New Insights into Tablet Sticking:

Characterization and Quantification of Sticking to Punch Surfaces during Tablet Manufacture by Direct Compaction

Dissertation

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"Sometimes the fastest way to get there is to go slow
and sometimes if you wanna hold on you got to let go.
I'm gonna close my eyes and count to ten.
I'm gonna close my eyes and when I open them again
everything will make sense to me then."

- Tina Dico -

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Summary

Tablets are the most widespread and popular dosage form for medical application. Despite the fact that tablets have been manufactured in large quantities for decades, there is still a need for a better understanding of the physical processes involved in tablet manufacture and the factors causing tableting problems. One of the most common problems observed during tablet manufacture is tablet sticking. Numerous studies have been conducted to elucidate the variables affecting the sticking tendency of pharmaceutical tablet formulations, but the underlying causes of tablet sticking are not yet fully understood.

In the present work, various pharmaceutical tablet formulations were investigated with regard to their physico-chemical properties, compaction behavior as well as their sticking propensity. The main objective was to provide new insights into tablet sticking, primarily focusing on the characterization and quantification of sticking to punch surfaces during tablet manufacture by direct compaction.

In a first study, various tablet formulations consisting of microcrystalline cellulose (Avicel® PH200) and sorbitol (Neosorb® P60W), a hygroscopic tableting excipient, were investigated for their sticking propensity. The main objective of this study was to evaluate the suitability of various lubricants for the prevention of tablet sticking. The efficiency of the most commonly used lubricant magnesium stearate was compared to that of sodium stearyl fumarate (Pruv®), microprilled poloxamer 407 (Lutrol® micro 127) and PEG 4000. It was found that the anti-adherent performance of the boundary lubricants Pruv® and magnesium stearate was sufficient for the prevention of sticking, whereas the fluid-film lubricants Lutrol® and PEG turned out to be inefficient.
In the same study, it could also be shown that the anti-adherent efficiency was considerably improved by using a physical mixture of Pruv® and magnesium stearate for lubrication of the tablet formulations. Lubrication with a 1:1 mixture of both lubricants allowed a reduction of the total lubricant content from 2 % to 1 %, thus indicating a synergistic effect between these two lubricants.

Secondly, the sticking propensity of tablet formulations containing various grades of ibuprofen, an adhesive drug substance, was evaluated and characterized by HPLC quantification of ibuprofen present in the sticking residue adhered to the punch surfaces.

It could be shown that the sticking propensity of the investigated tablet formulations was considerably affected by the ibuprofen grades and their mean particle size could be identified as a critical factor. The extent of ibuprofen sticking was found to be inversely related to the mean particle size of the powder particles. Hence, the smaller the ibuprofen powder particles, the higher the sticking propensity of the respective tablet formulation. In this study, the origin of the drug substance turned out to be less critical because ibuprofen grades purchased from different suppliers exhibiting similar particle sizes were found to cause sticking to a similar extent.

Furthermore, the suitability of take-off force measurements as an inline analytical technique for the detection and/or quantification of tablet sticking was studied. Although the tablet take-off force is reported to be a direct measure of the sticking tendency of tablet formulations, a correlation between the obtained take-off force data and the actual sticking extent quantified by HPLC analysis of the sticking residue could not be shown. It was concluded that the evaluation of take-off forces requires a more differentiated approach and therefore a new concept for the interpretation of take-off force data is presented. This concept takes into account that the measured take-off forces are not only affected by the mechanism of tablet detachment (no sticking vs. sticking), but are also influenced by the balance of the adhesion forces acting between tablet and punch surface in relation to the cohesion forces acting within the tablet.

In a final study, it was found that certain punch tip coatings had a synergistic effect on the anti-adherent performance of the lubricant magnesium stearate during direct compaction of six different tableting materials. It could be shown that application of Hard Chromium-plated punches and Chromium Nitride-coated punches provided supportive efficiency for the prevention of tablet sticking, partially allowing a reduction of the magnesium stearate content in the tablet formulation. However, from take-off force data it was concluded that the adhesive interactions taking place at the surface of the Chromium-Nitride-coated punches are higher than those observed with the Hard Chromium-plated punches, indicating a superior anti-adherent performance of the latter.

Zusammenfassung

Tabletten stellen auf dem Arzneimittelmarkt eine der bedeutendsten Darreichungsformen dar. Trotz ihrer vielfältigen Anwendung sowie der Tatsache, dass Tabletten bereits über Jahrzehnte hinweg in großen Mengen hergestellt werden, besteht nur ein begrenztes Verständnis der physikalischen Abläufe bei der Tablettierung sowie den Faktoren, die Probleme bei der Tablettierung verursachen können. Das Kleben von Tablettiermischungen an den Stempelflächen ist eine der am häufigsten auftretenden Komplikation während der Tablettierung. Obwohl bereits zahlreiche Studien zur Untersuchung des Klebeverhaltens von verschiedensten pharmazeutischen Tablettiermischungen durchgeführt worden sind, konnten die zugrunde liegenden Ursachen des Klebens noch nicht vollständig aufgeklärt werden.

Im Rahmen dieser Arbeit wurden daher verschiedene pharmazeutische Tablettiermischungen sowohl hinsichtlich ihrer physikochemischen Eigenschaften als auch ihrer Verpressbarkeit untersucht und deren Klebeneigung charakterisiert. Ziel der Untersuchungen war es, neue Einblicke in die Problematik des Klebens zu gewähren unter besonderer Berücksichtigung der Charakterisierung und Quantifizierung des Klebens von direkt verpressten Tablettiermischungen.

Zunächst wurde die Effektivität verschiedener Formentrennmittel bei der Tablettierung von Sorbitol-haltigen Pulvermischungen untersucht. Sorbitol weist eine starke Klebetendenz auf, welche hauptsächlich auf die Hygroskopizität dieses Hilfsstoffes zurückzuführen ist. In der vergleichenden Studie konnte gezeigt werden, dass für die Tablettierung der untersuchten Pulvermischungen die hydrophilen Substanzen Poloxamer 407 (Lutrol® micro 127) und PEG 4000 eine nur unzureichende Formentrennmittel-Wirkung aufwiesen, während durch die Verwendung der filmbildenen Schmiermittel Magnesiumstearat und Natriumstearylfumarat (Pruv®) das Kleben effektiv verhindert werden konnte.
Darüber hinaus konnte in dieser Studie gezeigt werden, dass die Formentrennmittel-Wirkung durch die Verwendung einer physikalischen Mischung (1:1) von Magnesiumstearat und Pruv® deutlich verbessert werden konnte. Die Gesamtkonzentration an Formentrennmittel konnte von 2 % auf 1 % reduziert werden, was auf einen synergistischen Effekt dieser beiden Substanzen hinweist.

In einer weiteren Studie wurde die Klebeneigung verschiedener Ibuprofen-haltiger Pulvermischungen untersucht und das Ausmaß des Klebens mittels HPLC-Analytik des Kleberückstands quantifiziert. Der Wirkstoff Ibuprofen ist in unterschiedlichen

Qualitäten auf dem Markt erhältlich. Daher wurde in dieser Studie der Einfluss verschiedener Ibuprofen-Qualitäten auf das Ausmaß des Klebens untersucht. Es konnte gezeigt werden, dass die Klebeneigung der Pulvermischungen erheblich durch die Qualität des Wirkstoffes beeinflusst ist, wobei die mittlere Korngröße der Pulver als kritischer Faktor identifiziert wurde. Die Klebeneigung der Pulvermischungen verhielt sich umgekehrt proportional zur mittleren Korngröße der Ibuprofen-Partikel, d.h. je kleiner die Ibuprofen-Partikel, desto stärker ausgeprägt war das Kleben der Tablettiermischung. Ibuprofen-Qualitäten, welche eine ähnliche Korngröße aufwiesen, zeigten auch ein ähnliches Klebeausmaß, sodass die Herkunft der unterschiedlichen Ibuprofen-Qualitäten als wenig kritischer Faktor bewertet wurde.

Im Folgenden wurde untersucht, ob die Messung von Abstreifkräften während des Tablettiervorganges eine geeignete analytische Methode ist, um das Kleben von Tablettiermischungen zu detektieren oder sogar quantifizieren zu können. Obwohl die Abstreifkraft in der Literatur als ein direkter Indikator für das Kleben von Tabletten beschrieben ist, konnte keine Korrelation zwischen den Abstreifkraft-Messwerten und dem mittels HPLC-Analytik quantifizierten Klebeausmaß der Tablettiermischungen festgestellt werden. Basierend auf diesen Ergebnissen wurde ein neues Konzept zur Beurteilung und Interpretation von Abstreifkräften vorgeschlagen. Dieses Konzept berücksichtigt das Zusammenspiel zwischen den vorherrschenden Adhäsionskräften an Stempel- und Tablettenoberfläche sowie den im Tabletteninneren auftretenden Kohäsionskräften und dem daraus resultierenden Mechanismus der Abtrennung der Tabletten von den Press-werkzeugen.

In einer abschließenden Studie konnte gezeigt werden, dass die Verwendung beschichteter Presswerkzeuge eine geeignete Maßnahme zur Vermeidung des Klebens darstellen kann. Durch die Verwendung sowohl von hartverchromten als auch Chromnitrid-beschichteten Stempeln konnte eine begünstigende Wirkung auf die Effektivität des Formentrennmittels Magnesiumstearat festgestellt werden, sodass die Magnesiumstearat-Konzentration in den Tablettiermischungen sogar teilweise deutlich reduziert werden konnte. Die Auswertung von Abstreifkräften ergab, dass die adhäsiven Interaktionen an der Oberfläche der Chromnitrid-beschichteten Stempel stärker ausgeprägt waren als an der Oberfläche der hartverchromten Stempel. Dies weist darauf hin, dass sich die hartverchromten Stempel besser zur Vermeidung des Klebens eignen als die Chromnitrid-beschichteten Stempel.

Contents

1. Introduction

1.1. Pharmaceutical tablets

Solid oral dosage forms such as tablets have been administered to patients for decades, and the fact that tablets still belong to one of the most widespread and popular dosage forms for medical application indicates their high acceptance. Tablets offer numerous advantages over other dosage forms such as the economic way of manufacture, the ease of handling during packaging, storage and distribution as well as the high chemical and microbial stability [1, 2]. From the patients' perspective, the convenient way of administration and dosing is one of the main reasons for their continued popularity. Moreover, the properties of conventional, uncoated tablets can be easily improved or modified by means of film coating which may also have a positive effect on the patient compliance. Film coatings can be applied to enhance the mechanical stability of the tablets [3], to facilitate swallowing, to mask unpleasant taste or odor [4], or to control drug release in the gastrointestinal tract [5, 6].

Tablets have to fulfil plenty of requirements. One of these requirements is that the tablet strength should be sufficiently high to withstand the mechanical strain encountered by the compacts during production, packaging, shipping and dispensing [7]. Furthermore, a tablet must exhibit a sufficient physico-chemical stability over its shelf life to maintain its physical attributes and to avoid alteration or degradation of the active pharmaceutical ingredient (API) and/or excipients [8]. After oral administration, the API must be released from the tablet in a predictable and reproducible manner to ensure drug absorption in the gastrointestinal tract, being a prerequisite for attaining adequate bioavailability of the API and consequently its therapeutic effect [9, 10].

In general, tablets are manufactured by powder compaction, during which the individual particles are compressed into a coherent compact [11]. To facilitate the compaction process as well as to achieve the desired tablet properties, the tablet formulation is basically composed of several components such as the API(s) and various excipients with different properties and functions. Excipients typically used in tableting are fillers (e.g. lactose, mannitol), binders (e.g. microcrystalline cellulose, povidone), lubricants (e.g. magnesium stearate, glyceryl behenate), glidants (e.g. colloidal silicon dioxide) and disintegrants (e.g. croscarmellose sodium, crospovidone).

Each excipient affects the tabletability and compactibility of the respective tablet formulation, and thus contributes to the final properties of the tablets [12, 13]. It is well known that excipients which are added to a tablet formulation even in low quantities can have considerable effects on the compaction process as well as on the tablet properties. For instance, the deleterious effect of the lubricant magnesium stearate on the tablet strength is well described [14-16]. Hence, when developing a new tablet formulation, it is fundamental to choose suitable excipients. Besides the choice of suitable excipients, appropriate tableting conditions need to be determined during the development phase.

Most pharmaceutical tablets are processed either by direct compaction or by compaction of granules obtained by a dry granulation or wet granulation process. Direct compaction means the tableting of powder blends which have been prepared only by dry mixing of the individual components. From Fig. 1 it is apparent that fewer steps and thus less equipment are required if the direct compaction technique is applied, resulting in lower labor costs, reduced processing time and lower energy consumption [17]. Particularly for the manufacture of tablets containing thermolabile and moisture-sensitive APIs, direct compaction is considered as the technique of choice [1]. However, to allow tablet manufacture by the direct compaction method, it is crucial that the powder blends to be compacted fulfil certain criteria, e.g. good flowability and compressibility [18, 19]. Various excipients specifically developed for the direct compaction technique are available on the market [20]. For instance, the concept of co-processing of excipients, introduced in the late 1980's, has led to an increasing number of co-processed excipients suitable for direct compaction on the pharmaceutical market [17, 21].

If a powder blend cannot be tableted by direct compaction, its processability can be improved by granulation of the powder blend, thereby obtaining uniform granules with narrow particle size distribution ultimately leading to superior flowability and compressibility. Moreover, segregation tendencies in the tablet manufacturing process are eliminated by granulation, and thus a homogeneous distribution of the API in the tablets is ensured. In the pharmaceutical industry, wet granulation is the most commonly used granulation technique [22, 23]. However, one limitation of wet granulation as method for tablet manufacture is that it is unsuitable for thermolabile or moisture-sensitive APIs. Further drawbacks

of the wet granulation technique are the long processing time and the product loss during the different processing steps [24].

Dry granulation methods such as slugging or roller compaction are particularly suitable for processing of APIs which are sensitive to moisture or heat because the granules are formed without addition of liquids and subsequent drying steps [25, 26]. Compared to wet granulation, the dry granulation process is less time-consuming. However, one of the disadvantages of dry granulation is that typically a high amount of fines is produced which has to be removed. In addition, dry granulation often results in tablets with inferior tensile strength compared to tablets prepared by wet granulation [25, 27].

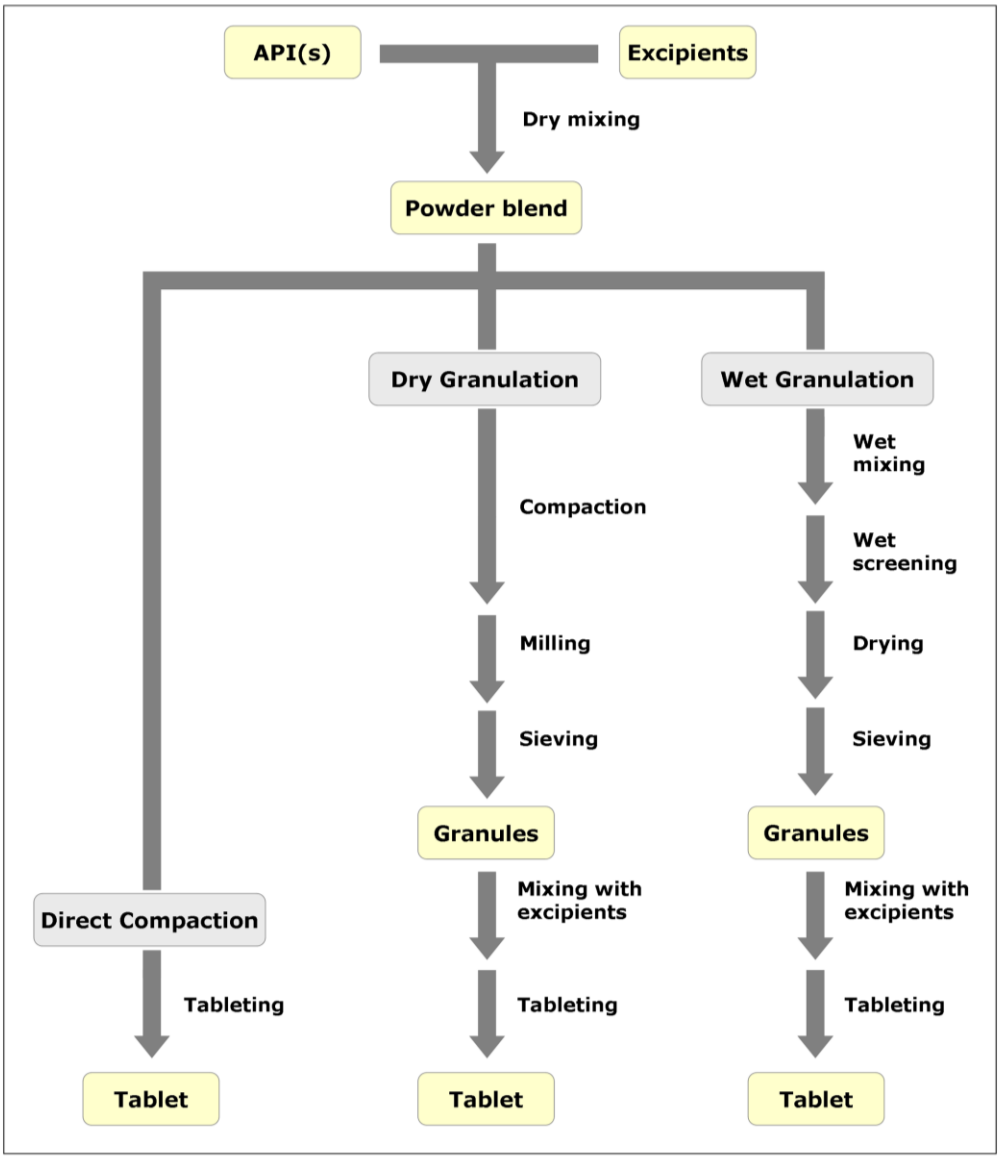

Fig. 1: Schematic outline of the process steps involved in direct compaction and compaction of granules obtained by dry granulation or wet granulation process.

1.2. Tableting equipment

About 170 years have passed since the first patent for a machine intended "for the shaping of pills, lozenges and black lead by pressure in a die" was granted to William Brockedon in 1843 [28]. Brockedon's machine worked basically with the same principle as nowadays tablet presses. However, modern tablet presses are substantially instrumented and computer-controlled machines providing a high degree of productivity, efficiency and flexibility [29]. Three general types of equipment used for compaction studies are available: eccentric tablet presses, rotary tablet presses and compaction simulators.

Eccentric tablet presses operate with one set of punches and a stationary die. The upper punch is attached to an eccentric arm that causes the upper punch to move up and down in a stamping motion [29]. The compaction force is adjusted by the depth of penetration of the upper punch into the die cavity, whilst the lower punch is inactive during powder compaction. Therefore, on eccentric tablet presses there is a one-sided inhomogeneous densification of the tableting material induced by the upper punch pressure. Tableting with an eccentric tablet press allows the compaction of even small amounts of material and thus single tablets can be prepared easily. Moreover, this kind of tablet press is easy to set up and to instrument. However, since these presses run at a relatively slow compression speed, eccentric tablet presses are traditionally used in compaction research and tablet formulation development as well as in commercial small-scale production.

Commonly, commercial tablet production is carried out with **rotary tablet presses**, some of which can have a tablet throughput of one million tablets per hour [30]. This high productivity results from the use of many punch and die sets as well as from the higher compression speeds that may be applied [31, 32]. The operation mode of rotary tablet presses differs significantly from that of eccentric tablet presses. In rotary tablet presses, many sets of tooling are fitted around the periphery of a rotating turret [30]. As the turret rotates, the vertical movement of the punches is induced by different cams (e.g. filling cam, dosing cam) and by the stationary pressure rollers, generating a continuous compaction cycle [31, 32]. In contrast to eccentric tablet presses, in rotary tablet presses both lower and upper punches move into the die while passing between the pressure rollers, ultimately leading to a two-sided homogenous densification of the tableting material.

Instrumentation of rotary tablet presses turned out to be more difficult than instrumentation of eccentric tablet presses, which is mainly attributed to the large number of tooling sets as well as to the rotation itself [33-35]. Furthermore, rotary tablet presses are predominantly utilized in pharmaceutical production rather than in pharmaceutical formulation development because of the larger amount of tableting material which is required to operate this type of tablet press.

Compaction simulators are single station presses with sophisticated instrumentation capable of imitating a modelled compaction event [36]. Thus, they are used to simulate the compaction process of commonly used tablet presses in terms of punch type, punch profiles and compression speed [29]. As with an eccentric tablet press, for compaction studies with a compaction simulator only small amounts of tableting material are required. Therefore, compaction simulators are typically used in pharmaceutical research and development as a tool for tablet formulation development and for the evaluation of influences of compaction process variables, particularly scale-up parameters [36]. In addition, compaction simulators may be used for troubleshooting to assess problems encountered in production-scale tableting.

In summary, for compaction studies, different types of tablet presses are available. However, the choice of the most suitable tableting equipment depends on the specific product requirements. The most important features of the three different types of tableting equipment are presented in Table 1.

Table 1: Comparison of tableting equipment; modified from [36]

Features	Eccentric tablet press	Rotary tablet press	Compaction simulator
Easy to set up	Yes	No	Yes
Easy to instrument	Yes	No	Yes
Small amount of material possible	Yes	(No)	Yes
Mimics production conditions	(No)	Yes	Yes
Mimics cycles of different presses	No	No	Yes
Comparably low equipment costs	Yes	No	No
Database in literature	Yes	Yes	Some

1.3. Theoretical aspects of compression

The tablet manufacturing process involves an essential unit operation of compaction, in which powders or granules are converted into a coherent compact through application of pressure. A tablet is typically formed by uni-axial compression using a set of tooling consisting of upper punch, lower punch and die [11]. The tableting process consists of several distinct stages including die filling, compaction and ejection [37]. A schematic description of the tableting process is displayed in Fig. 2.

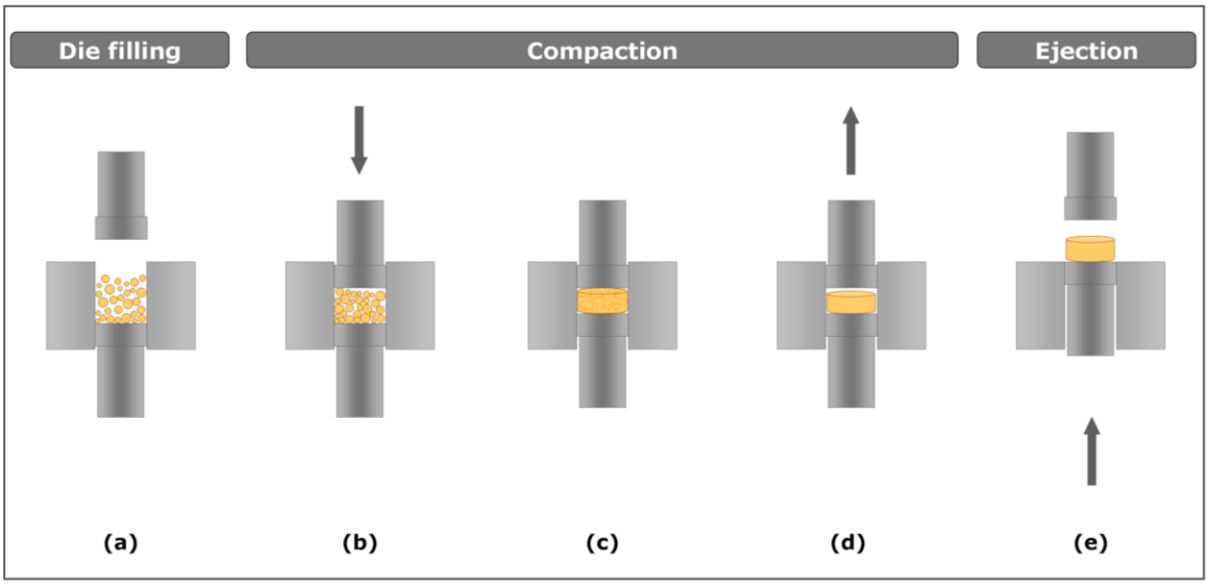

Fig. 2: Schematic description of the tableting process (eccentric tablet press): (a) die filling, (b) particle sliding and rearrangement, (c) particle fragmentation and deformation, (d) decompression, (e) ejection.

During die filling (Fig. 2a), the powder or granules are deposited into the die cavity under gravity with a filling shoe. At this stage, the only forces that exist between the individual particles are those that are related to the packing characteristics of the particles, e.g. particle shape, particle surface properties, the density of the particles and the total mass that is filled into the die [38]. The next step in the compaction process is initiated by the entrance of the upper punch into the die cavity (Fig. 2b). The proximity between upper and lower punch tips increases, thereby exerting pressure to the tableting material present in the die.

As a result of particle sliding and particle rearrangement, the bulk volume of the tableting material is progressively decreased leading to closer packing of the particles.

Subsequently, at a certain degree of density during the compaction process the particles are immobilized in the die and further rearrangement of the particles is prevented. At this stage, tablet formation is induced by numerous simultaneous internal processes that lead to particle fragmentation and deformation (Fig. 2c) and finally to the formation of bonds [39]. In the decompression phase, when the applied compaction pressure decreases (Fig. 2d), tablets generally show elastic recovery at least to some extent. Elastic recovery leads to volume expansion which is an effect of stress relaxation within the tablet [40]. This is caused by elastically deformed particles partially regaining their original shape. Finally, the compacted tableting material is ejected from the die (Fig. 2e). In general, the ejection process is divided into three phases [41, 42]: in the first phase the tablet ejection is initiated by overcoming frictional and adhesion forces at the interface between the tablet and the die wall. The subsequent second phase of the ejection process is characterized by sliding frictional forces which are required to push the tablet up the die wall, followed by the third phase where the tablet starts to emerge from the die until it is completely ejected [38].

In conclusion, as a result of compression, the final structure of a tablet is determined by the combined processes of particle deformation/fragmentation, interparticulate bonding and tablet relaxation.

1.3.1. Deformation behavior of tableting materials

Particles may deform during compaction by three possible mechanisms: elastic deformation, plastic deformation, and brittle fragmentation [43]. Elastic deformation is a reversible process where the individual particles regain their original shape when the compaction pressure decreases. In contrast, plastic deformation is the irreversible deformation of particles resulting in a permanent change of the particle shape dependent on the duration of the applied maximum pressure. During deformation by brittle fragmentation, the original particles break into smaller units which in turn are likely to undergo a secondary rearrangement, followed by further deformation processes.

Usually, pharmaceutical materials deform by more than one of the aforementioned mechanisms, and these mechanisms can occur at different stages of the compaction process [44].

However, one of the described mechanisms often predominates, mainly depending on the physical properties of the tableting material(s), e.g. particle size and morphology as well as their bonding characteristics. For example, it has been demonstrated that some materials exhibit a critical particle size at which the predominant deformation mechanism changes from brittle fragmentation into plastic deformation [45]. Some materials used as tableting excipients can be categorized as showing either brittle or plastic deformation behavior as a result of an either extremely low (e.g. anhydrous calcium phosphate) or high (e.g. microcrystalline cellulose) critical particle size [45]. However, materials such as lactose exhibit an intermediate deformation behavior, as lactose grades used for tableting exhibit particle sizes close to the critical particle size [46].

Generally, compaction parameters such as magnitude of compaction force, rate of force application and contact time during which the tableting material is exposed to the maximum pressure (dwell time) are also major factors affecting the degree of fragmentation, plastic and/or elastic deformation [47-49].

Various mathematical equations are used to quantitatively determine the deformation mechanism of a tableting material. The most frequently employed compression equation in pharmaceutical compaction research is the one described by Heckel [50, 51].

$$\ln\left(\frac{1}{\varepsilon}\right) = K \cdot P + A \qquad \text{(eq. 1)}$$

This equation is based on the assumption that the densification of the tableting material follows first-order kinetics, thus assuming a linear relationship between the logarithm of the reciprocal tablet porosity (ε) and the applied compaction pressure (P). K is the slope of the linear portion of the Heckel plot and A is a constant related to the initial particle rearrangement. The reciprocal of the slope K is the mean yield pressure (P_Y) which is a numerical parameter describing the deformation characteristics of a tableting material. A high degree of plastic deformation is indicated by a steep slope of the compression curve and a low mean yield pressure (P_Y < 100 MPa) [44, 52]. Although the Heckel equation is reported to have its limitations in describing the deformation behavior particularly at low and very high compression, it is widely accepted for characterization of the densification behavior of tableting materials [53, 54].

1.3.2. Bonding mechanisms

According to Hiestand "tableting is the process of sliding, fracturing and deforming particles" and "bonding is the summation of interatomic attraction between these particles" [55].

During compression, the contact area between individual particles is increased by rearrangement, fragmentation and deformation of particles, thereby facilitating the formation of bonds. Bonding between particles manifests itself in the mechanical tablet strength which reflects the number of bonds as well as the strength of each bond.
The predominant bonding mechanisms relevant in compaction of tablet formulations are intermolecular forces, solid bridges and mechanical interlocking of irregular particles [55, 56].
Intermolecular forces act over a certain distance between particles and include van der Waals forces, hydrogen bonding and electrostatic forces. These attractive forces are reported to contribute to the overall bonding strength of compacts to a large extent [57, 58]. Whilst van der Waals forces are assumed to be the most important type of intermolecular forces for bond formation [58, 59], electrostatic forces which may arise from triboelectric charging during mixing and compaction are not considered to be of significance due to quick neutralisation.
The nature of solid bridges strongly depends on the chemical structure of the tableting material, as this bonding type can only occur at solid-to-solid contacts between particles. Thus, solid bridges between particles are formed by processes such as sintering, solidification of the melting, crystallization, or chemical reactions such as salt formation [55]. Because of their structure, bonding through solid bridges usually leads to tablets with a high mechanical strength, which in turn may be associated with extended disintegration times of the tablets.
Bonding by mechanical interlocking is primarily attributed to particle irregularities as well as to surface texture and shape of the particles.

The predominating bonding type in tablets is difficult to predict and it certainly depends on various parameters including the physico-chemical properties of the tableting material and the degree and duration of compression [59].

1.3.3. Tablet relaxation

As a result of stress relaxation, tablets generally show elastic recovery during decompression [40]. However, the extent of elastic recovery strongly depends on the degree and the type of deformation and bonding [60]. Generally, the higher the degree of elastic deformation versus plastic deformation, the larger is the extent of tablet relaxation. It has been suggested that the elastically stored energy during compression is the driving force for tablet relaxation, whereas bonding is regarded as the counteracting force providing resistance to stress relaxation [40, 60].

As the stress during compression is applied in axial direction, dimensional changes are supposed to occur primarily in axial direction which means that the tablets increase in height rather than in diameter [61]. The percentage of elastic recovery (ER) can therefore be calculated following eq. 2:

$$ER = \left(\frac{h - h_P}{h_P} \right) \cdot 100 \qquad \text{(eq. 2)}$$

where h is the tablet height after ejection and h_p is the tablet height at the applied compaction pressure.

As with the deformation characteristics of particles, the tablet relaxation propensity can be influenced by the physical properties of the tableting material as well as by the compaction parameters such as compaction pressure and compression speed [62-64].

1.4. Common problems during tablet manufacture

Tablets must fulfill plenty of requirements such as being free from any organoleptic and/or functional defects. However, in industrial-scale tablet manufacture problems such as tablet weight variation, low tablet strength, capping or sticking are commonly observed. It is important to note that these problems may cause the rejection of whole batches for quality or safety reasons, and consequently commercial losses.

Tablet manufacturing problems and thus corresponding tablet defects are related to the tableting process, the tableting equipment, the composition of the tablet formulation, or a combination thereof. In 2010, the Journal *Pharmaceutical Technology Europe* conducted a survey on the most common problems encountered by tablet manufacturers [65]: the problems observed during tablet manufacture could mainly be attributed to poor weight/content uniformity (~ 27 %) and poor tablet formulation design (~ 34 %) rather than to inadequate (~ 14 %) or incorrect (~ 15 %) handling of the tableting equipment.

1.4.1. Tablet weight variation

One basic quality attribute of tablets is their content uniformity. During the compression process, dosing of tablets is conducted by volumetric filling of the die cavity. Thus at a given bulk density the volume of tableting material will directly correspond to the tablet weight. Therefore, a low variation of the individual tablet weights is regarded as an indicator for adequate content uniformity.
The main causes for high tablet weight variations and their common remedies are summarized in Table 2.

1.4.1.1. Formulation-related causes of high tablet weight variations

One fundamental reason for poor tablet weight uniformity is inconsistent filling of the die cavity as a result of the tableting material showing insufficient flowability [66]. In many cases, poor flow properties of the tablet material are caused by cohesive attraction forces acting between the particles which lead to aggregated powders exhibiting inferior flowability. As the cohesive attraction forces become effective only if the particles are in direct contact, the physical properties of the

tableting material such as particle size, particle shape and moisture content play an important role [67-69] and affect its flow properties. The problem of poor tablet weight uniformity may be solved by improving the flowability of the tablet material either by addition of a sufficient amount of glidant [70] or by optimization of the particle size distribution of the tableting material by means of granulation [24].

Table 2: Common causes and remedies for high tablet weight variations

Causes	Remedies
Formulation-related causes:	
▪ Poor powder flow properties	▪ Granulation or/and addition of glidant ▪ Compression at slower speed
▪ Inappropriate particle size distribution	▪ Granulation ▪ Avoidance/Removal of fines
▪ Inadequate moisture content	▪ Addition of moisture adsorbent or drying ▪ Addition of humectant
▪ Sticking	▪ Addition of lubricant (anti-adherent) ▪ Punch tip coatings
Machine-/Process-related causes:	
▪ Punch working length out-of-tolerance	▪ Adjustment of critical punch working length
▪ Inappropriate hopper and feeder settings	▪ Adjustment of machine and feeder speed ▪ Use of correct fill cams

High tablet weight variations may also be caused by sticking of powder material to punch surfaces. To prevent sticking, the addition of anti-adherents to the tablet formulation is the most commonly used measure.

1.4.1.2. Machine-/Process-related causes of high tablet weight variations

Another reason for high tablet weight variations is inconsistent filling of the die cavity during tableting resulting from incorrect settings of hopper or feeder [71]. What these machine-related problems are concerned, an optimization of the die filling process can be achieved by adjusting tableting parameters such as feeder speed, filling cam configuration or compression speed.

In case of rotary tablet presses, an additional source of high tablet weight variations is the dimensional variation in the punch working lengths [72]. The punch working lengths have to be monitored on a regular basis, where the punch working length tolerance applies to each punch within the same tooling set. If the punch working length is out-of-tolerance, the critical working length of the punches needs to be adjusted.

1.4.2. Insufficient tablet hardness

The tablet hardness is usually assessed as an in-process-control parameter during tablet manufacture, because it is one of the most relevant tablet properties, characterizing the compactibility of tableting materials and the mechanical tablet strength to withstand potential stresses during tableting, packaging, shipping and dispensing [7]. There are many formulation-related and machine-/process-related factors which can have a negative effect on the compactibility of a tablet formulation, leading to an insufficient hardness of the resulting tablets (Table 3).

Table 3: Common causes and remedies for insufficient tablet hardness

Causes	Remedies
Formulation-related causes:	
▪ Inadequate binding properties	▪ Addition/Replacement of dry binder ▪ Increase of binder content ▪ Granulation
▪ Excessive elastic recovery	▪ Reduction of the amount of elastic excipient(s) ▪ Granulation ▪ Co-processing
▪ Overlubrication	▪ Reduction of lubricant content ▪ Choice of different lubricant or lubricant type
Machine-/Process-related causes:	
▪ Compaction force too low	▪ Increase of compaction force
▪ Compression speed too high (insufficient dwell time)	▪ Decrease of compression speed (increased dwell time)
▪ Inconsistent die filling	▪ Adjustment of machine and feeder speed ▪ Use of correct fill cams

1.4.2.1. Formulation-related causes of insufficient tablet hardness

The most common formulation-related factors which may lead to insufficient tablet hardness are inadequate binding properties of the tableting material as well as excessive elastic recovery of individual components within the tablet.
The mechanical strength of tablets may therefore be improved either by addition of a more suitable dry binder or by an increase of the binder content within the tablet formulation. Furthermore, to reduce excessive elastic recovery, the elastically deforming component(s) within the tablet formulation may be replaced by more plastically deforming materials, e.g. suitable dry binders [73, 74]. The overall plasticity of the tableting material may also be increased by means of granulation or co-processing [17].

Another common cause of insufficient tablet hardness is overlubrication. Particularly the most frequently employed lubricant magnesium stearate is well known to have a negative effect on the compactibility of tableting materials resulting in decreased mechanical tablet strength [15, 16]. This phenomenon is explained by the formation of a thin lubricant film around each of the host particles during blending [75]. As a result of the physical barrier formed by the lubricant film, the interparticulate bonding strength between the particles is weakened. It has been shown that tablets consisting of excipients that undergo plastic deformation are greatly affected by the weakening of the interparticulate bonding, whilst brittle materials were found to be less susceptible to a reduction of tablet strength by magnesium stearate [14, 16]. As a remedy for overlubrication, the composition of the tablet formulation has to be changed with regard to the lubricant type and/or content.

