.5	0.85	0.1	2.2	1.2
1:3	303.0	2.47	2.0	0.87	0.7	3.1	5.4
1:3	377.3	2.34	0.2	0.89	0.4	4.0	5.3
1:1	78.4	2.58	3.0	0.73	0.7	0.2	31.0
1:1	154.8	2.48	0.4	0.78	0.5	1.3	3.1
1:1	230.6	2.38	4.6	0.81	0.4	2.3	2.4
1:1	304.1	2.37	4.3	0.83	0.2	2.9	9.6
1:1	377.0	2.29	1.8	0.85	0.4	3.6	11.3
3:1	78.8	2.43	2.7	0.68	0.1	0.4	8.8
3:1	156.1	2.30	1.3	0.72	0.3	1.4	9.8
3:1	231.8	2.16	1.8	0.75	0.6	2.6	13.8
3:1	305.5	2.13	1.4	0.77	1.2	3.3	7.3
3:1	377.1	2.18	1.7	0.78	1.8	2.9	10.4

Table 1h. Solid fraction and tensile strength of LYCATAB C and PEARLITOL 200 SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	73.8	3.19	6.6	0.73	0.3	0.5	8.4
1:3	148.8	3.00	5.8	0.81	0.2	1.4	1.3
1:3	224.5	2.91	1.0	0.85	0.7	2.4	0.9
1:3	299.5	2.71	3.3	0.88	0.9	3.2	4.1
1:3	373.1	2.85	3.1	0.88	0.9	3.8	2.6
1:1	73.4	3.40	3.8	0.70	0.3	0.2	8.8
1:1	149.1	3.08	3.0	0.80	0.5	1.0	5.3
1:1	226.6	2.95	1.4	0.83	2.1	1.6	0.2
1:1	303.2	2.80	1.0	0.85	1.9	2.1	2.3
1:1	377.4	2.84	3.6	0.86	0.5	2.4	1.5
3:1	72.6	3.68	8.0	0.69	0.5	0.2	5.5
3:1	148.7	3.14	2.0	0.79	0.5	0.9	1.1
3:1	227.5	3.07	2.7	0.83	0.1	1.4	1.6
3:1	304.4	2.99	1.7	0.83	1.8	1.6	2.4
3:1	381.9	2.79	3.7	0.84	0.7	1.8	2.2

Table 1i. Solid fraction and tensile strength of LYCATAB C and SuperTab 11SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	74.4	2.99	7.4	0.75	0.3	0.1	5.9
1:3	150.2	2.83	1.1	0.83	0.2	0.8	0.5
1:3	228.4	2.59	0.2	0.87	0.5	1.5	4.6
1:3	303.8	2.66	2.4	0.89	0.7	2.0	5.1
1:3	379.6	2.59	2.6	0.90	0.4	2.2	1.6
1:1	73.2	3.13	4.6	0.72	0.6	0.2	2.2
1:1	149.6	2.91	2.9	0.81	1.8	0.8	4.1
1:1	228.4	2.80	1.4	0.85	0.2	1.5	3.0
1:1	305.5	2.77	4.4	0.87	0.2	1.8	1.4
1:1	382.0	2.66	0.2	0.88	0.2	2.1	4.1
3:1	72.4	3.40	6.0	0.70	0.7	0.2	9.5
3:1	148.1	3.06	1.8	0.80	0.4	1.0	1.8
3:1	227.9	3.01	3.8	0.84	0.4	1.6	2.3
3:1	307.5	2.87	5.2	0.85	0.7	1.9	0.8
3:1	384.4	2.81	4.6	0.85	0.3	2.0	3.7

Table 1j. Solid fraction and tensile strength of PEARLITOL 200 SD and SuperTab 11SD (n=3).

