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Determination of the compressibility of excipients used for formulation of tablets with theophylline

Diploma Thesis

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Statement of originality

I declare that this diploma thesis is my own, original, personal work. All literature and other resources I used while processing are listed in the reference list and are properly cited.

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Table of contents

1 Abstract 6

2 The aim of study 7

3 List of abbreviations 8

4 Introduction 9

5 Theoretical section 10

5.1 Tablets 10

5.1.1 Excipients used in tablet preparations 10

5.1.2 Methods of tablet preparation 13

5.1.2.1 Wet granulation method 14

5.1.2.2 Dry granulation method 15

5.1.2.3 Direct compression 16

5.2 Typical properties of tableting materials and their influence on compressibility 17

5.2.1 Particle characterization 17

5.2.2 Powder density 20

5.2.3 Powder flow 21

5.2.4 Moisture content 24

5.3 Compression processes 24

5.3.1 Force-displacement method 26

5.3.2 Compaction equations 28

5.4 Tensile strength of tablets 32

6 Experimental section 34

6.1 Materials 34

6.2 Equipment 34

6.3 Methods 35

6.3.1 Measurement of particle size 35

6.3.2 Moisture content 35

6.3.3 Measurement of bulk density in volumeter 36
6.3.4 Angle of repose 36
6.3.5 Mass flow rate 37
6.3.6 Determination of apparent (bulk) and tapped volume of powders 37
6.3.7 Compression of tablets 37
6.3.7.1 Compaction equation method 38
6.3.7.2 Force-displacement method 38
6.3.8 Determination of crushing force and radial strength of tablets 39
7 Results 40
8 Discussion 54
8.1 Evaluation of powders properties 54
8.1.1 Testing of flowability 55
8.2 Evaluation of tablets 57
8.2.1 Compaction equation method 57
8.2.2 Force-Displacement method 58
8.2.3 Tensile strength 59
9 Conclusions 60
10 References 62

1 Abstract

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The current thesis is focused on the compressibility properties of five powders used in tablet formulation: Comprecel, Spherolac, DI-CAFOS D160, DI-CAFOS A150 as excipients and Theophylline as the active substance. The particle size, moisture content, bulk density and flowability of the powders are determined. The powders are compressed and the results are evaluated by means of the parameters of the compaction equation and the force-displacement method (compression under 5, 10, 15 kN). Then, the crushing strength of tablets prepared from each powder by the force-displacement method is measured. The average values of the crushing strength are used to calculate the tensile strength of the tablets. Best compressibility is found in Comprecel and Theophylline with tensile strength values of 1.31 MPa under 5 kN, 3.31 MPa under 10 kN, 4.75 MPa under 15 kN and 1.02 MPa under 5 kN, 2.27 MPa under 10 kN, 3.09 MPa under 15 kN, respectively.

2 The aim of study

In general, the aim of the certain study is to describe the properties of five powders which are used in the preparation of tablets.

In the theoretical section, the aim of this thesis is to present some general information about tablets as dosage forms, excipients used in their formulation, methods of preparation of tablets and description of the typical properties of powders and their influence on compressibility. The compression process is described in a more detailed manner.

In the experimental part, some of the typical characteristics of the five powders are evaluated, powders are compressed and the strength of the prepared tablets is estimated.

3 List of abbreviations

Symbol	Unit	Meaning
CI	%	Compressibility index
D	g/ml	Density of powder at pressure P
D, d	mm	Diameter
D_0	g/ml	Density of powder at zero pressure
E, E_{1-3}	J	Energies of the compression process
Elis	J	Energy used in the preparation on tablets
E_{max}	J	Total energy input
FDA	-	Food and Drug Administration
GIT	-	Gastrointestinal tract
HR	-	Hausner ratio
Ø	-	Average
P	MPa	Pressure
P, CF	N	Applied load, Crushing force
Pl	%	Plasticity
SD	-	Standard deviation
t, h	mm	Thickness, height
Tan (α), AOR	° (degrees)	Angle of repose
V	ml or mm^3	Volume of powder at given compression pressure
V_0	ml or mm^3	Initial, bulk volume, volume of powder before compaction
V_f	ml or mm^3	Tapped volume
y_0	ml or mm^3	Theoretical volume of reduction at infinite compression pressure
ρ_b	g/ml	Bulk density
ρ_t	g/ml	Tapped density
σ_0, TS	MPa	Tensile (radial) strength

4 Introduction

Tablets are dosage forms generally intended for oral administration of active ingredients within the gastrointestinal tract (GIT) including the oral cavity. They are formulated by compression of a powdered mixture of one or more active ingredients and excipients (Allen, 2013). Administration of tablets might be required for various reasons due to the convenience of the preparation and the accuracy in dosing.

The presence of excipients is vital and their choice must be taken into consideration, since they have a great impact on the manufacture, compressibility, handling and stability of the final dosage form, including the pharmacokinetic properties of the tablet, mainly the rate of delivery of the drug to the blood stream. Moreover, those auxiliary substances should be free from any pharmacological effect and compatible with the active ingredients i.e. they must not influence in any way the therapeutic action of a certain active ingredient. That being said, tablet production requires caution and control.

This thesis aims to study the methods that are used in the process of production of tablets and focuses on the compression of powders, being the starting material in tablet preparation. Also, the importance of the material properties, such as compressibility and flowability, to the characterization of the final tablets is going to be determined. Finally, the results of the measurements and processes that took place are going to be displayed in tables and figures, and the compressibility characteristics of the powders are going to be explained in correlation with the strength of the prepared tablets.

5 Theoretical section

5.1 Tablets

Tablets are solid dosage forms which contain a single dose of one or more active substances. They are considered as the most popular, advantageous, widely used pharmaceutical dosage form due to the simplicity and low cost of the manufacture, stability and convenience in packaging and transportation. These preparations are intended for oral administration; they can be swallowed whole, chewed and then swallowed, dissolved or dispersed in water prior to administration or placed into the mouth where they dissolve and release the active substance. As far as the patients are concerned, they find tablets an easy route of administration, portable, accurate in dosing and also a way of masking the unpleasant taste and odor of medicinal substances (Allen, 2013; Ph. Eur. 8.0, 2013).

As a group, they vary in shape, size and weight. Although tablets are usually straight, circular solid cylinders with discoid shape, they also can be round, oval, oblong, triangular or diamond-, pentagon- and hexagon-shaped (Allen, 2013; Ph. Eur. 8.0,2013).

Tablets are prepared mainly by compression of powder particles of uniform volumes, but also other technological procedures have been involved, such as extrusion, molding and lyophilisation (freeze-drying) (Ph. Eur. 8.0, 2013).

5.1.1 Excipients used in tablet preparations

In most cases, tablets are composed of one or more active pharmaceutical ingredients combined with some kind of inert material, known as excipient. It is of high importance for active ingredients and excipients in a formulation to be compatible, meaning that these “co-substances” must not react with the drugs (Gad, 2008).

Pharmaceutical excipients used in tablet preparations have many uses. They play an important role in the processing and compressibility properties of the formulation (diluents, binders, glidants, and lubricants), they improve the physical properties of the prepared tablet (disintegrants, surfactants, colors, flavors and sweetening agents) and ensure their stability and shelf-life (antioxidants). The choice of added excipients in the preparations is very important and they must be accepted by competent authorities.

Some categories of excipients used in tablets can be distinguished as described below (Allen, 2013; Gad, 2008).

Diluents or bulking agents are substances used mainly with small dose active ingredients, to increase their mass and enable successful compression. In this case, the most frequently used diluents are calcium hydrogen phosphate dihydrate, lactose, cellulose, dry starch, sucrose, calcium sulphate, sodium chloride, mannitol and kaolin. Certain diluents have the ability to improve the final properties of tablets such as tablet strength and disintegration time (mannitol, lactose, sorbitol etc). These agents can be used in the manufacture of chewable tablets. It is possible that diluents might interfere with the bioavailability of dosage form. In this case it could be better to use an alternative material that does not alter the pharmacokinetic or physicochemical parameters of active ingredients (Allen, 2013; Gad, 2008).

Binders are very important excipients due to their ability to keep powdered materials together. In this way, they give cohesive properties to tablet formulation and ensure that the tablet will not break after compression. When binders are used as excipients, it is important to consider the quantity which will be added. For example, if a high amount of binder or a too strong binder is used, the final tablets will be very hard resulting in a difficult disintegration and friction of punches and dies during compression. These excipients are incorporated into the formulation as a solution or as a dry powder. Most commonly used binders are microcrystalline cellulose, carboxymethyl cellulose (i.e. carmellose), methylcellulose, starch, lactose, gelatin, sodium alginate, tragacanth, acacia gum etc (Allen, 2013).

Many times the tableting materials tend to adhere on the surface of dies and punches during compression process and produce friction. In order to prevent this phenomenon, ensure a successful compression and increase the free flow of powders, **lubricants**, in concentrations less than 1%, are used. The most commonly used materials for this purpose include talc, polyethylene glycol, magnesium stearate, calcium stearate etc. Many lubricants are hydrophobic and have the tendency to repel water. That being said, the choice of the appropriate lubricant in desirable concentrations is vital i.e. small concentrations of lubricants must be used in the formulation, since higher amount can lead in the preparation of very hard tablets with poor disintegration or tablets with delayed dissolution (Allen, 2013; Gad, 2008).

In order to compensate the influence of lubricants on the formulation, **glidants** such as talc and colloidal silicon dioxide, are added to the mixture. These agents enhance the flowability properties of powder mixture, help to overcome powder cohesiveness and reduce friction between particles. Optimal flow properties can help to ensure the weight uniformity of tablets. Moreover, some glidants have moisture scavenging properties which results in improved stability of the tablets (Allen, 2013; Gad, 2008).

Other important excipients added to the tablet formulation are the **disintegrants**. They have the property to facilitate the disintegration (breakdown) of tablets after their administration. After disintegration, the active ingredients are released from the tablet and dissolved. Starch, croscarmellose, crospovidone, microcrystalline cellulose, methylcellulose, bentonite are some of the materials used as disintegrants (Allen, 2013; Gad, 2008).

Surfactants are also used as excipients in tablet formulations. They are surface active agents that tend to decrease surface tension of particles of the material by absorbing at the interphase. In case of coated tablets, surfactant addition enhances the uniform coating of the tablet core. Examples of materials used as surfactants are polyethylene glycols, sorbitan esters and sodium lauryl sulphate (Allen, 2013).

Coloring agents are used primarily to help the patients in identifying and distinguishing tablets and, also, for masking the unattractive tablet appearance. When coloring agents are used during preparation of tablets, some problems may occur such as migration of colors in wet granulations, resulting in "spotted" tablets. In order to prevent the uneven distribution of colors, drying must be performed slowly, at low temperature and with continuous stirring of the mixture. In addition, colorants must be approved by the FDA prior to their use in pharmaceuticals to exclude toxicity (Allen, 2013).

Flavors and **sweetening agents** are used to mask the unpleasant taste of drugs or other excipients mainly in the formulation of chewable tablets. They give a sweet taste to the preparation and also, when artificial sweeters are added to tablets (aspartame, saccharin, sucralose etc), those preparations are suitable for diabetic patients. Most important sweetening agent is sucrose (Allen, 2013).

Antioxidants used as excipients for tablets are citric acid, butylated hydroxyanisole, butylated hydroxytoluene and sodium metabisulphite. These agents are able to maintain the stability of the product by preventing the active ingredient's degradation in the presence of oxygen and peroxides (Allen, 2013).

5.1.2 Methods of tablet preparation

As mentioned above, tablets are compressed mixtures of substances (active ingredients and excipients). The material present in the mixture must be powdered or granular and have specific physical characteristics, which will be discussed in next chapter, to ease the compressibility of the mixture.

There are, mainly, three methods of tablet preparation: wet granulation, dry granulation and direct compression. If powders posses good compressibility and flow properties, it is possible to compressed directly into tablets. On the contrary, material with unsatisfactory compressibility and flow characteristics are processed by granulation in order to improve those characteristics. Wet and dry granulation

processes are also used in the preparation of granules as dosage forms (Allen, 2013; Gad, 2008).

5.1.2.1 Wet granulation method

Wet granulation is the most popular method for tablet preparation. The purpose of this method is to produce particles of improved, enlarged size which would, then, be compressed and form a tablet. It involves eight steps: weighing of the materials to be used, mixing, wetting, screening the wet mixture, drying, dry screening, lubrication and finally compression of the tableting mixture.

After weighing all the materials, active ingredients are mixed well, in special mixers/granulators, with the excipients (diluents, binders) and part of the disintegrant (Allen, 2013; Iveson et al, 2001). Mixing equipment used for this purpose can be low shear mixers, high shear mixers, fluid-bed granulators, spray dryers and extruders and spheronizers (formation of pellets from wet granulations). Details about them will not be mention, since the focus of the thesis is not about granulating equipment.

The next step involves the wetting of mixed powders by adding or spraying the mixture with a binder solution. This step is very crucial, since over-wetting can lead to the formation of hard granules, thus the pressure required for compression will be higher and the final tablets might have a spot-like appearance. On the other hand, if the wetting is not sufficient, soft granules will be formed and will break down in the lubrication phase, leading to unsuccessful compression. Thus, the presence of a binder in the granulation mixture ensures adequate mechanical strength of granules during processing and increase the binding ability of granules during compression (Çelik, 2011; Iveson et al, 2001).

