Mechanical deformation behavior of materials during compression

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Sabrina Berkenkemper

aus Witten

Düsseldorf, April 2023

Aus dem Institut für Pharmazeutische Technologie und Biopharmazie

der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der

Mathematisch-Naturwissenschaftlichen Fakultät der

Heinrich-Heine-Universität Düsseldorf

Berichterstatter:

1. Prof. Dr. Dr. h.c. Peter Kleinebudde
2. Jun.-Prof. Dr. Michael Hacker

Tag der mündlichen Prüfung: 15.06.2023

Für alle, die mein Herz zum Lächeln bringen

„The secret is to surround yourself with people who make your heart smile.
It is then, only then, that you will find Wonderland. “

The Mad Hatter

Table of contents

List of publications and contributions

Published manuscripts

Berkenkemper, S., Kleinebudde, P., Compressibility analysis as robust in-die compression analysis for describing tableting behaviour, *RPS Pharmacy and Pharmacology Reports 1 (2022) 1-7.*

Berkenkemper, S., Kleinebudde, P., Evaluation of alternative methods to derive particle density from compression data, *International Journal of Pharmaceutics 632 (2023) 122582.*

Berkenkemper, S., Klinken, S., Kleinebudde, P., Multivariate data analysis to evaluate commonly used compression descriptors, *International Journal of Pharmaceutics 637 (2023) 122890.*

Berkenkemper, S., Klinken, S., Kleinebudde, P., Investigating compressibility descriptors for binary mixtures of different deformation behavior, *Powder Technology 424 (2023) 118571.*

Congress contributions

Oral presentations

Berkenkemper, S., Kleinebudde, P., Comparison of two commonly used compression analyses for in-die and out-of-die performance, *4th Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science, Szeged 2022.*

Berkenkemper, S., Kleinebudde, P., Sensitivitätsanalyse bekannter Kompressionsanalysen bezüglich des Einflusses der Partikeldichte, *ProcessNet Annual Meeting Section Agglomeration and Bulk Handling, Leipzig 2022.*

Berkenkemper, S., Kleinebudde, P., Investigating the approach to derive particle density from compression data, *16th PSSRC Annual Meeting, Helsinki 2022.*

Poster presentations

Berkenkemper, S., Gupta, R., Hadamitzky, L., Kleinebudde, P., Vergleich zweier Methoden zur Untersuchung der Bruchkraft von Tabletten, *ProcessNet Annual Meeting Section Agglomeration and Bulk Handling, Leipzig 2021.*

Berkenkemper, S., Espinoza Luna, L.P., Kleinebudde, P., Impact of compression pressure on the performance of in-die Heckel analysis, *13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Rotterdam 2022.*

List of abbreviations

ab	Rearrangement index (Kawakita)
adj. R^2	Adjusted coefficient of determination
API	Active pharmaceutical ingredient
C^{-1}_{KL}	Plasticity parameter (Kuentz-Leuenberger)
CM	Continuous manufacturing
DC	Direct compression
DCP	Dibasic calcium phosphate anhydrate
HPC	Hydroxypropyl cellulose
K	Compressibility constant
KL	Kuentz-Leuenberger
MCC	Microcrystalline cellulose
MSP	Maize starch, pregelatinized
PAT	Process analytical technologies
ρ_p	Particle density
P_f	Pressure required for brittle fracture
P_y	Yield pressure
SEM	Scanning electron microscopy
SF	Solid fraction
TS	Tensile strength
V_0	Initial volume of powder bed (Kawakita)
x_{50}	Mean particle size

Section A.

Introduction

A.1 Tablets and tableting

A.1.1 General aspects

Tablets are single-dose, solid dosage forms that are typically manufactured by compressing a powder or granule. They remain one of the most important and most often used oral dosage forms in the pharmaceutical field. Due to their ease of handling by the patient, tablets ensure a high level of compliance [1]. In addition, as a solid, dry dosage form, tablets exhibit superior microbiological stability compared to other dosage forms [2]. The comparatively simple production process is another major advantage [3]. Tableting as it is applied nowadays, with two punches and a die, has been used in this way for over 150 years [4]. Powder mixtures, granules or mixtures of powders and granules can be used as starting materials. The compression of powder or powder mixtures without prior granulation steps is referred to as direct compression (DC). Especially if DC is applicable, cost-intensive production steps such as drying of an intermediate are no longer necessary.

Even though DC is the most effective way, there are some limitations. Many active pharmaceutical ingredients (APIs) do not have the necessary properties to be compressed into a tablet without further additives and prior processing steps [5], which means they do not meet the requirements of the critical quality parameters. One prerequisite is sufficient flowability to ensure uniform die filling [6]. Die filling usually takes place volumetrically, so that the filling of the die determines the dosing of the tablet. The better the flowability of the starting material, the more likely the uniformity of the dosage can be ensured. Another important quality feature of the resulting tablet is sufficient mechanical strength. The tablet must survive the coating and packaging process, further process steps such as transport of the finished product, and also handling by the patient [7]. The mechanical strength of a tablet is significantly influenced by the materials' behavior during the tableting process. The mechanical strength of the tablet is mostly determined by the solid fraction (*SF)*. In addition to the mechanical strength of the tablet, the *SF* significantly influences its disintegration and the dissolution of API. Therefore, the *SF* must be in a range that both mechanical strength and disintegration time contribute to optimal tablet properties. The greater the *SF*, the stronger the resulting tablet, which in turn prolongs the disintegration time. This is due to the disintegration medium taking longer to enter the tablet and thus initiate the disintegration process. In addition, a stronger tablet also means higher binding

forces that must be overcome during disintegration. For immediate-release tablets, a longer disintegration time is typically associated with a slower dissolution as well. Only if the release medium comes in contact with the API it can be dissolved and release can take place. Pharmaceutical tablets are typically manufactured in a *SF* range of 70-90% [8].

Figure 1 schematically shows the sequence of a tableting process for materials with different deformation behavior. The deformation behavior of materials is divided into plastic, elastic and brittle. Most materials are dominated by one of the three deformation behaviors, which largely determines their behavior during tableting. Very few materials exhibit only one of the three behaviors and no pharmaceutically used material does [9]. Usually, the tableting behavior is a mixture of all three deformation behaviors. The proportion of the respective deformation behavior in the overall behavior depends on the material properties as well as the tableting parameters, where the compression pressure, speed and the duration of the dwell time can be named as influencing parameters [9]. The particle size of the material also determines the deformation behavior. A brittle material (e.g., sodium chloride) can show predominantly plastic deformation if the particle size is beneath a certain limit [10]. The brittle-ductile transition is explained based on the pressure, which is required for either plastic flow or brittle fracture. The pressure required for brittle fracture (P_f) highly depends on the diameter of the respective particle. Large particles show low values for P_f. For those particles P_f will be lower than the pressure needed to achieve plastic flow (P_y, yield pressure). The smaller the particles become, the larger P_f becomes until a critical point is reached where plastic flow will take place instead of brittle fracture [10]. For sodium chloride the critical particle size is described to be around 20 µm. For those particles P_y will be smaller than P_f and the material will thus show predominantly plastic deformation behavior during compression.

Powder compression includes several steps (Figure 1). After dosing of the material, the powder bed is loosely packed in the die. The volume occupied by the powder bed is equal to the bulk volume of the material. As the distance between the punches decreases, particle rearrangement initially takes place. The powder is more densely packed when smaller particles fill voids between larger particles. This process requires only little force, so that no significant increase in compression pressure can be detected. The density of the powder bed at this stage is referred to as the deaeration

density. If the material cannot be rearranged because interparticular friction will hinder further packing [11], elastic deformation occurs. Every material has the capacity for reversible elastic deformation, but to varying degrees. The more elastic energy can be stored by the material, the later the compression pressure increases noticeably [12]. If the compaction process is stopped at this point, the particles can reexpand and return to the deaeration density state.

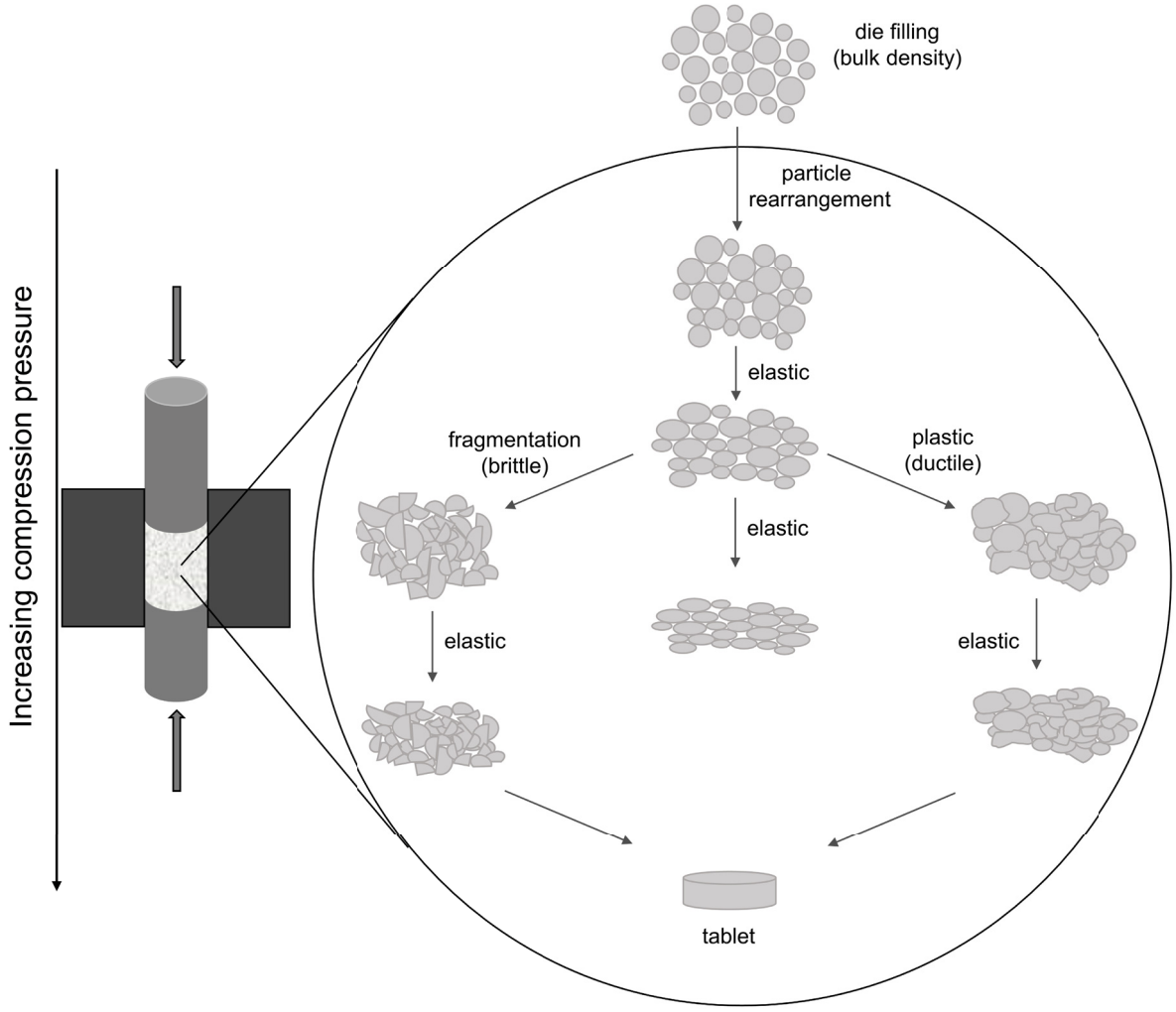

Figure 1. Deformation processes during tableting

When no further reversible elastic energy can be stored, the particles start to deform permanently and irreversibly at contact points with punches, die wall and other particles [1]. The pressure needed to overcome reversible elastic deformation is P_y for ductile materials and P_f for brittle materials [13]. Brittle materials fragment as the compression pressure exceeds P_f. This creates new surfaces that are available for bonding between the particles. Moreover, when the particles break – obtaining a higher specific surface area – the bonding area becomes larger, more contact points for particle interactions

are created and thus, the potential for bonding forces increases [14]. The strength of a tablet is determined by the bonding area and the bonding strength between the particles, which in turn is determined by the bonding mechanism [15]. Large bonding area linked with high bonding forces lead to strong tablets [16], which can withstand further processing steps and handling by the patient. The dominating bonding forces in a tablet are distance forces like van der Waals forces [17], hydrogen bonds, electrostatic forces [18] and solid bridges. Those adhesive forces are anti proportional to the distance between the particles. The closer the particles get to each other under increasing compression pressure, the stronger are the adhesive forces between them. Solid bridges play a minor role in the initial formation of bonding forces within the tablet, but strengthen existing bonds [19].

Much of the tablet strength during tableting is achieved by plastic deformation, even when fragmentation occurs simultaneously [19]. Plastic deformation takes place above the P_y and is also called cold flow. It facilitates the formation of permanent particle-particle contacts and thus bonding areas [13]. Plastic deformation takes place as a time-dependent process when the pressure is above the P_y [20]. The longer the pressure is above P_y, the more plastic deformation takes place and the larger is the resulting bonding area. Accordingly, plastic materials are more sensitive to changes in compression speed, which is of great relevance in scale-up processes [21]. At higher compression speeds - especially with rotary presses as used in industry - the dwell time becomes shorter. This results in less plastic deformation, which can significantly change the tablet properties [21]. Plastically deforming materials can also show fragmentation above a certain pressure limit, which is called ductile fracture [22].

Elastic deformation takes place throughout the entire tableting process to different extents at different stages [13]. After P_y or P_f is exceeded, mainly irreversible plastic deformation and fragmentation take place. Elastic deformation is less pronounced at this stage. However, the more the tablet is compressed, the more the elastic deformation increases again [23]. If the particles are irreversibly deformed to a large extent and the SF is high, a strong increase in elastic deformation occurs when the compression pressure is further increased. Here, even SF greater than 1 can be observed, as the particles are elastically deformed to such an extent that the particle density of the starting material is exceeded [24]. A large proportion of this elastic deformation at high compression pressure is reversed during decompression [25]. It is

described as the in-die elastic recovery, which characterizes the volume expansion of the tablet between the moment of minimal in-die thickness of the tablet and the moment when the upper punch loses contact to the tablet [26].

Elastic recovery does not only occur within the die. After the tablet is ejected, part of the elastic recovery takes place out-of-die, which together with the in-die elastic recovery is referred to as fast elastic recovery [27]. However, some elastic recovery takes place much slower and can last for hours to weeks, depending on the formulation ingredients of the tablet [28]. Which proportion of the elastic recovery takes place quickly and which slowly depends on the tableted materials.

The process described is similar for the tableting of granules. The main difference is that the granules as secondary particles first fragment into their primary particles from which they were fabricated. This also applies to excipients or active ingredients produced by agglomeration processes (e.g., spray-agglomeration, wet granulation). In such cases, the tensile strength of the agglomerates must be exceeded. This is mainly determined by the adhesive forces between the contact points of the primary particles and by the particle size of the processed primary particles determining the available area for adhesive forces [29]. When fragmented into the primary particles, the material can undergo some second rearrangement before irreversible deformation occurs likewise to DC [11].

A.1.2 Process monitoring

Up to now, pharmaceutical products have been manufactured primarily using batch-to-batch processes. A defined quantity of starting material is processed into a defined quantity of product. The processes required to manufacture the end product (e.g., blending, granulation, tableting) are separate. This means that each process step produces an intermediate product that can be analyzed for critical quality parameters and will be stored until further processing. After the last process step, the final product is generated, which will be assessed with regard to its quality and afterwards released if the corresponding requirements are met. In contrast, in continuous manufacturing (CM), all process steps are consecutively performed. The resulting intermediate product is transported within the system to the next process step. This results in a constant product flow that does not require storage of intermediate products [30].

For both, batch-to-batch process and CM, process understanding is an important prerequisite to control the process. Monitoring the process and thus the product quality is essential. Without process monitoring systems, subsequent steps in manufacturing, especially in CM, will be carried out even if the intermediate product does not meet the specified requirements, thus wasting time and resources. For this reason, analytical methods are used that allow real-time monitoring. These methods enable to find the sources of errors in the process itself and to optimize the process so that both intermediate products and the end product meet the requirements. The Food and Drug Administration refers to such methods as process analytical technologies (PAT) [31].

Although tableting has been carried out for over 150 years using the method described, the tableting process is not fully understood yet. There is a variety of factors that influence the tableting behavior of formulations and thus the resulting tablet properties. These include e.g., particle size [32-34], particle size distribution [35], particle shape [36, 37], particle density [9], deformation behavior [13, 38], and water content [39, 40]. Besides the properties of the formulation components, the tableting parameters like compression pressure [41, 42], compression speed [21, 43], punch diameter [44, 45], punch shape [46, 47], dwell time [48, 49], and compacted mass [50] significantly impact the tablet properties.

Process understanding helps in the development of tableting formulations and facilitates process monitoring to ensure product quality. PATs help to deepen such process understanding. Numerous PAT systems are already in use to monitor various process steps. These include, for example, near-infrared spectroscopy for assessing product moisture in wet granulation as well as homogeneity in mixing processes [51], temperature probes for monitoring of fluidized bed drying [52], and mass spectroscopy for monitoring freeze drying processes [53].

In continuous processes, the quality of the finished product and the intermediated can only be monitored using real-time quality control systems. For this purpose, suitable compression analyses may be used once their informative value about the tableting process has been proven. In contrast to the data typically used, such as tablet mass, tablet thickness and maximum compression force, compression analyses provide information about the behavior of the formulation during tableting. No further equipment than the tablet press itself with sufficient instrumentation is needed for applying compression analyses.

A.2 Compression analyses

A.2.1 General aspects

Compression analyses are techniques to describe the behavior of materials under applied pressure. The methods use data recorded during tableting from force and displacement sensors of the tableting press as well as further characteristics of the tablet. The obtained data is used to develop an equation capable of describing the given data in the best way. Typically, those equations focus on specific properties since none of them was found to describe all mechanism involved during tableting so far. Some equations can be used only as out-of-die methods [54, 55], but some can also be performed in-die [56, 57]. Out-of-die means that the characteristics of the tablet are measured after the ejection of the tablet. For in-die methods the characteristics of the tablet under pressure are used. Both approaches deliver information about the critical quality attributes of a tablet and can help to optimize its properties.

In order to obtain the optimum properties of a tablet, excipients are typically added, for example to increase the strength or to accelerate the disintegration time. Up to now, the selection of excipients has often been based on trial and error. This is time-consuming and cost-intensive, as drugs as well as excipients can be expensive and are consumed during the development of suitable formulations. In addition to understanding the process, knowledge of the behavior of the excipients to be used is of essential importance. The characterization of the deformation behavior of a powder provides information about key quality parameters of a tablet, such as the *SF* and the mechanical strength. Both parameters have a strong influence on other tablet properties such as disintegration time and drug release. Figure 2 shows how tablet properties are related to the tableting process. As the compression pressure increases, the *SF* and tensile strength (*TS*) of the tablet usually increase. A higher *SF* means reduced voids into which water can penetrate during disintegration and drug release. This results in longer disintegration times and slower release of the active ingredient. This exemplifies the influence that the tableting process can have on the resulting product properties. It has been described previously that the mechanical properties of a tablet made from the same formulation remain unchanged as long as the *SF* stays the same [17]. This also applies to different presses, so that scale-up processes from research tablet presses to production machines are possible as long as the *SF* is kept constant.

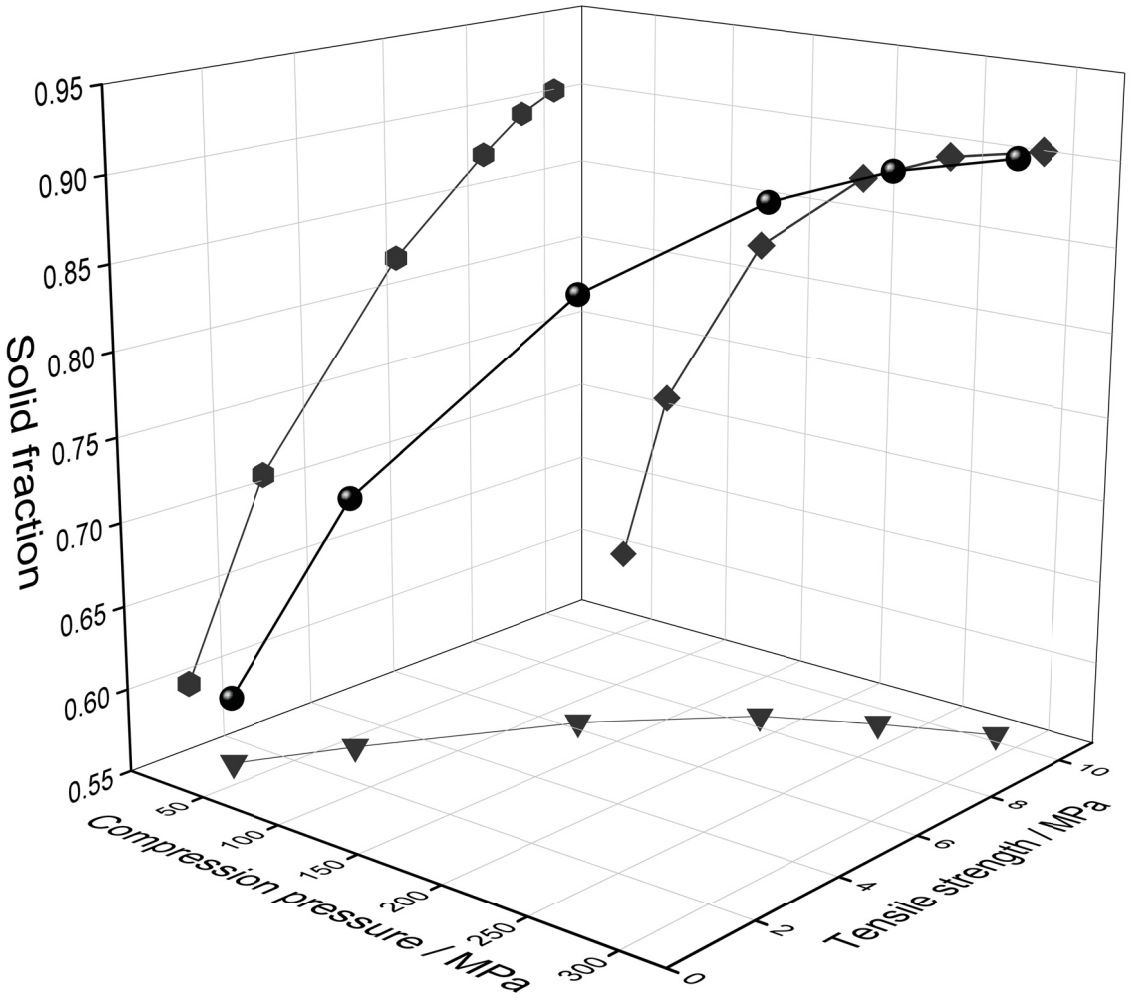

Figure 2. Three-dimensional compression profile

The search for methods to optimize and control the quality of a product within the production line is increasing as CM becomes more prevalent in the pharmaceutical industry. Destructive testing, such as tests of a tablet's breaking force to characterize mechanical strength, is more expensive than non-destructive methods. With non-destructive methods, the product can be saved, resulting in fewer resource loss. Particularly for high-cost drug substances, the avoidance of drug loss, for example, through destructive testing, should be aimed for.