Weight ratio	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	74.6	2.97	3.0	0.79	0.8	0.4	42.6
1:3	153.2	2.38	4.4	0.86	0.2	1.4	1.4
1:3	226.1	2.77	3.1	0.89	0.2	2.3	1.8
1:3	302.7	2.46	8.8	0.92	0.7	3.5	1.7
1:3	376.7	2.41	3.7	0.93	0.3	4.3	1.8
1:1	74.5	2.96	2.9	0.79	0.7	0.7	0.4
1:1	150.7	2.75	5.7	0.84	0.5	1.7	2.5
1:1	226.2	2.70	7.1	0.88	1.2	2.9	2.9
1:1	300.6	2.68	3.7	0.90	0.3	4.2	2.7
1:1	373.9	2.68	2.8	0.92	0.6	5.0	1.8
3:1	73.5	3.26	3.4	0.77	0.0	0.8	1.5
3:1	149.1	2.96	3.0	0.82	0.7	2.0	1.3
3:1	223.8	2.92	1.0	0.85	1.3	3.4	3.9
3:1	297.3	3.00	9.3	0.88	0.9	4.6	2.3
3:1	373.1	2.59	5.8	0.91	1.3	5.8	1.4

APPENDIX 6. Solid fraction and tensile strength of the binary mixtures at different compression pressures based on the FlexiTab experiments.

Table 1a. Solid fraction and tensile strength of Avicel PH-102 and DI-CAFOS D14 (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	83.5	2.65	4.3	0.67	1.0	0.9	6.3
1:3	50	197.8	2.25	5.9	0.76	0.8	2.8	4.1
1:3	50	305.6	2.20	7.5	0.78	1.8	3.9	13.4
1:3	50	412.2	2.18	7.5	0.79	0.7	5.1	13.2
1:3	50	509.4	2.12	4.6	0.82	1.6	5.8	10.1
1:1	50	79.7	3.01	3.1	0.70	1.8	1.4	8.7
1:1	50	195.6	2.41	6.5	0.79	1.1	4.0	6.2
1:1	50	306.0	2.40	6.1	0.86	0.7	5.8	4.1
1:1	50	410.8	2.45	1.8	0.85	1.4	7.2	3.9
1:1	50	509.5	2.42	3.9	0.86	1.3	7.8	1.8
1:1	1000	81.2	2.90	6.1	0.70	1.0	1.6	3.8
1:1	1000	198.4	2.36	4.0	0.78	1.7	4.2	4.4
1:1	1000	305.5	2.47	6.9	0.84	2.3	5.9	7.9
1:1	1000	409.7	2.34	4.6	0.82	1.0	6.8	3.1
1:1	1000	507.2	2.36	6.6	0.86	1.4	7.4	9.7
3:1	50	80.3	2.97	5.7	0.73	3.4	2.4	4.1
3:1	50	194.3	2.56	4.4	0.85	1.0	5.8	3.9
3:1	50	304.3	2.60	2.5	0.89	1.5	7.7	3.1
3:1	50	411.4	2.59	4.0	0.91	0.5	8.8	3.8
3:1	50	510.1	2.53	3.5	0.88	1.8	8.6	3.2

Table 1b. Solid fraction and tensile strength of Avicel PH-102 and LYCATAB C (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	81.2	3.46	0.4	0.69	0.5	0.4	5.8
1:3	50	196.5	2.91	1.8	0.83	1.4	2.0	5.7
1:3	50	308.5	2.84	1.4	0.85	1.1	2.4	5.3
1:3	50	412.8	2.74	2.1	0.86	0.3	2.5	4.9
1:3	50	518.2	2.78	1.4	0.81	2.6	2.5	3.8
1:1	50	79.9	3.25	1.2	0.71	0.9	0.9	11.5
1:1	50	188.5	2.78	1.5	0.83	1.2	2.8	6.6
1:1	50	314.9	2.66	1.4	0.82	3.2	3.4	10.4
1:1	50	416.9	2.65	2.0	0.80	2.1	3.7	4.6
1:1	50	517.4	2.65	0.9	0.86	2.3	3.7	3.6
1:1	1000	80.6	3.12	1.5	0.74	1.2	1.3	6.6
1:1	1000	194.2	2.66	1.6	0.86	0.9	3.2	7.2
1:1	1000	305.9	2.63	1.4	0.88	1.0	3.7	6.6
1:1	1000	412.5	2.67	1.8	0.83	3.3	3.6	5.0
1:1	1000	503.8	2.65	1.4	0.81	1.3	3.5	6.4
3:1	50	80.7	3.31	1.6	0.73	1.1	2.2	4.0
3:1	50	192.3	2.84	1.9	0.82	1.2	4.9	6.5
3:1	50	303.6	2.83	2.3	0.86	1.5	5.4	7.5
3:1	50	418.7	2.79	4.8	0.84	0.6	5.8	7.1
3:1	50	517.0	2.78	2.1	0.88	2.8	6.0	6.0

