Heinrich Heine Universität Düsseldorf

Influence of temperature on the tableting behavior of pure materials and complete formulations

Inaugural-Dissertation

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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aus Essen

Düsseldorf, November 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. Prof. Dr. Anne Seidlitz

Tag der mündlichen Prüfung: 21.02.2024

Für Mama und Bernd, wenn auch nur im Herzen.

TABLE OF CONTENTS

List of publications and contributions

Published manuscripts

Grumann, H.D., S. Klinken, and P. Kleinebudde, *Influence of temperature on the compression behavior of pharmaceutical excipients*. International Journal of Pharmaceutics, 2022. **628**: p. 122305

Grumann, H.D., S. Klinken, and P. Kleinebudde, *Evaluation of in-die compression data for a deeper understanding of altered excipient properties upon temperature rise*. AAPS PharmSciTech, 2023. **24**(4): p. 89.

Grumann, H.D. and P. Kleinebudde, *Investigating the heat sensitivity of frequently used excipients with varying particle sizes*. European Journal of Pharmaceutics and Biopharmaceutics, 2023. **192**: p. 1-12.

Grumann, H. D. and P. Kleinebudde*, Effect of tableting temperature on tablet properties and dissolution behavior of heat sensitive formulations.* International Journal of Pharmaceutics*,* 2023: p. 123603.

Congress presentations

Plappert, H. and P. Kleinebudde, 2022. *Einfluss der Temperatur auf das Tablettierverhalten binärer Mischungen*. Oral presentation, Jahrestreffen ProcessNet-Fachgruppe Agglomerations- und Schüttguttechnik, Leipzig, Germany

Plappert, H. and P. Kleinebudde, 2022. *Influence of temperature on the tableting behavior of a binary mixture*. Poster presentation, 13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Rotterdam, Netherlands

Grumann, H. D. and P. Kleinebudde, 2023. *Assessing temperature influence on tablet quality attributes*. Oral presentation, Medelpharm, Online-Webinar

Grumann, H. D. and P. Kleinebudde, 2023. *Influence of glass transition temperature on energy parameters during heated compression*. Poster presentation, 4th European Conference on Pharmaceutics, Marseille, France

Grumann, H. D. and P. Kleinebudde, 2023. *Relationship between yield pressure and energy parameters upon temperature rise*. Poster presentation, 4th European Conference on Pharmaceutics, Marseille, France

Grumann, H. D. and P. Kleinebudde, 2023. *Investigating the heat sensitivity of hyproloses with different particle sizes during tableting*. Poster presentation, 10th International Granulation Workshop – Granulation Conference, Sheffield, United Kingdom

List of abbreviations

ABC	Area between curves
API	Active pharmaceutical ingredient
AUC	Area under the curve
BA	Bonding area
BS	Bonding strength
DC	Direct compression
DT	Disintegration time
E	Energy
e.g.	Exempli gratia
ER	Elastic recovery
FDA	Food and Drug Administration
FEM	Finite element analysis
HPC	Hydroxypropyl cellulose
MCC	Microcrystalline cellulose
MDT	Mean dissolution time
PF	Plasticity factor
PSD	Particle size distribution
P_y	Yield pressure
SEM	Scanning electron microscope
SF	Solid fraction

T_c	Compression temperature
T_g	Glass transition temperature
T_m	Melting temperature
TS	Tensile strength
QbD	Quality by Design

Section 1. Introduction

1.1 Tablets and tableting

1.1.1 Introduction

Tablets represent one of the most common dosage forms within the pharmaceutical industry [1]. They are usually manufactured by the compression of a powder or granule. Besides one or more active pharmaceutical ingredients (APIs), they may contain excipients such as diluents, binders, disintegrants, lubricants and/or glidants. Reasons for their popularity include precise dosing, superior patient compliance and a comparably efficient manufacturing procedure [1, 2]. The simplest process for tablet production is the direct compression (DC) of a powder or powder mixture. If DC is feasible, no equipment for additional process steps such as the production and/or drying of granules or other intermediate products is necessary. This reduces costs, processing time and energy consumption [3, 4].

DC requires for a powder to possess sufficient flow, lubrication and cohesion [3-5]. Sufficient flow ensures a uniform filling of the die, which is usually volumetric on an industrial scale. If it is assumed that all particles within a powder mixture are homogenously distributed, a reproducible filling during production ensures weight and therefore content uniformity of the compact [6]. The flowability of a powder is affected by forces acting between particles including Van der Waals, electrostatic and capillary forces [6, 7]. After compression, the tablet needs to be ejected from the die. The corresponding ejection force is indicative of the friction between the tablet and the die wall. Excessive friction not only generates heat, but might also impede tablet quality and promote wear of the instruments [2, 8-10]. Moreover, powder particles might progressively accumulate on tooling, which is defined as punch sticking [8]. These effects might be prevented by lubrication [8-11]. If the optimum amount of lubricant for a specific formulation is exceeded, however, this might result in negative effects on mechanical strength, disintegration and dissolution [12]. The mechanical strength is determined by cohesive forces, which enable the formation of an integer compact. During production, the investigation of mechanical strength is a crucial parameter in the assessment of tablet quality. Sufficient mechanical strength enables packaging and transport as well as handling by patients. It might also have an impact on disintegration and dissolution [13].

Most excipients and APIs lack at least one of the above-mentioned properties. Therefore, formulation development puts a focus on the identification of suitable formulations and the production steps involved.

The complexity of the process is enhanced by the physical, chemical and mechanical properties of the used components (Fig. 1). The latter is essential for a material's deformation under stress during processing. The physical properties of a material include the particle size or particle size distribution (PSD), their shape and density. The investigation of chemical structures involves all aspects of a material's crystallinity and/or amorphousness, which is also related to its hygroscopicity [14]. The interaction of all properties has an impact on the processing conditions and vice versa [15]. It is therefore desirable to explore the behavior of different powders with varying process conditions to identify critical criteria during tableting, which define the final performance as a drug delivery system.

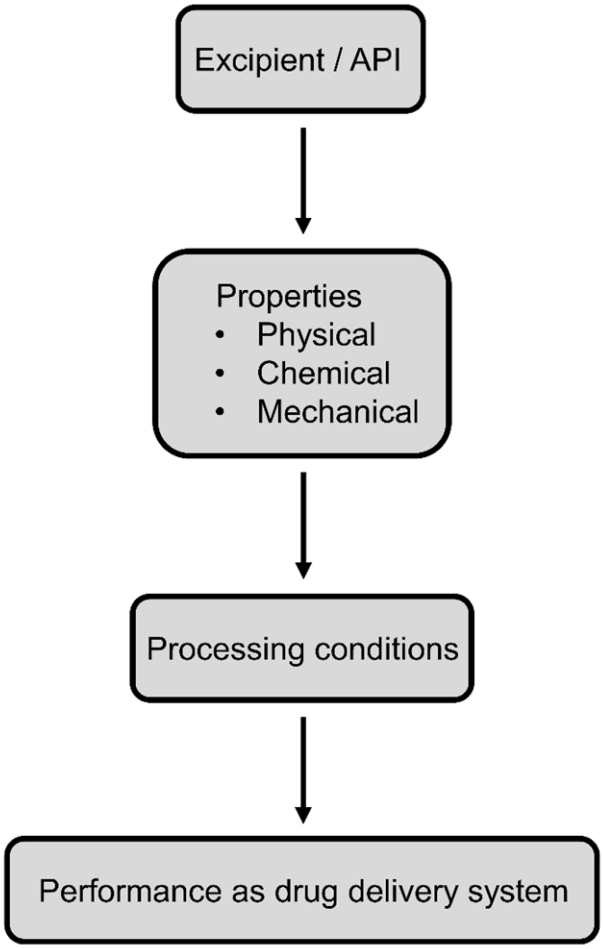

Figure 1. Excipient and API properties influencing drug delivery system performance.

1.1.2 Compression stages

The tableting process involves several compression stages. Initially, the powder particles are loosely packed in the die after filling. When the distance between the punches decreases, the particles are first rearranged without a notable pressure increase. As smaller particles fill the voids between larger particles, the initial bulk density of the material is replaced by the deaeration density. As the pressure continues to increase, interparticulate friction eventually prohibits a further approach [16]. The density subsequently increases by elastic deformation, which is energy stored reversibly. When the elastic limit of the particles is exceeded, they deform permanently, whereby plastic flow and fragmentation occur [14, 17, 18]. This leads to an enhanced contact area between the particles, which reaches its maximum at the end of the compression phase [19]. During and after decompression, the stored elastic energy is released [14]. Apart from the material properties, the processing conditions can strongly influence deformation characteristics [1, 2, 20]. This often enables an estimation of a powder's tableting behavior.

Depending on the response of a material, the deformation behavior can be classified as elastic, viscoelastic, plastic or brittle [21]. Although these characteristics are never isolated in pharmaceutical materials, one is usually prevailing for a substance [14, 15, 22].

Elastic deformation is energy stored reversibly, which can be quantified by the Young's modulus, Poisson's ratio or the elastic recovery (ER) [4, 23, 24]. It is detectable as tablet expansion when the stored elastic energy is released during and after decompression. It contains the fast in-die ER and the slow out-of-die ER, both of which are influenced by the time-dependent viscoelastic recovery [25, 26]. Their extent is dependent on the compression and decompression speed [27]. The in-die ER can directly be retrieved from the compression data even if the tableting properties of a material are poor, which is time and material saving. It is limited by the fact that no data is generated after the upper punch detaches from the tablet surface. Out-of-die analyses include the recovery after ejection, but require additional measuring equipment [25]. The ER can be calculated using Equation 1:

$$ER = \frac{V_r - V_m}{V_m} * 100\ \%$$

Equation 1

where V_m is the minimal volume retrieved from the minimum distance between both punches during tableting and V_r is the recovery volume (in-die or out-of-die). A high ER eliminates established bonds, which favors a higher porosity of a compact and might trigger capping and lamination [13, 18].

In contrast to elastic deformation, plastic flow is irreversible. It is a prerequisite for the establishment of a large bonding surface area. A sufficient amount of plastic deformation allows the release of stored elastic energy without bond breakage during decompression [28]. The interplay between the formed bonding area (BA) and the bonding strength (BS) determines the mechanical strength of a tablet [16, 29, 30]. The BS results from the work of adhesion [31]. Predominantly brittle materials irreversibly consolidate by fragmentation [2, 14, 32]. This increases the number of contact points available for bonding. After the formation of smaller discrete particles, elastic and plastic deformation might still occur [16, 17].

Irreversible deformation takes place when no more elastic energy can be stored during compression. This threshold is referred to as the yield pressure (P_y) of a material [14]. For ductile materials, the cold flow above P_y is time-dependent [33]. For this reason, they are especially responsive to process variations such as the compression speed [20, 34, 35]. At higher machine speeds, the dwell time available for the material to yield is decreased. The effect of compression speed on the fragmentation of brittle materials is only limited [35].

Both the fracture stress and the stress necessary for plastic flow are also influenced by the particle size of a material. When the particle size decreases, the fracture stress of a material increases. Plastic flow, on the other hand, is independent of particle size [36]. If a material exhibits both brittle and ductile characteristics, the fracture stress initially increases with decreasing particle size. When the fracture stress exceeds the yield stress, plastic flow will occur independent of particle size. This phenomenon might change the dominant compaction mechanism of the system and is referred to as the brittle-ductile transition [36-38].

1.1.3 Temperature evolution

During the tableting process, mechanical work is put into the system [39]. Physically, work (*W*) is defined as the multiplication of force (*F*) and distance (*x*) according to the following equation [40]:

$$W = \int F dx$$

Equation 2

The work performed determines the total energy input during compression, which is comprised of elastic and plastic deformation, fragmentation and friction. Friction occurs between neighboring powder particles, powder particles and the die-wall and between the machine components. The compression energy input contributes to the energy of adhesion between particles [41, 42]. It can be retrieved from the area under the force-displacement curve (AUC) [40]. The named processes trigger the generation of heat, when mechanical energy is transformed into thermal energy [43, 44]. Its transfer is directed from the powder to the tableting instruments and vice versa [45]. The first law of thermodynamics dictates that the heat added to or released by the system (*Q*) combined with the work done on the system (*W*) is the counterpart to the change in internal energy (ΔU) [39, 40, 44]:

$$\Delta U = dQ + dW$$

Equation 3

It is therefore desirable to assess the generated heat to fully grasp the tableting procedure and associated changes in material behavior. During tableting, the measured temperatures might exceed 50 °C [46]. Localized temperatures of > 100 °C have been postulated [47]. To determine the generated heat is challenging for several reasons. Firstly, the heat is promptly dispersed to its environment after compression. Secondly, the compact is not physically accessible before ejection, which prevents measurements at the assumed temperature maximum. Thirdly, the high pressures during compaction would destroy most possible measuring devices brought into the powder mixture [43]. Only one publication describes the complicated set-up of placing a thermocouple within the powder bed [48]. The complexity is enhanced when not single tableting cycles, but prolonged processes are investigated, which increases the

overall heat content. Back when the instrumentation of tablet presses and technical equipment lacked profound development, studies focused on the assessment of temperature changes by measuring the area beneath force-displacement curves with a planimeter [40] or by applying thermochromic methods [43]. The progressive development of modern instrumentation provided the opportunity to make use of more advanced techniques and a higher accuracy during measurement and evaluation. First attempts of modern instrumentation go back to the 1950's [49]. It requires for the applied force to be transferred to an electric voltage signal [18]. This is accomplished by strain gauges or piezoelectric transducers. The accurate transformation of data to a computer system is in need of sufficient resolution, accuracy, precision and sensitivity [50]. Nowadays, compression data can be displayed automatically. Compaction simulators combine the required data acquisition tools with the possibility to mimic specific processes on a small scale. This can be useful during research, development and production [51, 52].