Screening phase is important for the creation of granules of the desired shape and size. The moist mass is extruded through a mesh screen of a defined size. This can be achieved manually, when small quantities are to be considered, or mechanically, by using comminuting mills, for larger amount of material.

Afterwards, the wet granules are being dried sufficiently in fluid-bed dryers, microwave dryers or infrared dryers. Temperature and time of drying must be controlled and there must be no degradation of the ingredients during this process. Furthermore, optimum amount of residual moisture must be achieved in order to keep the ingredients of the granules moist and reduce the static electric charges on particles. After drying, the granulation is comminuted by forcing it through another mesh screen, smaller in size than the previous one, in order to form granules more uniform in size. The size of this screen is determined, mainly, by the diameter of the punches which will be used in the compression process.

In the end, a lubricant, in the form of a fine powder, is added onto the granulation by passing through a 60- or 100-mesh nylon cloth. Each granule must be sufficiently covered with the lubricant and blended with it in a gentle manner in order to retain the uniform size of granules.

Wet granulation is a desirable method for the preparation of tablets, since the final granules will have the appropriate physical characteristics (particle size, flow properties, appropriate density etc) for a successful compression (Allen, 2013; Çelik, 2011).

5.1.2.2 Dry granulation method

Dry granulation or pre-compression is a second method for preparation of granules used for tablet production. Active ingredients and excipients processed by this method are usually sensitive to moisture or they cannot keep their mechanical or chemical stability under elevated temperatures applied in wet granulation method during drying (Takasaki et al, 2013).
Dry granulation involves weighing of the material, mixing, slugging, dry screening, lubrication and then compression.

First, powders are weighted to the required amount and the active ingredients are mixed with diluents and part of the lubricant. For successful application of this method, the tablet ingredients must have a degree of cohesiveness.

The main task of dry granulation method is to press the powder mixture, under high pressures, in order to remove the air contained in the material, increase the contact area between particles and form a dense mass. This process is called slugging. Due to the pressure applied to the material during slugging, a degree of fragmentation or deformation may occur (Çelik, 2011). Moving forwards, the compressed slugs are forced through a mesh screen to create a uniform granule size (Gad, 2008).
Finally, the remaining amount of lubricant is added and then the tableting mixture is compressed to form tablets.

The main advantages of the method of slugging are simplicity, decrease of production time and formation of fine powders which have the property to flow better (Allen, 2013; Çelik, 2011).

5.1.2.3 Direct compression

Generally, compression (reduction in volume) of powders has been a very successful process for tablet manufacture. Compression consists mainly of three phases; consolidation of powders (pre-compression phase), elastic deformation of particles and plastic deformation of particles. More details about the compression processes will be found in Chapter 5.3.

In direct compression method, the tableting mixture is compressed directly, after mixing the materials, by the application of high pressures without prior granulation. Particles of component materials have differences in their density and this may cause segregation of blends during their handling prior to compression. In this case, particle size distribution and particle density of active ingredients and excipients must be equivalent.

Component materials, including active substances and excipients, must have good flow properties, must be cohesive, uniform in weigh and content of active ingredients in order to be compressed in a direct manner. Thus, direct compression process is correlated directly with the properties, mainly physical, of the starting material which must not be altered during compression (Allen, 2013; Çelik, 2011; Thoorens et al, 2014).

5.2 Typical properties of tableting materials and their influence on compressibility

In the development and manufacture of tablets by compression there are some general characteristics, of the powders which are used, that need to be taken into consideration. Those characteristics determine, mainly, the flowability and compressibility/compactibility of starting materials. Thus, it is of great importance to accurately define their typical properties, since they can influence the properties of the final tablets (Gad, 2008).

Powders, as the initial material for the production of tablets, are described as a special disperse system in which a large amount of fine particles are dispersed in air. They show a relatively low mechanical strength due to the weak interparticulate attractions. It is important that they posses some physicochemical properties, such as particle size, shape, density, porosity, surface area, flowability etc, which have a direct impact on the whole processing of solid dosage forms, especially tablets (Çelik, 2011).

5.2.1 Particle characterization

To begin with, is important to say that size, shape and size distribution of particles of a powder are essential characteristics that need to be considered during the design of tablets.

Particle size is one of the major properties of powders. It is considered as an important parameter in the formulation and production of tablets since it influences the density of powders, flowability, porosity, compressibility (volume reduction characteristics), strength and disintegration time of tablets and the speed of dissolution of active pharmaceutical substance/s (Allen, 2013).

Particle size is typically defined as the particle's diameter (Gad, 2008). Particles which have a spherical shape can be described by the diameter of the sphere. However, most particles are irregular in shape thus it is very difficult to determine their size. In this case, other, so-called diameters have been used to express the geometric size of particles; Feret's diameter, which is the distance between two imaginary parallel lines tangential to a particle randomly oriented; Martin's diameter which expresses the diameter (length) of a line that divides a particle into two equal projected areas. Moreover, dimensions of a particle can be measured according to the dimensions of a sphere (equivalent sphere) which has the same projected surface area as the irregularly-shaped particle (Ph. Eur. 8.0, 2013).

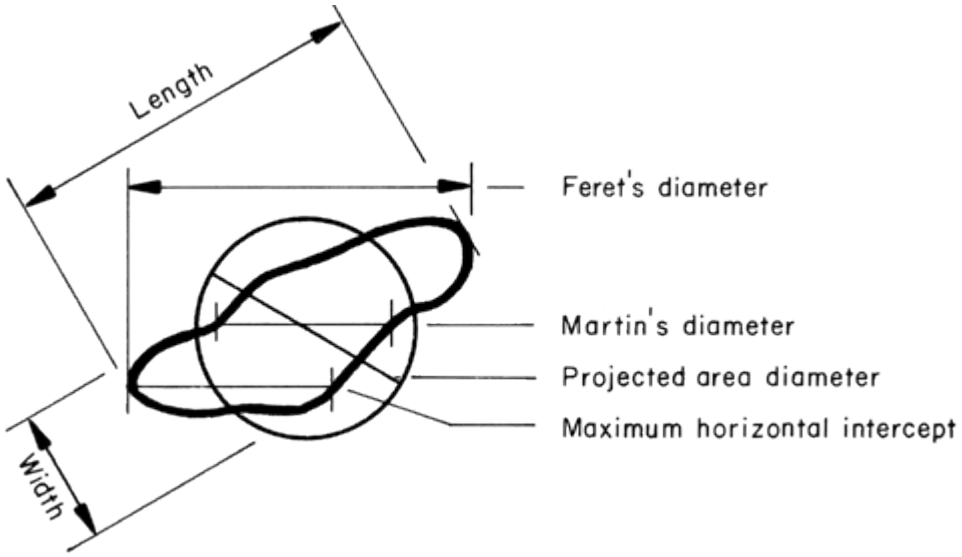

Figure 1: Measurements of particle size (Ph. Eur. 8.0, 2013).

Thus, the diameter of that sphere expresses the diameter of the particle (projected area diameter). At this point, it is important to mention that greater particles have a positive impact on flowability, since a great particle size causes a decrease in the

angle of repose (see later) resulting in a better content uniformity of substances in tablet preparations (Allen, 2013; Ph. Eur. 8.0, 2013).

Moving forwards, information about the shape of particles is very important in the technology of dosage forms made from powders. In general, the shape of particles strongly depends on the method used for particle formation and size reduction. That is why most particles have irregular shape and rough surface resulting in poor flowability. In this case, lubricants or glidants can be added to the powder; they fill the voids on the surface of particles, the surface becomes less rough, particles are separated and the frictional forces between them are decreased, thus improving the flowability. Also, the presence of agglomerates in a powder is unfavorable in the description of particle shape. However, it is important to mention if a powder has the tendency to form agglomerates, since agglomeration may affect the manufacture and handling of the final product (Allen, 2013; Nguyen et al, 2014).

According to US Pharmacopoeia, the most commonly used descriptors of particle shape are: *Acicular*, needle-like particle with similar width and thickness; *Columnar*, long, thin particle with greater width and thickness that the acicular one; *Flake*, thin, flat particle with similar width and length; *Plate*, flat particle with similar width and length but greater thickness than a flake particle; *Lath*, long, thin, blade-like particle; and *Equant*, similar width, thickness and length of a particle, can be cubical and spherical (USP 34/NF 29, 2001; PhEur 8.0, 2013).

Last but not least, particle size distribution must be taken into consideration since it is an essential factor in particle characterization. Size distribution is the percentage of particles within a specific size range. Since the majority of powders are polydisperse, the particle size distribution must be taken into account for better understanding of the uniformity and other properties of powders. Generally, the narrower the size distribution the more uniform the particles are i.e. monodispersity is more desirable (Allen, 2013; Gad, 2008).

Distribution can be evaluated by using some statistical characteristics and graphically. Statistical characteristics include the mean diameter which can be expressed by the mean of particle population, the median and the mode of a particle diameter. Mean describes the average particle size (diameter); Median represents the diameter at which 50 % of the particles are larger (coarser) and 50 % are smaller (finer); and Mode expresses the most frequent particle size. Graphically, particle size distribution is expressed as the frequency distribution and the cumulative frequency distribution. On the histogram (bar graph) which is created for frequency distribution, the frequency (i.e. size, number or weight percentage) is plotted on the y-axis and the diameter range is plotted on the x-axis. Thus, from those kinds of histograms one can determine the percentage of particles having a given diameter. Alternatively, on the histogram for the cumulative frequency distribution, the percentage of particles which are smaller or larger than the specified size limit is plotted on the y-axis and the particle diameter is plotted on the x-axis. This can be used in cases where more than one mode exists within a size distribution curve i.e. when a powder contains large, coarse particles and fine particles (Allen, 2013; Gad, 2008).

5.2.2 Powder density

The density of powders is an important physical characteristic which influences the technology of powdered dosage forms. It affects mainly the flowability and compressibility of powders which are the most crucial properties needed for tableting. Density is the ratio of mass of a powder to its volume. Thus, volume must be found first in order to obtain the density of powders.

Powder or particle density is classified according to the volume of particles into the true, bulk and tapped density. True density is the ratio of mass of a particle to the particle volume, in which interparticular spaces (pore volume and volume of gap between particles) are excluded; Particle density refers to the ratio of particle mass to its volume, where the pores within the particle (intraparticular pores) are included but volume of gap between particles is excluded; Bulk density can be defined as the ratio

of the mass of a powder to its volume, where interparticular spaces are included; and Tapped density, being correlated to the bulk density, is the increased bulk density obtain after mechanically tapping a vessel which contains the powder, but without causing particle deformation (Allen, 2013; Gad, 2008).

From the technological point of view, bulk and tapped density are the most significant types of densities, since their measured values are used in the calculation of the compressibility index and Hausner ratio which will be discussed later in this chapter (5.2.3) in details. Moreover, the bulk density of the powders 0must be constant during handling in order for the final tablets to have a constant and uniform mass (Ph. Eur. 8.0, 2013; Çelik, 2011).

5.2.3 Powder flow

Flowability of powders is considered to be an essential property which has a huge influence on compression process and the quality of powdered dosage forms. It expresses the convenience with which particles of powders flow under certain conditions. Powder flowability can cause variation in the weight of tablets within the same batch, thus compression processes require material with good flow properties and low degree of cohesiveness (Gad, 2008).

According to European Pharmacopoeia 8.0, the four most frequently used methods for testing powder flowability are: angle of repose, compressibility index or Hausner ratio, flow rate through an orifice and shear cell method. Generally, flowability data strongly depends on the method chosen.

Angle of repose (α) is the constant, three-dimensional angle between the surface of a powder mound and the horizontal plane. The angle is related to the interparticular friction of powders and it represents a measure of powder cohesiveness (Gad. 2008). It can be calculated from the following equation (Ph. Eur. 0.8, 2013):

$$\tan(a) = \frac{h}{0.5r} \quad (1)$$

Where h is the height of the cone in mm and r is the diameter of the cone in mm.

Angle of repose can be measured from the fixed height of a funnel through which the powder flows and forms a cone or from the fixed diameter of the base onto which the cone is formed. Powders with angle of repose range from 25 ° to 45 ° are proved to have good flow properties, since the lesser the angle the smaller the frictional forces between particles. On the other hand, when the angle is over 50 ° the flow of powders is poor and not favorable in manufacturing processes (Carr, 1965).

Flowability of powders can also be determined from the values of bulk and tapped volumes of the powder or from the bulk and tapped densities. Bulking properties of powders and powder flow are both influenced by the interparticular interactions. Therefore, from the comparison of those values, compressibility index and Hausner ratio can be calculated from volumes or densities according to the following formulas (Ph. Eur. 0.8, 2013):

$$CI = 100\frac{V_0 - V_f}{V_0} \quad (2)$$

Where CI is the compressibility index (%), V_0 is the bulk volume (ml) and V_f is the tapped volume (ml) after 1250 tappings.

$$HR = \frac{V_0}{V_f} \quad (3)$$

Where HR represents the Hausner ratio.

$$CI = 100\frac{\rho_t - \rho_b}{\rho_t} \quad (4)$$

Where ρ_t is the tapped density (g/ml) and ρ_b is the bulk density (g/ml)

$$HR = \frac{\rho_t}{\rho_b} \quad (5)$$

The compressibility index and Hausner ratio are measures of the ability of powders to flow, thus, determining the tendency with which powders will be compressed and assess the importance of interparticular interactions. When powders are characterized

by good flow properties, those interactions are not so important resulting in small differences between bulk and tapped densities. However, interparticular interactions in powders with poor flowability are greater and there is a great difference between bulk and tapped densities (Ph. Eur. 8.0, 2013).