Table 1c. Solid fraction and tensile strength of Avicel PH-102 and PEARLITOL 200 SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	77.5	3.39	0.9	0.73	1.2	1.0	8.4
1:3	50	191.9	2.94	0.8	0.83	0.8	3.4	5.5
1:3	50	300.9	2.79	1.0	0.87	3.0	4.9	6.3
1:3	50	406.9	2.79	1.0	0.87	3.0	4.9	6.3
1:3	50	511.0	2.70	1.0	0.94	0.5	6.3	6.0
1:1	50	78.7	3.23	0.8	0.75	0.6	1.4	3.5
1:1	50	194.7	2.76	1.1	0.89	0.6	4.1	2.5
1:1	50	301.1	2.73	1.7	0.90	0.9	5.5	2.0
1:1	50	412.4	2.67	1.8	0.91	0.6	6.5	4.0
1:1	50	519.2	2.65	1.7	0.93	1.0	6.8	3.1
1:1	1000	80.7	3.27	1.0	0.75	0.4	1.5	2.8
1:1	1000	196.6	2.82	1.0	0.86	1.3	4.2	4.0
1:1	1000	304.7	2.69	1.4	0.90	0.9	5.6	3.2
1:1	1000	410.3	2.67	1.0	0.91	0.8	6.1	2.9
1:1	1000	511.7	2.67	1.2	0.92	0.7	6.5	2.2
3:1	50	80.0	3.13	1.8	0.74	0.8	2.2	3.6
3:1	50	189.5	2.71	1.2	0.86	2.3	5.2	2.3
3:1	50	309.4	2.63	1.5	0.90	1.5	6.5	1.5
3:1	50	423.6	2.56	3.5	0.86	3.0	6.9	5.8
3:1	50	514.8	2.58	1.7	0.85	1.8	7.2	2.1

Table 1d. Solid fraction and tensile strength of Avicel PH-102 and SuperTab 11SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	81.5	3.07	1.0	0.76	0.5	0.7	7.0
1:3	50	194.1	2.71	1.0	0.85	0.7	2.2	5.5
1:3	50	301.7	2.61	1.9	0.89	1.9	3.4	4.7
1:3	50	406.6	2.50	1.5	0.87	1.3	3.9	3.2
1:3	50	505.8	2.50	1.3	0.91	1.6	4.3	2.9
1:1	50	79.5	3.17	0.9	0.75	0.9	1.2	5.3
1:1	50	195.7	2.73	1.7	0.86	1.7	3.4	4.1
1:1	50	308.3	2.61	1.7	0.90	1.4	4.5	3.2
1:1	50	413.0	2.58	1.5	0.88	2.3	5.1	2.9
1:1	50	517.1	2.49	2.0	0.92	2.6	5.7	4.2
1:1	1000	79.8	3.05	2.0	0.77	1.6	1.4	6.8
1:1	1000	191.7	2.65	2.4	0.86	3.2	3.5	3.9
1:1	1000	305.0	2.53	1.0	0.88	2.5	4.6	4.0
1:1	1000	411.2	2.49	1.4	0.86	1.8	5.0	2.0
1:1	1000	509.1	2.44	2.1	0.93	2.3	5.2	3.3
3:1	50	79.0	3.06	1.9	0.75	0.5	2.3	3.9
3:1	50	195.2	2.60	2.3	0.87	0.9	5.0	5.3
3:1	50	309.7	2.49	3.2	0.90	1.8	6.1	5.5
3:1	50	414.4	2.50	2.1	0.91	1.1	6.9	5.5
3:1	50	524.4	2.52	1.6	0.91	1.3	7.0	1.4

