About tablet disintegration

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List of abbreviations

API	active pharmaceutical ingredient
ASS	acetylsalicylic acid
AUC	area under the curve
CCS	croscarmellose sodium
CI	confidence interval
DCP	dibasic calcium phosphate dihydrate
DT	disintegration time
FD	fractal dimension
FLASH	fast low angle shot
GPU	graphical processing unit
ICH	international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
MCC	microcrystalline cellulose
MRI	magnetic resonance imaging
MRT	Magnetresonanztomographie
n	number of experiments
NLINV	nonlinear inversion
OD(M)T	orally disintegrating (mini) tablet
PP	polacrilin potassium
PSD	particle size distribution
PTFE	polytetrafluorethylene
PVC	polyvinyl chloride
r	correlation coefficient
rh	relative humidity
RMSEP	root mean square error of prediction
ρ	(relative) density
SFV	spatial filtering velocimetry
SSG	sodium starch glycolate
$t_{1/2}$	half-life
TA	texture analyser
TE	echo time

T_g	glass transition temperature
TR	repetition time
w/w	weight/weight
XPVP	crospovidone

1 Introduction

1.1 Tablet disintegration

The loss of structural coherence of a tablet is denoted as tablet disintegration. It is not to be confused with the slower acting erosion or dissolution processes. The disintegration process can greatly increase the surface area of the drug available to the solvent and enhances thereby the dissolution rate[1-3]. Depending on the properties of the incorporated drug, fast disintegration can lead to a quicker absorption of the active pharmaceutical ingredient (API) and a faster onset of the desired effect. Therefore, tablet disintegration can be understood as the first stage in the bioavailability cascade[4].

Tablet disintegration occurs when a force inside the tablet surpasses the sum of cohesive forces holding the tablet together. The cohesive forces comprise hydrogen bonds, capillary, van der Waals, and electrostatic forces, whereas solid and binder bridges and mechanical interlocking physically contribute to tablet strength[5]. Because tablets usually do not disintegrate by themselves, excipients are added, which generate the necessary force for the disintegration process, the tablet disintegrants.

The legally required test for disintegration is described in the European Pharmacopoeia[6]. Tablets are placed in open-ended transparent tubes with a 2 mm mesh attached to the bottom completely submersed in water. The tubes are moved up and down with a certain amplitude and frequency. The time point when "any residue of the unit, except fragments of insoluble coating" pass the mesh, is defined as the disintegration time of a tablet. This test is primarily used for quality control purposes and does not provide information about the mechanisms of actions or underlying processes of tablet disintegration. Therefore, scientists developed different methods in order to improve the understanding of disintegration (see section 1.2.1.2 and the following).

However, analytical and technical advances cannot resolve the basic constraints of disintegrants. The dissolution enhancing properties of disintegrants are limited, as even the best disintegrant cannot actively decrease the particle size of the incorporated API. Therefore, other techniques have been developed to further increase the dissolution rate. Besides chemical modification of the API itself, micronized API particles or solid dispersions and solutions are used to increase the contact area of the drug with the dissolution medium[7,8]. Despite these advanced techniques disintegrants will likely play an important role in the future, as most drugs in industrial development are poorly soluble[9]. Combining new techniques with tablet disintegrants can possibly increase the dissolution rate more than each approach alone.

Even though tablet disintegration can be controlled and directed with disintegrants, the disintegration process and efficacy of disintegrants is depending on many different factors. In the following, the influencing aspects will be introduced and a brief literature review will be given.