A better measure of powder flowability is flow rate through an orifice, which describes the ability or rate of powder particles to flow vertically under specified conditions. Generally, flow rate through an orifice, for a given material, depends on the particle size. With this method, mass flow rate or volume flow rate can be determined (Gad, 2008).

Mass flow rate refers to the measurement of mass of the sample within a specified time and volume flow rate represents the time needed for a known amount of the material to be emptied from the container. In general, high flow rate means better flowability (Allen, 2013; Ph. Eur. 8.0, 2013).

Last but not least, shear cell method had been employed as a more precise way to evaluate the flow properties of powders; it determines flowability as a function of the consolidation load and time. From this method, shear stress-shear strain relationship, angle of internal friction, cohesion, unconfined yield strength, tensile strength and other parameters can be obtained (Gad, 2008; Fitzpatrick et al, 2004).

Various types of shear cells have been developed in the study of pharmaceutical powders. A cylindrical shear cell forms a shear plane between the lower base of the shear cell ring, which is stationary, and the upper part of the ring, which is movable. After consolidation and shearing in a horizontal direction, the shear force needed to shear the powder by moving the upper ring is determined (Ph. Eur. 8.0, 2013). Another type, an annular shear cell, can be used. In this case, powder is not sheared in a uniform manner, since shearing is greater on the outside of the cell than on the inside region. In the third type, plate-type, of shear cell the powder is placed between a lower rough surface, which is stationary, and an upper rough surface, which is moveable (Fitzpatrick et al, 2004; Ph. Eur. 0.8, 2013).

The shear cell method, for characterizing powder flow, is very advantageous and a great degree of experimental control exists. However, this method is time-consuming and involves great amount of material (Ph. Eur. 0.8, 2013).

5.2.4 Moisture content

Generally, powders may contain a certain amount of water (moisture) considered optimum in conferring powders cohesive characteristics. During compression process, moisture enhances the rearrangement of particles and their deformation which results in tablets with lower porosity and increased area for interparticular bonding. Therefore, bonding between particles and tensile strength of the final tablets are increased. Also, water has a lubrication effect and it fill the gaps between the particles. However, when the content of water is above the critical moisture content the angle of repose is increased which results in a decrease in the flowability of powders (Allen, 2013; Marston et al, 2013; Wade et al, 2013).

5.3 Compression processes

As it was mentioned previously, the main process for tablet preparation is the compression/compaction of a powder bed consisting of mixtures of active ingredients and excipients. By applying high pressures to the tableting materials, the volume is reduced and the density is increased due to the decrease in the interparticular and intraparticular spaces, which results in the formation of a stable compact (Çelik, 2011; Gad, 2008).

The main principle for tablet preparation is the compression of mixtures of the component material by using a special aid; a lower punch fitted into a die and an upper punch fitted on top of the die after the mixture of the ingredients is filled in the die. As pressure is applied, tableting materials are compressed to form an intact, coherent dosage form (tablet). The size and shape of the die determines the shape of

the final tablet and the distance between punches determines its thickness (Allen, 2013; Çelik, 2011).

Compression process is described, mainly, by three distinct phases (volume reduction mechanisms) (Allen, 2013; Çelik, 2011). In the first phase, particles of the powder are rearranged and acquire a better and closer order and, for this procedure, only low pressure is required. At this level, interparticular friction and friction between particles and die occurs. Subsequently, when higher forced is applied and punches move towards each other, elastic deformation occurs and further consolidation of particles is achieved. This phase is also called reversible deformation since, if the applied force were removed, the particles would return to their initial state. At this point, fragmentation of particles may, also, take place. The third phase is the most vital in tablet formation. During plastic or irreversible deformation of particles, particle surfaces get into a very close contact and bonds (interparticulate attractions) are created between them resulting in the preparation of a dense powder compact. As a result of the high elasticity that a material may have, lamination (capping) of the tablets or formation of weak tablets may occur during ejection where the load is reduced (Allen, 2013; Çelik, 2011; Gad, 2008).

The whole process is mainly endothermal, since energy is consumed for volume reduction and, by this energy, surface area of particles is increased making possible the formation of interparticular attraction forces. However, in the phase of bond formation energy is released from the material (i.e. exothermal process). For the effective bonding of particles a certain degree of surface area increase must exists. This is determined by particle characteristics of the initial material and the changes caused by volume reduction (Çelik, 2011).

Several methods have been used to describe the entire compression process and the profile of the individual phases which take place. Compression of powders can be characterized by force-displacement method or by various compaction equations. Some of them will be described below.

5.3.1 Force-displacement method

Various methods have been developed in order to evaluate the profile of the compression process and the characteristics of the material to be compressed. Force-displacement method is one of them.

Force-displacement measurements describe the dependency of the compression force on the displacement of the upper punch (Gad, 2008). Data are obtained by accurate measurement of the punch force and punch displacement during decompression, but also the force of the lower punch. The latter, however, is neglected since lower punch is stationary. The profile of this method includes a compression and a decompression phase. For the compression of powders and formation of strong tablets to be achieved, energy input is needed (Gad, 2008; Velasco et al, 1997).

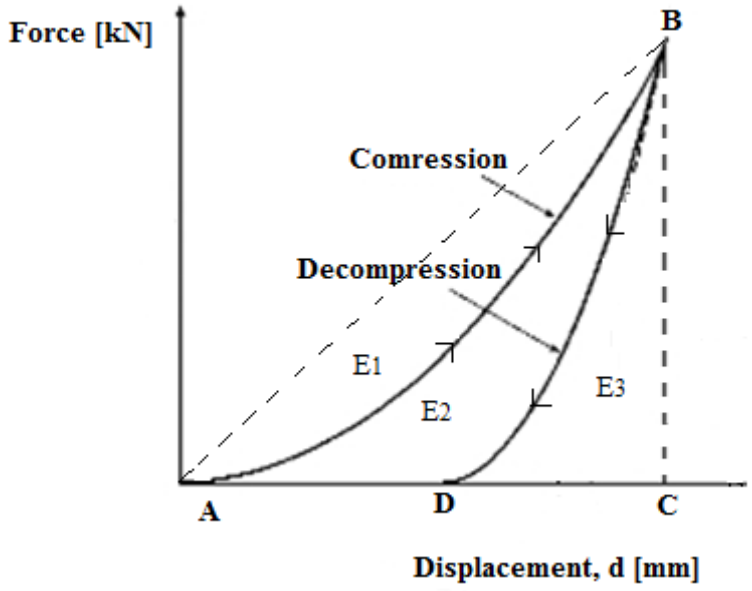

Figure 2: Schematical plot of the upper punch force versus the upper punch displacement (Çelik, 2011).

From the plot of the upper punch force (kN) against the upper punch displacement (d=mm), energy input (energy of compression) can be determined from the total area. These areas are correlated with the deformation properties of the material and their bonding mechanisms. It must be noted that, the properties of the compact are related, mainly, to the energy input rather than to compression pressure. As

illustrated in Figure 2, curve AB represents the increase of force during compression and BD curve represents the decrease of force during decompression. Thus, from the area ABD the total energy used for tablet formation and the energy needed to overcome die wall friction can be defined (Çelik, 2011).

Moreover, the energy consumed during each phase of the compression process should be determined. E_1 is the energy consumed during pre-compression, where particle rearrangement, friction between particles and friction between the particles and the die occurs. The friction causes the generation of heat which may damage the material, thus this energy should be as low as possible. E_2 represents the energy input used for plastic deformation and bond formation between particles and E_3 describes the energy recovered during decompression. This energy is a representative of the material elasticity, therefore it should be low (Çelik, 2011; Gad, 2008). Those characteristics can be described from the formulas below:

$$E_{\max} = E_1 + E_2 + E_3 \tag{6}$$

Where E_{max} is the total energy input (J)

$$\frac{E_2 + E_3}{E_1} \tag{7}$$

$$\frac{E_2}{E_3} \tag{8}$$

Those ratios should be as large as possible.

Another constant was introduced to determine the plasticity of the material:

$$Pl = 100\frac{E_2}{E_2 + E_3} \tag{9}$$

Where *Pl* describes the plasticity (%). The formula expresses the ratio of the energy needed to form a compact to the total energy input. When plastic materials undergo irreversible (plastic) deformation a large amount of energy is consumed. Thus, high value of Pl indicates a high energy input (Çelik, 2011).

5.3.2 Compaction equations

Compaction equation is a mathematical model which describes the dependency of reduction of volume on compression pressure. Many models of compaction equations exist (Řehula and Rysl, 2008). Some models, employed for example by Walker, Balshin or Heckel, expresses the compression process by a straight-line equation. Other models describe the compression process by parameters of a hyperbolic equation (Kawakita and Ludde). Some equations like for example Cooper and Eaton's, describe the compression process by a two-exponential equation.

Heckel equation

Heckel equation is a mathematical model which describes the compressibility of powders as the initial material for tablet formulation. The main aim is to determine the dependency of change of the density of powders on the applied pressure, which is needed to achieve that density. Powder compaction increases the density of the material and minimum porosity is achieved (Gad, 2008; Heckel, 1961).

According to Heckel, the density-pressure relationship can be estimated by measuring the densities of individual compacts, pressed at different pressures, after they were ejected from the die. This can be experimentally determined by calculating the change in volume of the material as a function of pressure (volume-pressure relationship). From this data, density-pressure relationship can be estimated from the known weight of the powder which was used and the volume-pressure relationship (Heckel, 1961).

Heckel equation was developed based on the first-order kinetics; it describes the rate of change of density as a function of pressure, assuming that this rate is directly proportional to the remaining porosity (Gad, 2008; Sonnergaard, 1999):

$$\frac{dD}{dP} = K(1 - D) \qquad (10)$$

Where P is the pressure (MPa), D is the density (g/ml) of the powder compact at pressure P and K is a constant.

By integration, equation (10) yields

$$\ln\left(\frac{1}{1-D}\right) = PK + A \tag{11}$$

Where *K* is the constant, mentioned above, obtained from the slope of the Heckel plot ln(1/(1-D)), which describes the densification of the powder, versus P (pressure in MPa). This constant is measured after particle rearrangement. *A* is the constant obtained from the intercept of the linear part of the same plot (Çelik, 2011; Gad, 2008; Sonnergaard, 1999).

Heckel, in his equation, correlates the constant A to the process of volume reduction and powder densification during filling the die and by rearrangement of particles in the powder. He, also, related the constant K with the plasticity of the tableting material. A large value of K designates the beginning of plastic deformation at low pressures (Gad, 2008).

Heckel equation is mainly valid at intermediate to high pressures and for material with low porosity (Çelik, 2011; Sonnergaard, 1999; Heckel, 1961).

Kawakita equation

As mentioned earlier, Kawakita equation expresses the compression process by a hyperbolic equation. It represents the dependence of volume reduction on the applied pressure (Gad, 2008; Kawakita and Lüdde, 1971):

$$C = \frac{V_0 - V}{V_0} = \frac{\alpha b P}{1 + bP} \tag{12}$$

Where *C* expresses the extend of volume reduction which is dependent on the initial packing state of particles, V_0 is the initial volume, *V* is the volume of the powder after pressing at a pressure *P* (MPa), α and *b* represent the constants which are characteristic to the compressed powder (Çelik, 2011).

If equation (12) is rearranged in linear form, it gives:

$$\frac{P}{C} = \frac{1}{\alpha b} + \frac{P}{\alpha} \tag{13}$$

From the straight line of the plot of P/C against P, evaluation of constants, α and b, can be achieved. Constant α represents the reciprocal slope of the linear part of the graph and is correlated with C when infinite compaction pressures are applied. Thus, it indicates the maximum reduction in volume. On the other hand, constant b expresses the tendency of volume reduction (Çelik, 2011).

Kawakita equation is applicable at low pressures for material with large or intermediate pososity. However, the use of this equation and the physical meaning of its parameters remain uncertain and unsuccessful in relating the physical and mechanical characteristics of powders to the densification process (Çelik, 2011; Denny, 2002).

Cooper-Eaton equation

Cooper and Eaton introduced an equation for the description of the compaction behavior of ceramic powders. According to this equation, the compression process takes place in two stages; filling the space created by particle movement and rearrangement and filling the space created by particle deformation (elastic, plastic or fragmentation). The two-exponential equation is given by (Gad, 2008; Cooper and Eaton, 1962):

$$\overset{*}{V} = a_1 \exp -\left(\frac{k_1}{P}\right) + a_2 \exp -\left(\frac{k_2}{P}\right) \tag{14}$$

Where $\overset{*}{V}$ accounts for the fractional volume reduction which can be also expressed as $\frac{1/D_0 - 1/D}{1/D_0 - 1}$. D_0 is the relative density (g/ml) at zero pressure or the ratio of bulk density to the particle density and D is the relative density (g/ml) at pressure P or the ratio of the apparent density of the powder to the particle density. Dimensionless constants, α_1 and α_2, represent the fraction of the theoretical maximum densification, which is accomplished by filling the spaces of the same size (α_1) and of smaller size (α_2) than the original particles. Pressures at which the individual densification processes take place are described by k_1 and k_2 constants (Çelik, 2011).

This model of compression equation is mainly suitable for hard, crystalline, monodisperse powders while for soft, polymeric, polydisperse systems is unsuccessful. However, Cooper-Eaton equation is very advantageous in describing with a great accuracy the initial stages of volume reduction (Çelik, 2011).