1.4.2.2. Machine-/Process-related causes of insufficient tablet hardness

The most evident machine- or process-related reasons for insufficient tablet hardness are incorrect settings of compaction force and compression speed.
The primary function of the compaction force is to increase the surface contact area between particles, thereby facilitating particle deformation and the formation of bonds [38]. Therefore, the higher the applied compaction forces, the higher the bonding strength between the particles and consequently the tablet hardness. However, for a specific tableting material this increasing tablet hardness is true only up to a certain compaction force, at which the tablet hardness will remain

constant, because the closest proximity between the particles has been reached [59].

The parameter compression speed may influence the deformation behavior of a tableting material. For some tableting materials, a change in the compression speed can have a considerable effect on the deformation mechanism occurring during compression [49]. Several investigators have found a decrease in tablet hardness with increasing compression speed. This observation was attributed to a decrease in interparticulate bonding caused by a reduction in the time available for plastic deformation [76, 77]. In the literature, this observation is referred to as viscoelasticity [62, 78, 79]. In contrast to the plastically deforming materials, brittle materials which primarily consolidate by fragmentation have shown to be much less sensitive to compression speed variations [48, 76-78].

1.4.3. Capping and lamination

Capping or lamination of tablets is a problem which frequently occurs during tablet manufacture or physical handling and/or testing of the tablets. Capping describes the splitting of parts of a tablet (Fig. 3a), whereas lamination refers to cracking manifesting itself in a separation of the tablet into two or more layers (Fig. 3b).

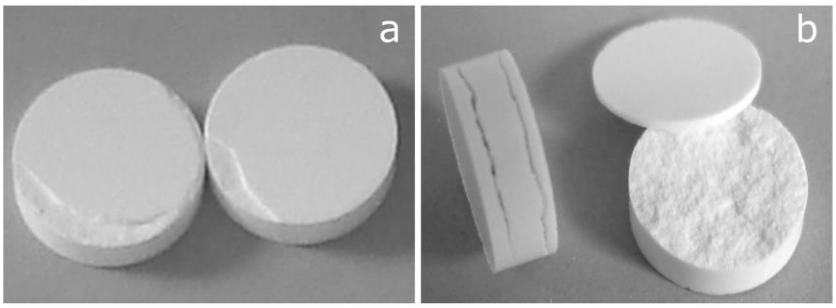

Fig. 3: Tablet capping (a) and lamination (b).

Numerous studies have been carried out to gain knowledge of the fundamental mechanisms behind tablet capping, and several mathematical estimations have been proposed to quantify the capping tendency of pharmaceutical tablet formulations [37, 80-86]. Some of the factors that may contribute to tablet capping and lamination are listed in Table 4.

Table 4: Common causes and remedies for tablet capping and lamination

Causes	Remedies
Formulation-related causes:	
▪ Insufficient binding properties	▪ Addition or Replacement of binder ▪ Increase of binder content ▪ Granulation
▪ Excessive elastic recovery	▪ Reduction of the amount of elastic excipient(s) ▪ Granulation ▪ Co-processing
▪ Overlubrication	▪ Reduction of lubricant content ▪ Choice of different lubricant or lubricant type
▪ Moisture content too low	▪ Use of humectant
▪ Inappropriate particle size distribution	▪ Granulation ▪ Avoidance or Removal of fines
Machine-/Process-related causes:	
▪ Entrapped air	▪ Tapered dies ▪ Decrease of compression speed (increased dwell-time) ▪ Pre-compression
▪ Residual die wall pressure too high	▪ Lubrication
▪ Compaction force too high	▪ Decrease of compaction force ▪ Pre-compression
▪ Incorrect adjustment of take-off bar (rotary tablet press)	▪ Correction of take-off bar position

1.4.3.1. Formulation-related causes of capping and lamination

Formulation-related causes of capping can be attributed to the bonding propensity and the deformation characteristics of tableting materials. It has been demonstrated that the capping incidence strongly depends on the ratio between the interparticulate bonding strength and the extent of elastic recovery [87, 88]. Basically, the most common formulation-related causes of tablet capping (and remedies) are those already described as having a negative effect on tablet hardness (see chapter 1.4.2.1.).

If interparticulate bonding formed during compression is too weak to withstand the counteracting stress induced by excessive elastic recovery during decompression, bonds may break, ultimately leading to tablet capping and/or lamination.

Particularly for tableting materials that primarily consolidate by plastic deformation, the relationship between interparticulate bonding and the elastic recovery is known to be considerably affected by the compression speed [78, 89]. Therefore, one key step to remedy tablet capping is to reduce the compression speed, thereby increasing the dwell time and thus the time a tablet is under maximum pressure. This prolongation of the dwell time provides more time for the particles to deform and to form bonds of sufficient strength. In addition, to compensate for the deleterious effect of excessive elastic recovery, either the content of the elastic excipient may be reduced or the interparticulate bonding strength may be increased by improving the tablet formulations' plasticity. Adequate plasticity of tablet formulations can generally be achieved either by using an appropriate type and amount of a suitable dry binder [73, 90-92] or by means of granulation or co-processing [18, 93]. In addition, some powder properties such as moisture content, particle shape and particle size distribution are other important parameters that contribute to the overall plasticity of the tableting material, thereby affecting the capping tendency of tablet formulations [94-97].

1.4.3.2. Machine-/Process-related causes of capping and lamination

One commonly accepted machine- or process-related factor contributing to capping and lamination is that of air being entrapped and compressed within the tablet pores during compaction [87, 98]. Particularly in high-speed tableting, the compressed air abruptly starts to expand and to leak from the tablet as soon as the punch pressure decreases, thereby causing the tablet to cap. It is generally recognized that the application of a degassing system such as tapered dies, the decrease in compression speed and/or the implementation of a pre-compression stage may be effective measures for the prevention of capping due to air entrapment [99, 100].

Other theories attribute capping to the process of cracking within a tablet induced by high residual die wall pressures which may occur during tablet decompression and ejection [84, 85]. Therefore, monitoring of residual die wall pressure changes is considered to be a valuable tool for detection of friction which may result in tableting problems such as capping or lamination [101, 102]. To quantitatively predict the capping tendency of tableting materials, a capping index has been defined as the ratio between the residual die wall pressure and the tablet bonding strength [85].
As a common remedy, high residual die wall pressures as a cause of tablet capping may be prevented by using an appropriate lubricant. However, excessive lubrication of tablet formulations should be avoided, as it may be counterproductive: overlubrication is an important factor which may lead to a reduction of the physical bonding strength within a tablet.

On rotary tablet presses, tablets are detached from the lower punch after ejection by bouncing against a stationary take-off bar. Due to the mechanical strain encountered by the tablets during detachment, an incorrect adjustment of the take-off bar may also be a reason for tablet capping or lamination. Therefore, an accurate adjustment of the stationary take-off bar will allow proper tablet detachment and thus contributes to the prevention of tablet capping or lamination.

1.4.4. Tablet Sticking

During tablet manufacture, sticking of tablet formulations is one of the most common problems observed. In general, tablet sticking refers to the tableting material adhering to the compression tooling such as punch surfaces and die walls, whereas picking describes a specific type of sticking in which the tableting material only sticks within the letters, numbers or logos being embossed on or engraved in the punch surfaces [103, 104].

Tablet sticking is caused by high adhesive forces acting between the surfaces of the compression tooling and the powder particles. Strong adhesion to the upper punch may lead to sticking of even whole tablets (Fig. 4a) and may cause a second compression of these tablets in the following compaction cycle together with the powder/granules already present in the die.

This double compression may result in serious damage to the punches and the tablet press. In contrast, sticking of whole tablets to the lower punch may cause demolition of the take-off bar on rotary tablet presses accompanied by a destruction of the tablets.
However, in most cases adhesion only leads to the sticking of a powder layer to the punches (Fig. 4b) resulting in rough tablet surfaces or incomplete engravings.

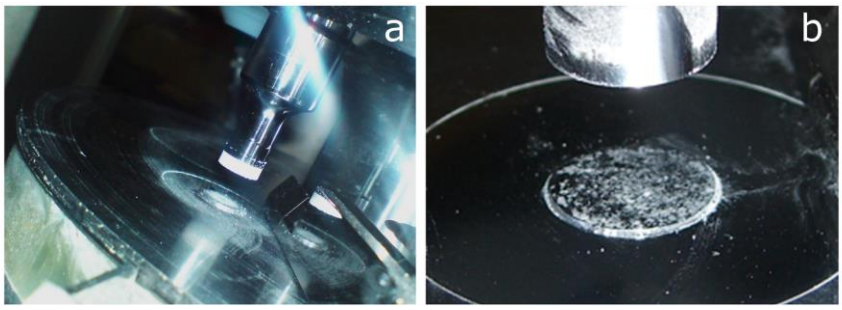

Fig. 4: Tablet sticking: (a) Sticking of a whole tablet to the upper punch, (b) powder layer sticking to the lower punch surface.

The various types of forces that are primarily responsible for the adhesion of powder particles to metal surfaces are intermolecular Van der Waals forces, electrostatic forces, electrical double layer formation, capillary forces and other interfacial events such as contact melting and mechanical interlocking [105-109]. It is important to recognize that many adhesive interactions may be caused by a combination of the aforementioned forces and mechanisms which can act concurrently or successively to different extents [105]. Moreover, it has been demonstrated in several studies that the eventual strength of adhesive interactions is also dependent on parameters such as surface roughness, mechanical properties of the powder particles as well as surface contact area [110-114].

During tableting, there are two distinct phases of the sticking process [115]: The first phase is characterized by an adhesive interaction between adhesive powder particles and the punch surface. If the adhesion forces exceed the cohesive bonding forces within the tablets, the powder particles adhere to the punch surface. In the second phase of the sticking process, an increase of powder layering is observed with prolonged run time of the tablet press. This build-up of a sticking layer on the punch surface is primarily caused by auto-adhesive interactions between the powder particles within the tablet formulation and those already adhered to the punch.

There are many variables affecting tablet sticking including the composition of the tablet formulation, the physical properties of the tableting material, the tooling properties as well as the compaction parameters (Table 5).

Table 5: Common causes and remedies for tablet sticking

Causes	Remedies
Formulation-related causes:	
▪ Inadequate lubrication (insufficient anti-adherent performance of lubricant)	▪ Increase of lubricant content ▪ Addition of another lubricant ▪ Choice of different lubricant or lubricant type ▪ Increase of lubricant mixing time ▪ External lubrication ▪ Punch tip coating
▪ Poor powder characteristics (e.g. particle size, crystal habit, polymorphism)	▪ Optimization of powder characteristics
▪ Contact melting: - components with low melting point - formation of eutectic mixtures	▪ Improvement of tablet formulation ▪ Addition of adsorbent, e.g. colloidal silica ▪ Co-processing
▪ Moisture content too high: - insufficient drying of granules obtained by wet granulation - hygroscopic components	▪ Addition of moisture adsorbent or drying ▪ Processing under low humidity conditions
Machine-/Process-related causes:	
▪ Rough or scratched punch surfaces	▪ Cleaning and polishing of punch surfaces ▪ Storage and transportation under suitable conditions
▪ Embossing/engraving	▪ Redesign of embossing/engraving ▪ Avoidance of certain letters/numbers, e.g. "A", "B", "8", "4"
▪ Compaction force too low	▪ Increase of compaction force ▪ Reduction of compression speed (increased dwell time)

1.4.4.1. Formulation-related causes of tablet sticking

One of the most obvious causes for tablet sticking is inadequate lubrication of the tablet formulation. In general, lubricants are added in small quantities to tablet formulations to improve tableting by reducing friction at the tablet-die interface during tablet compaction and ejection ("true" lubricant), enhancing flow properties (glidant), and preventing adherence to punch surfaces and the die wall (anti-adherent) [116-118]. If powder layer sticking is observed during tableting, the anti-adherent performance of the employed lubricant is to be considered as insufficient. Common approaches to prevent the tableting material from sticking are therefore to increase the lubricant content, to use an additional lubricant, or to choose a different lubricant or lubricant type.

Besides changing the composition of the tablet formulation, the lubricant mixing time may be increased to improve the anti-adherent performance of the lubricant. This is particularly applicable to boundary lubricants such as magnesium stearate, as these substances form a lubricant film around the host particles during the mixing process, which is essential for their anti-adherent efficiency [75, 119]. However, excessive lubrication and/or prolonged mixing time of the tableting material should be avoided because of the deleterious effects they may have on the tablet hardness [120, 121]. As mentioned before (see chapter 1.4.2.1), this is a result of the lubricant film acting as a physical barrier which consequently leads to a decreased bonding capacity of the host particles [14-16].

An alternative to internal lubrication is external lubrication, where a lubricant is suspended in air and directly sprayed onto the surfaces of the punches and the die wall. This type of lubrication process is particularly suitable when tablet properties such as tablet hardness or tablet dissolution are very susceptible to lubrication [118].

Apart from lubrication, another interesting approach to reduce the sticking tendency of a tablet formulation is the application of punches with a modified surface. Through punch tip modifications, the performance of the compression tooling can be improved by increasing surface hardness, wear resistance, corrosion resistance as well as anti-sticking efficiency [122, 123]. Chromium electroplating is the most prevalent method of surface modification for tablet tooling [104, 124].

In comparison with uncoated punches, hard chromium-plated punches provide a protection of the punch surfaces by enhancing corrosion and wear resisting properties and reducing friction and adhesion at least to some extent. However, Roberts et al. evaluated the effect of chromium plating of punch tips on the sticking tendency of model ibuprofen formulations and found it to be ineffective in reducing ibuprofen adherence [125].
Some other punch tip coatings such as Chromium Nitride have also proven their ability to increase the resistance to abrasive and adhesive wear and thus have found numerous applications in various industry sectors including pharmaceutical tablet manufacturing [126, 127]. Chromium Nitride coatings are characterized by a very smooth surface which is postulated to provide excellent anti-sticking properties [128].

Poor powder characteristics may also cause tablet sticking. It has been demonstrated that the compaction properties of a tableting material can be significantly affected by changing the particle size, crystal structure or crystal habit [112, 129-134]. For instance, the influence of the crystal habit on the compression and densification behavior of ibuprofen, a drug with a high sticking tendency to punch surfaces during tableting, has been widely investigated [129, 132, 134, 135]. The stickiness of this API could be effectively reduced by various crystallization techniques such as the solvent change crystallization technique [134]. Application of this technique in the presence of different water-soluble additives led to isomorphic crystals, which solely varied in particle shape. In contrast to powders containing needle-shaped ibuprofen particles, which is the common particle shape, powders consisting of the optimized plate-shaped particles were found to exhibit improved flowability, compactibility as well as drug dissolution.

Another reason for tablet sticking is contact melting of the tablet formulation at the punch surface under pressure. Contact melting can be attributed to either a component of the tablet formulation with an inherently low melting point or to the formation of an eutectic mixture [136]. Particularly for low-melting materials such as ibuprofen (T_m 75-78 °C), it is reported that localized high temperature zones caused by densification and friction during powder compaction could exceed the melting point, ultimately resulting in increased adhesion of powder particles to the punch surfaces [137-139].

To improve the melting behavior it has been suggested that low-melting materials may be adsorbed to suitable excipients such as colloidal silica or microcrystalline cellulose [140]. Moreover, co-processing of the tableting materials is possible. Co-processed tableting materials are usually manufactured by physical mixing of the components either as a homogenous dispersion or as a solution followed by co-drying, co-precipitation or co-crystallization resulting in improved flowability and compactibility [17-19].

Another common cause of tablet sticking is a high moisture content of the tableting material [141]. The most evident reasons for high moisture contents are insufficient drying of granules obtained from wet granulation and/or inherent hygroscopicity of the tableting material. Thus, to prevent tablet sticking, insufficiently dried or hygroscopic granules may be re-processed either by an additional drying step or by adding a moisture adsorbent. To prevent sticking of hygroscopic tableting materials, storage, handling and processing of these materials should be strictly conducted under low humidity conditions.

1.4.4.2. Machine-/Process-related causes of tablet sticking

The most evident machine- or process-related reasons for tablet sticking are inadequate compaction parameters, complex embossing/engravings and/or poor tooling properties. With regard to the compaction parameters, tablet sticking is most commonly attributed to incorrect settings of compaction force and compression speed [142]. As mentioned before, the primary function of the compaction force is to increase the surface contact area between the individual powder particles, thereby facilitating the formation of bonds [38]. Thus, the higher the applied compaction forces, the higher the cohesive bonding within the tablet.
In general, the extent of tablet sticking depends on the adhesive forces (F_{ad}) acting between tablet and punch surface in relation to the cohesive forces (F_{co}) acting within the tablet. Sticking to punch surfaces occurs if the cohesive bonding within the tablet is not as strong as adhesion to the punch surface ($F_{ad} > F_{co}$). Therefore, a simple method to overcome sticking is to increase the compaction force, ultimately leading to tablets with higher cohesive bonding strength.

Another common way to avoid tablet sticking is to reduce the speed of the tablet press, thus increasing the dwell time. This in turn will have a considerable effect on the cohesive bonding, mainly for plastically deforming tableting materials. However, the most eminent disadvantage of slowing down the compression speed is that of the productivity of the tablet press being reduced.

Furthermore, it is well known that certain letters (e.g. "A", "B") or numbers (e.g. "4", "8") embossed on or engraved in punch surfaces are prone to sticking, while the sticking residues are mainly observed within the enclosed "islands" of the engravings [103]. The excessive sticking to engravings is supposed to be caused by shear forces occurring at the lateral surfaces of the engravings during powder compaction and the main mechanism leading to adhesion is assumed to be mechanical interlocking [143]. Thus, by choosing an appropriate design of tablet engravings sticking may be prevented. For this purpose, the "islands" of problematic letters or numbers should be designed as large as possible, and the angles of strokes should be as flat as possible [104, 143, 144].

Besides embossing or engravings, the tablet shape was also found to be an important factor influencing the sticking propensity of a tableting material. It was observed that with increasing punch tip curvature, tablet sticking can be reduced [145]. Thus, for a tablet formulation known to show a high sticking tendency, application of concave punches may be preferred over application of bevelled-edged or flat-faced punches [146].

Poor tooling properties may be another cause of tablet sticking. As an essential preventive measure, punches and dies should be thoroughly cleaned from any residues of tableting material once the tooling is removed from the tablet press. After cleaning, the tooling should be inspected and either polished or replaced, if surface defects are detected. Moreover, the tooling must be protected from any deleterious conditions such as corrosion (oxidation) during the storage period. Ideally, to prevent damages to the delicate punch edges, for storage and transportation specific storage boxes may be used, which have special inserts for keeping the tooling separated [140].

1.4.4.3. Analytical techniques to examine tablet sticking

For a better understanding of the underlying causes of tablet sticking, several analytical techniques have been described to characterize and/or to quantify the sticking propensity of various tableting materials.

For instance, there are a number of experimental methods which have been developed for measuring adhesion forces between powder particles and metal surfaces. Among these methods, the centrifuge technique was widely used to investigate the adhesion properties of some commonly used pharmaceutical excipients [105, 110, 111, 147-149]. This method is based on the assumption that the adhesion force is equal in absolute values to the centrifugal force which is required to detach powder particles from a metal surface [105]. The determination of adhesion forces by measuring centrifugal forces is based on the principle that above a critical centrifuge speed, for a particle with a defined mass at a known distance to the rotation center, the centrifugal force resulting from the angular speed of rotation will exceed the adhesion force between the particle and the metal surface [148]. It could be shown that the centrifugal force required to detach the powder particles from a metal surface is dependent on the applied compression [105, 148], the time of application of contact pressure [111], the size of the powder particles [110, 148] as well as the temperature [149]. The development of the ultracentrifuge technique capable of measuring not only adhesion but also friction forces between powder particles and various surfaces was found to further improve the experimental options of the centrifuge procedure [150, 151].

To measure adhesion forces acting between particles, Shimada et al. introduced an apparatus equipped with a needle which applies an induced pulling force to the aggregated particles, thereby causing the particles to separate [113]. With this apparatus, the separation process of the particles can be observed and characterized by using a high-resolution camera system. This direct separation method has been applied to examine the influence of moisture content, particle shape and triboelectrification on the adhesion forces between particles.

Contact mode atomic force microscopy (AFM) was found to be another valuable tool to study adhesive interactions between two surfaces [114, 152-155]. For example, Wang et al. demonstrated that the AFM approach may be useful to differentiate the adhesive interactions between iron-coated AFM tips and different profen compounds (i.e. ketoprofen, ibuprofen and flurbiprofen) known to cause tablet sticking [114]. The rank order of the work of adhesion obtained in this study (ketoprofen > ibuprofen > flurbiprofen) was hypothesized to correspond to the rank order of the sticking propensity of tablet formulations containing these compounds. This hypothesis was verified in a second study using a compaction simulator and an instrumented tablet press [156].

Besides the inherent adhesiveness of powder particles to metal surfaces, punch surface roughness is another significant factor affecting tablet sticking. Therefore, several attempts have been undertaken to quantitatively evaluate the sticking propensity of tablet formulations by surface roughness measurements [125, 157-160]. For assessment of the surface quality, nowadays AFM and laser profilometry are the most common techniques used to determine the surface roughness of punches and/or tablets [161].

One simple method of sticking quantification is the determination of the punch weight increase during tablet manufacture [162, 163]. To circumvent the practical difficulties in accurately measuring very small quantities of adhered tableting material on a punch that weighs about 100 g, Mullarney et al. designed an upper punch with a removable punch tip exhibiting a low mass which allows the quantification of the sticking residue with a microbalance [162].

Chemical quantification of the drug substance present within the sticking residue was also found to be a useful method to assess tablet sticking. After complete collection of the sticking residue removed from the punch surface, quantification of the drug substance present in the sticking residue was conducted by using UV spectroscopy [125, 145, 164] or HPLC analysis [115]. Other techniques that provide information on the composition of the sticking residue and its molecular structure include scanning electron microscopy (SEM), Raman spectroscopy and X-ray photoelectron spectroscopy (XPS) [115, 161].

However, the disadvantage of all the aforementioned analytical techniques is that the measurements are carried out either after the compaction runs or entirely independent of tablet manufacture. Thus, methods that allow the determination of the sticking tendency of a tablet formulation during the compaction process are preferable.

Waimer et al. performed inline measurements with an eccentric press equipped with an instrumented upper punch that measures the adhesion force at the time-point of punch detachment from the upper tablet surface [143, 165]. It could be shown that this device is a helpful tool for quantification of tablet sticking providing reliable and reproducible information. However, this specially designed upper punch instrumentation is not easily transferable to a rotary tablet press.

A promising inline method for detection of sticking during tablet manufacture with a rotary tablet press is the measurement of take-off forces, which occur when tablets are detached from the lower punch surface. Two publications by Augsburger et al. deal with the measurement of take-off forces using a take-off bar instrumented with strain gauges [166, 167]. Take-off force signals obtained with this type of instrumentation are referred to as attenuated oscillations [168]. During compaction cycles tablets usually remain in front of the take-off bar for a certain period of time. Thus, multi-peak take-off force signals are obtained caused by repeated contact of the tablets with the measuring device. It has been reported that the sensitivity of strain gauge instrumented take-off bars might be too low for detection of rather low take-off forces of well lubricated tablet formulations [169]. Improvement of the sensitivity of take-off force measurements was achieved by using quartz load cell instrumentation [170]. However, for the measurement of take-off forces, rotary tablet presses are usually equipped with take-off bars instrumented with strain gauges, as they are easy to handle and comparably inexpensive. In the aforementioned second study by Wang et al. dealing with the sticking tendency of low dose tablet formulations containing ketoprofen, ibuprofen and flurbiprofen, respectively, sticking quantification was performed by visual inspection of the punch surfaces as well as by measurement of the ejection and take-off forces [156]. The authors postulated that the tablet take-off force is a direct indicator of the sticking tendency of the investigated tablet formulations.

1.5. Aim of the thesis

Despite the fact that numerous studies have already been conducted to elucidate the fundamental causes of tablet sticking, it is still one of the most common problems observed during production-scale tableting. Therefore, tablet manufacturers still seek for universally applicable measures to prevent and/or solve specific sticking problems more efficiently. Moreover, they are looking for analytical techniques that are capable of detecting, characterizing and/or quantifying tablet sticking during the compaction process.

As illustrated in Fig. 5, there are many variables affecting the sticking propensity of pharmaceutical tablet formulations including the properties of the API(s) and excipients as well as the compaction parameters. In general, the composition of a tablet formulation will be predetermined by the physico-chemical properties of the API(s) and excipients as well as their possible interactions. With this information a selection of suitable excipients at adequate amounts is possible. Finally, compaction parameters such as compaction force and compression speed play an important role for a certain tablet formulation to be compressed into a non-sticking tablet.

Fig. 5: Schematic representation of the parameters affecting tablet sticking.

The main objective of this thesis is to provide new insights into tablet sticking, primarily focusing on the characterization and quantification of sticking to punch surfaces during tablet manufacture by direct compaction.

A rotary tablet press is used for the compaction studies to mimic the process of production-scale tableting. This thesis investigates in a stepwise approach the influence of various formulation- or machine-/process-related factors on the sticking propensity of tablet formulations containing sticky components such as sorbitol, a hygroscopic tableting excipient, or ibuprofen, an adhesive API, and offers options for a quantitative characterization of the sticking process. For this purpose, a swabbing procedure is developed to remove the sticking residue from the punch surface and to quantify it by HPLC analysis. However, to detect sticking problems during production, tablet manufacturers prefer inline measurements of adhesion-indicating parameters. Therefore, the suitability of take-off force measurements for the detection of sticking during tableting is evaluated by correlating take-off force data with the actual extent of tablet sticking quantified by HPLC analysis. Finally, a new concept for the interpretation of take-off force data is presented, which will be applied to characterize the adhesive interactions between tablets and differently coated punch surfaces.

2. Evaluation of the suitability of various lubricants for direct compaction of sorbitol tablet formulations

Evaluation of the suitability of various lubricants for direct compaction of sorbitol tablet formulations

Abstract

There is an increasing interest in the use of polyols such as sorbitol in pharmaceutical tablet formulations due to their sweet taste but reduced calorie content and non-cariogenic characteristics. Sorbitol is a common tableting excipient and plays a major role in the manufacture of chewable and sublingual tablets. One limitation of sorbitol as a tableting excipient is that its hygroscopic nature may cause pronounced friction as well as sticking to the punch surfaces.

Therefore, the aim of the present study was to evaluate the suitability of various lubricants for reduction of friction and prevention of sticking during compaction of sorbitol-containing tablets. The efficiency of the most commonly used lubricant, magnesium stearate, was compared to that of sodium stearyl fumarate (Pruv®), microprilled poloxamer 407 (Lutrol® micro 127) and PEG 4000. Compaction studies were performed using both an eccentric tablet press and a rotary tablet press. In addition to their compaction properties, the effect of the investigated lubricants on the tablet properties was evaluated.

Considering both the lubricant efficiency and the influence on tablet properties of the investigated lubricants, Pruv® was found to be most suitable for compaction of the investigated sorbitol tablet formulations. However, the best overall lubricant performance, accompanied by excellent tablet properties, was observed with a mixture (1:1) of magnesium stearate and Pruv®, indicating synergism between these lubricants.

2.1. Introduction

Polyols (sugar alcohols) such as sorbitol are common excipients in pharmaceutical dosage forms as well as in food products. Due to their sweet taste but reduced calorie content and non-cariogenic characteristics, they are particularly used as sugar substitutes. Sorbitol is described as having a pleasant, cooling, sweet taste with a sweetness of approximately 60 % compared to that of sucrose [1]. Chemically, sorbitol is D-glucitol which is a hexahydric alcohol related to mannose and is an isomer of mannitol. Sorbitol occurs naturally in a wide variety of ripe berries. However, it is primarily produced industrially by high-pressure catalytic hydrogenation or by electrolytic reduction of D-glucose. Crystalline sorbitol occurs as an odorless, hygroscopic powder and it exhibits a complex monotropic polymorphism [171, 172]. Efforts have been made to identify the existing polymorphic forms: In addition to five different anhydrous crystalline polymorphic forms, one amorphous form and the hydrate of sorbitol have been identified [173, 174].

Because of its physico-chemical properties, sorbitol is commonly used in different pharmaceutical dosage forms as sweetening agent, humectant, plasticizer for soft gelatin capsules, or filler-binder in tablet formulations. Sorbitol was the first polyol that was modified for use as a suitable filler-binder in direct compaction [175]. Among the existing polymorphic forms γ-sorbitol, which is obtained by spray-drying or a special crystallization technique, is postulated to be the most stable polymorphic form with the best compaction properties [172, 175, 176]. However, one major limitation for the use of sorbitol as filler-binder in tablet formulations is that its hygroscopic nature may cause strong friction at the tablet-die interface during tablet compaction and ejection. Moreover, sticking of tablets to the punch surfaces during tablet take-off may also occur.

To reduce friction at the tablet-die interface, tablet formulations are mixed with lubricants, whereas anti-adherents are used for prevention of sticking. However, it is well known that efficient lubricants often also have anti-adherent properties [117]. Magnesium stearate is the most commonly used tablet lubricant because it reduces friction efficiently even at low concentrations of 0.25 – 0.5 % and it also exhibits good anti-adherent properties [177].

Despite its excellent lubricant performance, magnesium stearate is reported to have a negative effect on the compactibility of powder blends [15, 16]. Depending on the deformation behavior of the powder particles in a tablet formulation, magnesium stearate can reduce the physical strength of the tablets significantly which is attributed to the formation of a thin lubricant film around each of the host particles during blending [75]. As a result of this physical barrier, the interparticulate bonding strength between the particles is weakened. Therefore, tablets consisting of excipients that undergo plastic deformation are greatly affected, whilst brittle materials were found to be less susceptible to magnesium stearate [14, 16, 178]. In addition to the decreased bonding properties, magnesium stearate is also known to decrease the wettability due to its pronounced hydrophobic nature, and thus it can cause delayed tablet disintegration and prolonged dissolution rates [179-181].

Sodium stearyl fumarate has been suggested as another suitable lubricant in tableting. It has been shown that sodium stearyl fumarate has fewer negative effects on tablet strength and dissolution rate than magnesium stearate [119, 182]. If tablets are intended to be dissolved in water prior to ingestion, e.g. effervescent tablets, lubrication of the tablet formulation with water soluble excipients is most preferable. For this purpose solid polyethylene glycols, e.g. PEG 4000 and PEG 6000, have been used as lubricants [183]. Microprilled poloxamers are also readily soluble in water and therefore may also be used as hydrophilic lubricants in tableting [184].

The objective of the present study was to investigate the suitability of various lubricants for reduction of friction as well as for prevention of sticking during direct compaction of various Neosorb® P60W tablet formulations. The efficiency of the most commonly used lubricant magnesium stearate was compared to that of sodium stearyl fumarate (Pruv®), microprilled poloxamer 407 (Lutrol® micro 127) and PEG 4000.

2.2. Materials and Methods

2.2.1. Materials

In the present study sorbitol (Neosorb® P60W, Roquette Frères, France), microcrystalline cellulose (Avicel® PH200, FMC BioPolymer, Ireland), and crospovidone (Kollidon® CL, BASF, Germany) were used for the preparation of directly compressible powder blends.

The powder blends were lubricated with magnesium stearate (Fagron, Germany), sodium stearyl fumarate (Pruv®, JRS Pharma, USA), PEG 4000 P (Macrogol 4000 Powder, Fagron, Germany), and microprilled poloxamer 407 (Lutrol® micro 127, BASF, Germany), respectively.

The lubricants were used as purchased by the suppliers. Some physical properties of the employed lubricants are summarized in Table 6.

Table 6: Comparison of some physical properties of the employed lubricants

	MgSt	Pruv	Lutrol micro 127	PEG 4000
Particle Morphology	Fine powder, irregular-shaped particles	Fine Powder, flat circular-shaped particles	Waxy powder, free-flowing microprilled granules	Fine powder, spherical-shaped particles
Specific Surface Area [m²/g]	1.92 [a]	1.2 - 2.0 [b]	-	-
Melting range [°C] [c]	117 - 150	224 - 245	52 - 57	50 – 58
Lubricant classification	Boundary lubricant	Boundary lubricant	Fluid-film lubricant	Fluid-film lubricant
Lubricant concentration [%] [c]	0.25 - 5	0.5 - 2	2 - 10	2 - 5

[a] According to Certificate of Analysis issued by supplier; determination by gas adsorption (Ph. Eur. 2.9.26)

[b] According to supplier specification, gas adsorption method

[c] Data from reference [117, 185]

All other reagents used in this study were of analytical grade.

2.2.2. Methods

Physical characterization of Neosorb® P60W and Avicel® PH200

Particle Morphology

Samples of Neosorb® and Avicel® were coated with a thin carbon layer and the particle morphology was visualized by scanning electron microscopy (LEO 1525, LEO Elektronenmikroskopie, Oberkochen, Germany) at an accelerating voltage of 5 kV. For comparative purposes the investigated lubricants were also characterized by SEM with regard to their particle morphology.

Melting behavior

The onset of melting was determined by differential scanning calorimetry (DSC7, Perkin Elmer, Beaconsfield, UK). The samples of 10 mg each were heated up at heating rates of 10 K/min in aluminum pans under nitrogen atmosphere. The onset of melting was calculated using Pyris® software (Perkin Elmer, Beaconsfield, UK).

Powder densities

The true density of both excipients was measured by helium pycnometry using a 30 cm^3 sample cup (Accupyc 1330, Micromeritics, Aachen, Germany). Each measurement comprised 10 purge cycles followed by 10 measuring cycles. Bulk and tapped densities were determined according to the method of the European Pharmacopoeia (Ph. Eur.) (jolting volumeter, STAV 2003, J. Engelsmann, Ludwigshafen, Germany).

Flow properties

Flow properties were determined by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as the quotient of tapped and bulk density. The mass-related powder flow rate [g/s] was measured using a flowability tester (BEP2, Copley Scientific, Nottingham, UK) equipped with a stainless steel flow funnel (orifice diameter 10 mm). All measurements were performed in triplicate. The volume-related powder flow rate [cm^3/s] was calculated as the quotient of the mass-related powder flow rate and the bulk density of the excipients.

Particle size distribution

The particle size distribution was investigated via laser diffraction using a dry dispersion unit (HELOS/RODOS, Sympatec, Clausthal-Zellerfeld, Germany). Compressed air at 1.5 bar was used to disperse the powder.

Moisture sorption

Moisture sorption isotherms were obtained by gravimetric determination of the water vapor uptake using Schepky hygrostats [186]. Prior to the measurements, the samples were dried over phosphorus pentoxide until the weight remained constant. Subsequently, they were placed on watch-glasses above saturated salt solutions used to adjust the relative humidity to 23 % (potassium acetate sesquihydrate), 33 % (magnesium chloride hexahydrate), 44 % (potassium carbonate sesquihydrate), 66 % (ammonium nitrate), 75 % (sodium chloride), 85 % (potassium chloride) and 97.5 % (potassium sulfate), respectively [187]. The loaded hygrostats were stored at a temperature of 20 °C for 5 d.

Preparation and characterization of lubricated Neosorb® powder blends

The Neosorb® concentration in the investigated powder blends was 25, 50 and 75 % [w/w], respectively. Avicel® was chosen as filler, since it exhibits excellent compaction properties. Kollidon® CL was used as tablet disintegrant at a concentration of 2.5 %. Neosorb® was mixed with the filler and the disintegrant using a Turbula blender at 72 rpm for 10 min (T2F, W.A. Bachofen, Muttenz, Switzerland). After addition of 4 % [w/w] of the lubricants magnesium stearate, Pruv®, Lutrol® micro 127, and PEG 4000, respectively, to each powder blend, mixing was continued for 3 more min. All the lubricants were initially tested at 4 % [w/w] incorporation, since the performance of all lubricants was assumed to be sufficient at this relatively high lubricant concentration. As it is well known that magnesium stearate and Pruv® are very efficient lubricants, these two lubricants were also investigated at concentrations of 1 and 2 % [w/w]. In addition, the effect of lubrication with 1:1 mixtures of the two lubricants at total concentrations of 0.5, 0.75, 1 and 2 % [w/w], respectively, was studied. Prior to compaction, the powder blends were stored in an air-conditioned room at a temperature of 21 °C and a relative humidity of 45 % for at least 3 d. Flow properties of the lubricated powder blends were determined as described above.