The accurate application of compression parameters has been combined with temperature analyses such as infrared measurements [46, 53, 54], calorimetry [45, 55-57] and finite element analysis (FEM) [44, 58]. These methods require additional equipment or complex mathematical calculations and often lack the opportunity to still be used efficiently during scale-up. It therefore appears meaningful to directly link in-die compression data to material changes occurring from temperature rise. This has only been subject to few studies [54, 59, 60]. Besides the compression parameters and mechanical behavior, the physicochemical structure of a material needs to be known in order to interpret the generated data correctly.

For the above-mentioned reasons, the imitation of elevated temperatures on a small-scale has gained increasing interest. This often includes the modification of tablet presses for heated compression [47, 59, 60]. Recently, an additional tool for the modification of the STYL'One Evo tablet press (Medelpharm, France) has been developed. With this set-up, it is possible to mimic the temperature increase occurring on an industrial scale by thermally controlling the die. The details are depicted in Fig. 2. The die is surrounded by a heating element, which is connected to oil-containing pipes. The direct connection to a thermoelectric bath provides the opportunity to set the desired temperature for the tableting experiments. The maximum possible die temperature is 70 °C. Compression data can be recorded with a maximum acquisition

frequency of 10 kHz, whereby the accuracy of the punch displacement measurement is 1 µm.

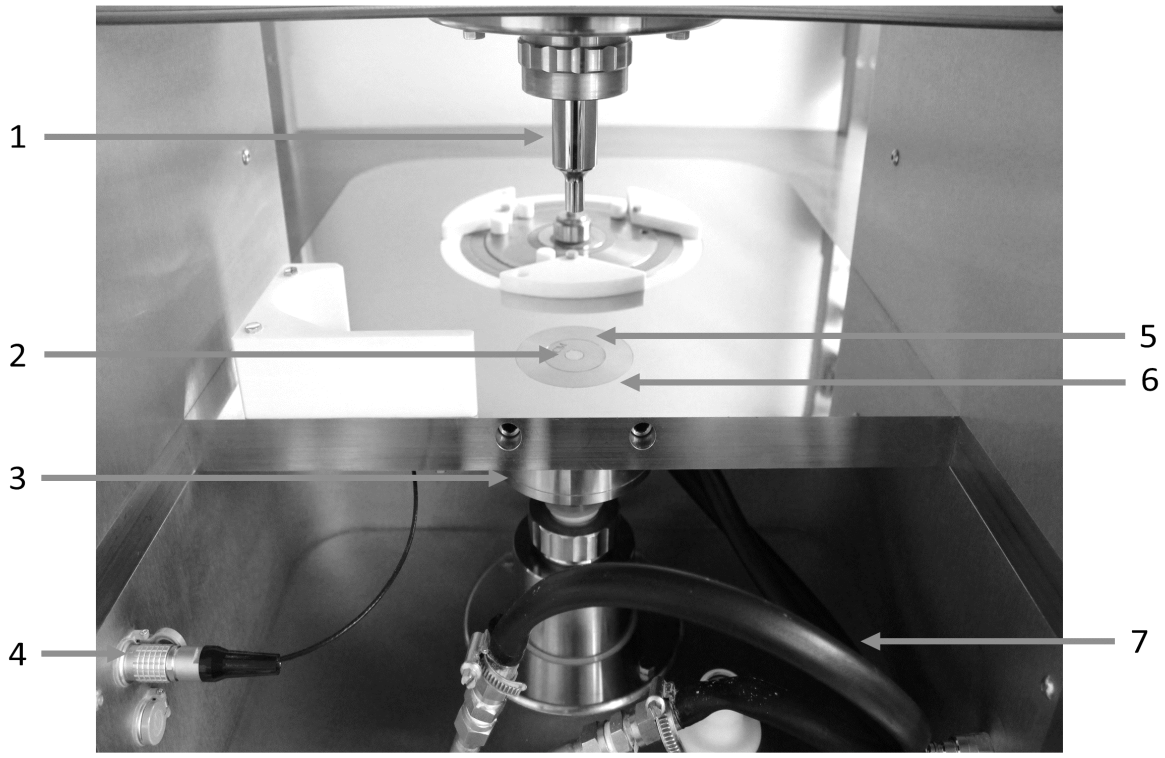

Figure 2. Set-up of the modified tablet press (STYL'One Evo, Medelpharm): (1) upper punch, (2) lower punch tip, (3) heating ring, (4) thermocouple, (5) die, (6) die holder, (7) pipes containing heating oil.

1.2 Structure of polymers

Polymers can be defined as long-chained molecules with a high molecular weight. At sufficiently low temperatures, all polymers are rigid solids. When the temperature rises, the additional thermal energy eventually allows for the material to transform to a liquid state [61]. The type of transformation depends on the polymer structure, which can be classified as either crystalline, semi-crystalline or amorphous (Fig. 3) [62, 63].

Crystalline substances exhibit an ordered structure. When the material is heated, the specific volume gradually expands until the melting temperature (T_m) is reached (Fig. 3a) [63]. T_m represents the temperature above which crystallinity completely disappears and the melt becomes amorphous [62-64]. Besides the volume, the energy,

enthalpy and entropy of the system increase [65, 66]. T_m is well-defined. Until T_m, the rigidity of a molecule is preserved [66].

The structure of amorphous polymers is different. The chains are arranged randomly, which prevents a long range molecular order. Short range orders are possible [61, 67]. Completely amorphous polymers are obtained if a cooled melt is prevented from crystal nucleation, which would subsequently lead to crystal growth [67]. Upon low temperatures, the polymer is in a glassy state [61]. Its rigidity hinders extensive bond vibration [68]. When the temperature is raised, the larger chain motion triggers the transformation to a plastified state close to and beyond its glass transition temperature (T_g) [63]. However, the thermodynamic properties do not change abruptly. The polymer gradually softens, as coordinated chain motions occur [62, 66]. This increases the specific volume (Fig. 3b). The change to a rubbery state or a viscous liquid induces an alteration of physicochemical properties [69, 70].

If both crystalline and amorphous areas are present, a polymer is classified as semi-crystalline. Generally, the combination of a long chain length and subsequently arising entanglements prohibits complete crystallinity of a molecule [62, 71]. Regions containing defects within the crystalline structure lead to areas of higher disorder. The crystals are arranged as lamellae, which are separated by amorphous areas [72, 73]. As a result, amorphous parts are interdispersed between crystalline parts [74]. Semi-crystalline polymers exhibit characteristics of both amorphous and crystalline polymers. The cool state of a semi-crystalline polymer is also rigid. When the polymer is heated, it first transforms to the plastified state when the T_g is transgressed (Fig. 3c). When the T_m of the crystalline areas is reached, the polymer converts to the liquid state. The T_m is always beyond the T_g [62].

The identification of the T_g or the T_m can be conducted via thermal analyses. The most popular technique is differential scanning calorimetry (DSC) [75, 76].

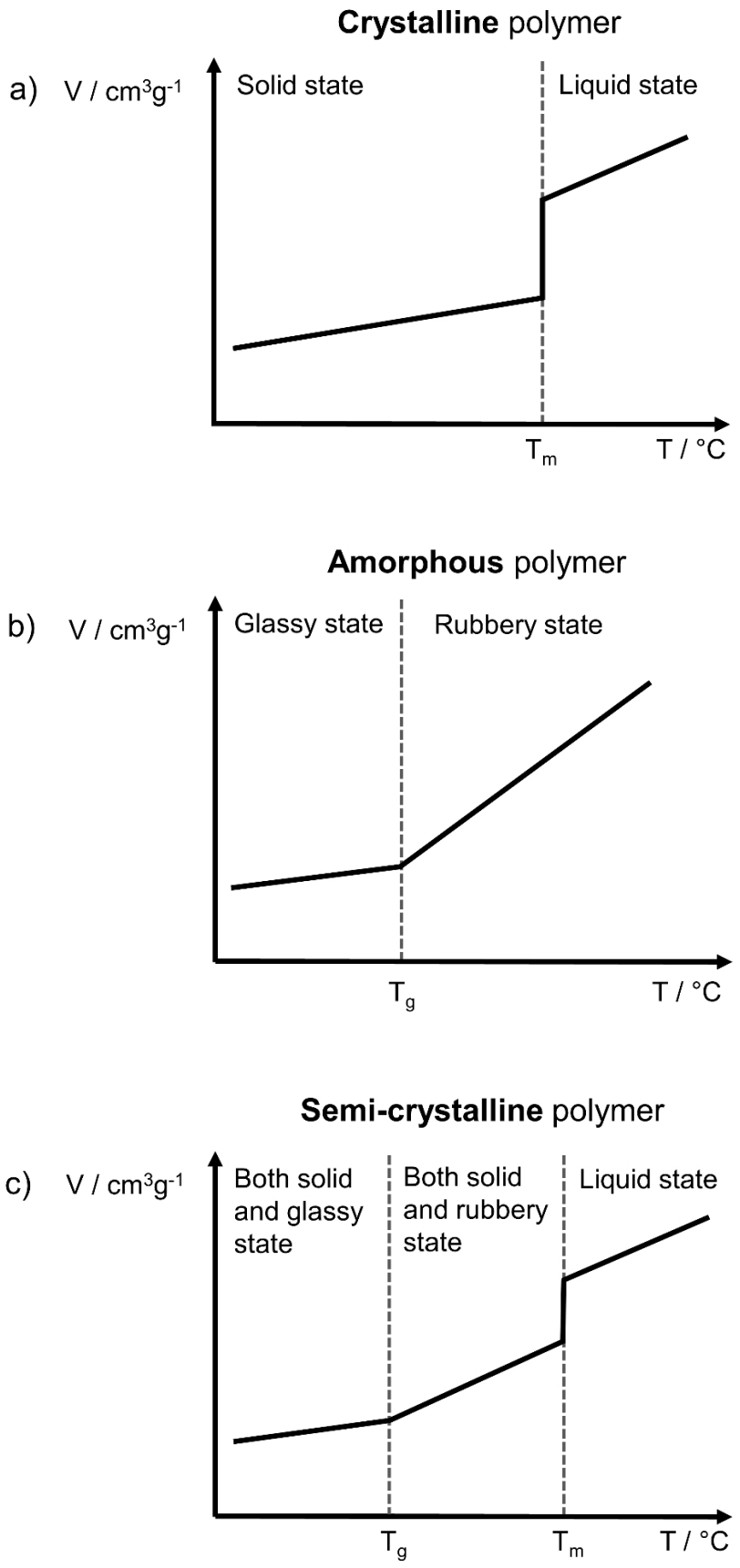

Figure 3. Specific volumes of polymers as a function of temperature (modified after [63]): (a) Crystalline (b) Amorphous (c) Semi-crystalline.

The degree of crystallinity can influence the deformation behavior of a material [77]. The number of imperfections within the crystal lattice might have a positive impact on the ease of fracture and deformation [78]. Amorphous and partially crystalline materials usually exhibit a high degree of plasticity. Within the pharmaceutical industry, a large number of materials are amorphous to varying degrees [79, 80]. Therefore, the T_g can serve as a critical parameter in several processes such as powder compression [80, 81], hot melt extrusion [82, 83], film coating [68, 84-86] and dissolution [69, 87]. If all process parameters can be controlled carefully, knowing the T_g of a material can be used as an advantage. For example, coating processes involve a curing step, during which the coated dosage form is subjected to elevated temperatures to aid the complete coalescence of the polymer particles. The coalescence is dependent on the T_g of the coating polymer [88, 89].

In compression processes, the T_g has been associated with alterations of tableting behavior [90]. The decreased rigidity of polymers results in a less pronounced resistance against deformation, which is also reflected in lower elastic moduli. The materials develop higher strain under the same pressure [80, 91]. The resulting tablets often obtain a lower porosity and therefore higher mechanical strength [47, 92]. However, problems during processing arise if the interdependence of temperature, the process and/or materials is not sufficiently understood. This includes the adherence of material onto the punch surface, which is referred to as sticking. Sticking phenomena might ultimately lead to defective tablets (e.g. lamination, capping), which compromises product quality [93-95]. Besides macroscopically visible defects of the compact, the alteration of material properties might influence other critical tablet attributes during development and production [47].