The three-exponential equation

According to equation developed previously by Řehula and Rysl (2008), the compression process is characterized be three phases which take place simultaneously: reduction of interparticular pores, reduction of intraparticular bonds and reduction of the solid substance without pores. The volume reduction (ratio of volume at a certain pressure to the volume of the tableting material prior to compression) can be estimated from the parameters of the three-exponential equation (Řehula and Rysl, 2008):

$$\frac{V}{V_0} = A_1 e^{-\frac{1}{t_1}P} + A_2 e^{-\frac{1}{t_2}P} + A_3 e^{-\frac{1}{t3}P} + y_0 \qquad (15)$$

Where V_0 is the initial volume (mm^3) of the material before compaction, V is the volume (mm^3) of the material at a given compression pressure, parameter A_1 is the reduction of interparticular pores, A_2 represents the reduction of intraparticular pores and parameter A_3 describes the reduction of a solid substance without pores. $1/t_{1\text{-}3}$ (MPa^{-1}) parameters represent the velocity constants of the appropriate reductions of volumes (speed of volume reduction), P are the compression pressures and y_0 represents the volume of the compact V_∞ at the endless compression pressure i.e. is a theoretical volume of reduction when infinite compaction pressure is used (Řehula and Rysl, 2008).

The sum of $A_{1\text{-}3}$ and y_0 parameters is the total volume of the compacted material at zero compression pressure. $A_{1\text{-}3}$ values represent the theoretical, maximum volume reduction. Parameters $t_{1\text{-}3}$ express the changes in compression pressure which cause the volume reduction. From these parameters energy of compression can be calculated as follows:

$$E = V_0 \sum_{i=1}^{3} (A_i\, t_i) \tag{16}$$

Where E is the total energy (J) consumed during the compression process, A_i represents the sum of parameters $A_{1\text{-}3}$ and t_i represents $t_{1\text{-}3}$ parameters.

Also, energies consumed during the individual stages of the compression process can be calculated according to the formula:

$$E_i = V_0 (A_i\, t_i) \tag{17}$$

Where E_i is the energy (J) consumed in particular phases ($E_{1\text{-}3}$).

5.4 Tensile strength of tablets

Strength of the tablets is an important characteristic of the mechanical properties of a compact. Tensile strength evaluation is a significant indicator of bonding strength of particles in a tablet which, eventually, becomes the basis for familiarization with the entire compression process.

Tensile strength can be defined as the maximum amount of tensile stress required to change permanently the shape of the tablet i.e. is the resistance of the tablet to a force, namely destruction force, before it fractures. Tablet strength determination is very crucial and needs caution and careful adjustment of pressures on the tableting machine. In general, tablets with adequate degree of hardness are desirable to resist breaking during handling and transportation, but without affecting the disintegration or dissolution after administration. If a very hard tablet is prepared, the disintegration time and dissolution can be influenced. On the other hand, a too soft tablet will not be able to withstand subsequent processing (Allen, 2013; Çelik, 2011; Gad, 2008).

Theoretically, tensile strength, it is expressed as the sum of the interparticular attractions within a compact. However, in practice is described as the distribution in interparticulate bonds (number of bonds as a function of bonding force), since a

variation in the strength of bonding forces between particles in the compact exists (Çelik, 2011).

Tablet tensile strength can be influenced by the properties of the initial tableting material as well as by the characteristics of the compression process. Therefore, the compressibility and dimensions of particles within a powder should be taken into consideration, since those properties are, mainly, involved in tablet strength characterization. Moreover, fragmentation and plastic deformation of the material should be encountered; fragmentation affects the number of interparticulate bonds, while plastic deformation affects the bonding force of interparticulate bonds. Dimensions of particles i.e. height, width, length and also their positions in the compact have a direct impact on the number of interparticulate bonds and the bonding force, by influencing the level at which fragmentation and deformation take place (Çelik, 2011).

According to Fell and Newton, tensile strength assessment is possible and successful when tablet fractures in a way where the main stress applied is the tensile stress. Stress development throughout the tablet is an important factor in determining the tensile strength. When tensile stress is constant across the load diameter, tensile strength can be calculated from the formula:

$$\sigma_0 = \frac{2P}{\pi D t} \tag{18}$$

Where σ_0 is the tensile strength of tablet in MPa, P represents the applied load (N), D is the diameter of the tablet in mm and t is the thickness (height) of the tablet in mm. (Fell and Newton, 1970).

6 Experimental section

6.1 Materials

Comprecel 102 (Microcrystalline cellulose)

Manufacturer: Mingtai Chemical Co., LTD., Taiwan

Batch number: C1307086

Spherolac 100 (Lactose monohydrate)

Manufacturer: Meggle, Wasserburg GmbH & Co. KG., Germany

Batch number: 5995

DI-CAFOS D160 (Dibasic calcium phosphate dihydrate-$CaHPO_4 \cdot 2H_2O$)

Manufacturer: Chemische Fabrik Budenheim KG, Germany

Batch number: MV 5030

DI-CAFOS A150 (Dibasic calcium phosphate, anhydrous-$CaHPO_4$)

Manufacturer: Chemische Fabrik Budenheim KG, Germany

Batch number: MV 4000

Theophylline

Ph. Eur. 6.0

Distributor: Dr. Kulich Pharma, s.r.o., Hradec Kralove, Czech Republic

Batch number: TAM/10071

6.2 Equipment

Optical Microscope, OLYMPUS BX51, (Olympus Optical Co., Ltd., Japan)

Moisture analyzer (KERN MLB 50-3, max 50g, d=1mg, KERN & SOHN GmbH, Germany)

Scott volumeter (COPLEY SCIENTIFIC, United Kingdom)

Tapped density tester (ERWEKA SVM 102, Erweka GmbH, Germany)

Flow tester (ERWEKA GT, Erweka GmbH, Germany)

Material testing equipment (ZWICK/ROELL T1-FRO 50, Zwick GmbH, Germany)

50 and 2kN force sensors (KAP-S 50 kN and KAP-TC 2 kN, A.S.T. GmbH Mess- & Regetechnik, Germany)

Micrometer screw (Mitutoyo Absolute, d=0.01mm, Mitutoyo Corp., Japan)

Analytical balance (AND HR-120, Max 120g, Min 10mg, d=0.1mg, A&D Company, Japan)

6.3 Methods

6.3.1 Measurement of particle size

I used an optical microscope to measure the size of the particles of the materials.
For the experiment, I placed a small amount of each powder on a microscopic glass with a spatula and spread it well, carefully and smoothly, in order to separate the individual particles but not to disrupt any agglomerates. Then, I put the glass onto the microscope table, focused on individual particles and took a picture of them (magnification-10 times). I measured the particle size of 100 particles manually using the vertical line tool (the largest diameter).
To estimate the mean, minimum and maximum diameters (μm) and the standard deviation (SD), the operation program (analySIS auto) was used.
The results will be found in Chapter 7 (Table 1 and Figures 3-7).

6.3.2 Moisture content

I had measured the decrease of mass of the material due to loss on drying.
I used Moisture analyzer (Kern MLB50-3). Firstly, I switched on the device. I weighted approximately 5 g of each sample (with precision of 0.001 g) on the empty aluminum bowl and I spread the sample evenly on the bowl. Afterwards, I covered the top part of the device, pressed the START button and heated the materials to 105 °C until equilibrium was achieved . Finally, the device expressed automatically the moisture content in %.
The results of the average of three measurements will be found in Chapter 7 (Table 2).

6.3.3 Measurement of bulk density in volumeter

According to European Pharmacopoeia 8.0 (2.9.34), I measured the bulk density of the powders by using Scott Volumeter.

The apparatus consists of a stainless steel top funnel which is fitted with a 1.0 mm sieve. This part is connected to a baffle box which contains four glass baffles over which the powder slides. At the bottom there is a stainless steel funnel which drives the powder into a cup placed directly below it. The cup I used had a cylindrical shape and the volume was 25.00 ml.

At the beginning of the experiment, I let an excess of the powder to flow through the apparatus and fall into the cup until it overflows. After that, I removed the excess of powder carefully from the top surface of the cup in order not to remove any powder from the cup and I measured the mass of the powder on an analytical balance (precision 0.1 mg). Before I proceeded to the next material, I cleaned the volumeter by using compressed air.

I repeated the measurement for each sample five times and I calculated the density (g/ml). The results of the experiment will be found in Chapter 7 (Table 2).

6.3.4 Angle of repose

For measurement of angle of repose I used the device Erweka GT.Before starting the experiment, I specified the settings for the measurement according to the instruction manual (nozzle-10 mm, stirrer steps-Off, measurements-3). Then, I allowed an excess quantity of powdered material to flow through a conical stainless steel hopper with a 10 mm orifice. Powders flew on a fixed base until a cone of powder was formed.

The angle was measured automatically by the device, using laser beam, and I recorded the results of three measurements for each powder.

The results of the measurements will be found in Chapter 7 (Table 3).

6.3.5 Mass flow rate

For the determination of mass flow rate, I used the device mentioned previously (Erweka GT) and designated the settings for the measurement according to the instructions (flow time-5 s, stirrer steps-Off, measurements-3). Then, I weighted 200 g of powder (precision 0.1 mg) and poured the weighted amount of the materials into a stainless steel, conical hopper fixed on the device. The diameter of the hopper orifice was 10 mm.

The determination of the mass of powder which flew from the hopper was done automatically by the device. Then, I filled hopper with new 200 g of powder and repeated measurement.

I read the results of the mass from three measurements and I calculated the mass flow rate in g/s. The results will be found in Chapter 7 (Table 3).

6.3.6 Determination of apparent (bulk) and tapped volume of powders

For the experiment I used a dry, graduated, 100ml cylinder into which I introduced 50 ml of the powder without tapping (the unsettled apparent volume V_0). Then, I placed the cylinder into the holder on top of the device (Erweka SVM 102). I turned on the device, set the number of tappings and determined the tapped volumes after 10, 100 (+90), 500 (+400) and 1250 (+750) tappings.

I used the results in calculation of the Hausner ratio according to Equation (3).

The results of the experiment will be found in Chapter 7 (Table 3).

6.3.7 Compression of tablets

For the compression of tablets I used the material testing machine Zwick/Roell T1-FRO 50. I used two methods which differed in the actual settings of the compression. The first one, called Compaction equation, and the second one called Force-displacement method. The details are written below.

The first step was to turn on the machine and weight on an analytical scale 500 mg of each powder. Then, I prepared the material by using the compaction aid ADAMUS

HT which consists of an upper and lower punch, a die and a blocking part. Firstly, I put the lower punch into the die, then the blocking part and, finally, the previously weighted powder and the upper punch. Afterwards, I put the compaction aid between plates into the material testing machine and started the pre-set program (TestXpert).
For the experiment, I also used a 50 kN force sensor for measuring force during compaction.

6.3.7.1 Compaction equation method

Settings of Compaction equation method: Measurement method-absolute displacement, Maximum force during the test-42000 N, Decompression detection-standard force 2 N, Displacement speed-0.5 mm/s, Shape of sample for volume calculation-round rod, Diameter-13 mm, Length of sample-13 mm, Plates displacement-13 mm, Speed of LE setting-100 mm/min.
After the procedure was finished, the results were recalculated according to compaction equation.
The results of the parameters of the compaction equation will be found in Chapter 7 (Tables 4A-4C and Figures 8-17).

6.3.7.2 Force-displacement method

Settings of Force-displacement method: Measurement method-differential displacement, Re-zero at pre-compression, Maximum force during the test-standard force 5, 10 and 15 kN, Decompression detection-standard force 2 N, Displacement speed-0.5 mm/s, Pre-compression-2 N, Speed of pre-compression-0.5 mm/s, Dwell time on pre-compression-No, Time to reach pre-compression-60 s, Re-zero at pre-compression-Yes, Shape of sample for volume calculation-Not defined, Length of sample-100 mm, Plates displacement-13 mm, Speed of LE setting-100 mm/min. After the procedure was finished, I recorded the results from the computer and used them for calculation of other parameters.
The results will be found in Chapter 7 (Tables 5A-7B).

6.3.8 Determination of crushing force and radial strength of tablets

In this experiment I determined the crushing and radial strength of tablets prepared by the Force-displacement method.

As I mentioned previously, the tablets were compressed by three different compression pressures (5, 10 and 15 kN). At the beginning, I chose ten tablets from each group and I measured their diameter and height by the micrometer screw with an accuracy of 0.01 mm. The device I used for the determination of crushing strength of the tablets was the same as the one I used for the compression procedures (Zwick/Roell T1-FRO 50). I put the tablet in between the crushing planes and turned on the pre-set program (measurement method-absolute displacement, maximum force during test-2000 N, speed of test-force increment 5 N/s, pre-compression-2 N, speed of pre-compression-0.01 mm/s, dwell time on pre-compression-No, time to reach pre-compression-60 s, re-zero ate pre-compression-No, shape of sample for volume calculation-Not defined, length of sample-13.2 mm, plates displacement-13.3 mm, speed of LE setting-100 mm/min, decrease of force-10% F_{max}, threshold force for the evaluation of breach-0.5% F_{norm}, maximal force, strain-2000 N). For the experiment I used a 2kN force sensor. After the crushing strength was determined, the radial strength was calculated according to the equation (18) in a modified form, shown below:

$$TS = \frac{2\,CF}{\pi\,d\,h}$$

where *TS* is the tensile (radial) strength in MPa, *CF* is the crushing strength in N, *d* is the diameter in mm and *h* is the height in mm. These abbreviations were used in Table 8 later in Result section.