Table 1e. Solid fraction and tensile strength of DI-CAFOS D14 and LYCATAB C (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	83.8	3.17	6.3	0.71	0.6	*	*
1:3	50	194.9	2.82	3.8	0.81	0.4	1.1	7.2
1:3	50	308.1	2.87	4.3	0.84	0.8	1.8	5.0
1:3	50	410.5	2.81	4.5	0.85	0.6	2.2	6.3
1:3	50	512.8	2.82	3.8	0.85	0.3	2.6	5.5
1:1	50	82.6	2.92	7.1	0.69	0.6	*	*
1:1	50	189.9	2.78	7.4	0.77	0.7	0.7	12.7
1:1	50	294.7	2.72	4.1	0.80	0.5	1.3	5.1
1:1	50	411.8	2.59	3.6	0.82	0.5	1.9	9.0
1:1	50	510.3	2.69	5.4	0.84	0.6	2.6	6.3
1:1	1000	81.9	3.18	2.6	0.69	0.5	*	*
1:1	1000	194.8	2.67	6.8	0.79	0.9	1.0	12.1
1:1	1000	287.9	2.69	6.9	0.81	0.3	1.7	8.3
1:1	1000	409.5	2.58	6.1	0.83	0.9	2.3	6.4
1:1	1000	509.6	2.55	7.2	0.84	0.6	2.5	6.4
3:1	50	83.2	2.40	9.4	0.67	0.5	*	*
3:1	50	206.5	2.33	5.5	0.74	0.7	1.1	9.2
3:1	50	300.5	2.17	6.2	0.77	0.5	1.8	15.2
3:1	50	409.2	2.20	5.2	0.79	0.8	2.3	5.0
3:1	50	510.4	2.14	9.3	0.80	0.5	2.8	5.1

* EasyCheck crushed the tablets without obtaining hardness values.

Table 1f. Solid fraction and tensile strength of DI-CAFOS D14 and PEARLITOL 200 SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	82.5	3.09	5.2	0.73	0.5	0.9	6.7
1:3	50	185.1	2.81	3.2	0.82	0.8	2.8	9.0
1:3	50	298.5	2.58	2.6	0.87	1.7	4.3	6.9
1:3	50	408.9	2.52	4.0	0.89	2.8	5.0	16.1
1:3	50	509.7	2.51	3.2	0.91	1.7	5.6	10.1
1:1	50	83.4	2.87	7.9	0.70	0.9	0.7	7.7
1:1	50	194.6	2.48	10.2	0.79	1.4	2.3	5.0
1:1	50	295.0	2.40	7.5	0.83	1.9	3.7	9.4
1:1	50	407.9	2.39	3.9	0.85	1.2	4.5	6.3
1:1	50	506.6	2.29	6.9	0.88	1.1	5.3	16.2
1:1	1000	85.3	2.81	6.0	0.71	1.1	0.9	11.5
1:1	1000	195.4	2.54	5.6	0.78	1.7	2.5	7.8
1:1	1000	298.1	2.46	4.0	0.84	0.8	3.5	7.7
1:1	1000	400.7	2.40	4.5	0.86	0.9	4.3	6.4
1:1	1000	500.8	2.29	4.4	0.86	0.6	4.7	12.8
3:1	50	82.7	2.61	6.7	0.67	0.9	0.7	9.0
3:1	50	193.4	2.40	4.1	0.75	2.4	2.3	8.0
3:1	50	300.1	2.22	4.9	0.78	1.2	3.6	5.5
3:1	50	407.5	2.04	5.8	0.78	2.9	4.3	7.7
3:1	50	508.0	2.14	6.2	0.82	3.0	5.1	12.3

