The application of lower punch vibration to improve the tableting process of a rotary tablet press

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Alexander Kalies

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Reviewer of the thesis:	**Professor Dr. Claudia S. Leopold**
	Professor Dr. Hans-Ulrich Moritz
Thesis defence committee:	**Professor Dr. Claudia S. Leopold**
	Professor Dr. Ralph Holl
	Priv. Doz. Dr. Christoph Wutz
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Zusammenfassung

Die Tablette als Arzneiform stellt aufgrund ihrer wirtschaftlich günstigen Produktionsmöglichkeiten, ihrer vorteilhaften physikalischen Eigenschaften sowie ihrer ausgesprochen hohen Patientencompliance einen besonders attraktiven Ansatz der Arzneistoffapplikation dar. Um den regulatorisch festgelegten Qualitätsanforderungen zu entsprechen, werden hohe Ansprüche an die Tablettenformulierung als solche sowie an die sich anschließenden Produktionsprozesse gestellt. So bedarf es oftmals teurer und speziell zugeschnittener Hilfsstoffe oder auch vorgeschalteter Produktionsprozesse wie der Granulierung, um die erforderlichen Eigenschaften wie Fließfähigkeit, Kompressibilität und Kompaktibilität der Pulvermischung für eine erfolgreiche Tablettierung zu gewährleisten. Eine Möglichkeit, den Tablettierprozess positiv zu beeinflussen, besteht in der Verwendung von Ultraschalvibration während der Tablettierung, wobei die bisher entwickelten Systeme nur eine begrenzte Anwendbarkeit im Labormaßstab zeigten. Aus diesem Grund beinhaltet die vorliegende Doktorarbeit die Entwicklung eines innovativen pneumatischen Vibrationssystems, welches den Tablettierprozess und insbesondere die Matrizenbefüllung verbessert. Durch eine gezielte pneumatische Vibration des Unterstempels innerhalb der Füllkurve soll die Fließfähigkeit der Pulvermischung aus der Fülleinheit optimiert, das Pulverbett innerhalb der Matrize verdichtet und Lufteinschlüsse innerhalb des Pulverbettes entfernt werden.

Hierzu wurde im Rahmen einer ersten Studie ein pneumatisch arbeitendes Vibrationssystem für den Labormaßstab entwickelt und in Bezug auf dessen Leistungsfähigkeit für ein späteres Scale-Up untersucht. Die Pulververdichtung innerhalb einer Matrize wurde mittels einer Hochgeschwindigkeitskamera aufgenommen und im Anschluss mit Hilfe eines Bildverarbeitungsprogramms

quantifiziert. Es zeigte sich, dass die zwei untersuchten Vibrationssysteme die benötigte Leistungsfähigkeit besaßen, um ein Pulverbett schnell und ausgeprägt zu verdichten. Auf dieser Grundlage wurde während einer zweiten Studie ein Vibrationssystem zur Implementierung in einer Rundläufertablettenpresse entwickelt und dessen Leistungsfähigkeit während der Tablettenproduktion untersucht. Das Vibrationssystem war in der Lage, die Matrizenbefüllung aufgrund der vibrationsinduzierten Neuordnung der Pulverpartikel innerhalb der Matrize stark zu verbessern. Als Folge dieser Pulverbettverdichtung wurden neue Kontaktflächen zwischen den Pulverpartikeln geschaffen, was sich positiv auf die Bindungskapazität und somit die mechanische Stabilität der Tabletten auswirkte.

Im Rahmen einer dritten Studie wurde die Anwendbarkeit der Unterstempelvibration im Hinblick auf die Reduktion und Vermeidung von häufig auftretenden Produktionsfehlern wie dem Deckeln oder dem Laminieren untersucht. Das Auftreten von Deckeln und/oder Laminieren während oder im Anschluss an die Tablettierung lässt sich häufig auf Lufteinschlüsse innerhalb der Tablette zurückführen. Mittels der Unterstempelvibration war es möglich, potentielle Lufteinschlüsse innerhalb des Pulverbettes schon vor der Kompaktierung zu entfernen und so das Auftreten von Deckeln und/oder Laminieren teilweise oder sogar vollständig zu verhindern.

In der letzten Studie wurde der Fokus auf den Einfluss der Unterstempelvibration auf verschiedene Tablettiereigenschaften (z.B. Bindungsfähigkeit, Kompaktierbarkeit) der verwendeten Pulver und den daraus resultierenden Qualitätsanforderungen (z.B. Bruchfestigkeit, Friabilität) der hergestellten Tabletten gelegt. Die Ergebnisse verdeutlichen, dass abhängig von der verwendeten Pulverformulierung wichtige Tablettiereigenschaften durch die Anwendung pneumatischer Unterstempelvibration

positiv beeinflusst und somit die mechanische Stabilität der Tabletten verbessert werden.

Zusammenfassend lässt sich sagen, dass die Anwendung von pneumatischer Unterstempelvibration einen vielversprechenden und innovativen Ansatz darstellt, um den Tablettierprozess zu optimieren und den Qualitätsanforderungen der Tabletten zu genügen.

Abstract

Because of the economically attractive production possibilities, the good physico-chemical properties and the high patient compliance, tablets are advantageous and present an attractive approach for API application. According to the regulatory quality requirements, high standards are expected for the tablet formulation as such and for the respective production process. Therefore, expensive and specially particle-engineered excipients as well as upstream production processes such as granulation are often necessary to meet the required tableting properties such as flowability, compressibility, and compactibility of the powders to be tableted. One possibility to improve the tableting process is the application of ultrasonic tool vibration during tablet compaction. However, the vibration systems developed so far show a limited applicability and may only be used on a laboratory scale. For this reason, the present thesis deals with the development of an innovative pneumatic vibration system that improves the tableting process and especially the die filling step. By means of a targeted pneumatic lower punch vibration within the filling cam, the die filling may be improved, the powder bed within the die may be densified, and entrapped air within the powder bed may be removed.

For this purpose, in a first study a pneumatically operating vibration system for laboratory scale was developed and investigated with regard to its performance characteristics and a subsequent scale-up. The powder bed densification within a die was recorded with a high-speed camera system and subsequently quantified with an image analyzing program. It was observed that the two investigated vibration systems met the required properties to allow a fast and significant densification of the powder bed within the die. In a second study, a respective vibration system was developed and implemented on a rotary tablet press. Subsequently, the performance

characteristics of both vibration systems were investigated during tablet production. It was shown that the application of lower punch vibration led to improved die filling as the consequence of the rearrangement of the powder particles within the die. Furthermore, new contact surfaces between the powder particles are created, which positively influence the bondability and thus the resulting mechanical tablet stability.

In a third project, the applicability of lower punch vibration was investigated with regard to the avoidance of production errors such as capping and/or lamination. The occurrence of capping and/or lamination during or after tablet manufacturing is often caused by entrapped air within the tablet. By lower punch vibration, it was possible to remove the entrapped air prior to the compaction step and thus the occurrence of capping and/or lamination was partially or completely prevented.

The last study dealt with the influence of lower punch vibration on various tableting properties of the powders to be tableted (e.g. bondability, compactibility) and the resulting quality attributes of the manufactured tablets (e.g. crushing force, friability). The results clearly showed that depending on the used powder formulation, important tableting properties are positively influenced by the application of pneumatic lower punch vibration, thus leading to an increased mechanical tablet stability.

In summary, the application of pneumatic lower punch vibration is a promising and innovative approach to improve the tableting process as well as to meet the quality requirements of the tablets.

Conference contributions and publications

In context with this work, the following contributions have been presented at conferences and journal articles have been published.

Conference contributions - oral presentations

Kalies, A., Heinrich, T., Leopold, C.S.
Application of lower punch vibration to improve the mechanical stability of tablets.
3rd International Symposium on Pharmaceutical Engineering Research – SPhERe 2019, Braunschweig, Germany

Conference contributions - poster presentations

Kalies, A., Özcoban, H., Leopold, C.S.
Application of pneumatic punch vibration for densification enhancement of pharmaceutical powders.
Meeting of the American Association of Pharmaceutical Scientists 2017, San Diego, USA

Kalies, A., Özcoban, H., Leopold, C.S.
Instrumentation of a lower punch vibration equipment on a rotary tablet press for enhanced die filling.
11th World Meeting on Pharmaceutics,Biopharmaceutics and Pharmaceutical Technology 2018, Granada, Spain

Kalies, A., Özcoban, H., Leopold, C.S.
A novel technique to reduce the tendency of capping and/or lamination during the tableting process.
Conference on Pharmaceutics 2019, Bologna, Italy

Journal articles with authors` contributions and reference chapters.

Title	Journal	Authors	Contribution to the work	Percentage	Reference chapters
Performance characteristics of a novel vibration technique for the densification of a powder bed within a die of a rotary tablet Press — a proof of concept	AAPS PharmSciTech (accepted)	Kalies. A. Özcoban. H. Leopold. C.S.	Project plan, experiments,data analysis, publication Supervisor Supervisor	100%	2.2.1., 2.2.2., 2.2.4., 2.2.6.1., 3.1.
Application of externally applied lower punch vibration and its effects on tablet manufacturing	Pharmaceutical Research (accepted)	Kalies. A. Özcoban. H. Leopold. C.S.	Project plan, experiments,data analysis, publication Supervisor Supervisor	100%	2.2.1., 2.2.2., 2.2.3.1., 2.2.3.2, , 2.2.5., 2.2.6.2., 3.2.
A novel approach to avoid capping and/or lamination by application of external lower punch vibration	International Journal of Pharmaceutics (accepted)	Kalies. A. Heinrich. T. Leopold. C.S.	Project plan, experiments,data analysis, publication Supervisor Supervisor	100%	2.2.1., 2.2.2., 2.2.3.1., 2.2.3.2., 2.2.3.4., 2.2.3.5., 2.2.6.2., 3.3.
The influence of lower punch vibration on the mechanical properties of tablets manufactured with a rotary tablet press	Pharmaceutical development and technology (under review)	Kalies. A. Heinrich. T. Leopold. C.S.	Project plan, experiments,data analysis, publication Supervisor Supervisor	100%	2.2.1., 2.2.2., 2.2.3.1., 2.2.3.2., 2.2.3.3., 2.2.3.4., 2.2.6.2., 3.4.

List of Abbreviations

APAP	Acetaminophen
API	Active pharmaceutical ingredient
CCS	Croscarmellose sodium
CI	Carr index
CM	Continuous manufacturing
DEM	Discrete element method
***ff*$_c$**	Powder flowability index
GMP	Good manufacturing practice
HR	Hausner ratio
Lac	Lactose monohydrate
MCC	Microcrystalline cellulose
$MgCO_3$	Basic magnesium carbonate
MgSt	Magnesium stearate
NIH	National Institutes of Health
PAT	Process analytical systems
Ph. Eur.	European Pharmacopoeia
SD	Standard deviation
SEM	Scanning electron microscope
SF	Solid fraction
US	Ultrasound
USP	United States Pharmacopeia

Contents

1. Introduction

1.1. Tablets for pharmaceutical use

1.1.1. General aspects

Up to 90 % of all APIs are administered orally, whereby solid dosage forms are mainly used for this purpose as they offer a number of advantages compared to semi-solid or liquid systems [1]. Currently, in the field of solid oral dosage forms, tablets present the highest share in the pharmaceutical market [2]. In comparison to other dosage forms, tablets represent an attractive way to administer APIs, because of their low manufacturing costs, high storage stability, easy handling, and acceptable patient compliance [3]. Furthermore, the physicochemical properties of a tablet may be modified with regard to the needs of the patients [4]. Especially the application of coatings offers the possibility to change a variety of tablet properties [5]. These include taste masking, increased storage and transport stability, easier tablet intake, and a possible controlled release of the APIs from the tablet [6–8].

According to the Ph. Eur., tablets are described as single dosage forms that can serve as a carrier for one or more APIs. They are usually administered via the oral route but may also be applied rectally or vaginally [9]. The administration of a tablet may vary depending on the target of the API within the organism and the preferred onset of action. Generally, tablets are either swallowed, chewed, sucked or have to be dissolved/dispersed in water before intake [10,11]. In this context, the Ph. Eur. divides tablets in several categories such as uncoated tablets, coated tablets, modified release tablets, tablets for use in the mouth, or soluble tablets. This variety enables a targeted-oriented therapy of the patient [12].

What all tablets have in common is the production process, whereby powder particles and/or particle aggregates are compressed to a uniform volume [13]. This consolidation process of the powder bed enables the powder particles -as a consequence of the reduction of the distance to each other- to form and build physical and chemical bonds [14]. Also suitable manufacturing processes are extrusion, lyophilization, molding, and 3-D printing [15–18].

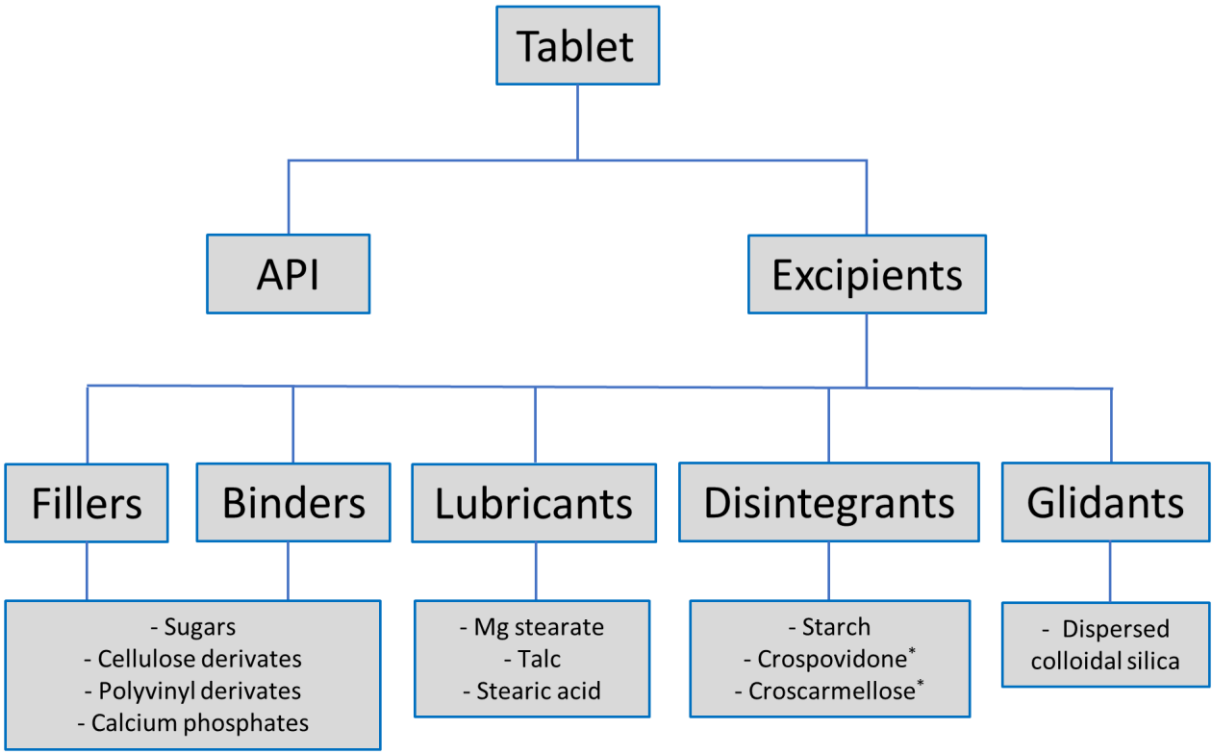
All of these manufactured tablets have to fulfill different requirements depending on the respective Pharmacopeia (e.g. Ph. Eur., USP). Within these Pharmacopeias, rules concerning various quality aspects of the tablets are listed regarding their mechanical stability, content or mass uniformity, disintegration, dissolution, and microbiological quality [19]. The shape of these manufactured tablets is commonly spherical, oval, or oblong, whereby the tablets may reveal flat or convex surfaces and might include snap tabs, marks, and imprints [20]. Especially the marks and imprints may be important for an unambiguous identification by the patient [21].

Although the process of tablet manufacturing is well-understood and constantly further developed, it still needs investigations to improve and optimize this process for economic and quality reasons [22,23]. Because of the intensified regulatory requirements special technical demands for the processing of newly developed APIs are needed [15].

1.1.2. Tableting materials and their functionality

The composition of a tablet is variable and strongly depends on the route of administration, the intended site of action, and the preferred release profile of the API [24–26]. Depending on the manufacturing method, a tablet is usually composed of either one or two phases (inner and outer phase). In the case of the two phases, the

inner phase consists of the API, the filler, the binder, and the disintegrant (in the form of aggregates), whereas the outer phase usually consists of the disintegrant, the lubricant, and the glidant (in the form of powders) [27,28]. The selection of excipients depends on the physicochemical properties of the APIs, the type of tablet, and the selected manufacturing process [29]. In Fig. 1, examples for the most commonly used excipients for pharmaceutical tablet manufacturing are shown, whereby in Table 1 the respective functions of the excipients are listed.



* *Superdisintegrant*

Fig. 1: Typical tablet composition consisting of the API and relevant excipients.

Table 1: Classification of commonly used excipients for tablet manufacturing and their functionality.

Excipient	Functionality
Fillers	• Dilution of the APIs (volume fill) • Prevention of agglomeration between the API particles
Binders	• Increased compactibility (plastic deformation) • Increased mechanical tablet stability (creation and enlargement of interparticle bonding)
Lubricants	• Decreased die wall friction (during the compression and ejection stage) • Decreased friction between die and punches • Decreased sticking between the tablet and the tooling equipment • Decreased energy input and heat generation
Disintegrants	• Enhanced tablet disintegration (porosity ↑, swellability ↑, “wick effect”, elastic deformation ↑) • Breaking of interparticle bonding points
Glidants	• Improved dosing accuracy (flowability ↑, segregation ↓) • Enhanced die disk speed (improved die filling)

In addition to the listed excipients, further additives are used in tablet compositions such as humectants, adsorbents, flavorings, colorants, and substances which influence the tablet dissolution [30,31]. Some excipients may possess more than one function [32]. Furthermore, the functionality and performance characteristics of the excipients strongly depend on the production process and/or pretreatment steps (milling, sieving, etc.) [33]. Hence, key parameters such as the flowability and

compactibility may vary within an excipient class despite the same chemical composition [34]. For instance, lactose which is used as filler/binder for tablet manufacturing differs regarding its physicochemical properties depending on its respective type: milled, sieved, agglomerated, spray-dried, and co-processed [35]. Co-processed means that excipients from different groups are processed together to build so-called compound excipients with advanced properties [36,37]. Depending on the co-processing steps, changes in the particle morphology, the crystallinity, the porosity, the surface area, and the binding forces occur, which in turn may positively affect the miscibility, flowability and compactibility of the excipients [38]. However, this “particle engineering” leads to an increase in costs because of the complex and time consuming pretreatment steps for these compound excipients (co-crystallization, agglomeration, granulation, spray-drying, and precipitation) [39].

In terms of economic efficacy, there is still a need for novel technologies and innovations to improve the tableting properties of the required excipients by introducing new strategies for direct compression or special equipment for tablet manufacturing.

1.2. Tablet Manufacturing

1.2.1. Tableting process

In the pharmaceutical industry, tableting is a well-established and important manufacturing process [14]. In comparison to other production techniques (e.g. the preparation of sterile formulations) the required effort for the manufacturing of tablets is comparatively low because the output is high, making tableting economic and cost-effective and thus, very attractive [2]. The tableting process with a rotary tablet press is displayed in Fig. 2., whereby the process usually comprises several steps.

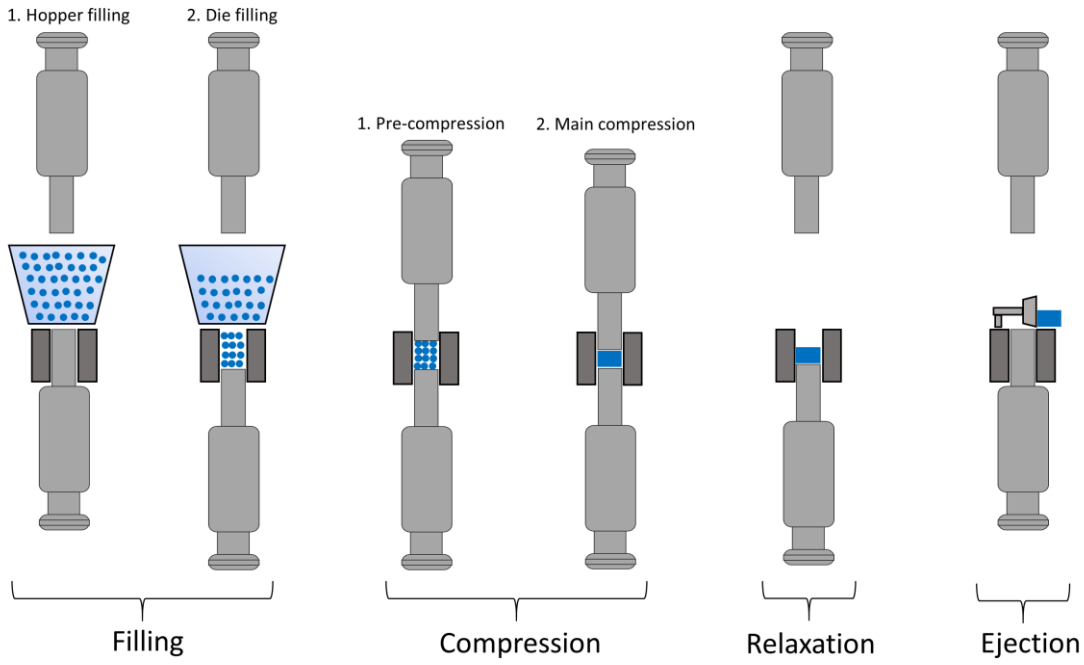


Fig. 2: Tableting process with a rotary tablet press comprising the required steps.

Depending on the type of the tablet press (see chapter 1.2.3.), the die filling process proceeds differently. It may proceed either passively by a driven moving shoe (excenter, single punch tablet press) or actively by using a stationary filling system (rotary tablet press) [40]. During the passive die filling, the die is filled by the powder caused by gravity [41], whereas the active die filling process combines the gravity filling

with the effect of “suction filling”, due to the lower punch moving down while passing the filling cam [42]. The die filling step of the rotary tablet press is more precisely displayed in Fig. 3.

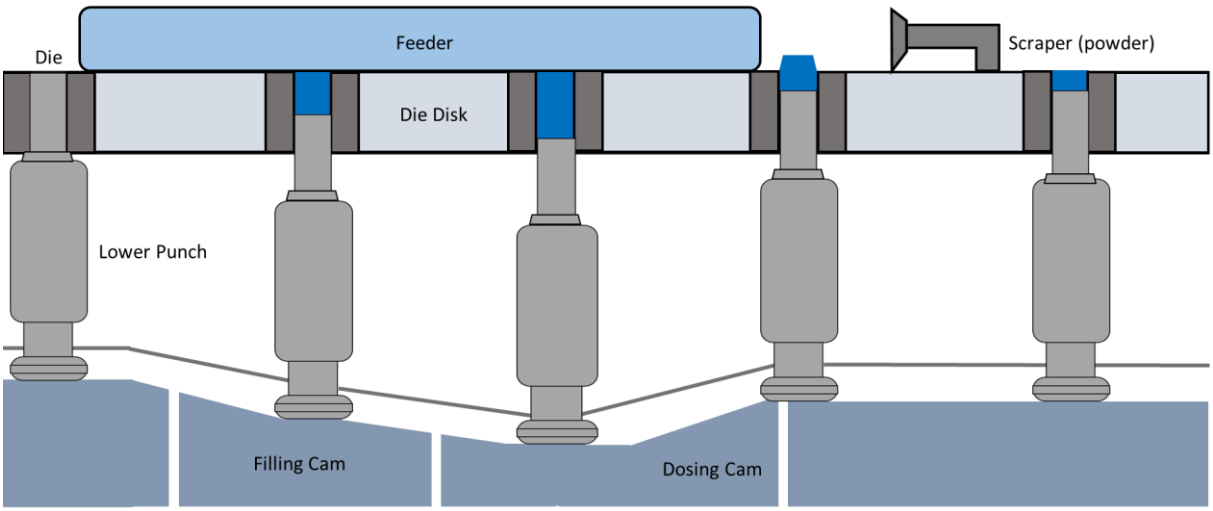


Fig. 3: Die filling during tableting with a rotary tablet press.

After the die filling step an out-dosing step takes place. By passing the dosing cam the lower punch moves upwards which leads to a defined powder volume within the die, depending on the predetermined machine settings. Accordingly, it is possible to adjust a defined tablet mass through the out-dosing step. Next to the mass adjustment of the tablet, the out-dosing step also leads to a removal of entrapped air which presents an additional benefit with respect to the resulting mechanical stability of the tablet [43]. Immediately after the out-dosing step the excessive powder is scraped into the filling chute. Usually, the scraped powder can be reused if suitable equipment is available. After the filling step, the compression and compaction steps follow, ultimately leading to the tablet formation. The compression/compaction process is exemplary illustrated in Fig. 4.

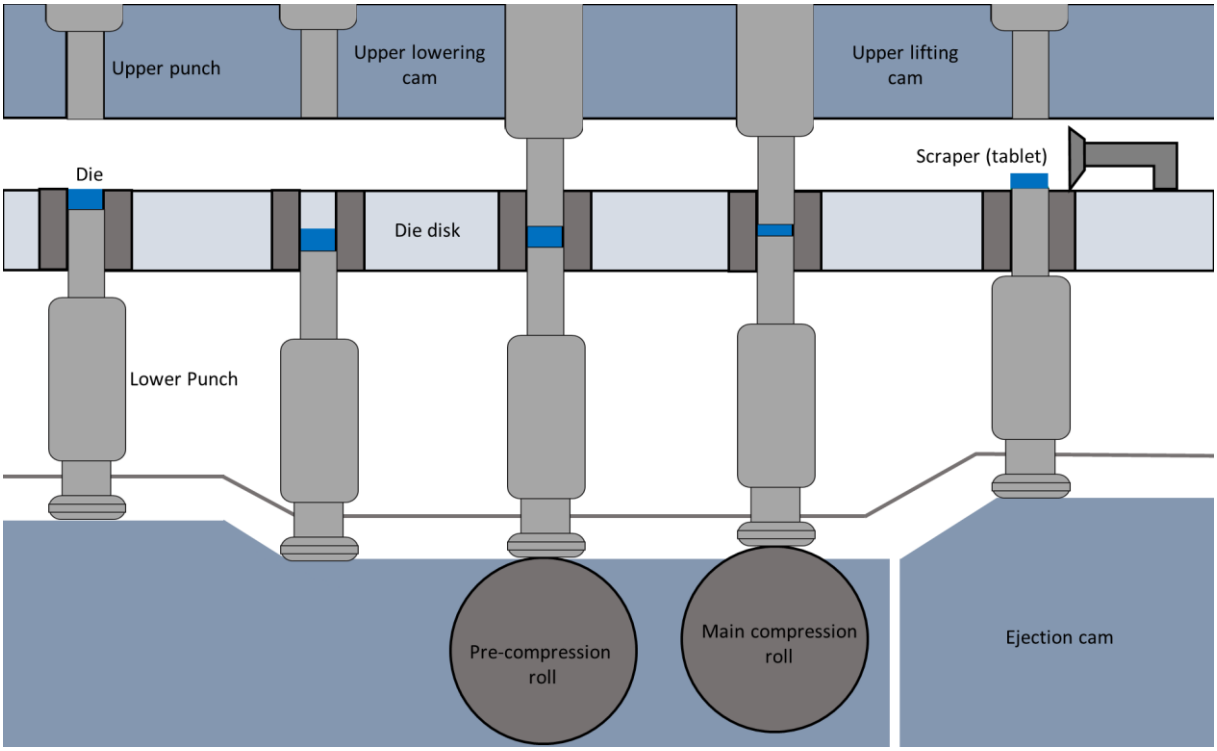


Fig. 4: Powder compression during tableting with a rotary tablet press.

Usually, the lower and upper punch pass two compression rolls, whereby the pre-compression step is optional and not available for all rotary tablet presses [44]. The use of a pre-compression roll is a well-established technical approach to remove entrapped air within the powder bed, to prevent manufacturing and product quality problems during the tableting process, and to improve the mechanical stability of the resulting tablets [45,46]. Hence, the applied compaction force during the pre-compression step is generally lower than the compaction force applied during the main compression step [47]. During the compression and compaction steps the mechanical tablet stability is adjustable by varying the penetration depth of the punches and thus the band height of the resulting tablet.

After powder compression and compaction, a relaxation step follows. The upper punch passes the upper lifting cam while the lower punch remains within the die. This relaxation step is important for the mechanical stability of the resulting tablet because

deformation occurs during this step [48]. Subsequently, the lower punch moves upwards by passing the ejection cam. Thereby, the manufactured tablets are ejected out of the die by assistance of a scraper tool and forwarded into a collecting vessel.

1.2.2. Powder compression and compaction

The compression and compaction processes as elementary steps during tablet manufacturing are very complex and influenced by a variety of factors. This includes machine settings (e.g. die disk speed, band height), the used tooling (e.g. punch shape, die geometry), and particularly the physicochemical properties of the powder to be tableted (e.g. deformation behavior, particle bonding strength). In this context, different powder deformation processes occurring during the compression and compaction steps are illustrated in Fig. 5.

During the first compression step (low compaction force), the particles undergo transitional packing and rearrangement, whereby the bulk density within the die usually increases (Fig. 5, 1. step) [49]. In this context, irregularly shaped particles as compared to spherical particles show a stronger rearrangement and thus often a closer particle packing within the die [50]. However, the extent of particle packing depends on the particle morphology such as the particle shape and/or size as well as on the particle size distribution of the investigated powder [51]. During the whole repacking/rearrangement processes, the particles are able to form interparticle bonds. However, the extent of particle packing depends on the particle morphology such as the particle shape and/or size as well as on the particle size distribution of the investigated powder [51]. During the whole repacking/rearrangement processes, the particles are able to form interparticle bonds.

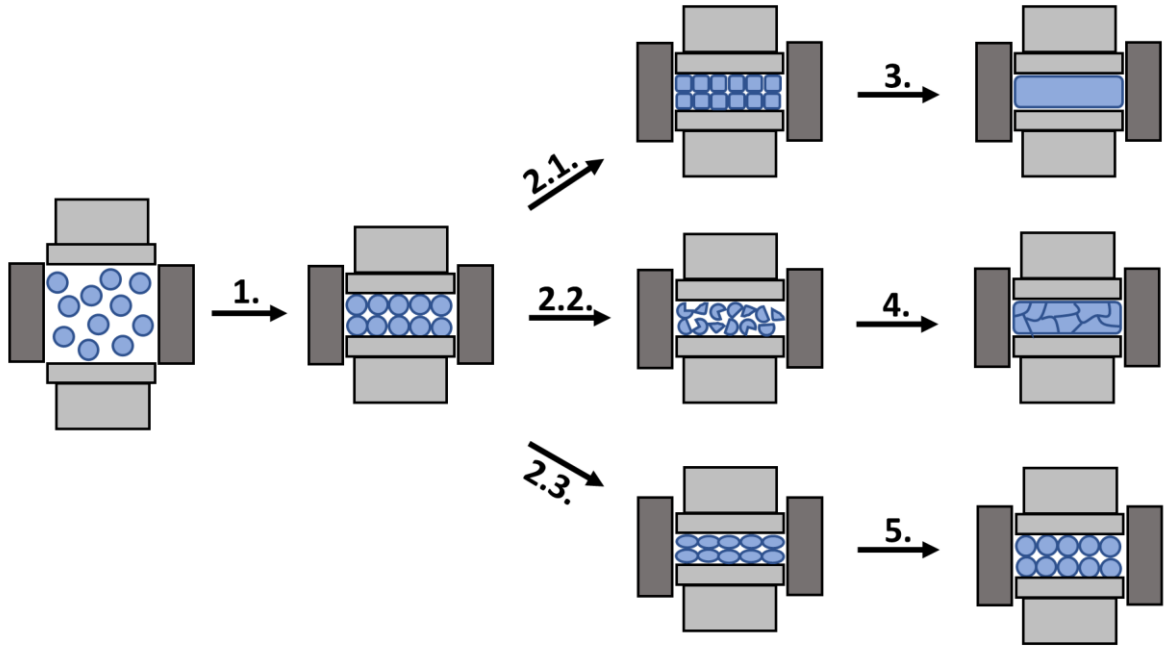


Fig. 5: Possible deformation properties of powders during powder compression/compaction (1. Transitional packing and rearrangement, 2. Particle deformation: 2.1 plastic, 2.2. brittle, 2.3. elastic).