# 1.2 Factors influencing tablet disintegration

1.2.1 Excipients and tablet properties


1.2.1.1 Tablet disintegrants

The employed disintegrant is the driving force behind the disintegration. Initially, natural polymers, such as starches, were used as excipient with disintegrating properties[10,11]. The influence of soluble disintegrant components on disintegration led to the crosslinking of the polymer chains to decrease the medium viscosity in the porous system of the tablets. Additionally, carboxyl functions were introduced to the polymer backbone to increase the hydrophilic properties[12-14]. The less soluble components are within disintegrants, the quicker is the absorption of disintegration medium. Subsequently, the disintegration time is shorter, as the medium viscosity does not increase during penetration. This dependency was first described by Washburn, who established an equation to describe the water uptake rate into capillaries[15]. Artificial polymers, such as crospovidone (cross-linked polyvinylpolypyrrolidone) and polacrilin potassium (a cross-linked copolymer of methacrylic acid and divinylbenzene), were designed and synthesized to further improve the desired properties[14,16]. This new class of modified and newly synthesized polymers is also called superdisintegrants because of their superior disintegration performance. In Figure 1.1 the structures of frequently used disintegrants are shown. Only for sodium starch glycolate and polacrilin potassium the cross-linking is known. For crospovidone a physical cross-linking has been reported, whereas no information is available for croscarmellose sodium. The carboxylic functions are placed exemplarily in Figure 1.1 as they are statistically distributed throughout the polymer.
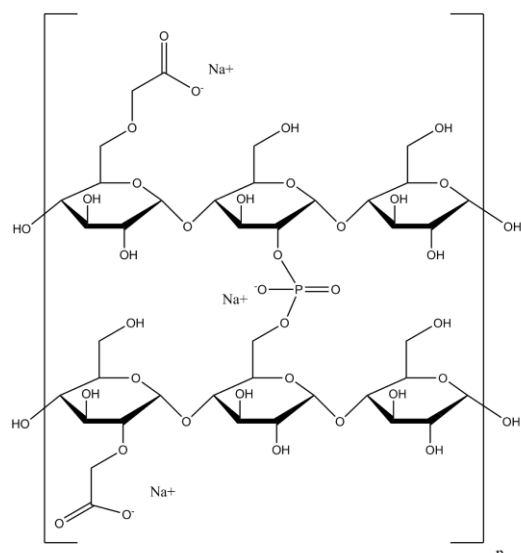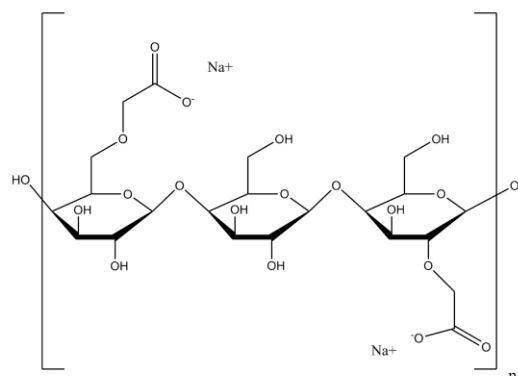
Sodium starch glycolate   (Cros)carmellose sodium
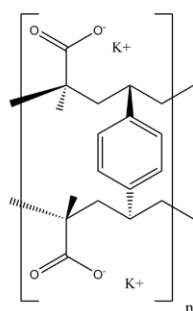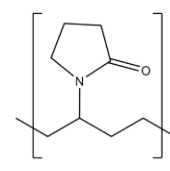
Polacrilin potassium   (Cros)povidone

Figure 1.1: Structures of commonly used disintegrants; the mode of crosslinking of croscarmellose sodium is unknown and therefore not shown

The disintegrant type, but also different characteristics of it can influence disintegration. Shotton and Leonard investigated the influence of disintegrant type and ratio on the disintegration time and resulting particle size of tablets, which they determined with custom built wet sieves[17]. The excipient blend was wet granulated beforehand and different amounts of either maize starch, microcrystalline cellulose (MCC), sodium calcium alginate, alginic acid, or a synthetic colloidal aluminum silicate were added as disintegrant. Even though these substances are only rarely used as disintegrants anymore, the results are nevertheless of interest. They demonstrated that depending on the disintegrant, the disintegration times and particle sizes were different, but also changed to different extents by increasing the disintegrant concentration. For example, disintegration lasted 2100 s when 1 % of alginic acid incorporated, when 8 % were added, disintegration time decreased to ~ 100 s. Tablets containing 1 % of sodium calcium alginate, on the other hand, disintegrated already within ~ 400 s, whereas an amount of 8 % reduced the disintegration time to approximately 90 s. A similar behavior was observed for the mean particle sizes.

Increasing the disintegrant concentration from 1 % to 8 %, the mean particle size decreases from 400 µm to 50 µm for alginic acid, and from 90 µm to 25 µm for sodium calcium alginate. Even though deviating behavior of different disintegrants had been described before, the authors did not interpret the results but only described the obtained data. Because the authors only briefly described the actual sieving process, it cannot be evaluated whether the obtained particle sizes are representative. Therefore, the data should be considered with caution.

The transition from classic disintegrants to the new superdisintegrants in the mid-1970s and early 1980s led to comparative studies of both classes, from which a variety of conclusions were drawn. Van Kamp investigated different disintegrants in wet granulated lactose-based formulations[18]. As potato starch is more effective in high concentrations, 20 % were added and compared to tablets prepared with 4 % of superdisintegrant or no disintegrant at all. When no disintegrant was added, tablets disintegrated in 664 s. With potato starch, this time decreased to 110 s when the disintegrant was added extragranularly. Extragranularly means that the disintegrant was added to the granules prior to tableting and not during the granulation process. When 4 % of crospovidone were added, tablets disintegrated within 43 s, with sodium starch glycolate, disintegration lasted 49 s. The disintegration times were in agreement with the water uptake rates of the different tablets. This confirmed the findings of Patel and Hopponen, who stated that water uptake is essential for disintegrant action[10].

Colombo et al. were among the first to measure the force produced by tablets during disintegration[19]. They produced tablets based on coated acetylsalicylic acid (ASS) at different compression levels (ranging from 4.3 kN to 28.7 kN) with several disintegrants. Either 13 % of corn starch or 2.5 % of other disintegrants plus 11.5 % of MCC were applied. Depending on the disintegrant, maximum forces between 34 N (corn starch) and 58 N (crospovidone) were detected. Additionally, the time at which 63.2 % of the maximum force was developed was calculated for each curve. This parameter also greatly depended on the choice of disintegrant and varied between 9 s (crospovidone) and 630 s (croscarmellose sodium). The influence of the compression force on the results will be discussed later on. The results were not interpreted further, but show that there are fundamental differences between different disintegrants.