The results of the experiment will be found in Chapter 7 (Table 8).

7 Results

Table 1: Results of particle size measurement by optical microscopy

Material	Mean diameter (µm)	SD	Minimum diameter (µm)	Maximum diameter (µm)
Comprecel	77,66	38,33	15,85	184,61
Spherolac	145,54	36,28	74,96	240,51
DI-CAFOS D160	202,19	48,56	104,51	387
DI-CAFOS A150	209,12	56,41	88,24	374,79
Theophylline	59,34	24,73	15,63	147,35

Figure 3: Picture of Comprecel obtained from optical microscope (magnification 10X)

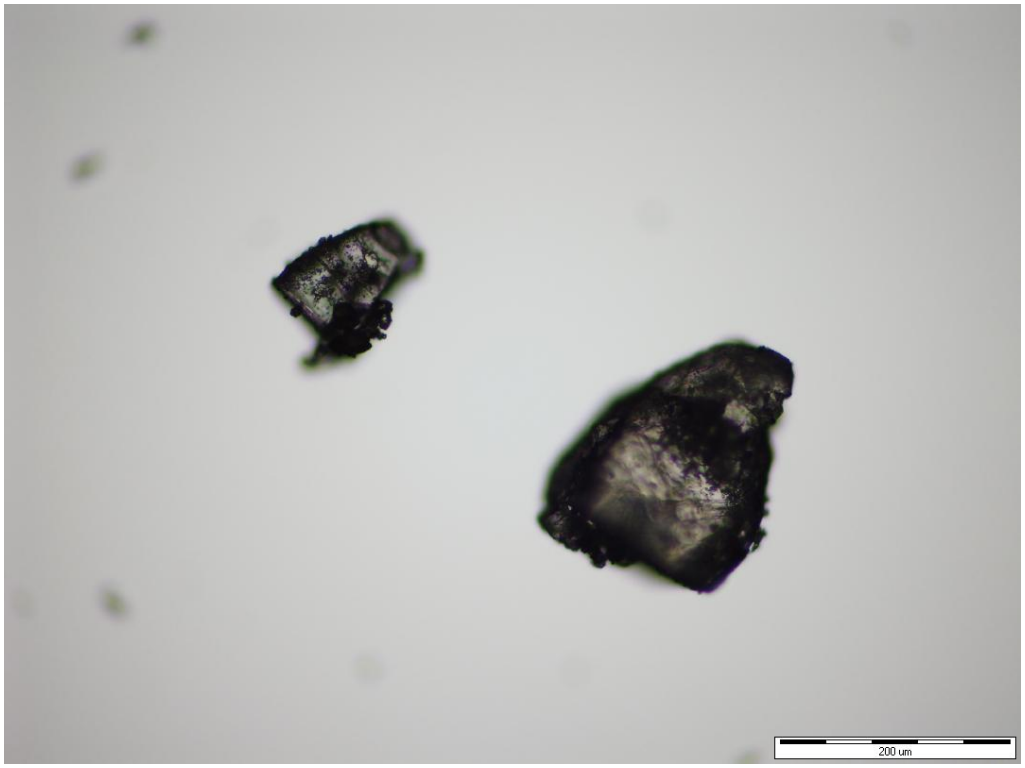

Figure 4: Picture of Spherolac obtained from optical microscope (magnification 10X)

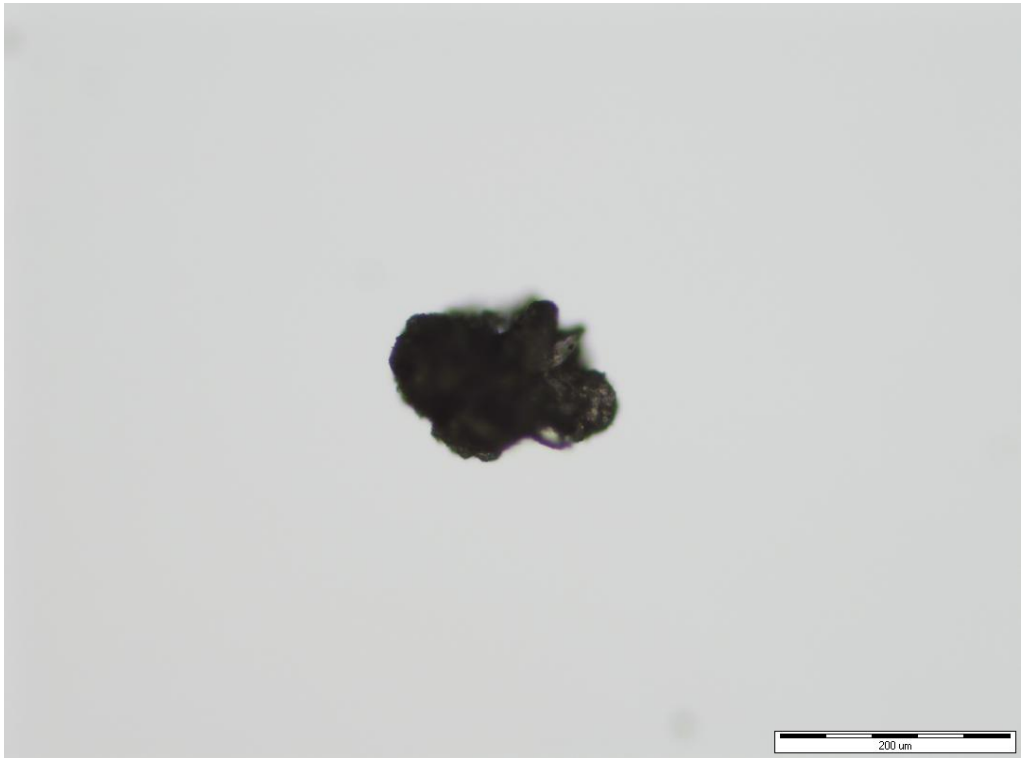

Figure 5: Picture of DI-CAFOS D160 obtained from optical microscope (magnification 10X)

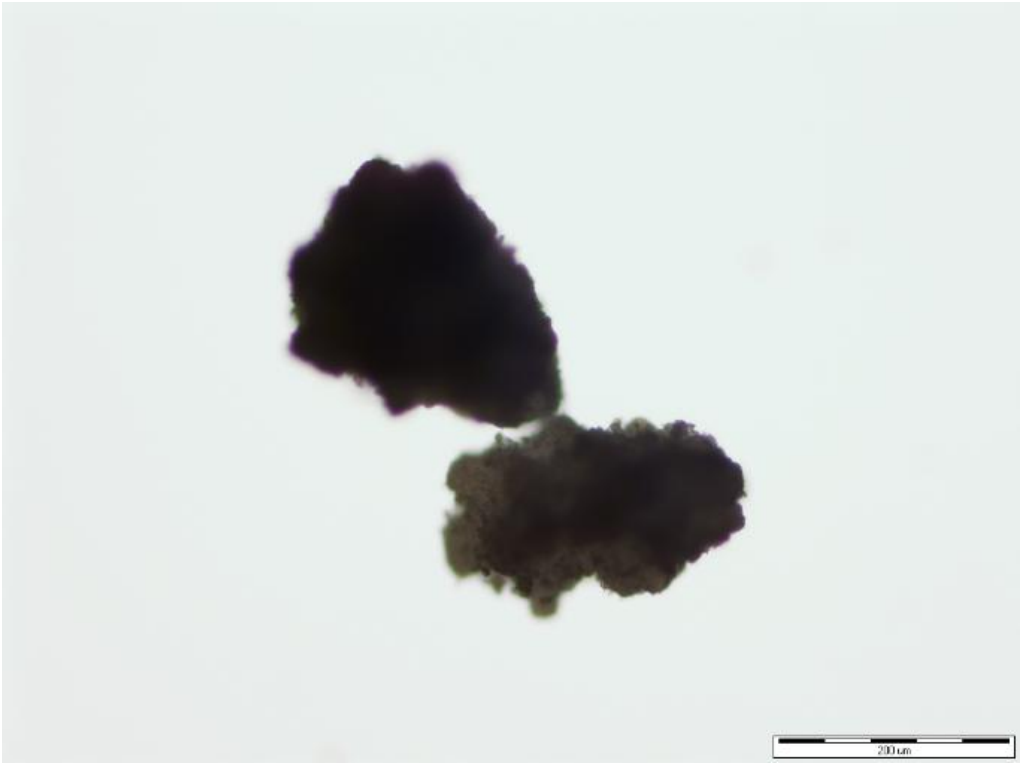

Figure 6: Picture of DI-CAFOS A150 obtained from optical microscope (magnification 10X)

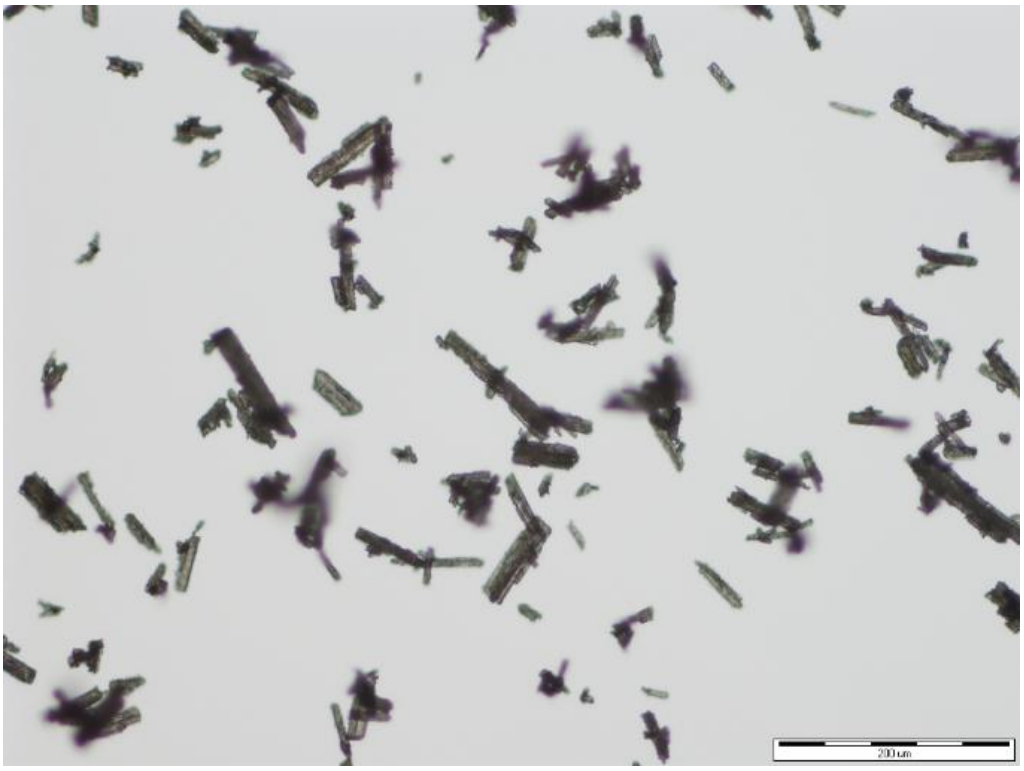

Figure 7: Picture of Theophylline obtained from optical microscope (magnification 10X)

Table 2: Results of moisture content and bulk density measurement

Material	Moisture content (%)		Bulk density (g/ml)	
	Ø	SD	Ø	SD
Comprecel	4,49	0,09	0,32	0,01
Spherolac	0,46	0,03	0,60	0,14
DI-CAFOS D160	3,89	0,36	0,81	0,01
DI-CAFOS A150	1,02	0,01	0,68	0,00
Theophylline	0,28	0,05	0,25	0,01

Table 3: Results of mass flow rate (g/s) and angle of repose AOR (°) measurements, Hausner ratio (HR)

Material	Mass flow rate (g/s)		AOR (°)		HR
	Ø	SD	Ø	SD	
Comprecel	9,75	1,39	47,33	1,46	1,39
Spherolac	16,22	2,18	44,50	1,04	1,16
DI-CAFOS D160	34,32	9,77	38,53	1,00	1,16
DI-CAFOS A150	32,91	0,16	39,90	0,30	1,13
Theophylline	0,53	0,16	48,13	1,19	1,35

Table 4A: Results of volume reduction parameters (a1-a3) of compaction equation

Material	a1		a2		a3	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	0,28	0,01	0,35	0,00	0,37	0,01
Spherolac	0,19	0,02	0,26	0,03	0,55	0,02
DI-CAFOS D160	0,15	0,01	0,29	0,01	0,56	0,01
DI-CAFOS A150	0,12	0,01	0,25	0,01	0,63	0,02
Theophylline	0,32	0,01	0,29	0,01	0,39	0,01