After particle repacking/rearrangement, further volume reduction is achieved by deformation processes of the particles during compaction. Depending on the physicochemical particle properties and the applied compaction force, plastic deformation and particle fragmentation (brittle fracture) as well as elastic deformation may occur, although one deformation type usually predominates (Fig. 5, 2.1.-2.3. step) [52]. During the compaction step, the transmitted force to the powder bed within the die increases and leads to the build-up of additional contact surface areas between the particles which results in an increased bondability of the respective powder [53].

Among all mentioned deformation behaviors, plastic deformation (Fig. 5, step 2.1.) is the most desired material property and appears if the particles remain in their deformed state after the compaction step (Fig. 5, 3. step) [54]. Usually, the rate and the magnitude of the applied compaction force have to be sufficiently high to overcome a

critical stress value, also referred as yield stress, to initiate plastic deformation [55]. Because filler and binder generally make up the largest portion within the powder composition, plastic deformation properties are generally required for these excipients [56]. Particularly MCC exhibits pronounced plasticity during tableting and is therefore a widely used filler and binder [57].

However, while increasing the compaction force and thus the compressional load, the particles may also start to undergo fragmentation (Fig. 5, 2.2. step) [58]. This so-called brittle fracture generally leads to the formation of increased particle surface areas and thus stronger bonding points between the particles [59]. The brittle deformation occurs if the shear stress within a powder overcomes the tensile strength of the resulting tablet (Fig. 5, 4. step). A powder which predominantly shows brittle deformation often leads to tablets with insufficient mechanical properties, especially with regard to the requested crushing force [60]. A typical powder which shows a pronounced brittle deformation behavior is calcium hydrogen phosphate dihydrate (e.g. Emcompress®) [61].

Both, plastic as well as brittle deformation may lead to tablets with sufficient properties regarding their mechanical stability. However, even brittle and plastic materials often exhibit a certain amount of elastic deformation and recovery, whereby especially polymers and disintegrants (e.g. modified starch) show a pronounced elastic behavior [62]. Elastic deformation is a time-dependent process and describes a reversible deformation behavior of the particles with regard to their original shape (Fig. 5, 5. step) [63]. After exceeding the critical stress value, the particles are no longer able to store the expended energy, ultimately leading to recovery events within the tablet, such as lamination or capping [55]. In terms of the occurrence of elastic deformation, the physicochemical particle properties play an important role [64]. In comparison with

plastic or brittle deformation, elastic deformation is an unwanted particle property and often leads to problems with regard to the mechanical stability of the tablets [64].

1.2.3. Tablet presses and tableting equipment

Commonly, tablet presses are classified into two types. In the field of experimental research and formulation development, eccentric tablet presses as well as compaction simulators are frequently used, whereas for production purposes mainly rotary tablet presses are used [65,66]. In addition, machines for special uses (e.g. multilayer tablets) are also common in the pharmaceutical industry, whereby these tablet presses are often based on the functionality of a rotary tablet press [67].

In contrast to the setup, functionality, and mechanisms of actions of a rotary tablet press (see sub-chapter 1.2.1.), especially the filling and compression step of an eccentric tablet press differs in comparison to the respective steps of a rotary tablet press. Usually, an eccentric tablet press contains a moveable filling shoe and a pressing station with one pair of punches, whereby only the upper punch is moving during the compression step [68]. The force transmission performed by the upper punch may lead to unequal density distributions within the tablet, which might result in problems with regard to the disintegration behavior and the mechanical stability of the resulting tablet [69]. Furthermore, the die disk is stationary and consists of one die. The tableting process of an eccentric tablet press is described by the force-time and the displacement-time compression profiles displayed Fig. 6A.

Nowadays, compaction simulators are frequently used and are capable of displaying the performance characteristics of eccentric as well as rotary tablet presses, especially with regard to the respective compression/compaction process [70]. However, the filling process is often not able to completely represent the real process conditions and thus leads to variations in the predictability of the tableting process [71].

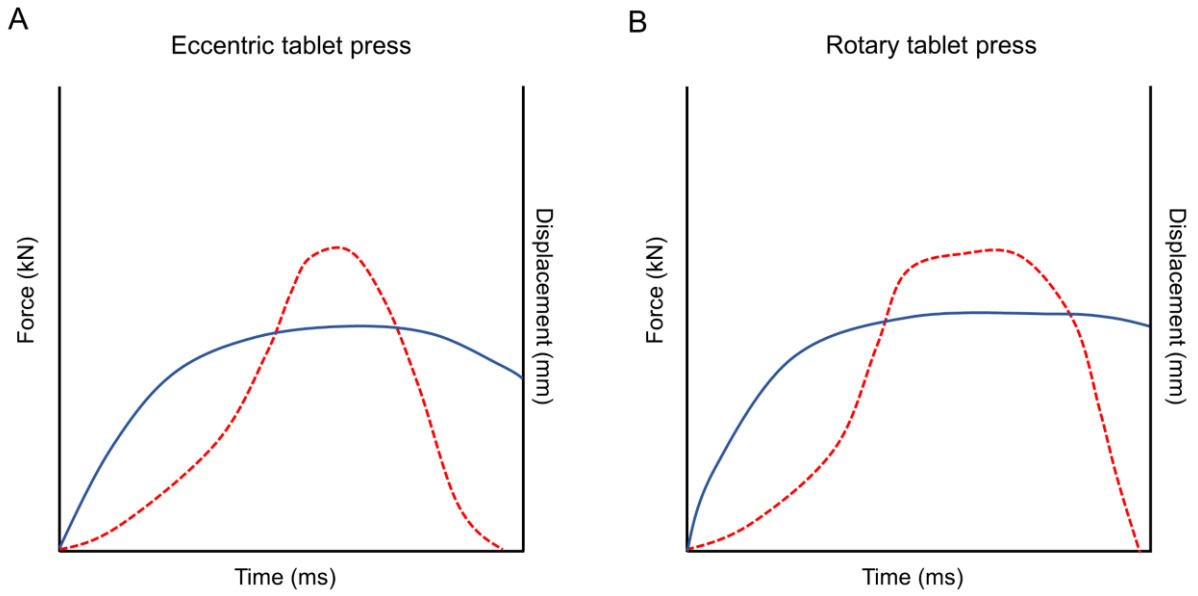


Fig. 6: Force-time as well as displacement-time compression profiles of an eccentric tablet press (A) and a rotary tablet press (B).

In comparison to eccentric tablet presses and to compaction simulators, rotary tablet presses contain a stationary filling system and multiple pairs of punches and dies as well as up to three pressing stations [72]. The die disk is moveable and rotates. Furthermore, both, the upper and the lower punches are involved in the compression/compaction steps leading to a more homogenous density distribution within the tablets in comparison to the tablets manufactured with an eccentric tablet press [69]. Moreover, the force-time compression profiles obtained with a rotary tablet press reach a plateau, whereby the length depends on the respective dwell time (Fig. 6B) [73]. The dwell time describes the time period during which the punch head remains in contact with the compression roll.

The duration of the dwell time and thus the resulting plateau of the force-time compression profile depends on several parameters as specified in Eq. 1 [74]:

$$\text{Dwell time} = \frac{\text{phf} \cdot \text{ns} \cdot 3600000}{\pi \cdot \text{cs} \cdot \text{ps}} \qquad \text{(Eq. 1)}$$

where phf is the diameter of the flat part of the punch head, ns is the number of compaction stations, cs is the diameter of the die disk, and ps is the turret speed in tablets per h.

The performance of a tablet press is usually measured as the respective output (number of manufactured tablets per h). An eccentric tablet press is able to produce up to 6,000 tablets/h, whereby a rotary tablet press has the ability to maximize the output up to 1.5 Mio. tablets/h. It can be summarized that a rotary tablet press shows distinct advantages over an eccentric tablet press with regard to the die filling, the tablet output, and the compression/compaction mechanisms. Nevertheless, eccentric tablet presses as well as compaction simulators show benefits concerning their flexibility, material expense, and the recording of compaction profiles [75].

1.2.4. Manufacturing methods for tablets in the pharmaceutical production

In addition to the classification of tablet presses, the tablet manufacturing process itself is principally divided into two production options: either “directly” or “conventionally” (Fig. 7) [76].

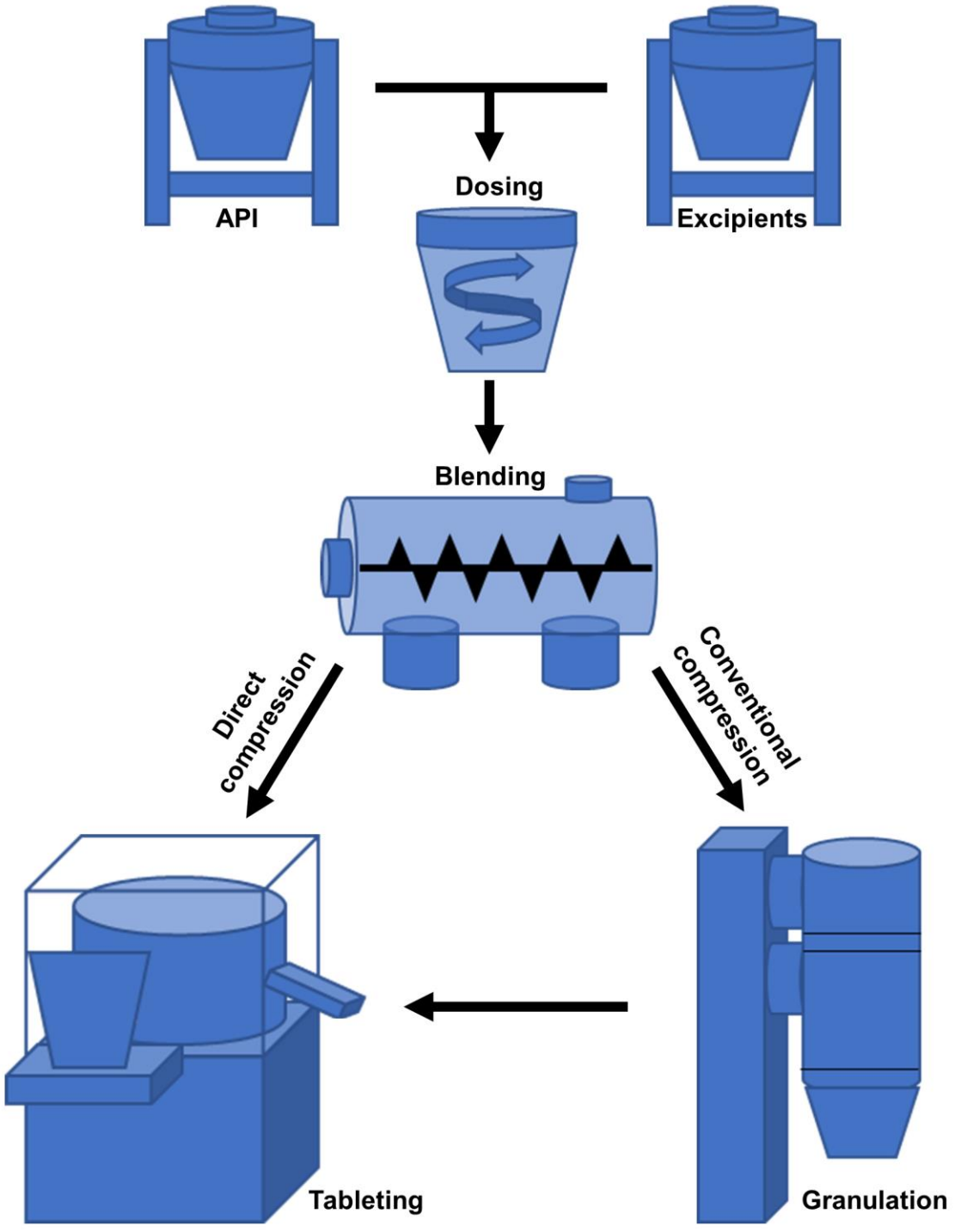


Fig. 7: Comparison between direct and conventional tablet manufacturing**.**

Direct compression means that the powder to be tableted is transmitted into the tablet press directly after the dosing and mixing steps without any further pretreatments of the powder [77]. Upon direct compression, the powder has to fulfill requirements regarding its tableting properties to ensure a trouble-free tablet manufacturing process [78]. On the one hand, the powder must show an adequate powder flow to ensure a fast and homogeneous filling of the die [79]. On the other hand, an acceptable compaction behavior of the powder is required to manufacture mechanically stable tablets that meet the quality specifications [80]. Especially the excipients have to fulfill further requirements beside flowability and compactibility, such as a sufficient miscibility, storage stability, compatibility with other excipients and APIs, and physiological tolerability [81]. Hence, the applicability of direct compression depends on the characteristics of the powder, the properties of which are often insufficient [3,80,82]. Usually, specially pretreated and/or co-processed excipients are selected, which fulfill the respective requirements for direct compression [83]. However, these modified excipients are often expensive in comparison to the respective untreated excipients [84]. Furthermore, an improvement of the excipient flowability may lead to an impaired compactibility reducing the mechanical stability of the manufactured tablets [84].

Because of the above mentioned disadvantages of direct compression, tablets are often manufactured by the “conventional” method, where an additional granulation step of the powder is performed before its compaction [36,85]. The agglomeration of the powder particles as a consequence of the granulation step is supposed to improve the properties of the powder, especially its flow, segregation, and compactibility [86–88]. The tableting performance of such granules depends on the properties of the contained powder particles (deformation behavior, compactibility, flowability etc.), the granulation

methods (wet, dry, or melt granulation), the used additives (solvents, binder solutions), and the process variables (temperature, humidity etc.) [89]. However, it is obvious that a preceding granulation step is costly and time-consuming. Therefore, direct compression is the preferred method for tablet manufacturing in the pharmaceutical industry, because of its shorter production time as well as lower energy consumption and cost-saving options in machinery and equipment. Thus, there is a special need for novel and innovative technical approaches to improve the compactibility and powder flow of powders to enable a direct compression.

A new and innovative approach to improve the tablet manufacturing process, especially with regard to economic aspects, production flexibility, and product quality is the concept of continuous manufacturing (CM) [90–92]. The basis for the change from batch towards continuous production is the application and implementation of methods in the field of process analytical technology (PAT) [93]. The implementation of novel PAT systems enables a real-time control of key quality attributes, a reduction of resources required for the manufacturing process, and a batch size flexibility [93]. In sub-chapter 1.3.4., a more detailed description of the commonly used PAT systems can be found. However, despite the mentioned advantages of CM compared to batch production, its implementation requires a detailed product and process understanding, which makes the introduction and establishment of such systems difficult [94].

1.3. Tablet quality

1.3.1. General aspects

To ensure that the intermediate and final products meet the required physicochemical quality attributes, measurement systems and assays defined by the different Pharmacopoeias have to be applied. These measurement systems and assays must be able to monitor the manufacturing process and the quality attributes of the tablets [95]. Furthermore, the required quality attributes of the Pharmacopeias depend on the respective tablet type. Usually, tablets are investigated regarding their appearance (size, color, form, engraving), their mechanical stability (Ph. Eur. monograph 2.9.8: crushing strength; Ph. Eur. monograph 2.9.7: friability), their porosity (Ph. Eur. monograph 2.9.32), their disintegration (Ph. Eur. monograph 2.9.1), their dissolution (Ph. Eur. monograph 2.9.3), and their mass/content uniformity (Ph. Eur. monograph 2.9.40).

The mentioned quality requirements are directly influenced by the properties of the plain powders as well as those of the powder blends [96]. Furthermore, process conditions such as the die disk speed and/or the compaction force also influence the quality attributes of the tablets [97]. In this context, it is also crucial to control and monitor upstream processes, such as dosing, blending, and granulation of the powders, as these processes have a decisive influence on the tableting performance [98]. For example, the monitoring of the blending process and thus the powder blend uniformity is of great importance regarding the dosing accuracy and content uniformity of the manufactured tablets [99]. Another example is the control of the particle morphology and particle size distribution after the granulation process to guarantee a sufficient powder flow as well as an acceptable compactibility [100]. The powder flow

as well as the compactibility are main influencing factors in terms of the processability and of the required tablet quality attributes [101].

1.3.2. Influencing process parameters

Aside from the mentioned plain powder and powder blend properties, the tableting process itself strongly influences the final tablet quality [97]. Because of the large number of adjustable process parameters (e.g. filling depth, band height, die disk speed) in combination with the exchangeable equipment (e.g. tooling, filling unit, scraper), tableting is a complex process [79,102]. The most important process parameters influencing the tablet quality attributes are listed in Table 2:

Two of the most influencing factors with regard to a variety of tablet quality attributes are the die disk speed and the compaction force [103,104]. Especially the die disk speed affects the die filling process and thus the tablet mass/content uniformity, the mechanical tablet stability, and the disintegration as well as the dissolution of the tablets [105]. Previous studies have shown that an increased die disk speed often results in a decrease of the tablet quality because the die filling time is reduced [106]. However, problems concerning die filling can be overcome with an appropriate filling system [107]. Within the last decades, three chamber- or cone filling systems were predominantly used, whereby also special filling units are available for certain applications (e.g. high die disk speeds) [108]. Depending on the die disk speed and the powder blend, the filling systems themselves can be further modified by the wheel geometries and the rotational speed of the wheels [109]. Nevertheless, various powders show such a poor flowability that a sufficient filling of the dies is not possible [110].

Table 2: Influencing process parameters with regard to the quality attributes of tablets.

Process parameter	**Tablet quality attributes**
Filling depth	• Tablet mass • Crushing force
Band height **(Compaction force)**	• Crushing force and tablet appearance • Friability • Disintegration • Dissolution
Die disk speed	• Crushing force • Mass/content uniformity
Filling unit speed	• Tablet mass • Mass/content uniformity
Process equipment	**Tablet quality attribute**
Tooling (punch & die)	• Tablet dimensions and appearance • Crushing force • Friability
Filling unit	• Mass/content uniformity • Tablet mass
Scraper	• Crushing force • Friability
External lubrication	• Crushing force • Friability

Next to the die disk speed, the applied compaction force significantly influences a variety of tablet quality attributes [47]. As mentioned in sub-chapter 1.2.2., the compaction force has to be high enough to induce plastic deformation for

manufacturing tablets with a sufficient mechanical stability according to the Ph. Eur. monographs 2.9.8. In this context, the used tablet press tooling is of special importance because the size, shape, and the appearance of the tablets are predetermined by the used punches and dies [111]. Therefore, the suitable tooling has to be selected to meet the required tablet specifications and to allow an appropriate production efficiency [112]. Actually, there are two main internationally recognized standards for tooling: the TSM (tablet specification manual) and the EU standard [113]. In the United States, the TSM is the common standard. Nevertheless, the EU standard is used more often than the TSM, whereby the tools of the EU standard are further distinguished between B and D tools depending on the punch and the die diameter [114].

With regard to the applied compaction force, the punch dimensions such as the punch head geometry or more precisely the flat part of the punch head determine the dwell time and thus the resulting compaction force [74]. It has been shown that depending on the tablet dimensions, the crushing force varies, although the same compaction force was applied. Therefore, the compaction force has to be converted into the compaction pressure as shown in Eq. 2:

$$P = \frac{F \cdot 1000}{A} \qquad \text{(Eq. 2)}$$

Where P is the compaction pressure (MPa), F is the compaction force (kN), and A is the cross-sectional area (mm^2). However, even the application of the same compaction pressure does not necessarily result in the same crushing force. Therefore, the crushing force has to be converted into the tensile strength to make different tablets comparable. The respective Eq. is shown in sub-chapter 2.2.3.2. The tensile strength is part of the compactibility and bondability profiles, in which the tensile strength is plotted vs. the compaction force respectively the solid fraction (SF) of the tablet. These

tableting profiles are best suited to compare and to predict the mechanical stability of tablets.

1.3.3. Influencing powder properties

As mentioned in sub-chapter 1.3.2., different process parameters may influence the resulting tablet quality depending on the tablet press equipment as well as on the tablet press settings. In addition, the physicochemical properties of the plain powders as well as of the powder blends to be tableted significantly influence a variety of tablet quality attributes [115]. The most relevant properties of the plain powders and the respective powder blends regarding the resulting tablet quality are displayed in Fig. 8.

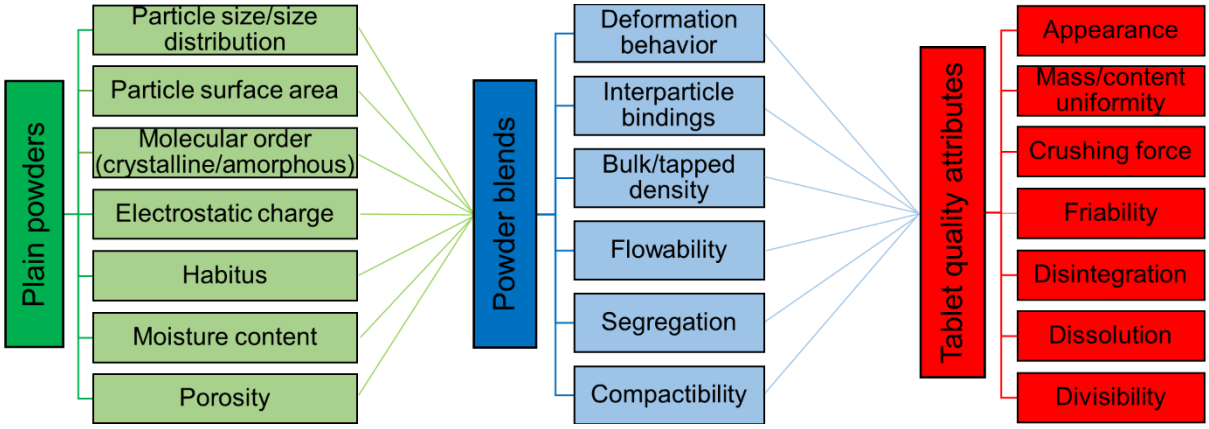


Fig. 8: Most relevant physicochemical properties of plain powders and powder blends with regard to the required tablet quality attributes.

Therefore, a selection of suitable plain powders for the preparation of powder blends for tableting is of particular importance for the manufacture of tablets meeting the respective quality requirements. Furthermore, the powder blend composition is also important with regard to the tableting performance because a variety of tableting settings have to be adjusted depending on the powder blend composition (e.g. die disk speed, filling depth, band height) [116]. Two of the main influencing factors in terms of

the resulting tablet quality and the performance characteristics of the tablet press are the flowability and the compactibility of the powder blend to be tableted [79].

It is generally acknowledged that the die filling process during tableting is a critical step because a continuous and homogeneous die filling is a prerequisite for a sufficient tableting process and for meeting the respective quality requirements of tablets [117]. Independent of the filling mechanism, the powder blend properties (e.g. the flowability), the tablet press settings (e.g. the die disk speed), and the used filling equipment (e.g. the paddle wheels) affect the die filling process [51,118,119]. If comparing these influencing factors, particularly the powder flow plays a major role and is often the most limiting factor [120]. The powder flow itself is very complex and depends on various particle properties such as the particle shape, the particle size, the particle size distribution, the moisture content, and the cohesiveness of the powder blend [43,121–123]. As mentioned in sub-chapter 1.3.2., the die disk speed defines the available filling time for the powder blend to fill the die and thus the available time for the removal of entrapped air [124]. Therefore, the relationship between the die disk speed and the flow properties of the powder blend obviously affects the efficiency of the tableting process [106]. Nevertheless, most of the currently used pharmaceutical excipients show an inadequate powder flow, resulting in tablet mass variations, segregation phenomena, deviations in the API content, and in a decreased efficiency regarding the tableting process [125]. An insufficient powder flow is usually the result of either a broad particle size distribution, an inappropriate particle shape (e.g. needle, plate), electrostatic charges, or an increased moisture content within the powder blend.

Besides the powder flowability, the compactibility of the powder blend is also a crucial and important physical property, especially with regard to the resulting mechanical stability of the tablet [126]. This mechanical stability such as the crushing strength or

the friability is required for subsequent processing steps of the tablets (e.g. coating), for the storage and transport of the tablets, and for the end-use of the tablets by the patient [127]. As already mentioned, the mechanical tablet stability is dependent on the physicochemical properties of the powders as well as on the adjustments of the tablet press [128,129]. The powder blend to be tableted has to provide an appropriate particle deformation behavior, a sufficient compactibility, as well as an adequate bondability [3,130,131]. As discussed in sub-chapter 1.2.2., especially the particle deformation behavior often causes tableting and tablet stability problems. Ideally, a powder blend shows pronounced plasticity and low elasticity which is difficult to realize [132]. Nonetheless, an excellent compactibility and bondability may overcome problems which occur as a consequence of the particle deformation behavior such as a marked elasticity [124,133].

An improvement of the compactibility and/or the bondability of a power blend may be achieved by changing the tableting parameters (e.g. compaction force, rotor speed) or the powder properties (e.g. particle morphology, molecular order, moisture content) [134]. However, these changes are not always feasible and are often associated with a decrease in the efficiency [2]. A novel and future-oriented approach to improve the compactibility and bondability of a powder blend is the application of externally applied lower punch ultrasound (US) vibration, whereby this approach is so far only implementable to compaction simulators [135].

1.3.4. Quality control systems

Nowadays, all operations and processes that influence tablet production are controlled by the regulatory authorities, which are usually the EMA and the FDA [136]. The basis for the required quality assurance are the so-called Good Manufacturing Practice (GMP) guidelines [137]. The GMP frameworks include extensive requirements with the

aim of an adequate and consistent tablet quality [138]. Aside from the defined product quality attributes, the regulation of further aspects, such as the personnel, the operation progress, the production facilities, or the entire documentation are also considered within the GMP frameworks [139,140].

With regard to tablet-relevant quality attributes, different analytical control systems are implemented at stations along or outside of the tablet manufacturing process [141]. Because tablets are predominantly manufactured batch-wise, the control of their quality attributes is primarily performed off-line and in external laboratories. However, the comprehensive quality monitoring of the intermediate products (e.g. granules) and the resulting tablets performed in these laboratories are time-consuming and cost-intensive [142,143]. Therefore, lately there has been a change in the use of the quality control systems, away from off-line measurement systems and towards on-line and/or in-line measurement systems [141]. These innovative measuring systems allow real-time monitoring of the most important quality attributes of tablets and are able to substitute the required laboratory work [93]. Therefore, process analytical techniques (PAT) are nowadays widely used because they are able to provide real-time or near real-time data [144]. Along the manufacturing line it is possible to implement these PAT systems to analyze and control specific parameters of the critical processing steps.

The data analysis may be performed off-line, at-line, on-line, or in-line [141,145]. For the in-line measurements special nondestructive analyzers and measuring techniques are applied. In this context, FT-NIR, UV-imaging, Raman spectroscopy, particle video monitoring, or terahertz spectroscopy are examples to determine the particle size distribution, the mass/content uniformity, and the moisture content of the powders to be tableted or the final tablet [95,146–150]. However, the implementation of such a PAT system is very complex and the manufacturing process itself has to be fully

understood in every respect [151]. Therefore, it is important to make the manufacturing processes as simple as possible, which means that tablets should be manufactured preferably by direct compression [152]. Generally, a comprehensive process as well as the product understanding in combination with a simplification of the manufacturing processes are of importance with regard to the transition from the traditional batch-wise production to a semi- or continuous production. Especially in view of the relevant aspects for CM a comprehensive process and product knowledge is mandatory [153]. Hence, the application of PAT systems is beneficial with regard to cost-efficient manufacturing processes [154,155].

1.4. Errors during tablet manufacturing

1.4.1. General aspects

Problems encountered during tablet manufacturing are principally divided into two categories, machine and powder induced problems [156]. Machine-induced manufacturing problems are often referred to the compression equipment such as the punch tooling, the punch lubrication, the selected filling unit, the applied compaction force, and the adjusted die disk speed [97]. In addition, powder-induced manufacturing problems are often related to the compositions of the powder blends, to their moisture content, and in particular to the physicochemical powder properties (flowability, compactibility, bondability) [157]. However, the occurrence of tableting errors and thus tablet failures is usually caused by an interplay between machine and powder-induced problems.

The problems which may occur during or after tableting are further distinguishable in visible and non-visible “failures” with regard to the tablet appearance [158]. However, both, the visible and non-visible failures have a pronounced impact on the required quality attributes of the tablets. Visible tablet failures are defined as failures which refer to the tablet appearance. These tablet failures usually include color changes, cracking, capping, lamination, and chipping. Especially capping, lamination, and chipping are serious and present the major problems during tablet manufacturing [159–161]. The causes for these problems are often complex and multifactorial which complicate the investigation of the respective causes [161]. In comparison to the visible tablet failures, non-visible tablet failures are usually undetectable by the eye [162]. These non-visible tablet failures especially include tablet mass/content variations as a result of segregation and/or insufficient die filling [163].

1.4.2. Capping, lamination, and chipping

The causes of capping and lamination are not yet completely understood and therefore only few problem-solving approaches are available so far [124]. Capping is often used as an “umbrella term” in the literature, whereby no difference is made between capping and lamination. Both, capping and lamination lead to non-reversible tablet failures, whereby their visual appearance differs: capping is accompanied by a complete parallel separation of the top or bottom part of the tablet, whereas lamination is characterized by horizontal multilayer cracks (Fig. 9) [164,165].

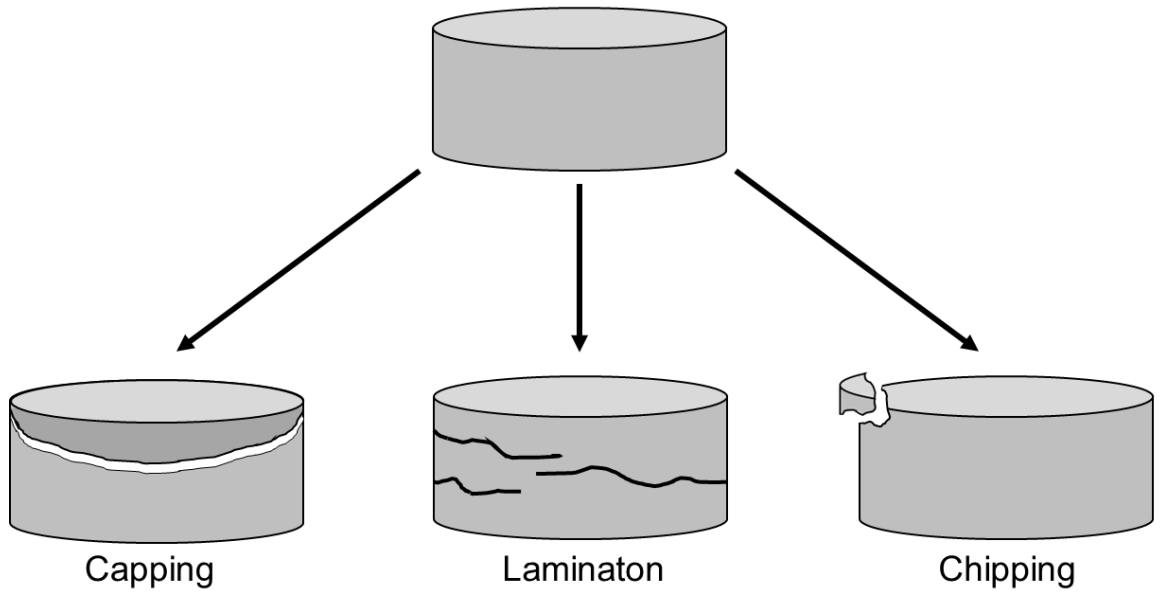


Fig. 9: Illustration of capping, lamination, and chipping.