Smallenbroek et al. investigated the impact of disintegrant particle size on the disintegration time of dibasic calcium phosphate dihydrate (DCP) tablets[20]. Either 4 % (sodium starch glycolate) or 20 % (potato starch) of disintegrant were employed and the disintegration times of tablets, compressed to similar porosities, determined. When no lubricant was used, the disintegration times of potato starch containing tablets decreased with increasing particle sizes of the disintegrant. This was found to be in accordance with results from List and Muazzam, who demonstrated that larger disintegrant particles produced a higher swelling force and shorter disintegration

times[21]. However, when magnesium stearate was used as lubricant, disintegration times severely increased with increasing particle size but also with the duration of mixing with magnesium stearate. The authors explained this with the formation of a lipophilic film around the disintegrant and DCP particles. The larger the disintegrant particles are, the smaller is the specific surface area leading to decreased water uptake capabilities. When the blending time increased, they hypothesized, the film was also more complete. Conversely, the disintegration times of tablets with the superdisintegrant sodium starch glycolate were hardly influenced by particle size and duration of blending. This was explained with the strong swelling of the disintegrant. A low amount of water is claimed to be adequate to increase the particle volume sufficiently to destroy the lipophilic lubricant film around the particles. Yet, observed disintegration times of tablets with different particle sizes of the sodium starch glycolate were similar and cannot be justified with this explanation of the authors.

The presented studies show that the disintegration behavior and/or time does not only change by choosing different disintegrants, it also varies to different extents with changing disintegrant concentrations and/or particle sizes. This makes the choice of the appropriate disintegrant during formulation development difficult. Classification systems based on different characteristics could facilitate the selection. The efficiency of disintegrants, i.e. the ability to cause a specific effect in short time, would be valuable. This could be the speed of force development, as measured by Colombo et al.[19] or the disintegration time. Another classification system could be based on the effectiveness of disintegrants, which describes the extent to which the desired effect takes place. In the study from Colombo et al., the most effective disintegrant would be the one producing the highest force. Another way to classify disintegrants based on the effectiveness could be the particle size during disintegration. Such classification systems could help to structure the findings in literature and greatly aid the formulation scientist.

However, to understand the behavior of different disintegrants, the differences between disintegrants had to be evaluated.

1.2.1.2 Quantifying disintegration

To examine the differences of disintegrants, scientists had to identify characteristics that are influenced by them.

The most basic approach is the determination of the disintegration time (see section 1.1). The disintegration time can be easily acquired and is used for quality control purposes. However, it does not provide any physical information about disintegration itself and is not capable of improving the understanding of the disintegration process.

A requirement for disintegration is the absorption of a disintegration medium. Without the incorporation of a disintegration medium, disintegrants are not able to

act and tablets do not disintegrate. The rate and amount of water uptake are hence recorded. Yet both, the water uptake as well as uptake rate reflect a variety of tablets and excipient properties and should be interpreted with caution[22,23].

In section 1.2.1.3.8 it is discussed that a volume increase of disintegrant particles is necessary to promote disintegration. To quantify this phenomenon, the swelling volume of disintegrants can be determined[10]. As the swelling volume does not necessarily correlate with disintegration time, the force that is exerted during disintegration seems to be a more appropriate factor[5]. The force is usually determined of tablets containing disintegrants and not the disintegrant itself[19].

Also, the main reason why disintegrants are added to tablet formulations is to improve the dissolution characteristics. Since the dissolution rate depends on the available surface area during disintegration, the tablet particle size generated during disintegration is of great interest. Prior to this work, it was not possible to continuously determine the particle size distribution of disintegrating tablets. Hence, the dissolution rate from disintegrating tablets can be determined to acquire information about disintegration[24]. As the dissolution rate is influenced also by other factors, it should also be carefully considered.

Most studies investigate one or more of the above mentioned factors, as they can be determined with reasonably low effort and provide a high degree of information about the underlying processes during disintegration. Still, to answer more questions and to further characterize disintegrants and disintegration, other factors are investigated, such as water sorption behavior of disintegrants[12] and morphologic changes of primary particles[25]. All of these characteristics were determined to investigate the feasibility of different proposed mechanisms of disintegrant action.

1.2.1.3 Mechanisms of action of tablet disintegrants

1.2.1.3.1 Introduction
An obvious explanation for the observed behavior of disintegrants are different mechanisms of action. Many studies were published between the 1960s and 1980s concerning the mechanistic studies of disintegrants. Beginning in the 1990s, the interest in the mechanisms of action decreased, as the focus shifted towards other characteristics of disintegrants. In the following, proposed mechanisms of action will be briefly introduced and discussed.

1.2.1.3.2 Swelling
Swelling is the volume expansion of a disintegrant particle upon contact with water, which acts as plasticizer for the polymers and increases the mobility of the polymer chains[26]. The polymer chains entangle to reach a lower energy state and thereby cause

a volume increase. When the expanding particles grow larger than the tablet pores, a force is exerted on the tablet matrix and disintegration will occur[10].