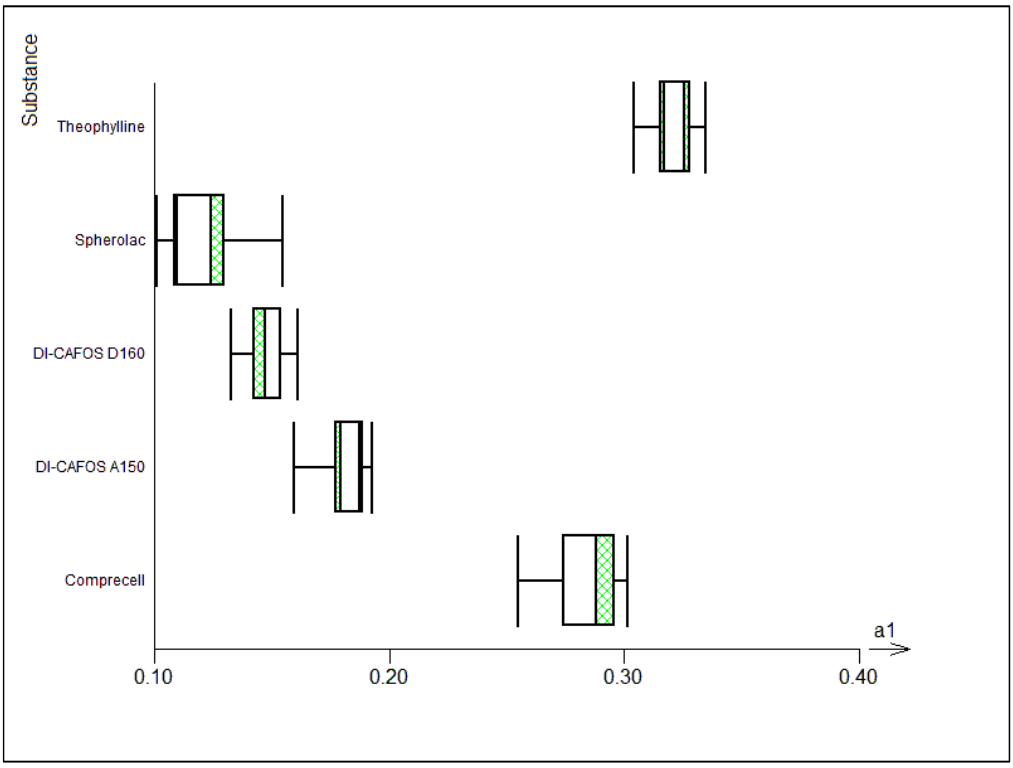

Figure 8: Volume reduction caused by particle rearrangement during pre-compression phase

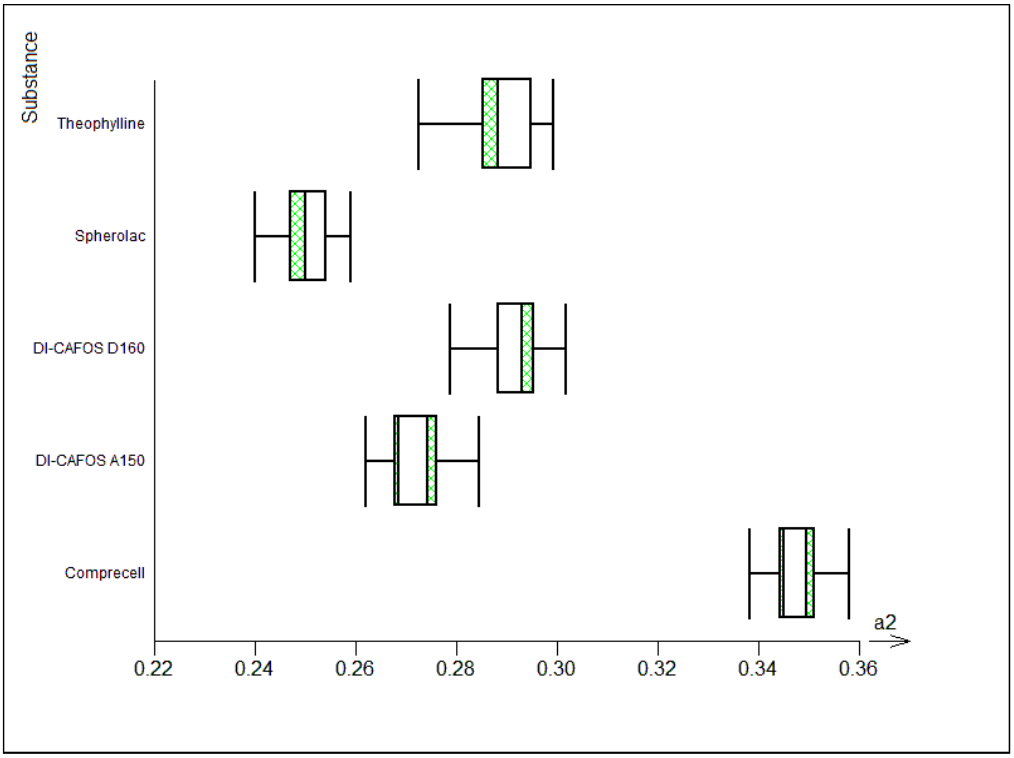

Figure 9: Volume reduction caused by elastic deformations of particles of the material

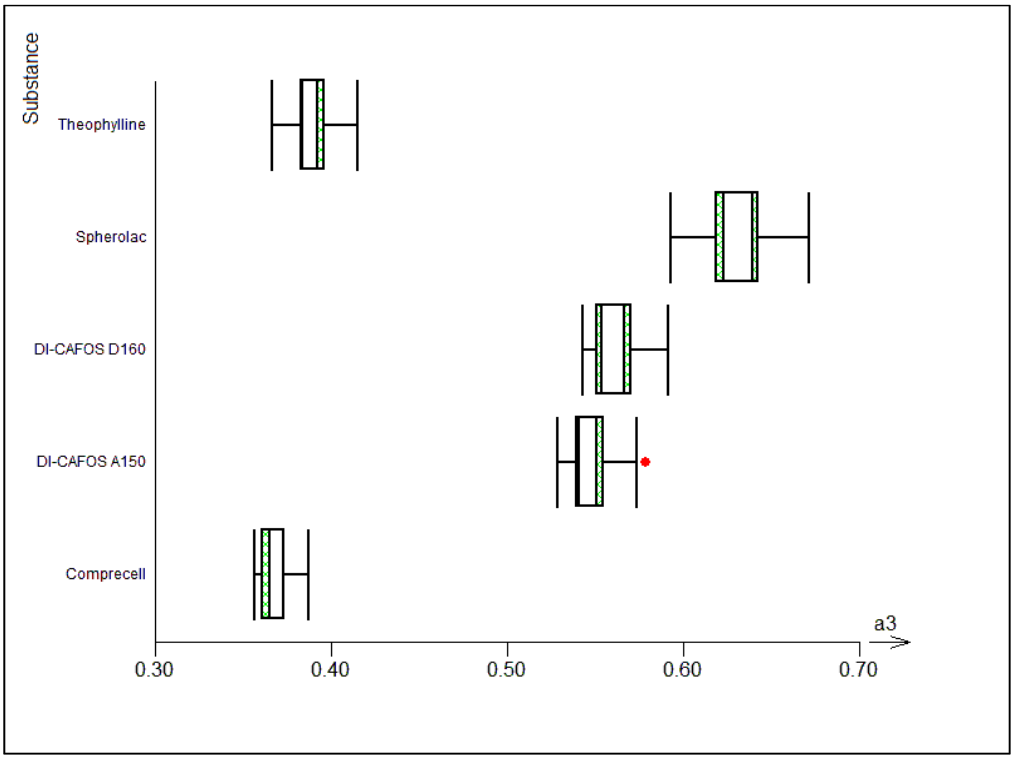

Figure 10: Volume reduction caused by plastic deformations of particles of the material

Table 4B: Results of speed parameters (1/t1-1/t3) of compaction equation

Material	1/t1 (MPa-1)		1/t2 (MPa-1)		1/t3 (MPa-1)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	1,95	0,23	0,10	0,01	0,01	0,00
Spherolac	1,17	0,34	0,15	0,18	0,00	0,00
DI-CAFOS D160	1,35	0,23	0,11	0,01	0,00	0,00
DI-CAFOS A150	1,89	0,44	0,10	0,01	0,00	0,00
Theophylline	2,31	0,25	0,14	0,01	0,01	0,00