Several studies have examined the influence of temperature on process and tablet characteristics [47, 60, 80, 90, 92, 96, 97]. Some findings have been linked to the closeness of the compression temperature (T_c) to the T_g [47, 97].

1.3 Compression analyses

1.3.1 Introduction

Pharmaceutical development and production aims at the manufacturing of a drug delivery system with a desired therapeutic performance. This requires a fundamental understanding of the interplay between process parameters and material characteristics. Trial-and-error approaches can be time- and resource-consuming and often lack adequate comparability to other processes and/or materials [98]. During the last years, systematic approaches have been put more into focus in course of the Quality by Design (QbD) recommendations by the Food and Drug Administration (FDA). The QbD approach aims at product- and process understanding and process control to ensure product quality [99].

Compression analyses focus on the behavior of materials under pressure. It is commonly acknowledged that the compression process is divided into different stages that tend to overlap. This has led to the development of rather complex mathematical models. It is therefore common practice not to examine all stages of compression simultaneously [100, 101]. The goal is to derive equations capable of adequately describing the obtained data. Predicting quality attributes of a compact after the assessment of density-pressure relationships and therefrom derived parameters is desirable.

The relation between the relative density and the applied pressure is material-dependent. Analyses include in-die (“at-pressure”) and out-of-die (“zero-pressure”) methods [91, 102, 103]. In-die methods evaluate the measured force-displacement data during compression. Consequently, they allow a non-destructive characterization with only little amount of material. As all the required information is retrieved directly from the compression data, the integration of these techniques into manufacturing lines is facilitated [104]. If no intact tablet is formed, the analysis of material behavior is still possible during early-stage development. Criticism of the in-die method arises from the fact that the relationship between porosity and pressure can be distorted by the elastic deformation of a sample under stress [105].

Out-of-die analyses require the collection of data after tablet ejection. The time-dependent relaxation of tablets can lead to deviations from in-die data [91]. They also

require additional equipment and generate higher costs when the use of destructive tests generates product loss.

The obtained compression parameters can be linked to key attributes of the resulting tablets. In that respect, the tensile strength (TS) and the solid fraction (SF) of a compact are of special interest. Disintegration and dissolution processes require for a solvent to penetrate into the tablet [106, 107]. If the TS and the SF are too high, the slower solvent ingress might decelerate disintegration and API release. The relationship between compression parameters and tablet quality attributes is depicted in Fig. 4. Compression pressure, solid fraction and tensile strength are interdependent. Their correlation can be investigated by three frequently used parameters: compressibility, tabletability and compactibility.

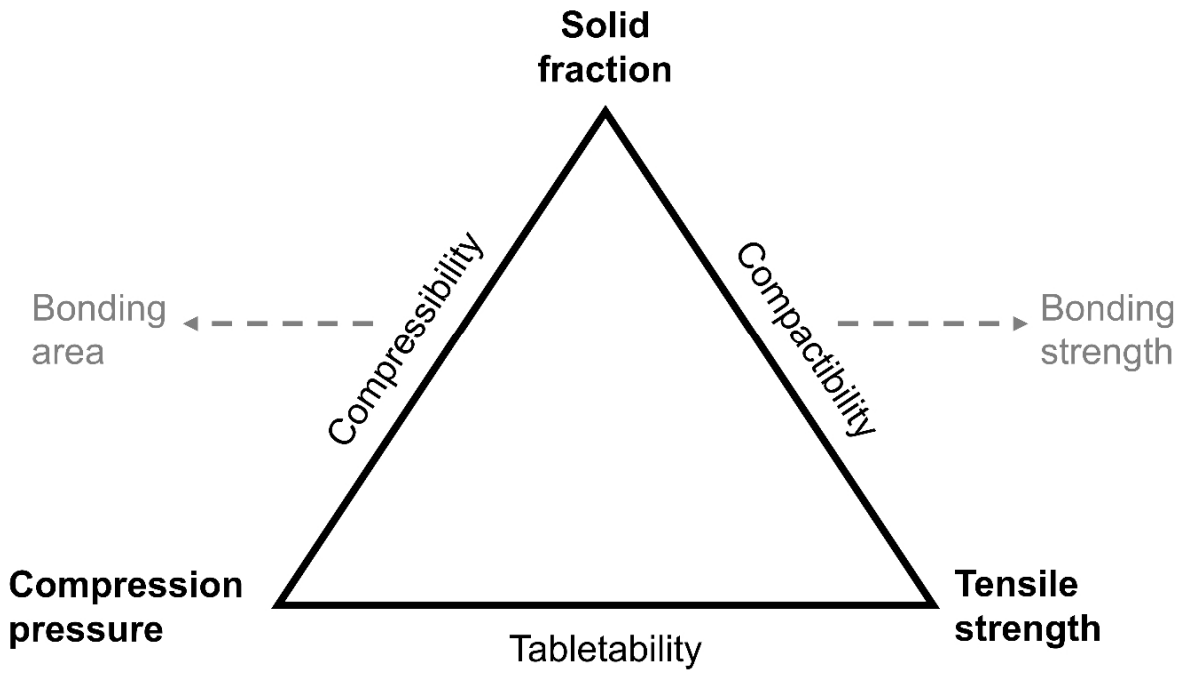

Figure 4. Relationship between compression parameters and tablet quality attributes (modified after [98, 108]).

1.3.2 Compressibility

1.3.2.1 General

Compressibility describes the dependance of solid fraction on the applied compression pressure. It refers to the ability of a powder to reduce its volume under stress [108]. The compressibility can be linked to a material's tableting performance. Numerous mathematical models for the density-pressure relationship have been established [109, 110].

1.3.2.2 Energy analysis

The conversion of mechanical to thermal energy during tableting contributes to elevated temperatures. Force-displacement profiles can be used to calculate the mechanical energy input [111-114]. Their shape is reliant on the tableting equipment, the applied settings and the material properties. It is therefore of great importance to keep the used equipment and parameters constant when comparing materials [115]. Force-displacement profiles have been the basis for the prediction of plastic flow, elastic recovery and brittle fragmentation by different methods [111]. These also include Heckel analysis, which is the most popular technique to describe powder compaction data within the pharmaceutical area [101, 116].

A typical force-displacement curve is depicted in Fig. 5 (solid line). The gross energy input is the AUC of the triangle between A, B and C (AUC_{ABC}). Initially, the distance between punches is large. As they approach each other, particle slippage and rearrangement during consolidation only lead to a minor force increase. As the distance between punches further decreases, the force rises significantly from deformation and fragmentation processes. The available energy for deformation is reduced by the dissipated energy E_1 from die-wall friction and particle interactions [43]. The remaining energy is referred to as the compressive work (E_{cw}). E_{cw} is composed of E_2 (AUC_{abD}) and E_3 (AUC_{DBC}). E_3 corresponds to the release of stored elastic energy during decompression, which compromises the established bonding area [1]. It is termed the elastic work. E_2 contains the residual stored elastic and the plastic energy. It is referred to as the net work of compaction and is used for the plastic deformation of particles. E_2 is of special interest during the analysis of force-displacement data, as it corresponds to the stored energy of the compact. It has been stated that the amount

of stored energy is associated with a large BA and might be used as a surrogate for the mechanical strength of tablets [117].

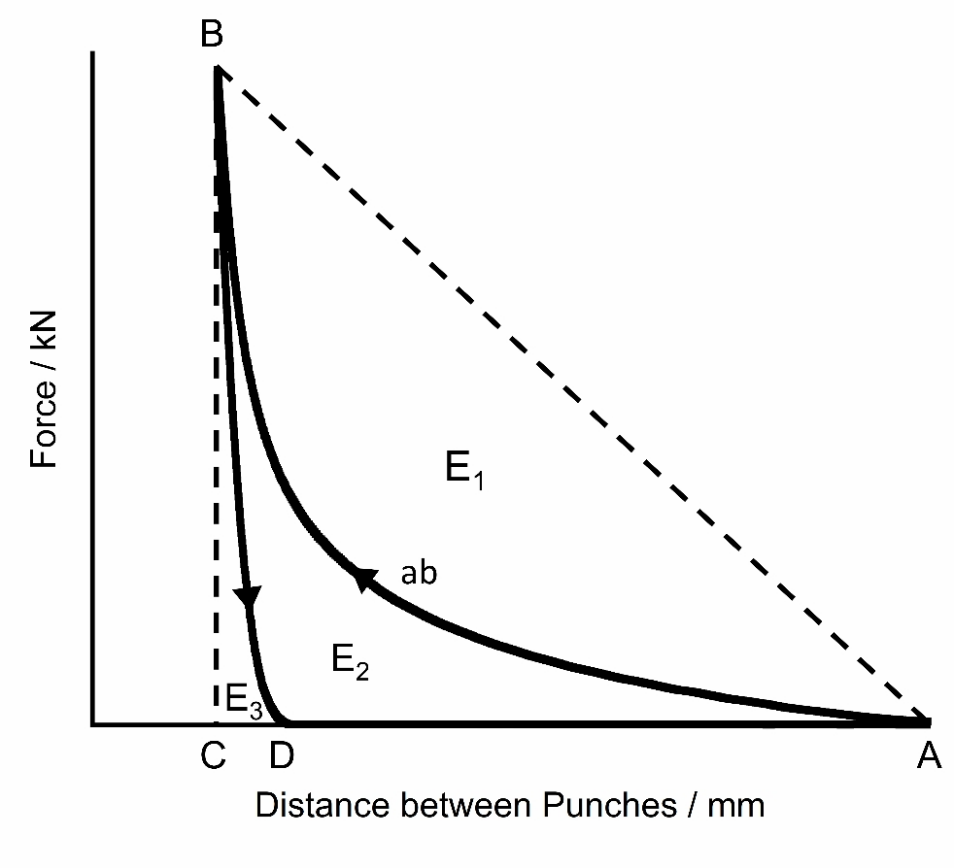

Figure 5. Example of a typical force-displacement curve.

For the area E_2, the following relationship can be established:

$$E_2 = AUC_{abC} - AUC_{DBC}$$

$$E_2 = E_{cw} - E_3$$

Equation 4

For its calculation, the trapezoidal rule is applicable [112, 118]:

$$E_2 = \int_{x_{max}}^{x_{min}} F(x) * dx - \int_{x_{0d}}^{x_{min}} F(x) * dx$$

Equation 5

x_{max} represents the distance between punches at which the force *F* exceeds 0 as a function of $F(x)$, x_{min} is the minimum distance between punches and x_{0d} is the punch separation when the force drops to 0 during decompression.

The association of E_2 with the plasticity of a material has led to the development of a plasticity factor (PF) [119]:

$$PF = \frac{E_2}{E_2 + E_3} * 100\ \%$$

Equation 6

Although the analysis of force-displacement profiles would offer a valuable tool to directly detect alterations of the tableting process, the influence of generated heat on the calculated energy values has rarely been studied. The PF, controversially described as the amount of plastic flow [115, 120, 121] or the necessary energy input during compression [122], has never been critically evaluated for temperature variations. This is probably rooted in the fact that corresponding assessments are rather challenging. To mimic the temperature evolution on an industrial scale either requires for the powder to be heated before compression or for the process to be run over a prolonged time period. For both scenarios, existing studies are scarce. Ketolainen et al. [54] made the effort to run a tableting process for up to 65 min on a small production scale. The compressed powder was composed of microcrystalline cellulose and dicalcium phosphate dihydrate either with or without lubrication. They stated that the energy parameters remained unchanged after an initial stabilization period despite a notable temperature increase. However, both materials do not show any thermal transitions < 100 °C, which were not reached during processing [123, 124]. In a study by Partheniadis et al. [97], unprocessed and hot-melt extruded polymers with T_g values up to 80 °C were compressed at 20 and 40 °C to improve their compaction performance. E_2 decreased for a polymer with a T_g close to the elevated tableting temperature. Hence, it is reasonable to link the investigation of energy parameters to the thermal sensitivity of polymers to examine the applicability of energy parameters as a tool for altered material properties upon temperature rise.

1.3.2.3 Heckel analysis

Within the pharmaceutical area, Heckel analysis has been the most frequently used technique to describe powder compression data [101, 116]. Reasons include the simplicity and speed of data collection using a small amount of material [91, 105]. For its application, it is assumed that the volume reduction of a powder bed under pressure follows first-order kinetics [125, 126]. Plotting the negative natural logarithm of the porosity (-ln(ε)) versus the applied compression pressure yields a characteristic compression curve (Fig. 6). It usually contains a linear region, which is enclosed by two curved sections in the low- and high-pressure regions. The first curvature can mainly be attributed to particle rearrangement and elastic deformation and is not considered in the analysis. Afterwards, irreversible deformation takes place, which can be either plastic or brittle. The respective curve section is linear. As the compression pressure further increases, the space for plastic flow diminishes. Eventually, the particles deform elastically when the porosity approaches extremely small values. Porosity values < 0.05 result in a steep increase of the corresponding -ln(ε). The interpretation of the second curvature is therefore impeded [91, 116].