Capping as well as lamination may occur directly after the compression/compaction step, the tablet ejection step, and/or during further tablet processing steps (e.g. coating) [166]. The occurrences of both, capping and lamination are linked to the process conditions, the composition of the tablet formulation, and to the physicochemical particle properties [128,167]. In this context, “process capping or lamination” is affected by the tooling [168], the die disk speed [169], and/or the

compaction force [105]. In contrast, “formulation capping or lamination” is especially influenced by the deformation characteristics of the powders/granules to be tableted (elastic recovery) [170,171], the binder content [172], the volume of entrapped air [173], and/or the resulting die wall friction [174]. It has to be noted that a precise distinction between “process and formulation capping or lamination” is often impossible because both phenomena influence each other [175].

Suitable approaches to decrease or prevent capping or lamination are the improvement of the mechanical tablet strength by varying the binder type and/or content, the residual moisture content of the tablet formulation, and the compaction force [103,176]. In many publications quantitative correlations between the tableting conditions and the tendency of capping or lamination are described [158,161,177]. These correlations include especially the rotary die disk speed, the compaction force, and the ejection force. An adjustment of these mentioned parameters may influence the resulting capping and/or lamination tendency. Furthermore, studies have been conducted to develop predictive tools to estimate the risk of a tablet formulation to show capping or lamination [124,166,178,179].

Possible attempts to avoid or reduce capping and lamination are the replacement of the chosen tableting material by a more suitable material (e.g. with plastic or brittle deformation properties), the alteration of the composition of the tablet formulation (e.g. increasing binder or lubricant concentrations), and the application of special tableting equipment or the adjustment of the tableting settings (e.g. reduced die disk speed, adjustment of the scraper, use of tapered dies) [180]. However, these attempts are usually costly and time-intensive. Therefore, there is an urgent need for innovative techniques to address capping and lamination.

In addition to capping and lamination, chipping is another frequently occurring problem during tableting and further processing steps (coating, packaging). The term chipping is defined as the breakoff of the tablet edges (Fig. 9) [181]. With regard to the causes of chipping the tablet formulation as well as the tablet press equipment and the tableting parameters may have a pronounced influence. Causes related to the tablet formulation are mainly the moisture content and the bondability characteristics of the powders. Accordingly, the use of humectants and dry binders are the most common remedies to prevent the occurrence of chipping [182]. Consequently, chipping may also occur as a result of the chosen tableting equipment, whereby in particular the tooling (pronounced punch concavity or damaged tools) play an important role [183]. In comparison to the tablet formulation induced-chipping, the tablet press-induced chipping is easier to solve.

1.4.3. Sticking

In the field of tablet manufacturing, the term sticking describes the adherence of powder particles to the punch surfaces or the die wall [175]. This so called “punch sticking” often occurs after the compaction step and may lead to irreversible tablet failures [184]. It is postulated that punch sticking is a consequence of a disbalance between the powder-punch adhesive forces and the powder-powder cohesive forces [185]. If the powder-punch adhesive forces outweigh the powder-powder cohesive forces the sticking tendency distinctly increases. The causes for these observations are complex and may primarily be attributed to several influencing factors such as the machine parameters (dwell time, compaction force), the selected punches (external damage, engravings, geometry), the manufacturing conditions (temperature, humidity) and the properties of the powders to be tableted (moisture content, cohesiveness,

lubricant concentration) [186–188]. The extent of punch/die wall sticking strongly depends on the respective influencing factors mentioned above, whereby the whole tablet surface or only regional areas of the tablet surface may be affected. With regard to punch sticking, especially the punch design (e.g. concavity, coating), a slow die disk speed (dwell time), and an increased compaction force mainly influence the sticking tendency of a powder [189,190].

The appearance of punch sticking may occur directly or shortly after starting tablet manufacture, but also at later stages of the production process. Usually, the majority of sticking events are dependent on the temperature of the tablet press (rotor). It is postulated that a tablet press reaches its highest temperature after 1-2 h of tablet production [191]. Often, sticking and thus the adherence of material to the tooling occurs at the sharp edges and corners of the tablet surface, which is commonly referred to as “picking” [192]. The reasons for this special type of sticking are particularly an excessive moisture content and an insufficient lubricant concentration of the powders to be tableted as well as tablet ingredients with low melting points [193]. Accordingly, different approaches are applicable to prevent the occurrence of sticking [189]. With regard to the machine parameters, the compaction force may be gradually adjusted or a preceding compression step may be added [194]. Furthermore, an increase in the die disk speed leads to shortened dwell times and thus to a decrease of the sticking tendency [194]. Moreover, special coatings for the punches and/or the die wall such as hard-chromium, chromium nitride or titanium nitride are available which may reduce sticking events [195].

Besides the machine induced-sticking, especially the environmental conditions influence the occurrence and extent of sticking [196]. For example, a decrease of the room temperature and humidity often leads to a reduction of sticking tendency during

tableting [195]. Furthermore, special tablet presses with a coolable rotor are available, especially for substances with low melting points. Nevertheless, it is known that sticky components in the tablet formulation mainly influence the occurrence of sticking [197]. In this context, the API is usually the sticky component which makes it difficult to change or modify the tablet formulation [198]. Possibilities to reduce or prevent sticking caused by the powder particles to be tableted are a decrease of the moisture content, and an increase of the binder and lubricant concentrations [199].

1.4.4. Tablet mass and content variability

As mentioned in sub-chapter 1.3.1., the mass and the content uniformity are relevant quality attributes of a tablet [19]. Various manufacturing processes before and during tableting are crucial to achieve the required mass/content uniformity. Usually, the dosing and mixing processes that are carried out prior to tableting are the basis for the resulting mass/content uniformity [200]. In this context, the mixing quality of the powder blend depends on the composition of the tableting formulation, the physicochemical properties of the powder particles (e.g. particle size distribution) as well as the applied blending process (blending time and type of blender) [201]. Nevertheless, independent whether the required mixing quality was previously achieved, segregation may still occur, especially during direct compression. The occurrence and extent of segregation is mainly influenced by different powder properties, first of all the powder flow and the particle size distribution, and secondly by adjustments of the tableting process (die disk speed) [202]. During tableting and even more precisely during the die filling processes, the powder to be tableted is exposed to a number of stress factors such as the paddle wheel speed and geometry [203].

In the last decade, segregation processes have been simulated by using the discrete element method (DEM) [204]. These simulations are able to predict and track the micro-macro dynamics of the particles inside the feed frame [205]. It has been shown that differences in the particle size often lead to segregation events within the feed frame and/or during the die filling step [204]. Hence, it was demonstrated that the paddle wheel speed and geometry are the most important factors to control and thus to prevent segregation within the feed frame [206]. Further factors are the adaptation of the particle size distribution, a reduction of the die disk speed, and the addition of glidants to improve the powder flow [207].

1.5. Vibration systems in tablet manufacturing

1.5.1. General aspects

In the pharmaceutical industry, vibration is already established as a useful and supportive technique for production processes such as the conveying of powders or the dedusting of tablets after their production [208,209]. However, vibration in mechanical engineering is generally an undesirable event, especially with regard to material densification and segregation [210]. In mechanics, vibrations are periodic, mostly applied at medium to high frequencies, and show low amplitude oscillations. In contrast to the term "oscillation", "vibration" suggests the immediate audibility or palpability of the process [211].

During the last years, the idea of applying vibration for improvement of the tableting process has frequently been discussed. However, this concept is comparatively new in the pharmaceutical industry, whereas the application of vibration is well established for compaction processes in the metallurgy, plastic, and ceramic industry [212].
Lately, the application of punch or die vibration prior to, during, or after the compression step, has been investigated to improve the compaction properties of powders [213]. In this context, different vibration systems were developed and investigated, whereby usually ultrasonically and pneumatically generated vibration was used [214]. These vibration systems differ in their torque, frequency, amplitude as well as in their complexity and their engineering effort. However, ultra-sound (US) -assisted vibration is primarily applied only on an experimental scale [215]. US systems show high frequencies and comparatively low amplitudes, whereas pneumatic vibration systems often exhibit only moderate frequencies but high amplitudes, depending on the used pneumatic system [216].

The objective of the majority of these vibration systems is a densification of the powder bed within the die prior or during the compaction step (Fig. 10). The application of vibration leads to a change of the flow properties of a powder, which usually results in a displacement and rearrangement of the powder particles [217].

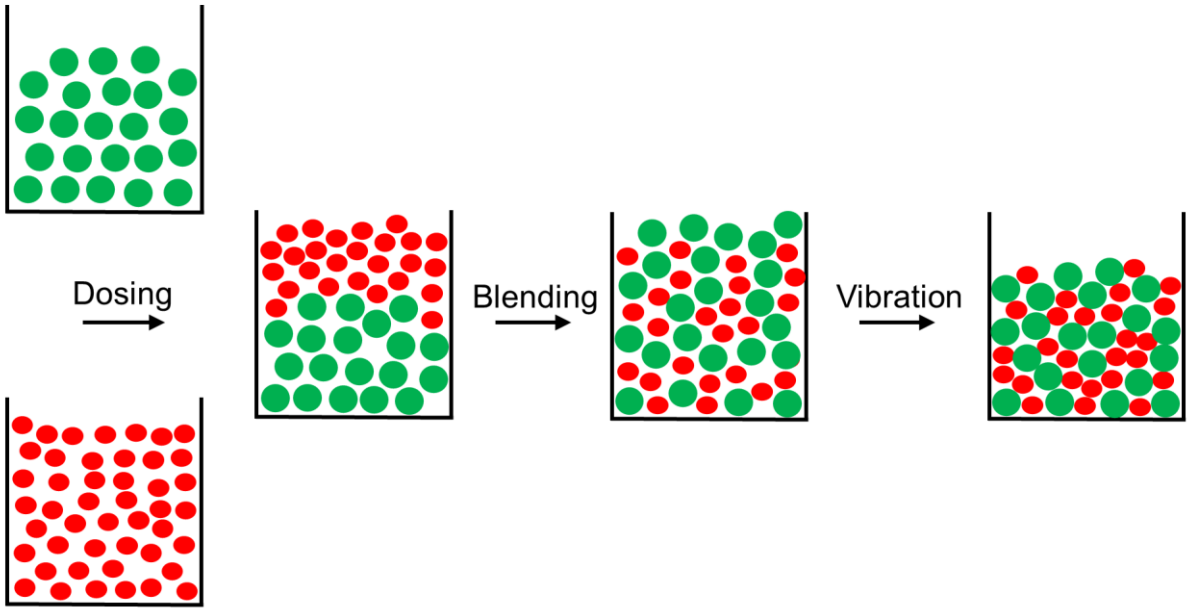


Fig. 10: The densification process of powder particles during dosing, blending, and vibration.

Therefore, densification of materials by vibration is particularly common in the construction industry, especially to make full use of e.g. coarse-grained mass concrete and to produce concretes of high strength and durability, which are impermeable for water and air [218].

The densification process as such leads to an increase of the bulk density of a powder, especially for powders that generally show a low bulk density [219]. Usually, this low bulk density mainly results from bridging as well as cohesive and adhesive forces between the individual powder particles and the container wall [220,221]. Under vibration, the static balance of the system shifts to a dynamic state [222]. As a result,

the cohesive and adhesive forces are reduced. In this regard, the efficiency of the densification process is determined by the particle properties and the engineering process parameters [223,224]. Because of the complexity of densification processes, there exists no general mathematical Eq. to predict the densification process.

Nevertheless, the essential vibration parameters can be described by the following Eq. 3 [225]:

$$a = k \cdot f^2 \cdot A \qquad \text{(Eq. 3)}$$

where a is the acceleration (m/s^2), f the frequency (s^{-1}), A the amplitude (m), and k a correction factor which is calculated as follows:

$$k = \frac{4 \cdot \pi^2}{9.81} \qquad \text{(Eq. 4)}$$

1.5.2. Ultrasound-assisted vibration

The term US describes the generation, transmission, and reception of energy in the form of sound waves above 18 kHz [226]. The industrial areas of US application are diverse, depending on the respective intensity level [227]. US vibration with low intensity and high frequencies is used for the investigation of materials with regard to their structural properties [228]. Because of these low intensities, US vibration does not lead to permanent structural or chemical changes within the investigated materials. Thus, the application of US at low intensities is non-destructive making it beneficial for structure analysis [229]. In contrast, the application of US vibration at high intensity levels leads to permanent chemical and structural changes in the respective material, whereby usually only low frequencies are required [230]. US vibrations at these high intensity levels are principally used for cleaning operations, chemical reactions, clinical imaging, plastic welding, foam extrusion, and powder compression [231,232]. The

application of US vibration at high intensity levels may lead to the generation of heat, movement processes (stirring, mixing), chemical reactions (oxidation, polymerization, depolymerization), and mechanical effects (ruptures, erosions, densifications) [233,234]. The required equipment for the generation of US depends on the respective type of material to be processed (metal, plastic, polymers, or powders). With regard to US-assisted tablet manufacturing, various of the above listed mechanisms influence the tableting process and the quality of the resulting tablets [235].

Previous studies showed that the application of US tool vibration leads to several benefits with regard to the tableting process itself as well as to the resulting tablet quality [236]. By application of punch or die vibration caused by US prior to, during, or after the compression step, the compaction properties of the tableting material may be significantly improve, whereby the application of US vibration during the compression step leads to the best results [135]. The improved compression and compaction properties of the investigated tableting materials are especially attributed to the densification of the powder bed within the dies as a consequence of the applied US vibration [237]. Hence, as a result of this densification process, additional interparticle bonding points are created and thus, the mechanical stability of the tablets is increased [238]. Furthermore, a densification and thus a closer particle arrangement of the powder particles within the dies is associated with a removal of entrapped air, which is one of the main causes for capping or lamination, especially under production conditions (high turret speeds) where the available deaeration time is short [239]. In addition to these observations, it is possible to reduce the required compaction force for tablet production by up to 40 % if US tool vibration is applied [240]. Further studies showed that lower punch vibration results in a homogeneous density distribution within the tablets, which is associated with an uniform disintegration of the tablet [240,241].

However, all these studies were performed with small laboratory compaction simulators and none of the developed vibration systems is suitable for implementation on a running rotary tablet press [216]. Furthermore, most of the introduced systems may influence the physicochemical properties of the powders to be tableted or of the manufactured tablets [242]. Beside these engineering challenges, US generated vibration shows various disadvantages. As mentioned above, US is associated with heat generation as a result of the high energy input [243]. Depending on the applied duration of vibration, temperatures of up to 100 °C were measured on the tablet surfaces [238]. This heat input may potentially lead to changes of the physicochemical properties of the tablets or specific compounds thereof [244]. Furthermore, oxidation and polymerization reactions may occur [245]. Consequently, US vibration is only applicable to tableting materials with high melting points and sufficient physicochemical stabilities. Also, the required time period to densify the powder bed within the dies during a running tableting process with high rotor speeds may not be reached because of the comparatively less pronounced amplitude. Moreover, the wear of the punches and the dies may be enhanced, and the generated US vibration may be transmitted to other parts of the tablet press. Because of the process complexity and the engineering effort [135], which is associated with the risk of heat development , up to now no US vibration system has been successfully implemented on a running rotary tablet [246].

1.5.3. Pneumatic vibration

Pneumatic vibrators are operated with compressed air, whereby their performance with regard to the generated frequencies and amplitudes depends on the respective vibration principle (linear, circular). Therefore, the application areas of pneumatic vibrators are diverse, whereby pneumatic vibration is mainly used in the fields of product conveying, filling, sieving, and densifying [247–249].

With respect to the efficiency of pneumatically generated vibrations and the instrumental effort, pneumatic vibrators may in theory be better suitable for implementation on an industrial rotary tablet press than US vibration systems. Also, pneumatically driven vibrators are in general easy to handle, economically efficient, and space saving, making the practical implementation on a rotary tablet press theoretically feasible. Additionally, these vibrators are able to generate higher centrifugal forces leading to an increased torque compared to US vibration systems [250]. This increased torque could be important with respect to a sufficient and fast powder bed densification during an industrial scale tableting process [251]. Furthermore, with pneumatically generated vibrations, heat generation is not observed. Thus, no physicochemical changes of the tablets and the incorporated ingredients are expected.

Furthermore, it appears to be advantageous to transfer the vibration process from the compaction step to the filling of the die with the aim to enable a homogeneous and continuous filling of the dies, which is important for the tableting process and the resulting tablet quality. In addition, it is assumed that a vibration of the lower punch during the die filling step may reduce or prevent the occurrences of capping and/or lamination caused by the removal of entrapped air from the powder bed within the dies. Similarly as wirt US vibration (see sub-chapter 1.5.2.) pneumatically generated

vibration also enables to a rearrangement of the powder particles, potentially leading to an increase of the mechanical stability of a tablet. This may additionally decrease the capping or lamination tendency caused by elastic recovery or die wall friction. Also, monodirectional pneumatic vibration may prevent an inhomogeneous density distribution within the tablet and allows a reduction of the required compaction force for tablet manufacturing.

Despite its advantages, so far no studies have dealt with the application of pneumatically tool vibration prior to the compaction step. Therefore, the purpose of the present study was to develop a suitable pneumatic vibration system for the implementation and application on a running rotary tablet press and to investigate the performance characteristics and the capability of this newly introduced system. Moreover, it was intended to investigate limitation parameters with regard to the pneumatic lower punch vibration [252]. Thus, a special experimental setup was designed to allow the visualization of the densification process of the powder bed within the die and to develop a suitable new image analyzing technique for quantification of the extent of densification [253,254].

1.6. Objectives of this work

Because of intensified regulatory requirements and the continuous development of challenging APIs, innovative technologies are needed to make the tableting process more flexible, robust and cost-effective. Especially in terms of the development of new production approaches (e.g. CM) and the economic efficiency of tablet manufacturing, direct compaction plays an important role. In this context, especially the powder flowability and thus the respective die filling process is crucial, as it has a significant influence on both, the respective tableting performance and the resulting tablet quality. In addition, the applicability of direct compaction is often limited by the properties of the powders to be tableted, whereby high requirements are expected with regard to the flowability, bondability, and compactibility which are often insufficient and may only be achieved by cost-intensive pretreatment steps.

Previous studies demonstrated that US tool vibration might be a powerful approach to improve both, the tableting process and the mechanical tablet stability. However, despite their potential benefit, the introduced systems are only applicable to compaction simulators so far, which may be related to the need of sophisticated equipment. Moreover, as a consequence of the pronounced heat development during the application of US, which may cause physicochemical changes of the powder properties, US vibration is only applicable to certain APIs and tableting materials. Therefore, the present work dealt with the development and implementation of a novel pneumatic lower punch vibration system in a rotary tablet press with the objective to improve the tableting process as well as the resulting tablet quality. A further aim of this work was the investigation of the performance characteristics, the application options, and the opportunities to influence the tableting process by pneumatic lower punch vibration.

In comparison to the introduced US vibration systems, it was intended to install the pneumatic vibration system at a position prior to the compaction step, more precisely during the die filling step, where the lower punch passes the filling cam. By passing the filling cam, the vibration may be transmitted especially to the lower punch. As a result of the lower punch vibration during the die filling step, the powder bed within the dies may undergo a defined densification, which may positively influence the die filling performance, the compression/compaction process as well as different quality attributes of the resulting tablets. Moreover, a densification of the powder bed usually leads to a removal of entrapped air ,which further positively affects the tableting process with regard to the prevention of capping and/or lamination as well as to the improvement of several mechanical stability aspects of the manufactured tablets. However, the application of vibration is often associated with the occurrence of segregation within the powder beds which may negatively influence certain tablet quality attributes. Consequently, the vibration system to be developed also had to be examined regarding the risk of segregation.

In summary, it was intended to develop and investigate a suitable and robust pneumatic vibration system which allows to improve the tableting process of a rotary tablet press under real conditions of manufacture. Because this is the first time that such an innovative pneumatic lower punch vibration system is applied during tablet manufacturing, the present work serves as a proof of concept.

2. Materials and Methods

2.1. Materials

2.1.1. Model drug (API)

The crystalline API acetaminophen (APAP) was purchased from Caelo (Hilden, Germany). APAP is a nonsteroidal anti-inflammatory drug usually used as a medication to treat pain and fever, which shows some characteristic properties with regard to its tableting behavior. Especially plain and unmodified APAP usually exhibits an insufficient compactibility and bondability. The poor tableting properties of APAP are mainly attributed to its high elastic behavior during compaction frequently leading to tablets with an insufficient mechanical strength and an increased capping/lamination tendency. Therefore, APAP is a well-suited API to investigate the fundamental performance characteristics of a novel lower punch vibration system developed and investigated in this thesis.

2.1.2. Model binder and filler

For conducting the tableting experiments different powders, predominantly fillers and binders, were selected. Fillers and binders are basic excipients for tablet manufacturing and are therefore present in almost every tablet formulation. Often, they even make up the largest percentage within a tablet formulation. Consequently, the flowability and tableting properties of the fillers and binders are of major importance for a successful tableting process. Especially with regard to direct tableting, the selected fillers and binders play a crucial role within the tablet formulation. For these reasons, in the present work different fillers and binders were investigated with regard to their

tableting behavior as well as their ability to form tablets with a sufficient mechanical stability.

Different grades of microcrystalline cellulose (MCC-1: Ceolus® KG1000, Lehman & Voss, Hamburg, Germany; MCC-2: Parmcel 102, Gustav Parmentier, Frankfurt, Germany; MCC-3: Vivapur® 200, JRS Pharma, Rosenberg, Germany; MCC-4: Avicel® 301, FMC, Brussels, Belgium; MCC-5: Microcel 12, Blanver, Sao Paulo, Brasil) and lactose (Lac-1: GranuLac® 200 and Lac-2 Tablettose® 80, both from Meggle, Wasserburg, Germany; Lac-3: Fast Flo® 316; Foremost Farms, Penny Lane, USA) were selected as model tableting excipients. Moreover, basic magnesium carbonate ($MgCO_3$, Pharmagnesia® MC Type F, Lehman & Voss, Hamburg, Germany), calcium hydrogen phosphate dihydrate (Emcompress® 200, JRS Pharma, Rosenberg, Germany), and calcium carbonate (Destab™ 90SE, Particle Dynamics, Saint Louis, USA) were investigated in the present thesis. The selected powders differ in their physical properties and their tableting behavior. The used short names of the MCC and lactose grades are listed in Table 3.

Table 3: Applied short names of the investigated MCC and lactose grades.

MCC grade	Ceolus® KG1000	Parmcel 102	Vivapur® 200	Avicel® 301	Microcel® 12
short name	MCC-1	MCC-2	MCC-3	MCC-4	MCC-5
Lactose grade	GranuLac® 200		Tablettose® 80		Fast Flo® 316
short name	Lac-1		Lac-2		Lac-3

2.1.3. Tableting excipients

Besides the mentioned model fillers and binders listed in sub-chapter 2.1.2., the tablets were partially manufactured with the addition of magnesium stearate (MgSt; Lehman & Voss, Hamburg, Germany) as lubricant and croscarmellose sodium (CCS; Fagron, Barsbüttel, Germany) as disintegrant.

2.1.4. Coloring agent

The blue food colorant indigo carmine (Carl Roth, Karlsruhe, Germany) was used as spray-colorant of MCC-3. Depending on the applied pH value, indigo carmine may appear blue (below pH 11.4) or yellow (above pH 13.0) in an aqueous solution.

2.2. Methods

2.2.1. Powder characterization

2.2.1.1. Particle morphology

To visualize the particle morphology of the investigated powders, images were obtained by a scanning electron microscope (SEM; LEO 1525, Carl Zeiss, Oberkochen, Germany). Therefore, powder samples were coated with a thin carbon layer prior to the imaging step. Depending on the particle size, the images were taken at different magnifications. The selected acceleration voltage was 5 kV and the samples were scanned at magnifications between 300 and 35,000.

2.2.1.2. Powder densities

With a jolting volumeter (Stav 2003; J. Engelsmann, Ludwigshafen, Germany) the bulk and tapped densities of the powders were measured and calculated according to the Ph. Eur. monograph 2.9.34 “Bulk density and tapped density of powders”. The determination of the true densities was performed with a helium pycnometer (AccuPyc 1330; Micrometrics, Norcross, USA). The density value was the mean of ten measurements of each powder sample. In addition, the relative density (ρ_0) which describes the relation between bulk and true density, was calculated by the following Eq. 5:

$$\rho_0 = \frac{\text{Bulk density}}{\text{True density}} \qquad \text{(Eq. 5)}$$

2.2.1.3. Particle size & particle size distribution

The particle size as well as the particle size distribution were determined by laser diffractometry (Helos KR; Sympatec, Clausthal-Zellerfeld, Germany). For the dispersion of the powder particles, compressed air of 1.5 bar was used. Depending on the respective particle size, different lenses with an effective range between 0.5 and 175 µm and 0.5 and 875 µm were used. The measurements were performed using the Fraunhofer´s theory. Furthermore, the particle span value was calculated (Eq. 6) to quantitatively compare the particle size distributions.

$$\text{Span value} = \frac{X_{90} - X_{10}}{X_{50}} \qquad \text{(Eq. 6)}$$

2.2.1.4. Powder flow

The powder flow was determined according to the Ph. Eur. monograph 2.9.36 “Powder Flow”. In this context, the angle of repose, the flow rate through an orifice, the Hausner ratio (HR) as well as the Carr index (CI), and ring shear cell measurements, were performed to describe the powder flow behavior of the investigated powders. The angle of repose and the flow rate through an orifice were performed with a cone (orifice Ø 10 mm). The HR (Eq. 7) as well as the CI (Eq. 8) were measured with a jolting volumeter (Stav 2003; J. Engelsmann, Ludwigshafen, Germany):

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \text{(Eq. 7)}$$

$$\text{Carr index} = 100\ \% \cdot \left(1 - \frac{\text{Bulk density}}{\text{Tapped density}}\right) \qquad \text{(Eq. 8)}$$

Shear cell measurements were performed with a ring shear tester (RST-XS; Dr. Dietmar Schulze Schüttgutmesstechnik, Wolfenbüttel, Germany) to determine the powder flow function (ff_c) of the powder samples by different applied mean consolidation stresses (2.5 kPa, 5.0 kPa and 10.0 kPa). The ff_c values were calculated by the following Eq. 9:

$$ff_c = \frac{\text{Major principal stress}}{\text{Unconfined yield strength}} \qquad \text{(Eq. 9)}$$

2.2.1.5. Specific surface area

The specific surface areas of the powder samples were measured with a gas adsorption porosimeter (Surfer; Porotec, Hofheim, Germany). Prior to the measurements, the samples were dried and degassed with the connected degasser module under vacuum at 40 °C for 3 h. Subsequently, the specific surface areas were calculated by the principle of static volumetric physical gas adsorption.

2.2.1.6. Residual moisture Content

The residual moisture content of each powder was determined thermogravimetrically (n = 3) by application of a moisture analyzer (MA 30; Sartorius, Göttingen, Germany). Therefore, approximately 3 g of the respective powder were used for each measurement.

2.2.2. Tablet preparation

In the present thesis, tableting was performed with and without lower punch vibration in single punch mode with a rotary tablet press (Fette 102i, Fette Compacting, Schwarzenbek, Germany). The manufacturing of tablets in single punch mode allows the determination of the compaction and ejection force for every single tablet. As filling unit, an automatically rotating filling wheel was selected, whereby only one chamber was used for the die filling process. Because the parameters used for blending, the batch sizes, the punches, and the selected tablet press settings (e.g. die disk speed, band height, filling depth) varied between the different studies, a more detailed description is given in the following paragraph.

For the measurements described in chapter 3.2., the investigated powders (Table 4) (batch sizes of 500 g) were blended for 3 min at 72 rpm after addition of the lubricant MgSt (0.5 % w/w) with a Turbula® T2F mixer (W.A. Bachofen, Basel, Switzerland). The prepared powder blends were compacted with 8 mm flat-faced faceted punches at a die disk speed of 15 rpm. During conventional tableting (without externally applied lower punch vibration), tablets with a tablet weight of 250 mg and a tensile strength of 2.0 MPa were manufactured. Therefore, the band height of the tablet as well as the filling depth were adjusted depending on the characteristics of each powder blend. The respective settings are listed in Table 4.

Table 4: Settings of the rotary tablet press.

Settings	MCC-1	MCC-2	Lac-1	Lac-2
Band height (mm)	1.5	2.0	1.8	2.2
Filling depth (mm)	9.5	8.0	6.0	6.0

After conventional tableting, externally lower punch vibration was applied and tablets were compacted under the same setting as illustrated in Table 4. Tableting with the assistance of lower punch vibration was performed with both, a piston and a turbine vibrator (see sub-chapter 2.2.6.), at two different levels of the inlet pressure (2 and 4 bar). Depending on the vibrator type, these levels correlate to frequencies of 48 Hz (2 bar) and 58 Hz (4 bar) for the piston vibrator, and to frequencies of 400 Hz (2 bar) and 475 Hz (4 bar) for the turbine vibrator.

The preparation of the tablets for the experiments presented in chapter 3.3. differs from the above-mentioned tablet preparation procedure and is described in the following. The respective MCC grades MCC-2, MCC-3, MCC-4, and MCC-5 were each blended for 3 min with a Turbula® T2F mixer (W.A. Bachofen, Basel, Switzerland) after addition of 2 % (w/w) MgSt as a lubricant. This amount of MgSt was chosen to definitely overcome possible die wall friction and to focus on capping or lamination caused by entrapped air [239]. Moreover, powder blends containing either 10 or 20 % (w/w) of APAP (APAP-10, APAP-20) were blended with MCC-5 for 5 min. Subsequently, 0.5 % (w/w) MgSt was added and each powder blend was mixed for additional 3 min. The batch size for each powder blend was about 2.5 kg. Afterwards, these powder blends were compacted at different turret speeds (8, 20, 42, 82, and 102 rpm) to tablets with and without the application of externally applied lower punch vibration. For tableting with lower punch vibration, a turbine vibrator was mounted and operated with an inlet pressure of 2 bar, which corresponds to a frequency of 400 Hz and amplitudes within a range of approximately 0.05-0.1 mm. The different turret speeds were selected with regard to the resulting dwell times of 80, 50, 20, 10, and 5 ms. Tableting was performed with round flat-faced punches (Ø 10 mm). All tablets, manufactured with and without lower punch vibration, were tableted to the same band height of 2.1 mm. The adjusted

filling depth for the tableting without vibration was set to 9.5 mm (maximum filling depth) to obtain tablets with a tablet weight of about 300 mg. In contrast, the filling depth for tablets manufactured with lower punch vibration was adjusted to 7.3 mm. Because of the fact that lower punch vibration leads to an improved die filling, a reduction of the filling depth for tablets manufactured with lower punch vibration was necessary to obtain the same tablet weight of 300 mg. The measured compaction forces and obtained tensile strengths depended on the applied turret speed and the investigated powder blend. The range of the measured compaction forces varied between 11-22 kN (MCC tablets) and 21-33 kN (APAP tablets), because of the different compaction behavior of the MCC and the APAP formulations.

A detailed list of the resulting compaction forces may be found in the following tables 5 and 6:

Table 5: Compaction forces (CF) of the manufactured MCC and APAP tablets (without vibration) at different turret speeds: CF-8 ≙ 8 rpm, CF-20 ≙ 20 rpm, CF-42 ≙ 42 rpm, CF-82 ≙ 82 rpm, and CF-102 ≙ 102 rpm (means ± SD, n = 20).