Table 1g. Solid fraction and tensile strength of DI-CAFOS D14 and SuperTab 11SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	82.5	3.07	4.3	0.78	0.5	0.5	15.9
1:3	50	198.0	2.73	3.3	0.86	0.4	1.5	10.0
1:3	50	295.1	2.66	3.3	0.89	0.8	2.6	11.2
1:3	50	405.8	2.61	3.9	0.91	0.6	3.6	5.9
1:3	50	507.6	2.44	5.6	0.90	1.5	4.1	4.1
1:1	50	81.0	2.64	5.5	0.74	0.6	*	*
1:1	50	199.8	2.31	8.0	0.81	0.8	1.5	5.0
1:1	50	307.3	2.14	4.4	0.83	2.0	2.4	6.1
1:1	50	412.0	2.21	7.3	0.84	0.3	3.3	3.7
1:1	50	509.0	2.30	4.5	0.85	1.9	4.2	7.4
1:1	1000	83.0	2.57	7.0	0.75	0.6	0.5	10.3
1:1	1000	197.1	2.39	5.1	0.81	1.0	1.5	9.1
1:1	1000	308.0	2.26	5.1	0.82	1.2	2.6	4.7
1:1	1000	405.3	2.10	6.3	0.83	1.1	3.2	6.6
1:1	1000	506.7	1.99	8.8	0.87	0.8	3.7	14.2
3:1	50	83.5	2.38	5.2	0.69	0.5	0.6	7.1
3:1	50	205.3	2.13	6.7	0.76	0.6	1.8	6.6
3:1	50	297.7	2.13	8.2	0.78	1.4	3.0	15.7
3:1	50	399.8	2.16	4.3	0.78	0.9	4.0	12.3
3:1	50	499.1	2.04	3.2	0.82	1.1	4.1	10.1

* EasyCheck crushed some of the tablets without obtaining hardness values.

Table 1h. Solid fraction and tensile strength of LYCATAB C and PEARLITOL 200 SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	81.2	3.42	1.6	0.76	0.9	0.4	6.0
1:3	50	191.9	3.00	1.5	0.87	0.8	1.4	14.1
1:3	50	300.2	2.89	1.2	0.86	0.5	2.2	9.2
1:3	50	408.3	2.81	1.4	0.88	0.6	2.7	8.6
1:3	50	503.4	2.78	1.5	0.91	1.0	2.9	12.7
1:1	50	82.0	3.59	1.2	0.73	0.4	*	*
1:1	50	193.2	3.12	1.5	0.85	0.4	1.0	13.6
1:1	50	301.0	3.03	1.4	0.86	0.8	1.5	11.7
1:1	50	410.4	2.99	1.1	0.87	0.4	1.8	5.2
1:1	50	512.4	2.95	1.9	0.89	0.6	2.0	3.3
1:1	1000	81.7	3.50	1.8	0.75	0.8	*	*
1:1	1000	196.9	3.07	2.2	0.83	1.4	1.2	17.0
1:1	1000	304.6	2.97	1.3	0.88	0.8	1.7	7.8
1:1	1000	412.1	2.94	1.1	0.86	1.1	1.8	7.5
1:1	1000	514.8	2.92	1.7	0.89	0.5	1.7	7.9
3:1	50	80.4	3.70	1.4	0.68	1.2	*	*
3:1	50	191.8	3.13	0.6	0.82	0.5	0.7	14.5
3:1	50	310.4	3.01	0.9	0.86	0.6	1.2	8.1
3:1	50	415.2	2.95	1.8	0.87	0.4	1.4	7.8
3:1	50	518.0	2.92	1.5	0.86	1.7	1.5	6.9

* EasyCheck crushed the tablets without obtaining hardness values.