In-die compression analyses can be performed non-destructively. In addition, the initial steps of formulation development do not require the formation of an intact tablet. Many drug substances cannot be compressed into a form-stable tablet that can be analyzed without the addition of the appropriate excipients. Nevertheless, the tableting behavior of such drugs can be characterized by means of in-die analyses. This provides information on the potential problems of the APIs during tableting. This facilitates the

selection of excipients to be added that can compensate for precisely these weak points [58].

When characterizing the deformation behavior of materials by compression analysis, three material properties are of most interest: tabletability, compactibility and compressibility.

A.2.2 Tabletability

Tabletability describes the relationship between the applied compression pressure and the *TS* [1]. In the three-dimensional compression profile (Figure 2), the tabletability is shown with triangles as symbols. With the aid of the tabletability, it is possible to identify which compression pressure is required to obtain a tablet with sufficient mechanical strength. Thus, tabletability is the most relevant property with regard to the manufacturability of the final product and further process steps, since sufficient strength of the tablet must be given for subsequent steps [59].

The course of the tabletability profile differs depending on the material investigated. Brittle materials often show a linear relationship of *TS* with compression pressure over a wide pressure range. Figure 3 illustrates an example tabletability plot for a ductile material with the dashed line representing the linear regression used for the evaluation of tabletability. Ductile materials, oftentimes show three stages within the tabletability plot [60]. In the beginning (Figure 3, part I) no sufficiently strong tablet is formed. If a specific compression pressure is exceeded, the *TS* increases linearly with increasing pressure (Figure 3, part II) [61]. After the linear range, a flattening of *TS* with increasing compression pressure can be seen until a plateau is reached (Figure 3, part III) [62]. Plastic materials show less resistance to deformation. As a result, higher densification is already achieved at lower compression pressure. With increasing compression pressure, the possibility of further compression decreases, since the *SF* is already high and the extent of irreversible deformation is largely exhausted. When the *TS* is decreasing again at increasing compression pressure, this is rooted in overcompression [1].

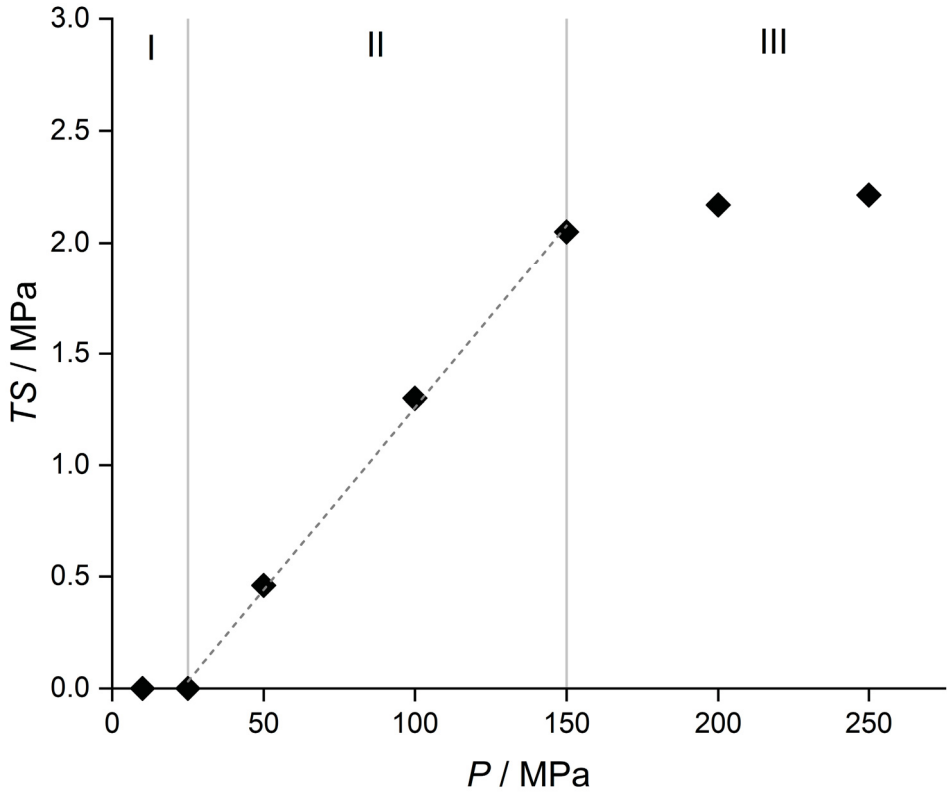

Figure 3. Example tabletability plot for a ductile material

With increasing compression pressure, the elastic deformation increases while the total bonding area after compression remains constant from a certain pressure upwards. This causes higher elastic recovery while the bonding forces are similar. The high elastic recovery causes the formed bonds to rupture and a lower *TS* is obtained at higher pressure [63].

The linear range of the tabletability profile can be described using Equation 1:

$$TS = T * P + D$$

Equation 1

T is the slope of the linear regression, *P* is the applied compression pressure and *D* is the y-axis intercept of the linear regression.

The comparison of tabletability profiles of the compression pressure necessary to reach a defined *TS* or of the slopes of linear regression have been described in literature and are commonly used to characterize tabletability [62-68]. There are other approaches to describe tabletability such as a recently postulated equation by Vreeman and Sun [59]. The advantage of this method is the inclusion of all data points in the analysis. Thus, not only the linear section at the beginning of the profile, but the

whole course is included for the characterization. The disadvantage of this method is that by combining two equations (Ryshkewitch-Duckworth and Kuentz-Leuenberger) a much more complicated method is necessary than in the classical characterization described above. Since linear regression in the *TS-P* plot already leads to a meaningful characterization of tabletability, it is questionable whether this effort is justified. The linear range of the tabletability profile is usually displayed in a pressure range typically used for pharmaceutical application (100-250 MPa [69]). Materials with pronounced plastic deformation (e.g., hydroxypropyl cellulose) show the linear section in the tabletability plot in a much lower range of compression pressure. In this work, Equation 1 was used to characterize the tabletability by comparing the slope of different materials.

In principle, the tabletability cannot be determined using an in-die method, because the *TS* must be measured out-of-die. Since it is one of the most relevant tablet properties in formulation development, it is of great interest to find alternative methods for the determination of tabletability which are in-die and non-destructive.

A.2.3 Compactibility

The compactibility describes the relationship between the *TS* and the *SF* of the tablet [1]. The compactibility is defined as the ability of a powder to be compressed into a tablet of defined strength [70]. In the three-dimensional compression profile (Figure 2), this interrelation is represented by hexagonal symbols. The property of compactibility not only plays an important role in tableting, but is also used, for example, in the construction of roadways and runways [71]. The compactibility combines two tablet properties that have a significant impact on the critical quality attributes of the final product: the mechanical strength of the product and its properties in terms of disintegration and dissolution. Both, the mechanical strength of the product and its properties in terms of disintegration and dissolution are closely related to the porosity and *SF*, respectively. When the *SF* increases, the particles will come closer to each other, which enlarges the potential of bonding forces. The more densified the material gets, and deformation takes place, the larger the contact area becomes and the more contact points between particles will be built. This relationship can be described by the equation of Ryshkewitch-Duckworth [55]. It can be used either as a nonlinear regression of the compactibility profile or as a linear regression after semilogarithmic plotting according to Equation 2. A typical semilogarithmic Ryshkewitch-Duckworth plot

is presented in Figure 4, where the dashed line represents the linear regression according to Equation 2.

$$\ln(TS) = \ln(TS_0) - k_b * \varepsilon$$

Equation 2

TS_0 is the maximum achievable *TS* of the compact at zero porosity, k_b is the bonding capacity of the material and ε is the out-of-die porosity of the tablet.

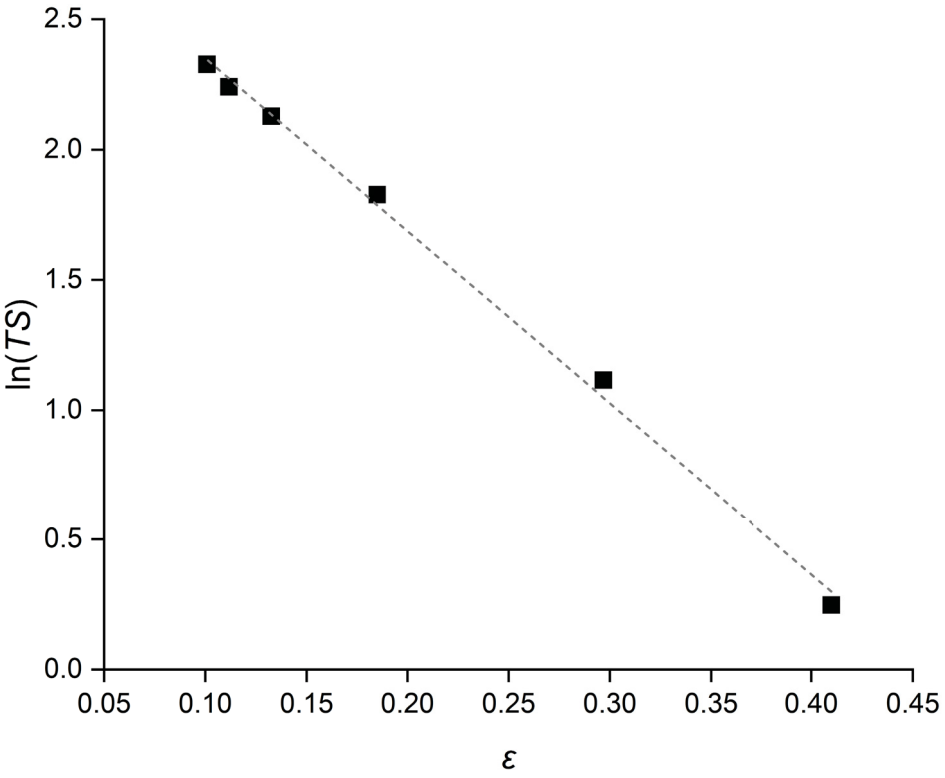

Figure 4. Example Ryshkewitch-Duckworth plot for a brittle material

The Ryshkewitch-Duckworth equation has been widely used in literature to characterize the compactibility of materials [8, 72-76]. The advantage of compactibility is the robustness against changes in compression speed. As long as the same *SF* is reached during tableting, the same mechanical properties of the tablet may be expected [17, 73]. The compactibility is therefore a more reliable property for scale-up processes than the tabletability.

Leuenberger [70] has established an equation that can also be used to describe compactibility. For the calculation of the corresponding parameter, however, the hardness of the tablet is required in addition to the *TS*. An instrument for measuring the hardness is, in contrast to the crushing force tester, a much less common device

in laboratories. Therefore, the more commonly accessible method was preferred in this work. Other works that have dealt with models for describing compactibility [77-79] have considered it as the relationship between the *TS* and the compression pressure. This relationship is defined as tabletability in the present work.

As with any analysis that includes porosity as a variable, the analyses for compactibility determination have been criticized for the fact that the measurement of particle density is an important source of error in the performance of the method [80]. The standard method for the determination of particle density is helium pycnometry. This has been criticized, among other things, for its susceptibility to materials containing water. The particle density of such materials (hydrates, solvates, or materials with a high content of adsorbed water) is overestimated due to the drying of surface associated water during purging cycles with dry helium gas. As a result, a smaller volume is determined than the material actually weighed in. Consequently, an overestimated value for particle density is obtained when materials with high water content are measured [81]. Furthermore, it has been criticized that the particle density is in turn underestimated for materials with closed pores. The effect of erroneous values of particle density on the evaluation of compression analyses has been described in some studies [80, 82, 83]. Different alternative methods have been postulated that can be used for a correct determination of particle density [81, 84]. They use compression data to obtain particle density. In the context of the evaluation of the compression analyses, these methods and the source of error of the particle density measurement shall be investigated in more detail.

The compactibility cannot be determined by the use of an in-die method. As with tabletability, *TS* is required, which can only be determined out-of-die and destructively. As with the characterization of tabletability, only one method was selected to describe compactibility. The focus of this work should be on in-die compression analyses, which in turn would be suitable for real-time monitoring.

A.2.4 Compressibility

Compressibility describes the relationship between the respective porosity (or *SF*) and compression pressure [1]. Compressibility is defined as the ability of a material to reduce its volume under applied pressure. In the three-dimensional compression profile (Figure 2), compressibility is represented as rhombus. The greater the volume

reduction, the more compressible is the material under study. Of the three properties in this section, compressibility has been subject to the most mathematical models to date. In a review, Çelik [85] summarized and explained 19 equations. All of them describe the variation of porosity as a function of compression pressure. In terms of tablet properties in industrial manufacturing, compressibility is of less interest than compactibility or tabletability. Nevertheless, compressibility provides information about the deformation behavior and thus initial conclusions about the properties the resulting tablet may have. In the following, the compression analyses for describing the compressibility, which were used in this work for material characterization, are explained in more detail.

Heckel [86]

Heckel analysis is one of the most commonly used compression analyses to characterize the compressibility of a material [87-89]. The analysis is based on the assumption that the porosity of the powder bed decreases with increasing compression pressure following first order kinetics [86]. The typical curve of a Heckel plot can be divided into three sections (Figure 5). The first section is nonlinear and shows the first curvature of the plot (Figure 5, part I). Mainly rearrangement processes take place in this section, whereby the powder bed is densified with only low force development. Elastic deformation also takes place at this point, but no significant irreversible deformation. After the first curvature a linear section of the plot follows, where irreversible deformation takes place (Figure 5, part II). The deformation can be both plastic and brittle. Elastic deformation also occurs throughout the tableting process, while the extent depends on the material. In this range, a linear regression can be performed for which the Heckel equation (Equation 3) is valid.

$$-\ln(\varepsilon) = \frac{1}{P_y} * P + a$$

Equation 3

ε as porosity of tablet, P_y^{-1} as slope of linear regression and a as y-axis intercept.

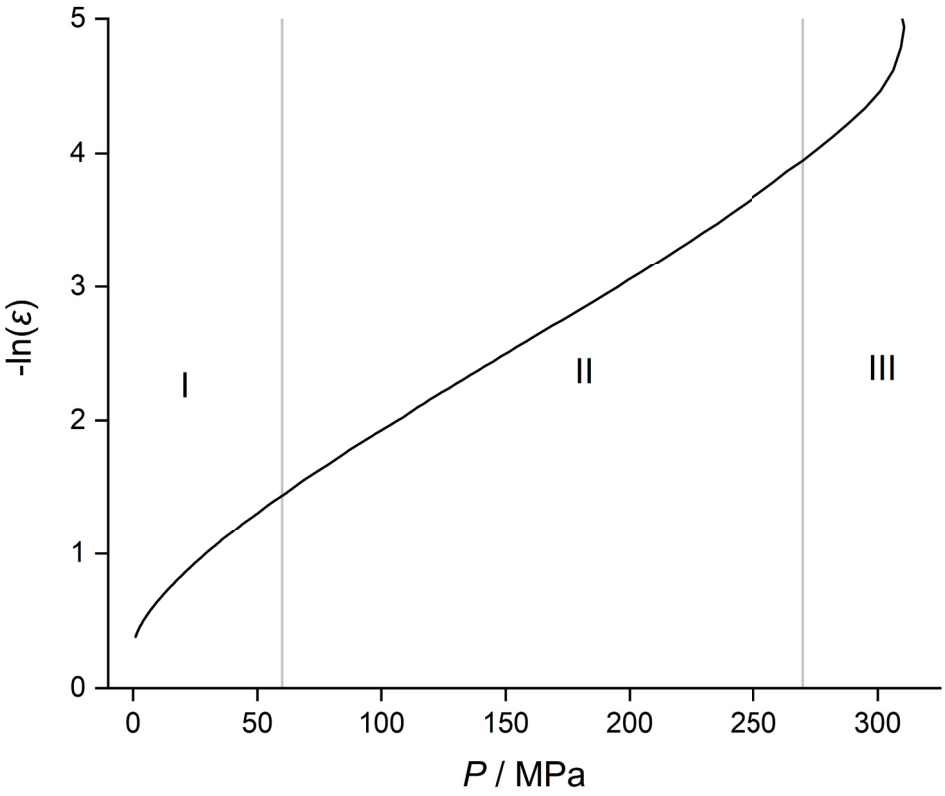

Figure 5. Example in-die Heckel plot for a ductile material

The more deformable a material is, which is reflected in the Heckel plot as a higher volume reduction and thus higher slope, the more compressible it is. From the linear section, the compression parameter P_y is calculated as the reciprocal value of the slope. P_y often serves as a measure of a material's resistance to irreversible deformation and is frequently considered equivalent to plasticity. The lower the yield pressure of a material, the more plastic the material is. The linear section is followed by a second curvature (Figure 5, part III). This occurs when the tablet density approaches the particle density during compaction. In this case, small changes in the volume of the tablet lead to large changes in the logarithmized values of the porosity. The occurrence of the second curvature has often been explained by elastic deformation under pressure [24], resulting in a temporarily higher tablet density compared to out-of-die. Even negative tablet porosities have been reported when performing the in-die Heckel analysis due to the tablet density exceeding the particle density [90]. For this reason, the Heckel analysis has been criticized by Ilkka and Paronen [89] as being inadequate to describe porosity changes in the range close to the particle density. This is only one of the numerous criticisms that were raised since the postulation of the Heckel equation in 1961. The susceptibility of the result to experimental changes was frequently criticized [91], with particular emphasis on

compression pressure [92]. Sonnergaard [93] emphasized the sensitivity with respect to particle density. Furthermore he stated that the reproducibility of Heckel analysis is too low, the method is unsuitable to distinguish between different materials and the linear section is only displayed at pressures above the practical used ones [93]. There have also been other studies claiming that the linear section could not be sufficiently displayed for different materials [94, 95]. Gabaude et al. [82] assessed the Heckel analysis to be useful only under certain conditions. These conditions include well-defined experimental parameters, usage of machines with sufficient accuracy and the availability of reference materials whose deformation behavior is known. In a recent study, on the other hand, it was shown that the yield pressure is a reliable material constant. Vreeman and Sun [96] have demonstrated that a representative value for P_y is given as soon as the second curvature is displayed at sufficiently high compression pressure. Above this pressure, the values of yield pressure were constant. In this study, the linear section could be defined for all used materials. This suggests that correct evaluation is essential for the reliability of the Heckel compression parameter P_y.

Heckel analysis as the most frequently used compression analysis in describing compressibility was used as a reference in this thesis. Furthermore, the robustness of the method was to be investigated comprehensively using materials with known deformation behavior and changing experimental parameters.

Compressibility [97]

The compressibility analysis was described by Johanson in 1965 [97]. The model is based on the observation that the density of the powder bed increases with increasing compression pressure. Double logarithmizing both the powder bed density and the compression pressure results in a linear relationship. The analysis has been performed in literature to describe the compressibility of materials for roll compaction [98, 99]. The density of the powder bed was replaced by the *SF* of the tablet in some studies [100, 101], while the linear relationship remained unchanged. The linearity is given in a certain pressure range, with a plateau of the *SF* being reached at some point as the compression pressure increases [98]. Figure 7 shows the in-die compressibility plot with a wide linear range before flattening of the curve at high compression pressure. The linear range can be described by the following equation:

$$\ln(SF) = K * \ln(P) + A$$

Equation 4

K is the slope of linear regression and represents the compressibility constant and *A* is the intercept of the linear regression.

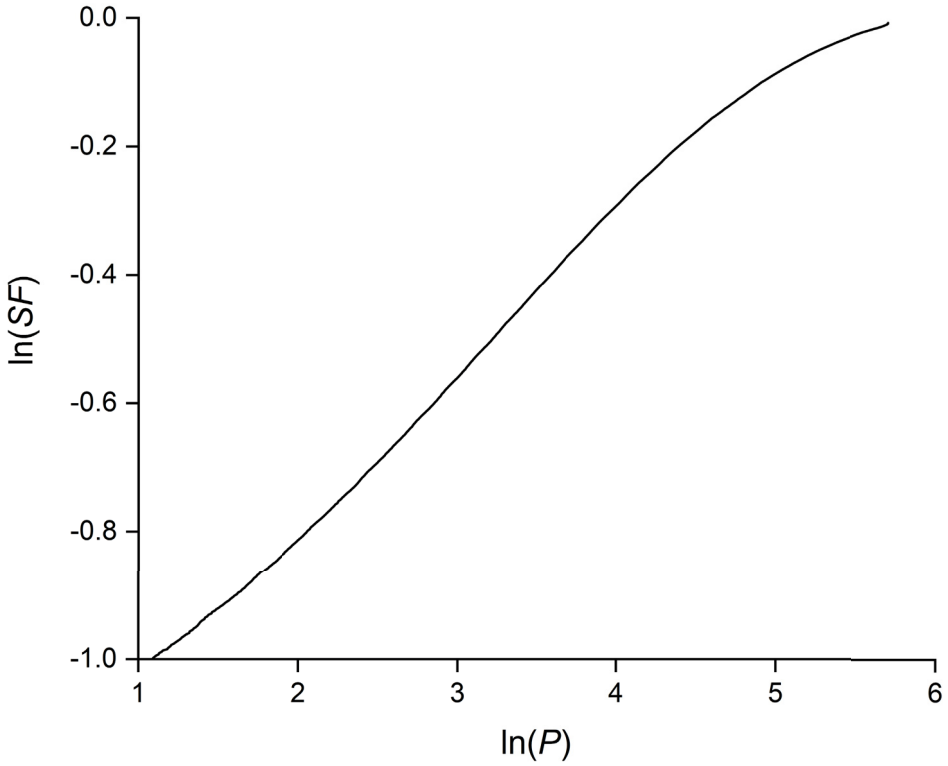

Figure 6. Example in-die compressibility plot for a ductile material

So far, the analysis has been used as a model in roll compaction. It has been criticized that uniaxial compression, as applied for implementation, is not suitable to represent the mechanical processes in roll compaction [102]. However, uniaxial compression is a valuable tool for describing tableting processes. The method was originally postulated as an out-of-die analysis and has primarily been performed as such for materials intended for dry granulation [98-101, 103, 104]. The compression parameter *K* should be investigated in more detail with regard to its suitability for characterizing the compressibility of materials for tableting. Furthermore, the applicability of compressibility analysis as an in-die method should be investigated. The comparison is made using Heckel analysis, which is considered as one of the standard methods for describing compressibility in the literature. In particular, the robustness to influencing parameters such as particle density, compression pressure and others should be investigated and compared with that of Heckel.