Tablet formulation	CF-8 (kN)	CF-20 (kN)	CF-42 (kN)	CF-82 (kN)	CF-102 (kN)
MCC-2	20.238 ± 0.91	20.261 ± 0.87	19.685 ± 0.91	11.252 ± 1.05	11.861 ± 0.86
MCC-3	14.931 ± 0.31	15.002 ± 0.19	14.301 ± 0.16	13.734 ± 0.53	13.315 ± 0.44
MCC-4	21.032 ± 0.81	20.984 ± 0.58	20.786 ± 1.41	15.051 ± 0.91	14.446 ± 0.54
MCC-5	20.852 ± 0.57	20.671 ± 1.12	20.013 ± 0.63	18.697 ± 0.83	18.727 ± 0.73
APAP-10	33.075 ± 1.02	33.171 ± 0.53	33.002 ± 0.86	27.259 ± 0.85	27.636 ± 1.06
APAP-20	29.980 ± 0.63	30.940 ± 0.75	30.391 ± 0.56	22.932 ± 1.32	21.454 ± 3.37

Table 6: Compaction forces (CF) of the manufactured MCC and APAP tablets (with vibration) at different turret speeds: CF-8 ≙ 8 rpm, CF-20 ≙ 20 rpm, CF-42 ≙ 42 rpm, CF-82 ≙ 82 rpm, and CF-102 ≙ 102 rpm (means ± SD, n = 20).

Tablet formulation	CF-8 (kN)	CF-20 (kN)	CF-42 (kN)	CF-82 (kN)	CF-102 (kN)
MCC-2	20.111 ± 0.63	19.382 ± 0.73	19.322 ± 0.83	12.878 ± 0.91	12.029 ± 0.82
MCC-3	15.273 ± 0.30	15.055 ± 0.24	15.252 ± 0.18	14.965 ± 0.29	13.626 ± 0.11
MCC-4	21.457 ± 0.33	20.079 ± 0.34	22.032 ± 1.21	21.299 ± 0.82	21.128 ± 0.69
MCC-5	20.797 ± 0.24	21.079 ± 0.28	22.031 ± 0.34	21.299 ± 0.48	21.128 ± 0.35
APAP-10	31.485 ± 0.53	31.369 ± 0.69	31.892 ± 0.70	30.988 ± 0.78	29.661 ± 0.62
APAP-20	29.501 ± 0.48	29.582 ± 0.71	30.864 ± 0.64	28.978 ± 1.06	27.862 ± 1.20

The comparably high compaction force for the APAP powder blends was required to obtain tablets with sufficient mechanical strengths at low turret speeds.

The MCC grades investigated in chapter 3.4. (MCC-2, MCC-3, MCC-4) were blended with 1 % (w/w) MgSt for 3 min with a Turbula® T2F blender (W.A. Bachofen, Basel, Switzerland). Furthermore, different reference powder mixtures were examined in this study. The compositions of these reference mixtures are shown in Table 7.

Table 7: Compositions of the investigated reference powder mixtures.

Powder	Reference A	Reference B	Reference C
MCC-3	60 % (w/w)	60 % (w/w)	60 % (w/w)
Lac-3	36 % (w/w)	0 % (w/w)	0 % (w/w)
Emcompress®	0 % (w/w)	0 % (w/w)	36 % (w/w)
Destab™ 90SE	0 % (w/w)	36 % (w/w)	0 % (w/w)
CCS	3 % (w/w)	3 % (w/w)	3 % (w/w)
MgSt	1 % (w/w)	1 % (w/w)	1 % (w/w)

The respective grades of filler and binder were blended together with CCS for 5 min. Subsequently, MgSt was added and the powder compositions were blended again for 3 min.

All of the investigated powders were compacted either with or without lower punch vibration with flat-faced (Ø 10 mm) punches, whereby the batch sizes were about 1.5 kg. The die disk speed was adjusted to 15 rpm and the compaction force was varied from 5 to 15 kN to investigate the influence of lower punch vibration on the

compactibility and bondability of the investigated powders. The filling depth for the tablets manufactured without vibration was set to 9.5 mm (maximum filling depth), whereby the respective band height was varied to achieve the required compaction forces. Because of the improved die filling during lower punch vibration, the filling depth for tablets manufactured with lower punch vibration had to be reduced to obtain equal tablet weights. The filling depths and band heights adjustments for tablets manufactured either with or without lower punch vibration are presented in Table 8:

Table 8: Tablet press settings.

Powder	Filling depth (mm)	Band height at 5 kN (mm)	Band height at 10 kN (mm)	Band height at 15 kN (mm)
MCC-2	9.50 mm 7.90 mm*	2.90	2.20	1.95
MCC-3	9.50 mm 7.90 mm*	3.30	2.60	2.35
MCC-4	9.50 mm 7.20 mm*	3.30	2.65	2.35
Reference A	9.50 mm 7.90 mm*	3.90	3.10	2.85
Reference B	9.50 mm 8.10 mm*	3.60	2.80	2.55
Reference C	9.50 mm 8.00 mm*	3.90	3.10	2.80

* Tablets manufactured with lower punch vibration

In the study presented in chapter 3.4., a turbine vibrator was mounted to the modified filling cam. The respective inlet air pressure was adjusted to 2 bar which corresponds to frequencies of 400 Hz and amplitudes between 0.05 and 0.1 mm during tableting with lower punch vibration.

2.2.3. Tablet characterization

2.2.3.1. Crushing force

The crushing forces of the tablets were determined with a multifunctional hardness tester (TBH 525; Erweka, Heusenstamm, Germany) and with a modified texture analyzer (Inspekt mini 3kN, Hegewald & Peschke, Nossen, Germany). The setup of the texture analyzer is illustrated in Fig. 11.

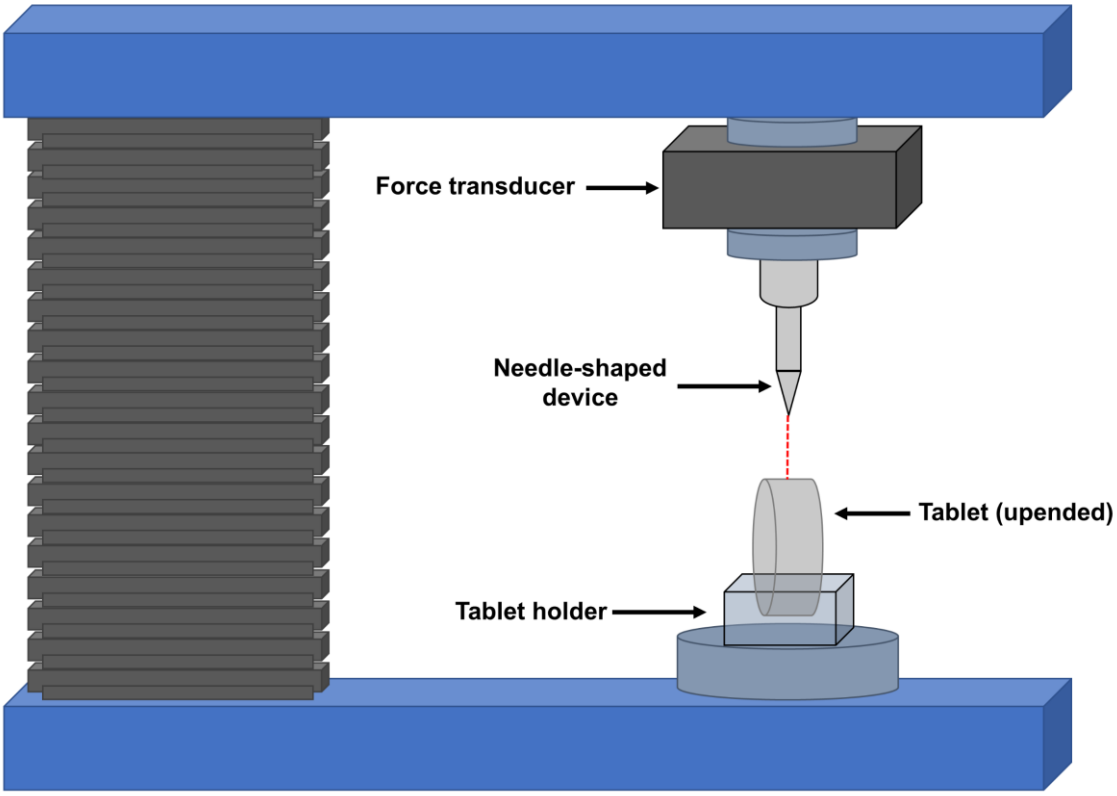


Fig. 11: Modified texture analyzer.

The tablets were placed upended in a specially formed fastening construction, whereby a needle-shaped device was used for the force transmission. The movement rate of the needle was adjusted to 1 mm/s, whereby a 200 N strain gauge load transducer was used to guarantee a high measuring accuracy. The measurement end was set to a force decrease of 50 %. Prior to the measurements, the tablets were placed upended

and centered in such a way that the needle hits the tablet at the center of its band height (Fig. 12).

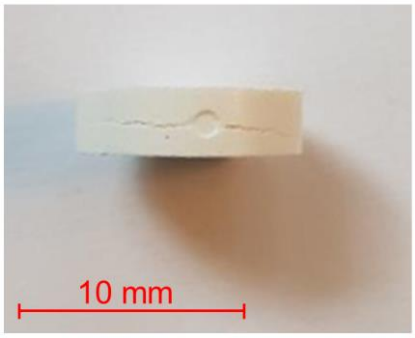


Fig. 12: Image of a tablet after measuring the crushing force with the modified texture analyzer.

In the case of flat-faced tablets, the center of the band height is usually the mechanically weakest point [240]. As the study presented in chapter 3.4. investigated if lower punch vibration allows to increase the crushing force and thus the mechanical strength of the tablets, tablets were tested at their weakest point.

2.2.3.2. Tensile strength

The tensile strength of tablets is a more precise parameter for determination of the mechanical tablet stability than the crushing force, as the tensile strength also takes into account the geometric conditions of the tablets. Therefore, the tensile strength σ of the investigated tablets was determined and calculated by the following Eq. 10:

$$\sigma = \frac{2 \cdot F}{\pi \cdot d \cdot t} \qquad \text{(Eq. 10)}$$

where F is the crushing force (N), d the tablet diameter (mm), and t the tablet thickness (mm) [255].

2.2.3.3. Friability

Friability tests were performed with a friability tester (TA 100; Erweka, Heusenstamm, Germany) according to the monograph 2.9.7 of the Ph. Eur. The tests were performed with approximately 6.5 g of tablets and a rotating speed of 25 rpm for 4 min.

2.2.3.4. Solid fraction

The SF serves as a parameter to quantify the solid content and thus the extent of porosity within the respective tablets. It was calculated according to Eq. 11, whereby the tablet density was divided by the true density of the powders:

$$\text{Solid fraction} = \frac{\text{Tablet density}}{\text{True density}} \quad \text{(Eq. 11)}$$

2.2.3.5. Capping & lamination index

The tablets, the manufacture of which is described in chapter 3.3., were investigated visually (with the naked eye) to detect possible occurrences of capping or lamination directly after tablet production. In this context, the Capping or Lamination Index of each examined powder blend after tableting was calculated according to Eq. 12:

$$\text{Capping or Lamination Index} = \frac{(5 \cdot N_{op} + N_h)}{N_t} \quad \text{(Eq. 12)}$$

where N_{op} is the number of capped or laminated tablets after tablet ejection, N_h is the number of tablets capped or laminated during hardness testing, and N_t is the total number of tested tablets [124]. The capping or lamination indices were determined in triplicate, whereby the total number of investigated tablets (N_t) was 20 for each measurement. Furthermore, a stereomicroscope (SteREO Discovery.V8; Carl Zeiss,

Oberkochen, Germany) was used to illustrate the differences between capping and lamination.

2.2.4. Characterization of the densification process within a die

2.2.4.1. High-speed camera imaging

The densification vs. time profiles shown in chapter 3.1. were monitored using the vibration rig in combination with an ultrahigh-speed camera system (Motion Pro Y4-S2; IDT Vision, Tallahassee, USA). Each powder sample was monitored maintaining the exactly same camera adjustments. The respective acquisition settings of the camera are listed in Table 9.

Table 9: High-speed camera acquisition settings.

Rate (Hz)	Exposure (µs)	Pixel Depth (bit)	Region of interest (ROI)	Binning
1000	639	8	1024 x 1024	1 x 1

A separate light source (KL 16000 LED; Schott, Mainz, Germany) was placed behind the plastic die directly opposite of the camera lens. Camera sequences of 6 s each were monitored, whereby the monitoring started 500 ms before and ended 500 ms after starting the vibration process. A frame rate of 1000 pics per s offered the possibility to visualize the process during every ms.

2.2.4.2. Image processing by ImageJ

The records from the high-speed camera (see sub-chapter 2.2.4.1.) were analyzed using the image analyzing system ImageJ, a freeware application available from the U.S. National Institutes of Health (NIH). The videos were imported in sequences of 6000 images per record (with regard to the frame rate of 1000 Hz and a record time of 6 s). In a first step, all images were cropped to obtain a uniform image. In a second

step a threshold technique was used to determine the densification processes within the die. Thresholding is based on the separation of pixels according to their intensity values. Every 8-bit greyscale image exhibits 256 intensities, which can be assigned to a pixel. As intensities of 0 are equivalent to “black”, intensities of 255 correspond to “white”. Hence, the image of a filled die appears “black”, whereas a decrease of the powder bed volume is associated with an intensity change from “black” to “white”. The underlying procedure is presented in Fig. 13, whereby the black area is converted to red during the thresholding procedure.

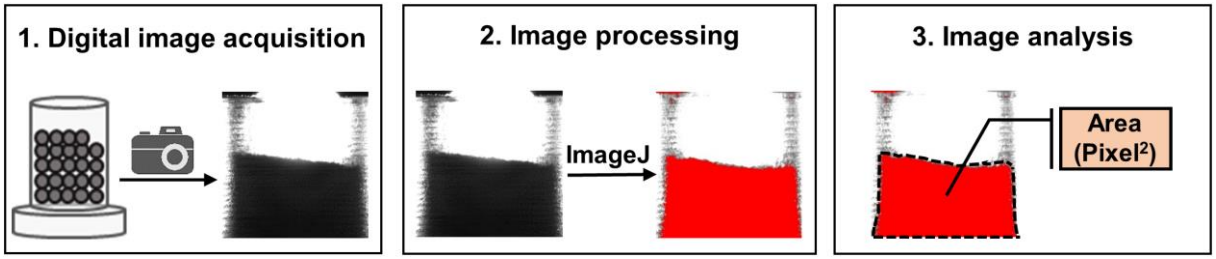


Fig. 13: Illustration of the image analysis procedure of the powder bed within the die.

The total extent of densification was determined by measuring the change in black to white in pixel^2. Therefore, threshold settings of saturation and brightness were standardized for each analyzed image to obtain comparable results. The possibility to calculate the area of every individual image at every single record time point enabled the monitoring of the densification process as a function of time.

2.2.5. Segregation analysis

2.2.5.1. Tablet preparation

In the study presented in chapter 3.2., a novel analyzing system for the determination of particle segregation within tablets is introduced. To investigate the extent of segregation depending on the externally applied lower punch vibration, two different powders, MCC-2 and MCC-3, were mixed in different mass ratios: 50:50 (w/w) and 80:20 (w/w). The 50:50 mixture is called blend 1 and the 80:20 mixture is called blend 2. Before mixing, MCC-3 was spray-colored with the blue food colorant indigo carmine to allow the analysis of segregation. For the spray-coloring process, 200 ml of a 0.25 % (w/w) aqueous solution of indigo carmine were added to 500 g of MCC-3 within a laboratory fluid bed system (Solidlab 1; Bosch, Waiblingen, Germany). Afterwards, the spray-colored MCC-3 was blended with untreated white MCC-2 for 8 min using the Turbula mixer. Subsequently, the powder blends were compacted with a rotary tablet press, whereby flat faced tablets with a diameter of 10 mm and a snap tab were prepared. The aim was to produce tablets with a target tablet weight of 250 mg and a tensile strength of 2 MPa.

After tableting, the tablets were treated and analyzed as shown in Fig. 14:

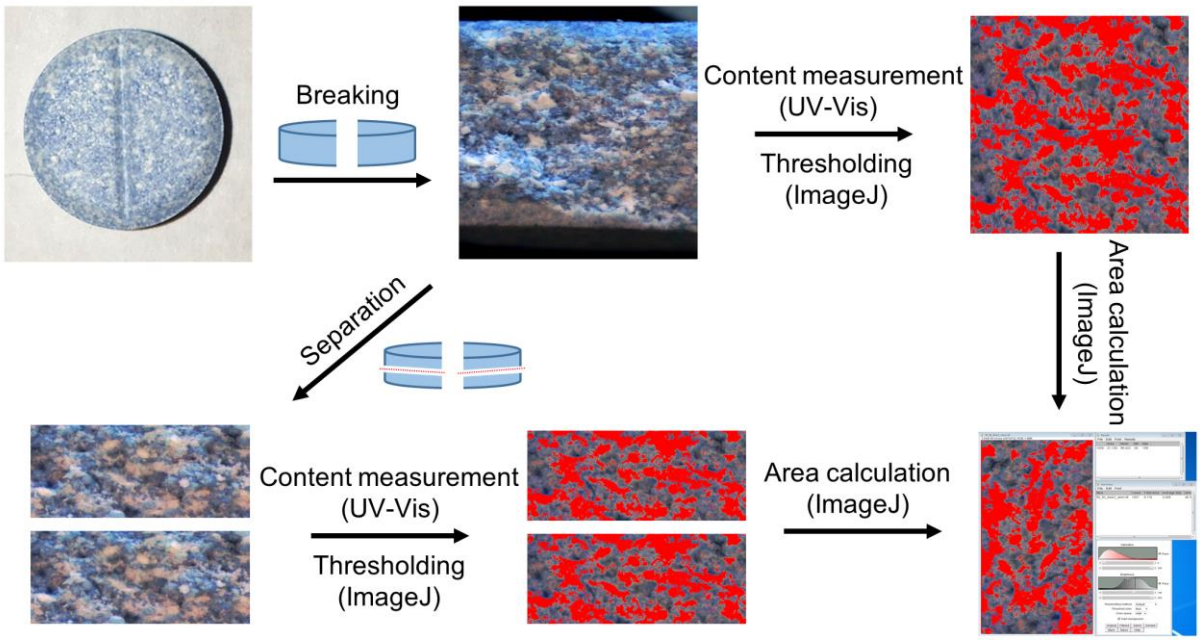


Fig. 14: Tablet treatment and analysis to determine the extent of segregation.

First, the tablet halves were examined. In addition, the tablet halves were cut horizontally using a scalpel. Both, the tablet halves and the horizontally cut tablet parts were first analyzed first with an image analyzing program (see sub-chapter 2.2.5.2.) and subsequently, the content of the spray-colored MCC-3 was determined by UV-Vis spectroscopy (see sub-chapter 2.2.5.3.). To detect possible differences between the resulting content of spray-colored MCC within the tablets, which were manufactured with and without externally applied vibration, a single-factor ANOVA was performed. In contrast, to determine differences between the two analyzing techniques, ImageJ and UV-Vis, a two-factor ANOVA was carried out. The concentration values of spray-colored MCC were considered as significantly different, if the p-value was lower than 0.05 (referring to a 95 % confidence level).

2.2.5.2. Imaging and image analysis of segregation events within tablets

To determine the content of spray-colored MCC-3 particles, the section along the snap tab of the tablet was analyzed by a stereo microscope (SteREO Discover.V8; Zeiss, Oberkochen, Germany) and images were recorded by an implemented camera (AxioCam ICc1, Zeiss, Oberkochen, Germany). Afterwards, the images were analyzed with the image analyzing software ImageJ. A threshold technique was used, which is based on the resolution of an image in pixels according to their color intensity values. The total extent of the pixels and the extent of the "blue pixels" were measured. Consequently, it was possible to determine the particle distribution and thus the extent of segregation for the whole tablet along the snap tab as well as for the top and bottom part of the tablet. The principles of the thresholding technique are described in detail in sub-chapter 2.2.4.2.

2.2.5.3. UV-Vis spectroscopy

To measure the concentration of the blue colored MCC-3 particles within the tablets, the tablet parts (tablet halves and horizontally cut top and bottom parts of the tablets) were disintegrated in demineralized water and the concentration of indigo carmine was determined by UV-Vis spectroscopy (Genesys^{TM}10S; Thermo Scientific, Pittsburgh, USA). Measurements were performed with 20 tablets (40 tablet halves and 80 horizontally cut tablet halves) at a wavelength of 608 nm. For validation purposes, powder blends with preassigned concentrations of indigo carmine were tableted and analyzed. In this context, the linearity of the calibration curve was verified within a concentration range between 0.10 and 0.90 (R^2 = 0.9994).

2.2.6. Vibration

2.2.6.1. Vibrator types

In the present work, two different pneumatic vibrator types were applied and compared to each other. On the one hand, a piston vibrator (MKK22; Mooser, Puchheim, Germany) with monodirectional generated vibrations [250] was implemented. On the other hand, a turbine vibrator (MTT13; Mooser, Puchheim, Germany) with circularly generated vibrations was used [256]. Both vibrator types differ in their generated frequencies and working torques. While the piston vibrator generates low vibrations frequencies with high amplitudes, the turbine vibrator generates high vibration frequencies with high amplitudes. With both vibrator types, the generated frequencies may be varied and adjusted through the inlet air pressure. Therefore, a compressor (Mega 400- 50 W; Metabo, Nürtingen, Germany) was used to generate the required inlet pressure (2 – 6 bar). For an exact adjustment of the inlet pressure a pressure reducer (LFR 1/4; Festo, Esslingen, Germany) was connected

2.2.6.1. Vibration rig - laboratory scale

For the study performed in chapter 3.1., a special vibration rig was developed to investigate the influence of external applied lower punch vibration on the densification behavior of a powder bed inside a filling die of a rotary tablet press. The basic equipment is presented in Fig. 15. The construction is composed of a metal scaffold and includes a moveable vibration table. The table is hanging on four springy pillars and modified with a special assembly to clamp a lower punch onto the table. Moreover, a device for mounting a vibration unit under the table is installed. The movement of the clamped lower punch into the die is controlled by a metal block.

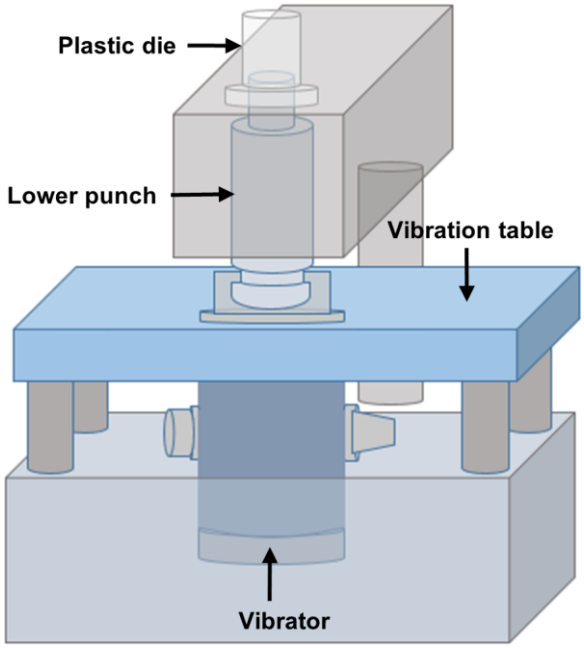


Fig. 15: Experimental assembly of the vibration rig.

Furthermore, the penetration of the lower punch into the die is variable and adjustable by the installed metal block. The plastic die is translucent to allow the monitoring of the powder bed densification. In the present study, a plastic die and a lower punch, both with a diameter of 10 mm, were used. Furthermore, a pneumatic piston vibrator (MKK22; Mooser, Puchheim, Germany) was applied to densify the powder bed in the die. The piston vibrator generates monodirectional vibrations by a free-vibrating reversing piston [250][256].

To visually comprehend the time-dependent densification it is important to start and stop the vibration immediately. For this purpose, a current relay with an operator display was programmed to trigger a high-speed two-way valve. This current relay was necessary to open and shut the air feed as quickly as possible. The inlet pressure was adjusted by a pressure reducer (LFR 1/4; Festo, Esslingen, Germany). Moreover, the opening time of the two-way valve was set exactly to 5 s. The experimental setup is

illustrated in Fig. 16 and consists of the air pressure source, the pressure reducer, the two-way valve in combination with the current relay and the vibration rig.

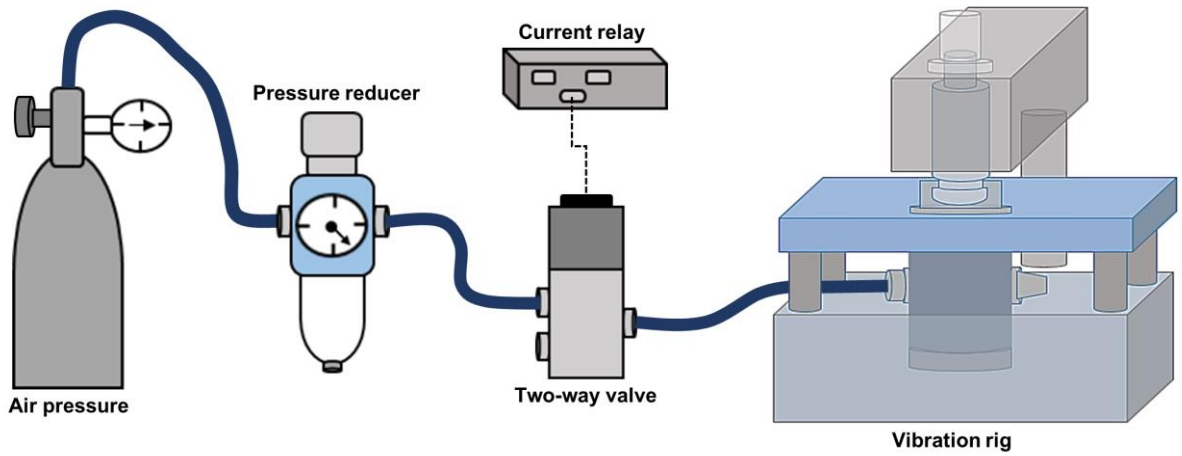


Fig. 16: Schematic representation of the experimental setup.

The experiments with the vibration rig were performed at the following three applied frequency levels of 48 Hz, 58 Hz, and 68 Hz, which resulted from the inlet pressures of 2 bar, 4 bar, and 6 bar, respectively. To obtain comparable results, a shaking rail was chosen to convey a defined amount of powder through a funnel into the die. The funnel (opening diameter 10 mm) was mounted closed to the die.

2.2.6.2. Vibration equipment for the rotary tablet press

A special vibration equipment was developed for the implementation on a rotary tablet press. The principles of the construction are presented in Fig. 17. The vibration equipment is basically composed of a modified filling cam and a vibrator, which is connected to the filling cam by springy pillars.

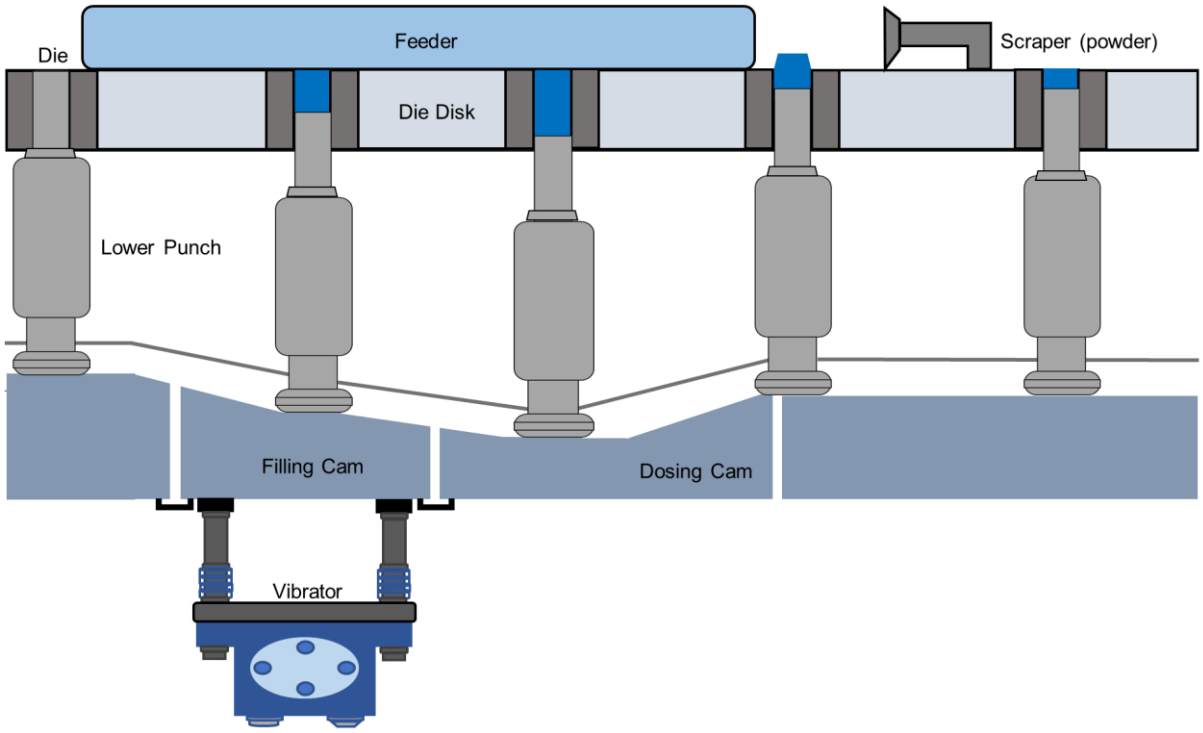


Fig. 17: Schematic overview of the implementation of a pneumatic vibrator connected to a modified filling cam.

The modified filling cam consists of two parts, the first directly mounted to the turret and the second part connected to the vibrator. This special two-part construction of the filling cam is necessary to convey the applied vibrations during the filling process only to the lower punch and not to other parts of the rotary tablet press. If the lower punch passes through the filling cam, vibration is transferred from the inner part of the filling cam to the lower punch and consequently to the inflowing powder.

3. Results and Discussion

3.1. Development of a novel vibration system for the densification of powders within the dies of tablet press

3.1.1. Powder characterization

To examine the effect of lower punch vibration to the densification of a powder bed within the die, in the present study powders with insufficient powder flow characteristics were investigated. Accordingly, powders with particularly high differences between bulk and tapped density were examined. The HR value and the CI serve as a measure of the powder flowability. Both investigated powders showed a comparatively high HR and high CI. While $MgCO_3$ showed a HR of 1.54, indicating a poor powder flow, MCC-1 revealed a HR of 1.69, which is attributed to an even inadequate powder flow. Moreover, $MgCO_3$ provided a CI of 48.76 % (inadequate powder flow) and MCC-1 a CI of 30.51 (poor powder flow). The corresponding values of bulk and tapped density and the respective standard deviations (SD) are listed in Table 10.

Table 10: Physical properties of the investigated powders (means ± SD, n = 3).

	$MgCO_3$	**MCC-1**
Particle shape	Plate	Needle
Particle size d_{50} (µm)	153.49	42.84
Bulk density (g/cm^3)	0.104 ± 0.0003	0.167 ± 0.0014
Tapped density (g/cm^3)	0.161 ± 0.0004	0.258 ± 0.0032
$V_{10} – V_{500}$ (ml)	56.3 ± 0.6	62.0 ± 0.1
Hausner ratio	1.54 ± 0.007	1.69 ± 0.008
Carr index (%)	48.76 ± 0.31	30.51 ± 0.55
True density (g/cm^3)	2.460 ± 0.040	1.646 ± 0.009
Relative density	0.042	0.102

The poor powder flow was confirmed by measuring the ff_c values of both powders at different applied consolidation stress values. The powder flowability index is illustrated as plot of the unconfined yield strength versus the consolidation stress (Fig. 18).

Both substances exhibit ff_c values < 5, which indicates a cohesive flow behavior. Apparently, $MgCO_3$ exhibits a stronger cohesive flow behavior than MCC-1. The V10-V500 value serves as an indicator for the presence of entrapped air within the powder bed. Hence, the measured values of 56.3 ml ($MgCO_3$) and 62.0 ml (MCC-1) indicate a high volume of entrapped air within the both powder beds. The relative density also serves as reference for the volume of entrapped air. The smaller the relative density values the higher the volume of entrapped air. A powder with no interparticle entrapped air shows values about $\rho_0 = 1$.