Compaction of lubricated Neosorb® powder blends

Compaction with an eccentric tablet press

To analyze the performance of the different lubricants, compaction of the Neosorb® powder blends containing 4 % [w/w] of lubricant was performed using an instrumented eccentric tablet press (E XI, Fette, Schwarzenbek, Germany) equipped with flat-faced punches of 10 mm diameter. The target tablet weight was 300 mg. Ten tablets were prepared with each powder blend at a compaction speed of 16 strokes/min and at compaction forces of 5, 10, and 15 kN, respectively. The efficiency of each lubricant was characterized by the ejection force measured during compaction as well as the R value. R values were calculated as the quotient of the maximum lower and upper punch forces (F_{max}) [188].

$$R = \frac{F_{max\,(lower\ punch)}}{F_{max\,(upper\ punch)}} \qquad \text{(eq. 3)}$$

The closer the R value is to unity, the better the efficiency of lubrication.

Compaction with a rotary tablet press

Tableting of selected Neosorb® powder blends was performed with an instrumented rotary tablet press (XL 100, Korsch, Germany) equipped with flat-faced punches of 10 mm diameter. The target tablet weight was 300 mg and the compression speed was 20 rpm with a corresponding dwell time of 74.7 ms. Based on the results obtained with the eccentric tablet press, only the powder blends containing 75 % Neosorb® were used for compaction. The performance of the lubricants magnesium stearate and Pruv® was investigated with Neosorb® tablet formulations at lubricant concentrations of 1, 2 and 4 % [w/w]. Powder blends lubricated with different concentrations of 1:1 mixtures of these two lubricants were also compacted.

Characterization of the tablets

After a relaxation time of at least 24 h following ejection of the tablets, the crushing strength, the diameter and the thickness of 10 tablets were determined using a hardness tester (TBH 30, Erweka, Heusenstamm, Germany).

The tablet tensile strength was calculated using the equation published by Fell et al. [189].

$$\sigma = \frac{2 \cdot F}{\pi \cdot d \cdot t} \qquad \text{(eq. 4)}$$

where σ is the tablet tensile strength (MPa), F the crushing strength (N), d the tablet diameter (mm), and t the tablet thickness (mm).

The disintegration times of six tablets were measured with a disintegration tester (ZT 72, Erweka, Germany) according to the method of the Ph. Eur. for uncoated tablets. The disintegration apparatus was operated with magnetic guided discs allowing for an automated determination of the tablet disintegration time.

2.3. Results and Discussion

Physical and bulk powder properties of Neosorb® P60W and Avicel® PH200

It is well known that the physical and bulk powder properties of crystalline sorbitol vary depending on the grade of sorbitol used [190]. In Table 7 several physical and bulk powder properties of the investigated sorbitol grade Neosorb® P60W are summarized. As Avicel® PH200 was chosen as filler for the Neosorb® tablet formulations, the bulk powder properties of this excipient are also displayed in Table 7.

Table 7: Physical and bulk powder properties of Neosorb® P60W and Avicel® PH200

	Neosorb® P60W	Avicel® PH200
Onset of melting [°C]	98.90 ± 0.72	–
Heat of fusion [J/g]	180.71 ± 2.58	–
True density [g/cm³]	1.492 ± 0.002	1.557 ± 0.001
Bulk density [g/cm³]	0.651 ± 0.001	0.358 ± 0.003
Tapped density [g/cm³]	0.732 ± 0.003	0.454 ± 0.003
Hausner ratio	1.12 ± 0.02	1.27 ± 0.01
Powder flow rate [g/s]	9.49 ± 0.08	4.60 ± 0.24
Powder flow rate [cm³/s]	14.54 ± 0.10	12.85 ± 0.11
Mean particle size (d_{50}) [µm]	191.1 ± 2.9	176.1 ± 4.2

– not determined

The melting behavior of sorbitol is a key parameter which characterizes the different polymorphic forms of the excipient. The endothermic event in the DSC thermograms of the investigated sorbitol grade is attributed to melting with a melting onset temperature of 98.9 °C and a heat of fusion of 180.71 J/g. This indicates that Neosorb® P60W consists of pure γ-sorbitol [171, 172] which is described to be the most stable polymorphic form and is postulated to exhibit the best compaction properties among the existing polymorphic forms [172, 176].

The flow properties of the plain excipients, Neosorb® and Avicel®, were determined by calculation of the Hausner ratio and by measurement of the powder flow rate. In accordance with the Ph. Eur. the Hausner ratio of the investigated sorbitol grade indicated good flowability, whereas Avicel® showed only passable flowability. These results appear to be in good agreement with the mass-related powder flow rate determined with these excipients. However, the difference in flow properties of the two excipients was found to be less pronounced if the volume-related powder flow rate was taken into consideration. This observation results from the large difference in the bulk density of the two compounds which is used to calculate the volume-related powder flow rate. The comparable small difference between the volume-related powder flow rates may furthermore be explained by an apparent similarity of both excipients with regard to particle morphology (Fig. 6) and mean particle size.

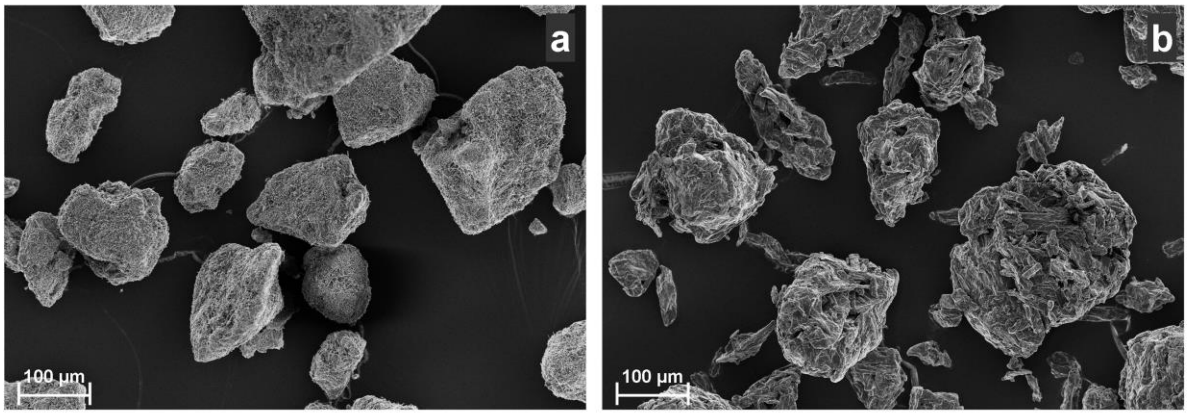

Fig. 6: SEM images of (a) Neosorb® P60W and (b) Avicel® PH200.

The physical stability of γ-sorbitol crystals towards moisture also plays a major role with regard to powder processing. Nikolakakis et al. provided evidence of a plasticizing effect of moisture on γ-sorbitol by plotting the logarithm of the ratio of the yield pressure (P_Y) and the elastic recovery as a function of the moisture content. It was shown that this ratio decreases linearly with increasing moisture content indicating high predominance of plasticity over elasticity at higher moisture content [191]. In Fig. 7 the water sorption isotherm for the investigated sorbitol grade is displayed. From the presented data it is obvious that the powder crystals resist moisture uptake up to a relative humidity of approximately 70 %. After a storage period of 120 h the water uptake at a relative humidity of 66 % amounted to only 3.4 % [w/w].

However, at a relative humidity above 70 % (critical hygroscopicity) the Neosorb® samples were observed to show deliquescence. Therefore, it is strongly recommended to avoid processing and storage of the excipient at relative humidities greater than 65 %.

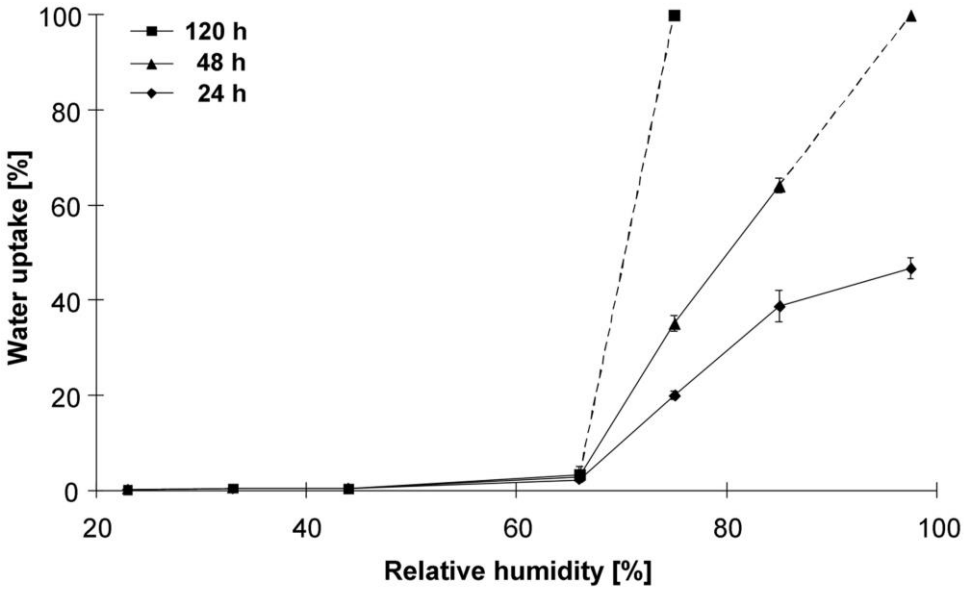

Fig. 7: Water sorption isotherm at 20 °C measured after a storage period of 24, 48, and 120 h; means ± SD, n = 3; - - - deliquescence was observed.

Flowability of lubricated Neosorb® powder blends

Each investigated powder blend was characterized with regard to its flowability by determination of the Hausner ratio (Fig. 8a) and by measurement of the powder flow rate (Fig. 8b). Apparently, an increase of the Neosorb® content leads to a decrease of the Hausner ratio and an increase of the powder flow rate, independent of the lubricant used in the powder blends. These results are in good agreement with the flowability data obtained with the plain excipients Neosorb® and Avicel® (Table 7) because the higher the content of readily flowable Neosorb® in the powder blends, the lower the amount of poorly flowable Avicel®.

With respect to the various excipients used for lubrication of the powder blends, considerable differences in terms of flowability were observed. The Hausner ratios of powder blends lubricated with either magnesium stearate (MgSt) or Pruv® were determined to be lower than 1.11, independent of the Neosorb® content (Fig. 8a). According to the Ph. Eur., Hausner ratios between 1.00 and 1.11 indicate excellent flow properties.

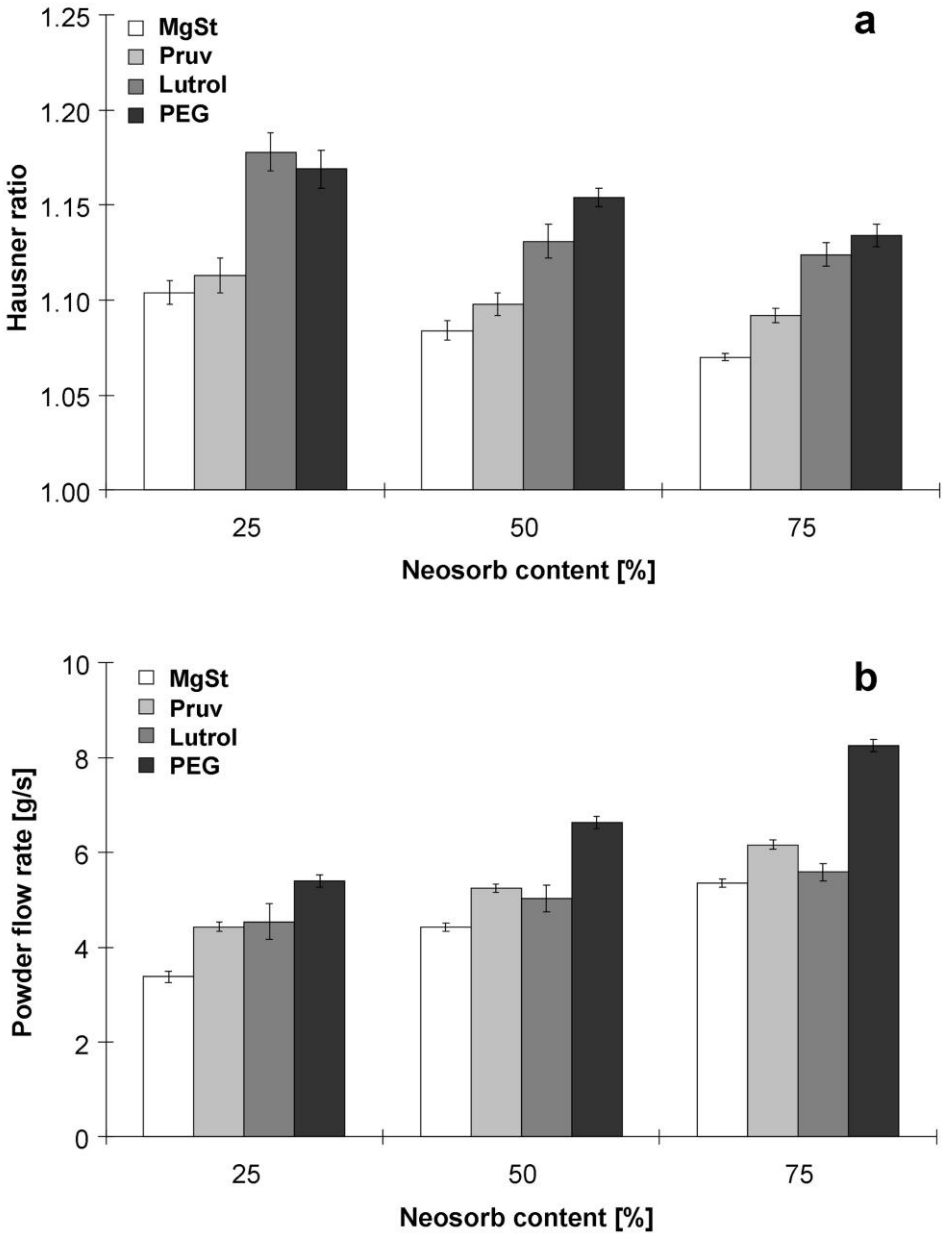

Fig 8: Flow properties of the lubricated powder blends: (a) Hausner ratio and (b) powder flow rate; means ± SD, n = 3.

In contrast, the Hausner ratios of the powder blends lubricated with Lutrol® or PEG were found to exceed 1.11, while they however remained lower than 1.18. Thus, according to the Ph. Eur., the flow properties of the powder blends lubricated with Lutrol® and PEG are still to be considered as good.

With regard to the powder flow rates (Fig. 8b), it is interesting to note that the flowability of the powder blends lubricated with magnesium stearate turned out to be worst, whereas the highest powder flow rates were obtained with the powder blends lubricated with PEG.

This observation may be explained by the particle morphology of the various lubricant powders. In Fig. 9 the SEM images of the different lubricants are shown. In comparison to the powder particles of the lubricants magnesium stearate, Pruv® and Lutrol®, the PEG particles are smooth and spherical leading to a considerable improvement of powder flowability.

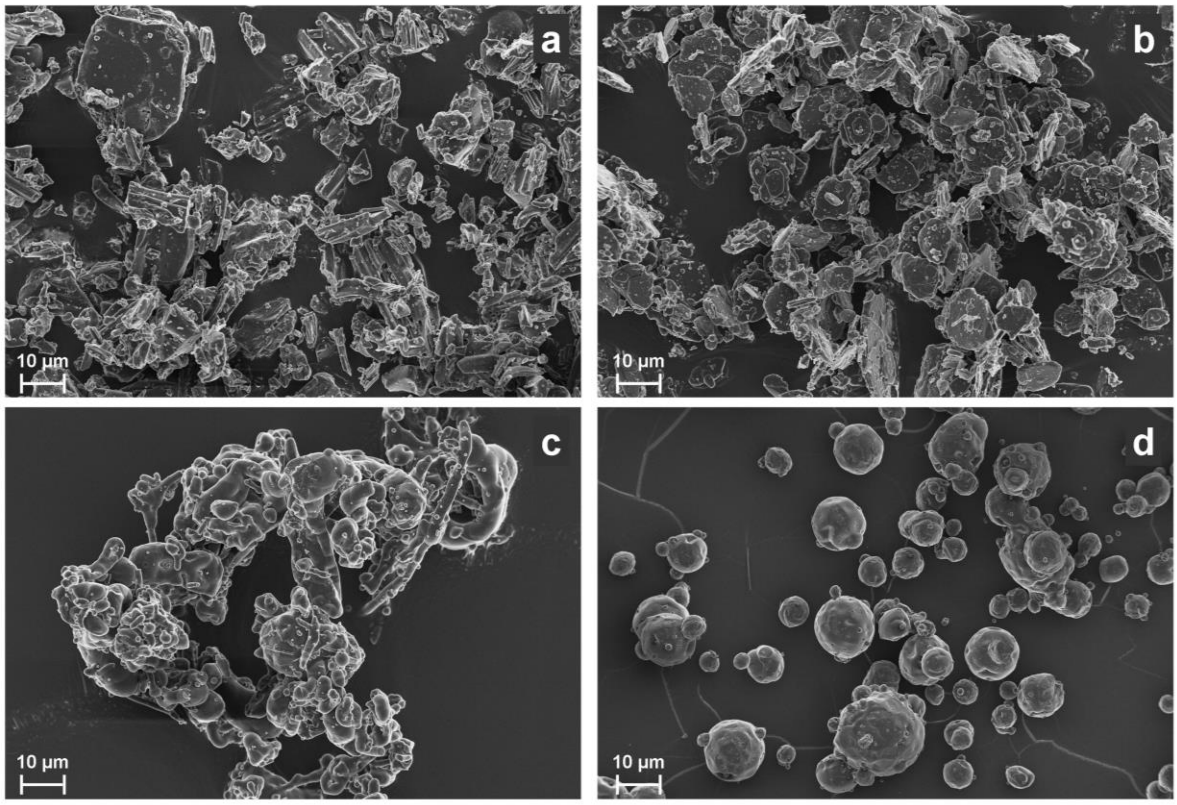

Fig. 9: SEM images of (a) magnesium stearate, (b) Pruv®, (c) Lutrol® micro 127, and (d) PEG 4000.

Tabletability and compactibility of lubricated Neosorb® powder blends

Compaction study using an eccentric tablet press

In the first part of the compaction study, tableting of the Neosorb® powder blends was performed using an instrumented eccentric tablet press in order to analyze the performance of the different lubricants. The efficiency of each lubricant was characterized by evaluation of the R values, ejection forces as well as the anti-adherent performance, i.e. the prevention of sticking to the punch surfaces.

In Table 8 the influence of the investigated lubricants and the Neosorb® content on the compaction properties indicated by the R values and the ejection forces measured during compaction is shown. The anti-adherent performance of the lubricants was determined by visual inspection of the punch surfaces after compaction.

Table 8: Influence of the Neosorb® content and various lubricants on the compaction and tablet properties; eccentric tablet press; compaction force 10 kN; lubricant concentration 4 % [w/w]; means ± SD, n = 10 (n = 6 for disintegration time)

	Neosorb [%]	MgSt	Pruv	Lutrol	PEG
Compaction properties:					
R value	25	0.956 ± 0.004	0.975 ± 0.005	0.849 ± 0.010	0.750 ± 0.018*
	50	0.960 ± 0.008	0.964 ± 0.002	0.830 ± 0.023*	0.735 ± 0.022*
	75	0.939 ± 0.009	0.971 ± 0.008	0.820 ± 0.025*	–
Ejection force [N]	25	50.5 ± 0.2	37.1 ± 0.1	88.3 ± 0.2	92.8 ± 0.6*
	50	54.0 ± 0.2	44.9 ± 0.2	87.1 ± 0.5*	100.4 ± 0.9*
	75	54.0 ± 0.4	45.1 ± 0.2	92.4 ± 0.7*	–
Tablet properties:					
Tensile strength [MPa]	25	1.19 ± 0.02	1.55 ± 0.03	3.79 ± 0.08	4.26 ± 0.18*
	50	1.74 ± 0.04	2.42 ± 0.02	4.18 ± 0.14*	5.18 ± 0.22*
	75	2.17 ± 0.05	3.03 ± 0.03	4.58 ± 0.15*	–
Disintegration time [s]	25	153 ± 10	189 ± 8	402 ± 14	186 ± 11*
	50	293 ± 13	231 ± 12	280 ± 13*	224 ± 18*
	75	308 ± 17	263 ± 12	158 ± 17*	–

* Sticking observed
– Tableting impossible

Obviously, with the powder blends lubricated with Pruv®, the highest R values and the lowest ejection forces were obtained which is attributed to a high efficiency of this lubricant. The R values derived from compaction of the powder blends lubricated with magnesium stearate were found to be similar to those of Pruv®. However, the measured ejection forces were higher, indicating a lower efficiency of magnesium stearate as lubricant. Nevertheless, the anti-adherent performance of both lubricants - Pruv® and magnesium stearate - turned out to be sufficient, as no sticking of powder to the punch surfaces was observed.

In contrast, from the results obtained with Neosorb® powder blends lubricated with either Lutrol® or PEG it is concluded that these two lubricants are inefficient at least at the chosen lubricant concentration of 4 %. Compaction of these powder blends led to low R values and high ejection forces, indicating a poor lubricant efficiency. Moreover, visual inspection of the punch surfaces after compaction revealed pronounced sticking of these powder blends, which results from a poor anti-adherent performance of the two lubricants. Only with the powder blend consisting of 25 % Neosorb® lubricated with Lutrol® no sticking to the punch surfaces occurred. The worst compaction properties were observed with PEG as lubricant: tableting of the powder blend containing 75 % Neosorb® turned out to be impossible because of pronounced friction induced by sticking of the tablets to the die wall.
In summary, from the data presented in Table 8 the rank order of lubricant efficiency was: Pruv® ≥ magnesium stearate > Lutrol® micro 127 > PEG 4000.

In addition to the compaction properties, the influence of lubrication on the properties of the Neosorb® tablets was analyzed. The tensile strength and the disintegration time of the tablets prepared with an eccentric tablet press at a compaction force of 10 kN are also presented in Table 8. It is obvious that the tablet properties are significantly affected by both the type of lubricant and the Neosorb® content within the powder blends. A general observation was that the higher the Neosorb® content, the higher the tensile strength of the tablets, independent of the lubricant used. As the tensile strength is an indirect measure of the bonding strength within tablets [192], it is hypothesized that an increase of the Neosorb® content leads to an increase of bonding within the tablets. In the literature, directly compactable sorbitol grades are reported to have excellent binding properties which are attributed to the high plasticity of the sorbitol particles as well as their particle structure [175, 176]. The particles of the sorbitol grade Neosorb® P60W consist of very small crystalline needles ultimately resulting in a porous particle structure providing a high surface area for bonding.

With regard to the investigated lubricants, it is interesting to note that lubrication of the Neosorb® powder blends with magnesium stearate led to tablets exhibiting the lowest tensile strength, whilst with the powder blends lubricated with Lutrol® or PEG high tablet tensile strengths were obtained.

This observation may be explained by the different mechanisms of lubrication: Magnesium stearate and Pruv® are boundary lubricants with amphiphilic activity and film-forming tendency, whereas Lutrol® and PEG are fluid-film lubricants [117, 118]. During the compaction process, fluid-film lubricants are supposed to melt leading to the formation of a continuous viscous fluid thin layer which separates tablet surface and metal surface [118]. After the compaction pressure is removed, solidification of the melted component is assumed to contribute to bonding within the tablets ultimately resulting in tablets with a higher tensile strength. However, one limitation for the use of fluid-film lubricants in conventional tablet formulations is their tendency to cause sticking to punch surfaces. In fact, as a result of sticking, an extremely rough tablet surface was obtained with the formulations lubricated with Lutrol® or PEG and thus the appearance of these tablets was unacceptable.

The Neosorb® content and the lubricant type also turned out to have a major effect on tablet disintegration. Though all tablets were found to disintegrate within several minutes, fulfilling the requirements for disintegration of uncoated tablets according to the Ph. Eur., considerable differences were observed. At a low Neosorb® content of 25 % the tablets lubricated with the boundary lubricants magnesium stearate and Pruv® disintegrated much faster than the tablets containing the water soluble lubricant Lutrol®. The comparably slow disintegration of the Lutrol®-containing tablets is an effect of the high tablet tensile strength. Interestingly, although lubrication with PEG also led to tablets with a high tensile strength, disintegration of these tablets was as fast as that of the Pruv®-containing tablets. This observation may be explained by the defects on the tablet surfaces caused by sticking which lead to a large contact area for water resulting in enhanced tablet disintegration.

With increasing Neosorb® content, disintegration of the non-sticking tablets was found to slow down. On the one hand, this may be attributed to the increase of the tablet bonding strength with increasing Neosorb® content. On the other hand, due to its high solubility, the predominant mechanism of disintegration of the tablets with a high Neosorb® content of 75 % is supposed to be tablet dissolution leading to slow disintegration rather than fast disintegration induced by rapid water penetration and subsequent widening of the pores [193].

As a result of the hydrophobizing effect through lubricant film formation on the surface of the Neosorb® particles, the surface wettability is reduced and thus the dissolution rate of the tablets is slowed down. In contrast, the disintegration of tablets lubricated with Lutrol® turned out to be considerably faster at a high Neosorb® content of 75 % than at a low Neosorb® content of 25 %. Poloxamers such as Lutrol® are known to exhibit a pronounced solubilizing efficiency leading to an enhancement of the wettability and the dissolution rate of poorly soluble substances [194]. In this study, with an increase of the content of water-soluble Neosorb®, the amount of the water-insoluble component microcrystalline cellulose is reduced in the tablet formulation, and thus tablet disintegration primarily occurs by tablet dissolution at a Neosorb® content of 75 %. The fast disintegration of the Lutrol®-containing tablets at this high Neosorb® content is therefore assumed to be attributed to the solubilizing effect of Lutrol® leading to an enhancement of the rate of dissolution.

Compaction study using a rotary tablet press

In the second part of the compaction study, only the two most efficient lubricants from the first part of the compaction study, magnesium stearate and Pruv®, were used for lubrication of the powder blends. Powder blends consisting of 75 % Neosorb® and lubricant at concentrations of 1, 2 and 4 %, respectively, were compacted using a rotary tablet press. It was confirmed that the efficiency of the lubricant Pruv® was superior to that of the most commonly used lubricant magnesium stearate, i.e. ejection forces derived from compaction of the powder blends lubricated with Pruv® were found to be lower than those obtained during compaction of powder blends lubricated with magnesium stearate (Table 9).

Interestingly, at the lowest lubricant concentration of 1 %, with both lubricants the measured ejection forces were drastically higher than those obtained at lubricant concentrations of 2 and 4 %, respectively. These high values are the result of die wall sticking, as friction is increased at the interface of tablet surface and die wall. Moreover, sticking to the punch surfaces was observed with both the powder blend lubricated with Pruv® and the powder blend lubricated with magnesium stearate. Therefore, at a lubricant concentration of 1 % the anti-adherent performance of both lubricants was considered inadequate.

Table 9: Influence of lubricant and lubricant concentration on the compaction and tablet properties; rotary tablet press; compaction force 10 kN; Neosorb® content 75 % [w/w]; means ± SD, n = 10 (n = 6 for disintegration time)

	Lubricant [%]	MgSt	Pruv
Compaction properties:			
Ejection force [N]	1	381.9 ± 12.4*	215.5 ± 6.2*
	2	54.0 ± 0.8	45.1 ± 0.7
	4	46.0 ± 0.4	37.7 ± 0.5
Tablet properties:			
Tensile strength [MPa]	1	3.17 ± 0.12*	3.84 ± 0.08*
	2	2.83 ± 0.07	3.74 ± 0.03
	4	1.75 ± 0.09	3.03 ± 0.02
Disintegration time [s]	1	253 ± 8*	184 ± 7*
	2	266 ± 16	188 ± 12
	4	299 ± 10	195 ± 14

* Sticking observed

This observation is contrary to the results presented in earlier publications where magnesium stearate concentrations between 0.5 and 1 % were found to be sufficient for compaction of various sorbitol tablet formulations. For instance, Michaud reported that placebo tablets containing only sorbitol (Sorbidex®) and 1 % of magnesium stearate could be successfully prepared by direct compaction without sticking [195]. For this reason, it is assumed that the anti-adherent performance of the employed lubricants is considerably affected by the physico-chemical properties of the investigated sorbitol grades.

Properties of tablets obtained with the rotary tablet press were examined by determination of the tabletability and by measurement of the disintegration times. Tabletability is the tensile strength of a tablet in dependence of the applied compaction force. The influence of the lubricant type and the lubricant concentration on the tabletability of the investigated Neosorb® powder blends is presented in Fig. 10. It is apparent that the tabletability of the powder blends is strongly affected by both the lubricant type and its concentration. The tensile strength of tablets containing magnesium stearate was considerably lower than that of tablets containing Pruv®.

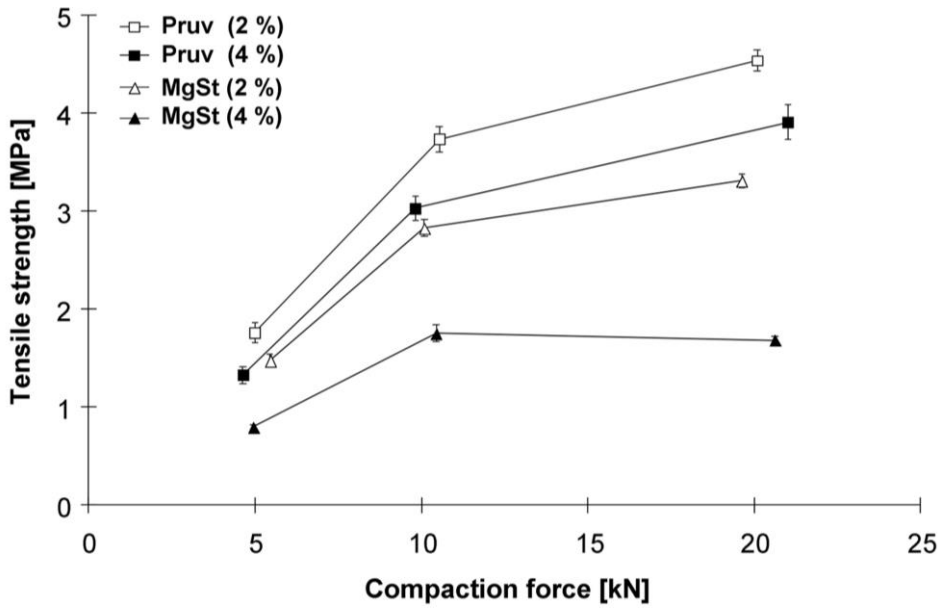

Fig. 10: Influence of the lubricant type and the lubricant concentration on the tabletability of Neosorb® tablet formulations; means ± SD, n = 10.

For example, at a compaction force of 10 kN and a lubricant concentration of 2 %, the tensile strength of tablets containing magnesium stearate was 2.83 MPa (± 0.07), whereas the tensile strength of tablets containing Pruv® was 3.74 MPa (± 0.03). With an increase of the lubricant concentration a decrease of the tablet tensile strength was observed. The tensile strength of the tablets containing magnesium stearate was reduced from 2.83 MPa to only 1.75 MPa (± 0.09). In contrast, the tensile strength of the tablets containing Pruv® decreased from 3.74 MPa to 3.03 MPa (± 0.02), which indicates an excellent tabletability even at a high lubricant concentration of 4 %.

The observed decrease of the tablet hardness with increasing concentrations of the two lubricants is caused by film formation of the lubricant around the host particles [75]. This lubricant film may act as a physical barrier, and it therefore interferes with the binding of powder particles resulting in comparably soft tablets. However, the effect of the lubricant film on the tablet hardness strongly depends on the lubricant type and on the deformation characteristics of the excipients used in the tablet formulation. Sorbitol and microcrystalline cellulose are examples of excipients with a high lubricant sensitivity resulting from their primarily plastic deformation behavior during compaction [52, 60, 175, 196, 197].

However, because brittle fragmentation is also likely to occur during compaction of crystalline sorbitol, the excipient is reported to be less susceptible to magnesium stearate than microcrystalline cellulose [15].

In addition to their excellent tabletability, the tablets lubricated with Pruv® also turned out to show better disintegration properties than those lubricated with magnesium stearate. In Fig. 11 the influence of the lubricant type and the lubricant concentration on the disintegration times of the Neosorb® tablets is shown. Tablets lubricated with Pruv® were observed to disintegrate more rapidly than tablets containing magnesium stearate. This observation is attributed to the pronounced hydrophobic nature of magnesium stearate compared to the relative hydrophilicity of Pruv®, which leads to poor wettability of the tablet surface ultimately resulting in prolonged tablet disintegration [75, 179, 180].

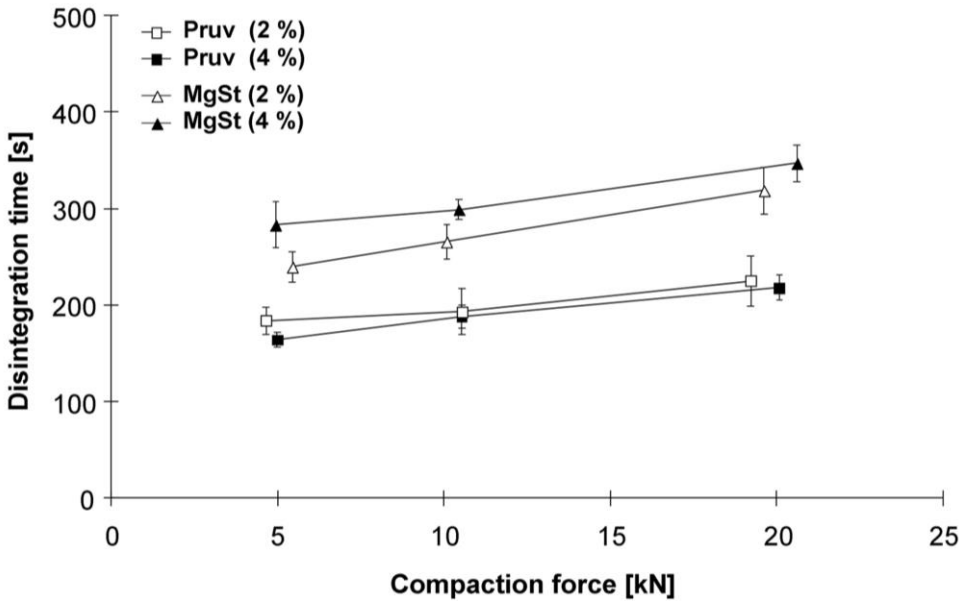

Fig. 11: Influence of the lubricant type and the lubricant concentration on the disintegration time of Neosorb® tablets; means ± SD, n = 6.

Considering both the lubricant efficiency and their effect on tablet properties, it is therefore concluded that lubrication of Neosorb® tablet formulations using Pruv® is preferable over lubrication with magnesium stearate.

Tabletability and compactibility of Neosorb® powder blends lubricated with 1:1 mixtures of magnesium stearate and Pruv®

Tableting of Neosorb® powder blends lubricated with 1 % of either magnesium stearate or Pruv® resulted in pronounced sticking to the punch surfaces, indicating that the anti-adherent performance of each lubricant was insufficient (see previous section). Nevertheless, preliminary studies revealed a possible synergistic effect of both lubricants, if a mixture of magnesium stearate and Pruv® was used for lubrication of the investigated Neosorb® tablet formulation. In order to analyze the lubricant efficiency of 1:1 mixtures of magnesium stearate and Pruv®, Neosorb® powder blends with a total lubricant concentration of 0.5, 0.75, 1 and 2 %, respectively, were prepared.

From the data presented in Fig. 12 it is obvious that the ejection forces measured during compaction of the powder blends were below 100 N at a total lubricant concentration of 1 %, indicating a good lubricant efficiency. Even at a total lubricant concentration of 0.75 % the ejection forces of approximately 200 N were considered acceptable. Moreover, it is interesting to note that sticking of powder to the punch surfaces was not detected with the powder blends lubricated with 0.75 % and higher. A total lubricant concentration of 0.5 % turned out to be inadequate, as compaction of the powder blends led to unacceptably high ejection forces of approximately 500 N and to sticking to the punch surfaces.