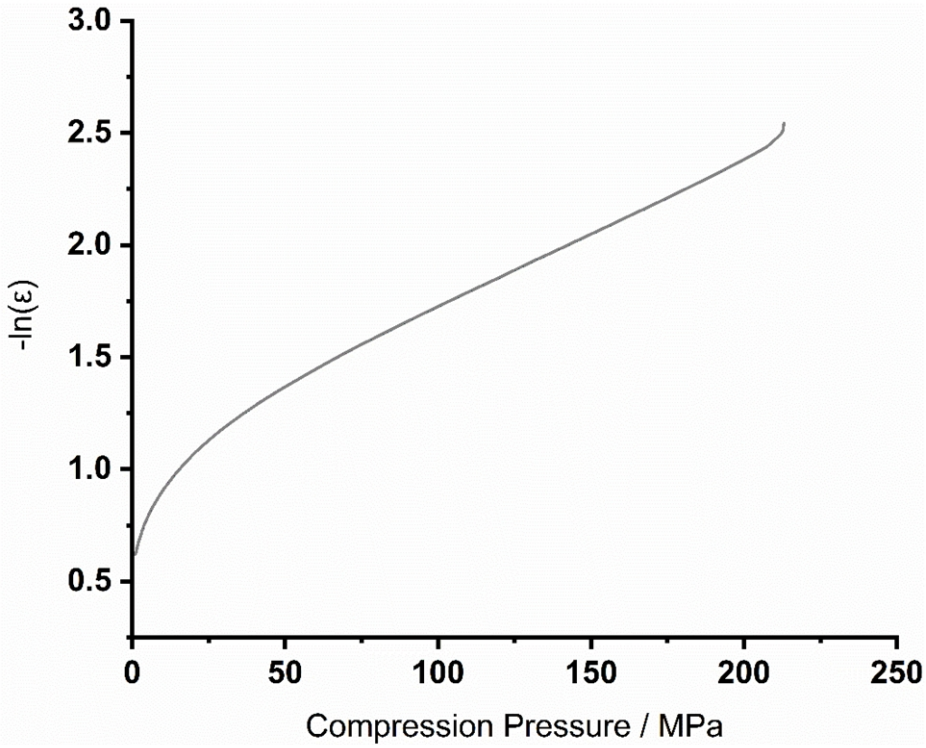

Figure 6. Example of a typical in-die Heckel plot.

The yield pressure P_y is referred to as a material's resistance against irreversible deformation. It can be derived from the reciprocal slope of the linear region after the following equation:

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

Equation 7

where P is the applied pressure and A is the y-axis intercept of the extrapolated linear section. The plasticity of predominantly ductile materials is reflected in low P_y values.

Besides the chemical characteristics, the particle size of materials also contributes to their deformation behavior [38]. Current literature on the effect of particle size on P_y is inhomogeneous. Most authors have found increasing P_y values with decreasing particle size [127-131], whereby it has also been stated that P_y increases with increasing particle size [132]. The effect of temperature on grades with varying particle sizes has not been subject to any studies. Smaller particles might exhibit a higher sensitivity to elevated temperatures due to a larger specific surface area [133].

Although frequently used, Heckel analysis has been criticized by several authors [101, 102]. One of the mentioned points refers to the susceptibility to errors during the measurement of particle density, which influences the calculated porosity. Systematic errors of its determination show substantial influence on the calculated P_y values [101]. Criticism has also arisen due to a lack of reproducibility and repeatability, which complicates the comparability of different materials. This can also be traced back to varying experimental conditions [20, 134, 135]. However, it has also been stated that Heckel analysis is practicable if the processing conditions are accurately controlled and deformation mechanisms of the materials are known [102]. Hence, the use of Heckel analysis is feasible, if modern equipment is used with commonly used excipients or APIs.

For a variation of tableting temperature, Heckel analysis has been proven to be sufficiently sensitive to analyze material behavior [59, 60]. For this it has to be kept in mind, that the particle density is assumed to be constant for the analysis of the same material. In that respect, errors in its determination would show no effect on the calculation of P_y for a given material for different temperatures. Moreover, the processing conditions do not necessarily vary during analysis. The temperature

change serves as the variable. Those limitations therefore account for the comparison between materials, but not for the comparison of different tableting temperatures for the same material.

It has frequently been stated that elevated temperatures lead to a decrease in P_y and therefore decreasing resistance against deformation. The extent is influenced by the T_g of a material [59, 60, 80, 81, 97]. However, a thorough investigation of Heckel analysis and its transfer to critical tablet characteristics under elevated temperatures is still missing. Often only few tablet characteristics were considered in isolation. Accordingly, comparisons between Heckel analysis and the assessment of energy parameters, which can directly be retrieved from the compression data without further calculations, are scarce. In the only existing studies, where the energy analysis was classified as being less sensitive, the thermal transitions of the investigated materials were rather high, so that the visible effects were of limited value. Only few materials were compared [59, 60]. In order to gain deeper insights, studies should aim at including several polymers with closely allied thermal transitions within a practicable temperature range. This would ensure a sufficient thermal sensitivity and open up the possibility of directly correlating the results to Heckel and energy parameters and to evaluate their respective applicability in the prediction of altered tablet characteristics.

1.3.3 Tablet quality attributes

1.3.3.1 Tabletability

Tabletability describes the dependence of tensile strength on the compression pressure [108]. In contrast to the measured breaking force during testing, the calculation of TS accounts for the geometry of the tablet [136]. Adequate TS is a crucial quality attribute, as it not only ensures tablet integrity during coating-processes, packaging and transport, but might also influence disintegration and drug release [13, 137]. The usual expectation is that higher compression pressures generate tablets with higher mechanical strength due to the creation of a larger BA [16]. However, the increase in TS is not infinite. It reaches a plateau. For some materials, the TS might even decrease with increasing pressure, which is referred to as overcompression [108, 138]. In course of the decreasing porosity at higher pressures, most voids are

eventually eliminated. The formation of a larger BA is therefore limited. For a given material, the BS is not affected by compression pressure [139]. If the available space for plastic deformation is exhausted, the stored elastic energy increases. Overcompression occurs when the resulting elastic recovery eliminates established bonds to a degree that the TS decreases despite higher pressures [140].

Conclusions about the tableting performance can be drawn from the necessary pressure to form a compact with specified strength or from a linear regression of appropriate data points to compare the slopes of different materials [108, 141]. Plastic materials exhibit less resistance against deformation than brittle materials, which favors the formation of a large BA. The established BA also varies with particle size and shape [13]. Smaller particles benefit from a large specific surface area available for bonding [133]. A large BA favors a high TS of the compact. For materials with a low T_g, the BA can be altered upon the application of higher temperatures [139]. When the temperature is raised, the decrease of P_y results in its transgression at an earlier stage. The prolonged dwell time above P_y yields a larger extent of plastic deformation and therefore a larger BA. The effect might be pronounced if the tableted particles are small. The larger specific surface area could promote a higher sensitivity for temperature variations.

The positive effect of temperature on the TS has been proven in several studies [47, 53, 90, 92, 142]. However, often pure materials or formulations with a high polymer content (≥ 50 %) were analyzed. Realistic polymer contents for the use as binding agents (~ 10 %) have rarely been investigated. A direct correlation to the T_g of materials was either missing or often only single tableting cycles were investigated. This neglects a possible temperature increase of the equipment during manufacturing. Moreover, the critical influence of particle size was not considered, although often several grades of a material are commercially available.

1.3.3.2 Compactibility

Compactibility profiles relate the TS to the SF or porosity [108]. They serve the assessment of BS. The plots usually yield an exponential relationship between TS and SF. A low SF corresponds to a lower mechanical strength of a compact [13, 143]. In contrast to tabletability profiles, compactibility profiles are not speed-dependent, which

could justify their preferred applicability during formulation development and scale-up. The SF might serve as a predictor of TS for a given material [35].

The SF also plays a crucial role for the disintegration and dissolution behavior. The disintegration process requires for the solvent to be absorbed by the tablet. Its components are hydrated and might start swelling or dissolving, depending on the formulation and its characteristics [107, 144, 145]. A fast disintegration ensures a rapid drug release [146-148]. Ideally, a reasonable compact porosity is combined with sufficient mechanical strength.

Ductile materials often yield tablets with a low porosity due to their high degree of plastic deformation. If the applied stress exceeds a material's capacity for plastic flow, however, the excess energy is stored reversibly. It is released during and after decompression. This relaxation favors a higher compact porosity. For thermally affected polymers, the stress relaxation propensity can be altered upon temperature rise. Initially, when the tableting temperature is far below the T_g, the amount of stored energy is comparably large. This changes as the T_g is approached. As P_y decreases, the enhanced plastic flow favors a lower porosity and therefore higher mechanical strength of the compact. This might also affect disintegration and drug release, which has not yet been explored in respect to temperature variations. When the T_g is exceeded, the elastic modulus of a polymer decreases drastically [80, 81]. At the same compressive stress, the strain is enhanced [91]. This can yield porous tablets after polymer relaxation. Established bonds might be broken, which compromises the compact strength. It has therefore been concluded by some authors, that the optimum tableting temperature is about 20 K below the T_g to attain minimum porosity and maximum strength [80, 81]. Although porosity changes under elevated temperatures have being investigated before, no comparison of compactibility profiles has been carried out. This provides the opportunity to display the interdependence of TS and SF as two parameters with significant impact on tablet attributes.

1.3.3.3 Disintegration

Disintegration of a tablet can be described as the state in which any remaining part, except insoluble fragments, is a soft mass without a firm core [149]. As mentioned above, a rapid disintegration is usually the prerequisite for a fast dissolution of the API

[146-148]. This is especially critical for immediate-release tablets, which are required to release the API within a short period of time. If the disintegration process is compromised, this might delay the release.

The solvent ingress is the first step during the disintegration process. The absorption of the medium by the compact leads to the breakage of interparticulate bonds. Mechanistically, capillary bridges built by the penetrating solvent create an attraction between neighboring particles. If the attractive forces exceed the interparticulate forces, the bonds are disrupted. The tablet disintegrates. If the porosity of a compact is critically low, the penetration of the solvent might be impeded [147, 150]. This decelerates the liberation of the API.

The effect of temperature on disintegration time (DT) has rarely been examined [151]. If produced tablets are intended for immediate-release, studies on the effect of elevated temperatures should also include disintegration.

1.3.3.4 Dissolution

Dissolution studies have been recognized as an essential aspect during pharmaceutical development. The dissolution of a drug is the prerequisite for its bioavailability [98]. Therefore, the development aims at the adjustment of the dissolution performance to a desired therapeutic effect. Generally, immediate-release dosage forms can be distinguished from modified release dosage forms. If a rapid drug release is required, the formulation components of a tablet need to ensure the API is released quickly upon contact with the dissolution medium. The formulation components therefore have a critical influence on API release [152, 153].
Numerous mathematical models have dealt with the prediction of dissolution behavior [154, 155]. The overall drug release from a dosage form can be described by kinetic models, whereby the dissolved amount of drug is related to the test time [153].
Most immediate-release dosage forms are designed to release an API immediately after oral administration and therefore follow first-order kinetics. Mathematically, first-order models can be described by the following equation [156]:

$$\ln(c_P - c_t) = -k * t$$

Equation 8

where c_p is the concentration of drug after complete release, c_t is the cumulative concentration at the time t and k is the first-order rate constant. To test its applicability has also been called the sigma-minus method [157]. The ICH Q6A specifications state that at least 80 % of drug need to be released within 15 min at pH 1.2, 4.0 and 6.8 for a rapidly dissolving product [158].
If tablet characteristics are altered upon temperature rise, the dissolution behavior of a dosage form might change.

If the fitting of the release curve fails to display a linear relationship, the release kinetics were altered. Provided that the drug release profile of a dosage form differs from that of a conventional one, the release is modified. Although modified release serves as a method to control drug release, the effect is unacceptable if the alteration arises from temperature variations. One of the first models developed to describe the drug release from a matrix system was the Higuchi model [156]. For the Higuchi model, the cumulative drug release is related to the square root of time after the following equation [159]:

$$c_t = k * t^{\frac{1}{2}}$$

Equation 9

where c_t represents the cumulative concentration at the time *t* and *k* is the Higuchi dissolution constant. The correlation of the data points with the square root of time yields a linear relationship. In most cases, the equation is only applied for data points up to 60 % of the release curve.