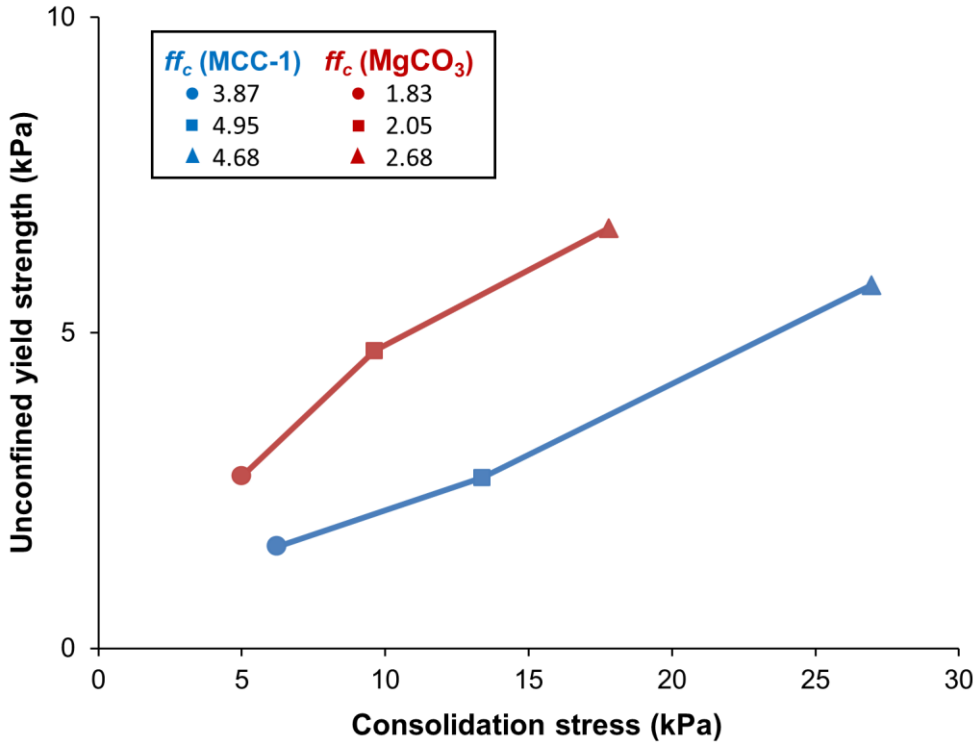


Fig. 18: Powder flow function plots and corresponding ff_c values of the investigated powders.

As both investigated powders, $MgCO_3$ and MCC-1, show relative density values of 0.102 and lower, it is obvious that the volume of entrapped air inside both powder beds is high. Furthermore, it is noticeable that $MgCO_3$ in comparison to MCC-1 (3.98 m^2/g) exhibits a larger specific surface area (28.45 m^2/g). Hence, electrostatic interaction between the particularly small $MgCO_3$ particles and thus, the tendency to form aggregates, is strong. Especially the aggregation tendency probably leads to a high volume of entrapped air caused by the generated cavities inside the formed aggregates.

Probably, the particle shape strongly influences these low relative density values. Images of both powders are displayed in Fig. 19.

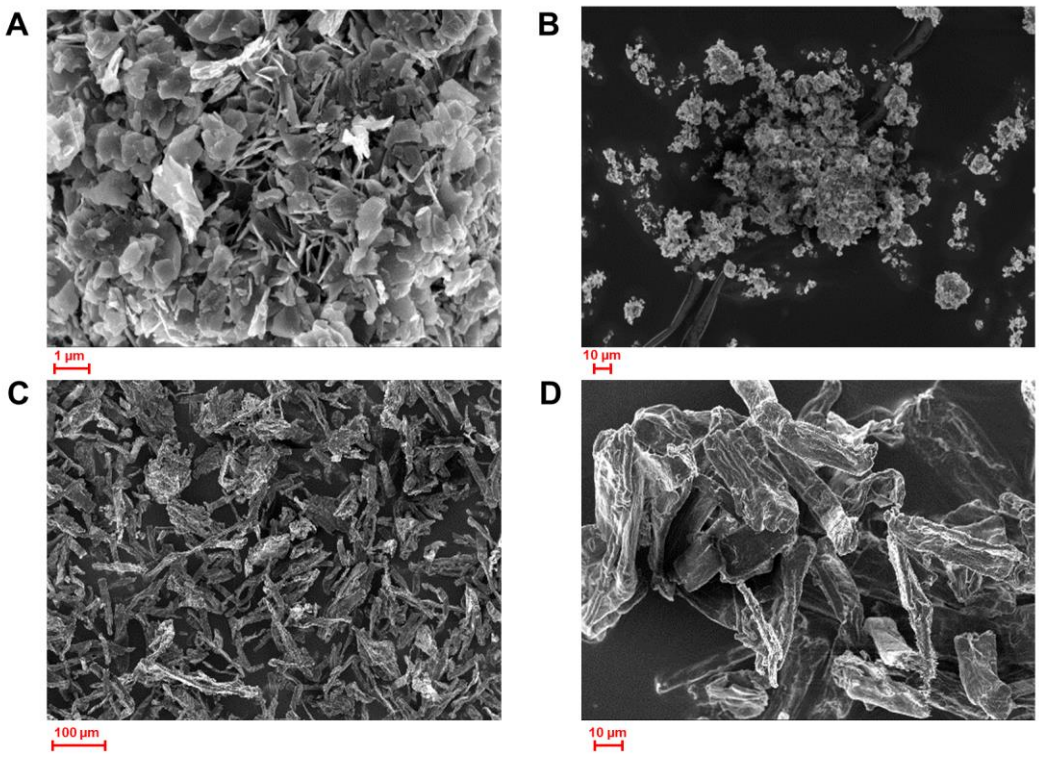


Fig. 19: SEM images of $MgCO_3$: (A) x = 2,000; (B) x = 1,000 and MCC-1: (C) x = 300; (D) x = 1,500.

In the present study, it was also intended to investigate powders with different particle shapes and particles sizes to examine the effect of the lower punch vibration on different types of powder. As it can be observed in Fig. 19A, $MgCO_3$ particles show a plate-like shape with sharp edges. In contrast, in Fig. 19B irregularly formed $MgCO_3$ aggregates are illustrated. The results of the particle size distribution, expressed as d50, showed that the value of $MgCO_3$ 153.94 µm (Table 10) described the size of the aggregates (Fig. 19B) and not the size of the single plate particles which were significantly smaller. However, the semi-crystalline polymer MCC-1 showed needle-formed fibers and filaments (Fig. 19C and D), and thus also led to an air entrapment. It is known that needle-formed particles, in particular those with a narrow minor axis, normally reveal low bulk densities. Such a low bulk density is caused by the arrangement of needle-shaped particles in the powder bed.

The moisture content of $MgCO_3$ was 6.17 ± 0.21 %, whereas MCC-1 showed a moisture content of 5.79 ± 0.10 %.

3.1.2. High-speed camera imaging

Image-analysis by thresholding is a valuable technique to measure the densification process within the die. The visualization of the densification process, performed by the high-speed camera system, is represented in Fig. 20.

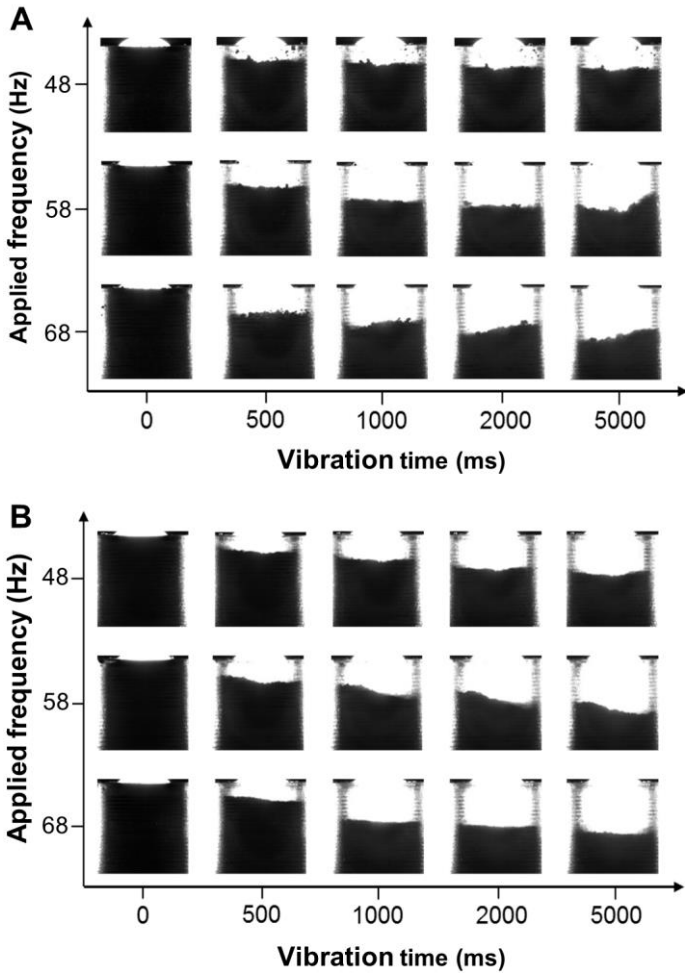


Fig. 20: Time-dependent densification of the investigated powder samples at different applied frequencies. High speed camera images of (A) $MgCO_3$ and (B) MCC-1.

It may be observed that both powders, MCC-1 and $MgCO_3$, showed a significant densification at all applied frequency levels. Dependent on the frequency level of the

applied vibration, a more or less pronounced densification was observed. It was shown that higher frequencies generally led to a more pronounced densification. However, the difference in the extent of densification is more distinct between 48 and 58 Hz than between 58 and 68 Hz. Especially with MCC-1 almost no alteration may be observed between 58 and 68 Hz (Fig. 20B). The various extents of densification of both powders illustrate the influence of the above-mentioned powder properties on the achieved densification levels. In addition, the applied vibration time had an important impact on the powder densification (Fig. 20). As shown in Figs. 20A and B, the highest extent of densification associated with a plateau level was already reached after the first 1,000 ms of vibration.

3.1.3. Image Analysis

Thresholding is an image processing technique, which allows the detection of complex and disjointed features in an image by the software ImageJ. Especially for the analysis of slight differences between similarly recorded images, thresholding presents a useful tool, as it may calculate the number of pixels in specified areas of an image. The powder beds represented as black areas in Fig. 20 correspond to the calculated image areas in Fig. 21.

This calculation enables the characterization and evaluation of the entire densification process of the investigated powders in the present study. Performance characteristics and detailed imaging sequences of each powder sample may be assessed time-dependently. The results referring to the time-dependent densification process of both investigated powders are shown in Figs. 21A and B.

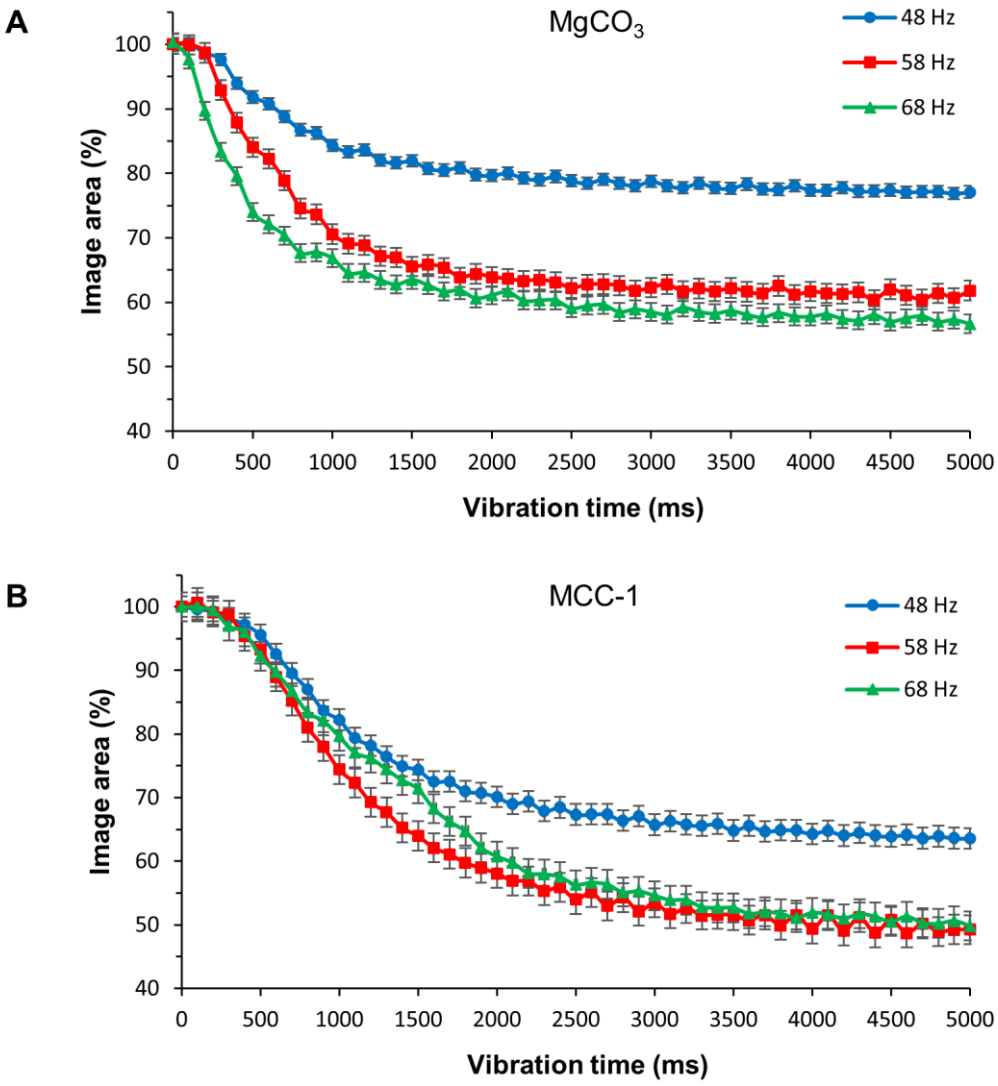


Fig. 21: Image area versus vibration time of (A) $MgCO_3$ and (B) MCC-1 at the applied frequencies (means ± SD, n=5).

As expected from the high-speed camera records in Fig. 20, the evaluation by the software ImageJ revealed similar trends of the densification behavior but allowed a more detailed insight into the densification process. In Fig. 21A ($MgCO_3$) it may be clearly observed that higher air pressures and thus, higher frequencies resulted in a more distinct image area decrease compared to lower frequencies. After the first 1,000 ms of applied vibration only comparably low changes of the image areas could be detected, which confirms the results of the high-speed images in Fig. 20. The unsteady pattern of the curve may be explained by the mounted piston vibrator, which

causes vibration by the fast up and down movements of the piston and thus the lower punch.

Despite the same curve patterns at all applied frequency levels, distinct differences in the extent of the image area decrease between the frequency levels are detectable particularly with $MgCO_3$ (Fig. 21A). The higher the applied frequency the higher the area decrease, whereby the difference between 48 and 58 Hz was much more pronounced than the difference between 58 and 68 Hz. As the difference between 58 and 68 Hz was very low, the applied frequencies generated by 4 bars led to an almost compacted powder bed.

In comparison to $MgCO_3$ (Fig. 21A), MCC-1 (Fig. 21B) showed a different trend. In contrast to $MgCO_3$, the highest extent of the image area decrease was detected only after 2,000 ms. The distinct change during the first 1,000 ms ($MgCO_3$) and 2,000 ms (MCC-1) is probably a consequence of a new particle rearrangement and increased air ventilation in the powder bed. Needle-shape MCC-1 particles require more time for dense packaging than the plate-shaped $MgCO_3$ particles, because the rearrangements of plate shaped particles occur faster.

The difference between the curve patterns of $MgCO_3$ and MCC-1 suggest that the densification process also depends on the physical properties of the investigated powders. Depending on the variations in the particle shape, particle size distribution, and particle density, different densification behaviors may be observed. This observation implies that each powder formulation exhibits a specific maximum densification level, which depends on the extent of the applied vibration. Hence, this fact may explain the observation that MCC-1 showed no significant changes in its densification level between 58 Hz and 68 Hz (Fig. 21B).

Together with the observed image area change of the investigated powder samples, the data displayed in Fig. 21 was used for calculation of the percentage of densification of the powder bed within the die for the different frequency levels. The corresponding results are depicted in Fig. 22.

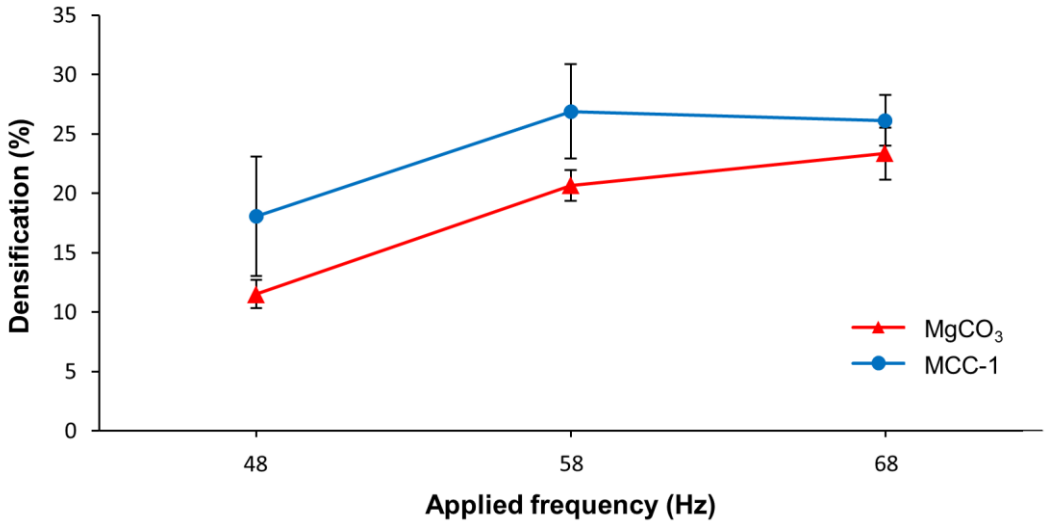


Fig. 22: Percentage of densification of $MgCO_3$ and MCC at the investigated frequencies (means ± SD, n=5).

The respective values of the image area decrease were converted and related to the die volume combined with the weight of the examined powder bed. It may be shown that the results corresponded to the data in Fig. 21. It is clearly observed in Fig. 22 that the differences between 48 and 58 Hz are more pronounced than those between 58 and 68 Hz. As previously mentioned, MCC-1 exhibited a higher extent of densification as $MgCO_3$. In comparison to the maximum amount of densification after US generated vibration (10–15 %), pneumatically generated vibration led to a 30–50 % increased densification of the powder bed [238]. This observation is attributed to the monodirectional vibration by the lower punch and the comparatively high working torque.

3.1.4. Comparison of the investigated densities

To assess the extent of densification of the powder bed by external lower punch vibration, the respective tapped densities were compared with the resulting densities after vibration, because it was assumed that the tapped density represents the maximum densification level of a powder bed. In Fig. 23, the densification levels of $MgCO_3$ and MCC-1 for the frequencies of 48, 58, and 68 Hz, in relation to the tapped densities are illustrated, whereby 0 % densification represents the bulk density of each powder.

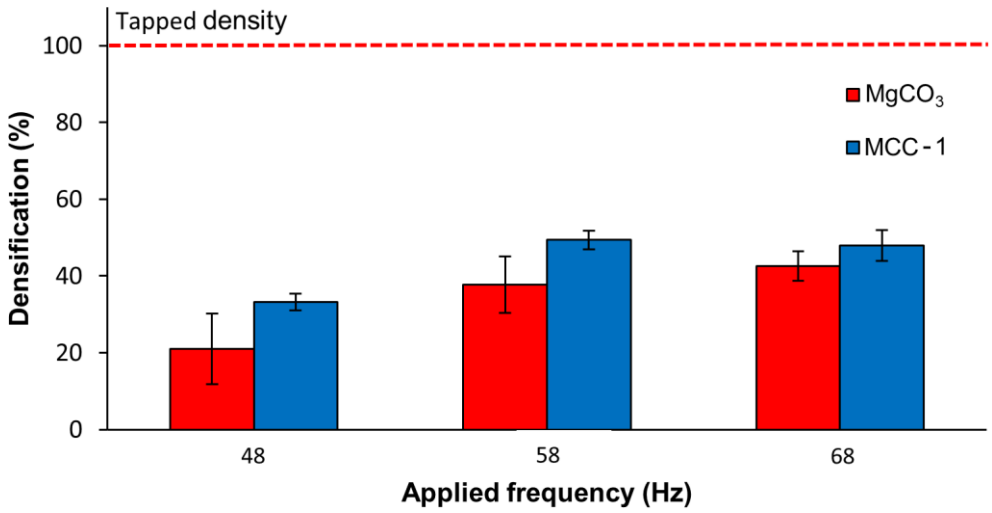


Fig. 23: Densification values calculated as percentage of the respective bulk (0 %) and tapped densities (100 %) of $MgCO_3$ and MCC-1. Vibration was applied for 5 sec at each applied frequency (means ± SD, n=5).

The results show that external vibration leads to an increase of the bulk density of the powder beds of up to 50 % in relation to the tapped density by application of a piston vibrator. Thus, for this experimental set-up, external vibration allows a densification of over 50 % of the maximum value within 5 sec of applied vibration.

In summary, externally applied lower punch vibration may be a promising approach to remove entrapped air from a powder bed inside a die and to densify the powder bed to a pronounced extent prior to the main compaction step. Furthermore, the extent of densification was shown to be dependent on the applied vibration, particles shapes, and the physical properties of the investigated powder samples.

3.1.5. Conclusion

The present study showed for the first time that a pneumatically generated vibration of the lower punch is able to densify a powder bed within the die. In comparison to previously investigated US vibration systems, the pneumatic vibration system presented in this study showed a higher extent of densification in a comparatively short time. Thus, the introduced concept of pneumatic lower punch vibration is the first vibration system, which meets the technical and instrumental requirements for the implementation on an industrial-scale rotary tablet press. Furthermore, it was observed that the extent of densification of the powder bed depended on the applied vibration and the physical properties of the selected powders. To quantify the extent and the time-dependent progress of densification an innovative measuring technique was developed. Thereby, it was possible to understand and describe the densification process within a die at a sufficient accuracy. Hence, it could be observed that the main densification occurred during the first 500 or 1000 ms and longer vibration time periods only marginally influenced the process. This observation is essential with regard to the

future implementation and feasibility of such a system on a running rotary tablet press. Additionally, such a vibration setup in combination with the presented measuring technique is suitable for the prediction of the densification process for different powder blends.

The presented concept of pneumatically lower punch vibration might be primarily applicable to reduce or prevent manufacturing problems such as capping and lamination as well as to improve the mechanical stability of the compact as the result of a homogeneously densified powder bed. In the following studies of this work, it will be investigated whether these benefits of lower punch vibration may also be observed in practice. Moreover, it is generally known that vibration might also lead to a segregation of powders. Therefore, in chapter 3.2., it will be dealt with this problem.

3.2. The effect of pneumatically lower punch vibration on tablet manufacture with a rotary tablet press under special consideration of the die filling step

3.2.1. Powder characterization

To investigate the influence of externally applied lower punch vibration on the die filling process and on the resulting mechanical stability of the tablets, powders with special attributes were selected. Because of the fact that a sufficient die filling depends on the flow behavior of the inflowing powder blend, powders with different flow properties were used in this study. Furthermore, excipients were selected that are widely used in the pharmaceutical industry as fillers and/or binders.

For comparative purposes, two grades of lactose (Lac-1, Lac-2) and MCC (MCC-1, MCC-2) were selected. Lac-1 and MCC-1 revealed an inadequate powder flow for tableting, whereas Lac-2 and MCC-2 showed acceptable flow properties. Because the process of the powder flow is complex and depends on different powder characteristics, a detailed powder characterization was performed and the results are presented in Table 11.

Table 11: Physical properties of the investigated powders (means ± SD, n = 3).

	MCC-1	**MCC-2**	**MCC-3**	**Lac-1**	**Lac-2**
Particle shape	Fibrous	Fibrous	Spherical	Cubic	Spherical
Particle size d_{50} (µm)	103.38 ± 2.36	98.23 ± 1.57	213.78 ± 4.78	16.91 ± 1.12	104.21 ± 1.67
Bulk density (g/cm^3)	0.17 ± 0.01	0.33 ± 0.01	0.35 ± 0.01	0.51 ± 0.01	0.60 ± 0.01
True density (g/cm^3)	1.646 ± 0.01	1.592 ± 0.01	1.558 ± 0.01	1.551 ± 0.01	1.513 ± 0.01
Relative density	0.102 ± 0.01	0.208 ± 0.01	0.366 ± 0.01	0.329 ± 0.01	0.397 ± 0.01
Hausner ratio	1.65 ± 0.01	1.33 ± 0.01	1.30 ± 0.03	1.61 ± 0.04	1.23 ± 0.02
Carr index (%)	39.57 ± 0.12	25.00 ± 0.56	23.16 ± 2.06	37.86 ± 1.70	19.19 ± 1.40

According to these results, MCC-1 and Lac-1 both revealed a high HR and CI, which indicates a very poor or extremely poor powder flow. In comparison, MCC-2 showed a moderate HR and CI, which corresponded to a passable powder flow. Lac-2 showed a fair or excellent powder flow. The powder flow of each powder was further characterized by shear cell measurements and the resulting ff_c values. The ff_c value of a powder describes the cohesiveness of the material depending on the consolidation stress. The corresponding ff_c values are shown in Fig. 24.

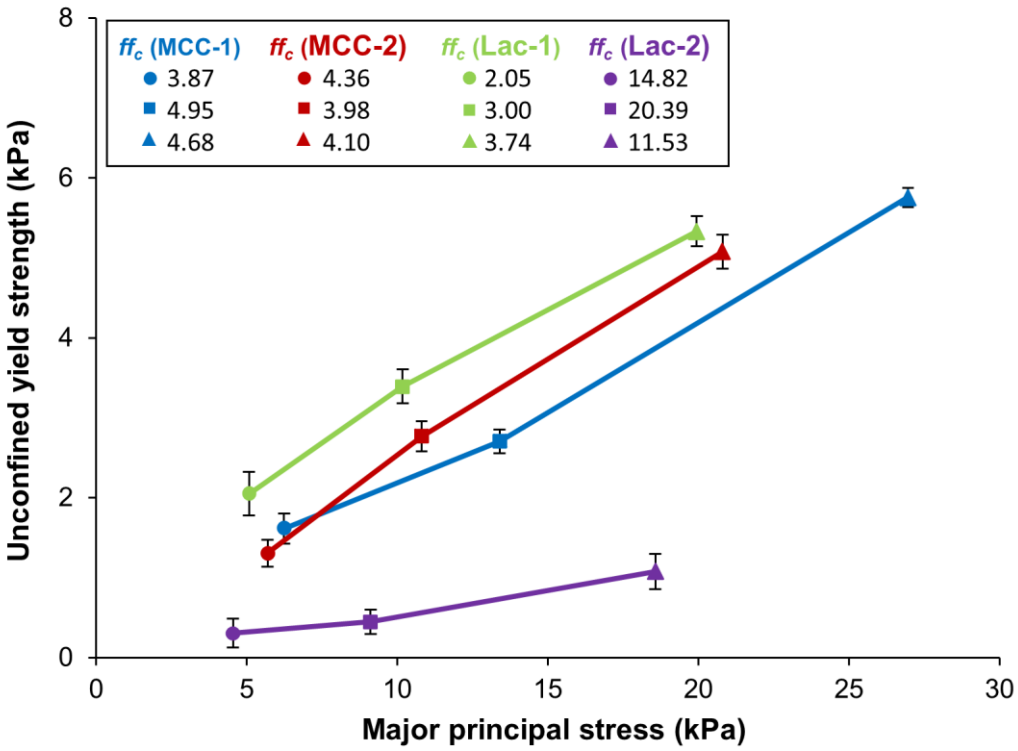


Fig. 24: Powder flow function plots and corresponding ff_c values of the investigated powders.

Both MCC grades showed similar ff_c values, which corresponded to a “cohesive” powder behavior and thus, a poor powder flow. The results are consistent with the powder flowability predicted from the HR and the CI. Also, the measured ff_c values of the two Lac grades (Lac-1 and Lac-2) supported the above-mentioned HRs and CIs. Lac-2 showed values above 10, which corresponds to an excellent flow behavior, whereas Lac-1 showed a cohesive powder behavior.

The relative density of each powder was calculated to determine the volume of entrapped air within the powder beds. The higher the relative density of a powder, the lower the entrapped air volume. A powder bed without any entrapped air shows a relative density of unity ($\rho_0 = 1$). It was observed that the relative densities of MCC-1 and MCC-2 were lower than those of Lac-1 and Lac-2 (Table 11), which indicates an insufficient die filling.

The volume of entrapped air, the powder bed buildup in the die, and the powder flow itself are directly linked to the particle shape and the particle size distribution of powder blends. Therefore, SEM was used to obtain images of the particle shape. As shown in Fig. 25, MCC usually shows fibrous and elongated particles, whereas MCC-1 exhibits a narrow minor axis and more elongated particles than MCC-2, which negatively influences the powder flow.

These needle-formed fibers lead to powder beds with a small bulk and small relative density and a high HR and CI. This observation corresponds to the results of the powder characterization (Table 11). The Lac powders show a completely different particle shape. As illustrated in Fig. 25, Lac-1 shows a cubic particle shape with sharp edges. The SEM image of Lac-2 differs completely from the SEM image of Lac-1. The particles form agglomerates and the approximately spherical particle shape may explain the good flow properties of Lac-2. Also, the particle size and particle size distribution, expressed as d_{10}, d_{50}, and d_{90}, are important factors to explain the powder flowability. It is known that a narrow particle size distribution in combination with a sufficiently large particle size (> 50 µm) results in a good flowability [110]. Thus, the small particle size of Lac-1, as well as its broad particle size distribution, lead to a poor powder flow. In comparison, the larger particle size and narrower particle size distribution of Lac-2 explain its good powder flow. It is reported that the residual moisture content of a powder distinctly influences the powder properties such as the true density, the flowability and the compressibility [257]. In the present study, the investigated powder samples showed moisture contents between 3 and 5 %, which are common for powder handling under ambient conditions of 43 % relative humidity and a temperature of 25 °C [176]. Therefore, the powders were not dried for the measurement of the true density. Hence, the true density values measured in this study

were slightly higher than reported for dry MCC. However, the residual moisture contents were in an adequate range for tablet manufacturing [134].