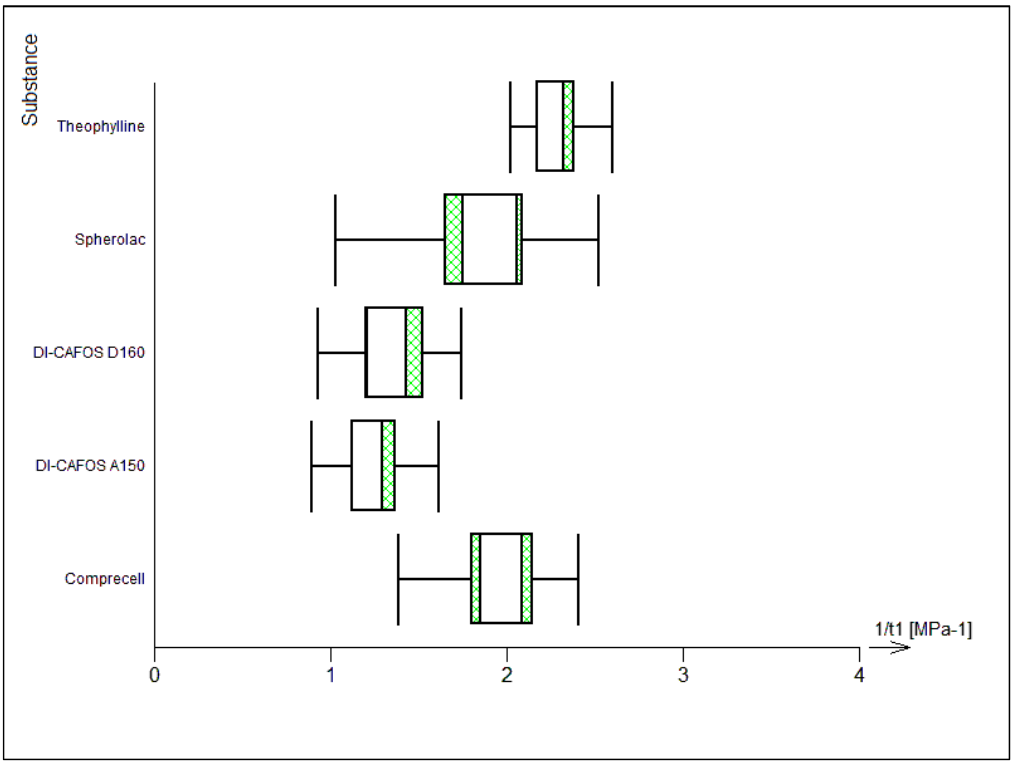

Figure 11: Speed of volume reduction during particle rearrangement

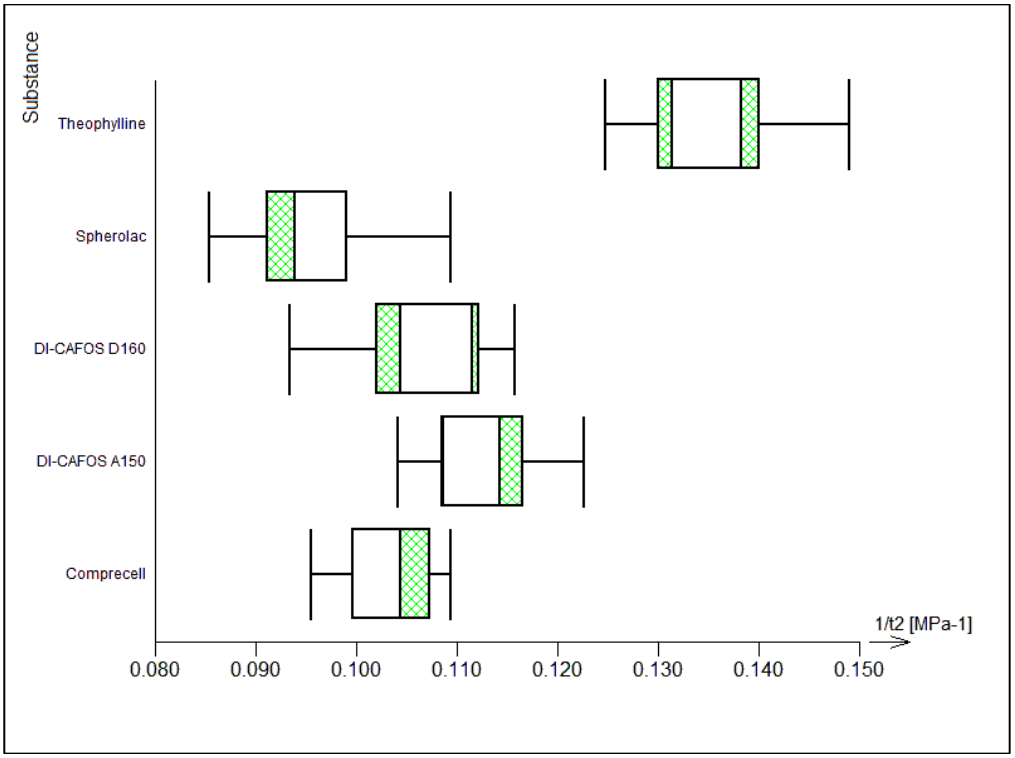

Figure 12: Speed of volume reduction during elastic deformation of particles

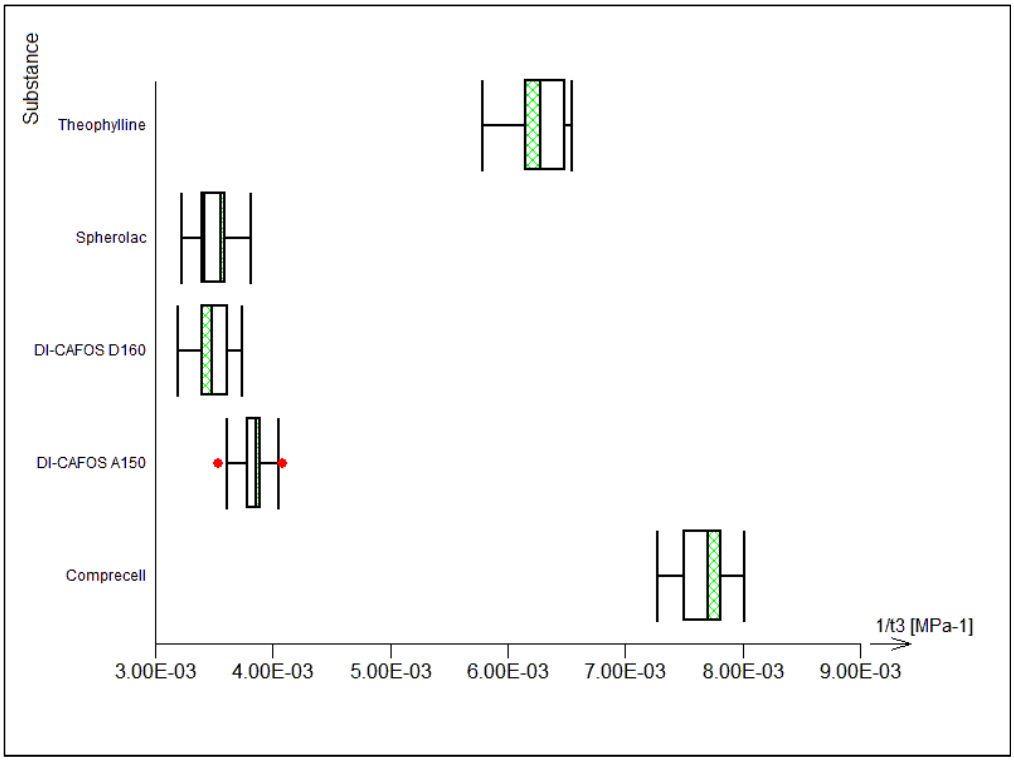

Figure 13: Speed of volume reduction during plastic deformation of particles

Table 4C: Results of energy parameters (E, E1-E3) of compaction equation

Material	E (J)		E1 (J)		E2 (J)		E3 (J)	
	Ø	SD	Ø	SD	Ø	SD	Ø	SD
Comprecel	42,77	2,19	0,12	0,01	2,80	0,17	39,84	2,02
Spherolac	121,94	10,33	0,23	0,45	1,93	0,42	119,78	10,21
DI-CAFOS D160	135,14	9,28	0,09	0,01	2,25	0,11	132,80	9,18
DI-CAFOS A150	150,65	11,17	0,05	0,01	2,16	0,13	148,44	11,15
Theophylline	53,01	3,77	0,12	0,01	1,74	0,10	51,15	3,78

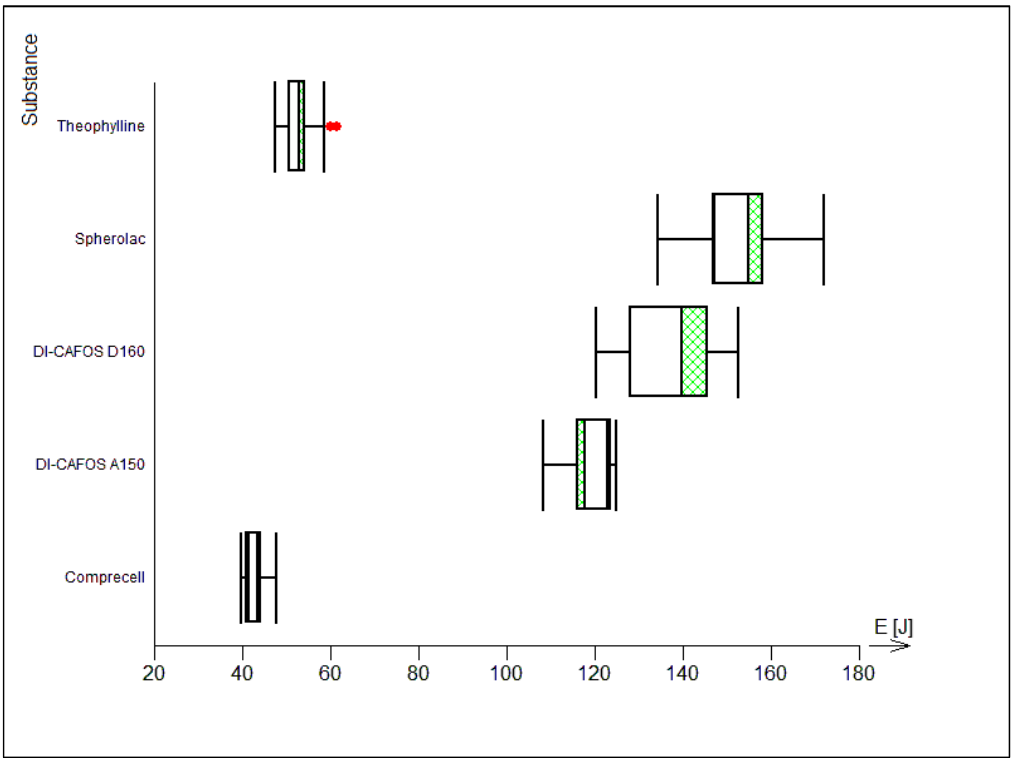

Figure 14: Total energy consumed during compression process

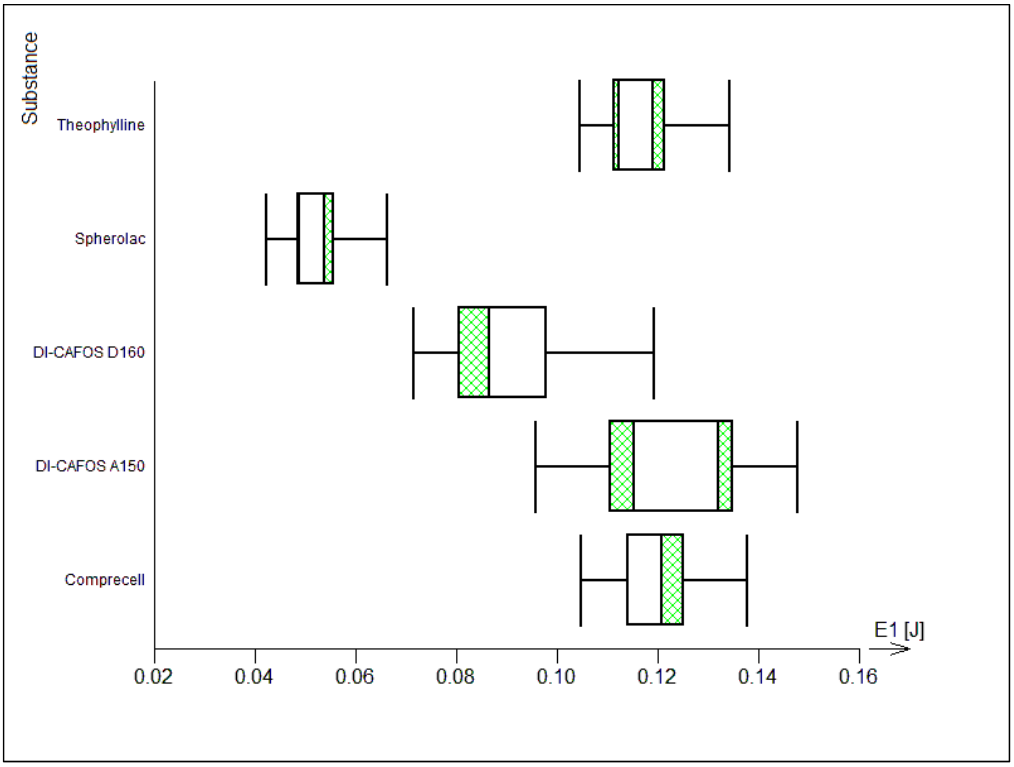

Figure 15: Energy consumed during particle rearrangement

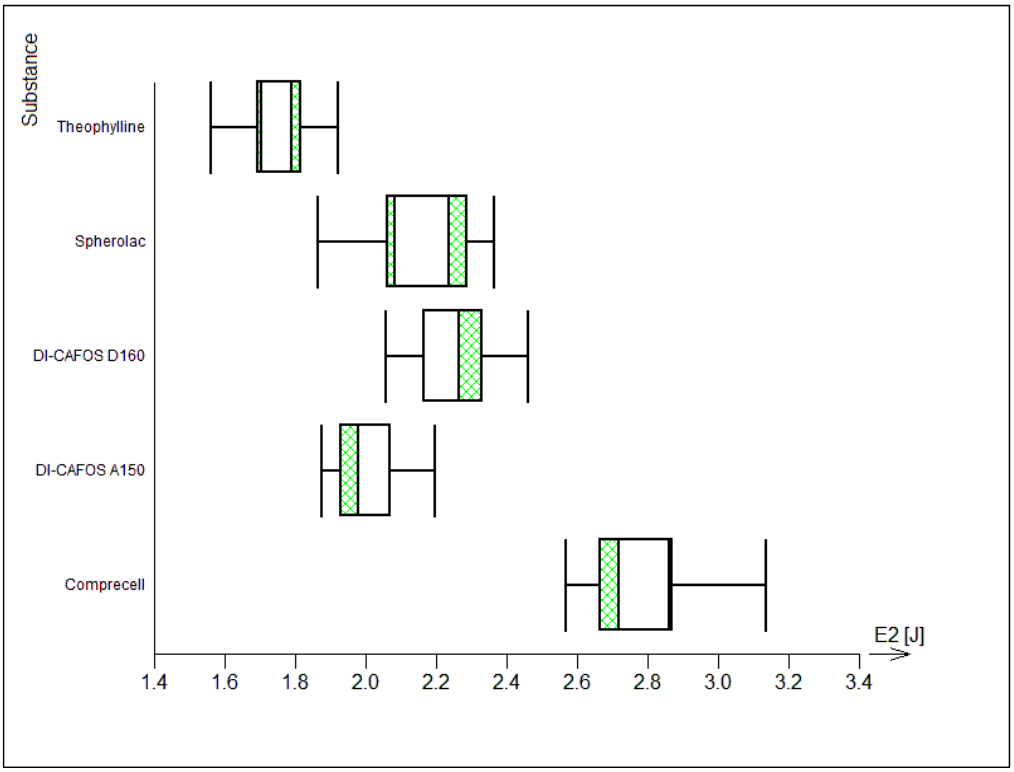

Figure 16: Energy consumed during elastic deformation of particles

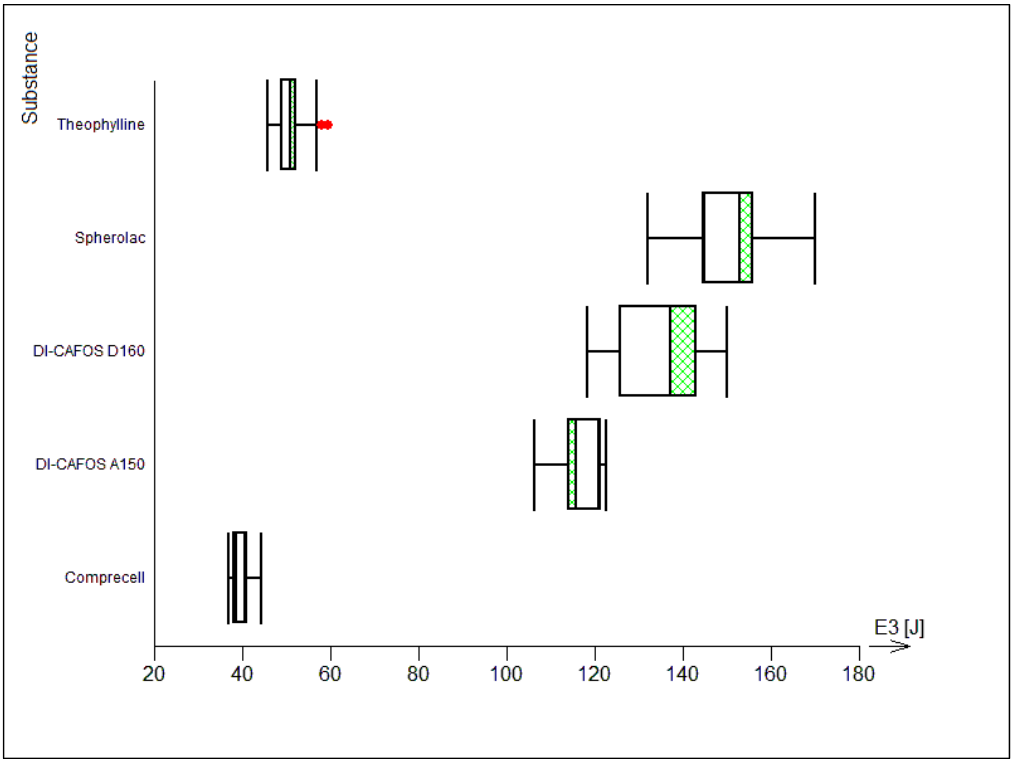

Figure 17: Energy consumed during creation of bonds between particles

Table 5A: Results of energy parameters (E1-E3) of Force-displacement method, 5 kN

Material	E1 (J)		E2 (J)		E3 (J)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	9,27	0,60	4,64	0,02	0,60	0,02
Spherolac	2,85	0,19	1,81	0,06	0,52	0,01
DI-CAFOS D160	3,60	0,31	2,09	0,03	0,52	0,02
DI-CAFOS A150	4,65	0,19	2,36	0,02	0,52	0,02
Theophylline	8,95	0,75	3,57	0,10	0,54	0,01