Kawakita [105]

The Kawakita analysis is based on the assumption that the tableting process is in equilibrium [106]. This equilibrium manifests itself as a constant volume reduction with increasing compression pressure. The volume reduction is described as the ratio between the volume change under pressure and the initial volume according to Equation 5. The initial volume is the apparent volume of the powder bed inside the die before increasing compression pressure is applied [106].

$$C = \frac{V_0 - V_P}{V_0}$$

Equation 5

C is the relative volume reduction, V_0 is the initial volume of the powder and V_P is the volume under pressure.

Assuming that the relative volume reduction is proportional to the compression pressure, the linear form of the Kawakita equation is obtained:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a}$$

Equation 6

a^{-1} being the slope of the linear course and $(ab)^{-1}$ being the intercept.

Figure *7* illustrates an in-die Kawakita plot. A typical initial curvature is visible at very low compression pressure, followed by the linear region. The extent of the initial curvature depends on the compressed material and results from the fact that *C* rises sharply at the beginning and then flattens out into a plateau [107]. Many compression analyses do not show a linear progression at the beginning of tableting, since the rearrangement processes and the initial elastic deformation of the material cannot be adequately described by those equations. However, the linear region following this initial curve is distinct in the Kawakita plot, so that linear regression can be performed exceptionally well in this section [108]. The method was originally postulated as an out-of-die analysis but has already been successfully applied to in-die data giving comparable results to the out-of-die application [57, 109-111].

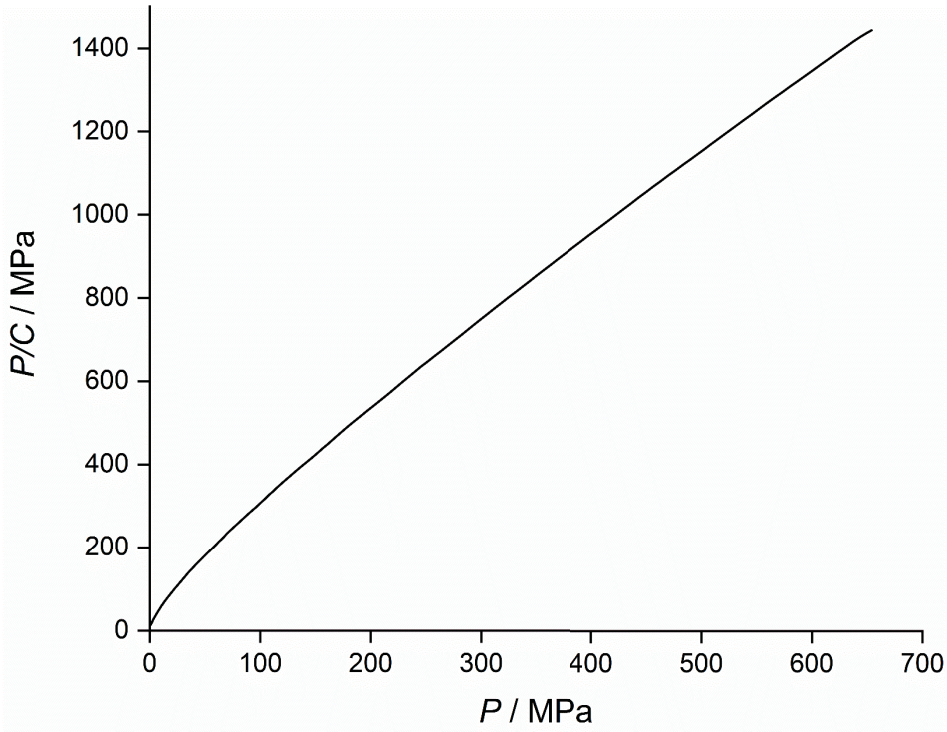

Figure 7. Example in-die Kawakita plot for a ductile material

Three compression parameters are obtained when performing Kawakita analysis: a, b^{-1}, and *ab*. The parameter *a* as the reciprocal value of the slope represents the maximum achievable consolidation of the material [107, 110]. The larger *a* is, the higher the compressibility of a material. High values for *a* are therefore mainly associated with ductile materials. The parameter b^{-1} is the product of the intercept $(ab)^{-1}$ and the parameter *a*. It is intended to provide information about the plasticity of a material [75, 85]. The physical meaning of b^{-1} is described as the initial compressibility of a material or the pressure required to achieve half-maximum compression (*a*/2) [112]. Small b^{-1} values are associated with high compressibility since low pressures are sufficient to achieve high degree of densification. This is typically the case for ductile materials with high compressibility. Furthermore, a proportionality between b^{-1} and the agglomerate strength of single particles was found [113]. This fits the interpretation of this parameter, since agglomerates with low resistance to deformation show small b^{-1} values and thus undergo consolidation more quickly. The parameter *ab* as the reciprocal value of the intercept is described as a rearrangement index [109, 114]. A positive correlation of *ab* with the tabletability capacity from the Power model was found [75]. This makes *ab* a promising parameter that could serve as a replacement for tabletability using an in-die method.

Like the Heckel analysis, Kawakita's equation has also been criticized. Kawakita and Lüdde [106] have emphasized that the equation is particularly suitable for soft and fluffy materials. In addition, they pointed out the problem of determining the initial volume V_0. Three methods are described in literature how to determine V_0. The first method uses the bulk density to calculate V_0 [75, 115]. The problem that arises is that not all materials are suitable for determining the bulk density experimentally. Materials that do not flow freely or have a particularly poor flowability give unrealistic values when measuring the bulk density, since they might have to be sieved into the measuring cylinder. The second method contains the approximation of the initial density by means of nonlinear regression and calculating the corresponding volume [116]. Additional experimental effort is also required for this method, since the particle density of the material is needed for the conversion of density into volume. In the third method, V_0 is extracted from the compression data of the in-die analysis. The initial volume is calculated from the die radius and the distance between the punches when a previously defined force - e.g. 34 N [107] - is exceeded. Neither bulk density nor particle density is needed for this method. This eliminates both additional experimental effort and sources of error due to poor flowability in bulk density determination or high water content in helium pycnometry. The importance of V_0 has already been underlined by Kawakita and Lüdde [106], as the initial volume has a significant influence on the resulting outcomes and especially on the comparability of the results. The parameter b^{-1} is highly dependent on the determination of V_0, while the parameter a is much less affected [107, 117]. In addition to this criticism, insufficient linearity in higher pressure ranges was reported. It was outlined that the method is only suitable for low pressure ranges and low porosities of the compact and thus only applicable for a limited number of materials [118].

Kawakita analysis will be examined in more detail in this thesis as an in-die method. Thereby, especially the points of criticism concerning materials of higher density as well as the insufficient linearity in higher pressure ranges shall be evaluated. The three parameters shall be investigated in more detail to evaluate and confirm the physical meaning described in literature.

Kuentz-Leuenberger [119]

Kuentz and Leuenberger described a modified Heckel equation considering the change in powder properties during the tableting process. They criticized that the

Heckel equation assumes that the powder behaves the same with respect to compressibility during all phases of compaction. They further argued that the powder shows a change in volume reduction under pressure due to the elimination of voids from the compact over time. The equation they established, and the compressibility parameter derived from it, take this change into account. The analysis is postulated as an out-of-die method and performed as a nonlinear regression of the entire pressure range, fitted according to the following equation.

$$P = {C^{-1}}_{KL} * \left[SF_c - SF - (1 - SF_c) * ln\left(\frac{1 - SF}{1 - SF_c}\right)\right]$$

Equation 7

C^{-1}_{KL} is the plasticity parameter and SF_c is the critical *SF* of the powder bed when the material starts to gain rigidity. Above this *SF*, a coherent tablet is formed [120].

Figure 8 shows an in-die Kuentz-Leuenberger plot, where the compression pressure increases exponentially with increasing SF until a constant *SF* is approached. The plasticity parameter C^{-1}_{KL} was reported to show comparable values to P_y [120], and a correlation between the parameters was shown. However, the values for C^{-1}_{KL} were reported to be two to four times higher than the values for yield pressure [119].

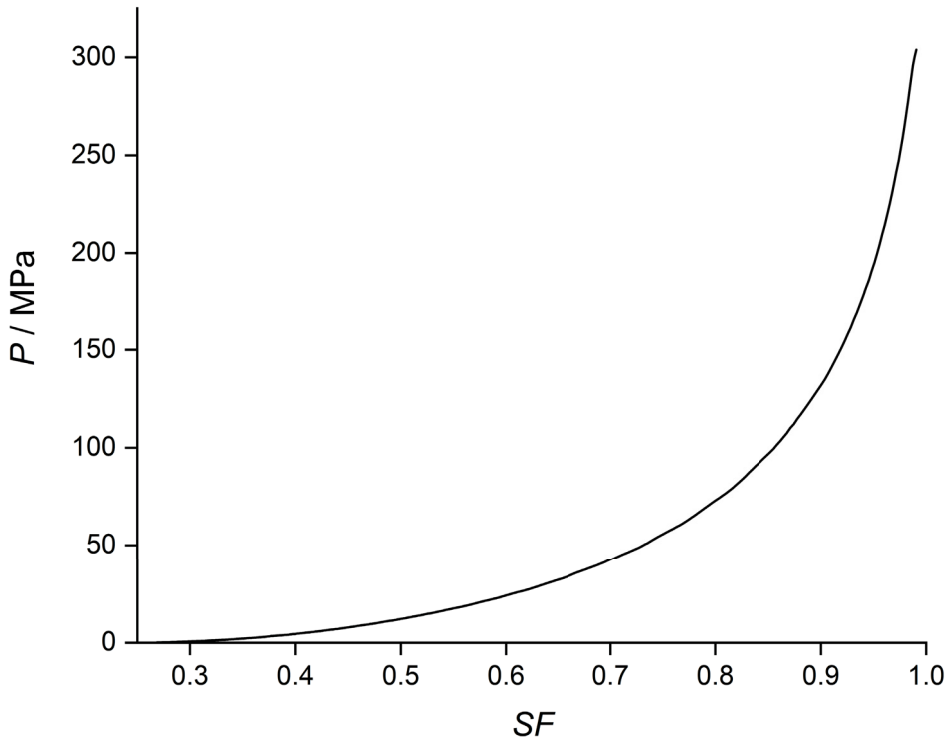

Figure 8. Example in-die Kuentz-Leuenberger plot for a ductile material

The applicability of the equation was demonstrated on the basis of various polymers. However, the authors stated that further investigations on the in-die application and especially on brittle materials are necessary to verify the applicability ranges. The advantage of C^{-1}_{KL} is that, unlike yield pressure, it includes the entire pressure curve and takes into account the elimination of pores. This should make the description of the compaction process by means of the Kuentz-Leuenberger (KL) equation more accurate than with Heckel [121]. However, the method has not found much application so far [120]. Most of the use of this equation is described in the form of the Sun equation [81]. Here, the particle density is also considered as an unknown variable in addition to the two unknown variables of the KL equation. Thus, an alternative determination method for the particle density is to be found by using the compression data. The Sun equation has already been frequently used as an out-of-die method [90, 122-125]. In this work, a further investigation of the KL equation will be made both as an in-die method and in its application to brittle materials.

Walker [126]

Walker was the first to describe the relationship between compression pressure and powder volume in the die in 1923 [127]. He established a linear relationship between the volume reduction - expressed as the reciprocal of the solids content - and the logarithm of the compression pressure. The typical Walker plot (Figure 9) has a strong curvature initially, followed by a descending linear range. At higher compression pressure, a second curvature will follow when the *SF* approaches the maximum achievable value of the material under applied pressure [126]. The evaluation is done by linear regression in the linear section according to the following equation:

$$\frac{V_i}{V_{pd}} = \frac{1}{SF} = -W * \log(P) + V_1$$

Equation 8

V_i is the volume of the powder under applied pressure, V_{pd} is the volume of the powder at zero porosity (which equals the particle density), $-W$ is the slope of the linear region and represents the compression parameter of interest, and V_1 is the intercept of linear regression and gives the reciprocal *SF* at a pressure of 1 MPa [127, 128].

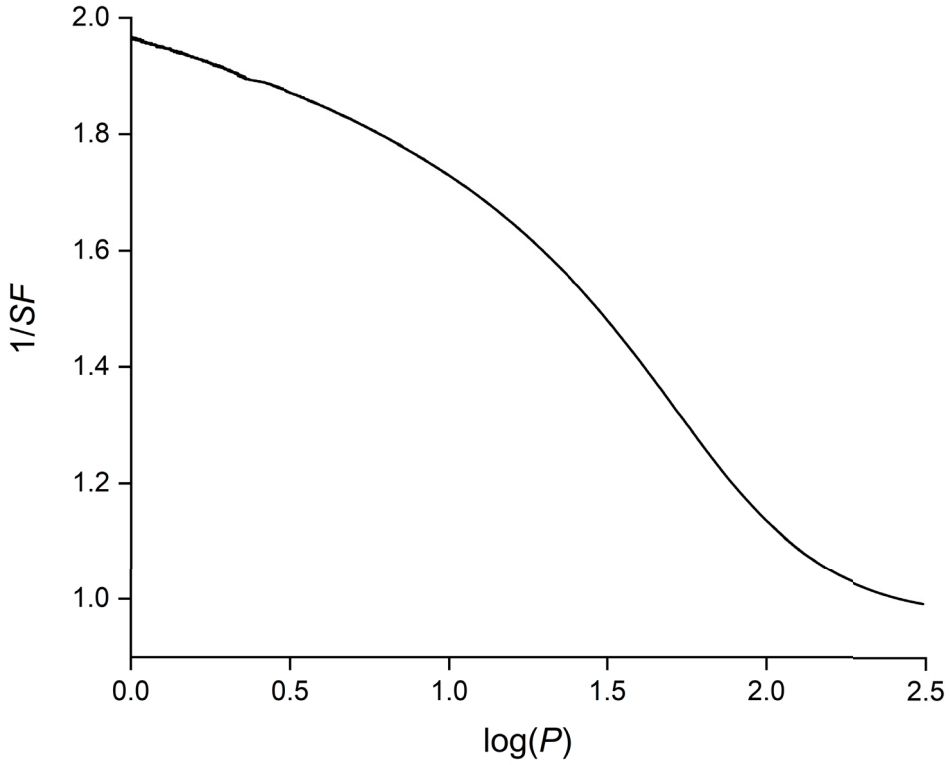

Figure 9. Example in-die Walker plot for a ductile material

Since the first part of the Walker plot shows a distinct bend, the recommendation was made to evaluate the linear regression only above a compression pressure of 10 MPa, which corresponds to a value of 1 on the abscissa in the Walker plot [129]. The compression parameter -*W*, also called Walker coefficient or pressing modulus [130], expresses the volume reduction corresponding to an increase in compression pressure by one decimal power. The higher the value for -*W*, the higher the compressibility of the material [85]. Here, -*W* describes the irreversible volume reduction under pressure or compressibility, which is relevant for the manufacture of pharmaceutical products [130, 131]. Walker analysis has been described as an out-of-die analysis and previously applied as such [128, 132, 133]. Although it was the first model to describe the tableting process, it is much less applied compared to Heckel and Kawakita equations, which were published about 30 years later [120]. Performing Walker analysis requires the same experimental effort as Heckel analysis, since particle density is needed to calculate V_{pd}. In addition, only the out-of-die tablet volumes are required at different compression pressures, as well as for other out-of-die methods. However, it has already been postulated that by modifying Walker's equation, it is possible to work without determining the particle density [132].

A positive correlation between yield pressure and Walker coefficient has been shown [128, 132]. Since Heckel analysis is often used to compare methods, comparative work has also been done for Walker's equation. The literature almost exclusively describes advantages of the Walker analysis over Heckel. The first mentioned advantage is a superior linearity of the Walker plot, often allowing the use of all data points of the out-of-die analysis [128]. The second superiority is the lower sensitivity to influencing parameters like particle density and tableting parameters [132]. In particular, the robustness to compression pressure was highlighted [130]. The yield pressure shows a high sensitivity to increasing compression pressure, while the Walker coefficient seems to be unaffected. This insensitivity is justified with the shape of the curve of the plot. The Walker curve shows the sharper curvature at the beginning, but tends to a linear course with increasing compression pressures [93]. Another advantage cited was better distinguishability between materials. This distinguishability refers both to different materials and to different grades of the same material [93, 128, 130]. The only limitation or inferiority of the Walker analysis to Heckel described is in the characterization of compressibility in powder mixtures containing liquid [133]. This is rather unusual in tablet formulations and therefore not of high relevance in the characterization of tableting behavior.

Although the advantages of Walker analysis are emphasized, the method is comparatively rarely used. In this thesis a closer examination of Walker's equation with focus on the applicability as in-die method should be carried out, since this has not been described so far.

Gurnham [134]

The Gurnham equation was first described in 1946 for the expression of liquids from fibrous materials [134]. Later, the equation has been used for the characterization of pharmaceutical solids during tableting [135]. The equation describes the relationship between porosity and compression pressure, establishing a linear relationship between porosity and the natural logarithm of compression pressure. The course of the Gurnham plot, illustrated in Figure 10, shows a pronounced linearity in the range of the pharmaceutically applied compression pressures. Only at low porosity values deviations from linearity are reported, which are described in nearly every compression analysis [69].

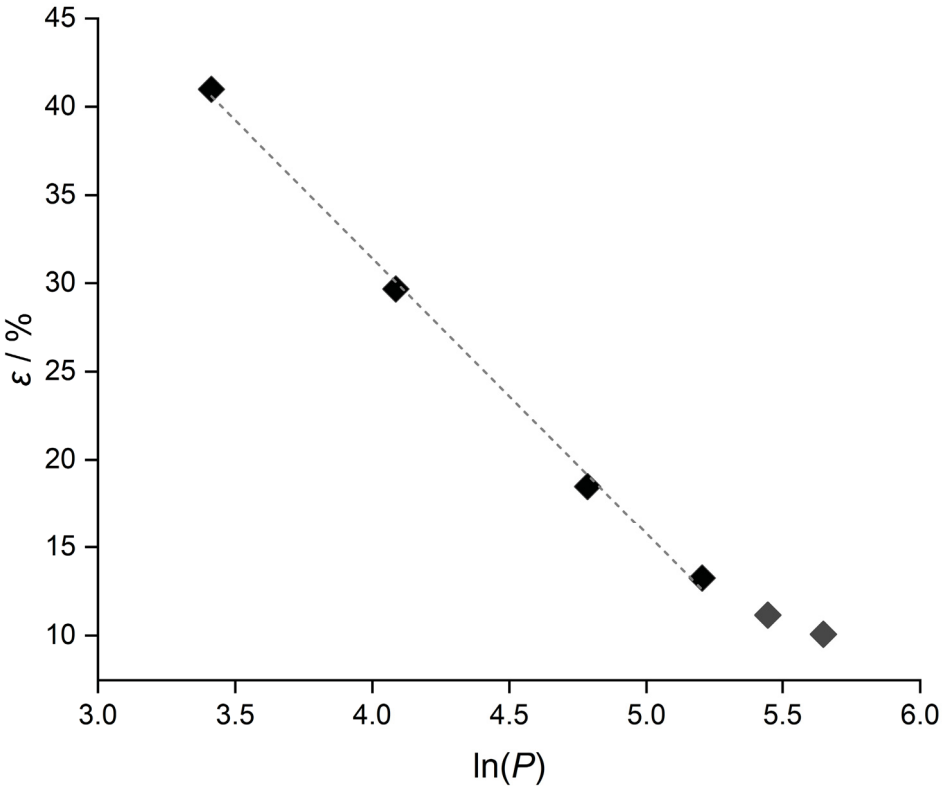

Figure 10. Example out-of-die Gurnham plot for a ductile material

The evaluation is performed as a linear regression of the linear section of the Gurnham plot according to Equation 9:

$$\varepsilon = -g * \ln(P) + d$$

Equation 9

-g is the slope of the linear regression and *d* is the intercept.

The compression parameter *-g* is considered as resistance to compressibility, which means to irreversible deformation due to volume reduction under pressure [75]. The larger the value for *-g*, the more compressible the material under study [135]. Zhao et al. [135] showed a linear relationship for five pharmaceutical materials based on the Gurnham equation. The linear range was given for all materials in the pressure range from 50 to 200 MPa with a high coefficient of determination. The method was postulated as an out-of-die analysis and as such has already been used repeatedly [75, 136-138]. Sonnergaard [139] recently described the successful use of the Gurnham analysis as an in-die method and highlighted the pronounced good fit for out-of-die as well as in-die data. Furthermore, he conducted a comprehensive evaluation of the Gurnham equation and postulated multiple advantages over the Heckel analysis.

He named the good fit of the data in the relevant pressure range as well as the independence from the maximum applied compression pressure. Furthermore, he stated that it is advantageous that the porosity remains untransformed, so that regression parameters are obtained without bias. Despite these advantages, the Gurnham equation has been much less used than the Heckel equation. This is presumably due to the late publication of its applicability for pharmaceutical materials. Dai et al. [75] criticized that there are not sufficient criteria for assessing *-g* yet, so that it is not possible to classify materials according to their compressibility. Further limitations of this method were expressed in the characterization of multi-component mixtures, where the Gurnham equation failed to describe changes in the composition of formulations accurately [137]. Nevertheless, it was concluded in this study that the Gurnham equation is a useful supplement to other compression analyses when characterizing the compressibility of a material.

In this work, the Gurnham equation is applied as a further analysis to characterize compressibility. The focus will be on the applicability as an in-die method.

Other compression analyses

In addition to the compression analyses described and used in this work, there are several other models. The modified Weibull function [140] and its simplification using only two parameters [141], is one of them. Since this equation is based on the shape of the force-time curve, it is extremely susceptible to the compression speed and other factors that influence the force-time curve. Therefore, it is not suitable for scale-up processes. The Shapiro equation [142] is also described in literature. It characterizes the first, non-linear section of the Heckel plot. Mainly rearrangement processes and elastic deformation are considered by this analysis. Since the focus should be on permanent deformation, this analysis was also not included. Furthermore, there is the Cooper-Eaton equation [143], which characterizes the compressibility of a material. This analysis is also widely used but includes four unknown material constants to be determined from a non-linear curve. Since this work was primarily intended to pursue a simple approach for implementation in running processes, the analyses described above in more detail were used instead of the additionally mentioned analyses.

From the required raw data aspect, all mentioned analyses are applicable in-die. However, it must be verified whether the equations established as out-of-die methods

are also suitable for the in-die curves of tableting. The analyses described before were selected because they have been established over a long period of time and, despite criticism of different aspects of each analysis, are among the most commonly used analyses. Should any of the in-die analyses be suitable for deriving properties such as tabletability or compactibility, it would be possible to obtain information about these properties in a non-destructive manner in real-time monitoring. The profound evaluation of the described analyses requires their application to different materials with varying properties.