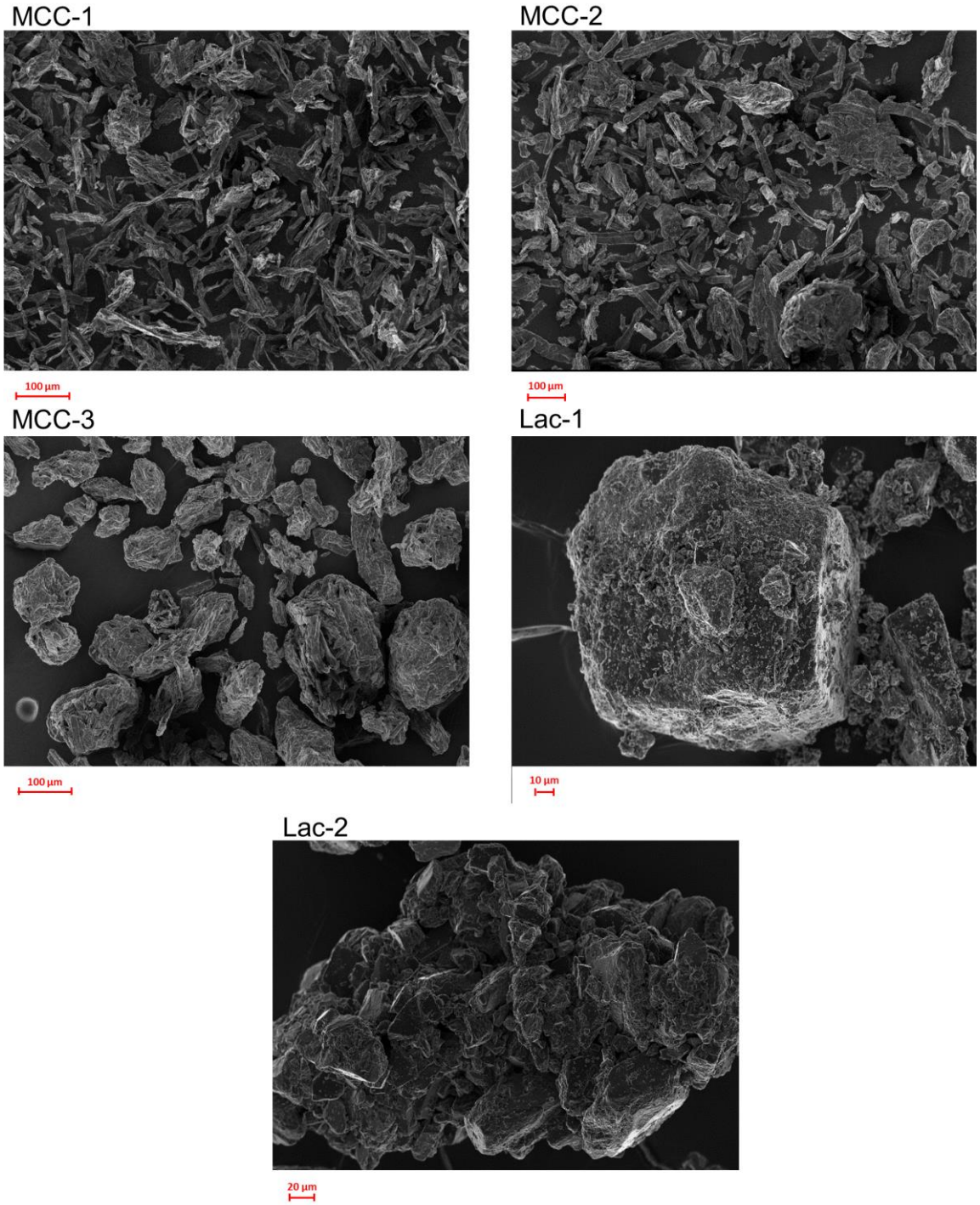


Fig. 25: SEM images of MCC-1, x = 300; MCC-2, x = 200; Lac-1, x = 1,000; Lac-2, x = 700; and MCC-3, x = 300.

3.2.2. Tablet characterization

In the present study, the recently introduced approach of externally applied lower punch vibration during the die filling process was designed and implemented for the first time on a running rotary tablet press. To determine the influence and performance of lower punch vibration on the filling process and the resulting tablet attributes, tablets were manufactured either with or without externally applied vibration but under the same conditions (Table 4, sub-chapter 2.2.2.). The obtained tablet weights and tensile strengths of the produced tablets are shown in Figs. 26 and Fig. 27. In Fig. 26, the very poor flowing Lac-1 was compared with the good flowing Lac-2, which is suitable for direct compression.

As expected, because of the good powder flow, the tablet weights and tensile strengths of the Lac-2 tablets were distinctly higher than for the Lac-1 tablets without the external application of lower punch vibration. In addition, the relative SD of the tablet weights was below 1 % for the Lac-2 tablets (Figs. 26C and D). These results are associated with the good flow properties of Lac-2 (see sub-chapter 3.2.1.). In comparison, the extremely poor flowing powder Lac-1 led to weak tablets with an inadequate tensile strength and high SDs of the tablet weights (Figs. 26A and B). By application of external lower punch vibration, generated by a piston vibrator (Fig. 26A), the tablet weights as well as the tensile strengths of Lac-1 tablets increased, while the corresponding SDs decreased. Thus, the tablet weights could be increased by over 50 mg without changing the tablet press settings. Additionally, the tensile strength reached values above 2.0 MPa by application of lower punch vibration.

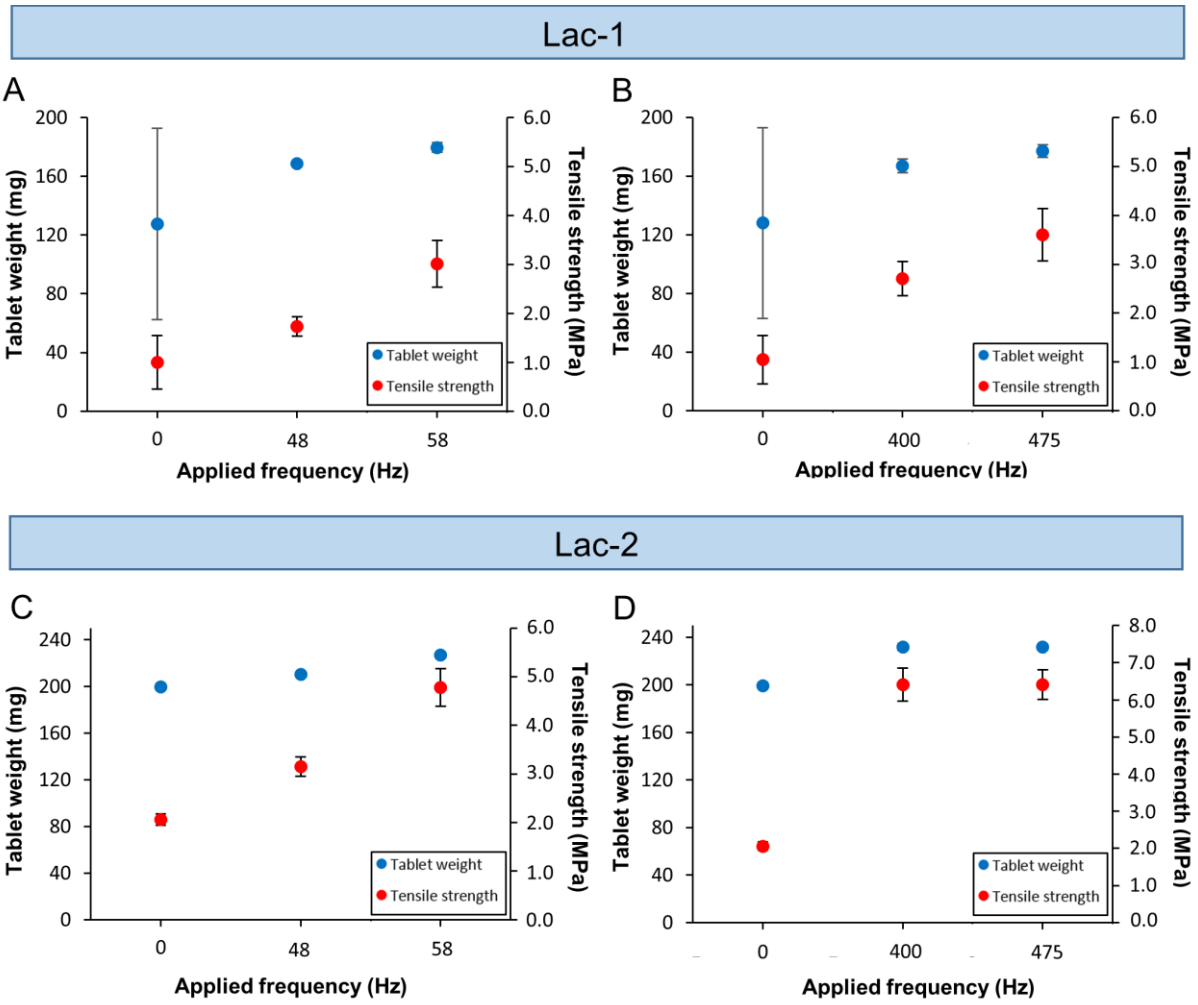


Fig. 26: Tablet weights and tensile strengths of the Lac-1 and Lac-2 tablets at the investigated frequencies and the different vibrator grades (A, C = piston vibrator; B, D = turbine vibrator) (means ± SD, n = 40).

With the turbine vibrator (Fig. 26B) the tablet weights were uniform and the resulting tensile strengths were higher compared to the values obtained with a piston vibrator (Fig. 26A). Although the Lac-2 tablets exhibited an already sufficiently high tensile strength if they were prepared without externally applied vibration, the tablet weight as well as the tensile strength of the tablets were even higher after application of lower punch vibration. Similar to Lac-1, with the turbine vibrator, the tensile strength of the Lac-2 tablets increased more distinctly if the same frequencies (400 and 475 Hz) were applied. It is noticeable that the results of the tablet weights and tensile strengths obtained at frequencies of 400 and 475 Hz (Fig. 26D) are equal. This observation

suggests that the powder bed was already completely densified at 400 Hz and a further increase in the frequency level was ineffective.

A comparable trend as with the Lac powders was observed with the investigated MCC powders (Fig. 27).

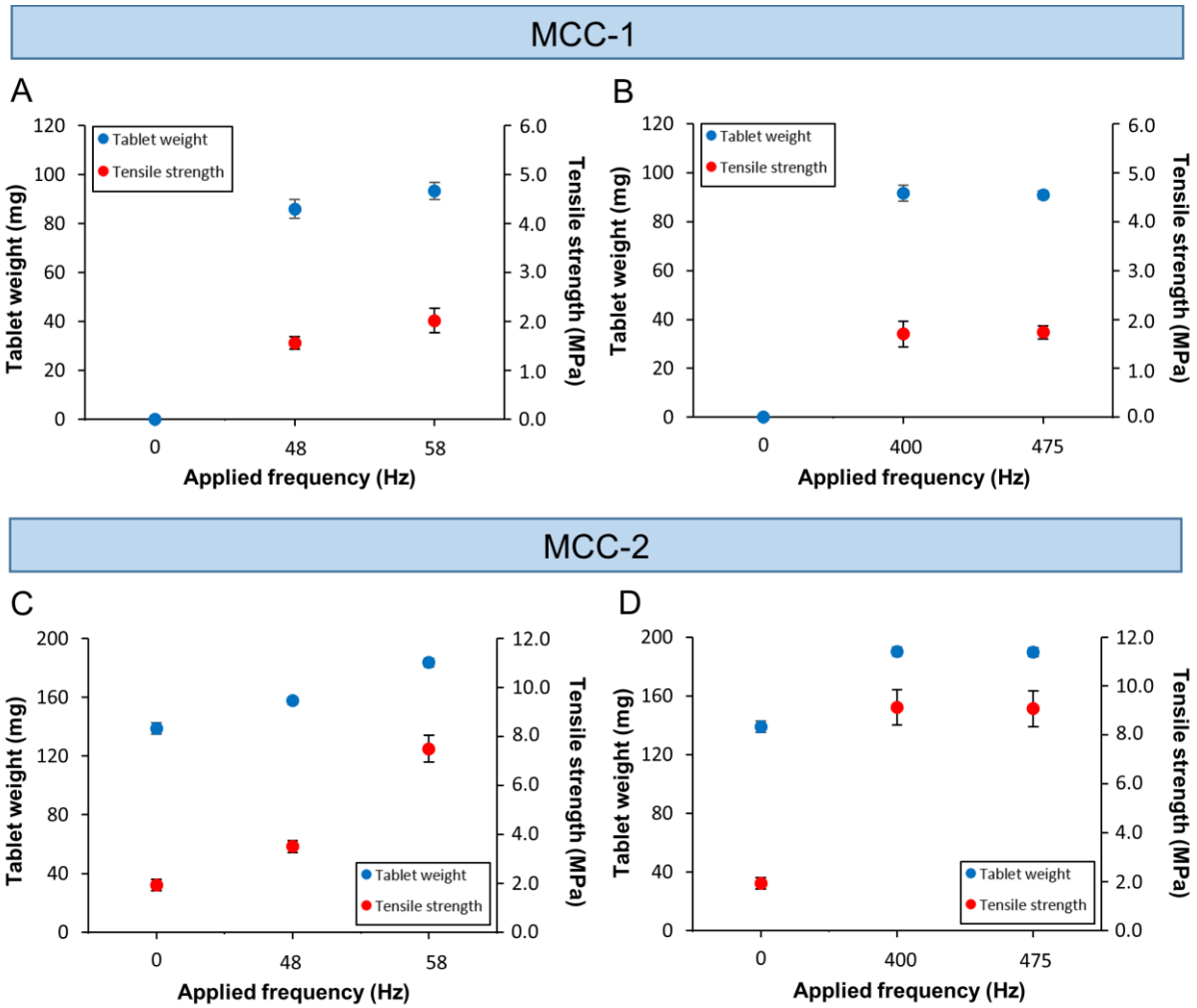


Fig. 27: Tablet weights and tensile strengths of the MCC-1 and MCC-2 tablets at the investigated frequencies and the different vibrator grades (A, C = piston vibrator; B, D = turbine vibrator) (means ± SD, n = 40).

However, without applying external lower punch vibration, it was impossible to produce tablets with MCC-1, independent of the filling depth or tablet height. The inadequate powder flow prevented a sufficient filling of the die during the filling process. Thus, no tablets could be manufactured as shown in Fig. 27A. Usually, MCC-1 is applied for dry granulation and has to be pretreated before it can be used for tableting. It may be

observed that after the application of vibration it was possible to produce tablets with sufficient quality attributes, independent of the vibrator type. Thus, it may be stated that the flow of MCC-1 into the dies was distinctly improved by the application of lower punch vibration. Although the powder exhibits a very poor powder flow, a broad particle size distribution, and a low relative density (Table 11), tablet weights with a SD below 5 % and a sufficient mechanical stability were obtained. Especially the bulk density as well as the relative density of the powder bed within the die increased resulting from a narrower particle arrangement after the applied vibration.

MCC-2 also profited from externally applied vibration (Figs. 27C and D). Similar to Lac-2, the variation in the tablet weights of both vibrator types was comparatively low and the increase of the tensile strength was more pronounced after application of the turbine vibrator. Overall, it was shown that the tablet weights as well as the tensile strengths and thus the mechanical stability of all investigated tablets increased with the application of external lower punch vibration.

To determine the extent of densification, the obtained tablets were also investigated regarding their SFs. An increase in the tablet density is associated with an increase of the SF. In Fig. 28, the obtained SF values of MCC-1, MCC-2, Lac-1, and Lac 2 depending on the applied frequencies of 48, and 58 Hz (piston vibrator, Fig. 28A), as well as of 400 and 475 Hz (turbine vibrator, Fig. 28B) are illustrated. As shown in Fig. 28A, the SF values increased with investigated powders after applied vibration. Higher SF values indicate an increase of the total volume of solid material within a tablet.

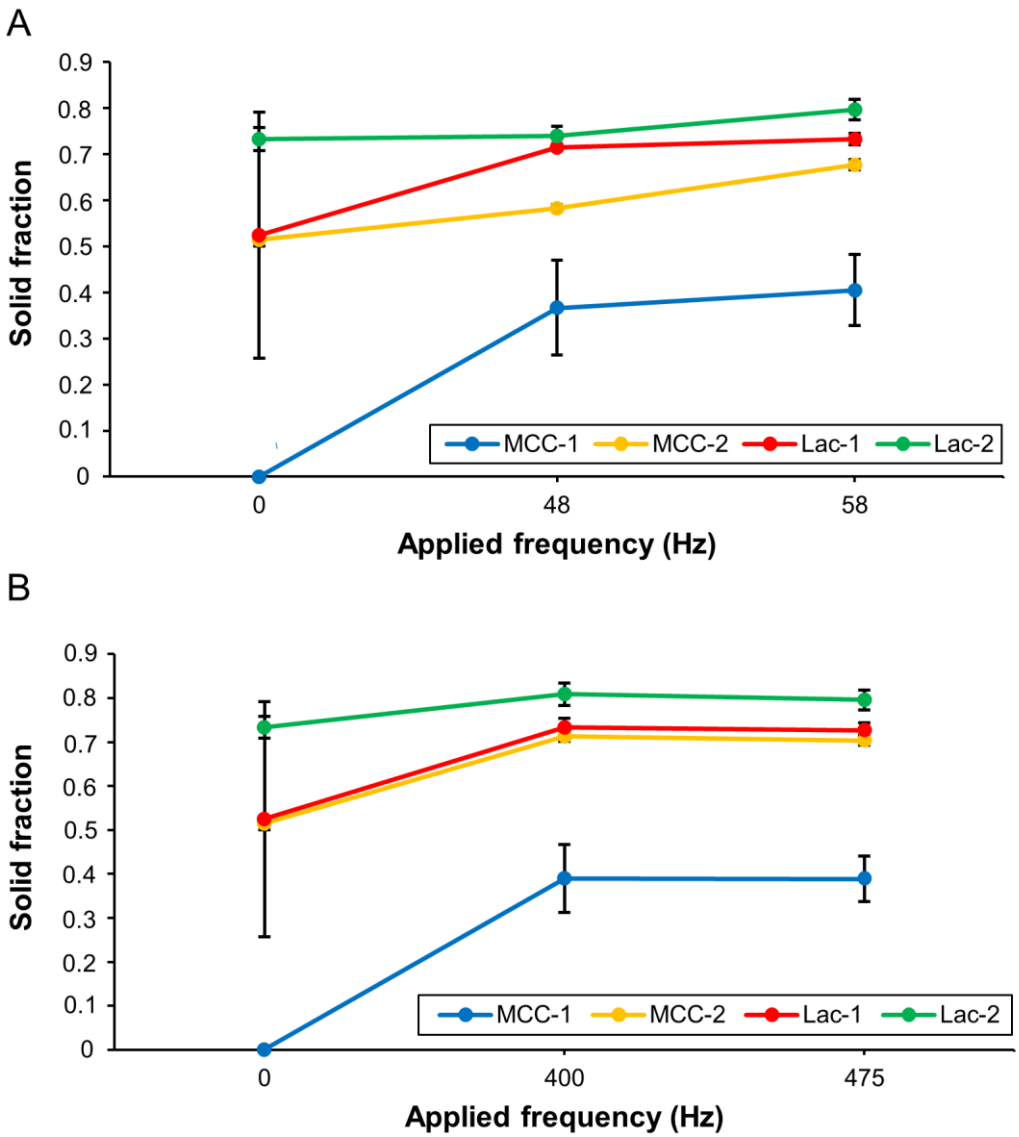


Fig. 28: Solid fractions depending on the applied frequency and the vibrator type. (A) = piston vibrator, (B) = turbine vibrator (means ± SD, n = 40).

The applied lower punch vibration led to a densification of the powder bed within the dies and consequently to a removal of entrapped air, which explains the increased SF values. Accordingly, especially powders with low bulk and low relative densities profit from the implemented vibration system. In this context, Lac-2 shows a less pronounced SF increase. Because of the high bulk density and the comparatively low relative density of Lac-2, the SF increase was less pronounced than with the other investigated powders (Figs. 28A and B).

The improvement of the mechanical stability of the tablets was confirmed by friability measurements. It was not possible to measure the friability of MCC-1 and Lac-1 after conventional tableting, because the tablets broke during the friability test. In contrast, friability values lower than 0.5 % were reached after applying external lower punch vibration. Furthermore, for the “directly compressible” powders MCC-2 and Lac-2, a decrease of the friability values of about 50 % after lower punch vibration was measured. This observation confirmed the results of the increased mechanical stability of the tablets after lower punch vibration (Figs. 26 and 27).

Thus, it was possible to manufacture tablets with a sufficient mechanical stability from powder blends, which are actually unsuitable for direct compression. Furthermore, it was shown that the high frequent turbine-generated vibration was advantageous in comparison to the low frequent piston-generated vibration.

3.2.3. Segregation analysis

The occurrence of segregation after application of external lower punch vibration was investigated by two different analyzing techniques. Most of the commonly used quantitative analyzing techniques such as UV-Vis or HPLC are time-consuming and do not allow a spatial resolution. Therefore, an image analyzing technique to analyze the occurrence of segregation within a tablet was introduced in this work. The aim was to develop a system with the ability to analyze defined parts within a tablet. It is known that segregation within a powder bed generally occurs vertically [210]. Therefore, the tablets were prepared as illustrated in Fig. 14. The tablets were broken along the snap tab and the tablet halves were horizontally cut to determine the occurrence of segregation at the top and bottom part of the tablets. For simplicity, a mixture of two directly compressible MCC grades (MCC-2 and MCC-3) was used. MCC-2 differs from MCC-3 in terms of particle size, particle shape, and flow characteristics (see Table 11 and Fig. 25). Resulting from the differences in the densities and the particle morphology between MCC-2 and MCC-3 the potential risk of segregation was given. As described in sub-chapter 2.2.5. “Segregation analysis” and as displayed in Fig. 14, the prepared tablet parts were analyzed by UV-Vis and ImageJ. The differences between both analyzing techniques are mainly the application options and the effort of the sample pretreatment. Especially for the determination of the occurrence of segregation in different parts of the tablet, the application of thresholding (ImageJ) might be an innovative technique. In comparison to conventional UV-Vis measurements, thresholding is able to determine the amount of both MCC grades in all segments of the recorded tablet profile. For this purpose, it is only necessary to take an image of the tablet profile after breaking the tablet into two parts. In contrast to the UV-Vis measurements, a further separation of the tablet into smaller parts to determine

the amount of the MCC grades at the top or bottom part of the tablet is not necessary. Despite these advantages of thresholding as an image analyzing technique, it has to be noted that the applicability of this technique is limited to differently colored powders in the investigated formulations. Depending on the used coloring substance as well as on the powder formulation, the coloring process might even lead to changes in the physical powder properties.

In contrast to the image analyzing technique, UV-Vis measurements only allow the determination of the total content of a colored MCC grade in one prepared segment of the tablet without an accurate localization of the occurred segregation. Furthermore, the tablet breaking for UV-Vis analysis in more than two tablet parts (under consideration of the horizontal separation) is inaccurate and because of the deformation behavior of the tablet (especially brittle fracture) often unfeasible. Consequently, UV-Vis analysis as well as further wet chemical analyzing techniques such as HPLC etc. are inappropriate for a precise determination of the segregation process within a tablet.

Therefore, it was necessary to examine the accuracy of this novel technique. Therefore, the content of spray-colored MCC in the tablets, composed of blend 1 was determined by ImageJ and directly compared to the UV-Vis results. The results of both analyzing techniques are displayed in Fig. 29.

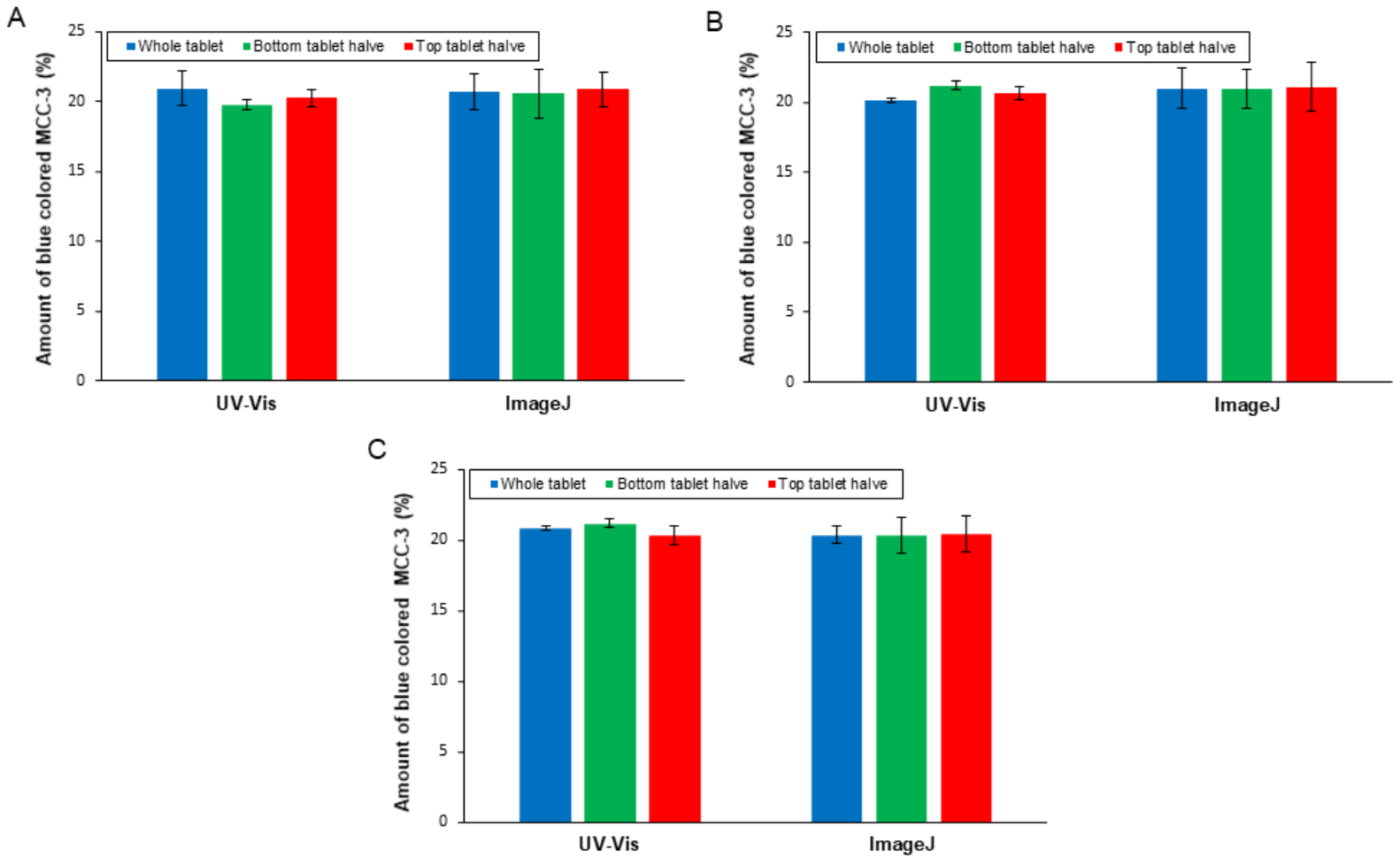


Fig. 29: Comparison of the two analyzing techniques, UV-Vis and ImageJ, with regard to the occurrences of segregation within tablets containing 80 % MCC-2 and 20 % blue colored MCC-3. Tablets were manufactured conventionally (A = 0 Hz) as well as by application of external lower punch vibration (B = 400 Hz, C = 475 Hz) (means ± SD, n = 20).

With respect to the accuracy of the image analyzing thresholding technique, it was shown that ImageJ was able to calculate similar data of “blue” MCC-3 as obtained by UV-Vis measurements. The SD of the respective data amounted to less than 2 %. Thus, it was demonstrated that the measurement accuracy of ImageJ is sufficient for the determination of the segregation within a tablet. It has to be noted that the SD of the thresholding values was slightly increased in comparison to the UV-Vis data. However, the performed two-factor ANOVA showed that the data points of both investigated analyzing techniques were not significantly different.

In addition to this “feasibility study”, one further purpose of this work was to examine the influence of externally applied lower punch vibration on the segregation within the manufactured tablets. Therefore, the tablets manufactured by the application of lower punch vibration at 400 and 475 Hz (turbine vibrator) were investigated with regard to the occurrence of segregation. It could be shown in Figs. 29B and C that independent of the applied vibration no significant segregation occurred at the top or bottom part of the tablet. Especially in comparison to the results in Fig. 29A, where no vibration was applied, no marked differences in the determined data of colored MCC-3 were detectable. As vibration was applied only for 0.432 ms to the lower punch at an adjusted die disk speed of 15 rpm, the available time for the segregation process was very short. Thus, during production conditions, the occurrence of segregation appears to be unlikely.

Thresholding was also used to determine the occurrence of segregation within manufactured tablets of blend 2 (MCC ratio: 50 % “blue” to 50 % “white”). It is shown in Fig. 30 that segregation occurred more distinctly within the tablets of blend 2 than within the tablets of blend 1.

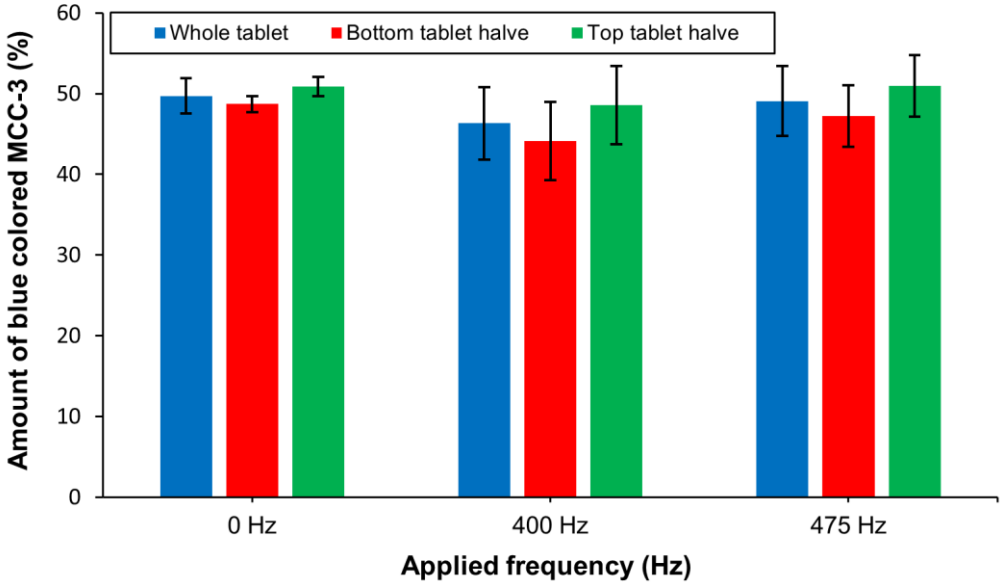


Fig. 30: Comparison of the two tablet manufacturing techniques (with and without vibration) regarding the occurrences of segregation within tablets containing 50 % MCC-2 and 50 % blue colored MCC-3. The tablets were manufactured conventionally (0 Hz) as well as by application of external lower punch vibration (400 and 500 Hz) and analyzed by ImageJ (means ± SD, n = 20).

The reason might be the higher amount of spray-colored MCC-3 (50 %) in blend 2 than in blend 1. The results of the single-factor ANOVA showed that the data points of tablets manufactured with lower punch vibration were not significantly different from the respective tablets manufactured without vibration. Furthermore, it is observed in Fig. 30 that the amount of the “larger” spray-colored MCC-3 particles was increased in the top parts of the tablet. This observation goes along with the assumption by C.F. Harwood [210] that segregation often proceeds vertically, whereby the larger particles migrate to the top. However, it was shown that studies in the field of segregation after tablet manufacturing are helpful and important for the understanding and application of externally applied lower punch vibration. Further studies have to be carried out to examine the influence of lower punch vibration prior to the compression step by different die disk speeds and/or powder blends.

3.2.4. Conclusion

For the first time, a pneumatic lower punch vibration system was directly implemented on a running rotary tablet press. It was shown that this externally applied vibration system was able to improve the filling process of the dies significantly. Hence, it was possible to compact powder blends, which are actually unsuitable for direct compression. Furthermore, as a consequence of an improved die filling, the mechanical stability of the investigated tablets increased distinctly, reflected by the SFs and measured tensile strengths. Moreover, in the present study it was shown that the higher vibration frequencies generated by a turbine vibrator lead to advantages in terms of tablet manufacturing in comparison to a piston vibrator system with lower frequencies.

To investigate possible segregation within a powder bed during the application of lower punch vibration, a novel image analyzing technique to determine the distribution of spray-colored ingredients within a tablet was introduced. In comparison to the commonly used wet analyzing techniques, the experimental effort could be distinctly reduced with this novel image analyzing technique. Certain segregation is often observed during conventional tableting. In this context, the results showed that segregation under the application of lower punch vibration occurred only marginally because of the short vibration times. The extent of segregation also depends on the manufacturing conditions (e.g. the filling unit and the die disk speed) and the composition of the tablet formulation.