Table 5B: Results of total energy consumed during compression process (Emax), energy consumed for the preparation of tablets (Elis), plasticity of the material (Pl) of Force-displacement method, 5 kN

Material	Emax (J)		Elis (J)		Pl (%)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	14,52	0,61	5,25	0,02	88,50	0,28
Spherolac	5,18	0,15	2,33	0,06	77,86	0,60
DI-CAFOS D160	6,20	0,34	2,61	0,04	80,10	0,55
DI-CAFOS A150	7,53	0,19	2,88	0,03	81,84	0,46
Theophylline	13,06	0,80	4,11	0,11	86,91	0,42

Table 6A: Results of energy parameters (E1-E3) of Force-displacement method, 10 kN

Material	E1 (J)		E2 (J)		E3 (J)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	23,56	0,78	8,18	0,03	1,82	0,01
Spherolac	7,23	0,11	3,39	0,12	1,78	0,02
DI-CAFOS D160	8,26	0,71	3,63	0,04	1,76	0,02
DI-CAFOS A150	10,59	0,37	4,24	0,06	1,78	0,01
Theophylline	19,84	0,87	5,92	0,28	1,81	0,01

Table 6B: Results of total energy consumed during compression process (Emax), energy consumed for the preparation of tablets (Elis), plasticity of the material (Pl) of Force-displacement method, 10 kN

Material	Emax (J)		Elis (J)		Pl (%)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	33,56	0,79	10,00	0,03	81,83	0,15
Spherolac	12,40	0,18	5,17	0,11	65,57	0,92
DI-CAFOS D160	13,65	0,72	5,39	0,05	67,30	0,35
DI-CAFOS A150	16,61	0,36	6,02	0,05	70,43	0,37
Theophylline	27,58	0,93	7,74	0,29	76,54	0,80

Table 7A: Results of energy parameters (E1-E3) of Force-displacement method, 15 kN

Material	E1 (J)		E2 (J)		E3 (J)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	37,12	0,96	11,13	0,20	3,76	0,03
Spherolac	11,84	0,67	4,80	0,24	3,80	0,08
DI-CAFOS D160	14,92	0,76	4,99	0,07	3,74	0,06
DI-CAFOS A150	17,22	0,54	6,05	0,08	3,76	0,04
Theophylline	31,38	0,78	7,99	0,38	3,85	0,05

Table 7B: Results of total energy consumed during compression process (Emax), energy consumed for the preparation of tablets (Elis), plasticity of the material (Pl) of Force-displacement method, 15 kN

Material	Emax (J)		Elis (J)		Pl (%)	
	Ø	SD	Ø	SD	Ø	SD
Comprecel	52,02	0,94	14,90	0,20	74,73	0,37
Spherolac	20,44	0,58	8,60	0,28	55,79	1,18
DI-CAFOS D160	23,65	0,78	8,73	0,09	57,19	0,52
DI-CAFOS A150	27,02	0,57	9,81	0,07	61,68	0,54
Theophylline	43,22	1,03	11,84	0,36	67,43	1,23

Table 8: Results of tensile (radial) strength measurement

Material	Compaction force (kN)	Tensile strength (MPa)	
		Ø	SD
Comprecel	5	1,31	0,07
	10	3,31	0,09
	15	4,75	0,30
Spherolac	5	0,11	0,04
	10	0,24	0,04
	15	0,40	0,08
DI-CAFOS D160	5	0,23	0,02
	10	0,43	0,06
	15	0,67	0,03
DI-CAFOS A150	5	0,14	0,01
	10	0,30	0,01
	15	0,54	0,06
Theophylline	5	1,02	0,09
	10	2,27	0,34
	15	3,09	0,74

8 Discussion

The importance of studying the compressibility characteristics of powders, as the initial material for tablet formulation, is great because those properties are responsible for the successful tablet production. More specifically, those properties are very significant characteristics that should be taken into account, since they influence the bioavailability, tablet strength, disintegration, dissolution and stability upon handling and storage.

In this experimental work, particle size, moisture content, bulk density and flow properties of five powders: Comprecel, Spherolac, DI-CAFOS D160, DI-CAFOS A150 and Theophylline were tested. Later, tablets were prepared from each powder and their strength was determined. The results obtained from those measurements were used to determine which of these powders has the best compressibility characteristics. The results are summarized in Tables 1-8 and Figures 3-17.

8.1 Evaluation of powders properties

Particle size was measured with an optical microscope. The results are summarized in Table 1 and Figures 3-7. From the results in Table 1, it is possible to say that Comprecel and Theophylline powders have smaller particle size 77.66 μm and 59.34 μm, respectively, than Spherolac, DI-CAFOS D160, DI-CAFOS A150 with average particle size values of 145.54 μm, 202.19 μm and 209.12 μm, respectively. Also, from Figures 3-7, it can be stated that all powders consist of irregularly shaped particles.

In Table 2 results of moisture content and bulk density measurements can be found. Moisture content was measured, with the use of a moisture analyzer, by heating the powders and automatically determining the moisture content (%) and the time needed for water evaporation. It could be seen that Theophylline, Spherolac and DI-CAFOS A150 have the least moisture content (0.28 %, 0.46 % and 1.02 %,

respectively) in comparison with DI-CAFOS D160 and Comprecel with moisture content 3.89 % and 4.49 %, respectively.

Bulk density was measured by using Scott volumeter. The results summarized in Table 2, show that Comprecel and Theophylline are the least dense powders, having bulk density values of 0.32 g/ml and 0.25 g/ml, respectively. On the other hand, DI-CAFOS D160, DI-CAFOS A150 and Spherolac, with bulk density values of 0.81 g/ml, 0.68 g/ml and 0.60 g/ml respectively, are more dense powders. All values are approximately in accordance with data referred to in literature (Rowe et al, 2012).

8.1.1 Testing of flowability

In order to describe the flowability of powders, the mass flow rate, angle of repose and bulk and apparent volume of powders were measured. Results are summarized in Table 3.

Mass flow rate describes the mass (g) of sample that passes per unit of time (s) though the orifice of hopper. The automatic powder flow tester was used with the diameter of the orifice 10 mm. From Table 3, it is obvious that DI-CAFOS D160 and DI-CAFOS A150 are the most free-flowing powders with the average mass flow rate values of 34.32 g/s and 32.91 g/s, respectively. On the contrary, Theophylline powder has the worst flow properties with average mass flow rate value of 0.53 g/s at the same experimental conditions.

Angle of repose (AOR) was measured automatically, by the device mentioned earlier, by using laser beam. For the evaluation of flow properties of the material according to the AOR the following Table 9 is the most representative (Ph. Eur. 0.8, 2013):

Table 9: Characterization of flow properties according to the AOR (Carr, 1965)

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

According to Table 9, Comprecel and Theophylline with AOR values of 47.33 ° and 48.13 °, respectively, have poor flowability; Spherolac with an angle 44.50 ° is considered passable and DI-CAFOS D160 and DI-CAFOS A150, with AOR values of 38.53 ° and 39.90 ° respectively have fair flow properties.

Hausner ratio was calculated from bulk and tapped volume of the powders according to the Equation 3 mentioned earlier.
According to PhEur 0.8, the generally accepted scale of flowability for Hausner ratio is given by the following Table 10:

Table 10: Characterization of flow properties according to the HR values (Carr, 1965)

Flow character	Hausner ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59
Very, very poor	>1.60

From Table 10, the following conclusions are derived: Comprecel and Theophylline, with HR values of 1.39 and 1.35 respectively, have bad flow properties and Spherolac, DI-CAFOS D160 and DI-CAFOS A150, with HR values of 1.16, 1.16 and 1.13 respectively, have good flowability.

8.2 Evaluation of tablets

8.2.1 Compaction equation method

After the evaluation of powder properties, the powders were compressed and the results were assessed by compaction equation and force-displacement method. Results of compaction equation parameters are found in Tables 4A-4C and Figures 8-17.

In Table 4A, the values of volume reduction parameters (*a1-a3*) are submitted; *a1* represents the particles rearrangement during the phase of pre-compression, where interparticular friction and friction between particles and die takes place. The parameter *α2* describes the elastic deformation and *α3* the plastic deformation and bond formation within particles of the powders (Ondrejček et al, 2014).

From Table 4B, the speed (reciprocal MPa) of individual phases of the compression process can be declared. The speed during particle rearrangement was higher with Theophylline, i.e. the reduction in the volume of the powder was faster, in comparison with the other powders. During elastic deformation of particles the speeds were approximately the same; however, with Spherolac the volume reduction happened faster. In the phase of plastic deformation, volume reduction in Comprecel and Theophylline was faster.

From Table 4C, the amount of energy (J) consumed during the entire compression process (E) and the energy consumed in the particular phases (E1-E3) can be assessed. The energy utilized during particle rearrangement was higher with Spherolac in comparison with the rest of the powders.

During an elastic deformation, Comprecel consumed the greatest amount of energy, since it is a highly elastic material. However, high elasticity is undesirable since it

can cause capping or lamination of the final tablet (Stasiak et al, 2010). Moreover, from this table it can be declared that Spherolac, DI-CAFOS D160 and DI-CAFOS A150 consumed huge amounts of energy for the creation of interparticular bonds due to their brittleness, while Comprecel and Theophylline, which exhibit plastic behavior, consumed approximately three times less energy for bond formation (Roberts and Rowe, 1987).

8.2.2 Force-Displacement method

The powders were compressed under three different compression pressures (5, 10 and 15 kN) by using the Force-Displacement method. This procedure comprises a compression and a decompression phase. The results are summarized in Tables 5A-7B.

The sum of the parameters E1-E3, presented in Tables 5A, 6A and 7A, express the total energy (J) consumption (Emax). Values of Emax are found in Tables 5B, 6B and 7B. E1 is the energy used during the compression phase, were particles within the powder are rearranged and friction occurs (Çelik, 2011). Comprecel and Theophylline, in the particular phase, consumed greater amount of energy than the other powders, due to the higher friction between their particles. E2 corresponds to the energy expenditure during interparticular bond formation and depends on the bonding mechanisms of the material (Çelik, 2011). Since this energy is correlated with the plastic behavior of the material, it is higher in Comprecel and Theophylline as well. On the other hand, E3 characterizes the elasticity of the materials; is the energy recovered in the decompression phase during displacement of the upper punch (Çelik, 2011). From the values of this energy it can be stated that Comprecel and Theophylline have great elasticity, thus the energy recovered is higher.

Additional parameters of this method are Emax, Elis and Pl and their values are submitted in Tables 5B, 6B and 7B. As it was mentioned earlier, Emax is the energy input (J) throughout the whole process and it is higher for Comprecel and Theophylline. Elis (E2+E3) stands for the energy utilized in the compression phase

and it is the energy used for tablet preparation. Elis values are also higher for Comprecel and Theophylline. Pl (%) is a parameter which describes the plasticity of the material, i.e. is the tendency of the material to undergo permanent deformation, under load, when they are compressed. This value is higher for Comprecel and Theophylline as well (Çelik, 2011).

Moreover, by comparing the values of Tables 5A-7B one can assume that, energies E1-E3, Emax and Elis increase with an increasing compression pressure, while plasticity of the material decreases.

8.2.3 Tensile strength

Radial (tensile) strength was estimated using the Fell and Newton equation in a modified form (Fell and Newton, 1970). Used tablets were prepared by the Force-Displacement method at given compression forces (5, 10, 15 kN). Crushing strength of those tablets was determined and the tensile strength was calculated from the values of crushing strength. The results of those measurements are summarized in Table 8.
From those results it can be seen that the strength of tablets prepared from Comprecel and Theophylline was approximately eight times higher than the strength of tablets prepared from Spherolac, DI-CAFOS D160 and DI-CAFOS A150.

Moreover, as the applied compression force increases, the strength of the final tablets was increased. This observation is in accordance with the literature (Augsburger and Hoag, 2008).

9 Conclusions

From the results of my work the following conclusions were drawn:

1. Particle size measurement:
    - Comprecel and Theophylline have smaller particles in comparison with the other excipients.
    - All used materials have irregular shape of particles.
2. Moisture content and bulk density measurements:
    - Spherolac, DI-CAFOS A150 and Theophylline have the least moisture content than the other materials.
    - Comprecel and Theophylline have the least values of bulk density.
3. Flowability measurements:
    - DI-CAFOS D160 and DI-CAFOS A150 have the best flow properties in comparison with the other powders.
4. Compression process-Compaction equation:
    - Faster volume reduction in the phase of particle rearrangement was found for Theophylline and energy consumed during this phase was higher for Spherolac.
    - In the phase of elastic deformation, the highest speed of volume reduction was found for Spherolac and the amount of energy consumed was greater for Comprecel.
    - During plastic deformation and creation of interparticular bonds, the volume reduction was faster for Comprecel and Theophylline and the energy consumed was higher for Spherolac, DI-CAFOS D160 and DI-CAFOS A150.
5. Compression process-Force-Displacement method:
    - Comprecel and Theophylline consumed the greatest amount of energy within the entire compression process.
    - Plasticity values were higher for Comprecel and Theophylline.
    - Energy utilized throughout the compression process increased and plasticity decreased with an increasing compression pressure.

6. Tensile strength measurement:
    - Tablets prepared from Comprecel and Theophylline were stronger than the tablets prepared from the rest of the materials.
    - As the compression force increases, the strength of the prepared tablets increases.

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