Similar to the Higuchi model, the data can be described by the Korsmeyer-Peppas model. In contrast to the Higuchi model, it is able to display different release exponents. The relationship is described by the following equation [160, 161]:

$$c_t = k * t^n$$

Equation 10

with c_t as the cumulative concentration at the time *t, k* as the release rate constant and the exponent *n* as the release exponent. The data is linearized by logarithmization of

both axes. Data points below 10 and above 60 % of the release curve are usually excluded from the investigation.

As not all kinetic models are applicable to all release curves, the mean dissolution time (MDT) as a model-independent method is useful to compare release curves with different kinetics. It can be calculated according to the following equation [153, 162]:

$$MDT = \frac{ABC}{c_p} = \frac{\sum_{i=0}^{\infty}\left[(c_{i+1} - c_i) * \frac{(t_i + t_{i+1})}{2}\right]}{c_p}$$

Equation 11

The area between curves (ABC) can be calculated with the trapezoidal equation. The concentration *c* is the API released over the time *t*. c_p represents the initial drug load. Only few publications concerning alterations of release curves upon temperature rise during tableting exist. Casettari et al. [60] investigated the effect of elevated temperatures on the modified release of matrix tablets, but found no significant effect of temperature. However, the lowest T_m of the investigated materials was beyond the maximum tableting temperature. More thorough investigations are still pending.

1.4 Excipient selection

1.4.1 Introduction

As described above, the material properties have a substantial influence on the resulting tablet characteristics. The T_g of the investigated materials was of critical essence in this work. Therefore, the selection of polymers was based on their amorphous or semi-crystalline character and moderate T_g. As a maximum tableting temperature of 70 °C could be set for the tablet press, only polymers with T_g values below 100 °C were included in most studies. The T_g values were determined via DSC. To account for the effect of particle size and morphology besides the processing conditions, different grades of the materials were used. Besides the pure polymers, the investigations included complete formulations to account for realistic binder contents during manufacturing. All used materials are introduced briefly.

1.4.2 Polymers with moderate T_g

1.4.2.1 Polymethacrylates

The functionality of polymethacrylates within the pharmaceutical area can be categorized as film-forming agents, tablet binders or tablet diluents for oral solid dosage forms. The most common is the use as film-coating agents [163]. They are marketed e.g. under the name Eudragit® (Evonik, Germany). All Eudragit® types are synthesized by polymerization of acrylic acid and methacrylic acids or their esters [164]. They exhibit an amorphous character, which suggests a high plasticity and justifies their use as binders [164]. In this work, three Eudragit® types with a moderate T_g were chosen for the investigation. Eudragit® E is a terpolymer composed of N,N-dimethylaminoethyl methacrylate with methylacrylate and butyl methacrylate [165]. It is soluble in gastric fluid (pH < 5). The T_g is ~ 49 °C. Eudragit® RS and RL are copolymers of ethyl acrylate, methyl methacrylate and methacrylic acid ester. The introduction of quaternary ammonium groups modifies the permeability [164, 166]. Eudragit® RL films have a higher permeability than Eudragit® RS films. As both polymers are not water-soluble, they are often used for sustained-release products. They have found applications in DC as matrix formers [167-171]. Their T_g values are 58 °C (Eudragit® RS) and 70 °C (Eudragit® RL), respectively. Experiments on thermal treatment of matrices after compression have been described [168, 169]. The investigated materials are commercially available as powders (Eudragit® E PO, Eudragit® RS PO, Eudragit® RL PO) or granules (Eudragit® E 100, Eudragit® RS 100, Eudragit® RL 100) [172]. The powder is obtained from milling the granules, which explains the irregular shape of its particles (Fig. 7a-c). Due to the broad range of products, the Eudragit grades played a key role in all studies.

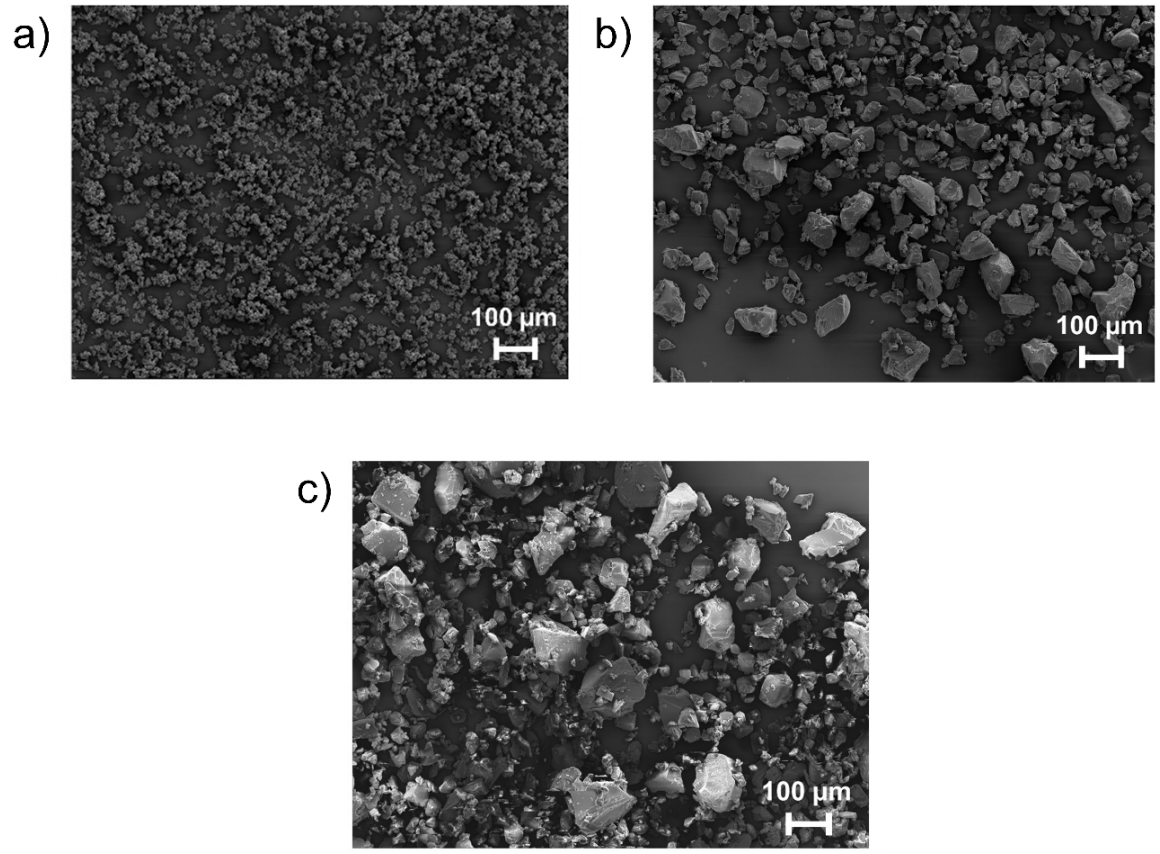

Figure 7. SEM images of a) Eudragit® E PO, (b) Eudragit® RS PO and (c) Eudragit® RL PO.

1.4.2.2 Hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is derived from cellulose by partially substituting hydroxy groups by hydroxypropyl moieties. Cellulose consists of β–(1-4)-linked D-glucose units. Its treatment with sodium hydroxide produces a more reactive type of cellulose, which is subsequently reacted with propylene oxide at elevated pressure and temperature [163, 173]. In contrast to the other polymers in this study, HPC is semi-crystalline. Its particles are of fibrous nature (Fig. 8a,b). Typical uses in solid oral dosage forms include tablet binding, film-coating and extended-release matrix systems. Commercially available grades differ in their particle size, degree of polymerization, degree of substitution and moles of substitution (MS). Its solubility in water is determined by its MS [163]. HPC grades of lower molecular weight have a lower T_g. In this work, HPC SSL SFP and HPC SSL (Nippon Soda, Japan) were

selected. They differ in their particle size, whereby HPC SSL SFP has finer particles than HPC SSL. The T_g value is ~ 82 °C [174].

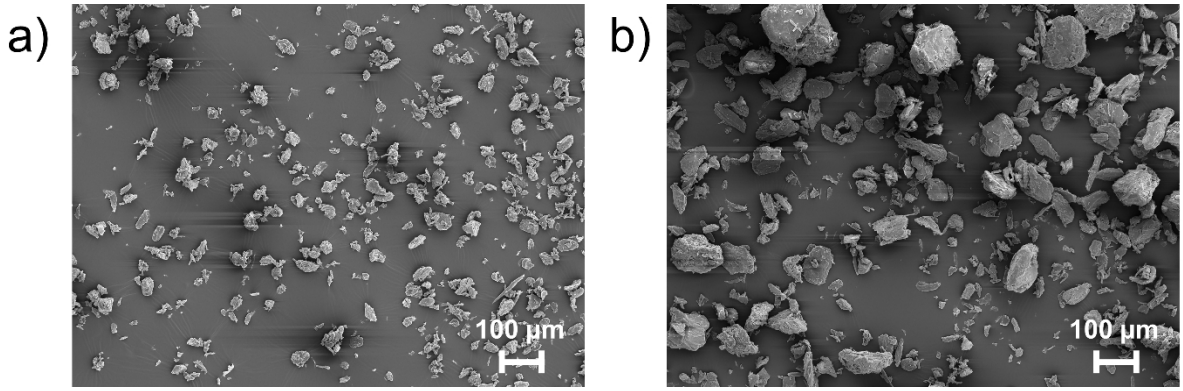

Figure 8. SEM images of (a) HPC SSL SFP and (b) HPC SSL

1.4.2.3 Polyvinylpyrrolidone (Povidone)

Polyvinylpyrrolidone consist of 1-vinyl-2-pyrrolidinone groups. The respective polymers are commercially available with varying molecular weights. They are typically characterized by their K-value, which represents their viscosity in aqueous solution relative to that of water [163]. Povidones with a K-value below 30 are manufactured by spray-drying and their particles are therefore of spherical shape (Fig. 9). The shape of povidone particles with K-values above 30 is different, as they are manufactured by drum-drying [163]. In solid dosage forms, povidones are often used as binders in wet-granulation processes [175]. Their use in DC is challenging, as they suffer from a pronounced hygroscopicity [176]. The T_g of the amorphous polymer varies with molecular weight. Kollidon® 12 PF (BASF, Germany) has the lowest T_g out of the commercially available products (~ 102 °C). It was only used in the first study of this work. The plasticizing effect of water on the hygroscopic powder impeded the reproducibility of experiments and promoted stickiness of the material. The polymer was subsequently excluded from further studies.

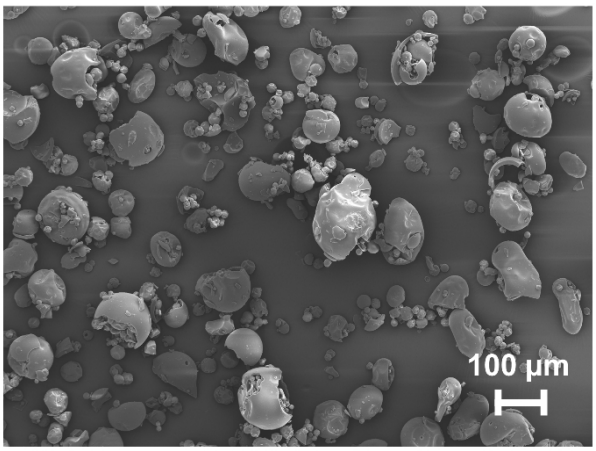

Figure 9. SEM image of Kollidon® 12 PF.

1.4.2.4 Mixture of polyvinylacetate and polyvinylpyrrolidone

The demand of excipients with improved compression properties has led to the development of coprocessed excipients. The coprocession includes two or more established excipients to obtain superior properties over the physical mixture [177]. The spray-dried mixture of 80 % polyvinylacetate and 19 % polyvinylpyrrolidone is traded as Kollidon® SR (BASF, Germany). Small amounts of sodium lauryl sulfate (0.8 %) and colloidal silica (0.2 %) are added for stabilization and flowability improvement. Spray-drying yields hollow particles with a spherical shape (Fig. 10). The excipient is mainly used as a filler, matrix former or as a film-coating agent. Although the povidone part is soluble in water, the insoluble polyvinylacetate part determines the overall solubility [172, 178]. KSR has frequently been used in DC [179-181]. The T_g of the amorphous polymer is ~ 42 °C, which was the lowest in this work.

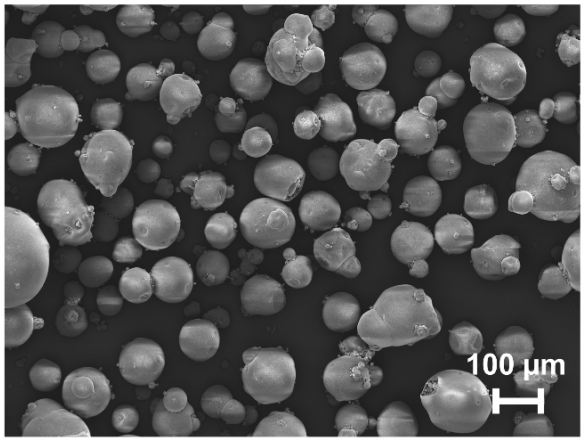

Figure 10. SEM image of Kollidon® SR.