The swelling behavior of starches has been known for a long time. Patel and Hopponen thoroughly examined swelling and the capillary effect of ASS or aluminum hydroxide tablets containing corn starch[10]. By measuring the disintegration time of the different tablets in water, ethanol, and glycerin, they concluded that swelling is the dominating mechanism of action of starch, as the tablets only disintegrated in media in which starch swelled.

The applicability of the swelling mechanism to other disintegrants was investigated by List and Muazzam[5]. The authors argued that most binding forces within tablets act only over very short distances and that, therefore, a high swelling volume is not necessary. Accordingly, they investigated whether the swelling volume or the force produced by disintegrants during water contact is decisive for quick disintegration. By modifying an electronic balance, they built an apparatus, which could measure the force of disintegrating tablets. It was demonstrated that tablets containing cross-linked superdisintegrants, which produce high swelling forces but have only a limited volume increase cause quicker disintegration than strongly swelling disintegrants. Tablets containing disintegrants that strongly swelled but produced little force caused only slow disintegration.

These studies demonstrate the feasibility of swelling as a dominant mechanism of action of tablet disintegrants. Yet, several observations contradict the general acceptance of this mechanism. For once, the swelling time of some disintegrant polymers is longer than the disintegration time of tablets formulated with these polymers. Also, some polymers that do not visibly swell are capable of promoting disintegration, e.g. crospovidone. Other disintegrants swell to such a low extent that the released energy might not be exerted on the matrix to disrupt the tablet[21,25,27,28]. This is possible because only disintegrant particles in the pore walls are initially wetted. When the disintegrant swells only little, the particle will mainly expand into the pore volume.

1.2.1.3.3 Repulsive force
Own observations and the controversies about the swelling theory led Guyot-Hermann and Ringard to the proposition of a particle-particle repulsive force for starches[28]. According to their hypothesis, penetrating water annihilates the hydrogen bonds, van der Waals and electrostatic forces and induces a repulsive force between incorporated starch grains. Yet, they do not explain the nature of the postulated repulsive force. Also, they used MCC as filler/binder and describe it as non-swelling excipient, which only absorbs water but does not exert a force on the tablet matrix, even though MCC is capable of volume expansion. Consequently, this hypothesis was not adapted by the scientific community.

1.2.1.3.4 Shape recovery

Shape recovery is a peculiar behavior of some polymers. When a force is applied on these substances, a semi-stable shape is programmed into the particles[29]. This can be due to interlocking of polymer chains or spontaneous crystallization of different polymer parts, which forces the polymer to remain in a high energy state. Heat or the contact with fluids can cause the destruction of the bonds and the stored energy is released by recovery of the original particle shape. In the case of tablets, the programming happens during compaction whereas the absorption of water or gastric fluid causes the shape recovery. Löwenthal did not find any evidence of a shape memory effect of cornstarch[30] but Erdös and Bezegh observed the return to the original shape of potato starch particles[31]. The feasibility of the hypothesis was confirmed when Desai et al. described crospovidone to be acting via a shape recovery[32]. Desai et al. applied high-speed video imaging to determine the movement of uncompacted and compacted disintegrant particles when they were brought in contact with water. Crospovidone displayed a much higher movement in the compacted than in the uncompated state, whereas the behavior of other disintegrants hardly changed. This behavior was attributed to shape recovery, because it is the only mechanism directly affected by compression. However, prior to the present work no information on the applicability of this theory to other disintegrants was available.

1.2.1.3.5 Wicking

Another frequently mentioned mechanism is wicking. It is caused by capillary action when water is drawn into the porous system of the tablet. The penetration of water is not only the prerequisite for swelling, shape recovery, and other proposed disintegration mechanisms, it might also cause the weakening of the tablet structure[13,33]. The high permittivity of water, which makes up most of the gastric fluid, causes the annihilation of hydrogen bonds as well as van der Waals and electrostatic forces. To systematically investigate the effect of wicking, Patel and Hopponen recrystallized ASS, sieved the crystals, and compressed tablets based on the obtained fractions[10]. When the largest fraction (850 µm to 1400 µm) was tableted with 5 % or 10 % of starch, the majority of starch grains was found in the capillaries forming a percolating network. The smaller the particles were, more and more discontinuities in the starch network were observed in the tablet. Consequently, the penetration of water and also the disintegration behavior changed when smaller ASS particles were used. When ASS crystals smaller 150 µm were used, only 9 % of the tablet were wetted within 10 s of contact with an iodine solution. When the crystals were > 850 µm, 49 % of the tablet were wetted in the same time. The tablets did not disintegrate at all when the starch was replaced by hydrophilic dextrose. From these results, the authors concluded that a percolating network of hydrophilic particles is beneficial for disintegration, but that wicking alone only weakens the tablet structure but does not cause disintegration. Wicking rather provides the necessary water for the actual disintegration process, caused by other mechanisms of action. Their

argumentation seems reasonable, since it could not be demonstrated that wicking causes an active disintegration but only slow eroding processes. However, a wicking mechanism has been reported for one brand of polacrilin potassium[34].