3.3. Influence of lower punch vibration on the capping and/or lamination tendency of tablets manufactured from different powders

3.3.1. Powder characterization

In the present study, MCC and APAP were selected as model substances to investigate the influence of externally applied lower punch vibration on the capping or lamination tendency of tablets. As mentioned in the introduction, the reasons for capping and lamination are complex and are often caused by interactions between several phenomena (e.g. die wall friction, entrapped air, and elastic recovery). In the present work, the experimental settings were selected with the focus on capping or lamination caused by entrapped air. Therefore, the turret speed was varied to alter the available time for powder bed deaeration within the die. The higher the applied turret speed, the lower the available deaeration time for the powder bed within the die and thus, the higher the volume of entrapped air. Besides the shortened deaeration time, a high turret speed often leads to a declined and inhomogeneous die filling which also influences the resulting powder bed packing and thus, the volume of entrapped air within the dies. Previous studies revealed that especially MCC shows lamination caused by entrapped air. This can be related to its low bulk density and poor powder flow, both leading to an inhomogeneous powder bed within the die and thus an increased volume of entrapped air within the powder bed after the die filling step [239]. Therefore, a detailed powder characterization was conducted to relate different physical properties with the occurrence of capping or lamination.

Different grades of MCC (MCC-2, MCC-3, MCC-4, and MCC-5), which differ in the particle morphology, the particle size distribution, and the powder flow, were chosen to evaluate and analyze the influence of these physical powder properties with regard to the resulting lamination tendency. As shown in Fig. 31, the particle shape of all MCC

grades varied, whereby MCC-2 showed the narrowest minor axis and the most needle formed particles in comparison to MCC-3, MCC-4, and MCC-5.

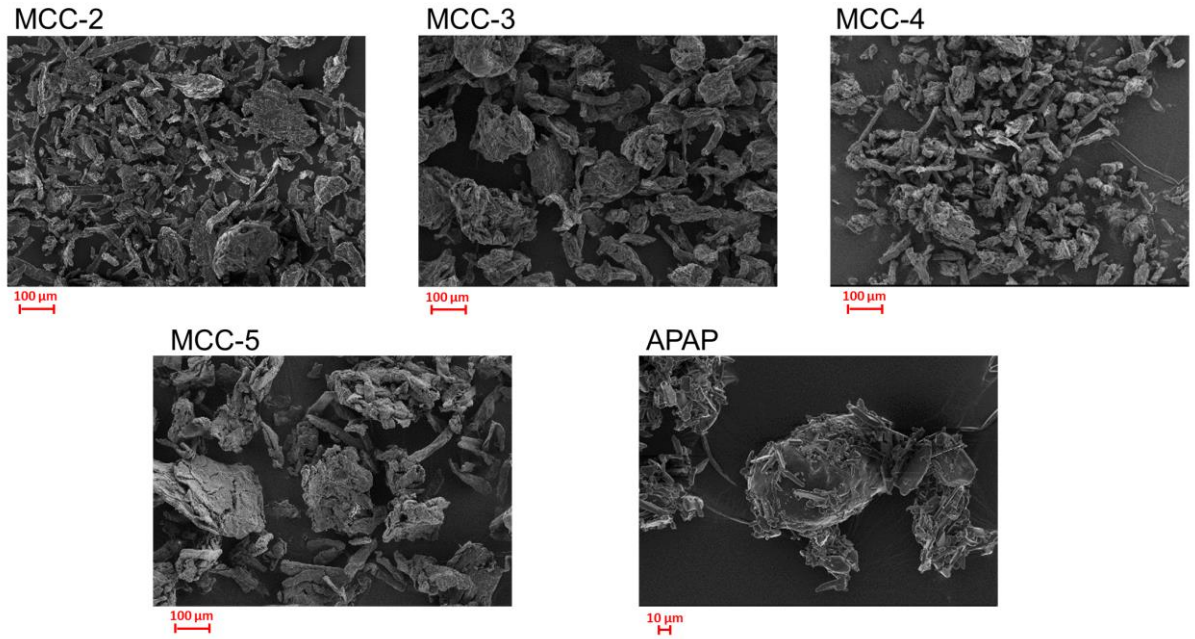


Fig. 31: SEM images of the MCC grades at a magnification of 250, and of APAP at a magnification of 900.

The particles of MCC-3 and MCC-4 were less needle-shaped and showed a more spherical particle shape. In contrast to the MCC grades MCC-2 – MCC-4, MCC-5 showed non-uniform particle shapes and sizes. This observation was confirmed by the measured particle size distribution of MCC-5, illustrated in Fig. 32. MCC-5 showed, in comparison to the other MCC grades, the broadest particle size distribution, whereas MCC-4 revealed the narrowest distribution. Furthermore, MCC-4 exhibited the smallest particles with a d_{50}-value of 58.44 µm and MCC-3 the largest particles with a d_{50}-value of 213.78 µm. Both, the particle morphology and the particle size distribution significantly influence the powder flow of the investigated powder blends and thus the filling of the die.

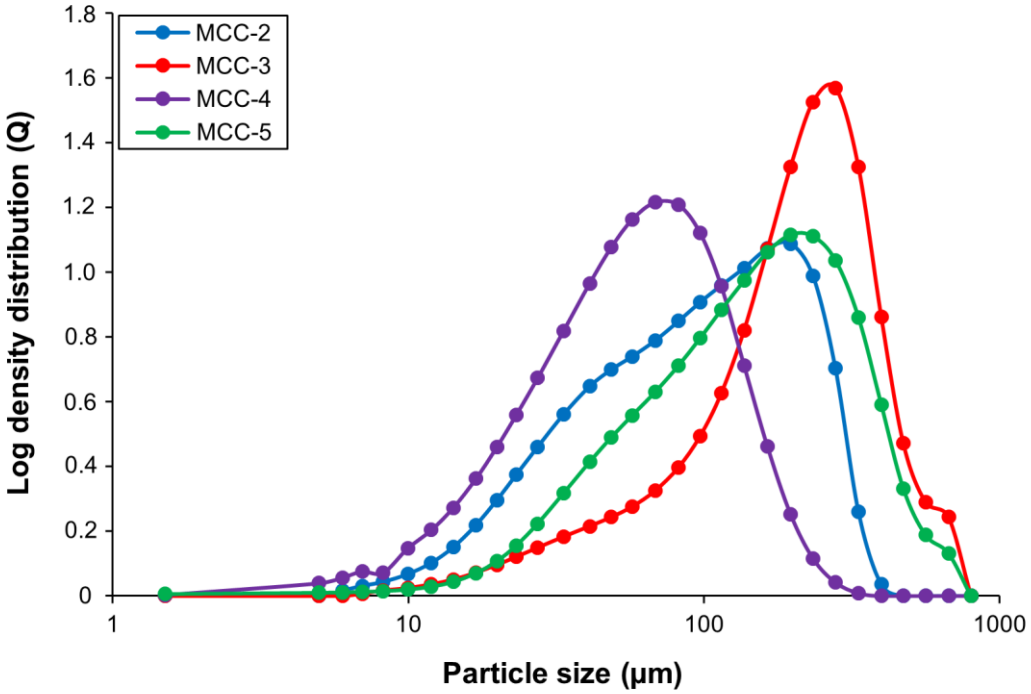


Fig. 32: Mean particle size distributions of MCC-2, MCC-3, MCC-4, and MCC-5 (n = 3).

To characterize the flow properties of the investigated powders, the HRs and CIs are presented in Table 12, and the measured ff_c values are illustrated in Fig. 33.

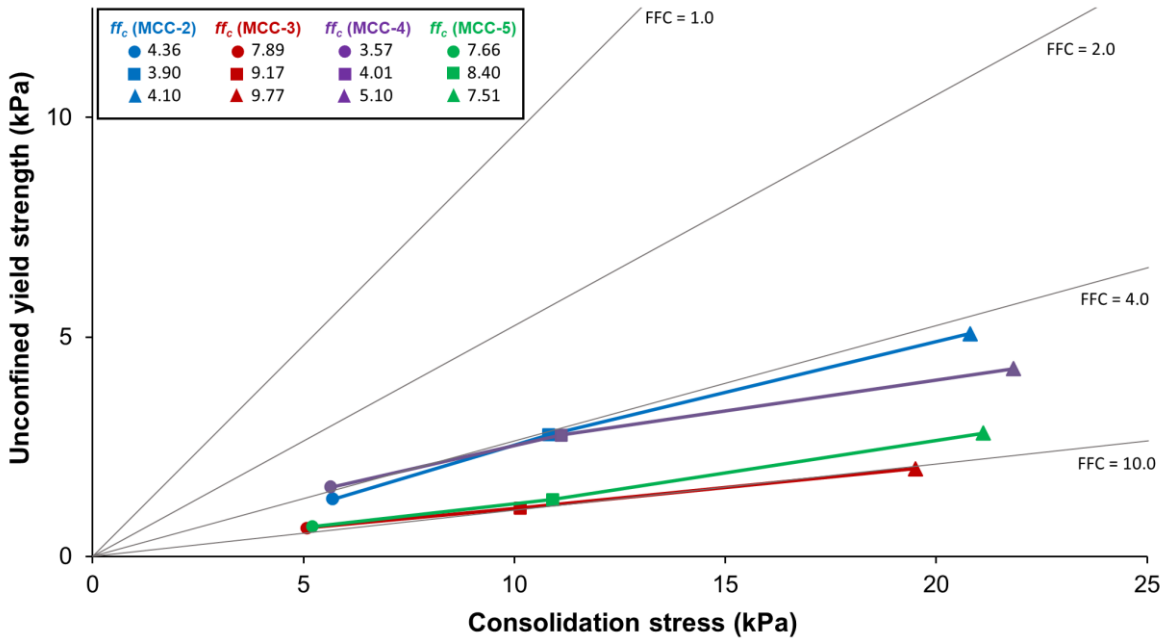


Fig. 33: Powder flow function plots and corresponding ff_c values of the investigated powders.

MCC-4 showed a fair powder flow and the measured ff_c values (Fig. 33) indicated a cohesive to “easy-flow” behavior. In contrast, MCC-2 and MCC-3 showed a passable powder flow according to the HRs and CIs. In addition, the ff_c values of MCC-2 and MCC-3 (Fig. 33) confirmed an “easy-flow” behavior. In comparison, the resulting powder flow characteristics of MCC-5 were different (Table 12). The respective HRs, and the CIs (Table 12) revealed a “poor powder” flow, whereby the ff_c values (Fig. 33) indicated an “free powder flow”. This observation may be attributed to the broad particle sizes distribution, high particle size span, and the non-uniform particle morphology.

Table 12: Physical properties of the investigated powders (means ± SD, n = 3-10).

Physical properties	**MCC-2**	**MCC-3**	**MCC-4**	**MCC-5**
Particle size d_{50} (µm)	98.23 ± 0.08	213.78 ± 4.88	58.44 ± 0.08	150.51 ± 2.19
Particle size span	2.206 ± 0.005	1.748 ± 0.063	2.011 ± 0.003	2.173 ± 0.004
Bulk density (g/cm^3)	0.33 ± 0.01	0.35 ± 0.01	0.47 ± 0.01	0.44 ± 0.01
True density (g/cm^3)	1.592 ± 0.003	1.558 ± 0.002	1.613 ± 0.003	1.600 ± 0.006
Hausner ratio	1.33 ± 0.01	1.30 ± 0.03	1.23 ± 0.01	1.35 ± 0.02
Carr index (%)	25.00 ± 0.12	23.16 ± 0.23	18.70 ± 0.77	25.93 ± 0.31
Specific surface area (m^2/g)	7.704 ± 0.023	3.607 ± 0.078	7.651 ± 0.052	5.055 ± 0.029

Besides the powder flow, the resulting density of the powder bed within the die is crucial with regards to the occurrences of capping or lamination as well as for the

resulting mechanical stability of the tablet. The bulk density appears to be best suited for estimation of the density of the powder bed within the die prior to the compaction step. However, depending on the filling system and the process conditions, the density of the powder bed within the die is often slightly higher than the bulk density [121]. In this context, MCC-2 revealed the lowest bulk density and MCC-4 the highest (Table 12). Moreover, the porosity of a powder, described as the ratio between the bulk and the true density, is an important factor for the determination of the volume of entrapped air within the powder bed. A high bulk density corresponds to a reduced volume of entrapped air within the powder bed, meaning that a powder with a bulk density corresponding to its true density exhibits no entrapped air. It was observed that MCC-2 revealed the lowest bulk density followed by MCC-3, MCC-5, and MCC-4. According to the calculated bulk density values (Table 12), MCC-2 possibly shows the highest volume of entrapped air and thus an increased capping or lamination tendency. Another important powder attribute, which particularly affects the powder flow into the die and the resulting mechanical stability of the tablet is the specific surface area. A high specific surface area influences the powder flow and thus the die filling by several factors: electrostatic charge [258], cohesiveness, and frictional force [259]. As shown in Table 12, MCC-1 and MCC-3 revealed the highest specific surface areas in comparison to MCC-3 and MCC-5. Usually, the specific surface area depends on the particle size and the pore volume of the powder particles. MCC-3 exhibited the largest particles (d_{50} = 213.78) and thus the specific surface area was comparatively low. It has to be noted that MCC-2 revealed a similar specific surface area as MCC-4.

3.3.2. Tablet characterization

To investigate the effect of the implemented lower punch vibration equipment with regard to the occurrences of capping or lamination during tableting, tablets were manufactured either with or without externally applied lower punch vibration. The tableting runs were performed at different turret speeds to vary the time for particle packing and rearrangement and thus to influence the volume of entrapped air within the powder bed. Usually, the higher the applied turret speed, the lower the time for air removal from the powder bed within the die.

The tablets manufactured from the MCC-2, MCC-3, and MCC-5 powder blends showed lamination, which was confirmed by the occurrence of typical horizontal “cracks” along the tablets. In Fig. 34A and B these observed “cracks” on the compact surfaces are exemplarily displayed for the MCC tablets. Also, an example for capping is given in Fig. 34C

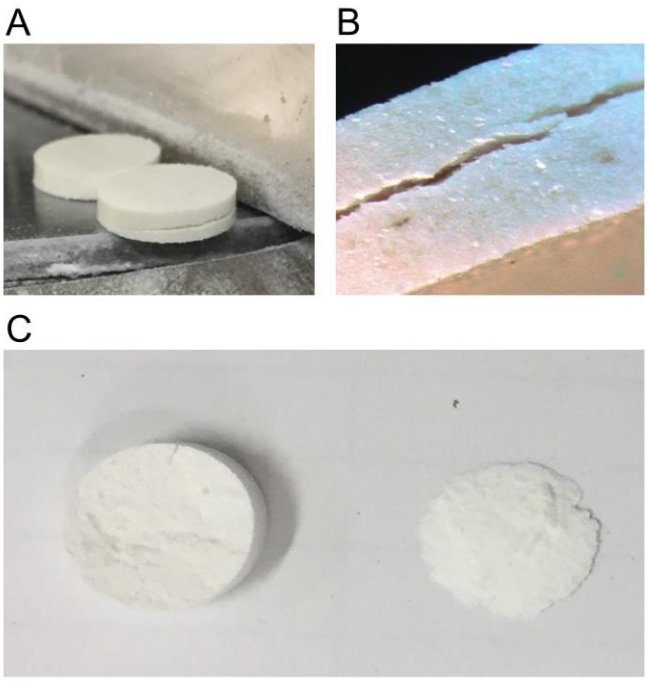


Fig. 34: Images of tablet failures: lamination (A and B), capping (C).

For tablets manufactured without vibration, the lamination index increased distinctly by increasing the turret speed (Fig. 35). At the highest turret speed (102 rpm), where the time for the removal of entrapped air is comparatively low, the lamination indices were partially maximal (MCC-2 and MCC-5), which means that every single tablet showed lamination directly after the ejection step (Fig. 35).

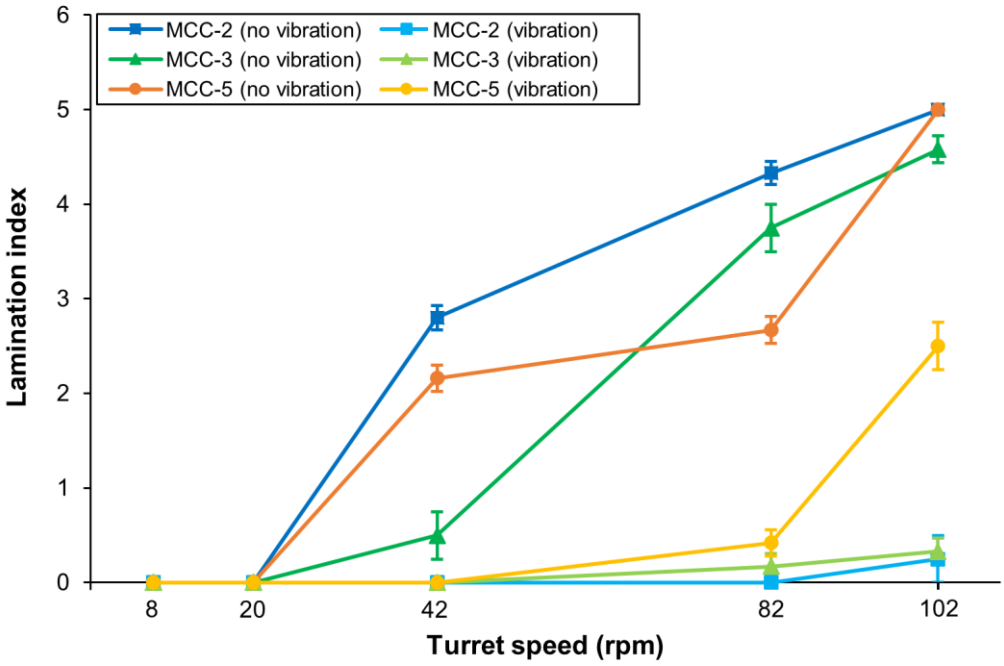


Fig. 35: Lamination indices of the investigated MCC tablets depending on the applied turret speed and the externally applied lower punch vibration (means ± SD, n = 3).

Furthermore, tablets manufactured from MCC-2 and MCC-5 (Fig. 35) showed a distinct increase of the lamination tendency at slow turret speeds between 20 and 42 rpm. In comparison, MCC-3 showed a slight steep in the lamination tendency between 20 and 42 rpm but a strong steep of the lamination tendency between 42 and 82 rpm. With applied lower punch vibration, the lamination tendency at all investigated turret speeds decreased significantly. Hence, it was possible to decrease the lamination tendency completely at lower turret speeds (until 42 rpm). Also, at higher turret speeds (> 42 rpm), lower punch vibration was able to decrease the lamination of MCC-2 and MCC-

3 significantly (below 0.5). These tablets showed only lamination during the hardness testing. The reason therefore may be the densification and new particle arrangement of the powder bed as result of the lower punch vibration prior to the compression steps. This densification of the powder bed leads to the removal of entrapped air from the powder beds within the die. Furthermore, the mechanical stability of the tablets is directly influenced. The narrower particle arrangement of the powder bed within the die leads to a higher bulk density, and thus increased the amount of potential contact areas between the powder particles.

In this context, the resulting tensile strengths of the tableted MCC powder blends (with and without lower punch vibration) are displayed in Fig. 36. The tensile strengths of all investigated powders decreased with increasing the turret speed. This observation was attributed to the previously mentioned insufficient filling step of the die and the limited removal of entrapped air. The decrease of the curve profiles in Fig. 36A is similar to the increase of the curve profiles displayed in Fig. 35. It is obvious that the tensile strength is related to the resulting capping or lamination tendency. As shown in Fig. 36A, MCC-2 and MCC-5 also showed a distinct decrease in the tensile strength within the turret speed range of 20 and 40 rpm, whereby MCC-3 revealed a distinct decrease at turret speeds above 42 rpm. At turret speeds above 82 rpm the tensile strengths obtained with MCC-2, MCC-3, and MCC-5 were below 1 MPa. Such low tablet tensile strengths are probably unsuitable for further processing steps (e.g. coating).

In comparison to the above-mentioned MCC tablets (MCC-2, MCC-3, and MCC-5), MCC-4 tablets did not show lamination independent of the applied turret speed. This observation may be explained by the physical powder properties of MCC-4 (see sub-chapter 3.3.1.).

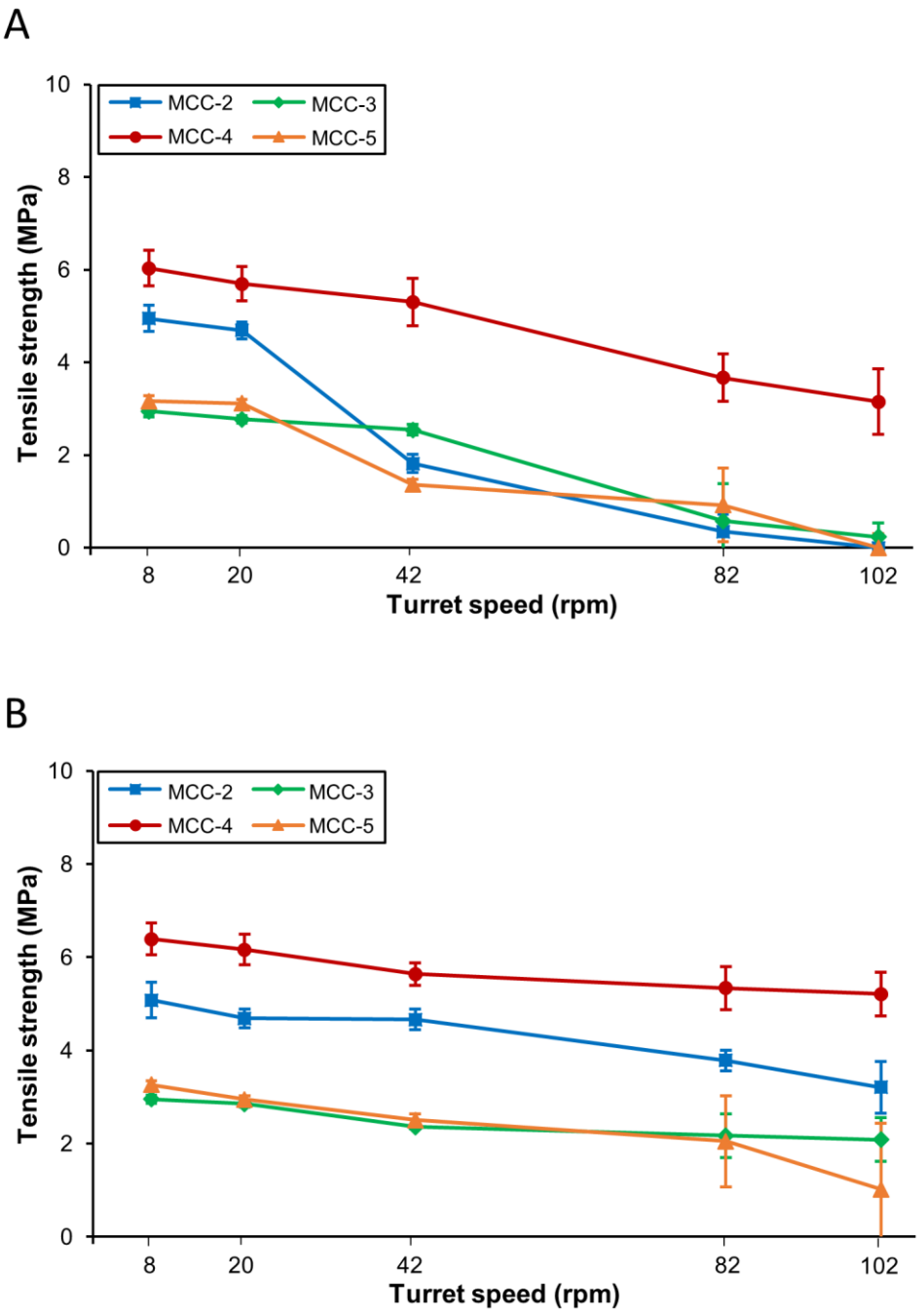


Fig. 36: Tensile strengths of the investigated MCC tablets depending on the applied turret speed. (A) without lower punch vibration, (B) with lower punch vibration (means ± SD, n = 20).

Despite its small particle size, MCC-4 showed the best powder flow and the highest bulk density in comparison to the other examined MCC grades. Thus, MCC-4 showed a more homogeneous die filling. Moreover, the high specific surface area of MCC-4 (7.651 m^2/g) influences the mechanical stability of the tablets because of the larger

contact areas (increased number of potential binding points). This observation was confirmed by the resulting tensile strengths of the MCC-4 tablets shown in Fig. 36A. Although all MCC powder blends were tableted under the same conditions (filling depth, and band height), MCC-4 showed by far the highest tensile strengths at the applied turret speeds. Moreover, a lower specific coverage of the surfaces with MgSt might be responsible for the performance of MCC-4.

In Fig. 36B, the tensile strengths of tablets manufactured with lower punch vibration are shown. In comparison to Fig. 36A, the decrease of the values is less pronounced with all investigated powder blends. Only MCC-5 showed a distinct decrease in the tensile strength between the turret speeds of 82 and 102 rpm. This observation probably results from its non-uniform particle shape (Fig. 31), and the associated poor powder flow of MCC-5. Surprisingly, MCC-5 showed a higher bulk density in comparison to MCC-2 and MCC-3, which usually indicates a lower volume of entrapped air within the powder bed. Thus, it was expected that MCC-5 leads to tablets with a higher tensile strength and a low lamination index. However, it has to be mentioned that the bulk density only serves as a surrogate parameter and does not represent the true state of the powder bed after the filling process within the die.

In general, the decrease of the tensile strength shown in Fig. 36 corresponds to the results displayed in Fig. 35, where the lamination indices are also significantly decreased by the application of lower punch vibration. Both, the results shown in Figs. 35 and 36 showed that lower punch vibration is able to improve the mechanical stability of the MCC tablets and to decrease their lamination index. These observations are mainly attributed to the more continuous and homogenous filling of the die caused by lower punch vibration during the die filling step, which leads to a deaeration and better filling of the die even at high turret speeds. The improved filling of the dies can also be confirmed by the resulting compaction forces (Table 5 and 6, sub-chapter 2.2.2.), as

the compaction forces of the manufactured tablets with lower punch vibration decreases more slowly than of the tablets manufactured without vibration.

Besides the investigated MCC formulations, two further powder blends containing MCC-4 and APAP (10 % and 20 %, respectively) were used to investigate if lower punch vibration also leads to a decrease of the capping or lamination tendency of tablets showing an elastic deformation behavior (APAP). In comparison to MCC, APAP tablets tend to cap rather than to laminate, which goes along with a radial separation of the top or bottom part of the tablet (Fig. 34C). Similar to the results of the MCC tablets, the capping indices of the APAP tablets increased at higher turret speeds (Fig. 37).

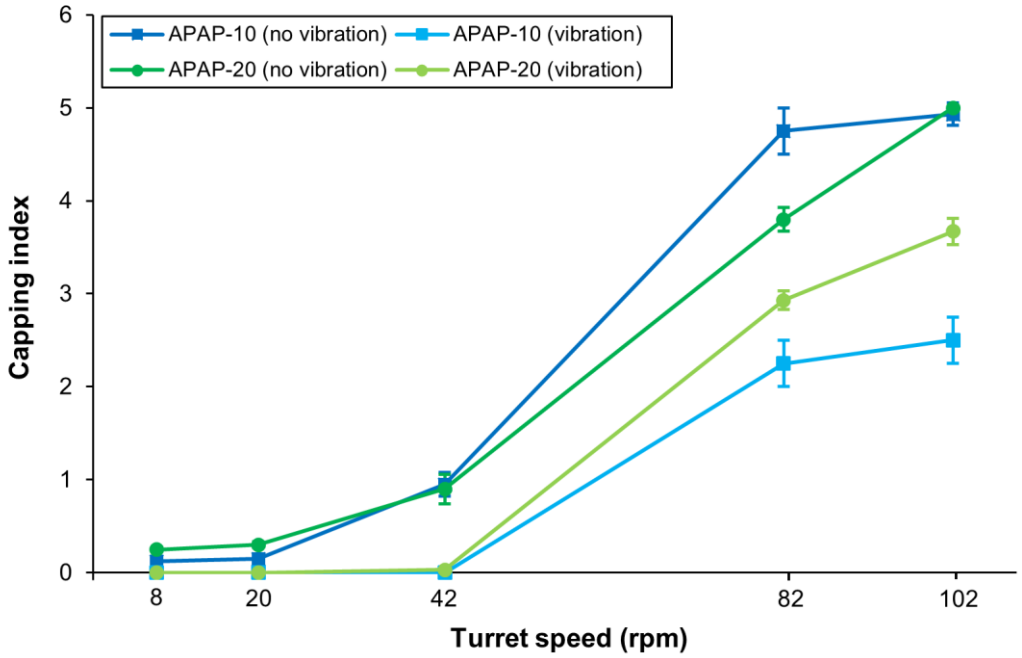


Fig. 37: Capping indices of the investigated APAP tablets depending on the applied turret speed and the externally applied lower punch vibration (means ± SD, n = 3).

Interestingly, only capping and no lamination occurred with the APAP tablets, although plain MCC-5 tablets just showed lamination. The APAP tablets showed a steep increase of the capping index (Fig. 37) starting at a turret speed of 42 rpm. In this

context, it has to be mentioned that even at the lowest turret speed (8 rpm) capping was observed only with APAP tablets manufactured without vibration. The respective capping index depended on the amount of APAP in the tablet formulation. Surprisingly, without vibration, the APAP-10 tablet formulation showed a steeper increase of the capping index in comparison to the APAP-20 formulation between the turret speeds of 42 and 82 rpm.

With lower punch vibration the capping index increased in a similar manner but to lower extent. Thus, the number of capped APAP-10 tablets manufactured at a turret speed of 102 rpm was decreased by 50 %, whereas the capping index of APAP-20 tablets was decreased by 25 % (Fig 37). This observation may be attributed to the more pronounced elastic recovery of the investigated APAP-20 formulation. In contrast, with lower punch vibration no capping was observed below turret speeds of 42 rpm. The obtained tensile strengths of the APAP tablets are presented in Fig. 38.

In principal, the data confirms the tendencies observed with the capping indices. Between turret speeds of 8 and 42 rpm the measured tensile strengths of the tablets manufactured with and without differ only marginally. Above 42 rpm the tablets manufactured without vibration showed a steep decrease of the measured tensile strength, whereby the tensile strength of the tablets manufactured with lower punch vibration showed only a slight decrease.

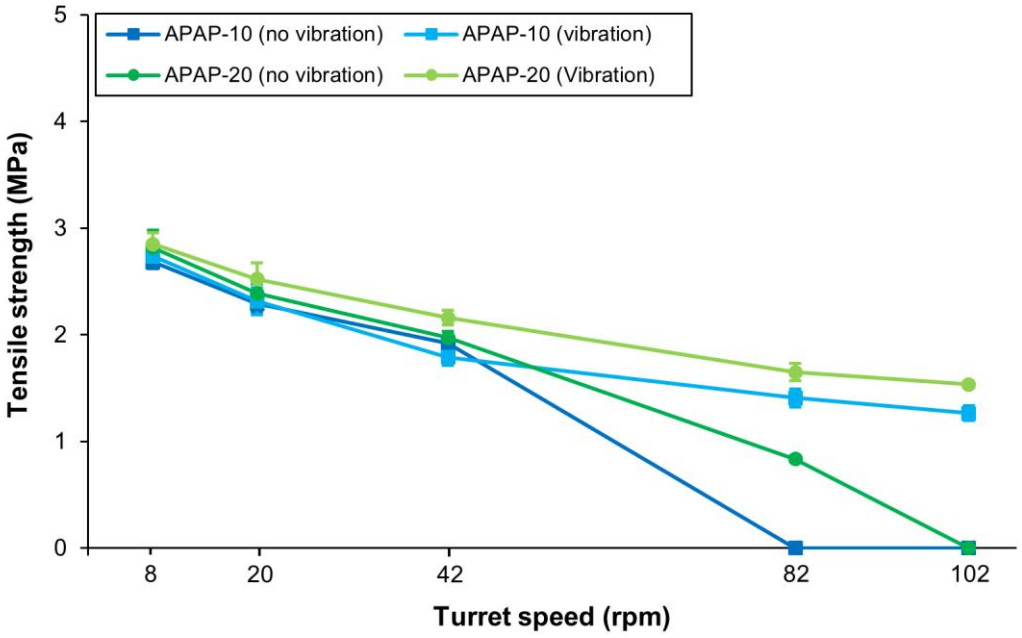


Fig. 38: Tensile strengths of the investigated APAP tablets depending on the applied turret speed and the externally applied lower punch vibration (means ± SD, n = 20).