Table 1i. Solid fraction and tensile strength of LYCATAB C and SuperTab 11SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	80.9	3.27	1.1	0.76	0.6	*	*
1:3	50	198.2	2.87	1.4	0.86	0.6	1.0	10.1
1:3	50	304.4	2.80	1.8	0.89	1.4	1.6	9.0
1:3	50	404.3	2.75	0.9	0.88	2.0	1.9	8.6
1:3	50	517.0	2.73	1.1	0.92	0.5	2.1	9.9
1:1	50	80.6	3.43	1.1	0.73	0.7	*	*
1:1	50	186.1	2.95	0.6	0.86	0.6	0.8	10.9
1:1	50	306.0	2.87	0.6	0.88	0.7	1.4	6.7
1:1	50	409.2	2.82	0.4	0.89	0.7	1.5	12.6
1:1	50	506.5	2.82	1.6	0.89	1.1	1.7	7.8
1:1	1000	80.8	3.39	1.1	0.74	0.6	*	*
1:1	1000	190.3	2.96	1.7	0.85	0.9	0.9	11.9
1:1	1000	298.8	2.90	0.8	0.88	0.9	1.4	8.2
1:1	1000	405.6	2.84	1.4	0.90	0.9	1.5	11.7
1:1	1000	510.0	2.82	0.7	0.85	1.3	1.6	5.8
3:1	50	79.9	3.54	1.2	0.69	1.1	*	*
3:1	50	188.4	2.99	0.6	0.83	0.4	0.8	7.0
3:1	50	312.7	2.87	0.7	0.84	2.0	1.2	11.3
3:1	50	411.1	2.85	0.9	0.83	0.7	1.4	8.0
3:1	50	516.7	2.83	0.6	0.88	0.5	1.4	5.5

* EasyCheck crushed the tablets without obtaining hardness values.

Table 1j. Solid fraction and tensile strength of PEARLITOL 200 SD and SuperTab 11SD (n=10).

Weight ratio	Dwell time (ms)	Compression pressure, average (MPa)	Thickness, average (mm)	Thickness, RSD (%)	Solid fraction, average	Solid fraction, RSD (%)	Tensile strength, average (MPa)	Tensile strength, RSD (%)
1:3	50	85.1	3.03	0.8	0.80	0.5	0.8	7.3
1:3	50	195.8	2.77	1.7	0.87	1.2	2.1	10.3
1:3	50	301.0	2.70	1.9	0.92	1.1	2.9	9.4
1:3	50	403.7	2.67	1.0	0.93	0.7	4.4	5.7
1:3	50	515.9	2.62	1.2	0.93	1.5	4.9	9.3
1:1	50	81.2	3.18	1.3	0.79	0.4	0.8	6.5
1:1	50	189.9	2.84	0.7	0.88	0.5	2.2	6.0
1:1	50	303.1	2.68	0.4	0.93	0.4	4.0	6.0
1:1	50	407.0	2.59	1.5	0.96	0.5	4.8	5.5
1:1	50	509.3	2.54	0.6	0.96	0.7	5.2	7.9
1:1	1000	82.2	3.09	1.2	0.79	1.0	0.9	8.6
1:1	1000	192.5	2.76	1.3	0.89	0.7	2.4	9.8
1:1	1000	297.3	2.63	1.6	0.94	1.0	3.6	7.5
1:1	1000	403.5	2.58	1.1	0.98	0.8	4.3	5.8
1:1	1000	508.8	2.54	0.4	0.96	1.0	5.2	4.9
3:1	50	81.9	3.07	0.9	0.77	1.7	1.0	9.6
3:1	50	189.9	2.83	1.0	0.87	1.5	2.8	11.1
3:1	50	297.4	2.67	2.1	0.92	0.8	4.2	10.0
3:1	50	412.4	2.71	1.4	0.95	1.0	5.5	12.0
3:1	50	506.6	2.72	1.1	0.94	0.9	5.8	11.7

APPENDIX 7. Solid fraction and tensile strength of Avicel PH-102 based on different measurement devices.

Table 1a. Solid fraction and tensile strength of Avicel PH-102 based on measurements with analytical balance, micrometer, and the Gamlen TTA.

	Solid fraction	Tensile strength (MPa)
	0.89	10.4
	0.89	10.7
	0.89	10.6
	0.89	10.0
	0.88	10.4
	0.89	10.6
	0.89	10.2
	0.89	10.4
	0.89	10.6
	0.88	10.6
Average	0.89	10.4
RSD (%)	0.5	1.8

Table 1b. Solid fraction and tensile strength of Avicel PH-102 based on measurements with the EasyCheck tablet combination tester.

	Solid fraction	Tensile strength (MPa)
	0.84	8.8
	0.86	8.8
	0.86	9.7
	0.83	8.6
	0.86	9.2
	0.86	9.6
	0.84	9.3
	0.82	9.6
	0.81	8.3
	0.82	9.1
Average	0.84	9.1
RSD (%)	2.0	5.0