1.4.3 Other excipients

1.4.3.1 α-Lactose monohydrate

Lactose is a disaccharide obtained from milk in which D-galactose is β–(1-4)-linked to D-glucose. It is one of the most frequently used fillers in DC [182-184]. The most commonly used form for oral solid dosage forms is α-lactose monohydrate [185]. Crystallization can also yield an anhydrous form, whereby the ratio of α- and β-lactose is determined by the temperature of crystallization [163]. A variety of products is available, which might vary in particle size, flow and compaction properties. The T_m of crystalline lactose is 216 °C.

Commercial products include milled, spray-agglomerated or spray-dried grades [186]. The milled products are usually used in wet- and dry granulation processes due to their small, sharp-edged particles, which trigger cohesiveness. However, the flowability for DC is insufficient. Spray-agglomerated products benefit from a better flowability of the crystalline particles. This makes them suitable for DC [187]. The spray-drying process introduces amorphous parts into the product, which are able to flow plastically and improve compaction performance. However, the amorphous content of marketed products is only between 10 - 15 %, so that the deformation behavior can still be classified as predominantly brittle [183, 188]. As the particles obtain a spherical shape after spray-drying (Fig. 11), the powder possesses sufficient flowability for DC. Depending on the storage conditions, the T_g of the amorphous content has been

reported to vary between 41.5 and 104 °C [189]. In this work, spray-dried lactose (FlowLac® 100, Meggle, Germany) was selected as a filler for all tableting experiments.

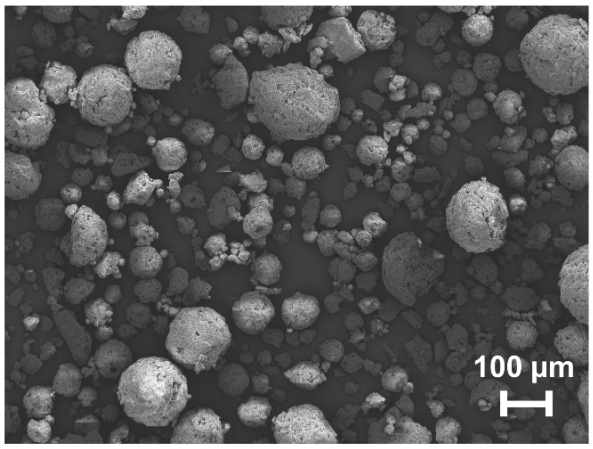

Figure 11. SEM image of FlowLac® 100.

1.4.3.2 Microcrystalline cellulose

Microcrystalline cellulose (MCC) is one of the most frequently used excipients for tablet formulations due to its excellent tableting properties [190, 191]. It consists of β–(1-4)-linked D-glucose units [173]. For its manufacturing, α-cellulose from fibrous plant materials is hydrolyzed in acidic environment, whereby amorphous regions are preferentially removed. While the crystallinity index increases, the average degree of polymerization decreases. The packed structure is broken up by shearing of a water slurry before the material is spray-dried. A fibrous structure is obtained (Fig. 12). Different commercially available grades arise from variations of hydrolytic, shearing and drying conditions [163, 191]. Despite its highly crystalline structure, MCC is characterized by a large amount of plastic flow [192, 193]. For oral solid dosage forms, it is mainly used as a capsule and tablet diluent, whereby it also exhibits disintegrant properties [163]. Although it is insoluble in water, the substance is hydrophilic. The tableting performance is dependent on the moisture content [173, 194]. MCC chars at 260 – 270 °C [163]. In this work, Vivapur® 102 (JRS Pharma, Germany) was used as a filler-binder during the investigation studies of complete formulations.

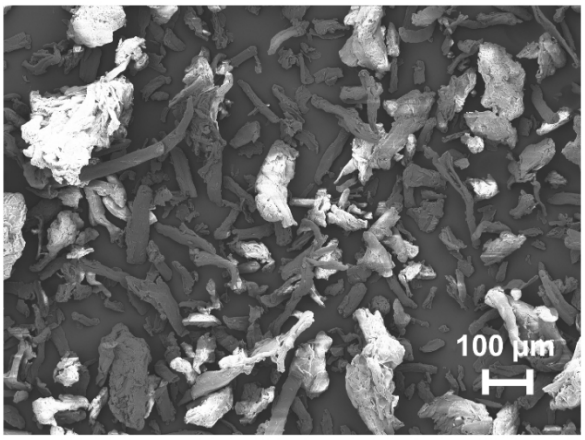

Figure 12. SEM image of Vivapur® 102.

1.4.3.3 Polyvinylpyrrolidone-vinyl acetate copolymer (Copovidone)

Copovidone is a synthetic copolymer of polyvinylpyrrolidone and ethenyl acetate at a ratio of 3:2. It is produced by free-radical polymerization. Spray-drying of the product yields an amorphous powder with spherical particles (Fig. 13a,b). Within pharmaceutical applications, it is mostly used as a tablet binder, coating agent or matrix former. Copovidone is suitable for wet-granulation and DC [163, 195]. Compared to povidone, it has a higher plasticity, which facilitates its deformation during tableting. Moreover, it is less hygroscopic [163]. The T_g is ~ 108 °C. Different grades are commercially available. In this work, Kollidon® VA 64 Fine and Kollidon® VA 64 (BASF, Germany) were of interest due to their varying particle size.

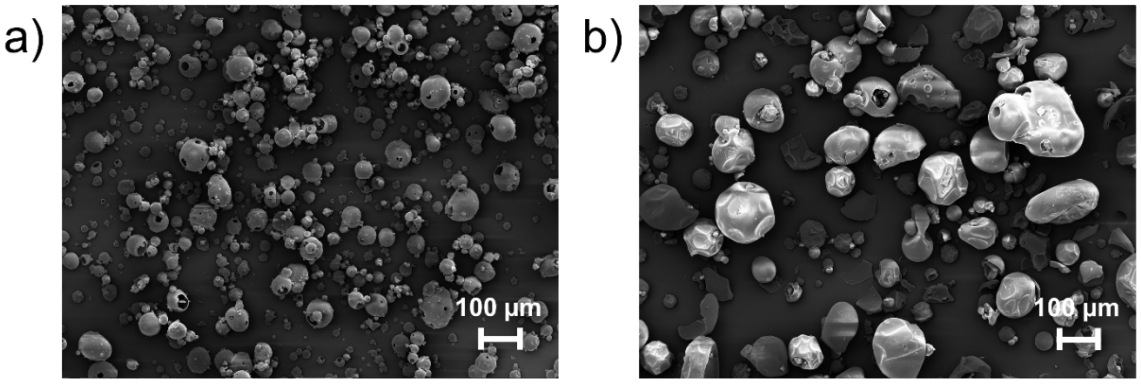

Figure 13. SEM images of (a) Kollidon® VA 64 Fine and (b) Kollidon® VA 64.

1.4.3.4 Polyvinylpolypyrrolidone (Crospovidone)

Crospovidone is a crosslinked polymer of N-vinyl-2-pyrrolidinone. It is prepared by a “popcorn polymerization” process. Crospovidone is frequently used as a tablet disintegrant [196, 197]. The rapid hydration of the polymer promotes its capillary activity. The disintegration capacity is influenced by the particle size. Crospovidone is practically insoluble in water [163]. The T_g is ~ 184 °C. Grades of different particle size are commercially available. Their shape is irregular, whereby the particles tend to agglomerate (Fig. 14a,b). Kollidon® CL-M and Kollidon® CL-F were used for the comparison of different material grades in one study. Later, Kollidon CL-F was used as a disintegrant in the dissolution studies.

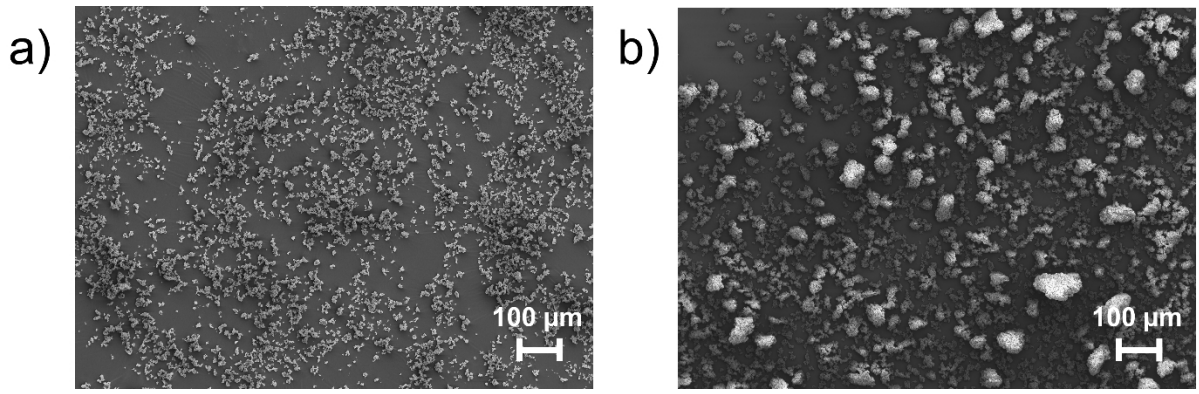

Figure 14. SEM images of (a) Kollidon® CL-M and (b) Kollidon® CL-F.

1.5 API selection

An active pharmaceutical ingredient is the component of a drug designed to develop a pharmacological activity. In this work, paracetamol (acetaminophen) was used as a model API (Atabay, Turkey). It is commonly used for the analgesic and antipyretic treatment of patients. Paracetamol crystallizes in three polymorphic forms with different crystal habits, whereby only form I and II are stable. The commonly marketed form I is known for its poor compression properties with only little plastic deformation [198-201]. Its particle shape is irregular (Fig. 15). The melting point is ~ 170 °C and it is soluble in water [202].

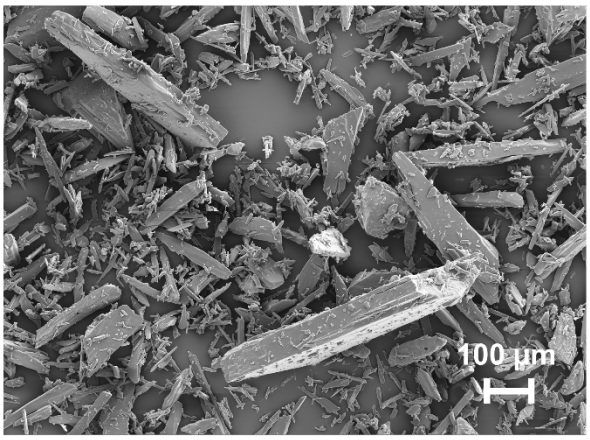

Figure 15. SEM image of Paracetamol.

Section 2. Aim of the thesis

Aim of the thesis

The aim of this work is to deepen the understanding of altered excipients properties upon temperature rise. The identification of influential process and material characteristics serves the prevention and elimination of tableting problems. On the other hand, some formulations might benefit from elevated tableting temperatures. The development and production processes of solid oral dosage forms could be improved, which saves production time and costs. A special focus will be put on polymers with a high binding capacity and a moderate T_g.

Recently developed equipment is used to heat the die before compression. Besides material characterization upon elevated temperatures, this allows for the simulation of production processes where heat evolves over longer time periods.

Systematic correlations between alterations of compression behavior and the T_g of the investigated polymers need to be identified. The first experiments serve the assessment of material deformation behavior and should ensure a homogenous temperature distribution within the powder bed. Therefore, the materials are equilibrated within the die after filling. Polymers are to be evaluated regarding their thermal response during compression. Binary mixtures containing a filler are to be analyzed regarding their resulting tablet quality attributes. This accounts for practicable binder contents on a full-production scale.

To mimic realistic tableting conditions on an industrial scale in the subsequent studies, the equilibration time of the powders is kept short. Besides the transfer of the previously obtained results, two existing in-die compression analyses are to be compared with regards to their applicability for heated compression. This would enable a direct detection of material alterations from compression data.

It was assumed that the particle size of materials is another critical criterion when it comes to temperature variations. Up to this point, no work has considered this aspect. Varying sensitivities of different grades would provide the opportunity of using a different grade of the same material if the formulation suffers from temperature-dependent tableting problems. No change in formulation components would be necessary.

The final objective is to transfer the results to complete formulations containing a model API. This also includes disintegration and dissolution studies. It is of central interest if alterations of tablet characteristics from the transgression of T_g can be applied to their disintegration and dissolution behavior. It may be possible to identify critical alterations of material behavior at an early development-stage before large investments are made or the eventual batch release is compromised.