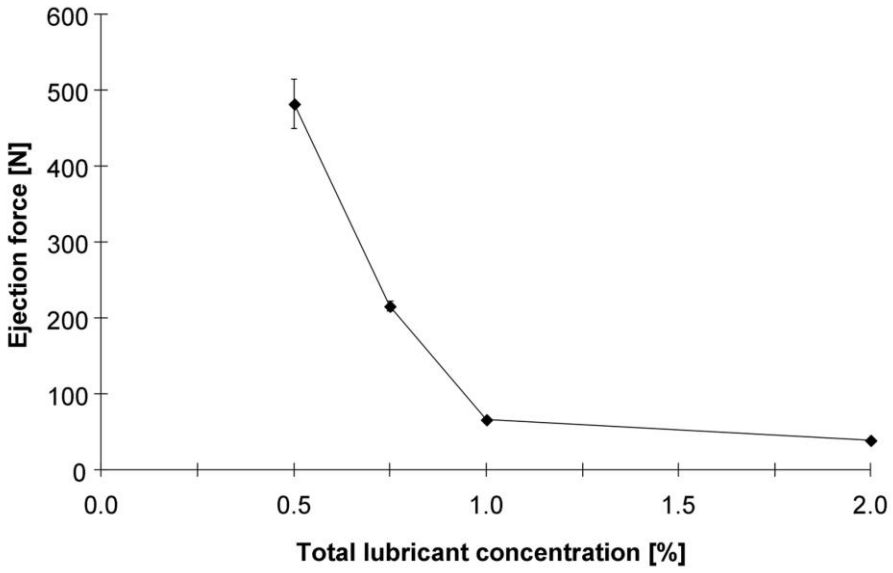

Fig. 12: Influence of the total lubricant concentration on the ejection force of Neosorb® tablets; magnesium stearate:Pruv (1:1); means ± SD, n = 10.

Lubrication of the powder blends with a 1:1 mixture of magnesium stearate and Pruv® resulted in tablets with excellent properties. The influence of the total lubricant concentration on the tablet tensile strength as well as on the disintegration time of tablets is displayed in Fig. 13. It is apparent that both the tablet tensile strength and the disintegration times of the tablets are only slightly affected by the total lubricant concentration. However, even at a comparably high lubricant concentration of 2 % the tablet tensile strength was found to exceed 3 MPa and the tablets disintegrated within 200 s.

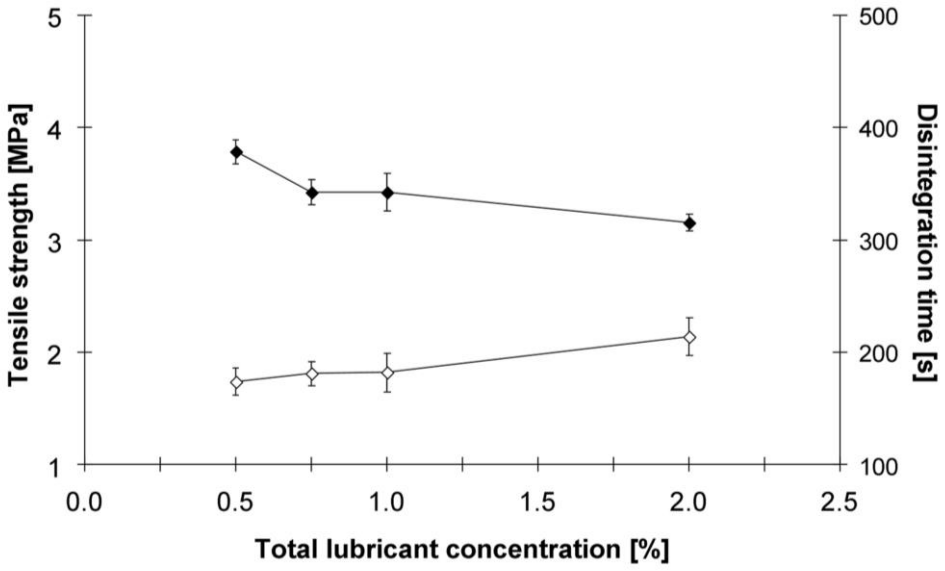

Fig. 13: Influence of the total lubricant concentration on the tensile strength (closed symbols; means ± SD, n = 10) and on the disintegration time (open symbols; means ± SD, n = 6) of Neosorb® tablets lubricated with magnesium stearate: Pruv (1:1).

In summary, a synergistic effect of the lubricants magnesium stearate and Pruv® was observed. In contrast to the lubrication with the plain lubricants, a 1:1 mixture of both lubricants allowed a reduction of the total lubricant concentration from 2 % to 1 %.

2.4. Conclusion

In contrast to the fluid-film lubricants Lutrol® micro 127 and PEG 4000, the boundary lubricants Pruv® and magnesium stearate turned out to be efficient lubricants for compaction of the investigated Neosorb® tablet formulations. However, tablets prepared with Pruv® as the lubricant were found to exhibit superior properties in terms of tablet tensile strength and disintegration time. Therefore, considering both the lubricant efficiency and the effect on tablet properties, it is concluded that lubrication of Neosorb® tablet formulations using Pruv® is preferable over magnesium stearate.

In addition, a synergistic effect between magnesium stearate and Pruv® can be postulated. Tableting of powder blends lubricated with 1 % of either magnesium stearate or Pruv® resulted in pronounced sticking to the punch surfaces, which indicated that the anti-adherent performance of each lubricant was insufficient. Interestingly, the required amount of lubricant for the investigated Neosorb® tablet formulations could be reduced to a total lubricant concentration of 1 %, if a 1:1 mixture of magnesium stearate and Pruv® was used. Lubrication with this mixture resulted in acceptable ejection forces during compaction (below 100 N), excellent tablet properties, and sufficient anti-adherent performance.

Finally, from the results obtained in this study and the results previously published it is obvious that the physico-chemical properties of sorbitol are of major relevance for its performance in tableting. It has to be taken into consideration that sorbitol as a tableting excipient is commercially supplied by numerous manufacturers and various sorbitol grades are available on the market. Sorbitol grades sourced from different manufacturers may be obtained from different manufacturing processes and thus they are likely to show variations with regard to their particle morphology and powder properties. This is also expected to account for the lubricant requirement of a certain tablet formulation.

3. Direct compaction of ibuprofen-containing powder blends – Influence of the ibuprofen grade on the flow and compaction properties of an ibuprofen tablet formulation

Direct compaction of ibuprofen-containing powder blends - Influence of the ibuprofen grade on the flow and compaction properties of an ibuprofen tablet formulation

Abstract

Ibuprofen powders exhibit poor flowability, poor compactibility, and ibuprofen tablets show a high tendency to stick to punch surfaces during tablet manufacture. Several ibuprofen grades are available on the market. The compaction properties of ibuprofen have been extensively investigated by several authors. However, a comparison of various ibuprofen grades with regard to flow and compaction properties has not been made so far.

Therefore, the objective of the present study was to investigate the influence of the ibuprofen grade on the flowability of powder blends and on the compaction properties of tablets prepared by direct compaction. Six different ibuprofen grades from three commercial suppliers were compared. A model tablet formulation containing 70 % of the drug was evaluated with regard to the flow and deformation characteristics, the sticking tendency of the tablets as well as the tablet properties such as tablet disintegration and drug dissolution.

It could be shown that flow and compaction properties of the investigated powder blends were considerably affected by the ibuprofen grade. Both flow and compaction properties were found to be strongly dependent on the mean particle size of the respective ibuprofen grade. Powder blends consisting of ibuprofen grades with larger particles showed appropriate flowability and compactibility, and the properties of resulting tablets were acceptable.

3.1. Introduction

Ibuprofen is a non-steroidal drug, which is widely used as an anti-inflammatory analgesic (NSAID). Solid oral dosage forms containing ibuprofen available on the market are tablets, granules, and soft gelatin capsules. Among these, tablets are the most frequently administered pharmaceutical dosage form, because tablets can easily be manufactured in large quantities, and they are easy to handle in terms of storage and distribution [1]. Further advantages over other dosage forms are the convenient way of administration to patients and the high stability of drug substances in dry formulations.

Ibuprofen is usually formulated in tablets with high drug contents (200 – 800 mg). However, the development of an ibuprofen tablet formulation poses a challenge with regard to the manufacturing process. In general, the drug has to be granulated prior tableting because of poor flow and compaction properties of ibuprofen powders as well as a high tendency to stick to punch surfaces during powder compression. The preferred technology for industrial production of tablets, however, is direct compaction of powder blends, as it is more economic due to lower labor costs, reduced processing time, and lower energy consumption [17].

Ibuprofen is commercially supplied by numerous manufacturers and various ibuprofen grades are available on the market. Independent of the drug origin, for a pharmaceutical application ibuprofen powders have to be chemically identical and must fulfill the regulatory and pharmacopeia requirements. Thus, pure ibuprofen grades vary only with regard to the mean particle size and / or the shape of the powder particles.

The compaction and deformation characteristics of ibuprofen have been extensively examined by several authors [112, 129, 156, 164, 198-201]. However, it has to be considered that in these studies the investigated ibuprofen powders were supplied by different manufacturers, and thus different ibuprofen grades were used for the compaction studies. A comparison of the compaction and deformation characteristics of different commercially available ibuprofen grades has not been made so far.

Therefore, the objective of the present study was to investigate the influence of the ibuprofen grade on the flowability of powder blends and on the compaction properties of tablets prepared by direct compaction. Furthermore, tablet properties such as tablet tensile strength, tablet disintegration und drug dissolution were determined.

3.2. Materials and methods

3.2.1. Materials

Six different ibuprofen grades were purchased from commercial suppliers (Table 10) and used as received. The following excipients were used for the tablet formulations: Ludipress®, a co-processed excipient consisting of 93 % α-lactose monohydrate, 3.5 % povidone, and 3.5 % crospovidone (BASF, Ludwigshafen, Germany); crospovidone (Kollidon® CL, BASF, Ludwigshafen, Germany); magnesium stearate (Fagron, Barsbüttel, Germany).
All other reagents used in this study were of analytical grade.

Table 10: Overview of the investigated ibuprofen grades

Ibuprofen grade	Manufacturer	Monograph
Ibuprofen 50 (IBU 50)	BASF, Ludwigshafen, Germany	USP, Ph. Eur., JP
Ibuprofen 70 (IBU 70)	BASF, Ludwigshafen, Germany	USP, Ph. Eur., JP
Ibuprofen 90 (IBU 90)	BASF, Ludwigshafen, Germany	USP, Ph. Eur., JP
Ibuprofen S250 (S 250)	Shasun Pharmaceuticals Ltd., Pondicherry, India	Ph. Eur., BP
Ibuprofen S500 (S 500)	Shasun Pharmaceuticals Ltd., Pondicherry, India	Ph. Eur., BP
Ibuprofen (IBU CH)	Hubei Biocause Pharmaceuticals Ltd., Jingmen, China	Ph. Eur.

3.2.2. Methods

Physical characterization of the investigated ibuprofen grades

Determination of the melting point

Onsets of melting and enthalpies of fusion (ΔH_f) of ibuprofen samples were determined with differential scanning calorimetry (DSC7, Perkin Elmer, Beaconsfield, UK). The samples (10 mg) were heated at scan rates of 10 K/min in aluminum pans under nitrogen atmosphere. The onsets of melting and the enthalpies of fusion were calculated by the Pyris® software (Perkin Elmer, Beaconsfield, UK).

Determination of the true density

True densities of the ibuprofen grades were measured by helium pycnometry using a 30 cm^3 sample cup (Accupyc 1330, Micromeritics, Aachen, Germany). Each measurement included 10 purge cycles followed by 10 measuring cycles.

Determination of the bulk and tapped density

Bulk and tapped densities were determined using a jolting volumeter (STAV 2003, J. Engelsmann, Ludwigshafen, Germany) according to the Ph. Eur. and the Hausner ratio was calculated as the quotient of tapped and bulk density.

Determination of the particle shape

The crystal habit of all investigated ibuprofen grades was analyzed by image analysis using a stereomicroscope (SteREO Discovery.V8, Zeiss, Jena, Germany) equipped with an AxioCam ICc and AxioVision software (Zeiss, Jena, Germany).

Determination of the particles size

Particle size distributions of ibuprofen samples were investigated via laser diffraction with a dry dispersion unit (HELOS/RODOS, Sympatec, Clausthal-Zellerfeld, Germany). Compressed air of 1.5 bar was used to disperse the powder.

All experiments were done in triplicate.

Preparation and characterization of powder blends

Preparation of powder blends

All ibuprofen samples were sieved (1000 µm mesh) prior to the preparation of the powder blends due to their high tendency to form powder agglomerates. The composition of the powder blends to be compacted is displayed in Table 11.

Table 11: Composition of the powder blends

Ingredients		**(%)**
Ibuprofen	active pharmaceutical ingredient (API)	70
Ludipress®	filler-binder	25
Crospovidone	disintegrant	4.5
Magnesium stearate	lubricant	0.5

The ibuprofen content in the investigated powder blends was 70 % (w/w). As filler-binder Ludipress® was chosen, as it exhibits excellent flow and compaction properties [202]. Although Ludipress® contains 3.5 % of the disintegrant crospovidone, supplemental addition of crospovidone (Kollidon® CL) was required to ensure tablet disintegration and drug dissolution.

Each ibuprofen grade was first mixed with the filler-binder and the disintegrant using a Turbula blender at 72 rpm for 10 min (T2F, W.A. Bachofen, Muttenz, Switzerland). Subsequently, the powder blends were lubricated with magnesium stearate and mixing was continued for 3 more minutes. Prior compaction, the powder blends were stored in an air-conditioned room at a temperature of 21°C and a relative humidity of 45 % for at least 72 h.

Flowability of powder blends

Flow properties of all powder blends were determined by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as described before. The mass-related powder flow rate [g/s] was measured using a flowability tester (BEP2, Copley Scientific, Nottingham, UK) equipped with a stainless steel flow funnel (orifice diameter 10 mm). All experiments were done in triplicate.

Compaction studies

Compaction with an eccentric tablet press

To analyze the deformation behavior of the powder blends, compaction was performed using an instrumented eccentric tablet press (EXI, Fette, Schwarzenbek, Germany) equipped with flat-faced punches of 10 mm diameter. Tableting was carried out in single stroke mode by filling 300 mg of the powder blends manually into the die. To avoid sticking, the die wall and punch surfaces were prelubricated with a magnesium stearate suspension (2 % in acetone [w/v]). Five tablets were prepared with each powder blend at a compression speed of 16 strokes / min and a compaction pressure of 150 MPa.

The deformation behavior of powder blends was analyzed using the equation described by Heckel [51]:

$$\ln\left(\frac{1}{\varepsilon}\right) = K \cdot P + A \qquad \text{(eq. 1)}$$

where ε is the porosity of the tablet at the applied pressure P, K is the slope of the linear portion of the Heckel plot, and A is a constant related to the initial particle rearrangement. The reciprocal of K is the mean yield pressure (P_Y), which was calculated from linear regression analysis within a pressure range between 50 and 120 MPa ($R^2 \geq 0.998$).

The percentage of elastic recovery (ER) of the tablets was calculated immediately after ejection (t_{0h}) and after a relaxation period of 24 h (t_{24h}) following eq. 2:

$$ER = \left(\frac{h - h_P}{h_P}\right) \cdot 100 \qquad \text{(eq. 2)}$$

where h is the tablet height immediately after ejection (t_{0h}) and after a relaxation period of 24 h (t_{24h}), respectively, and h_P is the tablet height at the applied compaction pressure.

Tablet porosity (ε) was calculated from the apparent density of the tablets and the true density of the powder blends:

$$\varepsilon = 1 - \frac{m_{tablet}}{\rho_{true} \cdot V_{tablet}} \qquad \text{(eq. 5)}$$

where m is the tablet weight (g) and V the apparent volume of the tablet (cm^3).

Compaction with a rotary tablet press

To investigate the influence of the ibuprofen grade on the compaction and tablet properties, flat-faced tablets with a target weight of 300 mg (RSD ≤ 1.5 %) and a diameter of 10 mm were prepared with an instrumented rotary tablet press (XL 100, KORSCH, Berlin, Germany) at different compaction forces (10, 20, and 30 kN). Due to poor flowability of the powder blends a speed force feeding system was used at 30 rpm. The compression speed was set to 20 rpm with a corresponding dwell-time of 74.7 ms.

Quantification of sticking

The sticking tendency of each tablet formulation was evaluated by HPLC quantification of ibuprofen within the sticking residue adhered to the punch surface. Following compaction runs of 50 tablets each, the sticking residue was removed from the punch surfaces with a swab method using a Q-tip soaked with methanol. Subsequently, the Q-tips were immersed in 5 ml of methanol. HPLC quantification of ibuprofen was carried out after an extraction period of at least 24 h.

The HPLC system (Kontron Instruments, Germany) was equipped with a LiChroCART® RP-18 (5 µm) column (Merck, Darmstadt, Germany). The flow rate was adjusted to 1 ml/min and the sample volume injected was 20 µl. The mobile phase consisted of 60 % acetonitrile and 40 % phosphate buffer (pH 3.0). UV detection of ibuprofen was performed at 242 nm. The absorbance was linear in a concentration range between 10 and 850 µg/ml (R^2 = 1.000). The limit of quantification was calculated to be 5 µg/ml. The extent of sticking is expressed as amount ibuprofen adhered to the punch surface area [µg/cm²].

Characterization of tablets

Determination of the tablet tensile strength

After a relaxation time of at least 24 h following ejection of the tablets, the crushing strength, the diameter and the thickness of 10 tablets were determined using a hardness tester (TBH 30, Erweka, Heusenstamm, Germany).

The tablet tensile strength was calculated using the equation published by Fell et al. [189]:

$$\sigma = \frac{2 \cdot F}{\pi \cdot d \cdot t} \qquad \text{(eq. 4)}$$

where σ is the tablet tensile strength (MPa), F the crushing strength (N), d the tablet diameter (mm), and t the tablet thickness (mm). A minimum tablet tensile strength of 0.85 MPa was regarded as sufficient, as this value corresponds to a tablet crushing strength of approximately 50 N.

Disintegration studies

Disintegration time of tablets was measured with a disintegration tester (ZT 72, Erweka, Heusenstamm, Germany) according to the conditions of the Ph. Eur. for uncoated tablets. The disintegration apparatus was operated with magnetic guided discs allowing for an automated determination of the tablet disintegration time.

Drug release studies

Drug release of tablets was determined according to the Ph. Eur. in 500 ml of phosphate buffer solution (pH 6.8) with a rotating paddle dissolution apparatus (Premiere 5100, Distek, North Brunswick, NJ, USA). The stirring speed was 100 rpm and the temperature was maintained at 37 ± 0.5 °C. Quantification of the dissolved amount of ibuprofen was done by UV spectroscopy at 264 nm (Spectrophotometer 8453, Agilent Technologies, Santa Clara, CA, USA).

3.3. Results and discussion

Physical and bulk powder properties

The influence of powder characteristics such as crystal habit and moisture content on compaction and deformation behavior of ibuprofen has already been published in several studies [96, 112, 129, 132, 200]. In the present study all investigated ibuprofen grades were found to exhibit needle-shaped drug particles, as it has been reported previously with common ibuprofen powder [134].

In Table 12 an overview of some physical and bulk powder properties of the different ibuprofen grades is presented. The onsets of melting, enthalpies of fusion and the true densities are approximately the same with all samples, indicating that the chemical structure of all ibuprofen grades is identical.

Table 12: Physical and bulk powder properties of the investigated ibuprofen grades

Ibuprofen grade	IBU 50	IBU 70	IBU 90	S 250	S 500	IBU CH
Physical properties:						
Onset of melting [°C]	76.4 (± 0.2)	76.5 (± 0.3)	76.5 (± 0.3)	76.7 (± 0.3)	76.6 (± 0.1)	76.1 (± 0.2)
Enthalpy of fusion (ΔH_f) [J/g]	118.8 (± 2.0)	119.3 (± 1.7)	119.4 (± 3.8)	118.1 (± 3.4)	119.4 (± 1.2)	121.1 (± 1.8)
True density [g/cm³]	1.117 (± 0.001)	1.118 (± 0.001)	1.118 (± 0.001)	1.116 (± 0.001)	1.116 (± 0.001)	1.117 (± 0.001)
Bulk powder properties:						
Mean particle size (d_{50}) [µm]	52.9 (± 0.5)	70.6 (± 0.7)	90.3 (± 0.7)	32.1 (± 0.2)	66.7 (± 0.3)	56.2 (± 0.3)
Bulk density [g/cm³]	0.34 (± 0.01)	0.41 (± 0.01)	0.50 (± 0.01)	0.32 (± 0.01)	0.40 (± 0.01)	0.35 (± 0.01)
Tapped density [g/cm³]	0.58 (± 0.01)	0.64 (± 0.01)	0.63 (± 0.01)	0.60 (± 0.01)	0.62 (± 0.01)	0.57 (± 0.01)
Hausner ratio	1.70 (± 0.05)	1.58 (± 0.04)	1.26 (± 0.02)	1.86 (± 0.06)	1.57 (± 0.03)	1.64 (± 0.04)

From the presented data it is obvious that the investigated ibuprofen grades clearly differ with regard to their mean particle size. The sample IBU 90 exhibits the largest particles, whereas the sample S 250 provides the smallest particles. The calculated Hausner ratios of the powders were found to correspond to the mean particle size of the ibuprofen grades. As the Hausner ratio is an indicator of the flowability of a powder, best flow properties were obtained with IBU 90 because of its lowest Hausner ratio of 1.26. In accordance with the Ph. Eur. a Hausner ratio exceeding 1.34 indicates poor flowability. In this study, all ibuprofen grades including IBU 90 were observed to be not free-flowing because of a pronounced cohesivity of the ibuprofen particles within the powder bed as well as a strong adhesivity of the powder particles to surfaces. Thus, a powder flow rate could not be determined with the raw ibuprofen samples.

Flowability of powder blends

The flow properties of the investigated powder blends (ibuprofen content 70 %) determined by measurement of the Hausner ratio and the powder flow rate are displayed in Fig. 14.

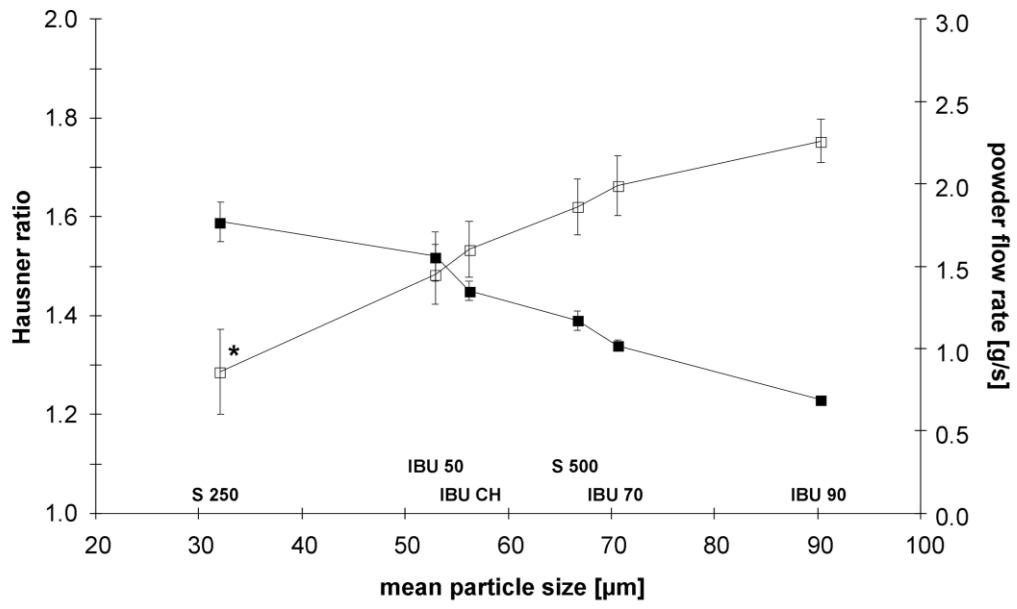

Fig 14: Flow properties of the investigated powder blends: Hausner ratio (closed symbols), powder flow rate (open symbols); means ± SD, n = 3.
*** Powder flow was induced by impulse to flow funnel.**

It is obvious that the flowability of the powder blends is strongly affected by the mean particle size of the different ibuprofen grades in the powder blends. With an increase of the mean particle size, a decrease of the Hausner ratio and an increase of the powder flow rate were observed. In accordance with the Ph. Eur. the Hausner ratio of the IBU 90-containing powder blend indicated fair flow properties, whereas the Hausner ratio of powder blends consisting of IBU 70 and S 500, respectively, showed passable flowability. With the powder blends containing the ibuprofen grades IBU CH and IBU 50, respectively, very poor flowability was observed, and the S 250 powder blend turned out to be not free-flowing. However, powder flow of the S 250 blend could be induced by a slight impulse to the flow funnel.

From these results it was concluded that for compaction studies with a rotary tablet press, a speed force feeding system should be used to ensure uniformity of the tablet weight.

Deformation characteristics of powder blends

To study the deformation behavior of the powder blends containing various ibuprofen grades, compaction was performed with an instrumented eccentric press. The deformation behavior of the raw ibuprofen samples could not be examined under the chosen conditions because of pronounced sticking to the punch surfaces. However, Di Martino et al. reported a plastic-elastic deformation behavior of ibuprofen with mean yield pressures ranging between 54 and 59 MPa depending on the crystal habit of the particles [129].

To estimate the influence of the deformation characteristics of the excipients used in the powder blends, analysis of Heckel plots were performed with Ludipress® and Kollidon® CL, respectively (Figs. 15 a, b). The curve profiles are significantly different with regard to the slopes of the compression and decompression curves. The mean yield pressure determined from the slope of the compression curve of Ludipress® was 90.4 ± 1.2 MPa, and that of Kollidon® CL was determined to be 61.5 ± 2.3 MPa. This indicates plastic deformation of both excipients, as mean yield pressures below 100 MPa usually represent a predominant plastic deformation behavior [203].

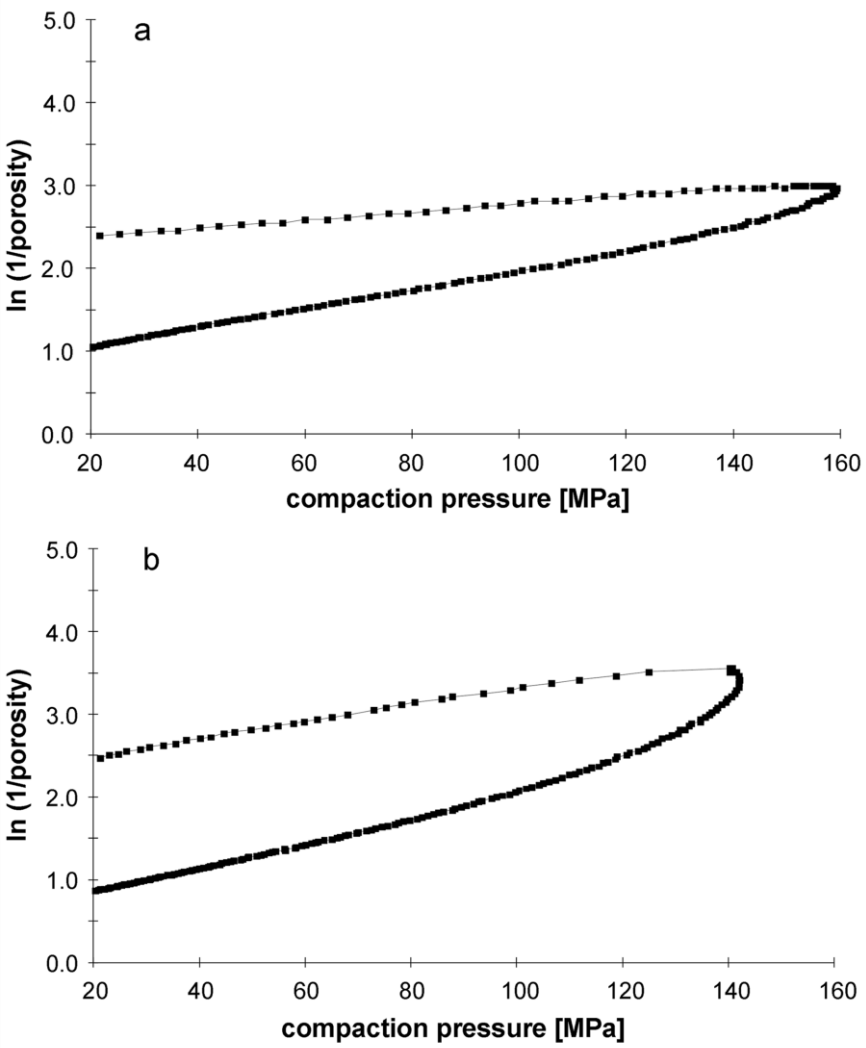

Fig. 15: Heckel plots of (a) Ludipress® and (b) Kollidon® CL.

However, it is apparent that the mean yield pressure of Ludipress® is considerably higher than that of Kollidon® CL. Kollidon® CL, i.e. crospovidone, undergoes pronounced plastic deformation during compaction due to the amorphous structure of the excipient [11]. In contrast to Kollidon® CL, Ludipress® is a multifunctional excipient consisting of α-lactose monohydrate coated with povidone and crospovidone. Due to the unique manufacturing process it exhibits dual deformation behavior: deformation by brittle fracture and plastic deformation. It is reported that crystalline α-lactose monohydrate shows primarily deformation by brittle fracture [204]. The plastic deformation behavior of Ludipress® is caused by the amorphous components povidone, crospovidone, and the amorphous portion of lactose, which is generated during co-processing of the excipients [202].

Typical Heckel plots recorded during compaction of the ibuprofen-containing powder blends are presented in Figs. 16 a-f.

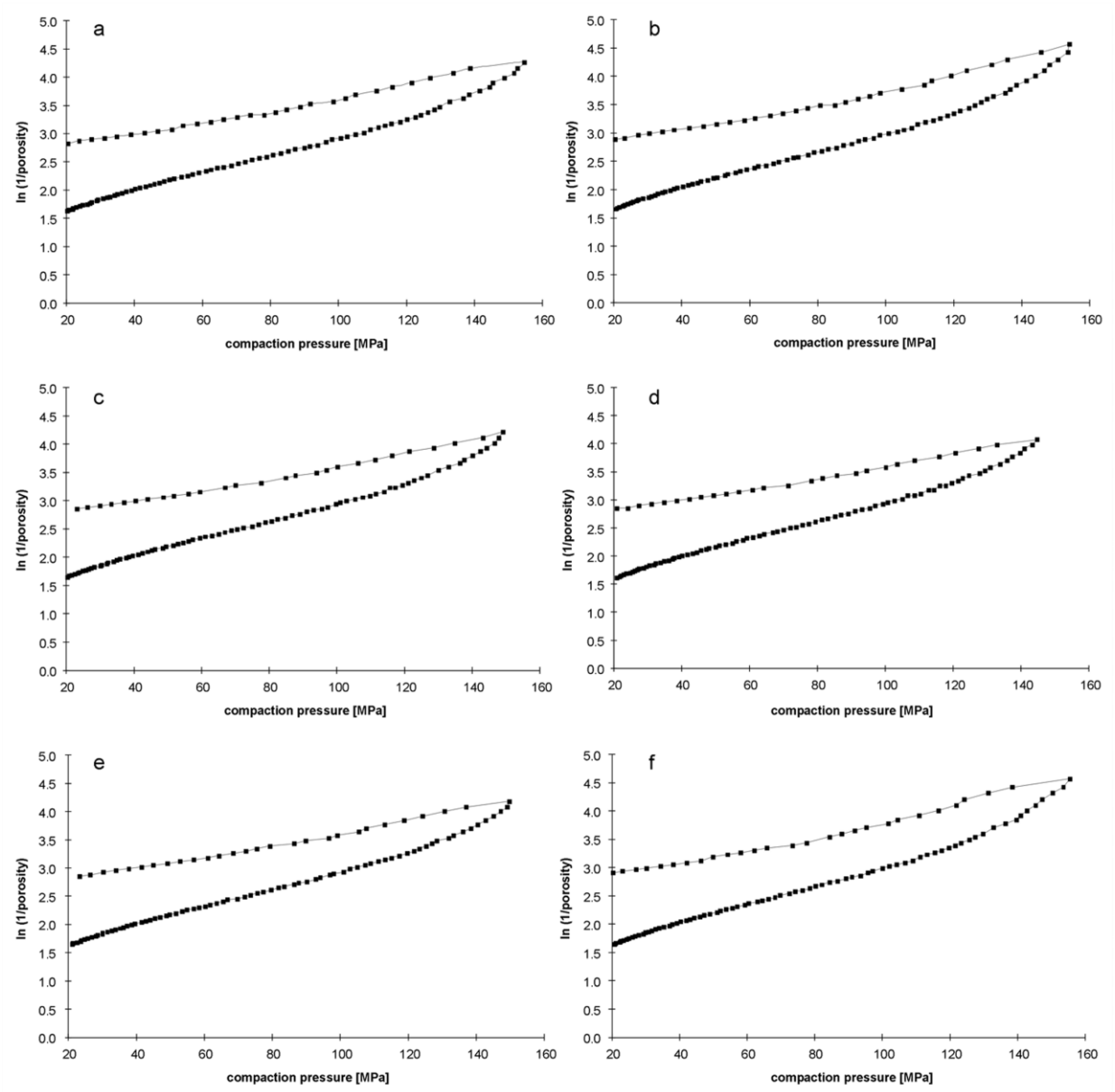

Fig. 16: Heckel plots of powder blends containing 70 % of (a) IBU 50, (b) IBU 70, (c) IBU 90, (d) S 250, (e) S 500, and (f) IBU CH.

The curve shape of the Heckel plots was found to be similar with all investigated powder blends, and mean yield pressures ranging between 60.5 MPa and 64.5 MPa were calculated from the slope of the compression curve (Table 13). These results are in good agreement with the plastic deformation behavior determined with Ludipress® and Kollidon® CL, respectively, as well as with the plastic-elastic deformation characteristics described with pure ibuprofen.

The elastic properties of compacted powders can also be estimated from the analysis of Heckel plots [78]. Elasticity of powder particles leads to an increase in the porosity of tablets during the decompression phase resulting in a descending slope of the decompression curve [205]. Thus, powders, which do not show elastic deformation, lead to Heckel plots with horizontal decompression curves. From the shape of the decompression curves obtained during compaction of the ibuprofen-containing powder blends a pronounced elastic deformation behavior can be postulated (Figs. 16 a-f). Furthermore, the degree of elasticity turned out to be independent of the ibuprofen grade used in the powder blends, as the slope of the decompression curves were found to be similar.

Table 13: Compaction properties of powder blends containing 70 % of ibuprofen (eccentric tablet press)

Ibuprofen grade	**IBU 50**	**IBU 70**	**IBU 90**	**S 250**	**S 500**	**IBU CH**
Mean Yield Pressure (P_Y) [%]	64.5 (± 1.4)	63.3 (± 1.3)	63.3 (± 1.4)	62.4 (± 1.4)	64.3 (± 1.7)	60.5 (± 1.0)
Elastic recovery (t_{0h}) [%]	5.13 (± 0.09)	5.06 (± 0.16)	5.00 (± 0.19)	4.96 (± 0.19)	5.06 (± 0.15)	5.03 (± 0.18)
Elastic recovery (t_{24h}) [%]	6.81 (± 0.10)	7.01 (± 0.10)	7.10 (± 0.11)	6.27 (± 0.06)	6.48 (± 0.06)	6.35 (± 0.10)
Porosity of tablets (t_{24h}) [%]	7.05 (± 0.09)	7.58 (± 0.08)	8.29 (± 0.05)	6.58 (± 0.03)	7.73 (± 0.07)	7.24 (± 0.08)
Tensile strength [MPa]	1.62 (± 0.03)	1.57 (± 0.05)	1.44 (± 0.05)	1.71 (± 0.07)	1.61 (± 0.07)	1.47 (± 0.06)

To confirm the elastic properties derived from analysis of the Heckel plots, the elastic recovery of tablets was calculated immediately after ejection as well as after a relaxation period of 24 h (Table 13). Rapid elastic recovery (t_{0h}) of tablets was found to be in good agreement with the observations derived from Heckel analysis: with all tablets an elastic recovery of approximately 5 % was obtained. Elastic recovery after a relaxation period of 24 h, however, appeared to be affected by the ibuprofen grade.

With ibuprofen grades of the same origin, e.g. IBU 50, IBU 70, and IBU 90, elasticity increased with increasing drug particle size in the tablets. A high elastic energy may lead to a breaking of bonds within the tablets resulting in increased tablet porosity. This ultimately leads to a reduced tablet hardness, and possibly to capping [87]. In fact, tablets with lower elastic recovery after relaxation and thus lower tablet porosity, showed a higher tablet tensile strength than those with higher elastic recovery. However, all tablets exceeded the desired tablet hardness and capping was not observed. Variations in elastic recovery of tablets were also determined with respect to the origin of the ibuprofen grades. Although IBU 70 and S 500 exhibit a similar mean particle size of approximately 70 µm, elastic recovery of tablets containing S 500 was considerably lower than that determined with IBU 70 tablets. This phenomenon was also observed with IBU 50 and IBU CH. It is hypothesized that the manufacturing process and thus slight differences in the particle shape might be the reason for this observation.

Evaluation of the sticking tendency

Apart from the poor flow and compaction properties of ibuprofen, its high tendency to stick to punch surfaces poses an additional challenge during tablet manufacture [112]. To investigate the influence of the ibuprofen grade on the sticking tendency of the powder blends, tableting was performed with an instrumented rotary tablet press.