A.3 Data analysis

A.3.1 Data measurement

Sufficient data generation is required for the successful application of compression analyses for material characterization and process monitoring. All required data have to be measured with sufficient precision and accuracy and then evaluated. In this work, the compaction simulator STYL'One Evo (Medelpharm, France) was used for the tableting experiments. It is a single-station tablet press able to simulate different compression profiles. The STYL'One records the following parameters during a tableting cycle: time, upper punch displacement, lower punch displacement, distance between punches, upper punch force, lower punch force, punches force difference, upper punch linear speed, and lower punch linear speed.

The displacement measurement is tared before the start of the experiments using a calibration block. This taring must be repeated at least every 12 h in the current series of experiments to ensure the accuracy of the displacement measurement. The displacement measurement is specified to the nearest 0.1 µm in the reporting of the tableting cycle, the accuracy is specified as 1 µm. [96]. In addition, a correction of the displacement measurement is made by the STYL'One software (Analis). For this purpose, the deformation of a new punch is measured when it is added to the software. It is done by moving the punches directly onto each other without filling the die and an increasing force is applied. The deformation of the punches is measured at the respective force. This deformation is used for a corrective calculation when processing the data of a tableting cycle in order to obtain the deformation of the material without the influence of the punch deformation.

The force of the STYL'One can be set from 0.5 kN to 51 kN, which is the security limit of the machine. The force is measured with the aid of two different instrumentations. Piezo crystals are installed for the force range below 5 kN, where greater sensitivity of the measuring system is required. Piezo crystals are quartz crystals carrying electrical charges at the surface. The measuring principle of piezo crystals is based on a displacement of these electrical charges when a force is applied to the crystal. The shifts of the electrical charge are proportional to the force applied [144]. Advantages of these piezoelectric force transducers are that they have high measurement sensitivity, reacting with a resonant frequency of above 10 kHz [145], and the linearity between the electric charge displacement and force application is good. In addition, they are insensitive to temperature. The disadvantage is that they have to be placed in cavities, which is not easy to implement in all tablet presses.

The force range above 5 kN is covered by strain gauges. The measuring principle of these strain gauges is that the electrical resistance in the wire changes proportionally to the change in length [145]. If the wire is subjected to a force, it changes in length and diameter. If the length decreases and the diameter increases, the electrical resistance decreases and vice versa. Advantages of strain gauges are that they are easy to attach and less expensive than piezo crystals. In addition, they exhibit high robustness over a wide pressure range. Disadvantages are that there is a risk of irreversible change and not all machine parts deform linearly. They are also temperature sensitive and exhibit some electrical noise. To compensate for the higher temperature sensitivity of this measuring method and the electrical noise, two measuring strips are usually bridged to form a Wheatstone bridge for signal balancing [144]. This ensures that the measured voltage is zero when no force is applied and that a voltage is only measurable when force is applied. In addition, the bridge coupling ensures that the measurement results do not change, even at different temperatures.

The force measurement of the STYL'One is given in the reporting file within 1 N, the accuracy is specified as 10 N [146]. The compaction simulator is calibrated each year to ensure the correctness of the measured values of both force and displacement sensors. The acquisition frequency of the STYL'One can be set to a maximum value of 10 kHz, which was used for the experiments to ensure sufficiently high data provision. Precision was checked by the agreement of the individual curves of the experimental replicates (n = 3 and n = 10, respectively). Figure 11 exemplarily

illustrates three single curves of force-displacement measurements of the STYL'One. A high degree of agreement between the curves was observed. Therefore, the precision was considered sufficiently high. An automatic tablet tester (SmartTest50, Sotax AG, Switzerland) was used to characterize the tablets out-of-die. The parameters measured were tablet mass, diameter, height, and crushing force.

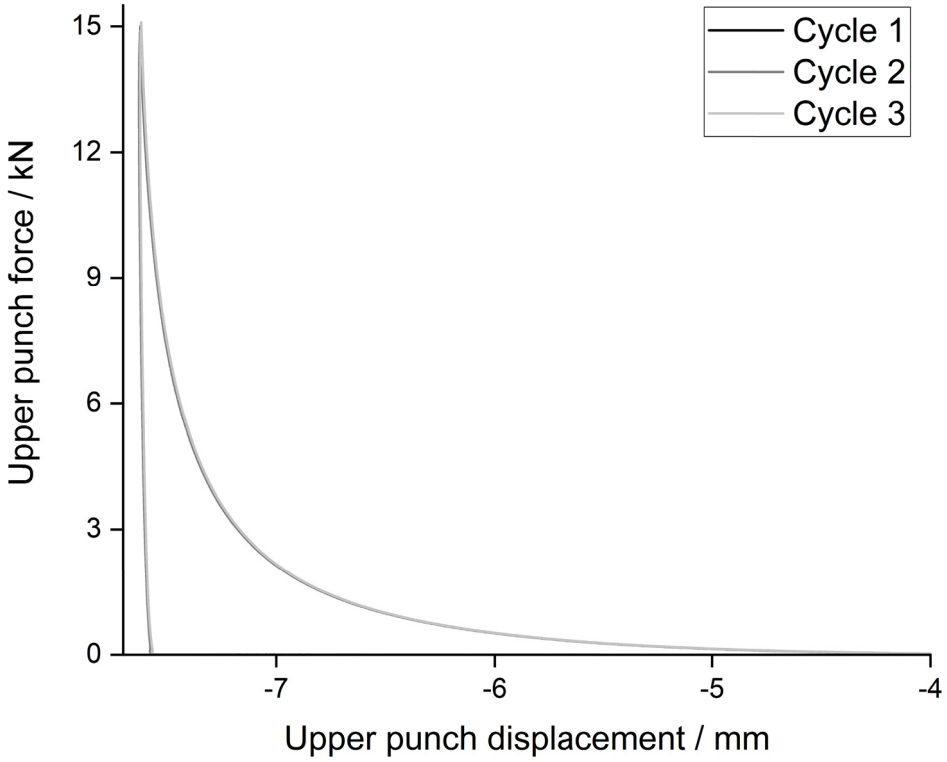

Figure 11. Example force-displacement plot with single curves of three tableting cycles

The influence of compression speed on tablet properties and compression analyses has been described frequently [21, 147, 148]. For this reason, the V-shape was selected as compression profile. The V-shape profile is characterized by a symmetric movement and a constant speed of both punches. This speed is adjustable in steps of 1 mm*s^{-1} and can be used from 1-300 mm*s^{-1}. Figure 12 shows an example of the course of a tableting cycle using the V-shape profile. At the beginning, the lower punch moves to zero position and then goes to the set dosage height (Figure 12, part I). The dosage height is held for a specific time (depending on the presetting of the tableting cycle) until the die is filled (Figure 12, part II). After the die filling is complete, both punches move downwards (Figure 12, part III). The upper punch moves to about 2 mm below the upper edge of the die and the lower punch moves back to zero position. Without this movement, the powder would be pressed out of the die when the upper punch enters the die. The lower punch starts moving first until the deaeration thickness

of the tablet is reached (Figure 12, part IV). This is defined as the height of the powder bed or the tablet, from which a further volume reduction leads to a measurable force, which exceeds the basic noise of the force measurement. From the deaeration thickness, both punches move at a constant, previously set speed until the specified thickness of the tablet is reached inside the die (Figure 12, part V). The punches then move a defined distance apart. This is followed by the ejection of the tablet and thus the completion of a tableting cycle (Figure 12, part VI).

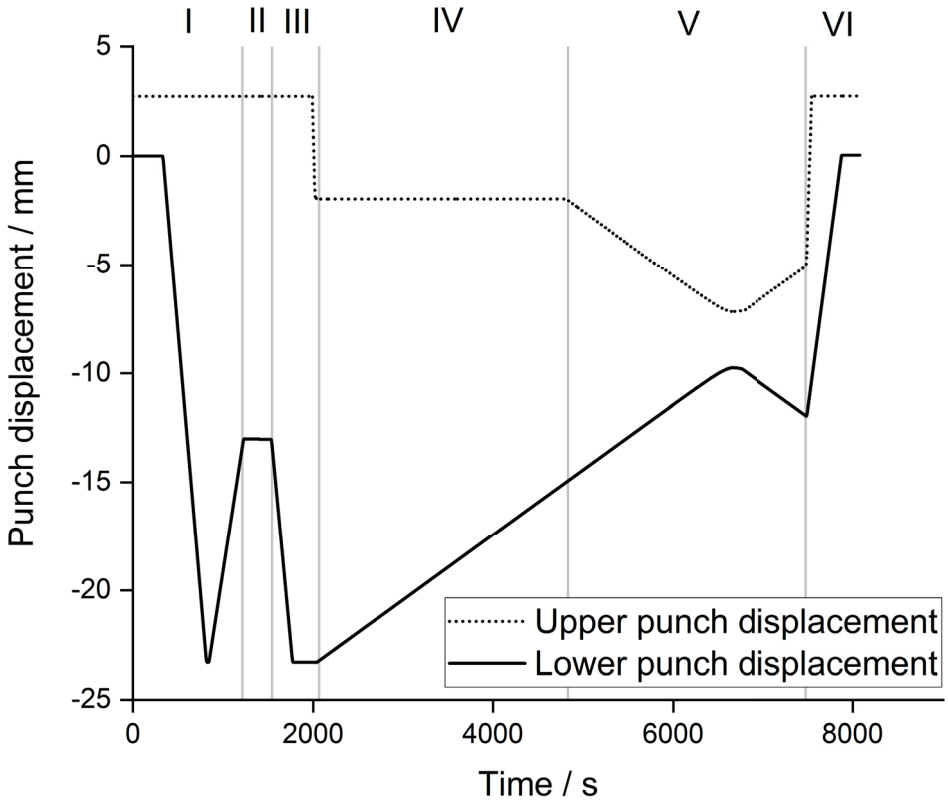

Figure 12. Punch displacement during compression of one tablet cycle

A.3.2 Data processing and evaluation

For the out-of-die compression analyses, the overview files of the STYL'One software and the SmartTest50 results were used. The following parameters were extracted from the overview file of the STYL'One software for each tableting cycle: maximum compression pressure of upper and lower punch, tablet thickness at maximum pressure, minimal tablet thickness, deaeration thickness, in-die recovery thickness, and ejection force. The lower punch compression pressure was used for evaluation of tabletability, Ryshkewitch-Duckworth, and Gurnham. The tablet mass and geometry of the SmartTest50 file as well as the particle density were used to calculate the out-of-die tablet *SF* or porosity respectively. The out-of-die compression analyses were

evaluated manually by applying linear regression to the data points that showed the highest coefficient of determination without systematic deviation.

Manual evaluation of the in-die compression analyses would have taken too long for the variety of data, so automatic evaluation was performed using an in-house written script based on Python source code. The execution of the script was performed using PyCharm (edition 2022.1.3) as a development environment with Python interpreter 3.7.

Before exporting the reporting csv files from STYL'One software, the reporting of punch forces was automatically transferred into the punch pressure. Both the tableting data as csv files from the STYL'One software and the csv files from the SmartTest50 were read into the script. Only the tablet mass was extracted from the SmartTest50 files. From the tableting data the distance between punches, the upper punch pressure and the lower punch pressure were loaded into the script. In addition, the punch diameter and the particle density of the respective material were loaded from an Excel file. The particle density was needed for calculation of the in-die porosity or *SF* of the tablet. For the evaluation of the tablet data only the actual compression of the tablet cycle was used (Figure 12, part V). The irrelevant sections of each tablet cycle were rejected. This was done by determining the noise of the force measurement as the mean value and defining the point from which the mean value plus one standard deviation was exceeded as the start of compression.

The distance between punches values were used to calculate the in-die tablet volume, porosity, or *SF* for the respective analyses. The following part shortly describes the evaluation of the corresponding compression analyses performed using the python script.

Heckel, Compressibility, and Walker

The same data processing was used for Heckel, Compressibility, and Walker analysis. To find the linear range for the regression, the data were divided into interpolation steps. Then a Savgol filter was used for the data with the window length set to one third of the interpolation steps. This was done to smooth the data so that small fluctuations in the measurement values would not affect the finding of the linear regression.

A linear regression was drawn over the entire data range up to the maximum compression pressure. Then, for each data point, the difference between the linear regression and the actual curve was calculated. At the point where the difference was the highest, the regression was started. This point approximately corresponds to the end of the first curve in the corresponding plot. A fitting loop was then performed to include as many interpolation steps of the data as possible and to obtain an adjusted coefficient of determination (adj. R^2) as high as possible. The target adj. R^2 was set to 0.999. For the fitting loop, interpolation steps from above the start point of linear regression was added and adj. R^2 was calculated in each loop. An additional side condition of the fitting loop was that at least 30 % of the data points of the compression had to be included in the linear regression.

All linear regressions were performed using the linregress function of scipy.stats. Output parameters of all executed evaluations of linear regression (Heckel, Compressibility, Kawakita, and Walker) were the slope of linear regression, the intercept of linear regression, and the adj. R^2.

Kawakita

Since the Kawakita plot has a pronounced linear range over almost the entire pressure range, a simpler processing of the data was performed here. Linear regression was first performed from a pressure of 10 MPa to the maximum pressure of the respective tablet cycle. If the adj. R^2 was greater than 0.999, the linear regression was adopted. If the adj. R^2 was less than 0.999, an interpolation step was removed at the beginning of the plot and the linear regression was performed again until an adj. R^2 greater than 0.999 resulted. Data points were only removed at the beginning, since the largest deviation of the linear range occurs in the first part of the Kawakita plot.

Kuentz-Leuenberger

For the nonlinear regression of the Kuentz-Leuenberger plot, the whole data of compression were used without preselection of a specific range. The nonlinear regression was done using the curve_fit function from scipy.optimize. Output parameters were the plasticity parameter C^{-1}, SF_c, and the adjusted coefficient of determination of the nonlinear regression.

A.4 Selection of excipients

A.4.1 General aspects

The properties of the starting materials influence the tablet characteristics. The influence of particle morphology, particle size and the manufacturing method on the tablet properties has frequently been studied [6, 64, 147, 149-153]. For the systematic investigation of different compression analyses, twelve pharmaceutically established excipients were used in this work. These were selected because they exhibit significantly different deformation behavior compared to each other. In addition, different grades of three substances were used to further investigate the influence of material properties such as morphology, manufacturing method and particle size on the compression analyses. The selected excipients for experiments are shortly introduced to provide an overview of their manufacturing method, powder properties and deformation behavior as described in literature.

A.4.2 α-Lactose monohydrate

Lactose is a disaccharide of D-galactose and D-glucose, which are β-1,4 glycosidic linked. It is derived from milk and is inexpensive to acquire because it can be obtained from whey, which is often a waste product [64]. There are three polymorphs of lactose which are relevant for pharmaceutical application: α-lactose monohydrate, β-lactose and anhydrous α-lactose [154]. α-lactose monohydrate is widely used as a filler in tablets and other oral, solid dosage forms [132]. Depending on the manufacturing process of the lactose grade, the powder is used for different applications. Milled lactose grades are mainly used for granulation processes, as the sharp-edged particles (Figure 13) have cohesive properties and the small particles

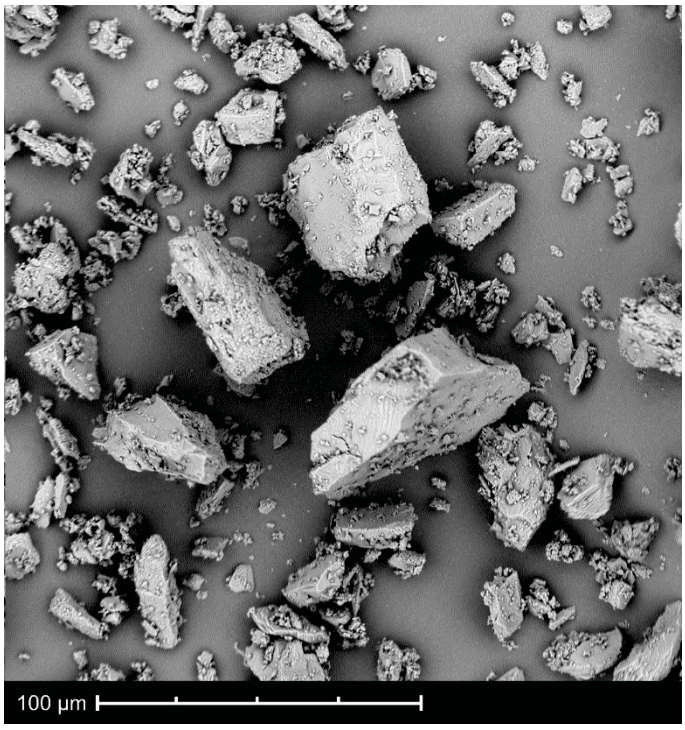

Figure 13. SEM image of GranuLac® 230

provide high specific surface area. These provide fresh surfaces for the formation of strong bonds during granulation [155]. Milled lactose is also suitable for tableting but does not have sufficient flowability for DC. Different manufacturing techniques were used to optimize lactose for DC. Especially the spray-dried and spray-agglomerated grades are widely utilized.

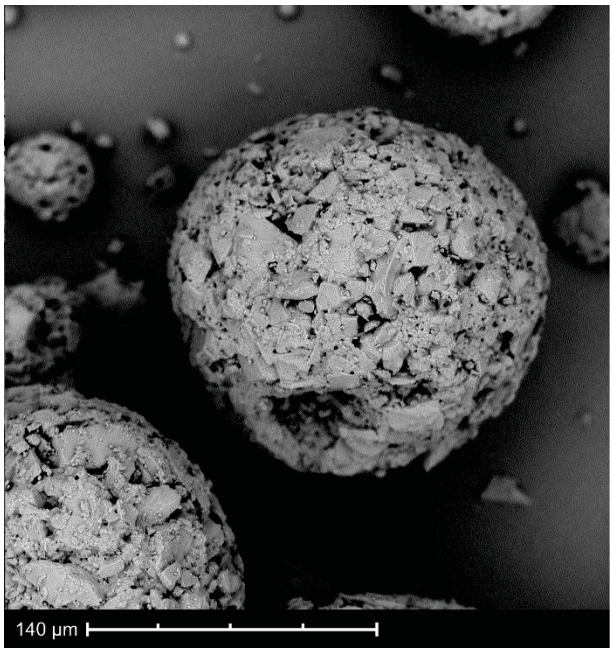

Figure 154. SEM image of FlowLac® 100

Spray-dried lactose is a mixture of crystalline lactose (α-lactose monohydrate) and amorphous lactose (1:1 mixture of α-lactose monohydrate and β-lactose) [154]. The proportion of amorphous lactose varies depending on the manufacturing method. If an ethanolic suspension is used, an entirely crystalline product is obtained, while the use of an aqueous solution leads to an almost completely amorphous product. The production of commercially available spray-dried lactose is usually done by using an aqueous suspension. The proportion of amorphous lactose in the available products is typically between 10-20% [154]. During storage of the spray-dried lactose, the amorphous particles can be converted into crystalline form, so that, depending on the storage conditions, pure crystalline lactose results. The particles obtained from spray-drying are of spherical shape (Figure 14), which provides excellent flowability. Due to its hollow spheres and thus the potential for eased densification, spray-dried lactose has an advantageous compaction capacity [156]. The amorphous content significantly affects the deformation behavior of the lactose particles. The bigger the amorphous fraction the more

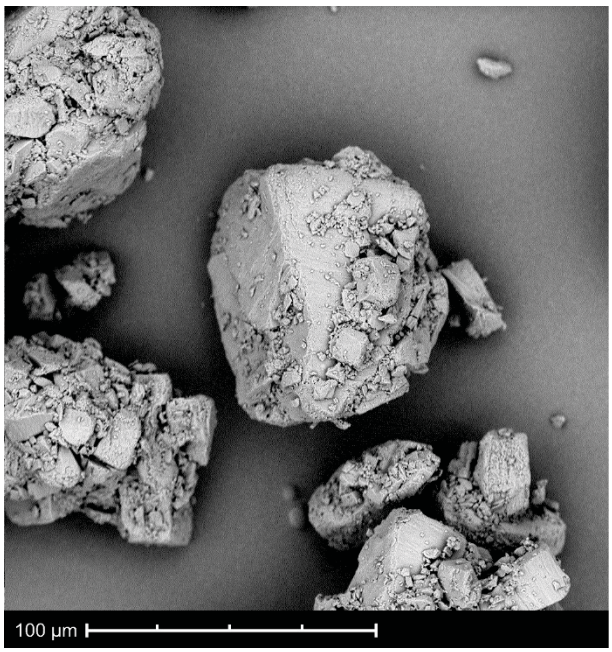

Figure 145. SEM image of Tablettose® 80

plastic deformation the material will show. Nevertheless, the crystalline portion predominates in the grades used, so that the deformation behavior can be classified as predominantly brittle.

Spray agglomerated lactose grades are produced by spraying water onto milled lactose crystals to agglomerate them into secondary particles. This increases the flowability, as larger particles with higher gravitational force are formed (Figure 15). At the same time, the secondary particles exhibit the good compressibility of the milled lactose [157]. Tablets of high mechanical strength are obtained using those agglomerated qualities. The agglomerates fragment into smaller particles with little force required. The smaller particles provide large bonding areas increasing the potential for bonding forces.

Different α-lactose monohydrate grades were used in this work to investigate the influence of the manufacturing method. GranuLac® 230 (Meggle, Germany) was chosen as finely milled grade with a mean particle size (x_{50}) of 22.4 µm. FlowLac® 100 (Meggle, Germany) was used as spray-dried lactose (x_{50} = 112.2 µm) and Tablettose® 80 (Meggle, Germany) as spray-agglomerated lactose (x_{50} = 124.0 µm).

A.4.3 Microcrystalline cellulose

Microcrystalline cellulose (MCC) consists of β-1,4 glycosidic linked D-glucose units. MCC is produced by acid hydrolysis of α-cellulose followed by purification [158]. The hydrolysis mainly takes place in the amorphous parts of the cellulose chains, which on the one hand reduces the average degree of polymerization and on the other hand increases the crystallinity index. The hydroxyl groups of the glucose units provide high potential for hydrogen bonding and high hydrophilicity. The crystalline domains (crystallites) are arranged in linear polymer chains, which are held together by van der Waals forces and hydrogen bonds [158]. MCC is known for being chemically inert and

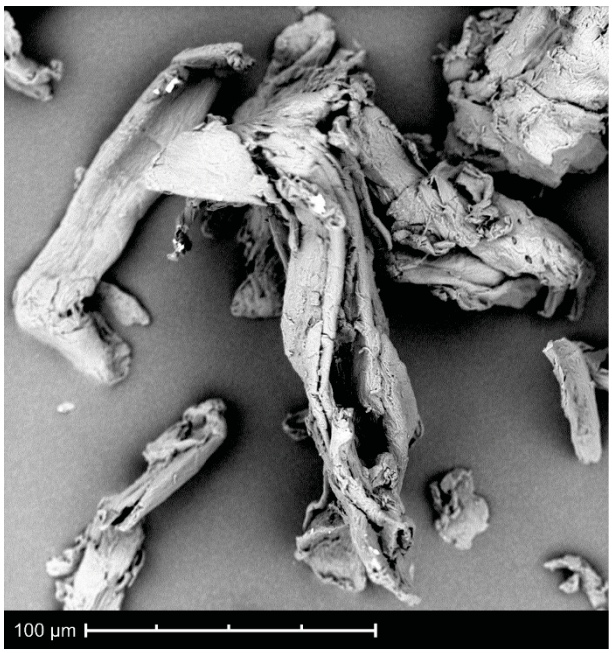

Figure 16. SEM image of Vivapur® 102

compatible with a wide range of APIs [159]. It has been described as one of the first effective dry binders [5] and also produces extraordinarily strong tablets compared to other dry binders [160]. The strength of the MCC tablets is achieved by the formation of hydrogen bonds [161].