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Section 3. Results and discussion

3.1. Influence of temperature on the compression behavior of pharmaceutical excipients

Pretext

This publication describes the initial investigations to correlate alterations in tableting behavior of polymers to their T_g. In this study, four different tableting temperatures ranging from 22-70 °C were investigated. To study the material behavior when the applied heat is homogenously distributed, the powder was equilibrated for 3 minutes per tablet after die filling. The highest T_g was 102 °C. At first, pure polymers were characterized for their temperature-dependent compressibility using Heckel-analysis. Afterwards, tableting was performed from binary blends composed of lactose and the respective polymers (ratio 9:1). The tableting behavior was evaluated in terms of tabletability and compactibility. Finally, recommendations were made which types of polymers could be useful when trying to avoid alterations of tablet properties or which could be of advantage if a change of material characteristics is desired.

The following paper has been published by the International Journal of Pharmaceutics in Volume 628 (2022): https://doi.org/10.1016/j.ijpharm.2022.122305

Weighting of the authorship / %:

Author	Idea	Study Design	Experimental	Evaluation	Manuscript
Hanna Dorothea Grumann	60	60	100	65	75
Stefan Klinken	0	0	0	20	5
Peter Kleinebudde	40	40	0	15	20

HDG provided contribution to the conception of the work, especially the selection of polymers and the specific temperatures studied. Furthermore, HDG acquired the data, while its analysis and interpretation was done together with SK and PK. HDG drafted the manuscript and changed the sections corrected by SK and PK. Some sections were changed by PK.

Influence of temperature on the compression behavior of pharmaceutical excipients

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International Journal of Pharmaceutics 628 (2022) 122305

Article available online at:

https://doi.org/10.1016/j.ijpharm.2022.122305

3.2. Evaluation of in-die compression data for a deeper understanding of altered excipient properties upon temperature rise

Pretext

In this work, the applicability of energy analysis as an indicator for altered excipient properties upon temperature rise was evaluated. This study only included the investigation of pure polymers with T_g values < 100 °C, whereby pure lactose served as a brittle reference material. The polymers were tableted at four different temperatures (22-70 °C). To mimic realistic conditions applicable to a full-production scale, the equilibration time was kept short. Alterations of net- and elastic recovery work during compaction were evaluated. A relationship between the change in energies and the T_g was established. The results from the energy analysis were compared to the results obtained from Heckel analysis. Lastly, the plasticity factor and its applicability for heated tableting was critically investigated. Recommendations were made which analyses should be preferred over others.

The following paper has been published by the AAPS PharmSciTech in Volume 24 (2023): https://doi.org/10.1208/s12249-023-02554-3

Weighting of the authorship / %:

Author	Idea	Study Design	Experimental	Evaluation	Manuscript
Hanna Dorothea Grumann	70	80	100	60	70
Stefan Klinken	10	0	0	35	10
Peter Kleinebudde	20	20	0	5	20

HDG provided contribution to the conception of the work, especially the correlation between energy analyses and temperature and the applicability of the plasticity factor. Furthermore, HDG acquired the data, while its analysis and interpretation was done together with SK and PK. HDG drafted most of the manuscript and changed the sections corrected by SK and PK.

Evaluation of In-Die Compression Data for a Deeper Understanding of Altered Excipient Properties upon Temperature Rise

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AAPS PharmSciTech (2023) 24(4):89

Article available online at:

https://doi.org/10.1208/s12249-023-02554-3

3.3. Investigating the heat sensitivity of frequently used excipients with varying particle sizes

Pretext

In this publication the influence of the particle size on the tableting characteristics of polymers upon temperature rise was investigated. It also included polymers with higher T_g values (> 100 °C) to increase the range of available grades. The grades were either commercially available or produced by ball-milling. Materials were categorized as “fine” or “coarse”. Changes in P_y and energy analysis were evaluated regarding their sensitivity to detect differences between particle sizes at standard ambient conditions and to detect temperature-dependent changes of compression parameters. Afterwards, binary blends containing lactose and the fine grade of a respective polymer were compared to binary blends containing the coarse grade. The comparison included changes in tabletability and compactibility.

The following paper has been published by the European Journal of Pharmaceutics in Volume 192 (2023): https://doi.org/10.1016/j.ejpb.2023.09.010

Weighting of the authorship / %:

Author	Idea	Study Design	Experimental	Evaluation	Manuscript
Hanna Dorothea Grumann	80	80	100	80	80
Peter Kleinebudde	20	20	0	20	20

HDG provided contribution to the conception of the work, especially the selection of polymers and their respective grades. Furthermore, HDG acquired and analyzed the data, while its interpretation was done together with PK. HDG drafted the manuscript and changed the sections corrected by PK.

Investigating the heat sensitivity of frequently used excipients with varying particle sizes

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European Journal of Pharmaceutics and Biopharmaceutics 192 (2023) 1-12

Article available online at:

https://doi.org/10.1016/j.ejpb.2023.09.010

3.4. Effect of tableting temperature on tablet properties and dissolution behavior of heat sensitive formulations

Pretext

In this publication the previously obtained knowledge was extended to complete formulations containing the model API Paracetamol. Six different formulations with varying binder type and concentration were tableted at the previously described temperatures. Besides the tabletability, the porosity, disintegration and dissolution of all formulations were studied. Where applicable, the underlying release kinetics for different tableting temperatures were investigated by the sigma-minus method, the Higuchi- and the Korsmeyer-Peppas equation. The comparison of all formulations included the calculation of the mean dissolution time. Besides the effect of binder type and concentration, the variation of the filler-binder components was evaluated for its significance.

The following paper has been published by the International Journal of Pharmaceutics (2023): https://doi.org/10.1016/j.ijpharm.2023.123603

Weighting of the authorship / %:

Author	Idea	Study Design	Experimental	Evaluation	Manuscript
Hanna Dorothea Grumann	70	70	100	80	80
Peter Kleinebudde	30	30	0	20	20

HDG provided contribution to the conception of the work, especially the selection of formulation components and dissolution parameters. Furthermore, HDG acquired and analyzed the data, while its interpretation was done together with PK. HDG drafted the manuscript and changed the sections corrected by PK.

Effect of tableting temperature on tablet properties and dissolution behavior of heat sensitive formulations

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International Journal of Pharmaceutics (2023) 123603

Article available online at:

https://doi.org/10.1016/j.ijpharm.2023.12360

Section 4. Core findings

Core findings

The heat generation from tableting processes can lead to challenges during formulation development and production. The transformation of mechanical into thermal energy might trigger an alteration of material properties and thereby influence their compression behavior [1]. Compromised critical tablet quality attributes can put batch release at risk. This results in additional production time, higher costs and energy consumption [2]. Amorphous or partially crystalline polymers with a low or moderate T_g are especially responsive to temperature variations. It was therefore the aim of this work to investigate the T_g as a critical parameter during tableting processes to establish a correlation between the T_g and the resulting tablet characteristics.

The mechanical and thermal energy of compression processes have often been studied separately. These days, modern instrumentation allows for accurate in-die data measurements [3]. The modified set-up of a laboratory tablet press provided the opportunity to set a specific temperature for the tableting equipment. Through this combination both components could be linked. The effect of T_g on temperature-dependent process and tablet characteristics could be evaluated.

Initially, the direct correlation between the T_g and altered excipient properties had to be proven. Heckel analysis is the most frequently used method for the compressibility investigation of pharmaceutical materials. Beyond P_y, a ductile polymer deforms plastically. The high propensity of plastic deformation justifies their suitability as binders. The sensitivity of Heckel analysis for temperature variations has previously been shown [4]. For heat-sensitive materials, P_y decreases when the temperature is raised. The earlier transgression of P_y favors an increased dwell time above yield pressure for heat-responsive polymers.

To provide a homogenous heat distribution within the powder bed, each sample was equilibrated within the heated die for 3 minutes prior to compression for the first experiments. This ensured that the powder was heated thoroughly and that all powder particles were subjected to the elevated temperature. This work included a broad range of polymers with moderate T_g. Direct correlations between the T_g and the resulting P_y value were found. The lower the T_g, the higher was the decrease in P_y. The changes observed for the brittle reference material lactose were only minor.

The transfer of the results to tablet characteristics included binary mixtures containing lactose and the polymer to be investigated (ratio 9:1). They were tableted under the same conditions. This accounted for practicable binder contents on an industrial scale. The mechanical strength of the tablets resulted from the combination of bonding strength and the established bonding surface area. The tabletability of polymers with a low or moderate T_g was enhanced. The compactibility analysis revealed that the relation between SF and TS was also temperature-dependent for those polymers. For tablets compressed under elevated temperatures, the TS (BS) was higher for a given SF (BA). It was assumed that the effect could be enhanced by the percolation of softened material for smaller particle sizes of sensitive polymers. No effects on the compactibility of lactose were observed. The data points formed one master curve. Therefore, the TS remained unchanged for a given SF.

As in the first study, the in-die compressibility for elevated temperatures has mainly been determined by Heckel analysis. Heckel analysis has often been criticized due to its susceptibility to errors [5]. As it is derived from parts of the force-displacement curve, it should be evaluated whether the direct analysis of energy parameters is also feasible in detecting material alterations upon temperature rise. The determination of the particle density would be obsolete, which would allow for a more meaningful comparison between materials. So far, only few studies have considered energy analysis as an alternative to Heckel. Its sensitivity for the detection of temperature alterations has not sufficiently been proven. As in all following studies, the equilibration time was kept short to imitate more practicable conditions on an industrial scale.

The investigated polymers showed a thermal response within the applied temperature range. It was found that E_2 decreased for ductile materials upon temperature rise. The relationship between the T_g and the decrease in E_2 could be described by an exponential equation. The lower the T_g, the more pronounced was the decrease in the size of the area E_2. A linear fit of the change in E_2 versus the change in P_y confirmed a good correlation of both parameters.

It has been hypothesized in the past that the amount of stored energy (area E_2) correlates with the TS of tablets [6]. As the previous study showed a clear increase in the TS when binary blends containing the same polymers were tableted, a positive correlation between the size of the area E_2 and the TS could not be confirmed. The

commonly acknowledged hypothesis was refuted. It appeared more accurate to describe E_2 as the necessary input for plastic deformation.

The investigations were expanded to the calculation of the PF. Similar to the above-mentioned hypothesis, the PF has been described as a surrogate for plastic flow [7]. The calculations proved that the opposite is the case. As E_2 is essential for the calculation of the PF, the PF also decreased with increasing temperature. The higher plasticity of polymers upon elevated temperatures was not reflected in the PF calculation. It also failed to distinguish between brittle and ductile materials, as lactose obtained the highest PF. As E_2 is an input variable for the calculation of the PF, it was concluded that the direct analysis of E_2 with its correct interpretation should be preferred over the calculation of the PF.

Besides the T_g, the particle size may act as a main contributor to tablet characteristics [8]. Its influence during heated tableting has never been investigated. It was postulated that the larger specific surface area of smaller particles might promote the heat sensitivity of a given material. The compressibility was evaluated by Heckel and energy analysis. Heckel analysis revealed a higher P_y value at standard ambient conditions for almost all materials if the median particle size was small. Smaller particles favored larger alterations of P_y upon temperature rise. Despite identical chemical composition, they exhibited a higher sensitivity to temperature variations. The initial hypothesis was therefore confirmed.

The energy analysis was less sensitive at standard ambient conditions. The energy parameters were independent of initial particle size. As energy analyses take the complete tableting cycle into account, a distortion of the results from material behavior during compression and decompression could not be excluded. The previously found sensitivity for temperature alterations was still confirmed. When the temperature was raised, the decrease of the area E_2 was dependent on the initial particle size.

The enhanced sensitivity of smaller particles could be verified in the tabletability studies. The increase in TS for binary blends with lactose was more pronounced for a given polymer with smaller particles. The comparison of the increase in TS for two grades of the same material revealed that the increase in TS might especially vary between two grades if the difference between their median particle size is large.

For the compactibility studies, the behavior was a little more complex. The visible effect of temperature for short equilibration times was comparably weak. This stood in contrast to the first studies with longer equilibration times. Although a more pronounced increase in the SF was visible for binary blends containing smaller particles, the extent was independent of the mean particle size difference of two grades. For this specific study, the tabletability analysis proved to be superior over the compactibility analysis.

For the final part of this work, the previously obtained knowledge was transferred to complete formulations containing the model API paracetamol. Initial studies put a large focus on compression data to deepen the understanding of material behavior, whereby tablet characteristics were evaluated in isolation. This last study served the assessment of temperature influence on a broad range of especially critical tablet characteristics. The influence of different formulation components on tablet properties was investigated by using different binder types and concentrations, whereby the filler composition varied.

Investigations regarding compressibility, tabletability and compactibility have the ultimate goal to ensure the desired disintegration and drug release profile during batch release. The temperature-dependent increase in TS during the tabletability studies was dependent on the polymer type and concentration. It was independent of the filler, as both investigated materials (lactose/MCC) had a rather high T_m.