Generally, there are two distinct phases of the sticking process [115]: The first phase is characterized by an interaction between powder particles and punch surface, whereat the adhesion forces exceed the cohesive bonding forces within the tablets. In the second phase of the sticking process an increase in powder layering is observed with long run times of the tablet press. This build-up of a sticking layer on the punch surface is primarily caused by auto-adhesive interactions between the powder particles within the tablet formulation and those already adhered to the punch. In this study, sticking was quantified after 50 compression cycles to reflect the first phase of the sticking process.

The extent of powder layer sticking of tablets containing the different grades of ibuprofen is displayed in Fig. 17.

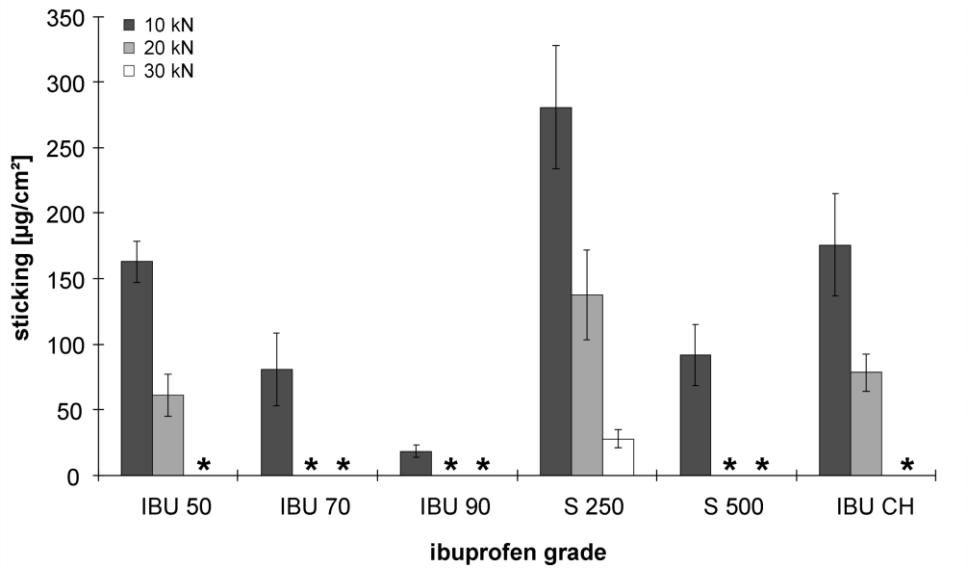

Fig. 17: Influence of the ibuprofen grade and the compaction force on sticking of the investigated powder blends; means ± SD, n = 3.
*** No sticking observed.**

The sticking tendency of the powder blends was found to be strongly affected by the compaction force. At a low compaction force of 10 kN, sticking was observed with all formulations. At a compaction force of 20 kN only the formulations consisting of IBU 50, IBU CH and S 250, respectively, showed a sticking tendency. At a compaction force as high as 30 kN only the S 250 tablet formulation turned out to stick to the punch surfaces. From the presented data it is apparent that the sticking tendency of each tablet formulation was considerably decreased with an increase of the compaction force. The benefit of high compaction forces to reduce the sticking tendency of a tablet formulation has been published previously, and it was explained by an increase of cohesion within the tablet at higher compaction forces [142, 145, 146].

The sticking tendency of the powder blends was also strongly affected by the ibuprofen grade. At a low compaction force of 10 kN, the highest extent of sticking was observed with the S 250 formulation, and the lowest with the IBU 90 formulation.

In consideration of all ibuprofen grades examined in this study, the sticking extent of the tablet formulations at a compaction force of 10 kN turned out to be inversely related to the mean particle size of the ibuprofen grades (Fig. 18).

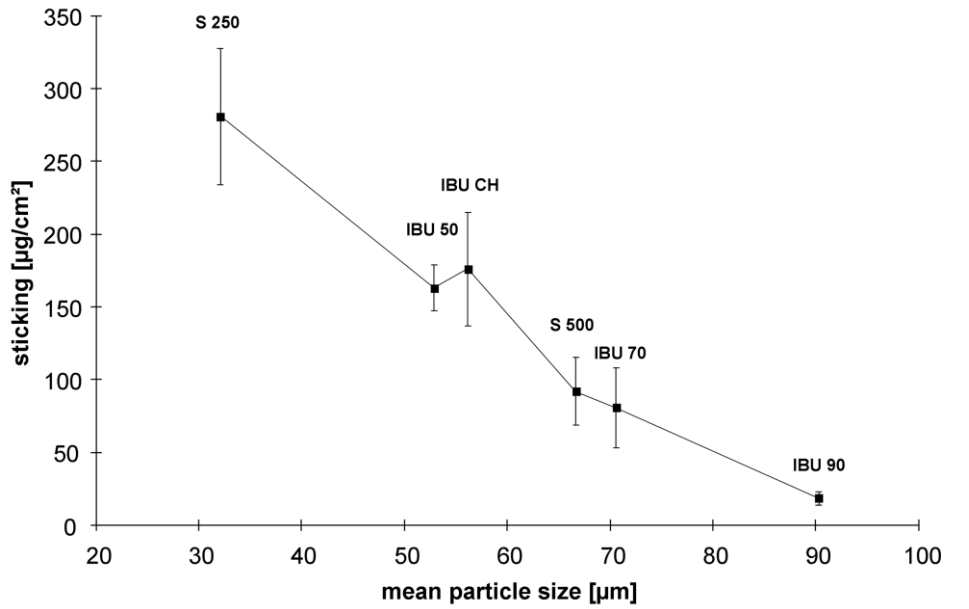

Fig. 18: Influence of the mean particle size on sticking of the investigated powder blends at a compaction force of 10 kN; means ± SD; n = 3.

Obviously, the larger the ibuprofen powder particles in the tablet formulations, the lower was the tendency to stick to the punch surfaces. Interestingly, ibuprofen grades with similar mean particle sizes such as IBU 70 and S 500 were found to cause sticking of the tablet formulations approximately to the same extent independent of their origin. The high sticking tendency of the tablet formulations, which contain small powder particles, may be explained by the increased surface area of these particles compared to that of larger powder particles. Thus, in the first phase of the sticking process small powder particles provide a larger contact area with the punch surface ultimately leading to more interactions at the interface and a higher sticking tendency. Moreover, as a consequence of the large surface area electrostatic charging of ibuprofen powder particles might be increased resulting in a stronger electrostatic attraction of these particles to the punch surface [125].

Tablet properties of non-sticking tablets

The properties of non-sticking tablets prepared with the rotary tablet press at a compaction force of 30 kN are summarized in Table 14. It is apparent that the properties of all tablets prepared with the different ibuprofen grades were acceptable with regard to the tablet tensile strength and tablet disintegration. However, the best tablet properties were obtained with the IBU 90-containing tablet formulation showing the lowest mass variation of tablets and the fastest tablet disintegration.

Table 14: Tablet properties of non-sticking tablets (rotary tablet press, compaction force 30 kN)

Ibuprofen grade	IBU 50	IBU 70	IBU 90	S 250 *	S 500	IBU CH
Mass variation [%]	0.80	0.54	0.43	1.42	0.70	0.58
Tensile strength [MPa]	1.85 (±0.17)	1.75 (±0.09)	1.73 (±0.12)	1.71 (±0.19)	1.61 (±0.09)	1.53 (±0.11)
Disintegration time [s]	34.0 (±1.1)	27.3 (±0.8)	15.3 (±0.5)	53.0 (±1.3)	26.0 (±0.6)	34.3 (±1.0)

* Sticking observed

The low mass variation of IBU 90 tablets may be explained by the appropriate flowability of the tablet formulation leading to uniform die filling during tableting. The fast disintegration of tablets prepared with IBU 90 is attributed to the porosity of the resulting tablets (Table 13). In comparison to tablets composed of the other ibuprofen grades, tablets with IBU 90 were more porous due to higher elasticity of the particles. Consequently, wicking, which is required for tablet disintegration, was promoted with IBU 90-containing tablets [193].

Apart from disintegration, the tablet tensile strength is also directly related to the porosity of the tablets. Thus, among ibuprofen grades of the same origin, the tablet tensile strength tended to decrease with an increase of the mean particle size. This results from the lower specific surface area of the larger powder particles, which provide less contact area for bonding and mechanical interlocking during compaction.

The drug release profiles of the tablets are displayed in Fig. 19. In accordance with the Ph. Eur. the investigated tablet formulations met the specification for immediate release tablets, as with all tablets drug release was finished within 10 min. However, drug release from IBU 90-containing tablets was much faster than that from tablets consisting of the ibuprofen grade S 250. The comparatively slow drug release from S 250 tablets may mainly be explained by the low porosity of the tablets resulting from the small particle size (Table 13). As a result of the low porosity, disintegration of S 250-containing tablets was decelerated and thus the drug dissolution rate was decreased.

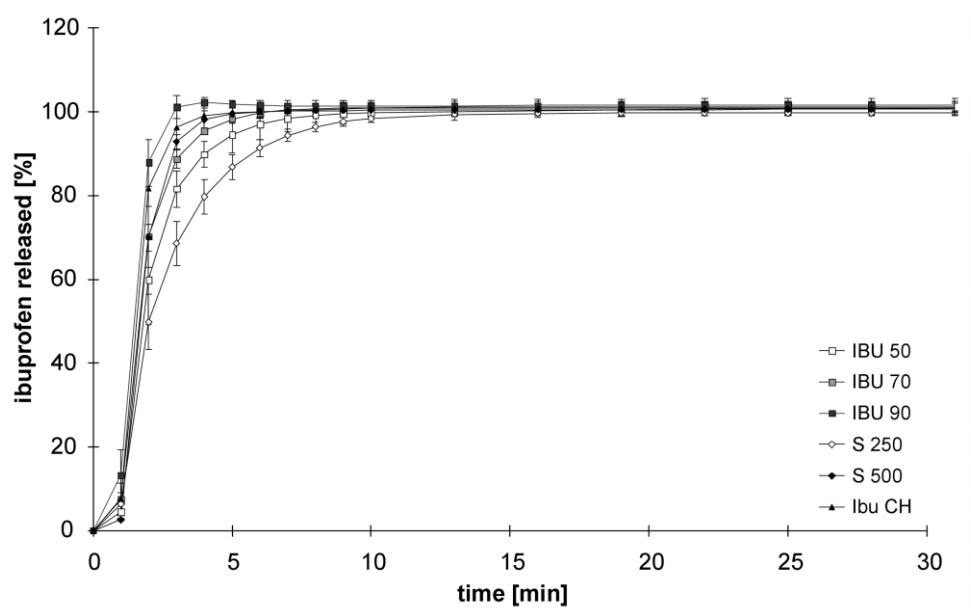

Fig. 19: Drug release profiles of tablets (ibuprofen content 70 %, compaction force 30 kN); means ± SD, n = 6.

3.4. Conclusion

The investigated ibuprofen grades showed a considerable effect on the flowability of the powder blends as well as on the compaction properties of the tablet formulations. It could be shown that flow and compaction properties are strongly dependent on the mean particle size of the different ibuprofen grades. The best compaction and tablet properties were observed with the tablet formulation containing IBU 90. Resulting from its large mean particle size, IBU 90 provided appropriate flowability and a low sticking tendency of the respective tablet formulation. Moreover, the IBU 90 formulation showed acceptable compactibility, fast disintegration of the tablets, and rapid drug dissolution.

In contrast, the ibuprofen grade S 250 with the smallest mean particle size accompanied by poor flowability, pronounced sticking, and slowest disintegration and drug dissolution was found to be unsuitable for direct compression.

The origin of ibuprofen was found to be less critical. Ibuprofen grades with a similar mean particle size purchased from different suppliers turned out to show similar flow and compaction properties.

4. How suitable is the measurement of take-off forces for detection of sticking during direct compaction of various ibuprofen tablet formulations?

How suitable is the measurement of take-off forces for detection of sticking during direct compaction of various ibuprofen tablet formulations?

Abstract

Sticking of tablet formulations to punch surfaces is one of the most common problems observed during tablet manufacture. An inline method proposed for detection of sticking during compression is the measurement of take-off forces, which occur when tablets are detached from the lower punch surface. It has been postulated that the tablet take-off force is a direct indicator of the sticking tendency of a tablet formulation.

In the present study, the take-off forces measured during direct compaction of sticking ibuprofen tablet formulations were evaluated and compared to the sticking extent of these tablets quantified by HPLC analysis of ibuprofen.

As expected, sticking to the lower punch was increased with an increase of the ibuprofen content in the investigated tablet formulations. However, data obtained from take-off force measurements did not correlate with the quantified amount of sticking. Although pronounced sticking was observed, the measured tablet take-off forces remained low even at high drug contents. These results indicate that the tablet take-off force is not a direct indicator of the sticking tendency of ibuprofen tablet formulations. It is suggested that the evaluation of take-off force data requires a differentiated approach. A new interpretation of take-off force data is presented in this chapter.

4.1. Introduction

During tablet manufacture sticking of tablet formulations to punch surfaces is one of the most common problems observed. It is caused by high adhesion forces between punch and tablet surface. Strong adhesion to the upper punch may lead to sticking of even whole tablets and may cause a second compression of these tablets in the following compaction cycle together with the powder/granules already present in the die. This may result in serious damage to the punches and the tablet press. In contrast, sticking of whole tablets to the lower punch may cause demolition of the take-off bar on rotary die tablet presses accompanied by a destruction of the tablets. However, in most cases adhesion only leads to a powder layer sticking to the punches resulting in rough tablet surfaces or incomplete engravings.

Sticking is usually detected after compaction runs by visual inspection of tablets and punch surfaces. In the literature, several analytical methods for characterization and/or quantification of sticking have been described with different excipients or powder blends. To estimate the sticking tendency of powder particles, direct measurement of adhesion forces between powder particles and metal surfaces were performed with contact mode atomic force microscopy (AFM) [114] and with a centrifuge technique measuring the required centrifugal force to detach powder particles from a stainless steel disk [105, 110, 111, 149].

With regard to tablet manufacture, chemical analysis of the drug within the sticking residue was found to be a useful method to assess tablet sticking [115, 125, 145, 164]. In a recent publication, Mullarney et al. introduced a removable upper punch to determine the sticking tendency of a tablet formulation by weighing the mass of powder adhered to the punch tip [162]. However, the disadvantage of these methods is that the measurements are carried out either after compaction runs or entirely independent of tablet manufacture. Thus, methods that allow the determination of the sticking tendency of a tablet formulation during the compaction process would be advantageous.

Waimer et al. performed inline measurements with an eccentric press equipped with an instrumented upper punch that measures the adhesion force in the moment of punch detachment from the upper tablet surface [165]. It could be shown that this device is a helpful tool for quantification of sticking providing reliable and reproducible information. However, this specially designed upper punch instrumentation is not easily transferable to a rotary tablet press.

Another promising inline method for detection of sticking during tablet manufacture with a rotary tablet press is the measurement of take-off forces, which occur when tablets are detached from the lower punch surface. Two publications by Augsburger et al. deal with the measurement of take-off forces using a take-off bar instrumented with strain gauges [166, 167]. Take-off force signals obtained by this type of instrumentation are described as attenuated oscillations [168]. During compaction cycles tablets usually remain in front of the take-off bar for a certain period of time. Thus, multi-peak take-off force signals are obtained caused by repeated contact of the tablets with the measuring device. It has been reported that the sensitivity of strain gauge instrumented take-off bars might be too low for detection of rather low take-off forces of well lubricated tablet formulations [169]. Improvement of the sensitivity of take-off force measurements was achieved by using quartz load cell instrumentation [170]. However, for the measurement of take-off forces rotary tablet presses are usually equipped with take-off bars instrumented with strain gauges, as those provide easy handling and cost-efficiency. Wang et al. examined the sticking tendency of low dose tablet formulations containing ketoprofen, ibuprofen and flurbiprofen, respectively, using visual inspection of punch surfaces and evaluation of ejection forces and take-off forces [156]. The authors postulated that the tablet take-off force is a direct indicator of the sticking tendency of the investigated powder blends, whereas the ejection force is not.

The aim of the present study was to evaluate the suitability of take-off force measurements for detection of sticking during direct compression of various high dose ibuprofen formulations. Ibuprofen was chosen as model drug because it shows a high tendency of powder layer sticking to punch surfaces during tablet manufacture [125, 145, 164].

The sticking tendency of ibuprofen is attributed to its poor compactibility, which is primarily caused by pronounced elastic relaxation of the powder particles resulting in a low tablet tensile strength [96, 129, 199, 200]. Another reason for the stickiness of ibuprofen might be its low melting point of 75 – 78 °C (Ph. Eur.). Bechard et al. reported that localized high temperature zones caused by consolidation and friction during powder compaction could exceed the melting point of low-melting materials ultimately leading to increased adhesion of powder particles to punch surfaces [137]. Moreover, electrostatic charging of powder particles is expected to affect the sticking tendency of ibuprofen depending on the punch surface material [125].

In the present study, the actual sticking extent of ibuprofen was examined by HPLC analysis of the drug within the sticking residue after each compaction run to estimate the suitability of take-off force measurements for detection of sticking during powder compaction. The sticking extent to the lower punch surface was quantified, as the take-off force is related to the detachment of tablets from this punch surface. The quantified amount of sticking was evaluated with regard to a possible correlation with the respective take-off forces recorded during compaction runs. Moreover, the influence of drug content and compaction force on the sticking tendency of ibuprofen tablet formulations was investigated.

4.2. Materials and methods

4.2.1. Materials

Ibuprofen (Caelo, Hilden, Germany); Ludipress®: co-processed excipient consisting of 93 % α-lactose monohydrate, 3.5 % povidone, and 3.5 % crospovidone (BASF, Ludwigshafen, Germany); Microcelac® 100: co-processed excipient consisting of 75 % α-lactose monohydrate and 25 % microcrystalline cellulose (Meggle, Wasserburg, Germany); Magnesium stearate (Fagron, Barsbüttel, Germany).
All other reagents used were of analytical grade.

4.2.2. Methods

Preparation of powder blends

Ibuprofen was disaggregated by sieving (1000 µm mesh) prior to the preparation of powder blends because of its high tendency of forming powder agglomerates. As filler-binder for the ibuprofen powder blends Ludipress® was selected, as it shows excellent flow and compaction properties [202]. In addition, Microcelac® was considered to be a useful filler-binder, as it is supposed to be suitable for compaction of poorly flowable and high dose active ingredients [206, 207]. The drug content in the investigated powder blends was 50 %, 70 % and 90 % [w/w], respectively.

Each formulation was prepared by blending the ingredients for 10 min using a Turbula blender at 72 rpm (T2F, W.A. Bachofen, Muttenz, Switzerland). After addition of 0.5 % [w/w] magnesium stearate as lubricant mixing of the powder blends was continued for 3 min. Prior compaction each formulation was stored in an air-conditioned room at 21°C and a relative humidity of 45 % for at least 72 h.

Flowability of powder blends

Flow properties of all powder blends were determined by measurement of the Hausner ratio and the powder flow rate. Prior to flowability testing of the plain filler-binders, magnesium stearate was added as lubricant (0.5 % [w/w]). Mixing was again performed with the Turbula blender at 72 rpm for 3 min. The Hausner ratio was calculated as the quotient of bulk and tapped volume. Bulk and tapped volumes were determined according to the Ph. Eur. with a jolting volumeter (STAV 2003, J. Engelsmann, Ludwigshafen, Germany). The mass-related flow rate [g/s] was measured using a flowability tester (BEP2, Copley Scientific, Nottingham, UK) equipped with a stainless steel flow funnel (orifice diameter 10 mm).

Compaction of powder blends

Compaction studies were performed in an air-conditioned room at 21 °C and a relative humidity of 45 %. Tablets were prepared with an instrumented rotary tablet press (XL 100, KORSCH, Berlin, Germany) equipped with flat-faced and hard-chromium plated punches of 10 mm diameter. A speed force feeding system was used at 10 rpm because of the poor flowability of the ibuprofen-containing powder blends. The target tablet weight was 300 mg (RSD < 1.5 %).

Tableting was performed at compaction forces of 7, 13, and 19 kN, respectively. The compression speed was set to 20 rpm with a corresponding dwell time of 74.7 ms.

Take-off force measurements

Generally, on a rotary tablet press tablets are detached by the stationary take-off bar after ejection. In the present study, tablet take-off forces were recorded using a take-off bar instrumented with strain gauges. Due to an initialization period of the data acquisition system, take-off force measurements were started after compaction of 10 tablets recording the take-off forces of the following 10 tablets. From each compaction run the highest value of take-off force was used for evaluation. Data acquisition was carried out with an updated and internally improved version of the Pharma Research® software (KORSCH, Berlin, Germany).

Quantification of powder layer sticking

The extent of powder layer sticking (called sticking throughout this paper) was quantified by HPLC analysis of ibuprofen present in the sticking residue adhered to the lower punch surface. In a preliminary study a gravimetric analysis of the sticking residue was performed to ensure that HPLC analysis of ibuprofen was representative for quantification of total sticking of the investigated formulations.
Following compaction runs of 25 tablets each, the sticking residue was removed from the lower punch surface with a swab method using a Q-tip soaked with methanol. Subsequently, the Q-tip was immersed in 5 ml of methanol. HPLC quantification of ibuprofen was carried out after an extraction period of at least 24 h ensuring total drug extraction from the Q-tip.

The HPLC system (Kontron Instruments, Germany) was equipped with a LiChroCART® RP-18 (5 µm) column (Merck, Darmstadt, Germany). The flow rate was adjusted to 1 ml/min and the sample volume injected was 20 µl. The mobile phase consisted of 60 % acetonitrile and 40 % phosphate buffer (pH 3.0). UV detection of ibuprofen was performed at 242 nm. The absorbance was linear in a concentration range between 10 and 850 µg/ml (R^2 = 1.000). The limit of quantification was calculated to be 5 µg/ml. The extent of sticking is expressed as amount ibuprofen adhered to the punch surface area [µg/cm²].

Characterization of tablets

After a relaxation time of at least 24 h following ejection of the tablets, the crushing strength, the diameter, and the thickness of 10 tablets were determined with a hardness tester (TBH 30, Erweka, Heusenstamm, Germany). The tablet tensile strength was calculated using the equation published by Fell et al. [189] (eq. 3):

$$\sigma = \frac{2 \cdot F}{\pi \cdot d \cdot t} \qquad \text{(eq. 4)}$$

where σ is the tablet tensile strength [MPa], F the crushing strength [N], d the tablet diameter [mm], and t the tablet thickness [mm].

The tabletability of the tablets was evaluated by plotting tablet tensile strength versus compaction force. A minimum tablet tensile strength of 0.85 MPa was regarded as sufficient, as this value corresponds to a tablet crushing strength of approximately 50 N.

4.3. Results and discussion

Flowability of ibuprofen and powder blends

In Table 15 the flow properties of ibuprofen and the investigated powder blends are summarized. It is well-known that ibuprofen exhibits very poor flow and compaction properties. The Hausner ratio of ibuprofen was determined to be 1.64. According to the Ph. Eur. a Hausner ratio exceeding 1.34 is considered to be an indication of poor flowability. In fact, ibuprofen was observed to be not free-flowing and thus, a powder flow rate was not determinable. The poor flowability of ibuprofen may be explained by the morphology (Fig. 20a) as well as the high cohesivity and adhesivity of the powder particles [112, 132].

Table 15: Flowability of the powder blends consisting of either Ludipress® (L) or Microcelac® (M) as filler-binders and varying percentages of ibuprofen; means ± SD; n = 3; all formulations contain 0.5 % (w/w) of magnesium stearate

Formulation	Hausner ratio	Powder flow rate [g/s]
Ibuprofen [a)]	1.64 ± 0.04	n.d. [b)]
L-0	1.19 ± 0.00	8.11 ± 0.06
L-50	1.34 ± 0.01	3.68 ± 0.97
L-70	1.46 ± 0.02	1.60 ± 0.94
L-90	1.59 ± 0.05	n.d [b)]
M-0	1.18 ± 0.00	6.43 ± 0.03
M-50	1.29 ± 0.00	2.45 ± 0.68
M-70	1.42 ± 0.02	0.84 ± 0.63
M-90	1.61 ± 0.06	n.d. [b)]

a) without magnesium stearate
b) not determined

In contrast, Ludipress® (L-0) and Microcelac® (M-0) showed good flowability manifesting itself in a low Hausner ratio and a high powder flow rate (Table 15). The excellent flow properties of these co-processed excipients result from the spherical shape and the relative smooth surface of the powder particles (Fig. 20b, 20c) [202, 207].

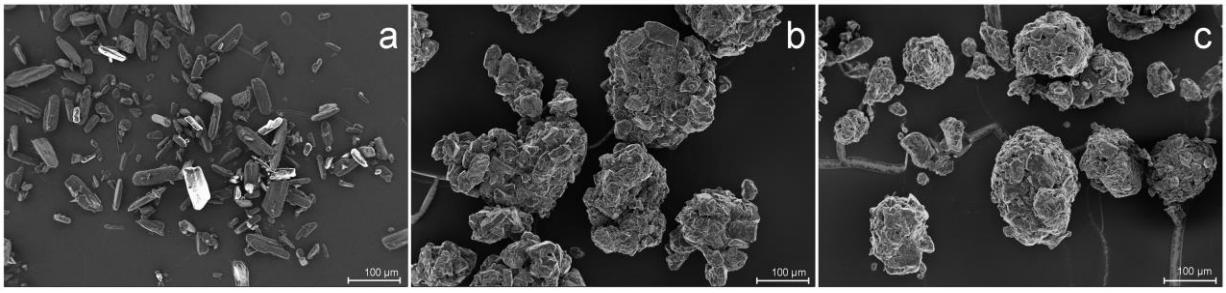

Fig. 20: SEM images of (a) ibuprofen, (b) Ludipress®, and (c) Microcelac® (LEO 1525, LEO Elektronenmikroskopie, Oberkochen Germany).

Furthermore, due to the unique manufacturing processes both excipients are reported to show good compaction properties. Whereas Ludipress® consists of α-lactose monohydrate coated with povidone and crospovidone, in Microcelac® α-lactose monohydrate is co-processed with microcrystalline cellulose using a spray drying technique. Because of their manufacturing processes, Ludipress® and Microcelac® exhibit dual deformation behavior: consolidation by brittle fracture as well as plastic deformation [17, 18]. Crystalline α-lactose monohydrate is reported to show primarily deformation by brittle fracture [204]. The good compactibility of Ludipress® however is attributed to the plastic deformation behavior of the amorphous components povidone, crospovidone and the amorphous portion of lactose, which is generated during co-processing of the components [202]. The good binding properties of Microcelac® are also attributed to increased plasticity of the co-processed powder particles as a result of the spray drying process.
Because of the excellent flow and compaction properties, Ludipress® and Microcelac® were considered to be useful filler-binders for direct compaction of the poorly flowable and compactible ibuprofen.

From the data presented in Table 15 it is obvious that the flowability of the ibuprofen-containing powder blends is strongly affected by the drug content. With an increase of the ibuprofen content in the powder blends, an increase of the Hausner ratio and a decrease of the powder flow rate were observed. In accordance with the Ph. Eur. the powder blends containing 50 % of ibuprofen (L-50, M-50) showed passable flow properties, whereas powder blends with a drug content of 90 % (L-90, M-90) turned out to be not free-flowing and the Hausner ratios indicated very poor flowability. Thus, to ensure uniformity of the tablet weight, a speed force feeding system was required for compaction studies with the rotary tablet press.

Tabletability of powder blends

Tabletability is the tensile strength of a tablet in dependence on the applied compaction force. The influence of the ibuprofen content on the tabletability of the investigated powder blends is displayed in Fig. 21. It is apparent that the tabletability of the formulations is also affected by an increase of the drug content. Interestingly, the tensile strength of tablets containing either Ludipress® or Microcelac® is influenced by the ibuprofen content to approximately the same extent. Obviously, the tablet tensile strength decreases with increasing ibuprofen content: at compaction forces as high as 19 kN the tensile strength of tablets was observed to decrease from 1.9 MPa (L-50) to 1.0 MPa (L-90) in the case of Ludipress® formulations, and from 2.0 MPa (M- 50) to 0.9 MPa (M-90) in the case of Microcelac® formulations. However, at compaction forces of 13 kN and higher, with all powder blends the desired minimum tablet tensile strength of 0.85 MPa was obtained independent of the composition of the blends.

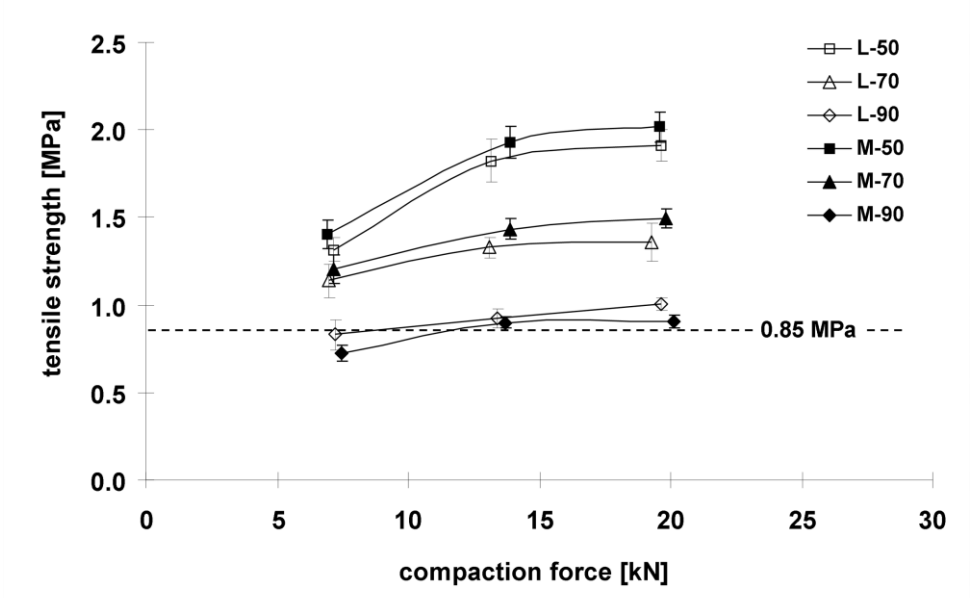

Fig. 21: Tabletability of the powder blends consisting of either Ludipress® (L) or Microcelac® (M) and varying percentages of ibuprofen; means ± SD, n = 10.

Quantification of powder layer sticking

Besides poor flow and compaction properties, ibuprofen exhibits a high tendency to stick to punch surfaces during tablet manufacture. Generally, the sticking process is divided into two phases [115]: the first phase is characterized by an interaction between adhesive powder particles and the punch surface. This interaction may lead to sticking to the punch surface if adhesive forces exceed the cohesive bonding forces within the tablet. In the second phase of the sticking process an increase of powder layering is observed with extended run time of the tablet press. This build-up of a sticking layer on the punch surfaces is primarily caused by auto-adhesive interactions between powder particles within the tablet formulation and those already adhered to the punch surface. In this study, the sticking extent was quantified after 25 compression cycles to reflect the first phase of the sticking process.

The extent of powder layer sticking of ibuprofen to the lower punch surface is displayed in Fig. 22. With the plain filler-binders (ibuprofen content 0 %) no sticking was observed. As expected, with increasing ibuprofen content in the tablet formulations the amount of ibuprofen adhered to the punch surface was also increased. Certainly, formulations with higher drug contents contain a higher number of adhesive ibuprofen particles, which are able to interact with the punch surface and thus, these interacting particles may adhere to it during powder compaction. Ibuprofen was observed to cause sticking only to the centre of the punch surfaces with formulations containing less than 50 % of the drug independent of the compaction force (data not shown). However, ibuprofen contents of 50 % and above lead to complete powder layering on the lower punch surface. Maximum sticking was observed at the lowest compaction force of 7 kN with both, Ludipress® and Microcelac® formulations containing 90 % of ibuprofen (Fig. 22).

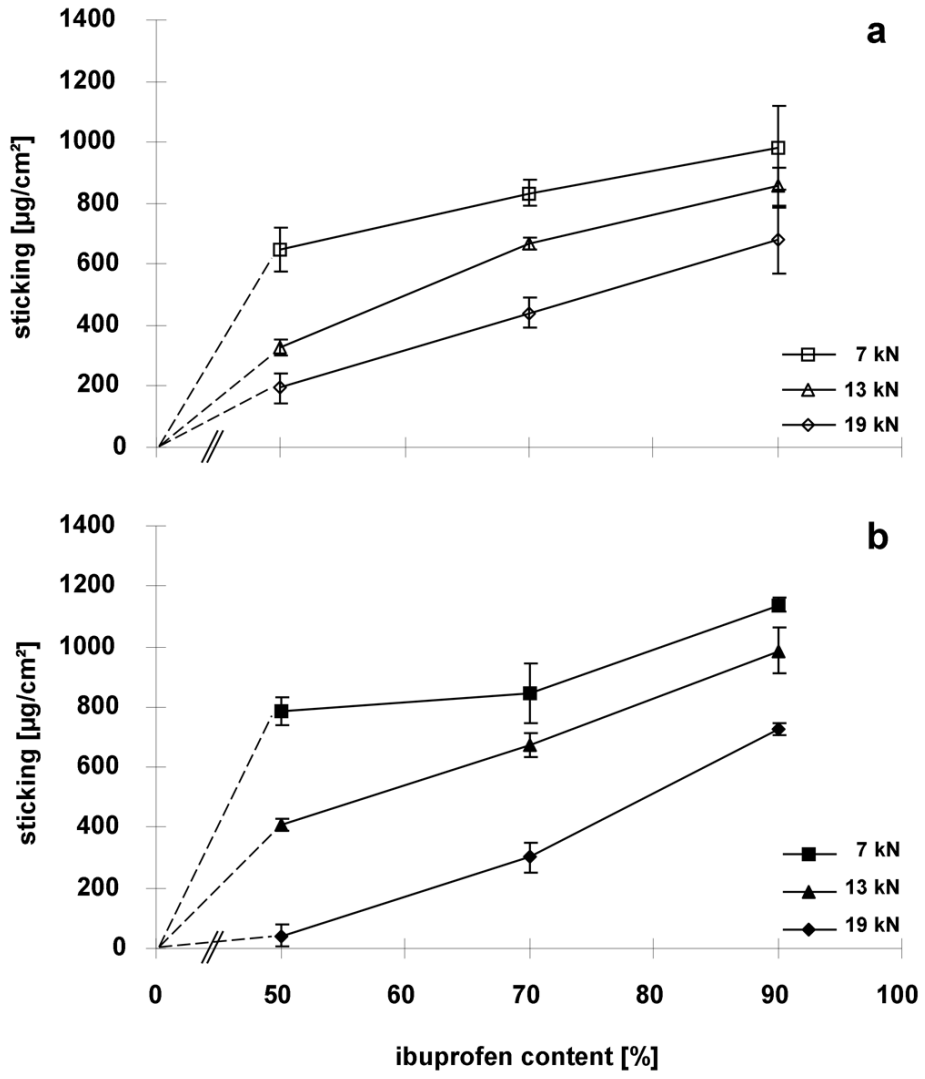

Fig. 22: Influence of the ibuprofen content on sticking to the lower punch surface at various compaction forces; means ± SD, n = 5; (a) Ludipress® formulations, (b) Microcelac® formulations.

The influence of the compaction force on the sticking extent of the investigated formulations is shown in Fig. 23. With all formulations the quantity of ibuprofen adhered to the punch surface at a compaction force of 19 kN was considerably lower than that at a compaction force of 7 kN. In general, the extent of sticking depends on the adhesion force (F_{ad}) between tablet and punch surface in relation to the cohesion force (F_{co}) within the tablet. Sticking to punch surfaces occurs if the cohesive bonding within the tablet is not as strong as adhesion to the punch surface ($F_{ad} > F_{co}$).