Due to the pronounced plastic deformation behavior of MCC, large bonding areas are created. This allows the powder particles to come close to each other which facilitates the formation of hydrogen bonds [19]. MCC already shows a high compactibility at low compression pressures, which, however, is highly dependent on the water content of the powder [162]. The advantageous properties in tableting behavior make MCC an effective dry binder for various formulations. The fibrous shape of MCC particles, visible in the scanning electron microscopy (SEM) image (Figure 16), are causing disadvantages regarding the flowability. However, this weakness can be compensated by combining MCC with well-flowing materials in a formulation [159]. MCC is one of the most widely used dry binders and tableting excipients. In this study Vivapur® 102 (x_{50} = 102.3 µm, JRS Pharma, Germany) was used as a MCC grade to represent materials with predominantly plastic deformation behavior in the evaluation of compression analyses.

A.4.4 Dibasic calcium phosphate anhydrate

Calcium phosphate is used in three different types in pharmaceutical production: as dibasic calcium phosphate anhydrate (DCP), as dibasic calcium phosphate dihydrate and as hydroxyapatite [154]. Dibasic calcium phosphate is prepared by a stoichiometric reaction of phosphoric acid with calcium hydroxide in an aqueous suspension. During subsequent drying, the temperature and duration of the drying process determine whether the dihydrate or anhydrate is formed [154]. The anhydrate can also be manufactured by the use of spray-drying. Both, dihydrate and anhydrate, are used as fillers and binders in the manufacture of tablets and in granulation processes

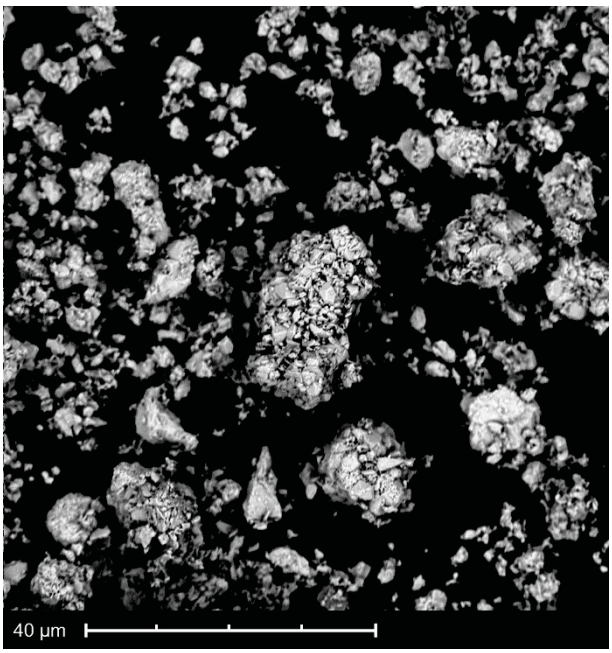

Figure 17. SEM image of DiCaFos® A7

because of their low cost, chemical purity and only few incompatibilities with APIs [163]. The milled grades are preferred for dry and wet granulation, since the small particles provide a large surface area (Figure 17). The finer grades are unsuitable for tableting, especially DC, due to their cohesiveness and the associated insufficient flowability.

For tableting, coarser grades are available (Figure 18, Figure 19) and in particular the spray-dried grades, which provide excellent flowability due to their higher gravitational force and spherical shape (Figure 20). In the case of dihydrate, the potential release of the water molecule must be taken into account, which may lead to a change in the critical quality parameters of the product [163]. Therefore, the use of the anhydrate is advantageous. The anhydrate grades provide slightly lower tensile strength values than the dihydrate grades. However, the alternative production by spray-drying can circumvent this problem.

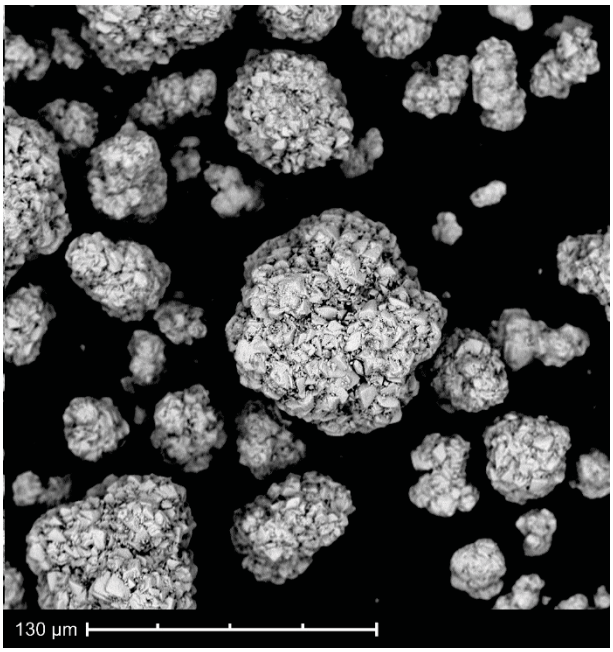

Figure 18. SEM image of DiCaFos® A60

Spray-dried DCP grades show significantly higher tablet strength than all other grades [164], despite their rather pronounced elastic recovery [165]. The spray-dried particles exhibit higher porosity and surface area, providing larger bonding areas and more contact points between the particles.

DCP exhibits a pronounced brittle deformation behavior with high resistance to deformation [166]. While the secondary particles of agglomerated or spray-dried DCP show a low P_f, the primary particles exhibit a pronounced high P_f. The low P_f of the secondary

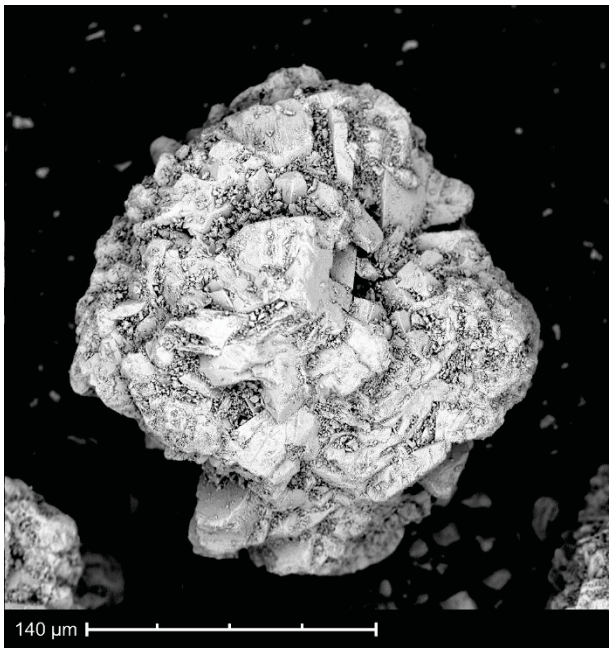

Figure 19. SEM image of DiCaFos® A150

particles can easily be exceeded during compression and the particles fragment into the primary particles.

By that, fresh surfaces are created, which provide high potential for interactions between particles. This property makes the material insensitive to the effects of compression speed and lubricants [159] because the surfaces created are free of lubricant. This eases the scale-up process on production machines. The resulting tablets show a high porosity and hydrophilic surface. This facilitates water penetration and promotes disintegration, which is driven by disintegrants. DCP is abrasive and shows high ejection forces after compression so the use of lubricants is necessary [154].

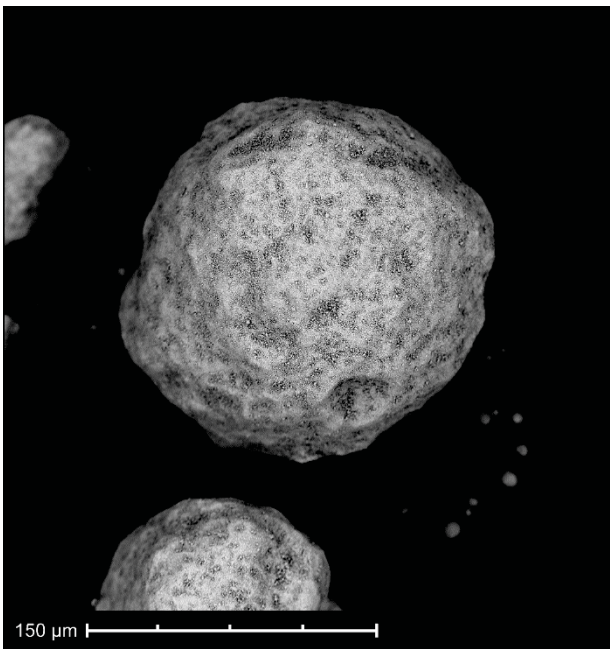

Figure 20. SEM image of Fujicalin®

Here, on the one hand, three DCP grades of the same production method but different particle size were used to investigate the influence of particle size on compression analyses. One finely milled DCP grade (DiCaFos® A7 (x_{50} = 10.3 µm, Figure 17), Budenheim, Germany) and two coarser grades (DiCaFos® A60 (x_{50} = 62.0 µm, Figure 18) and DiCaFos® A150 (x_{50} = 154.2 µm, Figure 19), Budenheim, Germany) were chosen for this purpose. On the other hand, a spray-dried DCP (Fujicalin® (x_{50} = 84.9 µm, Figure 20), Fuji Chemical Industries Co., Ltd., Japan) was used to investigate the manufacturing method and its influence on the tableting properties. Fujicalin® shows distinctly small primary particles and high porosity. In the evaluation of the compression analyses, the DCP grades serve as examples of pronounced brittle deformation behavior with high resistance to deformation.

A.4.5 Maize starch

Starch is a naturally occurring carbohydrate consisting of glucose units. The main components in starch are amylose and amylopectin. Amylose is a linear chain composed of α-1,4 glycosidically linked D-glucose units. Amylopectin is α-1,4 glycosidic-linked D-glucose, with α-1,6 glycosidic linkages intercalating, resulting in

branching of the chains. Starch is found in several plants (e.g., maize, rice, and potatoes), with maize starch being the most commonly used type of starch in tablet formulation [167]. It is produced by macerating maize in water followed by crushing the raw material and washing out the starch. The starch is then separated from the water-soluble components and dried [168]. Maize starch is used as a filler, binder and disintegrant in tablet formulations. Due to its low particle size (Figure 21) and high cohesiveness, it has poor flowability and is therefore not suitable for DC. Since it is inexpensive to obtain in large quantities and inert, modifications of native maize starch have been made to compensate for the poor flowability and optimize its properties for DC. These include pregelatinized maize starches.

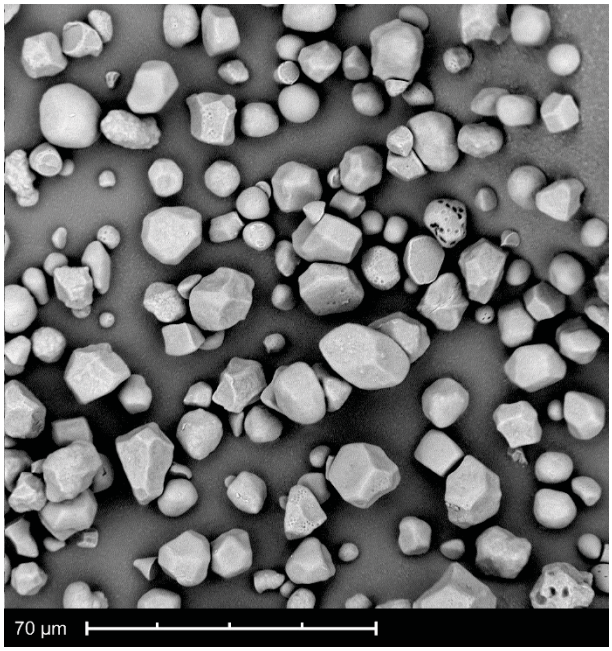

Figure 21. SEM image of C☆ PharmGel

Pregelatinized maize starches are obtained by heating a maize suspension. Native starch is semicrystalline with a crystallinity typically between 15-45 % [169]. Native maize starch is insoluble in cold water. When the temperature is increased, water penetrates into the amorphous regions and leads to an irreversible hydrolysis of the bonds between amylose and amylopectin. Depending on the amount of bonding, which is broken during the pregelatinizing, a partially or completely pregelatinized starch is obtained [170]. During the gelatinization, the semicrystalline starch transforms into a fully amorphous material [171]. Starch® 1500 was used as the pregelatinized maize starch, which will be referred to as MSP in the following. MSP

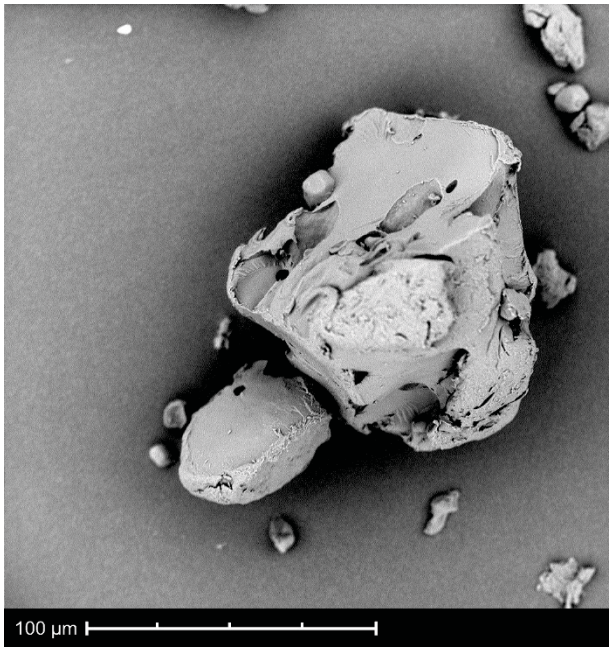

Figure 22. SEM image of Starch® 1500

has a larger particle size than native maize starch, which improves the flowability. It contains 5% free amylose, 15% free amylopectin and 80% unmodified starch [159]. Small starch particles are depicted next to bigger particles of MSP in Figure 22. Like native maize starch, MSP has a high proportion of elastic deformation. However, the higher proportion of free amylopectin ensures better binding capacity [13]. It has been widely used in DC and shows a pronounced densification behavior with low resistance to deformation [36]. The deformation behavior of MSP is described as being highly dependent on the compression speed and especially on the dwell time [172, 173]. The amount of plastic deformation, which also occurs for MSP, increases with decreasing compression speed resulting in less elastic deformation and causing stronger tablets [13].

In the present work, one quality of native maize starch (C☆ PharmGel (x_{50} = 13.3 µm), Cargill B.V., Netherlands) and one quality of partially pregelatinized maize starch (Starch® 1500 (x_{50} = 72.4 µm), Colorcon, United Kingdom) were selected. A comparison of native and partially pregelatinized maize starch should be drawn. Furthermore, these materials represent a predominantly elastic deformation behavior with pronounced fast elastic recovery in the evaluation of the compression analyses.

A.4.6 Carrageenan

Carrageenans are naturally occurring polysaccharides obtained from red seaweed by hot extraction followed by purification, evaporation, precipitation and drying [174]. Chemically, they consist mainly of sulfate esters of galactose and 2,6-anhydrogalactose joined by alternating α-1,3 und β-1,4 glycosidic linkages [175]. Three different types of carrageenans are used in the pharmaceutical field: κ-, ι-, and λ-carrageenan [176].

Figure 23. SEM image of Gelcarin® GP 911 NF

Due to their fibrous particle shape (Figure 23), carrageenans show rather insufficient flowability. In this thesis κ-carrageenan

(Gelcarin® GP 911 NF (x_{50} = 59.9 µm), FMC, United States) was used, which exhibits the lowest sulfate content of the three types of carrageenan [177]. All carrageenan types have a high water content and adsorb water quickly [175]. κ-carrageenan has been proven to be suitable for the manufacturing of pellets [174] as well as for matrix tablets with prolonged release [175, 178, 179]. The powder is already in the rubbery state at room temperature, since the glass transition temperature is below room temperature [175]. κ-carrageenan is a viscoelastic polymer with a high amount of elastic recovery during and after tableting [176, 179]. Nevertheless, tablets with sufficient mechanical strength have successfully been produced [176, 177]. κ-carrageenan was chosen in the present study to include a material with predominantly elastic behavior not only during but also after tableting.

A.4.7 Hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is a cellulose ether derivative in which the cellulose units are partially substituted with hydroxypropyl moieties. As is typical for cellulose derivatives, it is semi-crystalline [6] and shows fibrous particles (Figure 24). The production process is performed by adding sodium hydroxide to cellulose to obtain chemically reactive alkali cellulose, which is subsequently converted with propylene oxide at elevated temperature and pressure [154].

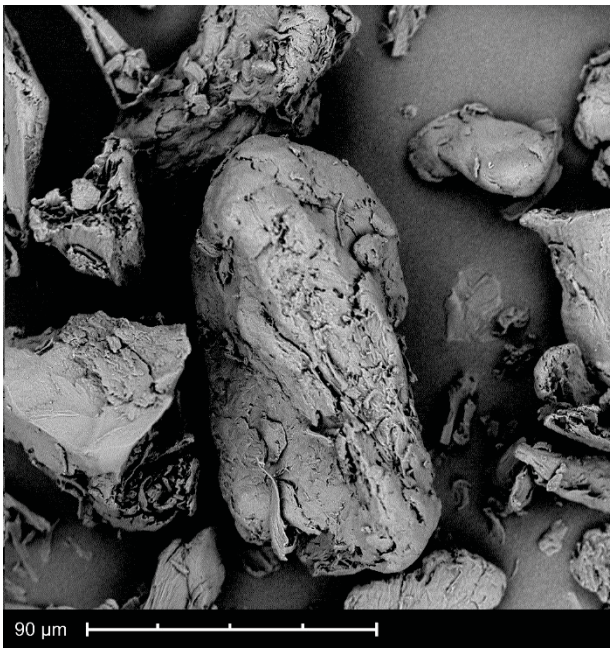

Figure 24. SEM image of HPC SL FP

HPC is available in numerous grades, varying in the average degree of polymerization and degree of substitution. In tablet formulation, it is mainly used as a coating agent, as a matrix former for prolonged release and as a binder [154]. As with many excipients, the binder effect depends on the particle size [6]. With decreasing particle size the binder effect increases and stronger tablets are obtained. The elastic recovery decreases with decreasing particle size, which also contributes to the formation of tablets with high mechanical strength [180]. The deformation behavior of HPC is predominantly plastic which favors a high

compressibility, compactibility, and tabletability. Even at low compression pressure, mechanically strong tablets are formed [180]. It has already been described that HPC tablets cannot be crushed during determination of their breaking force, merely deformed due to their high plasticity [160].

HPC SL FP (x_{50} = 80.9 µm, Nippon Soda, Japan), which has a small particle size and thus a strong binder effect, was used as the HPC grade. It was selected as a distinctively ductile material with exceptionally low resistance to deformation in order to extend the various properties of the starting materials.

A.5 References

1. U.S.P. Convention. *<1062> Tablet Compression Characterization*. In United States Pharmacopeia - National Formulary USP44-NF39, 2021. United Book Press.

2. Bos, C.E., Van Doorne, H. and Lerk, C.F. *Microbiological stability of tablets stored under tropical conditions.* International Journal of Pharmaceutics, 1989. **55**(2-3): p. 175-183, doi: https://doi.org/10.1016/0378-5173(89)90039-2.

3. Iqubal, M.K., Singh, P.K., Shuaib, M., Iqubal, A. and Singh, M. *Recent advances in direct compression technique for pharmaceutical tablet formulation.* International Journal of Pharmaceutical Research and Development, 2014. **6**(1): p. 49-57.

4. Çelik, M. *The past, present, and future of tableting technology.* Drug Development and Industrial Pharmacy, 1996. **22**(1): p. 1-10, doi: https://doi.org/10.3109/03639049609043867.

5. Shangraw, R.F. *Compressed tablets by direct compression.* In Pharmaceutical Dosage Forms: Tablets Volume 1, H.A. Lieberman, L. Lachman, and J.B. Schwartz, 1989. Marcel Dekker, Inc., New York, p. 195-246.

6. Arndt, O.R. *Einfluss von Trockenbindemitteln auf die Granulierung und Tablettierung.* Dissertation, Heinrich-Heine-Universität Düsseldorf, 2019.

7. Mangal, S., Meiser, F., Morton, D. and Larson, I. *Particle engineering of excipients for direct compression: understanding the role of material properties.* Current Pharmaceutical Design, 2015. **21**(40): p. 5877-5889.

8. Wu, C.Y., Best, S.M., Bentham, A.C., Hancock, B.C. and Bonfield, W. *A simple predictive model for the tensile strength of binary tablets.* European Journal of Pharmaceutical Sciences, 2005. **25**(2-3): p. 331-336, doi: https://doi.org/10.1016/j.ejps.2005.03.004.

9. Çelik, M. and Driscoll, C.E. *An overview of the effects of some physico-chemical and mechanical characteristics of particulates on the compaction and post-compaction properties of compacts.* Drug Development and Industrial

Pharmacy, 1993. **19**(17-18): p. 2119-2141, doi: https://doi.org/10.3109/03639049309047188.

10. Roberts, R.J., Rowe, R.C. and Kendall, K. *Brittle—ductile transitions in die compaction of sodium chloride.* Chemical Engineering Science, 1989. **44**(8): p. 1647-1651, doi: https://doi.org/10.1016/0009-2509(89)80007-7.

11. Nordström, J. *Compression analysis as a tool for technical characterization and classification of pharmaceutical powders.* Dissertation, Acta Universitatis Upsaliensis Uppsala, 2008.

12. Mohammed, H., Briscoe, B.J. and Pitt, K.G. *A study on the coherence of compacted binary composites of microcrystalline cellulose and paracetamol.* European Journal of Pharmaceutics and Biopharmaceutics, 2006. **63**(1): p. 19-25, doi: https://doi.org/10.1016/j.ejpb.2005.10.001.

13. Jain, S. *Mechanical properties of powders for compaction and tableting: an overview.* Pharmaceutical Science & Technology Today, 1999. **2**(1): p. 20-31, doi: https://doi.org/10.1016/S1461-5347(98)00111-4.

14. Carless, J.E. and Shear, A. *Changes in the particle size distribution during tableting of sulphathiazole powder.* Journal of Pharmacy and Pharmacology, 1976. **28**(1): p. 17-22, doi: https://doi.org/10.1111/j.2042-7158.1976.tb04016.x.