1.2.1.3.6 Heat of wetting

The heat of wetting hypothesis proposes the expansion of air trapped in a tablet due to the heat developed by the disintegrant particles upon contact with the disintegration medium[4,35]. List and Muazzam performed experiments that contradict this hypothesis, as tablets containing materials producing a high amount of wetting heat disintegrated slower compared to tablets with disintegrants that produced only little wetting heat[5]. As other studies found similar results, the hypothesis was generally rejected as potential disintegration mechanism.

1.2.1.3.7 Effervescence

Disintegration due to in situ generated gas by a chemical reaction of tablet excipients with water is called effervescence. This disintegration mechanism will not be discussed and investigated in this work, as the process is not induced by disintegrant polymers.

1.2.1.3.8 Further considerations

Neglecting disintegration by effervescence, volumetric expansion of disintegrants seems to be the cause for tablet disintegration. Other hypotheses, which proposed disintegration by different means, could not be supported with experimental data. A direct particle-particle contact is obviously necessary to transmit force in order to cause disintegration. Consequently, swelling and shape recovery are the most likely candidates as mechanisms of action of tablet disintegrants.

As swelling and shape recovery disintegrants should show different expansion behavior and react differently to increasing tableting pressure, a discrimination between the two should be possible.

1.2.1.4 Tablet filler/binder material

The tablet disintegrant is only one of several excipients used in tablet manufacturing. Usually, a filler and/or binder makes up most of the tablets mass. A large variety of inorganic and organic materials is used as filler/binder in tablet preparations. All of them differ in their binding capabilities, plastic and elastic behavior, solubility, hydrophilic properties, wettability and other parameters leading to different disintegration and dissolution characteristics. This great number of properties complicates the choice of the appropriate filler/binder. When the API alone is sufficiently compactible, only little or no filler/binder might be necessary at all. This further complicates predictions about the disintegration and dissolution behavior, as the physical characteristics of APIs are not well known. Therefore, several

investigations were performed to identify parameters of different materials that affect disintegration.

Patel and Hopponen demonstrated that when a poorly soluble API is used as core material, a continuous hydrophilic network of starch was necessary for rapid disintegration[10]. When the network was discontinuous, disintegration was delayed and incomplete because water penetration was hindered. Hence, either the filler/binder needs to have sufficient wicking capabilities or a hydrophilic network has to be set up by the disintegrant.

Nogami et al. discussed the importance of hydrophilic properties and adhesive and cohesive behavior of MCC and potato starch on the disintegration of ASS tablets[11]. They reported low disintegration times of potato starch based tablets containing 10 % and more potato starch. ASS/MCC tablets, however, showed a distinctive disintegration time minimum between 15 and 40 % of MCC. It was concluded that lower adhesive and cohesive forces of potato starch and more pronounced hydrophilic properties cause a quicker disintegration. The combination of two excipients can, therefore, lead to completely different behavior of the tablet system.

Ganderton and Fraser investigated the water uptake of tablets based on six fillers with and without starch[36]. The potential influence of the filler on disintegration was demonstrated by calculating the porosities of tablets based on the different materials after compression at 100 MPa. The porosity of ASS tablets based on wet massed granules was 6.0 %, the porosity of magnesium carbonate wet massed tablets was more than 6 times higher (36.4 %). It did not systematically influence the water uptake, even though water uptake vs. compaction pressure curves showed distinct behavior of tablets with different fillers. Tablets of pure ASS and phenidione compressed at 50 MPa absorbed almost immeasurable amounts of water. Calcium phosphate, magnesium carbonate, and lactose could be compressed at pressures of up to 150 MPa and still absorbed water almost 10 times faster than ASS and phenadione. Overall, lactose was found to be able to absorb the largest amounts of water over the complete pressure range (20 to 150 MPa). Because of contamination of the powders with granulation liquid, the influence of wettability could not be evaluated. The authors showed by air permeation measurements that the addition of up to 10 % of starch had only little effect on the pore structures of tablets. On the contrary, the impact on the water uptake is drastic. Lactose without starch absorbs 10 mg of water in 50 s. With starch, more than 30 mg are absorbed in the same time. It is discussed that the low absorption rate of pure lactose is due to the solubility of the material. When water penetrates the porous network, lactose dissolves from the pore walls and increases the viscosity of the water. This forms a viscous barrier, which slows down the water penetration. When starch is added, the lactose tablets disintegrate and the effect of the viscous barrier is nullified. The time point when 30 % of the tablet were saturated with water was used as marker for the water uptake capabilities of the

tablets. Without starch, phenidione required 600 s, with starch 215 s to reach 30 % saturation. The impact on ASS was even more pronounced. Without starch, the process lasted 300 s and with starch only 14 s. The authors, however, missed to provide more explanations for the observed deviations. Still, the results demonstrate the tremendous impact of filler/binder properties on tablet disintegration.

Gordon et al. found that, independent from the applied disintegrant, dissolution rates from tablets varied after storage at elevated temperature and relative humidity[37]. The storage conditions seem to unequally influence different base materials, as tablets compressed with lactose were affected most, followed by DCP and naproxene tablets, which were equally affected. Recrystallization of lactose was mentioned as potential cause for the stronger dissolution decrease of these tablets. The results hint towards the potential impact of the storage conditions on the dissolution rate (see section 1.2.3), but also demonstrate that the impact of storage conditions is different depending on the filler/binder material.