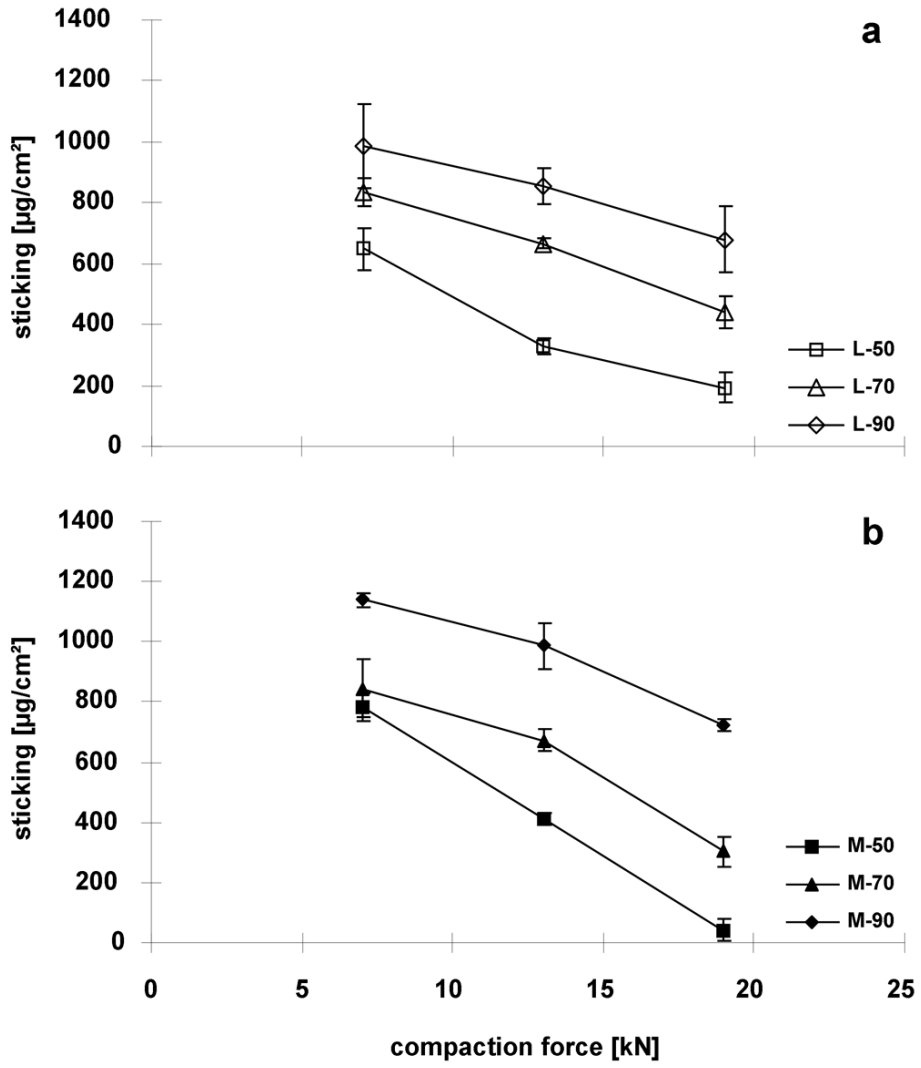

Fig. 23: Impact of the compaction force on sticking to the lower punch; means ± SD, n = 5; (a) Ludipress® formulations, (b) Microcelac® formulations.

From tabletability data (Fig. 21) it is apparent that tablets prepared with compaction forces of 19 kN exhibited a higher tensile strength than tablets prepared with lower compaction forces. As the tensile strength is an indirect measure of the bonding strength within tablets [192], it may be hypothesized that an increase of tablet hardness is a result of an increase of cohesive bonding within the tablets. Generally, tablet formation requires interparticulate attraction and the predominant bonding mechanisms during tablet formation are supposed to be mechanical interlocking of particles, intermolecular forces, and solid bridges resulting from localized melting [55, 58].

Consolidation of the powder bed and deformation of the particles initially leads to mechanical interlocking of the particles and thus, to an increase of the contact area between the particles. The higher the applied compaction force the higher is the contact area between compressed solid particles resulting in an increase of short range attractive forces such as Van der Waals forces and hydrogen bonding. The overall tablet strength is dependent on the magnitude of the compaction force, the deformation behavior of the particles, and the extent of elastic recovery [208]. Thus, cohesive bonding within tablets compacted at high compaction forces is usually stronger than that of tablets prepared with lower compaction forces. Therefore, high compaction forces lead to a shift of the balance between cohesive bonding within the tablet (F_{co}) and adhesion to the punch surface (F_{ad}) into the direction of higher cohesion ultimately resulting in a reduction of the sticking tendency.

Take-off force measurements

After ejection, tablet detachment is induced by the stationary take-off bar on rotary tablet presses. The forces, which are involved in tablet detachment from the lower punch surface, are displayed in Fig. 24. During the take-off event a tangential shear stress is applied to the tablet, and a certain detachment force (F_{det}) is required to overcome either the adhesive forces (F_{ad}) between tablet and punch surface in the case of non-sticking tablets or the cohesive force (F_{co}) within the tablet in the case of sticking tablets.

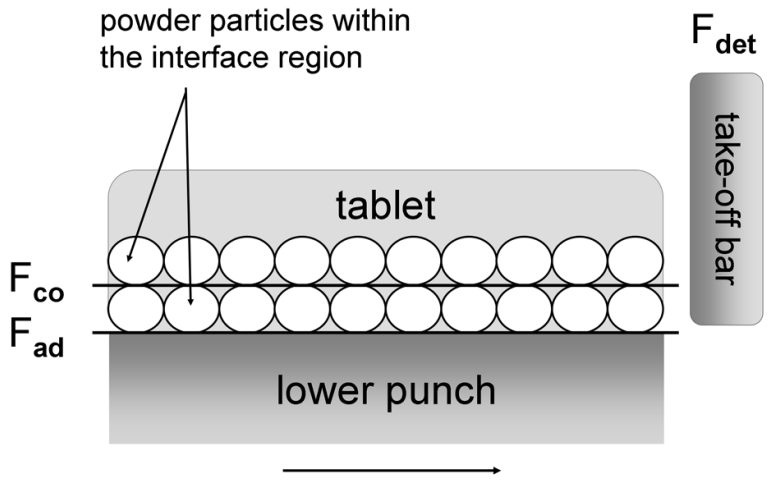

Fig. 24: Forces involved in tablet detachment from the lower punch: F_{det}, detachment force induced by the take-off bar; F_{ad}, adhesive force between tablet and punch surface; F_{co}, cohesive force within the powder layers/tablet.

The take-off forces required to detach sticking ibuprofen tablets from the lower punch are displayed in Fig. 25. The recorded take-off forces were low with all ibuprofen tablet formulations although pronounced sticking was observed. There is no obvious correlation between the extent of sticking and the take-off forces recorded during tablet detachment. While the sticking extent was found to increase at higher drug contents (Fig. 22), the measured take-off forces remained low independent of the filler-binder used. Furthermore, the take-off forces recorded with these tablet formulations showed no dependence on the compaction force at least at high drug contents of 70 % and 90 %, respectively. Again, these results are in contrast to the quantified amount of sticking to the lower punch surface, which was found to be strongly affected by both, the drug content and the compaction force (Fig. 23).

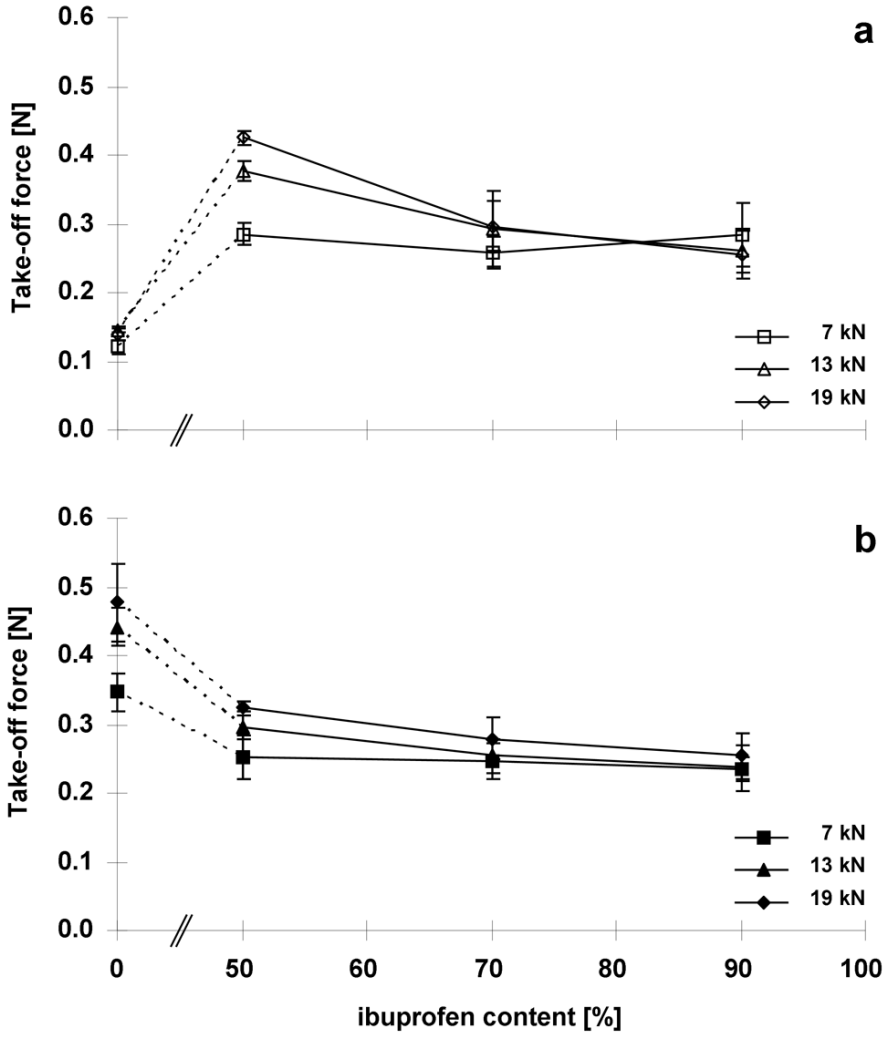

Fig. 25: Influence of the ibuprofen content and the compaction force on take-off forces recorded during tablet detachment; means ± SD, n = 5; (a) Ludipress® formulations, (b) Microcelac® formulations.

In addition to tablet take-off forces recorded during tablet detachment of sticking ibuprofen formulations, Fig. 25 also provides take-off force data of tablets composed of the non-sticking filler-binders Ludipress® and Microcelac® (ibuprofen content 0 %). With the Ludipress® formulation take-off forces lower than 0.150 N were measured independent of the applied compaction forces. In comparison, sticky ibuprofen- containing Ludipress® formulations lead to higher tablet take-off forces (Fig. 25a). From these results it might be postulated that sticking to the lower punch usually results in increased tablet take-off forces, as it is described in the literature [156, 170]. Thus, one might conclude that the measurement of tablet take-off forces is useful for detection of sticking during tablet manufacture.

However, it is interesting to note that the results of take-off force measurements obtained during tableting of the investigated Microcelac® formulations do not support the postulation mentioned before. It is noticeable that the take-off forces of non-sticking plain Microcelac® tablets were considerably higher than those recorded with the sticky, ibuprofen-containing Microcelac® formulations (Fig. 25b).

The take-off force of the non-sticking tablets composed of the plain filler-binders represents the true adhesion force between the tablets and the lower punch surface. The measured take-off forces of Microcelac® tablets were considerably higher than those of Ludipress® tablets. Obviously, during compaction of plain Ludipress® tablets less adhesive interactions to the hard-chromium plated punch surface occurred than during tableting of plain Microcelac®. Mitrevej and Augsburger investigated tablet adhesion of three commonly used direct compression filler-binders, namely microcrystalline cellulose, α-lactose monohydrate and compressible sugar (sucrose), using take-off force measurements [166, 167]. A strong adhesion of particularly microcrystalline cellulose to the punch surface was found, sticking however was not observed. Consequently, as Microcelac® contains 25 % microcrystalline cellulose, the comparably high take-off forces recorded during detachment of Microcelac® tablets in contrast to Ludipress® tablets might be attributed to the adhesion behavior of the microcrystalline cellulose portion.

These results indicate that the interpretation of take-off force data is more complex than proposed in the literature so far. First of all, two types of tablet detachment mechanisms have to be considered, namely tablet detachment either by adhesion failure or cohesion failure (Fig. 26).

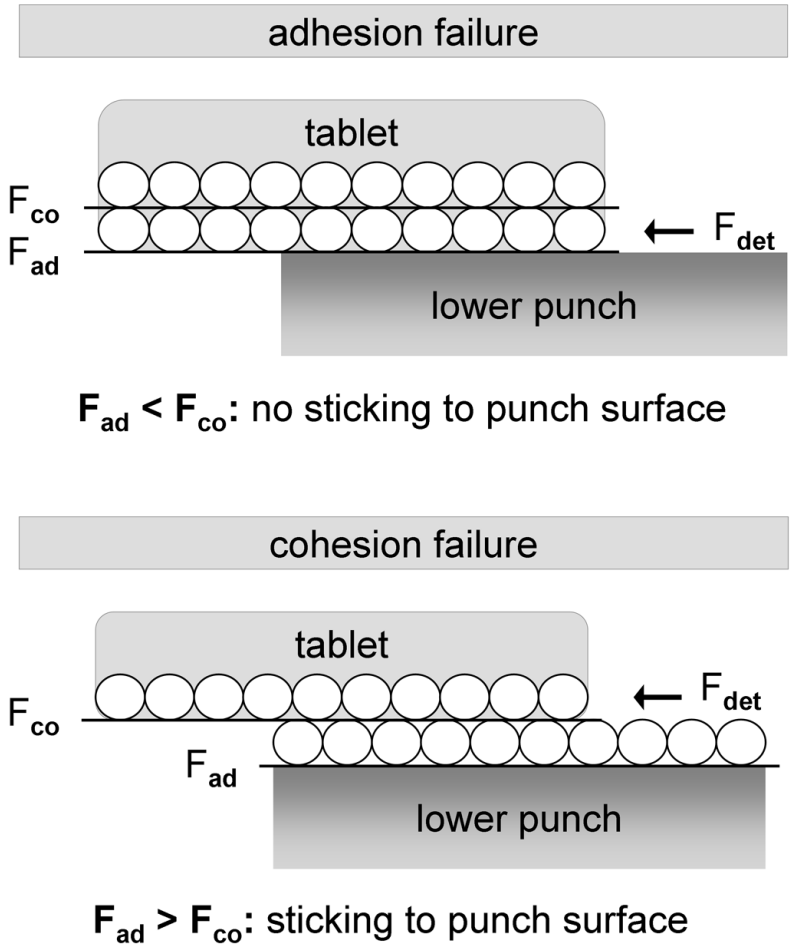

Fig. 26: Tablet detachment from the lower punch by adhesion failure and cohesion failure.

It is of great importance to distinguish between these mechanisms because a competition between adhesion forces (F_{ad}) and cohesion forces (F_{co}) takes place during tablet detachment from the lower punch affecting the take-off force.

If the adhesive forces between a tablet and the punch surface are lower than the cohesion forces within the tablet ($F_{ad} < F_{co}$), detachment of tablets from the lower punch surface takes place by the mechanism of adhesion failure. In this case powder layer sticking to the lower punch surface will not occur. It has already been reported that tablet detachment from punches by the mechanism of adhesion failure (leaving no sticking residue) leads to tablet detachment forces representing the true adhesive forces between the tablet and the punch surface [165].

In contrast, if the adhesive forces between a tablet and the punch surface exceed the cohesive bonding forces within the powder layers of the tablet ($F_{ad} > F_{co}$), tablet detachment from the lower punch occurs by the mechanism of cohesion failure. In that case, detachment of tablets takes place by disruption of weakly bound powder layers within the tablet leaving a sticking residue on the lower punch surface. Thus, take-off forces recorded during detachment of sticking tablets (cohesion failure) are a measure of the cohesive bonding strength within the tablet.

With regard to the presented data it is postulated that tablets composed of non-sticking Ludipress® or Microcelac®, respectively, were detached from the lower punch surface by adhesion failure, and consequently the measured take-off forces represent the true adhesion forces between the tablets and the punch surface. In contrast, detachment of sticking ibuprofen tablets occurred by cohesion failure and the recorded take-off forces represent rather the cohesive bonding strength within the tablets than adhesion to the punch surface. Therefore, it is concluded that the take-off forces resulting from the two different tablet detachment mechanisms cannot be compared and thus for evaluation of take-off force data a more differentiated approach is necessary.

In Table 16 a proposal for the interpretation of take-off force data is presented. High take-off forces represent either strong adhesion forces in the case of adhesion failure or strong cohesion forces in the case of cohesion failure.

Table 16: Interpretation of take-off force data

adhesion failure			cohesion failure		
$F_{ad} < F_{co}$ no sticking			$F_{ad} > F_{co}$ sticking		
Force balance	F_{ad}	$F_{take\text{-}off}$	**Force balance**	F_{co}	$F_{take\text{-}off}$
$F_{ad} \leq F_{co}$: F_{ad} — F_{co}	high	high	$F_{ad} \geq F_{co}$: F_{ad} — F_{co}	high	high
$F_{ad} \leq F_{co}$: F_{ad} — F_{co}	low	low	$F_{ad} \geq F_{co}$: F_{ad} — F_{co}	low	low
$F_{ad} \ll F_{co}$: F_{ad} — F_{co}	high	high	$F_{ad} \gg F_{co}$: F_{ad} — F_{co}	high	high
$F_{ad} \ll F_{co}$: F_{ad} — F_{co}	low	low	$F_{ad} \gg F_{co}$: F_{ad} — F_{co}	low	low

On the one hand, with non-sticking tablets (adhesion failure) which exhibit a high cohesive bonding strength that exceeds only marginally the adhesion forces ($F_{ad} \leq F_{co}$), a sufficiently high resistance to the shear stress applied during tablet take-off is present ultimately leading to high take-off forces and no sticking.

On the other hand, as the take-off force of sticking tablets (cohesion failure) is assumed to be a measure of the cohesive bonding strength, high take-off forces will be obtained during tableting of materials which exhibit good tablet binding properties, the adherence to the punch surface however still outweighing tablet cohesion ($F_{ad} \geq F_{co}$). Consequently, a high detachment force is required for breakup of the cohesive bonding within the powder layers of these tablets.

In contrast, rather low take-off forces will be measured with non-sticking tablet formulations (adhesion failure), the cohesive bonding strength of which strongly exceeds the adhesion forces between tablets and the lower punch surface ($F_{ad} \ll F_{co}$). Thus, these tablets are easily detached from the lower punch surface without showing sticking.
As a result of poor binding properties, low take-off forces will also be measured with sticking tablet formulations (cohesion failure) exhibiting weak cohesive bonding and pronounced adhesive interactions with the punch surface ($F_{ad} \gg F_{co}$).

In this study, take-off forces obtained with sticking ibuprofen formulations were rather low even at high drug contents. Results from sticking quantification indicate that adhesion forces between tablet and lower punch surface were increased with an increase of the ibuprofen content in the tablet formulations. However, the tablet tensile strength was reduced with increasing drug content suggesting a decrease of cohesive bonding. Resulting from these poor binding properties of high dose ibuprofen tablet formulations, tablets were easily detached from the lower punch surface by means of cohesion failure ultimately leading to pronounced sticking and low take-off forces.

4.4. Conclusion

A correlation between take-off force data recorded during direct compaction of high dose ibuprofen tablet formulations and the extent of sticking could not be shown. Despite pronounced sticking the measured tablet take-off forces remained low even at high drug contents. These results indicate that the tablet take-off force is not a measure of the sticking tendency of ibuprofen tablet formulations and thus, the measurement of take-off forces is unsuitable for detection of sticking during direct compression.

It is suggested that the evaluation of take-off forces requires a differentiated approach. First, the mechanism of tablet detachment from the lower punch surface has to be taken into consideration: tablets may be detached from punch surfaces either by adhesion failure (no sticking) or cohesion failure (sticking). Moreover, depending on the mechanism of tablet detachment, the level of the recorded take-off forces results from the balance of the adhesion force (F_{ad}) between tablet and punch surface in relation to the cohesion force within the tablet (F_{co}).

In conclusion, the sticking tendency of a tablet formulation is not necessarily be detected or predicted by means of take-off force measurements.

5. Investigation of the anti-adherent performance of the lubricant magnesium stearate during direct compaction of various excipients using differently coated punches

Investigation of the anti-adherent performance of the lubricant magnesium stearate during direct compaction of various excipients using differently coated punches

Abstract

Lubricants are added to tablet formulations in small quantities to reduce friction during compaction and tablet ejection ("true" lubricant), to enhance flow properties (glidant), and/or to prevent sticking to the punch surfaces (anti-adherent).

Sticking to punch surfaces is one of the most common problems observed during tableting and it is primarily attributed to an insufficient anti-adherent performance of the applied lubricant. If sticking is observed, the composition of the tablet formulation usually is changed with regard to the lubricant type and/or content. Apart from that, punch tip coatings are another approach affecting tablet adhesion to punch surfaces and thus may be useful in prevention of sticking.

In the present study, the anti-adherent performance of the most frequently used tablet lubricant magnesium stearate during direct compaction of various tableting excipients was investigated and the influence of different punch tip coatings on the anti-adherent performance was analyzed.

The anti-adherent performance of magnesium stearate was found to be affected by the investigated punch tip coatings, although to a different extent. In comparison to uncoated punches, sticking was successfully prevented by application of hard chromium-plated punches or Chromium Nitride-coated punches, allowing a reduction of the lubricant concentration in the tablet formulation. Thus, for these two types of punch surface modification a synergistic effect of lubricant and punch tip coating for prevention of sticking can be postulated. In contrast, tableting with Titanium Nitride-coated punches revealed no improvement of the anti-adherent performance of the lubricant.

5.1. Introduction

Lubricants are one of the most essential excipients in tablet manufacture and therefore have been used since the early days of tableting. Usually, lubricants are added in small quantities to tablet formulations to improve tablet manufacture by reducing friction at the tablet-die interface during tablet compaction and ejection ("true" lubricant), enhancing flow properties (glidant), and preventing sticking to punch surfaces and the die wall (anti-adherent) [116]. It is very important to distinguish between these three functions of a lubricant, since only few substances can simultaneously act as a "true" lubricant, glidant and anti-adherent.

A wide range of excipients are available for lubrication of tablet formulations. Magnesium stearate is by far the most frequently used tablet lubricant because it reduces friction efficiently even at low concentrations of 0.25 – 0.5 % and it also possesses good anti-adherent and glidant properties [42, 117, 177, 209]. However, despite its excellent lubricant performance, magnesium stearate is reported to have a negative effect on the tablet strength particularly at higher concentrations [16]. In addition, magnesium stearate is known to decrease the wettability due to its pronounced hydrophobic nature, and thus it can cause prolonged tablet disintegration and decreased dissolution rates [75, 179, 180].

Tablet sticking is one of the most common problems observed during tablet manufacture. It is caused by high adhesion forces between punch and tablet surface, in most cases leading to a powder layer sticking to the punch surface. In case powder layer sticking is detected, the anti-adherent performance of the applied lubricant is to be considered as insufficient. Therefore, traditional approaches to prevent the tablet formulation from sticking are to increase the lubricant concentration, to use an additional lubricant, or to choose a different lubricant.

Besides these traditional approaches, another possibility to reduce the sticking tendency of a tablet formulation is the application of punches with a modified surface. Through punch tip coatings, the performance of the tablet tooling can be improved by increasing surface hardness, wear resistance, corrosion resistance as well as anti-sticking efficiency [122, 123].

Chromium electroplating is the most prevalent method of surface modification for tablet tooling [124]. In comparison with uncoated punches, hard chromium plated punches provide a protection of the punch surfaces by enhancing corrosion and wear resisting properties and reducing friction and adhesion to some extent. Nevertheless, Roberts et al. evaluated the effect of chrome plating of punch tips on the sticking tendency of model ibuprofen formulations and they reported that it was ineffective in reducing ibuprofen adherence [125].

Hard coatings such as Titanium Nitride or Chromium Nitride have also proven their ability to increase the resistance to abrasive and adhesive wear and thus have found numerous applications in various sectors of industry including pharmaceutical tablet manufacturing [126, 127]. Titanium Nitride is a thin, gold colored coating with a very hard surface layer which is also supposed to exhibit a high resistance to heat transfer during tablet compaction [210, 211]. Therefore, application of Titanium Nitride-coated punches may be useful for compaction of low melting materials, e.g. ibuprofen, which show a high sticking tendency. Chromium Nitride coatings are characterized by a very smooth surface which is postulated to provide excellent anti-sticking properties [128].

The aim of the present study was to investigate the anti-adherent performance of magnesium stearate during direct compaction of various excipients which are usually used as filler-binders in tablet formulations. The anti-adherent performance of the lubricant was analyzed with respect to a possible synergistic effect of using punch tip coatings such as Hard Chromium, Chromium Nitride, and Titanium Nitride. The extent of tablet adhesion was evaluated by ejection and take-off force measurements as well as by visual inspection of the punch surfaces after each compaction run.

5.2. Materials and methods

5.2.1. Materials

The direct compression excipients used in this study were: Avicel® PH200 (microcrystalline cellulose), FMC BioPolymer, Cork, Ireland; Flowlac® 100 (spray-dried α-lactose monohydrate), Meggle, Wasserburg, Germany; Microcelac® 100 (co-processed excipient: 75 % α-lactose monohydrate and 25 % microcrystalline cellulose), Meggle, Wasserburg, Germany; Ludipress® (co-processed excipient: 93 % α-lactose monohydrate, 3.5 % povidone, and 3.5 % crospovidone), BASF, Ludwigshafen, Germany; Neosorb® 300 DC (sorbitol), Roquette Frères, France; Pearlitol® 200 SD (mannitol), Roquette Frères, France. Lubrication of the excipients was done with magnesium stearate (MgSt), Fagron, Barsbüttel, Germany. All other reagents used were of analytical grade.

5.2.2. Methods

Physical characterization of the excipients

Scanning electron microscopy

The morphology of the powder particles was analyzed with a LEO 1525 scanning electron microscope (LEO Elektronenmikroskopie, Oberkochen, Germany) at an accelerating voltage of 5 kV.

Determination of the powder densities

True densities of the excipients were measured by helium pycnometry using a 30 cm^3 sample cup (Accupyc 1330, Micromeritics, Aachen, Germany). Each measurement included 10 purge cycles followed by 10 measuring cycles. Bulk and tapped densities were determined according to the European Pharmacopoeia (Ph. Eur.) using a jolting volumeter (STAV 2003, J. Engelsmann, Ludwigshafen, Germany).

Determination of the particle size

Particle size distributions of the excipients were investigated via laser diffraction with a dry dispersion unit (HELOS/RODOS, Sympatec, Clausthal-Zellerfeld, Germany). Compressed air at 1.5 bar was used to disperse the powder.

Determination of flow properties

Flow properties of all powder blends were determined by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as the quotient of tapped and bulk density, which were determined according to the Ph. Eur. with the jolting volumeter mentioned above. The mass-related powder flow rate [g/s] was measured using a flowability tester (BEP2, Copley Scientific, Nottingham, UK) equipped with a stainless steel flow funnel (orifice diameter 10 mm).

All experiments were done in triplicate.

Preparation of the powder blends

The excipients were sieved (1000 µm mesh) prior to the preparation of the powder blends to destroy small powder agglomerates. Subsequently, each excipient was mixed with the lubricant magnesium stearate using a Turbula blender (T2F, W.A. Bachofen, Muttenz, Switzerland) at 72 rpm for 5 minutes. The lubricant concentration in the investigated powder blends was 0.25, 0.5, 1.0, 2.0 % [w/w], respectively. Prior to compaction studies, the powder blends were stored in an air-conditioned room at a temperature of 21°C and a relative humidity of 45 % for at least 72 h.

Compaction studies

Tableting of powder blends

To investigate the influence of various punch tip coatings on the anti-adherent performance of the lubricant magnesium stearate, beveled-edged tablets with a target weight of 300 mg (RSD ≤ 1.5 %) and a diameter of 10 mm were prepared with an instrumented rotary tablet press (XL 100, KORSCH, Berlin, Germany). Compaction forces of 5, 10, 15, and 20 kN, respectively, were applied, and the compression speed was set to 20 rpm with a corresponding dwell-time of 74.7 ms. The investigated punch tip coatings were Hard-Chromium, Chromium Nitride (CrN), Titanium Nitride (TiN), and uncoated punches served as reference. For all experiments uncoated dies were used.

Evaluation of the anti-adherent performance of magnesium stearate

To determine the anti-adherent efficiency of magnesium stearate at various lubricant levels, a visual inspection of the punch surfaces was performed after each compaction run. The anti-adherent efficiency of the lubricant was considered as sufficient, if no sticking of powder to the punch surfaces was detected. In addition, to evaluate the anti-adherent performance of the lubricant in non-sticking tablet formulations, ejection forces as well as tablet take-off forces recorded during compaction runs of 50 tablets each were analyzed. Due to an initialization period of the data acquisition system the measurement of ejection forces as well as take-off forces was started after compaction of 20 tablets recording the following 10 tablets. Data acquisition was carried out with an updated and internally improved version of the Pharma Research® software (KORSCH, Berlin, Germany).

Characterization of the tablets

After a relaxation time of at least 24 h after ejection of the tablets, the crushing strength, diameter and thickness of 10 tablets were determined using a hardness tester (TBH 30, Erweka, Heusenstamm, Germany). The tablet tensile strength was calculated using the equation published by Fell et al. [189]. The tabletability of the tablets was evaluated by plotting tensile strength versus compaction force. A minimum tablet tensile strength of 1 MPa was regarded as sufficient tablet hardness.

5.3. Results and discussion

Bulk powder properties of the investigated excipients

A general requirement for the lubrication process is the formation of a lubricant film on the surface of the host particles present in the powder blend [75]. Moreover, the lubricant performance depends on various parameters such as the physical and chemical properties of the lubricant, the composition of the powder blend, and the deformation behavior of the lubricated powder particles [15, 212-214]. Therefore, the bulk powder properties of the investigated excipients were considered as important factors relating to the anti-adherent performance of the lubricant magnesium stearate.

From the SEM images displayed in Fig. 27 a-f it is apparent that the excipients differ significantly from each other with regard to particle size as well as particle morphology.

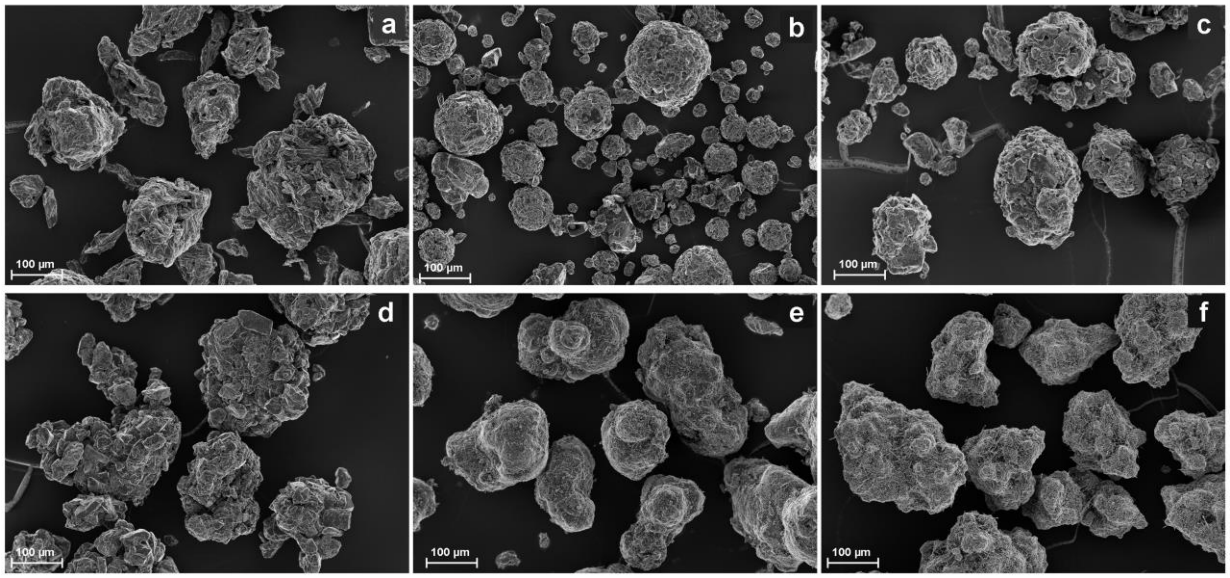

Fig. 27: SEM images of (a) Avicel® PH200, (b) Flowlac® 100, (c) Microcelac® 100, (d) Ludipress®, (e) Pearlitol® 200 SD, (f) Neosorb® 300 DC.

Flowlac® (Fig. 27b) showed the smallest powder particles with a mean particle size of 118.6 µm ± 1.1 (Table 17), whereas Neosorb® (Fig. 27f) provided the largest powder particles with a mean particle size of 300.5 ± 3.2. A general assumption is that the smaller the powder particles, the larger the provided surface area which needs to be covered by a lubricant film.

However, the SEM image of Neosorb® (Fig. 27f) shows that the powder particles of the excipient consist of very small crystalline needles ultimately resulting in an increased surface area.

Bulk density and flow properties are also postulated to have a major impact on the lubricant film formation [215]. In the case of a poor flowability of the host particles, the distribution of the lubricant particles and hence the lubricant film formation will be slow. From the data presented in Table 17 it is obvious that the bulk density as well as the flow properties of the excipient Avicel® were considerably less favorable than those of the other excipients. In accordance with the Ph. Eur. the Hausner ratio of Avicel® indicated only passable flowability, whereas the other excipients showed good flowability. As a result of the spherical shape and the favorable particle size distribution Pearlitol® turned out to have excellent flow properties in terms of powder flow rate.

Table 17: Bulk powder properties of the excipients

	Avicel	**Flowlac**	**Microcelac**	**Ludipress**	**Pearlitol**	**Neosorb**
Mean particle size (d_{50}) [µm]	176.1 (± 4.2)	118.6 (± 1.1)	140.6 (± 1.7)	193.3 (± 6.0)	146.7 (± 2.0)	300.5 (± 3.2)
True density [g/cm³]	1.557 (± 0.001)	1.549 (± 0.001)	1.555 (± 0.002)	1.510 (± 0.002)	1.491 (± 0.001)	1.501 (± 0.001)
Bulk density [g/cm³]	0.358 (± 0.003)	0.665 (± 0.002)	0.490 (± 0.001)	0.511 (± 0.001)	0.494 (± 0.001)	0.448 (± 0.002)
Tapped density [g/cm³]	0.454 (± 0.003)	0.764 (± 0.001)	0.577 (± 0.002)	0.608 (± 0.002)	0.564 (± 0.001)	0.512 (± 0.001)
Hausner ratio	1.27 (± 0.01)	1.15 (± 0.01)	1.18 (± 0.00)	1.19 (± 0.00)	1.14 (± 0.01)	1.14 (± 0.01)
Powder flow rate [g/s]	4.60 (± 0.24)	7.68 (± 0.10)	6.43 (± 0.03)	8.11 (± 0.06)	10.98 (± 0.16)	6.90 (± 0.05)

Compaction properties of the investigated excipients

In Fig. 28 the tabletability of the investigated excipients lubricated with 2 % magnesium stearate is shown. As expected, the higher the applied compaction force the higher the tablet tensile strength. However, particularly at high compaction forces of 15 and 20 kN the tablet tensile strength was found to differ significantly among the selected excipients.

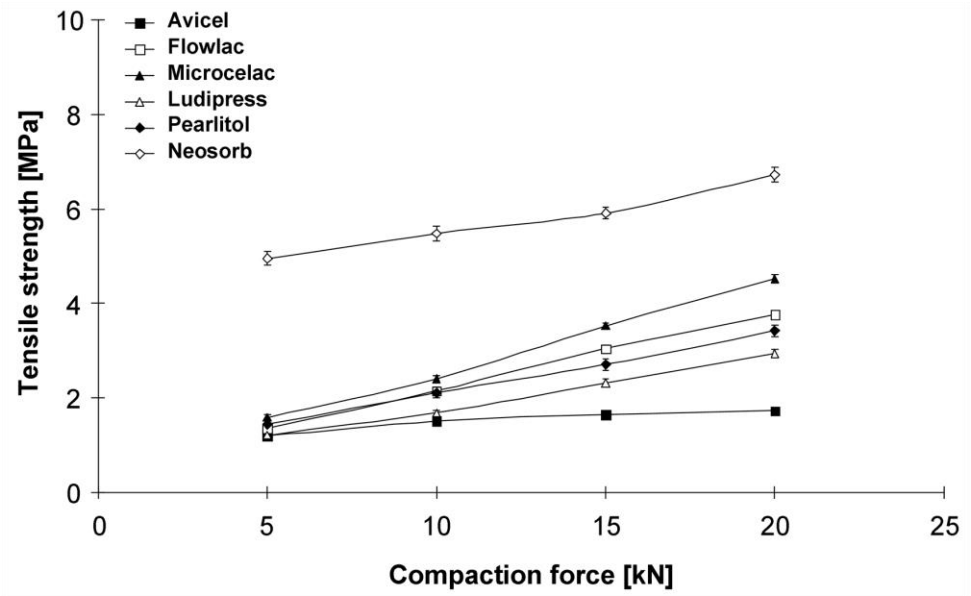

Fig. 28: Tabletability of the investigated excipients lubricated with 2 % magnesium stearate; means ± SD, n = 10.

The best tabletability by far was obtained with the Neosorb® tablets, whilst the tabletability of the Avicel® tablets was considered to be rather poor. At a compaction force of 20 kN, the calculated tensile strength of the Neosorb® tablets was 6.73 ± 0.15 MPa which corresponds to a tablet hardness of about 300 N. The excellent compaction properties of Neosorb® are attributed to the plasticity of the sorbitol particles as well as their particle structure [175, 176]. The sorbitol particles consist of small crystalline needles ultimately resulting in a porous particle structure, which provides a high surface area for bonding.