15. Nyström, C., Alderborn, G., Duberg, M. and Karehill, P.G. *Bonding surface area and bonding mechanism-two important factors for the understanding of powder compactability.* Drug Development and Industrial Pharmacy, 1993. **19**(17-18): p. 2143-2196, doi: https://doi.org/10.3109/03639049309047189.

16. Osei-Yeboah, F., Chang, S.Y. and Sun, C.C. *A critical examination of the phenomenon of bonding area-bonding strength interplay in powder tableting.* Pharmaceutical Research, 2016. **33**: p. 1126-1132, doi: https://doi.org/10.1007/s11095-016-1858-8.

17. Etzler, F.M. and Pisano, S. *Tablet tensile strength: Role of surface free energy.* Advances in Contact Angle, Wettability and Adhesion, 2015. **2**: p. 397-418.

18. Olsson, H. and Nyström, C. *Assessing tablet bond types from structural features that affect tablet tensile strength.* Pharmaceutical Research, 2001. **18**(2): p. 203.

19. Hiestand, E.N. *Principles, tenets and notions of tablet bonding and measurements of strength.* European Journal of Pharmaceutics and Biopharmaceutics, 1997. **44**(3): p. 229-242, doi: https://doi.org/10.1016/S0939-6411(97)00127-6.

20. Roberts, R.J. and Rowe, R.C. *The effect of punch velocity on the compaction of a variety of materials.* Journal of Pharmacy and Pharmacology, 1985. **37**(6): p. 377-384, doi: https://doi.org/10.1111/j.2042-7158.1985.tb03019.x.

21. Tye, C.K., Sun, C.C. and Amidon, G.E. *Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction.* Journal of Pharmaceutical Sciences, 2005. **94**(3): p. 465-472, doi: https://doi.org/10.1002/jps.20262.

22. Yazdi, A.K. and Smyth, H.D.C. *Implementation of design of experiments approach for the micronization of a drug with a high brittle–ductile transition particle diameter.* Drug Development and Industrial Pharmacy, 2017. **43**(3): p. 364-371, doi: https://doi.org/10.1080/03639045.2016.1253727.

23. Antikainen, O. and Yliruusi, J. *Determining the compression behaviour of pharmaceutical powders from the force–distance compression profile.* International Journal of Pharmaceutics, 2003. **252**(1-2): p. 253-261, doi: https://doi.org/10.1016/S0378-5173(02)00665-8.

24. Sun, C.C. and Grant, D.J.W. *Influence of elastic deformation of particles on Heckel analysis.* Pharmaceutical Development and Technology, 2001. **6**(2): p. 193-200, doi: https://doi.org/10.1081/PDT-100000738.

25. Hiestand, E.N., Wells, J.E., Peot, C.B. and Ochs, J.F. *Physical processes of tableting.* Journal of Pharmaceutical Sciences, 1977. **66**(4): p. 510-519, doi: https://doi.org/10.1002/jps.2600660413.

26. Keizer, H.L. *Hybrid Modelling of Roll Compaction.* Dissertation, Heinrich-Heine-Universität Düsseldorf, 2021.

27. Picker, K.M. *Time dependence of elastic recovery for characterization of tableting materials.* Pharmaceutical Development and Technology, 2001. **6**(1): p. 61-70, doi: https://doi.org/10.1081/PDT-100000014.

28. Keizer, H.L. and Kleinebudde, P. *Elastic recovery in roll compaction simulation.* International Journal of Pharmaceutics, 2020. **573**: p. 118810, doi: https://doi.org/10.1016/j.ijpharm.2019.118810.

29. Rumpf, H. *Zur Theorie der Zugfestigkeit von Agglomeraten bei Kraftübertragung an Kontaktpunkten.* Chemie Ingenieur Technik, 1970. **42**(8): p. 538-540, doi: https://doi.org/10.1002/cite.330420806.

30. Food and Drug Administration, Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing, available at: https://www.fda.gov/drugs/news-events-human-drugs/modernizing-way-drugs-are-made-transition-continuous-manufacturing; last accessed: 03.04.2023.

31. Food and Drug Administration, PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, available at: https://www.fda.gov/media/71012/download; last accessed: 01.04.2023.

32. Sun, C.C. and Grant, D.J.W. *Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder.* International Journal of Pharmaceutics, 2001. **215**(1-2): p. 221-228, doi: https://doi.org/10.1016/S0378-5173(00)00701-8.

33. McKenna, A. and McCafferty, D.F. *Effect of particle size on the compaction mechanism and tensile strength of tablets.* Journal of Pharmacy and Pharmacology, 1982. **34**(6): p. 347-351, doi: https://doi.org/10.1111/j.2042-7158.1982.tb04727.x.

34. Skelbæk-Pedersen, A.L., Vilhelmsen, T.K., Wallaert, V. and Rantanen, J. *Investigation of the effects of particle size on fragmentation during tableting.* International Journal of Pharmaceutics, 2020. **576**: p. 118985, doi: https://doi.org/10.1016/j.ijpharm.2019.118985.

35. Fichtner, F., Rasmuson, Å. and Alderborn, G. *Particle size distribution and evolution in tablet structure during and after compaction.* International Journal

of Pharmaceutics, 2005. **292**(1-2): p. 211-225, doi: https://doi.org/10.1016/j.ijpharm.2004.12.003.

36. Wong, L.W. and Pilpel, N. *The effect of particle shape on the mechanical properties of powders.* International Journal of Pharmaceutics, 1990. **59**(2): p. 145-154, doi: https://doi.org/10.1016/0378-5173(90)90089-M.

37. Sun, C.C. and Grant, D.J.W. *Influence of crystal shape on the tableting performance of L - lysine monohydrochloride dihydrate.* Journal of Pharmaceutical Sciences, 2001. **90**(5): p. 569-579, doi: https://doi.org/10.1002/1520-6017(200105)90:5%3C569::AID-JPS1013%3E3.0.CO;2-4.

38. Patel, S., Kaushal, A.M. and Bansal, A.K. *Compression physics in the formulation development of tablets.* Critical Reviews™ in Therapeutic Drug Carrier Systems, 2006. **23**(1), doi: https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v23.i1.10.

39. Szakonyi, G. and Zelkó, R. *The effect of water on the solid state characteristics of pharmaceutical excipients: Molecular mechanisms, measurement techniques, and quality aspects of final dosage form.* International Journal of Pharmaceutical Investigation, 2012. **2**(1): p. 18, doi: https://doi.org/10.4103%2F2230-973X.96922.

40. Takasaki, H., Yonemochi, E., Ito, M., Wada, K. and Terada, K. *The effect of water activity on granule characteristics and tablet properties produced by moisture activated dry granulation (MADG).* Powder Technology, 2016. **294**: p. 113-118, doi: https://doi.org/10.1016/j.powtec.2016.02.013.

41. Larhrib, H. and Wells, J.I. *Polyethylene glycol and dicalcium phosphate mixtures: effect of tableting pressure.* International Journal of Pharmaceutics, 1997. **159**(1): p. 75-83, doi: https://doi.org/10.1016/S0378-5173(97)00273-1.

42. Kakimi, K., Niwa, T. and Danjo, K. *Influence of compression pressure and velocity on tablet sticking.* Chemical and Pharmaceutical Bulletin, 2010. **58**(12): p. 1565-1568, doi: https://doi.org/10.1248/cpb.58.1565.

43. Larhrib, H. and Wells, J.I. *Compression speed on polyethylene glycol and dicalcium phosphate tableted mixtures.* International Journal of Pharmaceutics, 1998. **160**(2): p. 197-206, doi: https://doi.org/10.1016/S0378-5173(97)00309-8.

44. Sinka, I.C., Motazedian, F., Cocks, A.C.F. and Pitt, K.G. *The effect of processing parameters on pharmaceutical tablet properties.* Powder Technology, 2009. **189**(2): p. 276-284, doi: https://doi.org/10.1016/j.powtec.2008.04.020.

45. Shah, H.G., Dugar, R.P., Li, H., Dave, V.S. and Dave, R.H. *Influence of punch geometry (head-flat diameter) and tooling type ('B' or 'D') on the physical–mechanical properties of formulation tablets.* Drug Development and Industrial Pharmacy, 2019. **45**(1): p. 117-123, doi: https://doi.org/10.1080/03639045.2018.1525395.

46. Newton, J.M., Haririan, I. and Podczeck, F. *The influence of punch curvature on the mechanical properties of compacted powders.* Powder Technology, 2000. **107**(1-2): p. 79-83, doi: https://doi.org/10.1016/S0032-5910(99)00173-4.

47. Eiliazadeh, B., Pitt, K.G. and Briscoe, B. *Effects of punch geometry on powder movement during pharmaceutical tabletting processes.* International Journal of Solids and Structures, 2004. **41**(21): p. 5967-5977, doi: https://doi.org/10.1016/j.ijsolstr.2004.05.055.

48. Anbalagan, P., Sarkar, S., Liew, C.V. and Heng, P.W.S. *Influence of the punch head design on the physical quality of tablets produced in a rotary press.* Journal of Pharmaceutical Sciences, 2017. **106**(1): p. 356-365, doi: https://doi.org/10.1016/j.xphs.2016.10.016.

49. Anbalagan, P., Liew, C.V. and Heng, P.W.S. *Role of dwell on compact deformation during tableting: an overview.* Journal of Pharmaceutical Investigation, 2017. **47**(3): p. 173-181, doi: https://doi.org/10.1007/s40005-017-0306-z.

50. Wünsch, I., Friesen, I., Puckhaber, D., Schlegel, T. and Finke, J.H. *Scaling tableting processes from compaction simulator to rotary presses—Mind the sub-*

processes. Pharmaceutics, 2020. **12**(4): p. 310, doi: https://doi.org/10.3390/pharmaceutics12040310.

51. GEA, Consigma™ Kontinuierliche Direktkompression, available at: https://www.gea.com/de/products/tablet-presses/continuous-direct-compression-line/consigma-continuous-direct-compression-cdc.jsp; last accessed: 03.04.2023.

52. GEA, ConsiGma® 4.0: PAT-Compatible Continuous Manufacturing Solutions, available at: https://www.gea.com/de/stories/consigma-4-pat-compatible-continuous-manufacturing-solutions.jsp; last accessed: 03.04.2023.

53. GEA, Lyoplus™ PAT für Pharma-Gefriertrockner, available at: https://www.gea.com/de/products/dryers-particle-processing/lyophilizers/pat-lyoplus.jsp; last accessed: 03.04.2023.

54. Sun, C.C. *A classification system for tableting behaviors of binary powder mixtures.* Asian Journal of Pharmaceutical Sciences, 2016. **11**(4): p. 486-491, doi: https://doi.org/10.1016/j.ajps.2015.11.122.

55. Ryshkewitch, E. *Compression strength of porous sintered alumina and zirconia: 9th communication to ceramography.* Journal of the American Ceramic Society, 1953. **36**(2): p. 65-68, doi: https://doi.org/10.1111/j.1151-2916.1953.tb12837.x.

56. Ilić, I., Govedarica, B. and Srčič, S. *Deformation properties of pharmaceutical excipients determined using an in-die and out-die method.* International Journal of Pharmaceutics, 2013. **446**(1-2): p. 6-15, doi: https://doi.org/10.1016/j.ijpharm.2013.02.001.

57. Khomane, K.S. and Bansal, A.K. *Effect of particle size on in-die and out-of-die compaction behavior of ranitidine hydrochloride polymorphs.* AAPS PharmSciTech, 2013. **14**: p. 1169-1177, doi: https://doi.org/10.1208/s12249-013-0008-4.

58. Peck, G.E., Baley, G.J., McCurdy, V.E. and Banker, G.S. *Tablet formulation and design.* In Pharmaceutical Dosage Forms: Tablets Volume 1, H.A. Lieberman, L. Lachman, and J.B. Schwartz, 1989. Marcel Dekker, Inc., New York, p. 75-130.

59. Vreeman, G. and Sun, C.C. *A powder tabletability equation.* Powder Technology, 2022. **408**: p. 117709, doi: https://doi.org/10.1016/j.powtec.2022.117709.

60. Alderborn, G. *A novel approach to derive a compression parameter indicating effective particle deformability.* Pharmaceutical Development and Technology, 2003. **8**(4): p. 367-377, doi: https://doi.org/10.1081/PDT-120024690.

61. Persson, A.S. and Alderborn, G. *A hybrid approach to predict the relationship between tablet tensile strength and compaction pressure using analytical powder compression.* European Journal of Pharmaceutics and Biopharmaceutics, 2018. **125**: p. 28-37, doi: https://doi.org/10.1016/j.ejpb.2017.12.011.

62. Pazesh, S., Persson, A.S. and Alderborn, G. *Atypical compaction behaviour of disordered lactose explained by a shift in type of compact fracture pattern.* International Journal of Pharmaceutics: X, 2019. **1**: p. 100037, doi: https://doi.org/10.1016/j.ijpx.2019.100037.

63. Shi, L. and Sun, C.C. *Overcoming poor tabletability of pharmaceutical crystals by surface modification.* Pharmaceutical Research, 2011. **28**: p. 3248-3255, doi: https://doi.org/10.1007/s11095-011-0518-2.

64. Grote, S. *Untersuchungen zum Einfluss der Ausgangspartikelmorphologie in der Walzenkompaktierung und Tablettierung.* Dissertation, Heinrich-Heine-Universität Düsseldorf, 2018.

65. Narang, A.S., Rao, V.M., Guo, H., Lu, J. and Desai, D.S. *Effect of force feeder on tablet strength during compression.* International Journal of Pharmaceutics, 2010. **401**(1-2): p. 7-15, doi: https://doi.org/10.1016/j.ijpharm.2010.08.027.

66. Sun, C.C. and Himmelspach, M.W. *Reduced tabletability of roller compacted granules as a result of granule size enlargement.* Journal of Pharmaceutical Sciences, 2006. **95**(1): p. 200-206, doi: https://doi.org/10.1002/jps.20531.

67. Thoorens, G., Krier, F., Rozet, E., Carlin, B. and Evrard, B. *Understanding the impact of microcrystalline cellulose physicochemical properties on tabletability.*

International Journal of Pharmaceutics, 2015. **490**(1-2): p. 47-54, doi: https://doi.org/10.1016/j.ijpharm.2015.05.026.

68. Vanhoorne, V., Peeters, E., Van Snick, B., Remon, J.P. and Vervaet, C. *Crystal coating via spray drying to improve powder tabletability.* European Journal of Pharmaceutics and Biopharmaceutics, 2014. **88**(3): p. 939-944, doi: https://doi.org/10.1016/j.ejpb.2014.10.018.

69. Reynolds, G.K., Campbell, J.I. and Roberts, R.J. *A compressibility based model for predicting the tensile strength of directly compressed pharmaceutical powder mixtures.* International Journal of Pharmaceutics, 2017. **531**(1): p. 215-224, doi: https://doi.org/10.1016/j.ijpharm.2017.08.075.

70. Leuenberger, H. *The compressibility and compactibility of powder systems.* International Journal of Pharmaceutics, 1982. **12**(1): p. 41-55, doi: https://doi.org/10.1016/0378-5173(82)90132-6.

71. Felt, E.J. *Compactibility.* In Methods of Soil Analysis: Part 1 Physical and Mineralogical Properties, Including Statistics of Measurement and Sampling, C.A. Black, 1965. American Society of Agronomy, Inc., New York, p. 400-412.

72. Hernández, O.C., Baltazar, E.H., González, E.A. and Contreras, L.M.M. *Production of directly compressible excipients with mannitol by wet granulation: Rheological, compressibility and compactibility characterization.* Farmacia, 2019. **67**(6): p. 973-985, doi: https://doi.org/10.31925/farmacia.2019.6.7.

73. Osei‐Yeboah, F. and Sun, C.C. *A pitfall in analyzing powder compactibility data using nonlinear regression.* Journal of Pharmaceutical Sciences, 2013. **102**(3): p. 1135-1136, doi: https://doi.org/10.1002/jps.23456.

74. Yu, Y., Zhao, L., Lin, X., Wang, Y. and Feng, Y. *A model to simultaneously evaluate the compressibility and compactibility of a powder based on the compression ratio.* International Journal of Pharmaceutics, 2020. **577**: p. 119023, doi: https://doi.org/10.1016/j.ijpharm.2020.119023.

75. Dai, S., Xu, B., Zhang, Z., Yu, J., Wang, F., Shi, X. and Qiao, Y. *A compression behavior classification system of pharmaceutical powders for accelerating direct*

compression tablet formulation design. International Journal of Pharmaceutics, 2019. **572**: p. 118742, doi: https://doi.org/10.1016/j.ijpharm.2019.118742.

76. Shotton, E. and Ganderton, D. *The strength of compressed tablets: Part II. The bonding of granules during compression.* Journal of Pharmacy and Pharmacology, 1960. **12**(Supplement_1): p. 93T-96T, doi: https://doi.org/10.1111/j.2042-7158.1960.tb10459.x.

77. Higuchi, T., Elowe, L.N. and Busse, L.W. *The physics of tablet compression: V. Studies on aspirin, lactose, lactose-aspirin, and sulfadiazine tablets.* Journal of the American Pharmaceutical Association (Scientific ed.), 1954. **43**(11): p. 685-689, doi: https://doi.org/10.1002/jps.3030431118.

78. Newton, J.M. and Grant, D.J.W. *The relation between the compaction pressure, porosity and tensile strength of compacted powders.* Powder Technology, 1974. **9**(5-6): p. 295-297, doi: https://doi.org/10.1016/0032-5910(74)80056-2.

79. Leuenberger, H. and Jetzer, W. *The compactibility of powder systems-a novel approach.* Powder Technology, 1984. **37**(1): p. 209-218, doi: https://doi.org/10.1016/0032-5910(84)80018-2.

80. Sun, C.C. *Quantifying errors in tableting data analysis using the Ryshkewitch equation due to inaccurate true density.* Journal of Pharmaceutical Sciences, 2005. **94**(9): p. 2061-2068, doi: https://doi.org/10.1002/jps.20421.

81. Sun, C.C. *A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders.* Journal of Pharmaceutical Sciences, 2004. **93**(3): p. 646-653, doi: https://doi.org/10.1002/jps.10595.

82. Gabaude, C.M.D., Guillot, M., Gautier, J.C., Saudemon, P. and Chulia, D. *Effects of true density, compacted mass, compression speed, and punch deformation on the mean yield pressure.* Journal of Pharmaceutical Sciences, 1999. **88**(7): p. 725-730, doi: https://doi.org/10.1021/js9803050.

83. Sonnergaard, J.M. *Impact of particle density and initial volume on mathematical compression models.* European Journal of Pharmaceutical Sciences, 2000. **11**(4): p. 307-315, doi: https://doi.org/10.1016/S0928-0987(00)00119-6.

84. Krumme, M., Schwabe, L. and Frömming, K.H. *Development of computerised procedures for the characterisation of the tableting properties with eccentric machines: extended Heckel analysis.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **49**(3): p. 275-286, doi: https://doi.org/10.1016/S0939-6411(00)00067-9.

85. Çelik, M. *Overview of compaction data analysis techniques.* Drug Development and Industrial Pharmacy, 1992. **18**(6-7): p. 767-810, doi: https://doi.org/10.3109/03639049209058560.

86. Heckel, R.W. *Density-pressure relationships in powder compaction.* Trans Metall Soc AIME, 1961. **221**(4): p. 671-675.

87. Gentis, N.D. and Betz, G. *Compressibility of binary powder formulations: Investigation and evaluation with compaction equations.* Journal of Pharmaceutical Sciences, 2012. **101**(2): p. 777-793, doi: https://doi.org/10.1002/jps.22794.

88. Hassanpour, A. and Ghadiri, M. *Distinct element analysis and experimental evaluation of the Heckel analysis of bulk powder compression.* Powder Technology, 2004. **141**(3): p. 251-261, doi: https://doi.org/10.1016/j.powtec.2004.02.010.

89. Ilkka, J. and Paronen, P. *Prediction of the compression behaviour of powder mixtures by the Heckel equation.* International Journal of Pharmaceutics, 1993. **94**(1-3): p. 181-187, doi: https://doi.org/10.1016/0378-5173(93)90022-8.

90. Patel, D., Patel, V.D., Sedlock, R. and Haware, R.V. *Negative porosity issue in the Heckel analysis: A possible solution.* International Journal of Pharmaceutics, 2022: p. 122205, doi: https://doi.org/10.1016/j.ijpharm.2022.122205.

91. Rue, P.J. and Rees, J.E. *Limitations of the Heckel relation for predicting powder compaction mechanisms.* Journal of Pharmacy and Pharmacology, 1978. **30**(1): p. 642-643, doi: https://doi.org/10.1111/j.2042-7158.1978.tb13347.x.

92. Patel, S., Kaushal, A.M. and Bansal, A.K. *Mechanistic investigation on pressure dependency of Heckel parameter.* International Journal of Pharmaceutics, 2010. **389**(1-2): p. 66-73, doi: https://doi.org/10.1016/j.ijpharm.2010.01.020.

93. Sonnergaard, J.M. *A critical evaluation of the Heckel equation.* International Journal of Pharmaceutics, 1999. **193**(1): p. 63-71, doi: https://doi.org/10.1016/S0378-5173(99)00319-1.

94. Çelik, M. and Marshall, K. *Use of a compaction simulator system in tabletting research.* Drug Development and Industrial Pharmacy, 1989. **15**(5): p. 759-800, doi: https://doi.org/10.3109/03639048909058530.

95. York, P. *A consideration of experimental variables in the analysis of powder compaction behaviour.* Journal of Pharmacy and Pharmacology, 1979. **31**(1): p. 244-246, doi: https://doi.org/10.1111/j.2042-7158.1979.tb13487.x.

96. Vreeman, G. and Sun, C.C. *Mean yield pressure from the in-die Heckel analysis is a reliable plasticity parameter.* International Journal of Pharmaceutics: X, 2021. **3**: p. 100094, doi: https://doi.org/10.1016/j.ijpx.2021.100094.

97. Johanson, J.R. *A rolling theory for granular solids.* Journal of Applied Mechanics, 1965. **32**(4): p. 842-848, doi: https://doi.org/10.1115/1.3627325.

98. Nesarikar, V.V., Patel, C., Early, W., Vatsaraj, N., Sprockel, O. and Jerzweski, R. *Roller compaction process development and scale up using Johanson model calibrated with instrumented roll data.* International Journal of Pharmaceutics, 2012. **436**(1): p. 486-507, doi: https://doi.org/10.1016/j.ijpharm.2012.06.027.

99. Bi, M., Alvarez-Nunez, F. and Alvarez, F. *Evaluating and modifying Johanson's rolling model to improve its predictability.* Journal of Pharmaceutical Sciences, 2014. **103**(7): p. 2062-2071, doi: https://doi.org/10.1002/jps.24012.

100. Moroney, K.M., Cronin, P., Adeleye, O.A., Schaller, B.E., Howard, M.A., Castro-Dominguez, B., Ramachandran, R. and Walker, G.M. *An evaluation of the Johanson model for roller compaction process development for a high dose API.* Powder Technology, 2020. **366**: p. 82-95, doi: https://doi.org/10.1016/j.powtec.2020.02.058.