The SF was evaluated in connection with the disintegration and dissolution. The SF usually has a strong effect on disintegration and dissolution, as the medium needs to be able to penetrate into the compact [9]. The SF was similar for all formulations upon temperature rise. Still, the disintegration and dissolution were visibly affected.

The disintegration studies suggested that the effect was strongly reliant on the binder type, concentration and its respective binding capacity. All formulations contained a disintegrant.
Weak interactions and a higher T_g of a binder type favored a rapid disintegration despite elevated temperatures. The effect was independent of the TS. A different binder type with lower T_g yielded an exponential relationship between DT and TS. As the mechanical strength was generally higher, the DT was decelerated from stronger interactions within the compact.

For higher binder concentrations, the analysis focused on tablets compressed at lower pressures. Preliminary trials revealed a pronounced deceleration of the DT at standard ambient conditions. It was found that the tablets from both investigated formulations with higher binder content completely failed to disintegrate when the tableting temperature was high. It is likely the high binder concentrations led to the formation of a percolating cluster.

The obtained results were reflected in the dissolution studies. If the tablets disintegrated rapidly for a given binder type and concentration, the drug release was determined by the dissolution rate of the paracetamol particles. For formulations with a lower binder content, the drug release was only sustained if its enhanced binding capacity yielded in tablets with higher TS.
For the former formulation, the drug release was too rapid to accurately calculate the underlying release-kinetics. For the latter formulation, the sigma-minus method confirmed underlying first-order kinetics.
For the formulations with a higher binder concentration, the dissolution was clearly sustained despite the application of a lower compression pressure. The underlying release-kinetics changed from first-order (22 and 30 °C) to a controlled release (50 and 70 °C). The latter was confirmed by the Higuchi- and the Korsmeyer-Peppas equation. Upon the comparison of all formulations, the MDT also changed most drastically for formulations with a high binder concentration.

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Section 5. Summary and perspectives

Summary and perspectives

This work has deepened the knowledge about critical material characteristics that can trigger an alteration of tablet quality attributes upon temperature rise on an industrial scale. A broad range of frequently used polymers within the pharmaceutical industry was systematically correlated to changed tablet characteristics. The T_g was identified as the main contributor to the identified changes. The studies included pure materials, binary blends and complete formulations containing a model API. The work included aspects of chemical composition, physical properties and mechanical behavior of materials. The findings could be used to prevent and eliminate problems occurring in tableting processes due to elevated temperatures, but could also be useful during formulation development, if an alteration of material properties is desired.

An important part of this work was the establishment of a direct connection between altered excipient properties and in-die compressibility data. Both Heckel and energy analysis proved to be suitable for the detection of material alterations. The lower the T_g, the larger was the decrease in the yield pressure P_y and the energy E_2, respectively. The change in P_y versus the change in E_2 showed a good correlation of both parameters. Differences were observed concerning their sensitivity in regard to particle size variations. In that respect, Heckel analysis was superior in identifying different material characteristics for varying excipient grades.

Moreover, literature statements concerning E_2 were revised critically. The common hypothesis that the size of the area E_2 is the stored energy directly associated with tensile strength was refuted. Although E_2 decreased, the higher plasticity of heated materials promoted a higher mechanical strength. The same findings could be applied to the calculation of the plasticity factor. It was concluded that the direct analysis of E_2 including its correct interpretation should be preferred over the calculation of the plasticity factor.

The studies of binary blends provided first insights into the behavior of formulations with a realistic binder content upon temperature rise. Tablets containing polymers with relatively low T_g values showed an enhanced tabletability and compactibility. For a given bonding area, the bonding strength was pronounced. Where binary blends contained finer grades of the same material, the effect was more pronounced for the

fine grades. For the increase in tensile strength, the difference between two grades could be associated to the difference in the median particle size of the compared polymers. For the solid fraction, no systematic effect was found.

The final part of this work focused on the investigation of more complex formulations containing the model API paracetamol. Besides the tabletability and porosity, disintegration and dissolution studies proved a critical alteration of tablet properties. Disintegration and dissolution behaved similarly for a given binder type and concentration. The application of kinetic models substantiated the statement that the dissolution was clearly sustained for polymers with a high binding capacity and concentration but comparably low T_g.

Further process improvements would include a systematic collection of the findings to evaluate alternatives for critical binders rationally during development. Although this work included several valuable findings, not all influential parameters have been thoroughly understood. This would further reduce empirical approaches by creating a profound knowledge network.

One remaining issue is the connection of temperature evolution and glass transition to sticking phenomena during tableting. Sticking leads to a variety of problems during processing including capping, lamination and heat generation. In course of this work, sticking sometimes prohibited the analysis of a material or promoted the wear of the tableting equipment. Ongoing work should focus on the identification of critical parameters for sticking, which also includes its accurate quantification. This would further assist in the prevention of tableting problems and might eliminate the need for excessive lubrication.

Lastly, it should be kept in mind that the used equipment is not fully developed yet. It is unclear, what scale-up processes could look like if formulations were to benefit from temperature control in either direction. This provides a range of opportunities for future development.

Danksagung

Zuallererst möchte ich mich bei meinem Doktorvater Prof. Dr. Dr. h.c. Peter Kleinebudde für die Aufnahme in seinen Arbeitskreis und das mir damit entgegengebrachte Vertrauen bedanken. Mit Ihrer Hilfe haben sich meine Fähigkeiten wissenschaftlich zu arbeiten und zu denken enorm weiterentwickelt. Sie waren stets ein Ansprechpartner bei Problemen aller Art und haben nie den Blick für das Wesentliche verloren. Auch wenn das Ziel zwischenzeitlich weit entfernt schien, haben Sie Verständnis gezeigt und mich stets motiviert. Die zahlreichen Anregungen und Diskussionen haben zu einem Großteil zum Gelingen dieser Arbeit beigetragen und mich nachhaltig geprägt.

Im Zuge unserer Arbeitskreis-Treffen durften wir Sie auch von Ihrer persönlichen Seite kennenlernen. Sowohl ihre Geburtstage, als auch die Weinverkostung bei Ihnen Zuhause haben uns viel Freude bereitet. Dabei haben wir mit Schrecken feststellen müssen, dass es die edelsten Tropfen wohl doch nicht an jeder Ecke gibt und Weine durchaus unterschiedlich schmecken können! Die interessanten und auch humorvollen Gespräche werden mir für immer in guter Erinnerung bleiben. Dafür möchte ich mich herzlich bei Ihnen bedanken.

Prof. Dr. Anne Seidlitz möchte ich für die Übernahme des Koreferats danken. Das Betreuungssemester mit dir hat viel Spaß gemacht und ich bin froh, dass du mit deiner verständnisvollen und offenen Art das Institut bereicherst.

Der Firma Medelpharm danke ich für die Bereitstellung der beheizbaren Matrize und die schnelle Hilfe bei jeglichen Fragen und Maschinenproblemen.

Bei Stefan Klinken möchte ich mich für die Erstellung des Python-Skripts und die mühevolle Unterstützung bei fachlichen Fragen bedanken. So hat die Arbeit deutlich an Qualität gewonnen.

Ein riesiger Dank geht an Dr. Sabrina Berkenkemper. Ich bin unendlich froh, dass ich so einen liebevollen Menschen wie dich kennenlernen durfte und sich daraus eine tiefe Freundschaft entwickelt hat. Auch wenn du anfangs noch nicht so überzeugt von meinen technologischen Fähigkeiten warst („Da kannst du ewig rühren, das wird sich nicht lösen!“), sind wir schnell unzertrennlich geworden. Mit keiner anderen Person hätten die zahlreichen Abende mit Cocktails und/oder 1,5 kg Süßigkeiten so viel Spaß

gemacht. Ohne dich hätte ich mir die Promotionszeit nicht vorstellen können! Ich hoffe, dass ich eines Tages von deinen exzellenten Spanisch- und Französischkenntnissen profitieren kann (oder deiner Fähigkeit, Publikationen unauffällig auf Deutsch zu schreiben). Danke, dass du so ein toller Mensch bist!

Bei Arne Schulzen möchte ich mich für seine Treue als Büro-Kollegen und später auch guten Freund bedanken. Obwohl wir beide genügend Hürden zu meistern hatten, konnten wir immer gemeinsam lachen und uns hervorragend von der Arbeit ablenken. Dein offenes Ohr und die guten Ratschläge haben mir immer gut getan. Ich bin froh, dass sich in der gemeinsamen Zeit eine so schöne Freundschaft entwickelt hat.

Dr. Jerome „Schromi“ Hansen, dir danke ich besonders für die herzliche Aufnahme ins Institut mit einer Menge Spaß vor allem zu Anfang der Promotionszeit. Dass ich bei unseren gemeinsamen Abenden immer ein Nickerchen machen musste, lag bei weitem nicht an deiner einschläfernden Art, sondern wohl eher an den zahlreichen Schoki-Exzessen (und 2-3 Jelly-Shots). Uns hat es definitiv nie an Humor gefehlt und ich hoffe, dass wir unsere Freundschaft noch lange beibehalten werden.

Dr. Sebastian „Ronny“ Pohl, dir danke ich für deine Einzigartigkeit, die dich zu einem so besonderen Menschen macht. Obwohl es eher Liebe auf den zweiten Blick war, sind wir schnell zusammengewachsen. Neben zahlreichen Lachanfällen konnten wir auch ernste Momente teilen, in denen wir uns unterstützt und aufgemuntert haben. Du hast mich immer wieder motiviert nicht aufzugeben und dafür danke ich dir nebst unserer Freundschaft ganz herzlich.

Katharina Kiricenko möchte ich ebenfalls für die zahlreichen schönen Momente und ihre Unterstützung danken. Dank dir haben die Instituts-Abende und „bottomless“ Konferenzen besonders Spaß gemacht. Danke für deine Freundschaft.

Lukas „Luki“ Lammerding möchte ich für seine stets gute Laune und hilfsbereite Art danken. Ich freue mich, dass wir den Kontakt noch lange beibehalten werden.

Bei Jennifer Kuck, Clara Grawe und Annika Frings möchte ich mich für das stete Auffüllen der „Diabetes-Schublade“ bedanken, an der ich mich doch das eine oder andere Mal bedient habe. Ich werde die Kaffee-Pausen mit euch vermissen.

Andrea Michel, dir möchte ich neben deinem grenzenlosen Einsatz bei den DSC-Messungen für deine liebevolle und empathische Art danken. Deine Tür stand immer

offen und das werde ich für immer zu schätzen wissen. Dorothee Eikeler, dir danke ich vor allem für deine Unterstützung bei den Freisetzungsversuchen (bis die Finger bluten!). Im Verdünnen von Schnappis sind wir nun beide Profis. Besonders gefallen haben mir ebenfalls die Gespräche mit zahlreichen Geschichten von früher und heute. Ihr seid beide eine absolute Bereicherung für das Institut.

Bei meinen beiden WPP-Gruppen, Fulya Cansiz und Sien Duski, sowie Madeleine de Vos und Paulina Schmidt bedanke ich mich für ihren Einsatz bei den Granulier- beziehungsweise Tablettierversuchen.

Dr. Robin Meier möchte ich für die Unterstützung bei meinen ersten Granulierexperimenten danken, auch wenn sie leider nicht von Erfolg gekrönt waren. Im gleichen Zuge möchte ich mich bei Stefan Stich für die Anfertigung der Schneckenvorrichtung bedanken.

Steffen Köhler vom Center for Advanced Imaging danke ich für seine Bemühungen im Zuge der REM-Aufnahmen.

Allen weiteren Personen vom Institut für Pharmazeutische Technologie und Biopharmazie möchte ich für eine unvergessliche Zeit danken. Egal ob Konferenzen, Weihnachts- oder Karnevalsfeiern – dank euch wird mir die Promotionszeit für immer in positiver Erinnerung bleiben!

Mein wohl größter Dank gilt meinem Ehemann Marcel. Du hast mir durch deine liebevolle Unterstützung und Geduld immer wieder Kraft gegeben. Dies in wenige Worte zu fassen, ist unmöglich. Ich danke dir von ganzem Herzen für alles!

Zuletzt möchte ich meiner Familie und vor allem meinem Vater Mahmoud Hajij danken. Einen besseren Papa könnte ich mir nicht wünschen.
Auch wenn nicht alle Familienmitglieder den Abschluss dieser Arbeit erleben durften, haben sie doch alle zu ihr beigetragen. Meinem Onkel Dr. Bernd Plappert danke ich in Gedanken dafür, dass er mein Interesse für Wissenschaft entfacht hast. Meiner Mutter Dr. Birgit Plappert möchte ich von Herzen für ihren Ansporn danken, meine Ziele und Träume zu verwirklichen. Ohne euch wäre diese Arbeit nicht entstanden.

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.

Hanna Dorothea Grumann