In contrast, although Avicel® is also reported to exhibit extremely good binding properties as a dry binder in direct compaction [17, 216], the tensile strength of the Avicel® tablets (1.73 ± 0.04 MPa) was found to be approximately fourfold lower than the tensile strength of the Neosorb® tablets. This comparably low tensile strength of the Avicel® tablets may be explained by the high magnesium stearate concentration of 2 % in the powder blend.

It is well known that Avicel® shows a high lubricant sensitivity affecting tabletability and compactibility of the excipient. The high lubricant sensitivity is primarily attributed to the pronounced plastic deformation behavior during compaction [14]. As a result of the physical barrier caused by the lubricant film, the interparticulate bonding strength between the particles is weakened resulting in a low tablet tensile strength [75].

Although Neosorb® also shows plastic deformation it is apparent that its lubricant sensitivity is considerably lower than that of Avicel®. This low lubricant sensitivity is supposed to be an effect of a dual deformation behavior; i.e. besides plastic deformation, brittle fragmentation also occurs during compaction of Neosorb®. In the literature it is described that excipients that deform by brittle fragmentation are less susceptible to magnesium stearate than those that undergo pronounced plastic deformation [14]. The other investigated excipients also show a dual deformation behavior accompanied by a low lubricant sensitivity resulting in tablets with a higher tensile strength than Avicel® tablets, but a lower tensile strength than Neosorb® tablets.

Anti-adherent performance of the lubricant magnesium stearate

To study the influence of different punch tip coatings on the anti-adherent performance, tableting of the investigated excipients lubricated with magnesium stearate at concentrations of 0.25, 0.5, 1, and 2 % was performed using hard chromium plated punches as well as Titanium Nitride (TiN)- and Chromium Nitride (CrN)-coated punches. Uncoated punches served as reference tooling. The anti-adherent performance of the lubricant magnesium stearate was evaluated by visual inspection of the punch surfaces as well as by measurement of the ejection forces and take-off forces.

a. Evaluation of the anti-adherent performance by visual inspection of the punches

The influence of different punch tip coatings on the anti-adherent performance of the lubricant magnesium stearate evaluated by visual inspection of the punches is presented in Fig. 29.

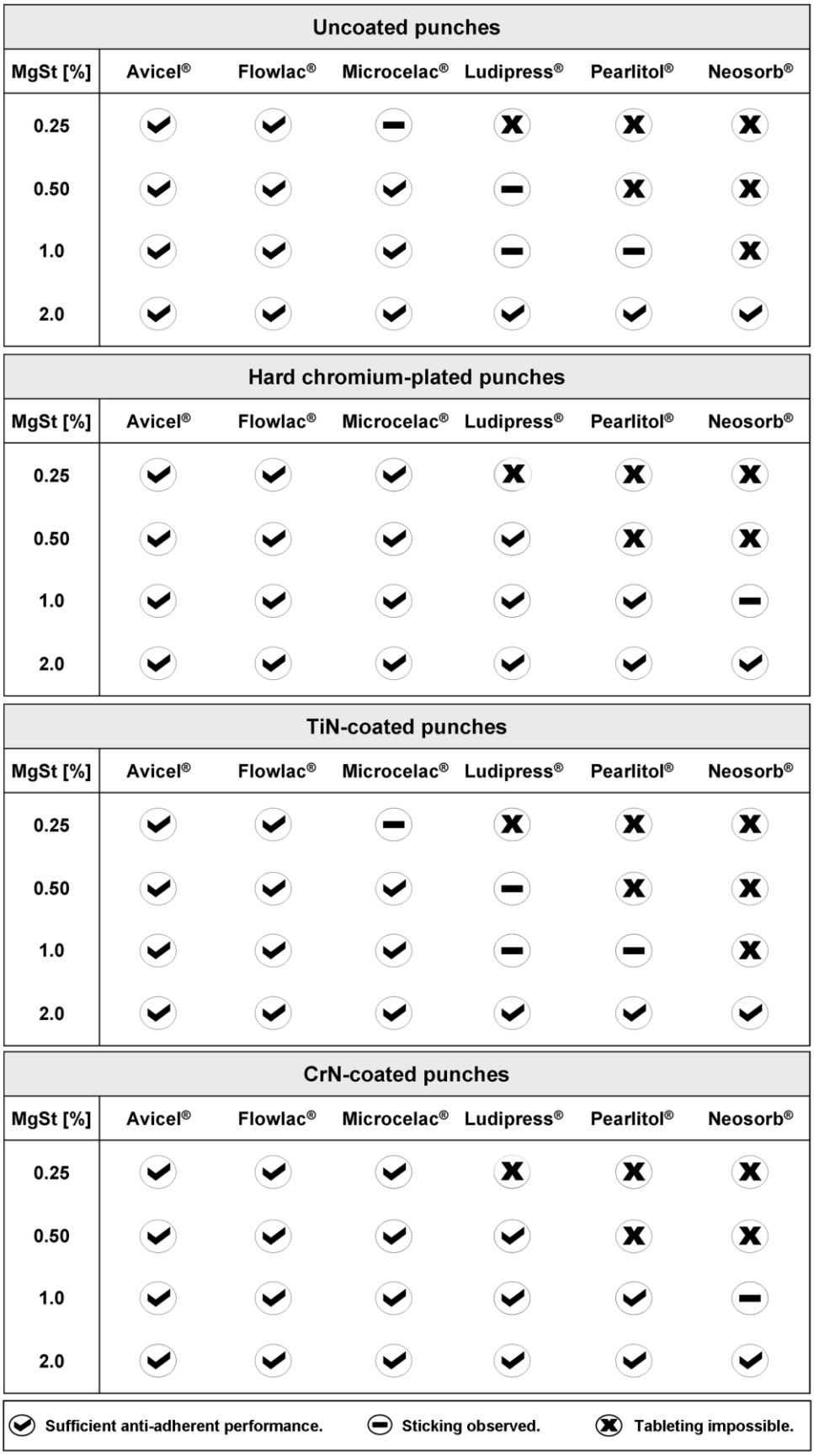

Fig. 29: Influence of different punch tip coatings on the anti-adherent performance of the lubricant magnesium stearate evaluated by visual inspection of the punch surfaces.

With uncoated punches it was found that for compaction of the excipients Avicel® and Flowlac® an amount of only 0.25 % magnesium stearate was sufficient to prevent powder sticking to the punch surface. In contrast, this low magnesium stearate concentration turned out to be insufficient for tableting of the other investigated excipients. With the Microcelac® formulation, powder layer sticking to the uncoated punches was observed, leading to a rough surface of the corresponding Microcelac® tablets. However, for direct compaction of Microcelac® a slightly higher magnesium stearate concentration of 0.5 % resulted in a sufficient anti-adherent performance of the lubricant. Interestingly, tableting of the excipients Ludipress®, Pearlitol® and Neosorb® was impossible at a lubricant concentration of 0.25 % due to unacceptably high ejection forces caused by pronounced die-wall sticking. With these three excipients a sufficient anti-adherent performance was only achieved at a magnesium stearate concentration of 2 %. From the presented data it is apparent that the anti-adherent performance of the lubricant is not only dependent on its concentration, but also dependent on the excipient used.

It is interesting to note that with the TiN-coated punches the same results as with the uncoated punches were obtained. Thus, in comparison with the reference punches, no improvement of the anti-adherent performance of the lubricant magnesium stearate was observed with application of TiN-coated punches.

In contrast, the anti-adherent performance of the lubricant was effectively improved by application of hard chromium-plated punches or CrN-coated punches. With both punch tip coatings, a magnesium stearate concentration of 0.25 % was sufficient for prevention of sticking not only during tableting of Avicel® and Flowlac®, but also during direct compaction of Microcelac®. Moreover, the required minimum lubricant concentration could be reduced from 2 % to 0.5 % for compaction of Ludipress® and from 2 % to 1 % for compaction of Pearlitol®.

b. Evaluation of the anti-adherent performance by ejection force measurements

Generally, the ejection process is divided into three phases [41, 42]: in the first phase the tablet ejection is initiated by overcoming frictional and adhesion forces at the interface of the tablet and the die wall, ultimately leading to a peak force noticeable within the ejection force-time profiles. The subsequent second phase of the ejection process is characterized by sliding frictional forces which are required to push the tablet up the die wall, followed by the third phase where the tablet starts to emerge from the die until it is completely ejected [38, 217].

In the present study, the peak ejection forces recorded during tableting were used as a measure of the lubricant efficiency. The influence of the magnesium stearate concentration on the ejection forces measured during direct compaction of the investigated excipients is displayed in Fig. 30. The measured ejection forces did not differ significantly with regard to the investigated punch tip coatings and therefore only the data obtained with the uncoated punches are presented.

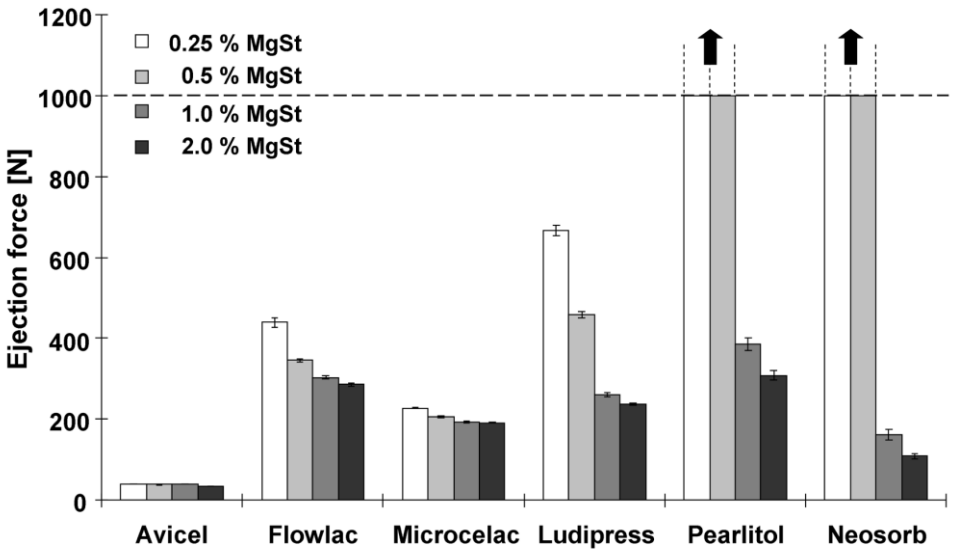

Fig. 30: Influence of the magnesium stearate concentration on the ejection forces measured during direct compaction of various excipients; compaction force 20 kN; means ± SD, n = 10; --- upper limit of data acquisition system.

From the data shown it is apparent that an increase of the magnesium stearate concentration leads to a decrease of the ejection forces, independent of the excipient used in the compaction study.

It is well known that the lubricant concentration affects the lubricant efficiency with regard to the compaction process and thus increased ejection forces are measured at low magnesium stearate concentrations. However, as already mentioned before, the lubricant efficiency is also affected by the properties of the host particles such as particle size distribution and flow properties. As the bulk powder properties of the excipients were found to differ significantly, the measured ejection forces were also found to vary considerably with respect to the excipients used in this compaction study. Obviously, the lowest ejection forces were recorded during compaction of Avicel®. Even at a lubricant concentration as low as 0.25 %, the ejection forces remained lower than 50 N, indicating an excellent lubricant efficiency. Although the ejection forces measured during compaction of Flowlac® (439.4 ± 12.2 N) and Microcelac® (227.9 ± 1.9 N) were found to be significantly higher than those obtained with Avicel® (39.5 ± 1.1 N), this low magnesium stearate concentration also turned out to be sufficient for tableting of these two excipients, as no sticking to the die wall was observed.

In contrast, the ejection forces derived from compaction of Ludipress® (666.1 ± 13.5 N) lubricated with 0.25 % of magnesium stearate were considered unacceptably high, as ejection of these tablets was accompanied by an atypical scratching noise caused by pronounced sticking of the excipient to the surface of the die wall. The tablet bands showed a rough surface and there were sticking residues at the die wall. However, no die wall sticking was observed if a concentration of 0.5 % was used for lubrication of Ludipress®, indicating a sufficient anti-adherent performance of magnesium stearate at this lubricant level.

Moreover, it was noticed that for tableting of the excipients Pearlitol® and Neosorb® a minimum lubricant concentration of 1 % was required. At lubricant concentrations below 1 % the ejection forces were found to exceed the upper limit of the data acquisition system (1000 N).

c. Evaluation of the anti-adherent performance by take-off force measurements

After a compressed tablet is ejected from the die, it will be detached from the lower punch surface by getting into contact with the stationary take-off bar on rotary tablet presses. During tablet detachment a tangential shear stress is applied to the tablet, and a certain take-off force is required to overcome the adhesive forces between tablet and punch surface [218].

In Fig. 31 the influence of the magnesium stearate concentration on the take-off forces recorded during direct compaction of the selected excipients is shown with regard to the investigated punch tip coatings. It is obvious that the measured take-off forces strongly depend on the excipient used for tableting as well as on the lubricant concentration, which was already observed with the aforementioned ejection force data. In addition, it was found that the occurrence of sticking to the punch surfaces also had an unexpected effect on the take-off force values. A general observation was that the take-off forces of non-sticking tablets (Avicel® and Flowlac®) increased with decreasing magnesium stearate concentrations. This is attributed to an increase of adhesion forces between the tablet and the punch surface, suggesting a reduction of the anti-adherent performance of the lubricant. For example, the take-off forces measured during compaction of Avicel® increased from 0.44 ± 0.04 N at a lubricant concentration of 2 % to 1.46 ± 0.16 N at a lubricant concentration of 0.25 % if the uncoated punches were used. The same trend was observed with Microcelac® at lubricant concentrations of 0.5, 1 and 2 %, respectively. However, it was surprising that the measured take-off forces of the sticking Microcelac® tablets at a magnesium stearate concentration of 0.25 % were lower (1.20 ± 0.13 N) than those of the non-sticking tablets with 0.5 % magnesium stearate (1.77± 0.14 N). This observation conflicts with the previously published hypothesis reporting that for the detachment of sticking tablets higher take-off forces are required [156]. Interestingly, with Ludipress® and Pearlitol® it was also observed that the take-off forces of sticking tablets were lower than those of non-sticking tablets. Therefore, it is assumed that in the case of sticking, the tablet take-off force does not represent the "true" adhesion force between the tablet and the punch surface, but rather the force to overcome cohesion between the tablet and the sticking powder layer, ultimately leading to decreased take-off forces [218].

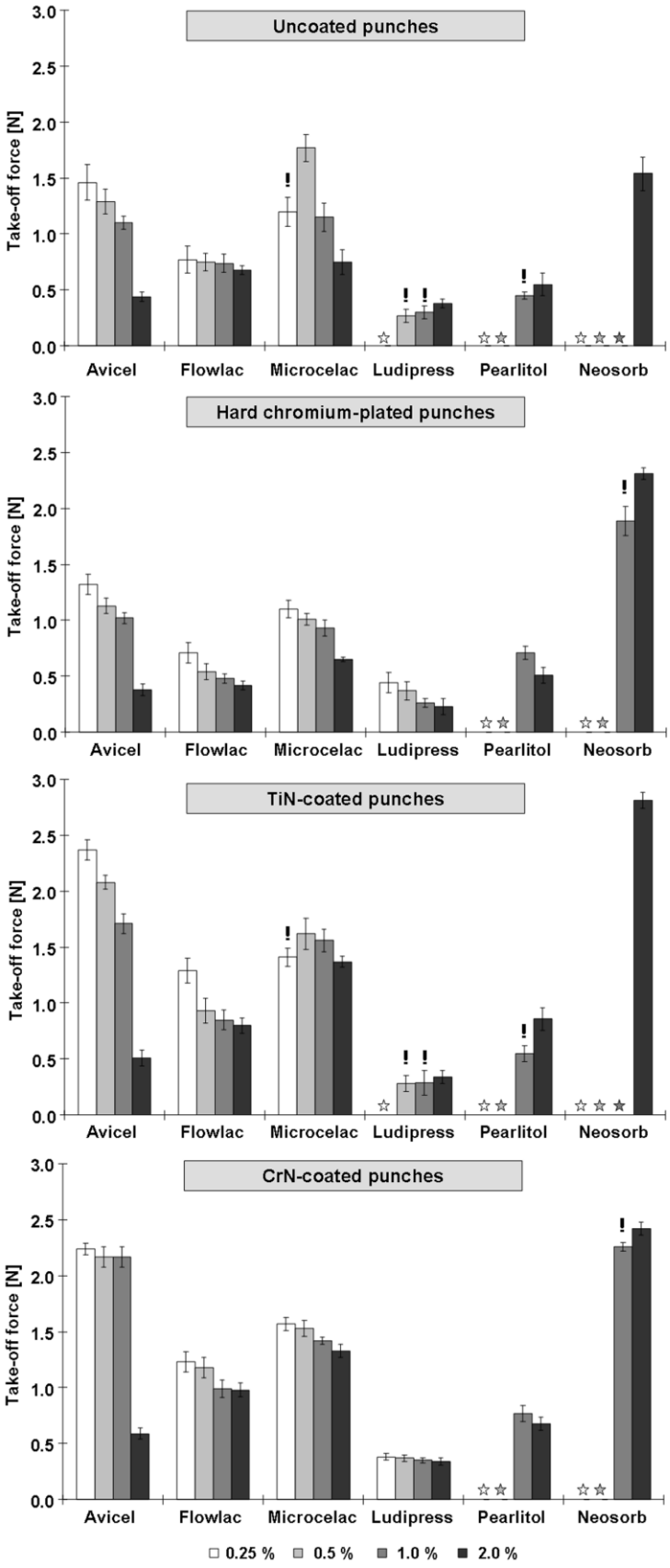

Fig. 31: Influence of the magnesium stearate concentration on the take-off forces measured during direct compaction of various excipients; compaction force 20 kN; means ± SD, n = 10. ! Sticking observed; * tableting impossible.

Moreover, from the data presented in Fig. 31 it is apparent that the take-off forces are highly affected by the applied punch tip coating. With the Avicel® powder blend containing less than 2 % of magnesium stearate the strongest tablet adhesion was measured during compaction with TiN- and CrN-coated punches. However, although the recorded take-off forces were as high as 2.4 N, sticking of material to the punch surfaces was not observed. During compaction of Flowlac® the take-off forces were found to be considerably lower than those measured during compaction of Avicel®, particularly at low magnesium stearate concentrations, indicating an excellent anti-adherent performance of the lubricant for compaction of this excipient. Again, tablet take-off forces measured with TiN- and CrN-coated punches were found to exceed those measured with hard chromium-plated and uncoated punches, but sticking to the punch surfaces was not observed. Independent of the punch tip coating, the anti-adherent performance of magnesium stearate at a concentration of only 0.25 % was sufficient to prevent sticking of Avicel® and Flowlac® tablets.

In contrast, with Microcelac® tablets lubricated with 0.25 % magnesium stearate pronounced sticking to the surfaces of the TiN-coated and the uncoated punches was observed, whereas compaction with hard chromium-plated or CrN-coated punches revealed no sticking tendency at this lubricant concentration. This implies that sticking of Microcelac® could be successfully prevented by application of hard chromium-plated as well as CrN-coated punches. However, from the measured take-off forces it is obvious that the adhesion forces occurring at the surface of the CrN-coated punches (1.57 ± 0.04 N) are considerably higher than those obtained with the hard chromium-plated punches (1.00 ± 0.08 N), indicating a superior anti-adhesive efficiency of the latter.

Furthermore, take-off forces recorded with Ludipress® tablets were found to be comparably low with all investigated tooling. With regard to the different punch tip coatings it was found that sticking to the surfaces of TiN-coated and uncoated punches was observed up to a magnesium stearate concentration of even 1 %, whereas a lubricant concentration of 0.5 % turned out to be sufficient, if hard chromium-plated and CrN-coated punches were used. Interestingly, compaction of Ludipress® revealed no superiority of the hard chromium-plated punches over CrN-coated punches with regard to their anti-sticking properties, as similar take-off forces were recorded with both tooling.

Pearlitol® and Neosorb® showed the worst compaction properties. With the Pearlitol® powder blend a magnesium stearate concentration of 1 % was found to be sufficient for prevention of sticking if hard chromium-plated or CrN-coated punches were used, whilst application of uncoated and TiN-coated punches was insufficient. In the case of Pearlitol® lubricated with 1 % magnesium stearate, the take-off forces measured during compaction with the hard chromium-plated punches (0.71 ± 0.06 N) were found to be only slightly lower compared to those recorded during compaction with CrN-coated punches (0.77 ± 0.08 N). However, at a lubricant concentration of 2 % the difference in tablet take-off forces turned out to be more evident, suggesting that compaction with hard chromium-plated punches is preferable over compaction using CrN-coated punches.

Magnesium stearate was least efficient for lubrication of Neosorb®, as concentrations of 1 % either led to sticking (hard chromium-plated and CrN-coated punches) or to unacceptable tableting conditions (TiN-coated and uncoated punches). Even at a lubricant concentration of 2 % the measured take-off forces were extremely high, indicating strong tablet adhesion to the differently coated punch surfaces.

An overview of the anti-adherent performance of the lubricant magnesium stearate with respect to the different excipients and various punch tip coatings is given in Table 18.

Table 18: Overview of the minimum magnesium stearate concentration required for direct compaction of various excipients to obtain a sufficient anti-adherent performance with respect to the investigated punch tip coatings

	Avicel	Flowlac	Microcelac	Ludipress	Pearlitol	Neosorb
Uncoated punches	0.25	0.25	0.5	2.0	2.0	2.0
Hard chromium-plated punches	0.25	0.25	0.25	0.5	1.0	2.0
TiN-coated punches	0.25	0.25	0.5	2.0	2.0	2.0
CrN-coated punches	0.25	0.25	0.25	0.5	1.0	2.0

The best anti-adherent performance of the lubricant magnesium stearate was observed during direct compaction of Avicel® and Flowlac®, as a lubricant concentration of 0.25 % was sufficient to prevent the tablet formulations from sticking.

With respect to the investigated punch tip coatings it was found that in the case of Microcelac®, Ludipress® as well as Pearlitol®, the application of hard chromium-plated punches and CrN-coated punches allowed a reduction of the magnesium stearate concentration in the tablet formulation. This indicates that with these two types of punch surface modification the sticking tendency of the tablet formulations could be successfully reduced. However, from take-off force data it is obvious that tablet adhesion forces to the surface of the hard chromium-plated punches were lower than those to the surface of the CrN-coated punches. This is assumed to be primarily attributed to the different surface microstructure of these punches. In comparison to the rather rough surface of the hard chromium-plated punches because of asperities and micro-cracks, the surface microstructure of the investigated CrN-coated punches was very smooth resulting from the plasma-based coating process. Consequently, the adhesion forces acting between tablet and punch surface are uniform across the entire surface area of the CrN-coated punches. In contrast, the asperities and micro-cracks at the surface of the hard chromium-plated punches lead to decreased adhesive forces between punch and tablet surface. This may be explained by the comparably rough surface resulting in a discontinuity of the adhesion forces across the punch surface and thus the adhesive attraction between tablet and punch is reduced [124, 125].

Unfortunately, with Neosorb® no improvement of the anti-adherent efficiency of the lubricant was achieved by application of the differently coated punches.

5.4. Conclusion

The anti-adherent performance of the lubricant magnesium stearate may be supported by punch tip coatings depending on the composition of the tablet formulation. With Avicel® and Flowlac® powder blends the anti-adherent performance of the lubricant was found to be sufficient to prevent sticking independent of the investigated magnesium stearate concentrations and punch tip coatings. However, from the take-off force data it was apparent that tablet adhesion to TiN- and CrN-coated punches was more pronounced than that to hard chromium-plated and uncoated punches.

With the Microcelac® powder blend containing 0.25 % magnesium stearate pronounced sticking to the surfaces of TiN-coated and uncoated punches was observed, whereas sticking of Ludipress® to these punches was apparent up to a magnesium stearate concentration of 1 %. However, with both excipients the sticking tendency of the tablets was reduced by application of hard chromium-plated or CrN-coated punches, allowing a reduction of the lubricant concentration.
The lubricant performance of magnesium stearate turned out to be rather poor during compaction of Pearlitol® and Neosorb®, as tableting of these excipients was impossible at magnesium stearate concentrations of 0.25 and 0.5 %. A lubricant concentration of 1 % was found to be sufficient for compaction of Pearlitol®, if hard chromium-plated or CrN-coated punches were used, whilst with the TiN-coated and the uncoated punches pronounced sticking was observed. With Neosorb® a magnesium stearate concentration of 2 % was required for an acceptable anti-adherent performance of the lubricant independent of the punch tip coating used for compaction.

In conclusion, for prevention of sticking both, the conventional hard chromium-plated punches and the CrN-coated punches turned out to be most efficient. However, with regard to the adhesive behavior of the investigated excipients during direct compaction, take-off force data reveal a slight superiority of the hard chromium-plated punches over CrN-coated punches. Moreover, hard chromium-plated punches are less expensive and therefore also preferable from a commercial point of view.

6. References

References

[1] Jivraj, M., Martini, L.G., Thomson, C.M.
An overview of the different excipients useful for the direct compression of tablets.
Pharm Sci Technol Today 3: 58-63 (2000)

[2] Ahmat, N., Ugail, H., Gonzales Castro, G.
Method of modelling the compaction behaviour of cylindrical pharmaceutical tablets.
Int J Pharm 405: 113-121 (2011)

[3] Fell, J.T., Rowe, R.C., Newton, J.M.
The mechanical strength of film-coated tablets.
J Pharm Pharmacol 31: 69-72 (1979)

[4] Sohi, H., Sultana, Y., Khar, R.K.
Taste masking technologies in oral pharmaceuticals: recent developments and approaches.
Drug Dev Ind Pharm 30: 429-448 (2004)

[5] Fites, A.L., Banker, G.S., Smolen, V.F.
Controlled drug release through polymeric films.
J Pharm Sci 59: 610-613 (1970)

[6] Ozturk, S.S., Palsson, B.O., Donohoe, B., Dressman, J.B.
Kinetics of release from enteric coated tablets.
Pharm Res 5: 550-565 (1988)

[7] Wu, C.-Y., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W.
A simple predictive model for the tensile strength of binary tablets.
Eur J Pharm Sci 25: 331-336 (2005)

[8] Bharate, S., Bharate, S., Bajaj, A.N.
Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review.
J Excipients and Food Chem 1: 3-26 (2010)

[9] Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R.
A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability.
Pharm Res 12: 413-420 (1995)

[10] Löbenberg, R., Amidon, G.L.
Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards.
Eur J Pharm Biopharm 50: 3-12 (2000)

[11] Mullarney, M.P., Hancock, B.C.
Mechanical property anisotropy of pharmaceutical excipient compacts.
Int J Pharm 314: 9-14 (2006)

[12] Patel, S., Bansal, A.K.
Prediction of mechanical properties of compacted binary mixtures containing high-dose poorly compressible drug.
Int J Pharm 403: 109-114 (2011)

[13] Wu, C.-Y., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W.
Predicting the tensile strength of compacted multi-component mixtures of pharmaceutical powders.
Pharm Res 23: 1898-1905 (2006)

[14] De Boer, A.H., Bolhuis, G.K., Lerk, C.F.
Bonding characteristics by scanning electron microscopy of powder mixed with magnesium stearate.
Powder Technol 20: 75-82 (1978)

[15] Zuurman, K., Van der Voort Maarschalk, K., Bolhuis, G.K.
Effect of magnesium stearate on bonding and porosity expansion of tablets produced from materials with different consolidation properties.
Int J Pharm 179: 107-115 (1999)

[16] Vromans, H., Lerk, C.F.
Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate.
Int J Pharm 46: 183-192 (1988)

[17] Bolhuis, G.K., Armstrong, N.A.
Excipients for direct compaction - an update.
Pharm Dev Technol 11: 111-124 (2006)

[18] Saha, S., Shahiwala, A.F.
Multifunctional coprocessed excipients for improved tabletting performance.
Expert Opin Drug Deliv 6: 197-208 (2009)

[19] Gohel, M.C., Jogani, P.D.
A review of co-processed directly compressible excipients.
J Pharm Pharmaceut Sci 8: 76-93 (2005)

[20] Armstrong, N.A.
Selection of excipients for direct compression tablet formulations.
Pharm Technol Eur 9: 24-30 (1997)

[21] Rojas, J., Buckner, I., Kumar, V.
Co-processed excipients with enhanced direct compression functionality for improved tableting performance.
Drug Dev Ind Pharm 38: 1159-1170 (2012)

[22] Tousey, M.D.
The granulation process 101. Basic technologies for tablet making.
Pharm Technol 26: 8-13 (2002)

[23] Faure, A., York, P., Rowe, R.C.
Process control and scale-up of pharmaceutical wet granulation processes: a review.
Eur J Pharm Biopharm 52: 269-277 (2001)

[24] Meeus, L.
Direct compression versus granulation.
Pharm Technol Eur 23: 30-31 (2011)

[25] Herting, M.G., Kleinebudde, P.
Studies on the reduction of tensile strength of tablets after roll compaction/ dry granulation.
Eur J Pharm Biopharm 70: 372-379 (2008)

[26] Kleinebudde, P.
Roll compaction/dry granulation: pharmaceutical applications.
Eur J Pharm Biopharm 58: 317-326 (2004)

[27] Teng, Y., Qiu, Z., Wen, H.
Systematical approach of formulation and process development using roller compaction.
Eur J Pharm Biopharm 73: 219-229 (2009)

[28] Brockedon, W.
Shaping pills, lozenges, and black lead by pressure in dies.
British Patent No. 9977: 1-5 (1843)

[29] Ruegger, C.E., Celik, M.
Advanced compaction research equipment: compaction simulators.
in: Pharmaceutical Powder Compaction Technology, 2nd ed. (Celik, M., Ed.): 99-128, Informa Healthcare, London (2011)

[30] Armstrong, N.A., Ridgway Watt, P.
Instrumented tablet presses.
in: Tablet and capsule machine instrumentation, 1st ed. (Ridgway Watt, P. and Armstrong, N.A., Ed.): 99-138, Pharmaceutical Press, London (2008)

[31] Konkel, P.
Untersuchungen zur Vergleichbarkeit von Parametern der Tablettierbarkeit pharmazeutischer Haufwerke an Exzenter- und Rundlauf-Tablettiermaschinen.
PhD Thesis, University of Hamburg, Germany (1995)

[32] Palmieri, G.F., Joiris, E., Bonacucina, G., Cespi, M., Mercuri, A.
Differences between eccentric and rotary tablet machines in the evaluation of powder densification behaviour.
Int J Pharm 298: 164-175 (2005)

[33] Oates, R.J., Mitchell, A.G.
Calculation of punch displacement and work of powder compaction on a rotary tablet press.
J Pharm Pharmacol 41: 517-523 (1989)

[34] Oates, R.J., Mitchell, A.G.
A new method of estimating volume during powder compaction and the work of compaction on a rotary tablet press from measurements of applied vertical force.
J Pharm Pharmacol 46: 270-275 (1994)

[35] Charlton, B., Newton, J.M.
Theoretical estimation of punch velocities and displacements of single-punch and rotary tablet machines.
J Pharm Pharmacol 36: 645-651 (1984)

[36] Celik, M., Marshall, K.
Use of a compaction simulator system in tableting research.
Drug Dev Ind Pharm 15: 759-800 (1989)

[37] Wu, C.-Y., Hancock, B.C., Mills, A., Bentham, A.C., Best, S.M., Elliott, J.A.
Numerical and experimental investigation of capping mechanisms during pharmaceutical tablet compaction.
Powder Technol 181: 121-129 (2008)

[38] Wray, P.E.
The physics of tablet compaction revisited.
Drug Dev Ind Pharm 18: 627-658 (1992)

[39] Hiestand, E.N., Wells, J.E., Peot, C.B., Ochs, J.F.
Physical processes of tableting.
J Pharm Sci 66: 510-519 (1977)

[40] Van der Voort Maarschalk, K., Zuurman, K., Vromans, H., Bolhuis, G.K., Lerk, C.F.
Stress relaxation of compacts produced from viscoelastic materials.
Int J Pharm 151: 27-34 (1997)

[41] Delacourte, A., Guyot, J.C., Colombo, P., Catellani, P.L.
Effectiveness of lubricants and lubrication mechanism in tablet technology.
Drug Dev Ind Pharm 21: 2187-2199 (1995)

[42] Patel, S., Kaushal, A.M., Bansal, A.K.
Lubrication potential of magnesium stearate studied on instrumented rotary tablet press.
AAPS Pharm Sci Tech 8: E1-E8 (2007)

[43] Siiria, S.-M., Antikainen, O., Heinamaki, J., Yliruusi, J.
3D simulation of internal tablet strength during tableting.
AAPS Pharm Sci Tech 12: 593-603 (2011)

[44] Duberg, M., Nyström, C.
Studies on direct compression of tablets. XVII. Porosity-pressure curves for the characterization of volume reduction mechanisms in powder compression.
Powder Technol 46: 67-75 (1986)

[45] Roberts, R.J., Rowe, R.C.
Brittle/ductile behaviour in pharmaceutical materials used in tabletting.
Int J Pharm 36: 205-209 (1987)

[46] Sebhatu, T., Ahlneck, C., Alderborn, G.
The effect of moisture content on the compression and bond-formation properties of amorphous lactose particles.
Int J Pharm 146: 101-114 (1997)

[47] Jain, S.
Mechanical properties of powders for compaction and tableting: an overview.
Pharm Sci Technol Today 2: 20-31 (1999)

[48] Garr, J.S.M., Rubinstein, M.H.
The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium phosphate mixtures.
Int J Pharm 73: 75-80 (1991)

[49] Roberts, R.J., Rowe, R.C.
The effect of punch velocity on the compaction of a variety of materials.
J Pharm Pharmacol 37: 377-384 (1985)

[50] Heckel, R.W.
An analysis of powder compaction phenomena.
Trans Metall Soc, AIME 221: 1001-1008 (1961)

[51] Heckel, R.W.
Density-pressure relationships in powder compaction.
Trans Metall Soc, AIME 221: 671-675 (1961)

[52] Ilkka, J., Paronen, P.
Prediction of the compression behaviour of powder mixtures by the Heckel equation.
Int J Pharm 94: 181-187 (1993)

[53] Sonnergaard, J.M.
A critical evaluation of the Heckel equation.
Int J Pharm 193: 63-71 (1999)

[54] Sun, C., Grant, D.
Influence of elastic deformation of particles on Heckel analysis.
Pharm Dev Technol 6: 193 (2001)

[55] Hiestand, E.N.
Principles, tenets and notions of tablet bonding and measurements of strength.
Eur J Pharm Biopharm 44: 229-242 (1997)

[56] Buckton, G.
Intermolecular bonding forces: where materials and process come together. in: Pharmaceutical Powder Compaction Technology, 2nd ed. (Celik, M., Ed.): 1-8, Informa Healthcare, London (2011)

[57] Ferrari, F., Bertoni, M., Bonferoni, M.C., Rossi, S., Caramella, C., Nyström, C.
Investigation on bonding and disintegration properties of pharmaceutical materials.
Int J Pharm 136: 71-79 (1996)

[58] Luangtana-Anan, M., Fell, J.T.
Bonding mechanisms in tabletting.
Int J Pharm 60: 197-202 (1990)

[59] Adolfsson, A., Nyström, C.
Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads.
Int J Pharm 132: 95-106 (1996)

[60] Van der Voort Maarschalk, K., Zuurman, K., Vromans, H., Bolhuis, G.K., Lerk, C.F.
Porosity expansion of tablets as a result of bonding and deformation of particulate solids.
Int J Pharm 140: 185-193 (1996)

[61] Picker, K.M.
Time dependence of elastic recovery for characterization of tableting materials.
Pharm Dev Technol 6: 61-70 (2001)

[62] Van der Voort Maarschalk, K., Vromans, H., Bolhuis, G.K., Lerk, C.F.
The effect of viscoelasticity and tabletting speed on consolidation and relaxation of a viscoelastic material.
Eur J Pharm Biopharm 42: 49-55 (1996)

[63] Katikaneni, P.R., Upadrashta, S.M., Rowlings, C.E., Neau, S.H., Hileman, G.A.
Consolidation of ethylcellulose: effect of particle size, press speed, and lubricants.
Int J Pharm 117: 13-21 (1995)

[64] Van der Voort Maarschalk, K., Vromans, H., Groenendijk, W., Bolhuis, G.K., Lerk, C.F.
Effect of water on deformation and bonding of pregelatinized starch compacts.
Eur J Pharm Biopharm 44: 253-260 (1996)

[65] Tabletting: the issues facing today's manufacturers.
Pharm. Technol. Eur. 22: (2010)