Altogether, the results of the MCC based tablets (Figs. 35 and 36), as well as those of the tablets containing APAP (Figs. 37 and 38), showed that the application of lower punch vibration was able to decrease the tendency of capping and lamination and to improve the mechanical stability of the tablets manufactured from the investigated powder blends. It was shown that the extent of the reduction of capping or lamination depended on the powder blend composition, the physical powder properties as well as on the manufacturing conditions (turret speed).

3.3.4. Conclusion

The present work showed that the occurrences of capping and lamination depend on the powder blend composition and on several physical powder properties such as the particle morphology or the powder flow, as well as on the selected production conditions (turret speed). The results demonstrated that a non-uniform particle shape, in combination with a broad particle size distribution and a poor powder flow increased the capping or lamination tendency caused by entrapped air. Furthermore, the capping or lamination tendency of the investigated tablets also increased at high turret speeds. Thus, it was impossible to manufacture tablets with a sufficient mechanical stability at turret speeds of up to 102 rpm. By application of externally applied lower punch vibration prior to the pre- and main compression step, the occurrences of capping or lamination were significantly decreased. Hence, it was possible to completely eliminate the capping tendency of the APAP tablets up to a turret speed of 42 rpm as well as the lamination tendency of two MCC blends (MCC-2 and MCC-3), even partially at high turret speeds. In this context, the application of lower punch vibration is mainly applicable to powder blends which show capping or lamination caused by entrapped air. Moreover, it was possible to increase the tensile strength of the tablets manufactured with lower punch vibration in comparison to the tablets manufactured without vibration. Thus, the application of lower punch vibration is a promising approach to reduce the occurrences of capping and lamination during and after tablet manufacturing, and to improve the resulting mechanical stability of the tablets. Nevertheless, there is still a need for further studies dealing with the developed lower punch vibration system. For example, the process conditions such as the used filling system, the punch shape, and the number of punches should be varied to generate a better understanding of the performance of the lower punch vibration system.

3.4. Investigation of the tableting behavior of different powders under application of vibration to the lower punches of a rotary tablet press.

3.4.1. Powder characterization

Previous studies of this thesis showed that the performance of lower punch vibration depends on the physical properties of the investigated powder blends. In this context, the particle morphology, the powder flow, the bulk density, and the specific surface area were shown to have a distinct influence. For interpretation of the tableting results, the data of the powder characterization is shown in Table 13.

Table 13: Physical properties of the investigated powders (means ± SD, n = 3).

Powder	Hausner ratio	Flow rate (s/100 g)	Bulk density (g/cm^3)	Particle size span	Specific surface area (m^2/g)
MCC-2	1.33 ± 0.01	24.56 ± 5.62	0.33 ± 0.01	2.206 ± 0.005	7.704 ± 0.023
MCC-3	1.30 ± 0.03	9.42 ± 0.12	0.35 ± 0.01	1.748 ± 0.063	3.607 ± 0.078
MCC-4	1.23 ± 0.01	n.d	0.44 ± 0.01	2.011 ± 0.003	7.651 ± 0.052
Ref. A	1.14 ± 0.02	9.30 ± 0.23	0.52 ± 0.02	1.778 ± 0.037	n.d
Ref. B	1.13 ± 0.01	8.06 ± 0.19	0.57 ± 0.01	1.493 ± 0.013	n.d
Ref. C	1.11 ± 0.02	7.12 ± 0.18	0.59 ± 0.01	1.563 ± 0.029	n.d

According to the data in Table 13, the investigated MCC powders differed in all listed powder properties despite their same chemical structure. For example, MCC-4 revealed the best HR and the highest bulk density, MCC-2 the largest specific surface area, and MCC-3 200 the best flow rate and the smallest particle size span. It is noticeable that MCC-2 revealed comparably high values for the flow rate and particle size span as well as the lowest bulk density. These results may be attributed to the

thin needle-shaped particles and the rather broad particle size distribution. With regard to the reference mixtures, the powder characteristics showed minor but measurable differences.

3.4.2. Compactibility and bondability

The mechanical stability of tablets particularly depends on the physical properties of the powder blends (e.g. powder flow, particle morphology) as well as on the tableting settings (e.g. die disk speed, compaction force). Because the fillers/binders generally represent the major part of a powder blend, their tableting behavior may affect the product quality of the tablets. Therefore, in the present study, different grades of fillers/binders as well as reference mixtures were selected to investigate the influence of lower punch vibration on the resulting mechanical stability of the manufactured tablets. Because previous studies indicated that especially MCC´s benefit from the application of lower punch vibration during tableting, the present work primarily focused on different MCC grades which all play an important role in tablet manufacturing.

As mentioned in the introduction, the compactibility as well as the bondability are two crucial properties which particularly influence the resulting mechanical stability of tablets. Usually, both properties are determined by the physical characteristics of the powder blend ingredients and the tableting settings. Therefore, the powders were investigated with regard to their tableting performance at different compaction forces either with or without lower punch vibration.

In Fig. 39 the resulting compactibility and bondability plots of MCC-2, MCC-3, and MCC-4 are shown. It is clearly observed that the compactibility as well as the bondability of MCC-2 and MCC-3 significantly increased if lower punch vibration was applied. For example, in Fig. 39A the measured tensile strength of MCC-2 compacted

at 10 kN with lower punch vibration was considerably higher than the tensile strength of the tablets manufactured at 15 kN and without lower punch vibration.

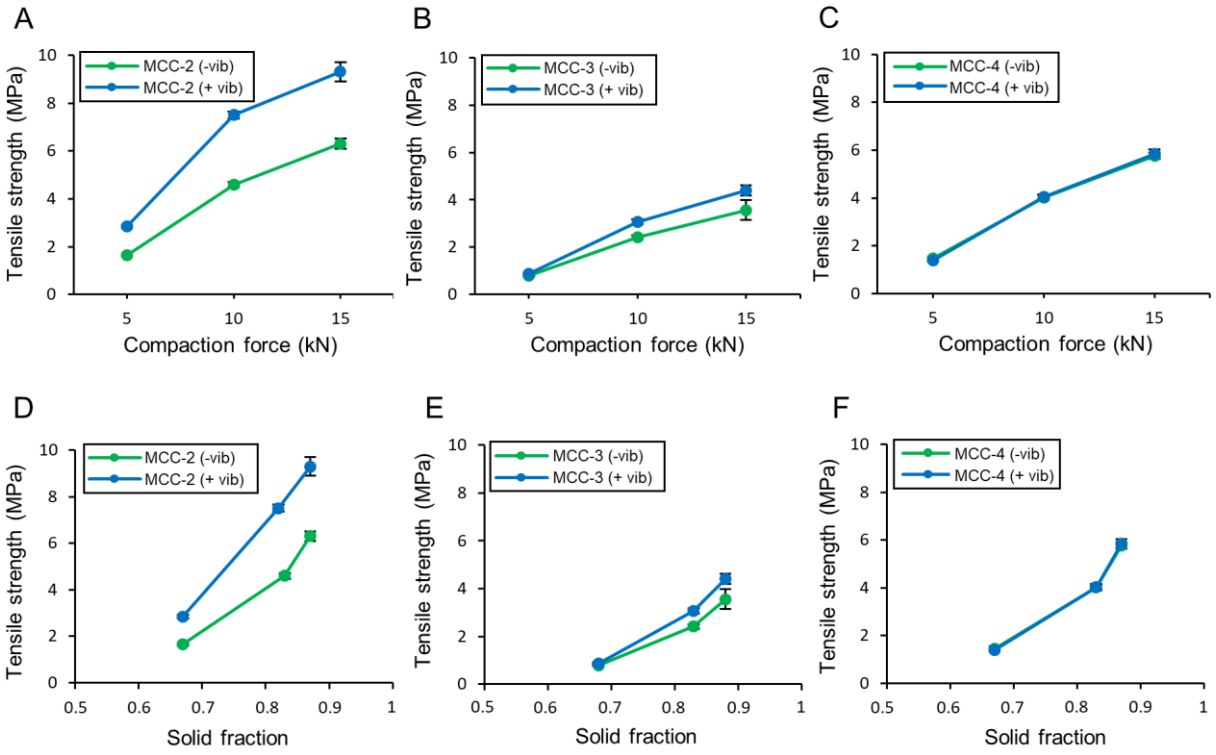


Fig. 39: Compactibility profiles of MCC-2 (A), MCC-3 (B), and MCC-4 (C) as well as bondability profiles of MCC-2 (D), MCC-3 (E), and MCC-4 (F) (means ± SD, n = 20).

Furthermore, as shown in Figs. 39D and E, the SFs of the tablets manufactured from MCC-2 and MCC-3 were slightly increased if compacted with vibration, which may be attributed to a denser and more compact particle packing within the tablet. Usually, an increase of the SF is associated with a decrease in the volume of entrapped air within the tablet and an increase of the bonding capacity between the particles. As a consequence, the tensile strength of the tablets manufactured from MCC-2 and MCC-3 with lower punch vibration increased in comparison to the tablets manufactured without lower punch vibration. It is noticeable that the higher the compaction force the more effective is the lower punch vibration. Apparently, at low compaction forces, the

newly generated bonding capacity seems not to be advantagous, probably due to the low SF.

However, as shown in Figs. 39C and F, MCC-4 does not show any differences in the compactibility and bondability behavior between the tablets manufactured either with or without lower punch vibration. The varying influence of lower punch vibration on the tableting properties of the investigated MCC powders may be explained by the different physical powder properties. In comparison to MCC-2 and MCC-3, MCC-4 shows a small particle size and narrow particle size distribution which results in an increased bulk density leading to a denser particle packing within the die. Furthermore, MCC-4 revealed a rather low HR which also leads to a homogeneous and dense particle package within the die. Moreover, MCC-4 exhibits a high particle surface area and thus an improved bonding capacity. Hence, it is almost impossible to further densify the powder bed within the die and thus to improve the tableting performance of MCC-4 with regard to the compactibility and bondability to a noticeable extent by the application of lower punch vibration.

To get a better insight into the performance characteristics of the lower punch vibration, also the three reference mixtures were investigated with regard to their compactibility and bondability. The respective results are displayed in Fig. 40. It was observed that lower punch vibration also improved the compactibility and bondability of the reference mixtures but only to a minor extent. The reference mixture A was most positively affected by application of lower punch vibration (Figs. 40A and D). As shown in these Figs., the influence of lower punch vibration was most pronounced at a compaction force of 10 kN, at which the tensile strength as well as the SF was notably improved. In comparison, the compactibility and bondability of the reference mixtures B and C were only slightly affected.

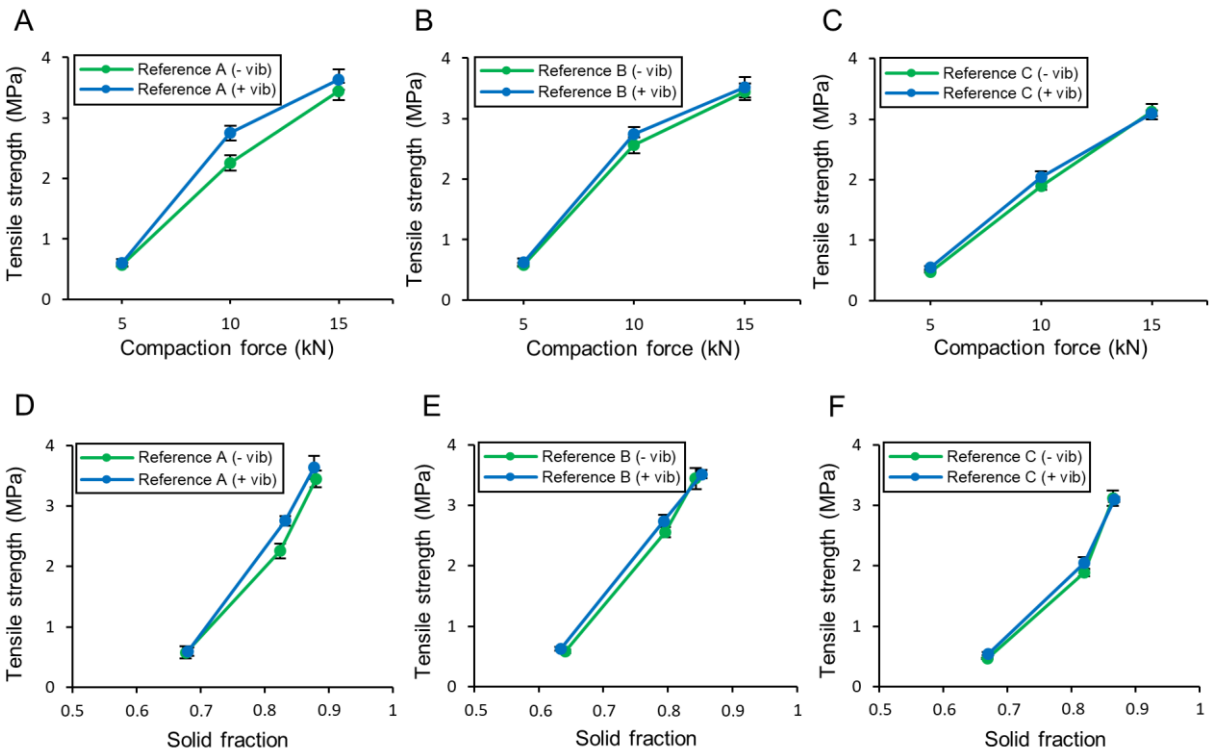


Fig. 40: Compactibility profiles of reference A (A), reference B (B), and reference C (C) as well as bondability profiles of reference A (D), reference B (E), and reference C (F) (means ± SD, n = 20).

However, all of the investigated reference mixtures exhibited high bulk densities and comparatively good powder flow characteristics (Table 13). The bulk density increased from reference mixtures A to C, whereas the HR and the flow rate decreased from A to C, which explains the influence of lower punch vibration on the compactibility and bondability behavior of the respective reference mixtures A to C. Hence, the influence of lower punch vibration on the tableting behavior of powders increased if the powders revealed low bulk densities and poor powder flow characteristics.

In summary, the results obtained with the MCC powders and the reference mixtures confirm that lower punch vibration improves the compactibility and bondability and thus the tableting behavior of powders without altering the composition of the powder or adjusting the tableting settings. Nevertheless, the influence of lower punch vibration depends on the physical properties of the powders and the applied compaction forces.

3.4.3. Tensile strength

It is known that the density distribution within tablets is inhomogeneous which leads to areas of different mechanical strength [241]. In the case of a flat faced tablet, the top and the bottom layer usually show more compact and densified regions, and thus a higher mechanical strength as compared to the center of the tablet [260]. Therefore, all manufactured tablets were also investigated with the texture analyzer in terms of their tensile strength (see sub-chapter 2.2.3.1.). The respective results are displayed in Figs. 41 and 42.

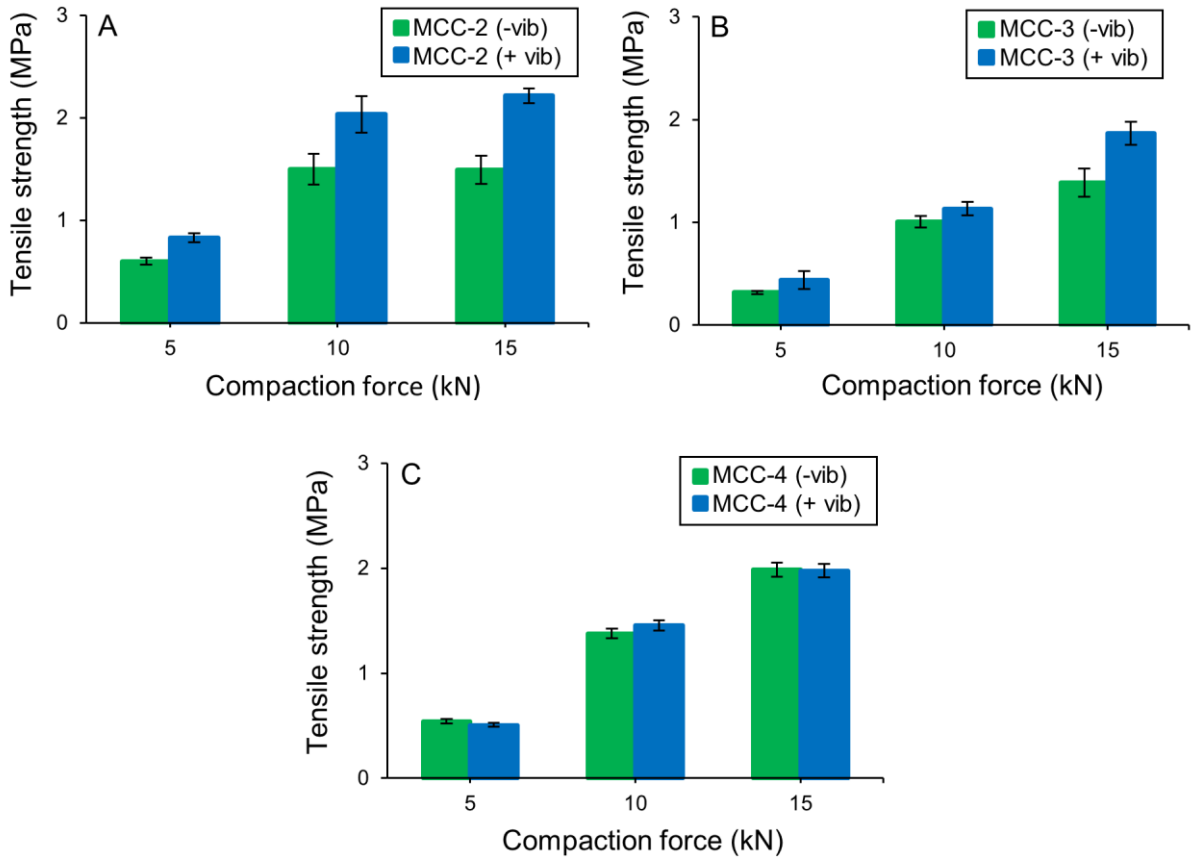


Fig. 41: Tensile strengths of MCC-2 (A), MCC-3 (B), and MCC-3 (C) depending on the applied compaction forces, measured with the modified texture analyzer (means ± SD, n = 10).

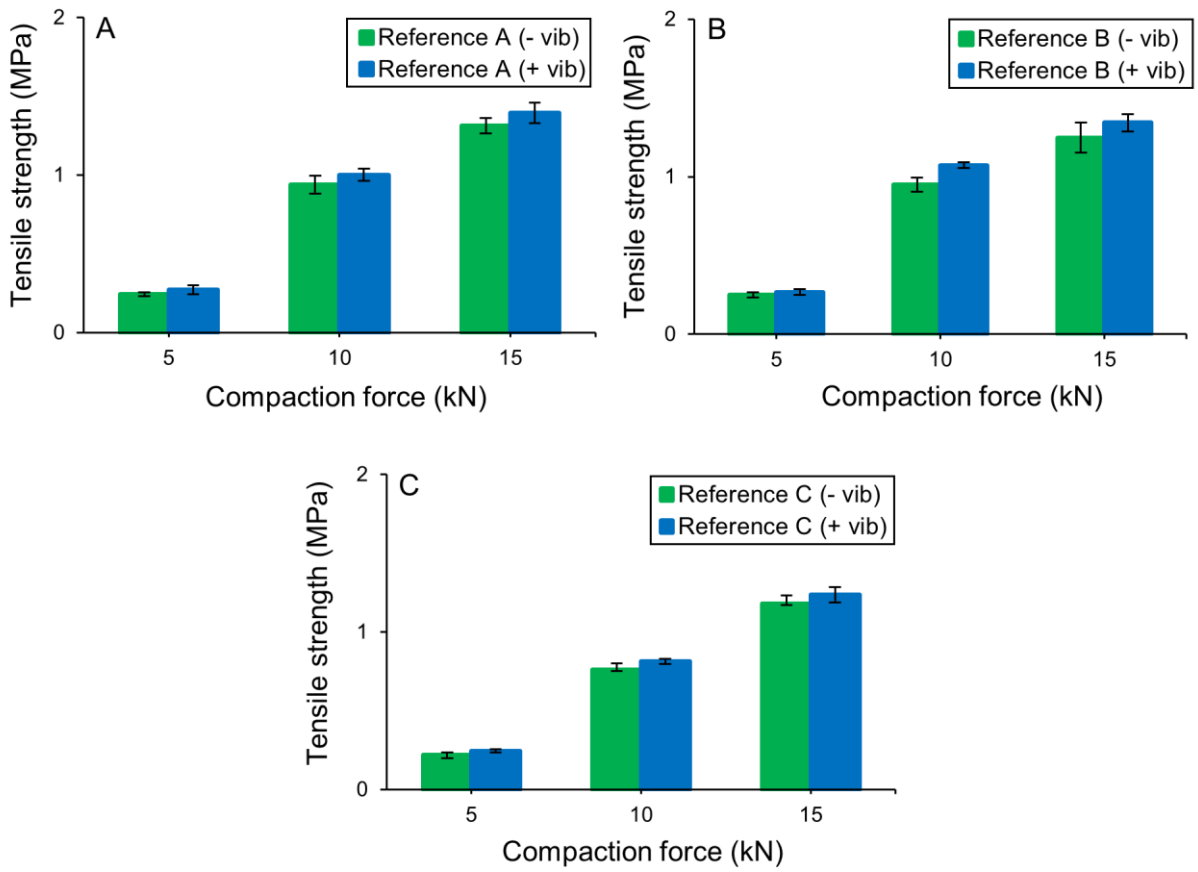


Fig. 42: Tensile strengths of reference A (A), reference B (B), and reference C (C) depending on the applied compaction forces, measured with the modified texture analyzer (means ± SD, n = 10).

It was observed that all investigated tablets showed a lower tensile strength values than those that were obtained with the conventional hardness tester (Figs. 39 and 40). For example, in Fig. 39A the MCC-2 tablets, manufactured without vibration at 10 kN, revealed a tensile strength of 4.5 MPa, whereas the tensile strength based on the results obtained with the texture analyzer was only 1.5 MPa (Fig. 41A). Thus, there is a distinct difference between the tensile strengths measured at the different locations of the tablets. This observation might be explained by the behavior of the tablets during hardness testing, where tablets usually break horizontally along the center of the band height.

However, lower punch vibration led to an increase of the tensile strength at the center of the band height of all tablets except for MCC-4, the tensile strength of which only marginally changed (Figs. 41C). Generally, the increase of this tensile strength varied, whereby the results were similar to those shown in Figs. 39 and 40. This increase may be attributed to a more homogeneous density distribution within the tablets. Thus, lower punch vibration may increase the mechanical stability of tablets at the center of their band height (weakest point), whereby the variation in the tensile strength may be explained by the different physical powder properties (see sub-chapter 3.4.1).

3.4.4. Friability

The friability is an important property for conformation of the mechanical stability of tablets, especially prior to subsequent processing steps such as coating or packaging. Therefore, the friability of all tablets manufactured either with or without lower punch vibration was determined. In Fig. 43, the friability values of the tablets manufactured at different compaction forces are displayed. It was shown that the friability of all MCC tablets decreased significantly if lower punch vibration was applied (Fig. 43). Interestingly, also the friability of MCC-4 tablets was significantly reduced (Fig. 43C), although MCC-4 tablets showed no difference in their tensile strength or SF as shown in Figs. 39C and F as well in Fig. 41C. Thus, lower punch vibration was also able to influence the mechanical strength of the MCC-4 tablets with regard to their friability. Nevertheless, all investigated MCC tablets passed the friability test according to the Ph. Eur. monograph 2.9.7. (weight in loss < 1 %).

The results of the friability test performed with the tablets from the reference mixtures showed similar results (Figs. 43D-F). The friability of these tablets was lower after vibration. It has to be noted that the tablets manufactured from the reference mixtures

A and B at 5 kN compaction force and without vibration (Figs. 43D and E) did not meet the regulatory requirements (weight in loss < 1 %). However, after application of lower punch vibration, the friability of these tablets was significantly decreased: reference mixture A by 55 % (5 kN) and reference mixture B by 59 % (5 kN). Hence, lower punch vibration was able to decrease the friability of the tablets from reference mixture A to a sufficient extent (weight in loss < 1 %). All tablets from reference mixture C met the friability test, no matter whether vibration was applied or not (Fig. 43F). However, lower punch vibration was even able to decrease the friability of these tablets by up to 50 %. Therefore, lower punch vibration is also regarded as a useful tool to decrease the friability of tablets.

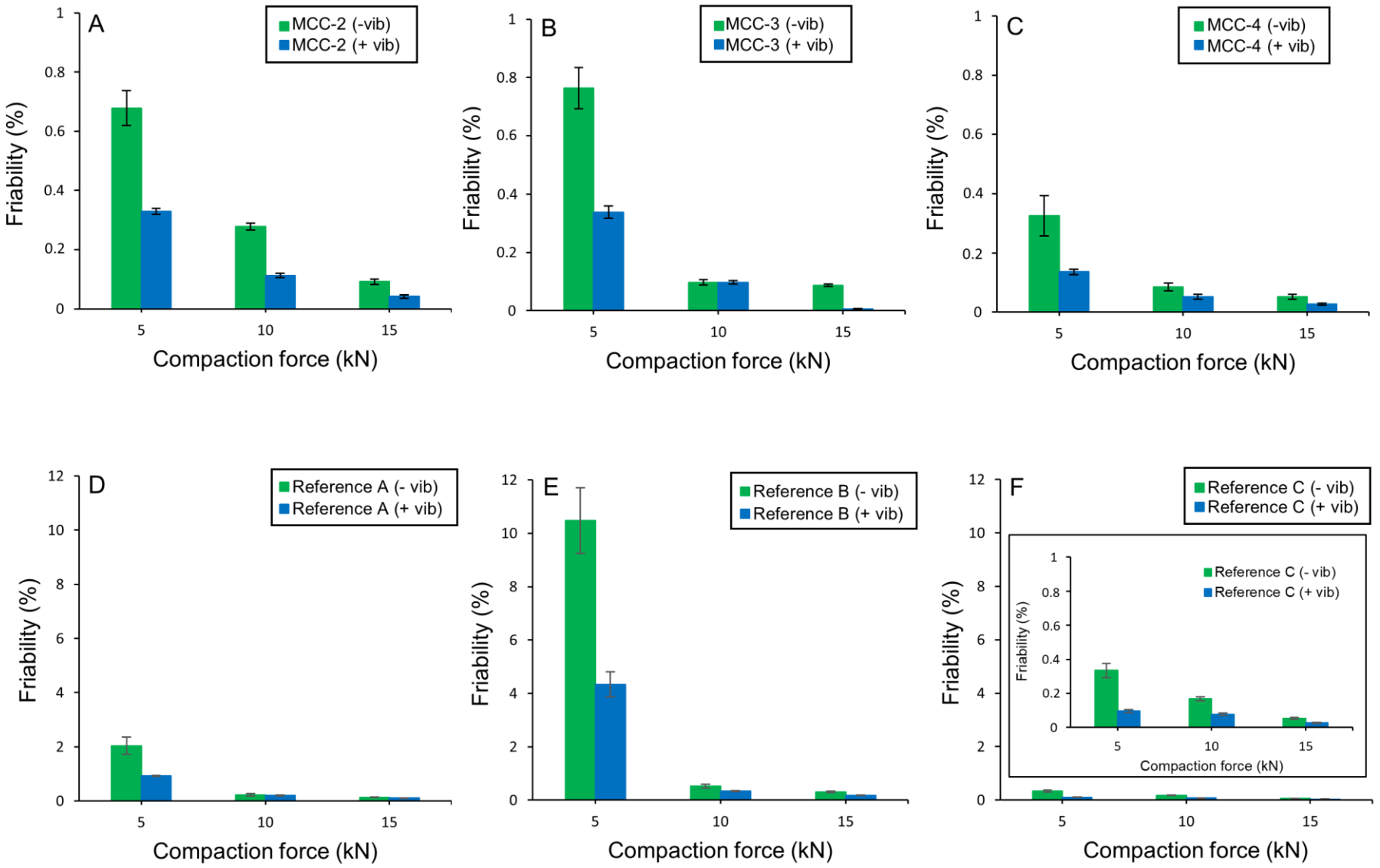


Fig. 43: Friability values of the MCC grades Parmcel 102 (A), Vivapur® 200 (B), Avicel® 301 (C), and the reference mixtures reference A (D), reference B (E), and reference C (F) (means ± SD, n = 10).

3.4.5. Die filling

As shown in chapter 3.2., lower punch vibration affects the die filling process by improving the powder flow into the die caused by a fast powder densification within the die. The present study confirmed these results because all tablets manufactured with lower punch vibration required a lower filling depth in comparison to the tablets manufactured without lower punch vibration to reach the same tablet weight. As shown in Table 8 (see sub-chapter 2.2.2.), the filling depth of several powder blends decreased up to 2.30 mm (24.2 %) to reach the same tablet weight. This observation clearly shows that the performance level as well as the applicability of lower punch vibration is remarkable, especially for powders with a poor powder flow. Therefore, the application of lower punch vibration appears very promising for tablets manufactured by direct compression, where the powder flow is a primary reason for production problems.

3.4.6. Conclusion

The present study showed that the application of lower punch vibration allows to improve the compactibility and bondability and thus the mechanical strength of tablets to a significant extent. Moreover, the required compaction forces for the manufacture of tablets with a sufficient mechanical stability were reduced, which might be beneficial with regard to the prevention of tableting failures. These results are primarily attributed to a pre-densification of the powder bed within the die prior to the pre-compaction and main compaction. Consequently, the particle arrangement within the powder bed changed, leading to the generation of new potential interparticle bonding points as well as to the removal of entrapped air. Hence, the SF and the tensile strength of the manufactured tablets increased. However, the extent of pre-densification and therefore the influence of lower punch vibration differed depending on the physical properties (especially particle morphology, particle size distribution, and powder flow) of the investigated powders. Thus, lower punch vibration is preferably applicable to powder compositions with a poor powder flow and a low bulk density. Nevertheless, the friability of all investigated tablets was decreased by application of lower punch vibration, independent of their physical powder properties. Moreover, the die filling was significantly improved, which confirmed the assumptions made in previous studies. However, additional investigations with regard to the performance characteristics of lower punch vibration have still to be performed to gain further knowledge regarding the applicability of lower punch vibration for the manufacturing of tablets.

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Appendix

A Hazardous materials

Substance	Supplier	Danger symbol	Hazard statements	Precautionary statements
Acetaminophen	Caelo, Germany		H302, H315, H317, H319	P260, P273
Indigo carmine	Carl Roth, Germany		H302	

B Curriculum vitae

Name:	Kalies, Alexander	Date of birth:	Jan 5th, 1991
Marital status:	Unmarried	Place of birth:	Hamburg

Professional experience	since 11/2020	GMP Coordinator Production Assembly & Packaging medac GmbH, Wedel
Education	11/2016 – 10/2020	Ph.D. student, Division of Pharmaceutical Technology, University of Hamburg, Supervisor: Prof. Dr. C.S. Leopold Co-Supervisor: Thomas Heinrich
	12/2016	Licensure as a pharmacist (Approbation)
	10/2011 – 10/2015	Study of Pharmacy, University of Hamburg
Specialization	since 11/2016	“Fachapotheker für Pharmazeutische Technologie”
Internships	05/2016 – 10/2016	Intern, Fette Compacting GmbH, Schwarzenbek
	11/2015 – 04/2016	Intern, Cranach Apotheke, Hamburg
School	06/2010	A-level diploma, Ida-Ehre Gesamtschule, Hamburg

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Declaration on oath (affirmation in lieu of oath) / Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, die vorliegende Dissertation selbst verfasst und keine anderen als die angegebenen Hilfsmittel benutzt zu haben. Die eingereichte schriftliche Fassung entspricht der auf dem elektronischen Speichermedium. Ich versichere, dass diese Dissertation nicht in einem früheren Promotionsverfahren eingereicht wurde.

Datum, Unterschrift