In another study, Gordon et al. investigated the dissolution rates of tablets with different disintegrants and base materials[38]. The dissolution rates did not merely depend on the mode of disintegrant incorporation (intra- or extragranularly), but also on the applied filler/binder material. Lactose was chosen as soluble filler, DCP as insoluble one, and naproxen as intermediate with a self-determined solubility of 6 g/l. When no disintegrant was used, 40 % of p-aminobenzoic acid were liberated from the lactose base within 15 min, 5 % from the naproxen matrix, and 20 % from the DCP matrix. After addition of crospovidone, similar amounts were released from DCP and naproxen (both around 40 %) but 90 % from the lactose matrix. When croscarmellose sodium was used, 75 % were liberated from DCP, 80 % from naproxen, and 100 % from lactose. The authors only briefly mentioned that the solubility of the materials is likely causing the observed effects but did not explain any further. Still, the fact that dissolution from lactose was always highest suggests that the available surface area of the API was larger in this case compared to the poorly and intermediate soluble tablets. This indicates that particles dissolved quickly after the initial disintegration and left behind pure drug substance. The dissolution of the generated particles of DCP and naproxen with the included drug is likely progressing much slower, which causes the observed effects. The more rapid dissolution of tablets with croscarmellose sodium could therefore be because of the generation of smaller particles when this particular disintegrant is used.

Ferrari et al. also examined disintegration of tablets with varying formula solubility[39]. They used the "force equivalent" as measure for the disintegration propensity of tablets. The force equivalent was originally introduced by Caramella and is the highest slope of force vs. water uptake curves after fitting with the Weibull equation[40]. It is supposed to represent the "ability of disintegrants to transform water uptake into disintegrating force". Sodium starch glycolate was used as disintegrant. The

disintegration characteristics of formulations based on DCP, calcium sulphate dihydrate, α-lactose monohydrate, and mannitol were as expected. Disintegration of insoluble tablets was quicker than of soluble tablets as no viscous barrier was formed (8.6 to 12.1 s for insoluble and 16.3 s to 88.3 s for soluble formulations). The results appear to differ from those acquired by Gordon et al. in the previously mentioned study, but in this case the disintegration time and not the drug dissolution is investigated. Depending on the tableting force, mannitol tablets require up to 5 times the disintegration time compared to the α-lactose tablets. This was not discussed in the article, yet could be due to lower detected porosity and mean pore size values for mannitol, which could slow down water penetration.

The studies show that the filler/binder solubility seems to be a decisive parameter for disintegration ability. The formation of a viscous barrier due to dissolved material hinders water penetration and thereby delays disintegration of soluble tablet matrices. The results of Ferrari et al. suggest that also the porosity plays an important role. It was demonstrated that α-lactose tablets disintegrate quicker than mannitol tablets even though their solubility is similar. A possible reason is that porosity and mean pore diameter of mannitol tablets were considerably lower than of α-lactose, despite similar compression pressures. This could delay water absorption. The investigation of Patel and Hopponen demonstrated the impact of particle filler/binder particle size (see section 1.2.1.2.5)[10], a factor that has not been systematically investigated, yet.

These parameters represent only a fraction of potentially influencing parameters. In combination with other excipients, the behavior of the matrix will become less predictable. It is questionable, if extensive investigations of large numbers of parameters of fillers/binders actually help with the excipient choice, as interdependencies of the parameters strongly increase the system complexity. A better approach might be the investigation of rather few parameters, such as solubility, porosity, and particle size. After these factors and their interplay have been understood, investigations could be extended.

1.2.1.5 Lubricants

As already mentioned in section 1.2.1.1, lubrication has a major effect on disintegration. The purpose of lubricants is the reduction of friction and cohesion between the die, the punches, and the tablet itself. To decrease the friction and cohesion, usually a fatty substance is added to the excipient blend before tableting. During compaction, parts of the lubricant are pressed out of the tablet core and form a thin layer around it.

Smallenbroek et al. demonstrated the dependency of disintegration time on the particle size of ASS and blending time with magnesium stearate[20]. The larger the particles were or the longer the blending time, the less permeable was the lubricant film around them and the slower disintegration was (see section 1.2.1.1). Van Kamp

et al. showed that superdisintegrants are less sensitive towards magnesium stearate than potato starch[18]. When 0.5 % of magnesium stearate were added as lubricant to a formulation containing potato starch, the disintegration time more than doubled from 50 s to 110 s. In contrast, the disintegration time did not change, when sodium starch glycolate was used. The authors explained the superiority of the superdisintegrants with insensitivity to magnesium stearate, as the particles swell to a greater extent. Therefore, only little liquid has to penetrate the lubricant film to cause a larger volume increase, leading to the rupture of the film.