[66] Soppela, I., Airaksinen, S., Murtomaa, M., Tenho, M., Hatara, J., Räikkönen, H., Yliruusi, J., Sandler, N.
Investigation of the powder flow behaviour of binary mixtures of microcrystalline celluloses and paracetamol.
J Excipients and Food Chem 1: 55-67 (2010)

[67] Doelker, E.
Comparative compaction properties of various microcrystalline cellulose types and generic products.
Drug Dev Ind Pharm 19: 2399-2471 (1993)

[68] Doelker, E., Massuelle, D., Veuillez, F., Humbert-Droz, P.
Morphological, packing, flow and tableting properties of new Avicel types.
Drug Dev Ind Pharm 21: 643-661 (1995)

[69] Lahdenpää, E., Niskanen, M., Yliruusi, J.
Crushing strength, disintegration time and weight variation of tablets compressed from three Avicel PH grades and their mixtures.
Eur J Pharm Biopharm 43: 315-322 (1997)

[70] Ohta, K.M., Fuji, M., Chikazawa, M.
Effect of geometric structure of flow promoting agents on the flow properties of pharmaceutical powder mixture.
Pharm Res 20: 804-809 (2003)

[71] Bundenthal, M.
Battling off-weight tablets: training, calibration and preventive maintenance help prevent over- and underweight tablets.
Pharm Technol Eur 26: 32-33 (2014)

[72] Ling, W.C.
Tooling as a factor in tablet weight variation and control.
Pharm Technol 62: 2007-2011 (1973)

[73] Joneja, S.K., Harcum, W.W., Skinner, G.W., Barnum, P.E., Guo, J.H.
Investigating the fundamental effects of binders on pharmaceutical tablet performance.
Drug Dev Ind Pharm 25: 1129-1135 (1999)

[74] Malamataris, S., Hatjichristos, T., Rees, J.E.
Apparent compressive elastic modulus and strength isotropy of compacts formed from binary powder mixes.
Int J Pharm 141: 101-108 (1996)

[75] Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T., De Boer, A.H.
Film formation by magnesium stearate during mixing and its effect on tabletting.
Pharm Weekbl 110: 317-325 (1975)

[76] David, S.T., Augsburger, L.L.
Plastic flow during compression of directly compressible fillers and its effect on tablet strength.
J Pharm Sci 66: 155-159 (1977)

[77] Ruegger, C.E., Celik, M.
The effect of compression and decompression speed on the mechanical strength of compacts.
Pharm Dev Technol 5: 485 (2000)

[78] Malamataris, S., Rees, J.E.
Viscoelastic properties of some pharmaceutical powders compared using creep compliance, extended Heckel analysis and tablet strength measurements.
Int J Pharm 92: 123-135 (1993)

[79] Rees, J.E., Rue, P.J.
Time-dependent deformation of some direct compression excipients.
J Pharm Pharmacol 30: 601-607 (1978)

[80] Casahoursat, L., Lemagnen, G., Larrouture, D.
The use of stress relaxation trials to characterize tablet capping.
Drug Dev Ind Pharm 14: 2179-2199 (1988)

[81] Jarosz, P.J., Parrott, E.L.
Factors influencing axial and radial tensile strength of tablets.
J Pharm Sci 71: 607-614 (1982)

[82] Jetzer, W.E.
Measurement of hardness and strength of tablets and their relation to compaction performance of powders.
J Pharm Pharmacol 38: 254-258 (1986)

[83] Nakamura, H., Sugino, Y., Watano, S.
In-die evaluation of capping tendency of pharmaceutical tablets using force-displacement curve and stress relaxation parameter.
Chem Pharm Bull 60: 772-777 (2012)

[84] Sugimori, K., Kawashima, Y.
A new practical index to predict capping occuring during the tableting process.
Eur J Pharm Biopharm 44: 323-326 (1997)

[85] Sugimori, K., Mori, S., Kawashima, Y.
Introduction of a new index for the prediction of capping tendency of tablets.
Chem Pharm Bull 37: 458-462 (1989)

[86] Kuppuswamy, R., Anderson, S.R., Augsburger, L.L., Hoag, S.W.
Estimation of capping incidence by indentation fracture tests.
AAPS Pharm Sci 3: 1-12 (2001)

[87] Garr, J.S.M., Rubinstein, M.H.
An investigation into the capping of paracetamol at increasing speeds of compression.
Int J Pharm 72: 117-122 (1991)

[88] Malamataris, S., Baie, S., Pilpel, N.
Plasto-elasticity and tableting of paracetamol, Avicel and other powders.
J Pharm Pharmacol 36: 616-617 (1984)

[89] Akande, O.F., Rubinstein, M.H., Rowe, P.H., Ford, J.L.
Effect of compression speeds on the compaction properties of a 1:1 paracetamol-microcrystalline cellulose mixture prepared by single compression and by combinations of pre-compression and main-compression.
Int J Pharm 157: 127-136 (1997)

[90] Adolfsson, A., Caramella, C., Nyström, C.
The effect of milling and addition of dry binder on the interparticulate bonding mechanisms in sodium chloride tablets.
Int J Pharm 160: 187-195 (1998)

[91] Sugimori, K., Mori, S., Kawashima, Y.
The role of binders in the prevention of capping within a tablet.
Chem Pharm Bull 37: 1064-1067 (1989)

[92] Mattsson, S., Nyström, C.
Evaluation of strength-enhancing factors of a ductile binder in direct compression of sodium bicarbonate and calcium carbonate powders.
Eur J Pharm Sci 10: 53-66 (2000)

[93] Adam, A., Schrimpl, L., Schmidt, P.C.
Factors influencing capping and cracking of mefenamic acid tablets.
Drug Dev Ind Pharm 26: 489-497 (2000)

[94] Garr, J.S.M., Rubinstein, M.H.
The influence of moisture content on the consolidation and compaction properties of paracetamol.
Int J Pharm 81: 187-192 (1992)

[95] Lin, M.-C., Duncan-Hewitt, W.C.
Deformation kinetics of acetaminophen crystals.
Int J Pharm 106: 187-200 (1994)

[96] Nokhodchi, A., Rubinstein, M.H., Larhrib, H., Guyot, J.C.
The effect of moisture content on the energies involved in the compaction of ibuprofen.
Int J Pharm 120: 13-20 (1995)

[97] Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.
Formation and compression characteristics of prismatic polyhedral and thin plate-like crystals of paracetamol.
Int J Pharm 187: 77-89 (1999)

[98] Mann, S.C., Roberts, R.J., Rowe, R.C., Hunter, B.M., Rees, J.E.
The effect of high speed compression at sub-atmospheric pressures on the capping tendency of pharmaceutical tablets.
J Pharm Pharmacol 35 Supplement: 44P (1983)

[99] Ebba, F., Piccerelle, P., Prinderre, P., Opota, D., Joachim, J.
Stress relaxation studies of granules as a function of different lubricants.
Eur J Pharm Biopharm 52: 211-220 (2001)

[100] Tanino, T., Aoki, Y., Furuya, Y., Sato, K., Takeda, T., Mizuta, T.
Occurrence of capping due to insufficient air escape during tablet compression and a method to prevent it.
Chem Pharm Bull 43: 1772-1779 (1995)

[101] Abdel-Hamid, S., Betz, G.
Study of radial die-wall pressure changes during pharmaceutical powder compaction.
Drug Dev Ind Pharm 37: 387-395 (2011)

[102] Doelker, E., Massuelle, D.
Benefits of die-wall instrumentation for research and development in tabletting.
Eur J Pharm Biopharm 58: 427-444 (2004)

[103] Tousey, M.D.
Sticking and picking: some causes and remedies.
Reprinted from Tablets & Capsules 10/2003: www.tabletscapsules.com (2003)

[104] Sabir, A., Evans, B., Jain, S.
Formulation and process optimization to eliminate picking from market image tablets.
Int J Pharm 215: 123-135 (2001)

[105] Lam, K.K., Newton, J.M.
Investigation of applied compression on the adhesion of powders to a substrate surface.
Powder Technol 65: 167-175 (1991)

[106] Visser, J.
Particle adhesion and removal: A review.
Particul Sci Technol 13: 169-196 (1995)

[107] Rowley, G.
Quantifying electrostatic interactions in pharmaceutical solid systems.
Int J Pharm 227: 47-55 (2001)

[108] Lachiver, E.D., Abatzoglou, N., Cartilier, L., Simard, J.S.
Insights into the role of electrostatic forces on the behavior of dry pharmaceutical particulate systems.
Pharm Res 23: 997-1007 (2006)

[109] Eilbeck, J., Rowley, G., Carter, P.A., Fletcher, E.J.
Effect of contamination of pharmaceutical equipment on powder triboelectrification.
Int J Pharm 195: 7-11 (2000)

[110] Lam, K.K., Newton, J.M.
Influence of particle size on the adhesion behavior of powders after application of an initial press-on force.
Powder Technol 73: 117-125 (1992)

[111] Lam, K.K., Newton, J.M.
The influence of the time of application of contact pressure on particle adhesion to a substrate surface.
Powder Technol 76: 149-154 (1993)

[112] Rasenack, N., Müller, B.W.
Crystal habit and tabletting behavior.
Int J Pharm 244: 45-57 (2002)

[113] Shimada, Y., Yonezawa, Y., Sunada, H.
Measurement and evaluation of the adhesive force between particles by the direct separation method.
J Pharm Sci 92: 560-568 (2003)

[114] Wang, J.J., Li, T., Bateman, S.D., Erck, R., Morris, K.R.
Modeling of adhesion in tablet compression - I. Atomic force microscopy and molecular simulation.
J Pharm Sci 92: 798-814 (2003)

[115] McDermott, T.S., Farrenkopf, J., Hlinak, A., Neilly, J.P., Sauer, D.
A material sparing method for quantitatively measuring tablet sticking.
Powder Technol 212: 240-252 (2011)

[116] Armstrong, N.A.
Lubricants, glidants, and anti-adherents.
in: Pharmaceutical Dosage Forms: Tablets, Vol. 2, 3rd ed. (Augsburger, L.L. and Hoag, S.W., Ed.): 251-267, Informa Healthcare, New York (2008)

[117] Miller, T.A., York, P.
Pharmaceutical tablet lubrication.
Int J Pharm 41: 1-19 (1988)

[118] Wang, J., Wen, H., Desai, D.
Lubrication in tablet formulations.
Eur J Pharm Biopharm 75: 1-15 (2010)

[119] Bolhuis, G.K., Hölzer, A.W.
Lubrication issues in direct compaction.
in: Pharmaceutical Powder Compaction Technology, 2nd ed. (Celik, M., Ed.): 205-234, Informa Healthcare, London (2011)

[120] Bolhuis, G.K., De Jong, S.W., Van Kamp, H.V., Dettmers, H.
The effect on tablet crushing strength of magnesium stearate admixing in different types of labscale and production-scale mixers.
Pharm Technol 11: 36-44 (1987)

[121] Bolhuis, G.K., Reichman, G., Lerk, C.F., Kamp, H.V., Zuurman, K.
Evaluation of anhydrous alpha-lactose, a new excipient in direct compression.
Drug Dev Ind Pharm 11: 1657-1681 (1985)

[122] Jehn, H.A.
Multicomponent and multiphase hard coatings for tribological applications.
Surf Coat Technol 131: 433-440 (2000)

[123] König, W., Fritsch, R., Kammermeier, D.
Physically vapor deposited coatings on tools: performance and wear phenomena.
Surf Coat Technol 49: 316-324 (1991)

[124] Schumann, S., Searle, G.D.
The effects of chromium nitride ion bombardment treatment of tablet tooling on tablet adherence.
Drug Dev Ind Pharm 18: 1037-1061 (1992)

[125] Roberts, M., Ford, J.L., MacLeod, G.S., Fell, J.T., Smith, G.W., Rowe, P.H.
Effects of surface roughness and chrome plating of punch tips on the sticking tendencies of model ibuprofen formulations.
J Pharm Pharmacol 55: 1223-1228 (2003)

[126] Cunha, L., Andritschky, M., Rebouta, L., Silva, R.
Corrosion of TiN, (TiAl)N and CrN hard coatings produced by magnetron sputtering.
Thin Solid Films 317: 351-355 (1998)

[127] Stoiber, M., Panzenböck, M., Mitterer, C., Lugmair, C.
Fatigue properties of Ti-based hard coatings deposited onto tool steels.
Surf Coat Technol 142-144: 117-124 (2001)

[128] Dörfel, I., Österle, W., Urban, I., Bouzy, E.
Microstructural characterization of binary and ternary hard coating systems for wear protection. Part I: PVD coatings.
Surf Coat Technol 111: 199-209 (1999)

[129] Di Martino, P., Beccerica, M., Joiris, E., Palmieri, G.F., Gayot, A., Martelli, S.
Influence of crystal habit on the compression and densification mechanism of ibuprofen.
J Cryst Growth 243: 345-355 (2002)

[130] Kaul, D., Nguyen, N.T., Venkataram, S.
Crystal habit modifications and altered tabletting characteristics.
Int J Pharm 88: 345-350 (1992)

[131] Nokhodchi, A., Amire, O., Jelvehgari, M.
Physico-mechanical and dissolution behaviours of ibuprofen crystals crystallized in the presence of various additives.
DARU J Pharm Sci 18: 74-83 (2010)

[132] Rasenack, N., Müller, B.W.
Properties of ibuprofen crystallized under various conditions: a comparative study.
Drug Dev Ind Pharm 28: 1077-1089 (2002)

[133] Umprayn, K., Luengtummuen, A., Kitiyadisai, C., Pornpiputsakul, T.
Modification of crystal habit of ibuprofen using the phase partition technique: effect of Aerosil and Tween 80 in binding solvent.
Drug Dev Ind Pharm 27: 1047 (2001)

[134] Rasenack, N., Mueller, B.W.
Ibuprofen crystals with optimized properties.
Int J Pharm 245: 9-24 (2002)

[135] Jbilou, M., Ettabia, A., Guyot-Hermann, A.M., Guyot, J.C.
Ibuprofen agglomerates preparation by phase separation.
Drug Dev Ind Pharm 25: 297-305 (1999)

[136] Danjo, K., Kamiya, K., Otsuka, A.
Effect of temperature on the sticking of low-melting point materials.
Chem Pharm Bull 41: 1423-1427 (1993)

[137] Bechard, S.R., Down, G.R.B.
Infrared imaging of pharmaceutical materials undergoing compaction.
Pharm Res 9: 521-528 (1992)

[138] Rankell, A.S., Higuchi, T.
Physics of tablet compression XV. Thermodynamic and kinetic aspects of adhesion under pressure.
J Pharm Sci 57: 574-577 (1968)

[139] York, P., Pilpel, N.
Effect of temperature on the frictional, cohesive and electrical conducting properties of powders.
Mater Sci Eng 9: 281-291 (1972)

[140] Ritschel, W.A., Bauer-Brandl, A.
Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitäts-sicherung.
ECV Editio Cantor Verlag, Aulendorf (2002)

[141] Danjo, K., Kojima, S., Chen, C.Y., Sunada, H., Otsuka, A.
Effect of water content on sticking during compression.
Chem Pharm Bull 45: 706-709 (1997)

[142] Kakimi, K., Niwa, T., Danjo, K.
Influence of compression pressure and velocity on tablet sticking.
Chem Pharm Bull 58: 1565-1568 (2010)

[143] Waimer, F., Krumme, M., Danz, P., Tenter, U., Schmidt, P.
The influence of engravings on the sticking of tablets. Investigations with an instrumented upper punch.
Pharm Dev Technol 4: 369-375 (1999)

[144] Young, L.
Tableting specification manual.
American Pharmaceutical Association, Washington DC (1995)

[145] Roberts, M., Ford, J.L., MacLeod, G.S., Fell, J.T., Smith, G.W., Rowe, P.H., Dyas, A.M.
Effect of punch tip geometry and embossment on the punch tip adherence of a model ibuprofen formulation.
J Pharm Pharmacol 56: 947-950 (2004)

[146] Aoki, S., Danjo, K.
Effect of tableting conditions on the sticking of tablet using ibuprofen.
J Pharm Soc Jpn 118: 511-518 (1998)

[147] Booth, S.W., Newton, J.M.
Experimental investigation of adhesion between powders and surfaces.
J Pharm Pharmacol 39: 679-684 (1987)

[148] Felicetti, M.A., Salazar-Banda, G.R., Coury, J.R., Aguiar, M.L.
Influence of particle size, applied compression, and substratum material on particle-surface adhesion force using the centrifuge technique.
Ind Eng Chem Res 48: 877-887 (2009)

[149] Lam, K.K., Newton, J.M.
Effect of temperature on particulate solid adhesion to a substrate surface.
Powder Technol 73: 267-274 (1992)

[150] Podczeck, F., Newton, J.M.
Development of an ultracentrifuge technique to determine the adhesion and friction properties between particles and surfaces.
J Pharm Sci 84: 1067-1071 (1995)

[151] Podczeck, F., Newton, J.M., James, M.B.
Influence of relative humidity of storage air on the adhesion and autoadhesion of micronized particles to particulate and compacted powder surfaces.
J Colloid Interf Sci 187: 484-491 (1997)

[152] Butt, H.-J., Cappella, B., Kappl, M.
Force measurements with the atomic force microscope: technique, interpretation and applications.
Surf Sci Rep 59: 1-152 (2005)

[153] Louey, M.D., Mulvaney, P., Stewart, P.J.
Characterisation of adhesional properties of lactose carriers using atomic force microscopy.
J Pharmaceut Biomed 25: 559-567 (2001)

[154] Hooton, J.C., German, C.S., Allen, S., Davies, M.C., Roberts, C.J., Tendler, S.J.B., Williams, P.M.
An atomic force microscopy study of the effect of nanoscale contact geometry and surface chemistry on the adhesion of pharmaceutical particles.
Pharm Res 21: 953-961 (2004)

[155] Weber, D., Yu, P., Cooney, C.L.
Quantification of Lubricant Activity of Magnesium Stearate by Atomic Force Microscopy.
Drug Dev Ind Pharm 34: 1097-1099 (2008)

[156] Wang, J.J., Guillot, M.A., Bateman, S.D., Morris, K.R.
Modeling of adhesion in tablet compression. II. Compaction studies using a compaction simulator and an instrumented tablet press.
J Pharm Sci 93: 407-417 (2004)

[157] Hyvärinen, V., Peiponen, K.-E., Silvennoinen, R., Raatikainen, P., Paronen, P., Niskanen, T.
Optical inspection of punches: flat surfaces.
Eur J Pharm Biopharm 49: 87-90 (2000)

[158] Hyvärinen, V., Silvennoinen, R., Peiponen, K.-E., Niskanen, T.
Diffractive optical element based sensor for surface quality inspection of concave punches.
Eur J Pharm Biopharm 49: 167-169 (2000)

[159] Seitavuopio, P., Rantanen, J., Yliruusi, J.
Tablet surface characterisation by various imaging techniques.
Int J Pharm 254: 281-286 (2003)

[160] Toyoshima, K., Yasumura, M., Ohnishi, N., Ueda, Y.
Quantitative evaluation of tablet sticking by surface roughness measurement.
Int J Pharm 46: 211-215 (1988)

[161] Bouhroum, A., Blanchard, R.
Using analytical techniques to examine tablet sticking.
Pharm Technol Eur 25: 35-37 (2013)

[162] Mullarney, M.P., MacDonald, B.C., Hutchins, A.
Assessing tablet-sticking propensity: weighing accumulated powder on a removable punch tip.
Pharm Technol Eur 36: 57-62 (2012)

[163] Sendall, F.E.J., Staniforth, J.N.
A study of powder adhesion to metal surfaces during compression of effervescent pharmaceutical tablets.
J Pharm Pharmacol 38: 489-493 (1986)

[164] Roberts, M., Ford, J.L., MacLeod, G.S., Fell, J.T., Smith, G.W., Rowe, P.H., Dyas, A.M.
Effect of lubricant type and concentration on the punch tip adherence of model ibuprofen formulations.
J Pharm Pharmacol 56: 299-305 (2004)

[165] Waimer, F., Krumme, M., Danz, P., Tenter, U., Schmidt, P.C.
A novel method for the detection of sticking of tablets.
Pharm Dev Technol 4: 359-367 (1999)

[166] Mitrevej, A., Augsburger, L.L.
Adhesion of tablets in a rotary tablet press. I. Instrumentation and preliminary study of variables affecting adhesion.
Drug Dev Ind Pharm 6: 331-377 (1980)

[167] Mitrevej, K.T., Augsburger, L.L.
Adhesion of tablets in a rotary tablet press. II. Effects of blending time, running time, and lubricant concentration.
Drug Dev Ind Pharm 8: 237-282 (1982)

[168] Schmidt, P.C., Steffens, K.-J., Knebel, G.
Vereinfachung der Registrierung physikalischer Parameter bei der Tablettierung. 3. Mitteilung: Quantitative Erfassung des Klebens von Tabletten.
Pharm Ind 44: 1278-1283 (1982)

[169] Ritter, A., Dürrenberger, M., Sucker, H.
Messmethoden zur Quantifizierung des Klebens von Tabletten.
Pharm Ind 40: 1181-1183 (1978)

[170] Neuhaus, T.
Investigation and optimisation of the Presster - A linear compaction simulator for rotary tablet presses.
PhD Thesis, University of Bonn, Germany (2007)

[171] Quinquenet, S., Ollivon, M., Grabielle-Madelmont, C., Serpelloni, M.
Polymorphism of hydrated sorbitol.
Thermochim Acta 125: 125-140 (1988)

[172] DuRoss, J.W.
Modification of the crystalline structure of sorbitol and its effects on tableting characteristics.
Pharm Technol Eur 8: 42-53 (1984)

[173] Bolhuis, G.K., de Waard, H.
Compaction properties of directly compressible materials.
in: Pharmaceutical Powder Compaction Technology, 2nd ed. (Celik, M., Ed.): 143-204, Informa Healthcare, London (2011)

[174] Nezzal, A., Aerts, L., Verspaille, M., Henderickx, G., Redl, A.
Polymorphism of sorbitol.
J Cryst Growth 311: 3863-3870 (2009)

[175] Bolhuis, G.K., Rexwinkel, E.G., Zuurman, K.
Polyols as filler-binders for disintegrating tablets prepared by direct compaction.
Drug Dev Ind Pharm 35: 671-677 (2009)

[176] Guyot-Hermann, A.M., Draguet-Brughmans, M.
Gamma sorbitol as a diluent in tablets.
Drug Dev Ind Pharm 11: 551-564 (1985)

[177] Lee, J.
Intrinsic adhesion force of lubricants to steel surface.
J Pharm Sci 93: 2310-2318 (2004)

[178] Hwang, R., Parrott, E.L.
Effect of a lubricant on wear rate of tablets.
Drug Dev Ind Pharm 19: 1379-1391 (1993)

[179] Dansereau, R., Peck, G.E.
The effect of the variability in the physical and chemical properties of magnesium stearate on the properties of compressed tablets.
Drug Dev Ind Pharm 13: 975-999 (1987)

[180] Lerk, P.C., Sucker, H.
Interaction of magnesium stearate and talc upon tabletting mixtures II: Effect on wettability of powder blends.
Acta Pharm Technol 34: 72-76 (1988)

[181] Uchimoto, T., Iwao, Y., Takahashi, K., Tanaka, S., Agata, Y., Iwamura, T., Miyagishima, A., Itai, S.
A comparative study of glycerin fatty acid ester and magnesium stearate on the dissolution of acetaminophen tablets using the analysis of available surface area.
Eur J Pharm Biopharm 78: 492-498 (2011)

[182] Shah, N.H., Stiel, D., Weiss, M., Infeld, M.H., Malick, A.W.
Evaluation of two new tablet lubricants - sodium stearyl fumarate and glyceryl behenate. Measurements of physical parameters (compaction, ejection, and residual forces) in the tabletting process and the effect of the dissolution rate.
Drug Dev Ind Pharm 12: 1329-1346 (1986)

[183] Delacourte, A., Predella, P., Leterme, P., Provasi, D., Colombo, P., Conte, U.
A method for qualitative evaluation of the effectiveness of the lubricants used in tablet technology.
Drug Dev Ind Pharm 19: 1047-1060 (1993)

[184] BASF
Technical information brochure.
BASF AG, Ludwigshafen, Germany (2009)

[185] Rowe, R.C., Sheskey, P.J., Quinn, M.E.
Handbook of Pharmaceutical Excipients.
Pharmaceutical Press, London (2009)

[186] Schepky, G.
Preformulation - The role of moisture in solid dosage forms.
Drug Dev Ind Pharm 15: 1715-1741 (1989)

[187] Stahl, P.H.
Feuchtigkeit und Trocknen in der pharmazeutischen Technologie.
Steinkopff, Darmstadt (1980)

[188] Nelson, E., Naqvi, S.N., Busse, L.W.
The physics of tablet compression. IV. Relationship of ejection, upper and lower punch forces during the compressional process.
J Amer Pharm Assoc 43: 596-602 (1954)

[189] Fell, J.T., Newton, J.M.
The tensile strength of lactose tablets.
J Pharm Pharmacol 20: 657-659 (1968)

[190] Schmidt, P.C., Vortisch, W.
Einfluss der Herstellungsart von Füll- und Bindemitteln auf ihre Tablettierfähigkeit. Vergleich von 8 marktüblichen Sorbit-Typen.
Pharm Ind 49: 495-503 (1987)

[191] Nikolakakis, I., Newton, J.M., Malamataris, S.
Solid state 'adsorption' of fine antibiotic powders onto sorbitol: effects of particle size, state of sorbed water and surface free energy characteristics.
Eur J Pharm Sci 17: 229-238 (2002)

[192] Hoag, S.W., Dave, V.S., Moolchandani, V.
Compression and compaction.
in: Pharmaceutical Dosage Forms: Tablets, Vol. 1, 3rd ed. (Augsburger, L.L. and Hoag, S.W., Ed.): 555-630, Informa Healthcare, USA (2008)

[193] Caramella, C., Colombo, P., Conte, U., Ferrari, F., Gazzaniga, A., LaManna, A., Peppas, N.A.
A physical analysis of the phenomenon of tablet disintegration.
Int J Pharm 44: 177-186 (1988)

[194] Ahuja, N., Katare, O.P., Singh, B.
Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers.
Eur J Pharm Biopharm 65: 26-38 (2007)

[195] Michaud, J.
Crystalline sorbitol. A pharmaceutical excipient for direct compression.
PharmaChem 1/2: 62-64 (2003)

[196] Kothari, S.H., Kumar, V., Banker, G.S.
Comparative evaluations of powder and mechanical properties of low crystallinity celluloses, microcrystalline celluloses, and powdered celluloses.
Int J Pharm 232: 69-80 (2002)

[197] Picker, K.M.
The 3D model: explaining densification and deformation mechanisms by using 3D parameter plots.
Drug Dev Ind Pharm 30: 413-425 (2004)

[198] Gohel, M.C., Parikh, R.K., Brahmbhatt, B.K., Shah, A.R.
Improving the tablet characteristics and dissolution profile of ibuprofen by using a novel coprocessed superdisintegrant: a technical note.
AAPS Pharm Sci Tech 8: E1-E6 (2007)

[199] Marshall, P.V., York, P., Maclaine, J.Q.
An investigation of the effect of the punch velocity on the compaction properties of ibuprofen.
Powder Technol 74: 171-177 (1993)

[200] Nokhodchi, A., Rubinstein, M.H., Larhrib, H., Guyot, J.C.
The effect of moisture on the properties of ibuprofen tablets.
Int J Pharm 118: 191-197 (1995)

[201] Romero, A.J., Savastano, L., Rhodes, C.T.
Monitoring crystal modifications in systems containing ibuprofen.
Int J Pharm 99: 125-134 (1993)

[202] Schmidt, P.C., Rubensdörfer, J.W.
Evaluation of Ludipress as a "multipurpose excipient" for direct compression. Part I: Powder characteristics and tableting properties.
Drug Dev Ind Pharm 20: 2899-2925 (1994)

[203] Celik, M.
Overview of compaction data analysis techniques.
Drug Dev Ind Pharm 18: 767-810 (1992)

[204] Lerk, C.F.
Consolidation and compaction of lactose.
Drug Dev Ind Pharm 19: 2359-2398 (1993)

[205] Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.
Effect of compression force, compression speed, and particle size on the compression properties of paracetamol.
Drug Dev Ind Pharm 27: 935-942 (2001)

[206] Meggle
Technical information brochure.
Molkerei Meggle GmbH & Co KG, Wasserburg, Germany (2010)

[207] Michoel, A., Rombaut, P., Verhoye, A.
Comparative evaluation of co-processed lactose and microcrystalline cellulose with their physical mixtures in the formulation of folic acid tablets.
Pharm Dev Technol 7: 79-87 (2002)

[208] Hiestand, E.N., Peot, C.B.
Tensile strength of compressed powders and an example of incompatibility as end-point on shear yield locus.
J Pharm Sci 63: 605-612 (1974)

[209] Podczeck, F., Miah, Y.
The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders.
Int J Pharm 144: 187-194 (1996)

[210] Hedenqvist, P., Jacobson, S., Hogmark, S.
Tribological PVD coatings - characterisation of mechanical properties.
Surf Coat Technol 97: 212-217 (1997)

[211] Wiedemann, R., Oettel, H., Bertram, T., Weihnacht, V.
Mechanical Properties of TiN Coatings.
Adv Eng Mater 3: 865-870 (2001)

[212] Barra, J., Somma, R.
Influence of the physicochemical variability of magnesium stearate on its lubricant properties: possible solutions.
Drug Dev Ind Pharm 22: 1105-1120 (1996)

[213] Rao, K.P., Chawla, G., Kaushal, A.M., Bansal, A.K.
Impact of solid-state properties on lubrication efficacy of magnesium stearate.
Pharm Dev Technol 10: 423-437 (2005)

[214] Riepma, K.A., Vromans, H., Lerk, C.F.
A coherent matrix model for the consolidation and compaction of an excipient with magnesium stearate.
Int J Pharm 97: 195-203 (1993)

[215] Vromans, H., Bolhuis, G.K., Lerk, C.F.
Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties.
Powder Technol 54: 39-44 (1988)

[216] Tobyn, M.J., McCarthy, G.P., Staniforth, J.N., Edge, S.
Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose.
Int J Pharm 169: 183-194 (1998)

[217] DeCrosta, M.T., Schwartz, J.B., Wigent, R.J., Marshall, K.
Thermodynamic analysis of compact formation; compaction, unloading, and ejection: II. Mechanical energy (work) and thermal energy (heat) determinations of compact unloading and ejection.
Int J Pharm 213: 45-62 (2001)

[218] Saniocki, I., Sakmann, A., Leopold, C.S.
How suitable is the measurement of take-off forces for detection of sticking during direct compression of various ibuprofen tablet formulations?
Pharm Dev Technol 18: 257-265 (2013)

7. Appendix

Curriculum vitae

Personal Data:

Name:	Ines Saniocki
Date of birth:	09. September 1982
Place of birth:	Brandenburg an der Havel
Marital status:	married

Job History	since 05/2012	Project Manager Technical Service/ Quality, Alfred E. Tiefenbacher GmbH & Co. KG, Hamburg
	05/2008 – 04/2012	Ph.D. student, University of Hamburg, Department of Chemistry, Division of Pharmaceutical Technology; Supervisor: Prof. Dr. Claudia S. Leopold
Specialization	12/2012	Pharmaceutical Specialist for Pharmaceutical Technology
Education	12/2008	Licensed Pharmacist
	10/2002 – 10/2007	Pharmaceutical studies, University of Hamburg
Internships	05/2008- 10/2008	University of Hamburg, Division of Pharmaceutical Technology
	11/2007- 04/2008	Helms Apotheke am Sande, Lüneburg
School	06/2002	A-level diploma, Friedlieb-Ferdinand-Runge-Gymnasium, Oranienburg

Publication List

Publications

Saniocki, I., Sakmann, A., Leopold, C.S.
Direct compression of ibuprofen-containing powder blends – Influence of the ibuprofen grade on the flow and compaction properties of an ibuprofen tablet formulation.
Pharm. Ind. 74, Nr. 11, 1842-1852 (2012)

Saniocki, I., Sakmann, A., Leopold, C.S.
How suitable is the measurement of take-off forces for detection of sticking during direct compression of various ibuprofen tablet formulations?
Pharm. Dev. Technol. 18(1), 257-265 (2013)

Saniocki, I., Sakmann, A., Leopold, C.S.
Evaluation of the suitability of various lubricants for direct compaction of sorbitol tablet formulations.
J. Excipients and Food Chem. 4 (4), 169-182 (2013)

Saniocki, I., Sakmann, A., Leopold, C.S.
Impact of punch tip coating on the anti-adherent performance of the lubricant magnesium stearate during direct compaction of various excipients.
In preparation (2014)

Oral presentations

Saniocki, I.
Tableting: Common problems and how to avoid them.
In-house training at KORSCH AG, Berlin, Germany (2009)

Saniocki, I.
Interpretation of the data recorded during tableting.
In-house training at KORSCH AG, Berlin, Germany (2011)

Poster presentations

Hentzschel, C.M., Saniocki, I., Sakmann, A., Leopold, C.S.
Particle size, surface area and flowability of novel tableting excipients.
XIV. Workshop Porotec, Bad Soden, Germany (2008)

Saniocki, I., Sakmann, A., Leopold, C.S.
Compactibility and sticking properties of ibuprofen-containing Microcelac® 100 tablets.
7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Valletta, Malta (2010)

Saniocki, I., Sakmann, A., Leopold, C.S.
Characterization of the sticking tendency during tablet manufacture – Take-off force measurement and quantification of material adhering to the punch surface.
37th Annual Meeting & Exposition of the Controlled Release Society , Portland, USA (2010)

Saniocki, I., Sakmann, A., Leopold, C.S.
Quantification of sticking to the punch surfaces during tablet manufacture.
Annual meeting of the DPhG, Braunschweig, Germany (2010)

Poster presentations (continued)

Saniocki, I., Sakmann, A., Leopold, C.S.
Investigation of the sticking tendency during tablet manufacture – Compaction of binary mixtures of ibuprofen and Ludipress®.
FIP PSWC/AAPS Annual Meeting and Exposition, New Orleans, USA (2010)

Saniocki, I., Sakmann, A., Leopold, C.S.
Effect of punch tip coating and geometry on the sticking tendency of an ibuprofen tablet formulation.
38th Annual Meeting & Exposition of the Controlled Release Society , National Harbor, USA (2011)

Saniocki, I., Sakmann, A., Leopold, C.S.
Impact of the lubricant type on compaction and tablet properties of sorbitol formulations.
Joint meeting of the ÖPhG and DPhG, Innsbruck, Austria (2011)

Saniocki, I., Klukkert, M., Sakmann, A., Leopold, C.S.
Compaction of tablet formulations based on Ludipress® containing high-dose poorly compressible and pressure-sensitive drugs.
AAPS Annual Meeting and Exposition, Washington D.C., USA (2011)

Saniocki, I., Sakmann, A., Leopold, C.S.
Impact of punch tip coating on the anti-adherent performance of the lubricant magnesium stearate during direct compression of various excipients.
8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Istanbul, Turkey (2012)

Hazardous materials

Substance	Supplier	Danger symbol	Code letter	Hazard statements	Precautionary statements
Ibuprofen	Caelo, Germany BASF, Germany Shasun, India Hubei, China		Xi	H302	P301, P312
Acetone	Merck, Germany		F, Xi	H225, H319, H336	P210, P233, P303+P361+P353 P305+P351+P338
Acetonitril	Prolabo, Germany		F, Xn	H225, H302, H312, H319, H332	P210, P233, P301+P312 P302+P352 P303+P361+P353 P304+P340 P305+P351+P338 P403+P235
Isopropanol	-		F, Xn	H225, H319, H336	P210, P233, P303+P361+P353 P305+P351+P338 P403+P235

Substance	Supplier	Danger symbol	Code letter	Hazard statements	Precautionary statements
Methanol	Merck, Germany	  	T, F, Xn	H225, H301, H311, H331, H370	P210, P280, P301+P310 P302+P352 P303+P361+P353 P304+P340 P307+P311 P403+P235
Sodium hydroxide (1N)	Carl Roth, Germany		C	H314	P301+P330+P331 P303+P361+P353 P304+P340 P305+P351+P338
Ammonium nitrate	Merck, Germany	 	O, Xi	H272, H319	P220, P280, P305+P351+P338 P370+P378
Magnesium chloride hexahydrate	Merck, Germany		Xi	H315, H319	P261, P280, P305+P351+P338
Potassium carbonate sesquihydrate	Merck, Germany	 	C, Xi	H335, H314, H302, H318	P261, P280, P301+P312 P301+P330+P331 P305+P351+P338 P310

Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, die vorliegende Arbeit selbstständig und ohne fremde Hilfe sowie nur mit den angegebenen Hilfsmitteln und Quellen erstellt zu haben. Ich versichere zudem, keinen weiteren Promotionsversuch an einer anderen Einrichtung unternommen zu haben.

Hamburg, den

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Ines Saniocki