101. So, C., Leung, L.Y., Muliadi, A.R., Narang, A.S. and Mao, C. *Simplifying Johanson's roller compaction model to build a "Virtual Roller Compactor" as a predictive tool – Theory and practical application.* International Journal of

Pharmaceutics, 2021. **601**: p. 120579, doi: https://doi.org/10.1016/j.ijpharm.2021.120579.

102. Patel, B.A., Adams, M.J., Turnbull, N., Bentham, A.C. and Wu, C.Y. *Predicting the pressure distribution during roll compaction from uniaxial compaction measurements.* Chemical Engineering Journal, 2010. **164**(2-3): p. 410-417, doi: https://doi.org/10.1016/j.cej.2009.12.022.

103. Yusof, Y.A., Smith, A.C. and Briscoe, B.J. *Roll compaction of maize powder.* Chemical Engineering Science, 2005. **60**(14): p. 3919-3931, doi: https://doi.org/10.1016/j.ces.2005.02.025.

104. Yu, S., Gururajan, B., Reynolds, G., Roberts, R.J., Adams, M.J. and Wu, C.Y. *A comparative study of roll compaction of free-flowing and cohesive pharmaceutical powders.* International Journal of Pharmaceutics, 2012. **428**(1-2): p. 39-47, doi: https://doi.org/10.1016/j.ijpharm.2012.02.033.

105. Kawakita, K. and Tsutsumi, Y. *An empirical equation of state for powder compression.* Japanese Journal of Applied Physics, 1965. **4**(1): p. 56, doi: https://doi.org/10.1143/JJAP.4.56.

106. Kawakita, K. and Lüdde, K.H. *Some considerations on powder compression equations.* Powder Technology, 1971. **4**(2): p. 61-68, doi: https://doi.org/10.1016/0032-5910(71)80001-3.

107. Nordström, J., Klevan, I. and Alderborn, G. *A particle rearrangement index based on the Kawakita powder compression equation.* Journal of Pharmaceutical Sciences, 2009. **98**(3): p. 1053-1063, doi: https://doi.org/10.1002/jps.21488.

108. Paul, S. and Sun, C.C. *The suitability of common compressibility equations for characterizing plasticity of diverse powders.* International Journal of Pharmaceutics, 2017. **532**(1): p. 124-130, doi: https://doi.org/10.1016/j.ijpharm.2017.08.096.

109. Klevan, I., Nordström, J., Tho, I. and Alderborn, G. *A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials.* European Journal of Pharmaceutics and

Biopharmaceutics, 2010. **75**(3): p. 425-435, doi: https://doi.org/10.1016/j.ejpb.2010.04.006.

110. Nordström, J., Welch, K., Frenning, G. and Alderborn, G. *On the physical interpretation of the Kawakita and Adams parameters derived from confined compression of granular solids.* Powder Technology, 2008. **182**(3): p. 424-435, doi: https://doi.org/10.1016/j.powtec.2007.07.009.

111. Nicklasson, F. and Alderborn, G. *Analysis of the compression mechanics of pharmaceutical agglomerates of different porosity and composition using the Adams and Kawakita equations.* Pharmaceutical Research, 2000. **17**(8): p. 949-954, doi: https://doi.org/10.1023/A:1007575120817.

112. Frenning, G., Nordström, J. and Alderborn, G. *Effective Kawakita parameters for binary mixtures.* Powder Technology, 2009. **189**(2): p. 270-275, doi: https://doi.org/10.1016/j.powtec.2008.04.016.

113. Adams, M.J., Mullier, M.A. and Seville, J.P.K. *Agglomerate strength measurement using a uniaxial confined compression test.* Powder Technology, 1994. **78**(1): p. 5-13, doi: https://doi.org/10.1016/0032-5910(93)02777-8.

114. Salbu, L., Bauer-Brandl, A., Alderborn, G. and Tho, I. *Effect of degree of methoxylation and particle size on compression properties and compactibility of pectin powders.* Pharmaceutical Development and Technology, 2012. **17**(3): p. 333-343, doi: https://doi.org/10.3109/10837450.2010.535831.

115. Odeku, O.A. *The compaction of pharmaceutical powders.* Pharmaceutical Reviews, 2007. **5**(2).

116. Sonnergaard, J. *Investigation of a new mathematical model for compression of pharmaceutical powders.* European Journal of Pharmaceutical Sciences, 2001. **14**(2): p. 149-157, doi: https://doi.org/10.1016/S0928-0987(01)00165-8.

117. Schmidtke, R., Schröder, D., Menth, J., Staab, A., Braun, M. and Wagner, K.G. *Prediction of solid fraction from powder mixtures based on single component compression analysis.* International Journal of Pharmaceutics, 2017. **523**(1): p. 366-375, doi: https://doi.org/10.1016/j.ijpharm.2017.03.054.

118. Denny, P.J. *Compaction equations: a comparison of the Heckel and Kawakita equations.* Powder Technology, 2002. **127**(2): p. 162-172, doi: https://doi.org/10.1016/S0032-5910(02)00111-0.

119. Kuentz, M. and Leuenberger, H. *Pressure susceptibility of polymer tablets as a critical property: A modified Heckel equation.* Journal of Pharmaceutical Sciences, 1999. **88**(2): p. 174-179, doi: https://doi.org/10.1021/js980369a.

120. Blynskaya, E.V., Markeev, V.B., Alekseev, K.V., Tishkov, S.V., Bueva, V.V. and Bogunova, I.V. *Application of the Kuenz–Leuenberger equation as a predictive model of the direct tablet compression process.* Pharmaceutical Chemistry Journal, 2021. **55**(6): p. 604-615, doi: https://doi.org/10.1007/s11094-021-02465-2.

121. Sun, C.C. *Microstructure of tablet—pharmaceutical significance, assessment, and engineering.* Pharmaceutical Research, 2017. **34**(5): p. 918-928, doi: https://doi.org/10.1007/s11095-016-1989-y.

122. Al-Hmoud, L., Abu Fara, D., Rashid, I., Chowdhry, B.Z. and Badwan, A.A. *Influence of chitin source and polymorphism on powder compression and compaction: Application in drug delivery.* Molecules, 2020. **25**(22): p. 5269, doi: https://doi.org/10.3390/molecules25225269.

123. Trementozzi, A.N., Leung, C.Y., Osei-Yeboah, F., Irdam, E., Lin, Y., MacPhee, J.M., Boulas, P., Karki, S.B. and Zawaneh, P.N. *Engineered particles demonstrate improved flow properties at elevated drug loadings for direct compression manufacturing.* International Journal of Pharmaceutics, 2017. **523**(1): p. 133-141, doi: https://doi.org/10.1016/j.ijpharm.2017.03.011.

124. van der Haven, D.L.H., Ørtoft, F.H., Naelapää, K., Fragkopoulos, I.S. and Elliott, J.A. *Predictive modelling of powder compaction for binary mixtures using the finite element method.* Powder Technology, 2022. **403**: p. 117381, doi: https://doi.org/10.1016/j.powtec.2022.117381.

125. Wang, K. and Sun, C.C. *Direct compression tablet formulation of celecoxib enabled with a pharmaceutical solvate.* International Journal of Pharmaceutics, 2021. **596**: p. 120239, doi: https://doi.org/10.1016/j.ijpharm.2021.120239.

126. Walker, E.E. *The properties of powders. Part VI. The compressibility of powders.* Transactions of the Faraday Society, 1923. **19**(July): p. 73-82, doi: https://doi.org/10.1039/TF9231900073.

127. Mallick, S. *Rearrangement of particle and compactibility, tabletability and compressibility of pharmaceutical powder: A rational approach.* Journal of Scientific and Industrial Research, 2014. **73**: p. 51-56.

128. Šantl, M., Ilić, I., Vrečer, F. and Baumgartner, S. *A compressibility and compactibility study of real tableting mixtures: The impact of wet and dry granulation versus a direct tableting mixture.* International Journal of Pharmaceutics, 2011. **414**(1-2): p. 131-139, doi: https://doi.org/10.1016/j.ijpharm.2011.05.025.

129. Bauer-Brandl, A. and Ritschel, W.A. *Die Tablette - Handbuch der Entwicklung, Herstellung und Qualitätssicherung*. Ed. 4. 2022, Aulendorf: ECV - Editio Cantor Verlag.

130. Patel, S., Kaushal, A.M. and Bansal, A.K. *Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility.* Pharmaceutical Research, 2007. **24**(1): p. 111-124, doi: https://doi.org/10.1007/s11095-006-9129-8.

131. Llusa, M., Faulhammer, E., Biserni, S., Calzolari, V., Lawrence, S., Bresciani, M. and Khinast, J. *The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification.* International Journal of Pharmaceutics, 2014. **471**(1-2): p. 182-188, doi: https://doi.org/10.1016/j.ijpharm.2014.04.073.

132. Ilić, I., Kása Jr, P., Dreu, R., Pintye-Hódi, K. and Srčič, S. *The compressibility and compactibility of different types of lactose.* Drug Development and Industrial Pharmacy, 2009. **35**(10): p. 1271-1280, doi: https://doi.org/10.1080/03639040902932945.

133. Mamidi, H.K., Mishra, S.M. and Rohera, B.D. *Determination of maximum flowable liquid-loading potential of Neusilin® US2 and investigation of compressibility and compactibility of its liquisolid blends with PEG (400).* Journal

of Drug Delivery Science and Technology, 2019. **54**: p. 101285, doi: https://doi.org/10.1016/j.jddst.2019.101285.

134. Gurnham, C.F. and Masson, H.J. *Expression of liquids from fibrous materials.* Industrial & Engineering Chemistry, 1946. **38**(12): p. 1309-1315.

135. Zhao, J., Burt, H.M. and Miller, R.A. *The Gurnham equation in characterizing the compressibility of pharmaceutical materials.* International Journal of Pharmaceutics, 2006. **317**(2): p. 109-113, doi: https://doi.org/10.1016/j.ijpharm.2006.02.054.

136. Eftaiha, A.F., El-Barghouthi, M.I., Rashid, I.S., Al-Remawi, M.M., Saleh, A.I. and Badwan, A.A. *Compressibility and compactibility studies of chitosan, xanthan gum, and their mixtures.* Journal of Materials Science, 2009. **44**: p. 1054-1062, doi: https://doi.org/10.1007/s10853-008-3186-9.

137. Akin-Ajani, O.D., Itiola, O.A. and Odeku, O.A. *Application of the Gurnham equation in characterizing the compressibility of fonio and sweet potato starches and their paracetamol tablet formulations.* Nigerian Journal of Pharmaceutical Research, 2018. **14**(1): p. 25-33.

138. Aburub, A., Mishra, D. and Buckner, I. *Use of compaction energetics for understanding particle deformation mechanism.* Pharmaceutical Development and Technology, 2007. **12**(4): p. 405-414, doi: https://doi.org/10.1080/10837450701366952.

139. Sonnergaard, J.M. *A simplified model structure for compression characterization of pharmaceutical tablets.* Journal of Pharmaceutical Sciences, 2022. **111**(11): p. 3088-3095, doi: https://doi.org/10.1016/j.xphs.2022.07.007.

140. Dietrich, R. and Mielck, J.B. *Parametrisierung des zeitlichen Verlaufs der Verdichtung bei der Tablettierung mithilfe der modifizierten Weibull-Funktion. I: Gedanklicher und experimenteller Ansatz.* Pharmazeutische Industrie, 1984. **46**(8): p. 863-869.

141. Konkel, P. and Mielck, J.B. *Associations of parameters characterizing the time course of the tabletting process on a reciprocating and on a rotary tabletting machine for high-speed production.* European Journal of Pharmaceutics and

Biopharmaceutics, 1998. **45**(2): p. 137-148, doi: https://doi.org/10.1016/S0939-6411(97)00132-X.

142. Shapiro, I. *Compaction of powders XI. Application of the general equation to both metal powders and ceramic powders.* Advances in Powder Metallurgy and Particulate Materials, 1994. **3**: p. 41-55.

143. Cooper Jr, A.R. and Eaton, L.E. *Compaction behavior of several ceramic powders.* Journal of the American Ceramic Society, 1962. **45**(3): p. 97-101, doi: https://doi.org/10.1111/j.1151-2916.1962.tb11092.x.

144. Levin, M. *Tablet press instrumentation.* In Encyclopedia of Pharmaceutical Technology, J. Swarbrick, 2002. Marcel Dekker, Inc., New York, p. 1-26.

145. Ridgway Watt, P. *The measurement of force.* In Tablet and Capsule Machine Instrumentation, P. Ridgway Watt and N.A. Armstrong, 2008. Pharmaceutical Press, London, p. 11-50.

146. Mazel, V., Busignies, V., Diarra, H. and Tchoreloff, P. *Lamination of pharmaceutical tablets due to air entrapment: direct visualization and influence of the compact thickness.* International Journal of Pharmaceutics, 2015. **478**(2): p. 702-704, doi: https://doi.org/10.1016/j.ijpharm.2014.12.023.

147. Garekani, H.A., Ford, J.L., Rubinstein, M.H. and Rajabi-Siahboomi, A.R. *Effect of compression force, compression speed, and particle size on the compression properties of paracetamol.* Drug Development and Industrial Pharmacy, 2001. **27**(9): p. 935-942, doi: https://doi.org/10.1081/DDC-100107674.

148. Danjo, K., Ertell, C. and Carstensen, J.T. *Effect of compaction speed and die diameter on Athy-Heckel and hardness parameters of compressed tablets.* Drug Development and Industrial Pharmacy, 1989. **15**(1): p. 1-10, doi: https://doi.org/10.3109/03639048909040192.

149. Grote, S., Osthues, H., Schaeffer, F. and Kleinebudde, P. *The influence of isomalt particle morphology on tabletability after roll compaction/dry granulation.* Powder Technology, 2019. **341**: p. 59-65, doi: https://doi.org/10.1016/j.powtec.2018.01.077.

150. Blattner, D., Kolb, M. and Leuenberger, H. *Percolation theory and compactibility of binary powder systems.* Pharmaceutical Research, 1990. **7**(2): p. 113-117, doi: https://doi.org/10.1023/A:1015864415693.

151. Riepma, K.A., Veenstra, J., De Boer, A.H., Bolhuis, G.K., Zuurman, K., Lerk, C.F. and Vromans, H. *Consolidation and compaction of powder mixtures: II. Binary mixtures of different particle size fractions of α-lactose monohydrate.* International Journal of Pharmaceutics, 1991. **76**(1-2): p. 9-15, doi: https://doi.org/10.1016/0378-5173(91)90338-O.

152. Zheng, J., Carlson, W.B. and Reed, J.S. *The packing density of binary powder mixtures.* Journal of the European Ceramic Society, 1995. **15**(5): p. 479-483, doi: https://doi.org/10.1016/0955-2219(95)00001-B.

153. Liu, L.X., Marziano, I., Bentham, A.C., Litster, J.D., White, E.T. and Howes, T. *Influence of particle size on the direct compression of ibuprofen and its binary mixtures.* Powder Technology, 2013. **240**: p. 66-73, doi: https://doi.org/10.1016/j.powtec.2012.07.006.

154. Rowe, R.C., Sheskey, P. and Quinn, M.E. *Handbook of Pharmaceutical Excipients 6th Edition*. 2009, London: Pharmaceutical Press.

155. Meggle, GranuLac® 230, available at: https://www.meggle-pharma.de/de/lactose/4-granulac-230.html; last accessed: 01.04.2023.

156. Meggle, FlowLac® 100, available at: https://www.meggle-pharma.de/de/lactose/10-flowlac-100.html; last accessed: 01.04.2023.

157. Meggle, Tablettose® 80, available at: https://www.meggle-pharma.de/de/lactose/7-tablettose-80.html; last accessed: 01.04.2023.

158. Trache, D., Hussin, M.H., Chuin, C.T.H., Sabar, S., Fazita, M.R.N., Taiwo, O.F.A., Hassan, T.M. and Haafiz, M.K.M. *Microcrystalline cellulose: Isolation, characterization and bio-composites application—A review.* International Journal of Biological Macromolecules, 2016. **93**: p. 789-804, doi: https://doi.org/10.1016/j.ijbiomac.2016.09.056.

159. Jivraj, M., Martini, L.G. and Thomson, C.M. *An overview of the different excipients useful for the direct compression of tablets.* Pharmaceutical Science & Technology Today, 2000. **3**(2): p. 58-63, doi: https://doi.org/10.1016/S1461-5347(99)00237-0.

160. Arndt, O.R. and Kleinebudde, P. *Towards a better understanding of dry binder functionality.* International Journal of Pharmaceutics, 2018. **552**(1-2): p. 258-264, doi: https://doi.org/10.1016/j.ijpharm.2018.10.007.

161. Reier, G.E. and Shangraw, R.F. *Microcrystalline cellulose in tableting.* Journal of Pharmaceutical Sciences, 1966. **55**(5): p. 510-514, doi: https://doi.org/10.1002/jps.2600550513.

162. Khan, K.A., Musikabhumma, P. and Warr, J.P. *The effect of moisture content of microcrystalline cellulose on the compressional properties of some formulations.* Drug Development and Industrial Pharmacy, 1981. **7**(5): p. 525-538, doi: https://doi.org/10.3109/03639048109057729.

163. Schmidt, P.C. and Herzog, R. *Calcium phosphates in pharmaceutical tableting: 1. Physico-pharmaceutical properties.* Pharmacy World and Science, 1993. **15**: p. 105-115, doi: https://doi.org/10.1007/BF02113938.

164. Grote, S. and Kleinebudde, P. *Roll compaction/dry granulation of dibasic calcium phosphate anhydrous—does the morphology of the raw material influence the tabletability of dry granules?* Journal of Pharmaceutical Sciences, 2018. **107**(4): p. 1104-1111, doi: https://doi.org/10.1016/j.xphs.2017.12.003.

165. Schlack, H., Bauer-Brandl, A., Schubert, R. and Becker, D. *Properties of Fujicalin®, a new modified anhydrous dibasic calcium phosphate for direct compression: Comparison with dicalcium phosphate dihydrate.* Drug Development and Industrial Pharmacy, 2001. **27**(8): p. 789-801, doi: https://doi.org/10.1081/DDC-100107242.

166. Schmidt, P.C. and Herzog, R. *Calcium phosphates in pharmaceutical tableting: 2. Comparison of tableting properties.* Pharmacy World and Science, 1993. **15**: p. 116-122, doi: https://doi.org/10.1007/BF02113939.

167. Svačinová, P., Mužíková, J. and Ondrejček, P. *Comparison of compressibility, compactability, and lubricant sensitivity of two partially pregelatinized starches.* Starch, 2021. **73**(3-4): p. 2000166, doi: https://doi.org/10.1002/star.202000166.

168. VGMS, Stärkeindustrie - Herstellung, available at: https://www.vgms.de/staerkeindustrie/staerkeindustrie/herstellung; last accessed: 03.04.2023.

169. Zobel, H.F. *Molecules to granules: a comprehensive starch review.* Starch - Stärke, 1988. **40**(2): p. 44-50, doi: https://doi.org/10.1002/star.19880400203.

170. Bolhuis, G.K. and de Waard, H. *Compaction properties of directly compressible materials.* In Pharmaceutical Powder Compaction Technology, Ç. Metin, 2016. CRC Press, Boca Raton, p. 143-204.

171. Jane, J.J.M.S. *Starch properties, modifications, and applications.* Journal of Macromolecular Science, Part A: Pure and Applied Chemistry, 1995. **32**(4): p. 751-757, doi: https://doi.org/10.1080/10601329508010286.

172. Rees, J.E. and Rue, P.J. *Time-dependent deformation of some direct compression excipients.* Journal of Pharmacy and Pharmacology, 1978. **30**(1): p. 601-607, doi: https://doi.org/10.1111/j.2042-7158.1978.tb13340.x.

173. Anuar, M.S. and Briscoe, B.J. *The elastic relaxation of starch tablets during ejection.* Powder Technology, 2009. **195**(2): p. 96-104, doi: https://doi.org/10.1016/j.powtec.2009.05.019.

174. Bornhöft, M., Thommes, M. and Kleinebudde, P. *Preliminary assessment of carrageenan as excipient for extrusion/spheronisation.* European Journal of Pharmaceutics and Biopharmaceutics, 2005. **59**(1): p. 127-131, doi: https://doi.org/10.1016/j.ejpb.2004.05.007.

175. Picker, K.M. *Matrix tablets of carrageenans. II. Release behavior and effect of added cations.* Drug Development and Industrial Pharmacy, 1999. **25**(3): p. 339-346, doi: https://doi.org/10.1081/DDC-100102179.

176. Picker, K.M. *Matrix tablets of carrageenans. I. A compaction study.* Drug Development and Industrial Pharmacy, 1999. **25**(3): p. 329-337, doi: https://doi.org/10.1081/DDC-100102178.

177. Picker-Freyer, K.M. *Carrageenans: Analysis of tablet formation and properties.* Pharmaceutical Technology Europe, 2005. **17**(8): p. 37-44.

178. Baishya, H. *Carrageenan as release controlling polymer in insoluble anti-psychotic drug matrix.* World Journal of Pharmacy and Pharmaceutical Sciences, 2017. **6**(5): p. 118-128, doi: https://doi.org/10.20959/wjpps20175-9093.

179. Picker, K.M. *The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **48**(1): p. 27-36, doi: https://doi.org/10.1016/S0939-6411(99)00009-0.

180. Picker-Freyer, K.M. and Dürig, T. *Physical mechanical and tablet formation properties of hydroxypropylcellulose: in pure form and in mixtures.* AAPS PharmSciTech, 2007. **8**(4): p. 82-90, doi: https://doi.org/10.1208/pt0804092

Section B.

Aim of the thesis

Aim of the thesis

The aim of this thesis is to further deepen the understanding of the tableting process on the foundation of existing work. The comprehension of the process and in particular the factors influencing the process is the prerequisite for optimizing the production of dosage forms. A special focus of this work will be put on factors influencing the tableting process regarding the raw materials as well as varying tableting parameters.

To increase the understanding about the tableting process, several well-known compression analyses are applied and evaluated. The evaluation is to be carried out with respect to the applicability, robustness and informative value of the respective compression parameters. Preference should be given to methods that show high robustness to adjustable process parameters such as compression speed, compacted mass and punch diameter. Those will most likely be suitable as tools for scale-up processes and useful for different formulations as well as tablet presses. Furthermore, those analyses that are easy to use and yet have the same information content as comparable methods should be preferred. This ensures that the methods can be integrated into process control strategies quickly and with minimal complications.

Existing compression analyses are to be modified or extended so that they can be optimized for the characterization of tableting behavior. In particular, in-die methods will be investigated in more detail. For this purpose, methods that are established for out-of-die application are reviewed for their suitability as in-die methods. The key aspects of tableting, in terms of material characterization, should be highlighted. By this, cost- and time-intensive steps in the development of tablet formulations can be eliminated. A combination of compression analyses should be found to apply when new materials for tableting are to be characterized.