In a further study, van Kamp et al. measured the volumetric water uptake and the penetration rate of powders and tablets with and without 0.5 % of magnesium stearate[23]. The penetration rate into a bed of loose crospovidone powder was not affected by lubrication, whereas the penetration rate of potato starch showed a pronounced lag time, yet absorbed similar amounts of water. The penetration rate of sodium starch glycolate powder was also severely slowed down (2250 mg water uptake without lubricant compared to 1000 mg with lubricant in the same time). The results of tablets based on different fillers (α-lactose, calcium sulphate dihydrate, and DCP) showed similar trends. When magnesium stearate was added, the volumetric water uptake and the water uptake rates decreased. However, the change was least pronounced for DCP, a very brittle material, which fractures during compression. The newly created surfaces are not covered by lubricant and the lipophilic effect is thereby minimized.

Other substances than magnesium stearate can be used as lubricants as well. Late et al. evaluated the optimum amount of magnesium stearate in a fast disintegrating tablet formulation and replaced it with other lubricants in the same concentration[41]. Talc and stearic acid did not affect disintegration time compared to magnesium stearate. Glycerol dibehenate, though, significantly increased the disintegration time from 20 s to approx. 30 s. The hydrophilic l-leucin significantly decreased the disintegration time but also tablet hardness. The disintegration times were connected to the penetration rate of the disintegration liquid and the hydrophilic and lipophilic properties of the lubricants.

It can be concluded, that the use of a lipophilic lubricant has a negative effect on disintegration. However, filler/binder properties can be specifically used to control the extent of the lubrication effect. Potentially, the use of hydrophilic lubricants can decrease disintegration time.

1.2.1.6 Tablet porosity

According to the Washburn equation, the penetration rate of a liquid is proportional to the diameter of pores (Equation 1.1)[15]. Hence, it is expected that the porosity of tablets directly influences disintegration.

$$\frac{dl}{dt} = \frac{r * \gamma * \cos\theta}{4 * \eta * l}$$ 1.1

r represents the radius of the pore, *l* the length of the pore already filled with liquid, *γ* the surface tension and *η* the viscosity of the penetrating liquid, and *θ* the contact angle between liquid and matrix material.

Equation 1.1 describes the penetration behavior into an ideally straight, perfectly cylindrical, and horizontal pore (the tortuosity and changing diameter of naturally occurring pores are not considered, for example). Yet, it summarizes most of the factors that directly influence water penetration into pores. Characteristics of the penetration liquid as well as of the matrix substance directly influence penetration. Wider pores, increased surface tension of the liquid, and cosine of the contact angle between liquid and matrix lead to an increase of the penetration rate into the pore. An increased liquid viscosity or already partially filled pores decrease the penetration rate. In terms of tablet disintegration and tablet properties, it is expected that with wider pores, disintegration proceeds faster than with narrow pores.

The opposite was found by List and Muazzam[21]. The higher the compression pressure of DCP tablets, the quicker they disintegrated and the quicker the swelling force increased. Apparently, the penetration rate and length is not the limiting factor for disintegration but the rapidity with which the disintegrant transfers force onto the tablet matrix. When the pores are wide, the disintegrant needs to expand more until it touches the pore walls, which takes more time. It also requires energy that cannot be exerted on the tablet matrix anymore. When the disintegrant is placed in narrow pores it has to expand only slightly to transfer energy on the tablet. This behavior has been reported several times[12,19,32].

This observation appears to be only true when the pores do not become too narrow. Then, water penetration can be heavily impeded. The same is true when the filler/binder material is soluble[39]. The Washburn equation states that the penetration rate is inversely proportional to the medium viscosity. When the filler/binder dissolves, the medium viscosity increases and the water uptake will be strongly delayed. On the other hand, not only the viscosity changes dynamically but also the radius of the pores and the matrix stiffness. Even when the viscosity increases, some of the disintegrant particles will be wetted and will cause a widening of the pores, thereby facilitating water penetration. Also, especially when it is soluble, the matrix will soften upon contact with water. Thereby, the force transmission from disintegrant particle on tablet matrix will decrease as the matrix will simply adapt to the changing shape of the disintegrant.

The influences of tablet porosity and the dynamic changes during water uptake on disintegration are only superficially understood, as they have only been briefly discussed for swelling disintegrants. The behavior of shape recovery disintegrants in tablets of different porosity has not been investigated, yet. The investigation of such a system could improve the understanding of the interplay between compression force, porosity, and disintegration.

1.2.2 The manufacturing process

1.2.2.1 Introduction
Most tablets look similar: the steps that were necessary to produce them cannot be identified by the outer appearance. Yet, these steps, necessary for a smooth tableting process, can greatly interfere with disintegrant action. Direct compression is considered to be the most simple production process, where the excipients are only blended before tableting. Consequently, disintegrant action should only be influenced by other excipients and tablet properties but not the manufacturing technique. Direct compressed tablets are used as reference to investigate the impact of other manufacturing procedures. Yet, not all excipients are suitable for direct compression. Different granulation techniques are used to alter the characteristics of the applied excipient blend. Granulation improves flow characteristics, handling, decreases dust formation, and segregation tendencies[42]. Unfortunately, granulation can greatly influence the disintegration properties of the final dosage form. While most studies on tablet disintegration were conducted on direct compressed tablets, other manufacturing scenarios are possible and have, in part, been investigated.