The aim of this work is further to point out compression analyses that have the potential to be used as in-line methods for quality control of the tableting process. If the tablet properties can be analyzed by applying compression analyses during the process, the product quality can be monitored in real-time for every single tablet. It may be possible to use those analyses as PAT tools in the future.

Section C.

Results and discussion

C.1 Evaluation of methods to determine particle density

C.1.1 Evaluation of alternative methods to derive particle density from compression data

Pretext

Different approaches to determine the particle density of powders were evaluated in this publication. Two methods described in literature were compared to helium pycnometry, used as a standard in the pharmaceutical field. Additionally, one of the methods was modified and investigated in more detail. The alternative methods utilize compression data to calculate particle density. An assessment of the robustness of the methods to changes in tableting parameters was performed in this section. Finally, recommendations which method is advantageous to use for specific purposes and laboratory scenarios were included in this work.

The following paper has been published by the International Journal of Pharmaceutics in Volume 632 (2023).

https://doi.org/10.1016/j.ijpharm.2023.122582

Weighting of the authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Sabrina Berkenkemper	70	60	100	80	80
Peter Kleinebudde	30	40	0	20	20

Evaluation of alternative methods to derive particle density from compression data

---

Sabrina Berkenkemper[1], Peter Kleinebudde[1]

[1]Institute of Pharmaceutics and Biopharmaceutics,

Heinrich Heine University, Düsseldorf, Germany

International Journal of Pharmaceutics 632 (2023) 122582

Article available online at:

https://doi.org/10.1016/j.ijpharm.2023.122582

C.2 Evaluation of common compression analyses

C.2.1 Compressibility analysis as robust in-die compression analysis for describing tableting behaviour

Pretext

This publication describes the application of a common compression analysis as an in-die method. The compressibility analysis, so far used as an out-of-die method, was compared with the Heckel analysis, which is widely used and accepted. Both methods are intended to characterize the compressibility of a material. Both compression parameters, the yield pressure (P_y) of the Heckel analysis and the compressibility constant (K) of the compressibility analysis, were investigated and conclusively evaluated. In addition, a sensitivity analysis of both methods was performed with respect to tableting parameters, particle density, and punch displacement measurements.

The following paper has been published by RPS Pharmacy and Pharmacology Reports in Volume 1 (2022).

https://doi.org/10.1093/rpsppr/rqac004

Weighting of the authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Sabrina Berkenkemper	40	70	100	80	80
Peter Kleinebudde	60	30	0	20	20

Compressibility analysis as robust in-die compression analysis for describing tableting behaviour

---

Sabrina Berkenkemper[1], Peter Kleinebudde[1]

[1]Institute of Pharmaceutics and Biopharmaceutics,

Heinrich Heine University, Düsseldorf, Germany

RPS Pharmacy and Pharmacology Reports 1 (2022) 1-7

Article available online at:

https://doi.org/10.1093/rpsppr/rqac004

C.2.2 Investigating compressibility descriptors for binary mixtures of different deformation behavior

Pretext

In this section, compressibility descriptors were used regarding their applicability to predict binary mixtures. Three different material combinations were chosen to analyze different deformation behaviors. All compression analyses applied were performed as in-die methods. The objective was to examine which of the analyses is most suitable to describe binary mixtures. Furthermore, the linear mixing rule was applied for both volume and mass fractions and the applicability was evaluated. In addition, the compressibility descriptors were evaluated in terms of their informative value with respect to material characterization.

The following paper has been published by Powder Technology in Volume 424 (2023).

https://doi.org/10.1016/j.powtec.2023.118571

Weighting of the authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Sabrina Berkenkemper	40	60	100	60	70
Stefan Klinken	40	30	0	20	10
Peter Kleinebudde	20	10	0	20	20

Investigating compressibility descriptors for binary mixtures of different deformation behavior

---

Sabrina Berkenkemper[1], Stefan Klinken[1], Peter Kleinebudde[1]

[1]Institute of Pharmaceutics and Biopharmaceutics,

Heinrich Heine University, Düsseldorf, Germany

Powder Technology 424 (2023) 118571

Article available online at:

https://doi.org/10.1016/j.powtec.2023.118571

C.2.3 Multivariate data analysis to evaluate commonly used compression descriptors

Pretext

In this study, a multivariate data analysis of all experimentally collected tablet data was performed. Material and tablet properties as well as the compression descriptors described in the previous publications were used as input variables. The aim was to deepen the understanding of the tableting process and find compression analyses best suitable to characterize new materials for tableting. The influence of tableting parameters on tableting behavior should further be assessed. Similarities and differences of the previously used compression analyses should be investigated. Recommendations on a combination of compression analyses to use for material characterization regarding their tableting behavior should be given.

The following paper has been published by the International Journal of Pharmaceutics in Volume 637 (2023).

https://doi.org/10.1016/j.ijpharm.2023.122890

Weighting of the authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Sabrina Berkenkemper	40	45	100	45	65
Stefan Klinken	40	45	0	55	25
Peter Kleinebudde	20	10	0	0	10

Multivariate data analysis to evaluate commonly used compression descriptors

---

Sabrina Berkenkemper[1], Stefan Klinken[1], Peter Kleinebudde[1]

[1]Institute of Pharmaceutics and Biopharmaceutics,

Heinrich Heine University, Düsseldorf, Germany

International Journal of Pharmaceutics Volume 637 (2023) 122890

Article available online at:

https://doi.org/10.1016/j.ijpharm.2023.122890

C.3 Discussion

Material characterization using compression analysis is a widely accepted technique for describing the behavior of materials during tableting. Knowledge of deformation behavior provides key information essential for formulation development. Compression analyses have been used for 100 years, and accordingly many equations are available. In the present work, a selection of commonly known compression analyses was examined in more detail in order to answer the question which compression analyses are useful to apply.

Heckel analysis is considered one of the standard methods for describing tableting behavior. It is often criticized due to its susceptibility to influencing parameters such as the compression pressure, but also the particle density [1]. The particle density is part of most compression analyses, since it is needed for the calculation of the porosity or the *SF*, respectively. The correct determination of the particle density of a material is therefore essential for the performance of compression analyses. The traditional method for the determination of particle density in the pharmaceutical field is helium pycnometry. This has been criticized due to the tendency for errors in the measurement of materials containing water [2]. The associated water on the surface of a material can be removed by helium gas during the purging cycles of the measurement. The measured sample volume does not correspond to the actual volume of the substance. As a result, the volume is underestimated, and the particle density subsequently overestimated. Such an overestimation of the particle density can lead to misleading results in the calculation of compression analyses. Sonnergaard [1] showed that a relative error in particle density of 1% can lead to a deviation of the yield pressure determined by Heckel analysis of more than 10%. For this reason, the alternative methods for particle density determination using compression data according to Sun [2] and Krumme [3] were investigated in more detail. Sun's method showed a significant underestimation of the particle density of materials containing water. Water-free materials, on the other hand, can be determined using this method as long as the yield pressure of the material is not too high. Materials with pronounced resistance to permanent deformation could not be densified to sufficiently high *SF* and are therefore unsuitable for Sun's method. The method according to Krumme also proved to be unsuitable for materials with high yield pressure, since the particle density was considerably underestimated. Such materials are still to be measured with the proven

method of helium pycnometry. However, for water-containing materials or materials with lower yield pressure, this method was found to be a useful alternative to helium pycnometry. The method was modified so that the tablet height immediately after rapid elastic recovery was used instead of the minimum tablet height under pressure. This modification showed good agreement with theoretically calculated particle densities considering the respective water content. The modified Krumme method can be used in the future for materials containing water or if no helium pycnometer is available. For the method according to Krumme, no additional experimental effort is necessary. The raw data of the tableting process as well as the mass, as it is required for most compression analyses, are sufficient for the implementation of the method.

Compressibility represents a special interest due to the possibility of in-die analysis of material behavior under pressure. The method of Johanson [4] provided promising results out-of-die with a linearity valid over a wider range than in Heckel analysis. So far, compressibility has only been performed out-of-die. In this work, it was investigated in detail with respect to its applicability as an in-die method as well as its robustness to influencing parameters such as compression pressure, particle density, and compression speed. A direct comparison with Heckel analysis was performed to evaluate the method with a standard method. The Heckel analysis was identified as being sensitive against the compression pressure and changes in particle density. The compression speed, punch diameter and compacted mass had less influence on the results of P_y. The compression pressure only influenced the evaluation of P_y as long as the second curvature of the plot was not reached yet. As soon as the second curvature has been reached in the Heckel plot, the P_y was constant. This proved Heckel analysis to be a reliable method for determining the compressibility of a material despite the criticism [1]. A proper evaluation is the key aspect for a correct interpretation of the results. A correlation of the out-of-die to in-die results of compressibility analysis was shown using the twelve materials and the fitting of the in-die data gave high coefficients of determination for all batches. K as the compression parameter of the analysis was robust to the different experimental influences. The particle density as well as the compression pressure in particular showed no significant influence on the results. Thus, the compressibility analysis proved to be superior to the Heckel analysis. However, no correlation could be found between K and P_y. Therefore, the two analyses seem to describe different material properties during tableting.

The validity of different analyses with respect to compressibility should be further investigated with a special focus on the description of mixtures. For this purpose, the analyses describing compressibility were applied to binary mixtures. In order to cover a wide range of possible deformation behaviors, three material combinations were tableted: a binary mixture of two plastic materials, one of two brittle materials and one with both a plastic and a brittle material. Three analyses showed promising results in describing binary mixtures. The compression parameters of the Kawakita, compressibility, and Walker analyses (*ab*, *K*, and *-W*) showed a linear relationship with the composition of the mixture. Thus, these analyses are advantageous in their application to mixtures, although mixtures with more components need to be investigated to assess the overall applicability of the analyses. If the methods are applicable to multi-component mixtures as well, these analyses could be suitable for the use as a PAT tool. Even small changes in the composition of a blend can alter the resulting tablet and its critical quality attributes. A combination of different compression analyses to monitor tableting behavior would thus be useful especially for CM, but also for batch-to-batch processes.

With the use of binary mixtures, promising compression analyses could already be highlighted. In a final multivariate analysis of the tablet data, commonalities and differences of all compression analyses investigated should be examined. This was to further evaluate the informative value of the analyses as well as their ability to characterize materials. Tabletability plays a central role in formulation development. Since it can only be determined out-of-die, an alternative determination method should be identified in this work. The rearrangement index *ab* showed a strong correlation to tabletability. The Kawakita analysis is feasible in-die, so it could represent a non-destructive method to determine tabletability. Further investigation with more materials with diverse properties and multi-component blends is advisable at this point to verify the correlation. Furthermore, no additional information or experiments are needed to perform the Kawakita analysis. The tablet raw data is sufficient to perform the method. However, the determination of V_0 has been problematic in the past, and different methods have been postulated [5, 6]. Since the particle density is not required when determining V_0 using the compression data, this approach was chosen for the present work. Comparable values to the literature were found and the materials were successfully classified. It is therefore considered to be an advantageous method over the other options described.

With the variety of compression analyses available, deciding which method to use is often not easy. Using multivariate data analysis, a combination of three compression analyses was found to give a fairly thorough picture of the tableting behavior of a material. These methods include the Kawakita, compressibility and Kuentz-Leuenberger analysis. The Kuentz-Leuenberger analysis showed a positive correlation with P_y and superiority over Heckel in terms of informative value as well as robustness to experimental parameters. It is therefore a promising alternative to the Heckel analysis. The compressibility analysis was already shown to be advantageous due to its high robustness to influencing parameters and its ability to describe binary mixtures. The multivariate data analysis showed an orthogonal position to Heckel and KL, covering a material property that these two methods do not describe. The robustness of the methods to influencing parameters is also an important aspect in the evaluation of the analyses. The compression pressure showed by far the greatest influence on the tablet properties. *K* and *ab* showed a high robustness to compression pressure, making them particularly advantageous to use. C^{-1}_{KL} showed lower sensitivity to tableting parameters than P_y, making KL analysis appear advantageous over Heckel. All three methods (Kawakita, compressibility, Kuentz-Leuenberger) are in-die applicable, so they could be used as real-time monitoring of the tableting process. Should the three methods be able to detect small changes in composition and thus mechanical behavior, each tablet during the manufacturing could be monitored in real-time. An evaluation of this combination with multi-component mixtures could verify the applicability as a PAT tool.

The characterization of a material in terms of deformation behavior always applies only to the grade that has been investigated. The influence of the manufacturing method and the particle size on the deformation behavior and thus the tableting behavior has already been shown [7]. This conclusion could be confirmed in the present work. Therefore, it is only possible to draw conclusions about the grade of the material used in each case. This underlines the importance of the complete specification of the materials used in the literature.

C.4 References

1. Sonnergaard, J.M. *A critical evaluation of the Heckel equation*. International Journal of Pharmaceutics, 1999. 193(1): p. 63-71, doi: https://doi.org/10.1016/S0378-5173(99)00319-1.

2. Sun, C.C. *A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders*. Journal of Pharmaceutical Sciences, 2004. 93(3): p. 646-653, doi: https://doi.org/10.1002/jps.10595.

3. Krumme, M., Schwabe, L. and Frömming, K.H. *Development of computerised procedures for the characterisation of the tableting properties with eccentric machines: extended Heckel analysis*. European Journal of Pharmaceutics and Biopharmaceutics, 2000. 49(3): p. 275-286, doi: https://doi.org/10.1016/S0939-6411(00)00067-9.

4. Johanson, J.R. *A rolling theory for granular solids*. Journal of Applied Mechanics, 1965. 32(4): p. 842-848, doi: https://doi.org/10.1115/1.3627325.

5. Sonnergaard, J. *Investigation of a new mathematical model for compression of pharmaceutical powders*. European Journal of Pharmaceutical Sciences, 2001. 14(2): p. 149-157, doi: https://doi.org/10.1016/S0928-0987(01)00165-8.

6. Nordström, J., Klevan, I. and Alderborn, G. *A particle rearrangement index based on the Kawakita powder compression equation*. Journal of Pharmaceutical Sciences, 2009. 98(3): p. 1053-1063, doi: https://doi.org/10.1002/jps.21488.

7. Rue, P.J. and Rees, J.E. *Limitations of the Heckel relation for predicting powder compaction mechanisms*. Journal of Pharmacy and Pharmacology, 1978. 30(1): p. 642-643, doi: https://doi.org/10.1111/j.2042-7158.1978.tb13347.x.

Section D.

Summary and perspectives

Summary and perspectives

Based on existing works, this thesis has generated a comprehensive evaluation of some well-known and widely used compression analyses. It helped to further deepen the understanding of the processes during tableting. A systematic study of tableting parameters including compression pressure, compression speed, punch diameter, and compacted mass was conducted. Compression pressure was found to be the most important influencing parameter, while the other tableting parameters played a minor role. This can have a positive effect in a scale-up process, since the compression pressure can be kept constant, while the compression speed usually increases when transferring to production machines. It was shown that the properties of the raw material, such as the manufacturing method and particle size, have a significant influence on the deformation and subsequently on the tableting behavior. The accurate and complete specification of the material grade in literature is therefore essential to obtain comparability of results in material characterization and description of the tableting behavior.

Compressibility as well as KL analysis have successfully been established as in-die methods and can be applied as such in the future. KL has been found to describe the same material properties as Heckel analysis. A strong correlation of the results was shown. In direct comparison, KL showed a higher informative value concerning the given data set as well as a slightly lower sensitivity to influencing parameters. Thus, it is superior to Heckel analysis and should be applied preferentially. A detailed evaluation of KL analysis as an in-die method with greater material diversity could not be carried out in this work. This should be done in the future to further prove the applicability of the analysis as an in-die method. The compressibility analysis has been shown to be a complementary method that focuses on different material properties than KL and Heckel. The high robustness of this method, especially with respect to compression pressure and particle density, is particularly valuable. This robustness makes compressibility analysis a method that can achieve high comparability and is exceptionally suitable for scale-up processes. The rearrangement index *ab* from the Kawakita analysis was found to be a suitable parameter for describing the tabletability. This makes it possible to obtain statements about tabletability using a non-destructive in-die analysis and saves time and resources in formulation development. A further

evaluation of the correlation with more materials and especially with multi-component mixtures should be carried out.

A promising combination of three in-die compression analyses - Kawakita, compressibility, and KL - was found that could be applied as PAT tools for real-time monitoring of tableting. These three compression analyses already show a fairly thorough picture of a material's tableting behavior. In addition, the compressibility and Kawakita analyses show promising qualities in describing binary mixtures. This triple combination should be evaluated for its applicability as a PAT tool. For this purpose, a formulation with different concentrations of active ingredient could be investigated. This can be used to check if the three compression parameters are able to reflect the change in composition. If this is the case, the combination of compression analyses highlighted in this work could be used as a PAT tool in the manufacturing of tablets in the future. A real-time monitoring of the tableting process including the content of the dosage form could be enabled using this approach. Finally, the accomplishments of this work can contribute to a more standardised characterization of materials for the tableting process.

Danksagung

Zuallererst möchte ich mich bei meinem Doktorvater Prof. Dr. Dr. h.c. Peter Kleinebudde bedanken, dass er mir die Promotion in seinem Arbeitskreis ermöglicht hat. Sie waren immer sehr verständnisvoll für alle kleineren und größeren Pannen, haben stets Verbesserungsvorschläge parat gehabt und Ihre Tür stand immer offen. Die Diskussionen über meine Daten und Publikationen mit Ihnen haben meine Arbeit zu dem gemacht, was sie ist, worauf ich sehr stolz bin. Auch wenn meine Begeisterung für das Promotionsthema anfangs zu wünschen übriggelassen hat, haben Sie es geschafft, mir Durchhaltevermögen einzutrichtern. Ebenfalls bedanke ich mich für die Arbeitskreis-Abende abseits des Instituts zu Ihren Geburtstagen und der Weinverkostung. Wir Doktoranden durften Sie an diesen Abenden von Ihrer persönlichen Seite kennenlernen, was nicht selbstverständlich ist. Diese fröhlichen Abende werde ich in guter Erinnerung behalten. Ich habe in meiner Zeit am Institut sehr viel Fachliches aber auch Menschliches gelernt und möchte mich dafür ganz herzlich bei Ihnen bedanken.

Jun.-Prof. Dr. Michael Hacker möchte ich für die Übernahme des Koreferats danken. Du hast mir einen anderen Blickwinkel auf meine Daten ermöglicht und mit konstruktiver Kritik meine Arbeit weitergebracht. Du stellst für das Institut eine große Bereicherung dar.

Ein riesiger Dank geht an Hanna „Plappi“ Grumann. Es war die große Freundschaft auf den zweiten Blick (nachdem ich klargestellt habe, dass ich immer böse gucke). Wir konnten von Anfang an stundenlang über alle Themen sprechen und es hat sich superschnell eine sehr tiefe Freundschaft gebildet. Ich freue mich, dass du in unserem Arbeitskreis angefangen hast und wir uns kennenlernen durften. Wir sind in den zwei Jahren durch dick und dünn gegangen, haben zusammen gelacht und geweint und ich habe eine Freundin fürs Leben gefunden. Danke für deine Freundschaft!

Bei Laura Falkenstein möchte ich mich für 2,5 tolle Jahre in unserem („Aquarium“) Keller-Büro bedanken. Du hast mich so herzlich aufgenommen und wir konnten immer sehr viel lachen. Bei zahlreichen Tees und Kaffees haben wir uns angefreundet und konnten über alles reden – ob privat oder fachlich. Ich konnte immer auf deine Unterstützung zählen. Vielen Dank dafür!

Felix Reichel danke ich, dass er die Leere im Büro gefüllt hat, als Laura fertig wurde. Wir hatten sehr viel Spaß und die „Sho(r)t“-Friday Tradition werde ich in Ehren halten.

Dr. Björn Fischer danke ich, dass er mich die letzten drei Monate meiner Promotion bei sich im Büro aufgenommen hat. Mit vollem Kühlschrank und Kaffeeregal haben sich die Paper fast von allein geschrieben. Die Gespräche über Tennis, Bier, Wärmeleitfähigkeit und viele weitere Themen habe ich sehr genossen.

Ein großer Dank geht an Stefan Klinken, der mir bei fachlichen Fragen hilfsbereit zur Seite stand. Du hast mir die Auswertung der Daten extrem erleichtert und mit tollen Ideen zur Entwicklung meiner Arbeit beigetragen, danke dafür.

Ein weiterer Dank gilt Dr. Annika Wilms und Dr. Dina Kottke, die mich als „alte Hasen“ sehr herzlich in die Mädelsgruppe aufgenommen haben. Ihr habt mir das Gefühl gegeben, direkt dazuzugehören und die gemeinsamen Pizza- und Weinabende, Wasserski-Events und Switch-Contests haben mir die Promotionszeit versüßt.

Dr. Sebastian „Ronny“ Pohl möchte ich dafür danken, dass er er ist! Mit deiner offenen, herzlichen und fröhlichen Art hast du immer für jede Menge Lachen gesorgt. Mit dir hat sogar Auswertung für Firmenprojekte Spaß gemacht. Auch hast du es immer geschafft, das Positive zu sehen und mich aufgemuntert, wenn ich mal das Gefühl hatte, in meinen Daten unterzugehen. Deine Lache werde ich niemals vergessen!

Arne Schulzen möchte ich für seine ruhige und besonnene Art danken. Du hast es stets geschafft mir andere Standpunkte näherzubringen, wenn ich aufgebracht zu euch ins Büro kam. Dank dir konnte ich dann wieder die „bright side of life“ erkennen.

Meinen beiden WPP-Gruppen mit Lara Hadamitzky und Rishika Gupta sowie Niklas Carstensen und Meryem Carikci möchte ich für den Einsatz im Labor danken.

Auch allen ungenannten - ehemaligen und derzeitigen - Instituts-Mitgliedern möchte ich danken. Egal ob Doktorandenvorträge, Konferenzfahrten oder Karnevals- und Weihnachtsfeiern, ihr alle habt meine Promotion zu einer wunderbaren und unvergesslichen Zeit gemacht. Ich werde das Institut mit euch allen sehr vermissen!

Lukas Lammerding möchte ich dafür danken, dass er im Institut angefangen hat zu promovieren. Ohne diese Entscheidung hätte ich nicht meinen Lieblingsmenschen auf der ganzen Welt gefunden. Du bist meine bessere Hälfte und bereicherst mein Leben auf so vielen Ebenen. Danke für deine Liebe und Unterstützung!

Zuletzt möchte ich meiner Familie danken, ohne die ich nicht zu dem Menschen geworden wäre, der ich heute bin. Ihr habt mich immer voller Liebe und Tatendrang bei all meinen Vorhaben unterstützt. Ich schulde euch unendlichen Dank, dass ihr mir all das ermöglicht habt!

Eidesstattliche Erklärung

Ich versichere an Eides statt, dass die vorliegende Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.

Düsseldorf, den 26.06.2023 _____

Sabrina Berkenkemper