1.2.2.2 Direct compression
Direct compression is the process of directly tableting the excipient powder mixture after blending without prior treatment[43]. It is a preferred process for moisture sensitive and thermo-labile drugs as the lack of intermediate steps assures unaltered API quality[44] and low production costs. The incorporated disintegrant particles are also not altered, which avoids other effects to be superimposed on the experimental results. This is the reason why most studies on disintegration are based on direct compressed formulations.

1.2.2.3 Dry granulation
When the excipient mixture shows extensive static charge, poor flowability, or high segregation tendencies, a granulation step is introduced. Due to the lack of process heat and/or process fluids, dry granulation is the favored granulation process for heat and moisture sensitive APIs[43]. Roller compaction/dry granulation is the standard industrial dry granulation technique. During roller compaction/dry granulation, a powder blend is fed into the gap between two counter rotating rolls. The rolls densify

the blend and more or less coherent ribbons result. These ribbons are then forced through a sieve of a defined mesh width by the granulator and the final granules are produced.

It was demonstrated by Zhao and Augsburger that precompression has only little influence on the intrinsic swelling of different disintegrants but that the disintegration times of sodium starch glycolate and crospovidone disintegrants increased [45]. The disintegration times of a croscarmellose disintegrant remained similar. Water uptake and water uptake rates of disintegrants were unaffected by the precompression step. They describe a dependency of disintegration time and disintegration time variation on the deployed disintegrant particle size. Smaller disintegrant particles led to lower variations and shorter disintegration times. However, the authors deviated from the usual techniques and procedure of dry granulation. Precompression was performed on a rotary tablet press whereas granulation was done with mortar and pestel until a fine powder was obtained. The results might not be directly transferable to other preparation techniques.

Other studies did not systematically investigate the impact of dry granulation on tablet disintegration. Because roller compaction/dry granulation is receiving more attention from the industry lately in the wake of continuous manufacturing initiatives, further studies should be conducted to examine what parameters influence disintegration to what extent.

1.2.2.4 Wet granulation

During wet granulation, liquid is added to an agitated powder blend until agglomerates of the desired particle size distribution (PSD) are acquired. After the target PSD is reached, granules are dried and tableted in the following. Wet granulation is usually performed in fluid bed granulators or high shear mixers[46]. Both techniques differ fundamentally from each other. In a fluid bed granulator, the powder is fluidized by air flowing through the particle bed. The binder liquid can be sprayed on the fluidized bed from different directions and angles. Granule growth is mostly due to adhesion of particles to the liquid droplets from the spraying nozzle. During the agglomeration process, drying continuously occurs because of the high amount of air necessary to fluidize the particles, whereas the main drying step takes place after spraying is stopped and the inlet air temperature is increased.

In a high shear mixer, the permanent movement of the powder particles is caused by a rapidly rotating impeller. The sprayed on liquid causes the formation of granule nuclei in the powder. The high shear forces of the process densify small granules and liquid is pressed out to the surface where more powder can adhere. Drying does not usually occur in the high shear mixer but in separate equipment.

Due to different applied temperatures, drying times and methods, energy input, and particle growth mechanisms, it is likely that depending on the granulation technique,

different tablet disintegration times and characteristics will result. However, conducted studies did not compare the influence of the manufacturing technique but generally focus on the mode of disintegrant incorporation, i.e. intra- and/or extragranularly. Besides, the results were not compared to direct compressed formulation. Hence, the studies discussed in the following can only be seen in the context of other examinations with a similar focus.

Shotton and Leonard manually wet granulated sulfadiazine with disintegrants[47]. They concluded that extragranular starch resulted in a quicker disintegration, as the starch was found to form a coherent hydrophilic network in the porous system of the tablet, which supposedly led to quicker water absorption and disintegration. With a custom built wet sieving apparatus they determined intragranular disintegrant incorporation to be more effective as smaller mean particle sizes resulted[17,47]. According to the authors, this is due to disintegration of the granules when disintegrant is incorporated, which does not occur when the disintegrant is only added externally.

Gould and Tan also produced tablets with intra- and extragranular disintegrant. They wet massed a powder blend of MCC, a soluble API, and (optionally) different disintegrants (croscarmellose sodium, crospovidone, and sodium starch glycolate) and prepared tablets at different compression forces from the resulting granules[48]. Parts of the tablets were milled, wet massed again and the obtained granules then tableted at different compression forces. If no disintegrant was added in the first granulation step, it was added during the second granulation step. The areas under the curves (AUCs) of disintegration time vs. compression pressure graphs were calculated for tablets wet massed once and tablets wet massed twice. The ratio of the AUCs was then defined as "rework efficiency". The disintegration times of all tablets increased after rework, however Explotab, a sodium starch glycolate, was affected least when incorporated extragranularly prior to compression, as it showed the highest "rework efficiency". This was explained with a size reduction of the disintegrant during the rework process and the sensitivity of the disintegrants to magnesium stearate. Whereas the size reduction of the disintegrant particles should affect all disintegrants equally, the lubricant sensitivity may play a more important role. Smallenbroek et al. argued that strongly swelling disintegrants are less sensitive towards lubrication (see section 1.2.1.1)[20], which could explain the better results of sodium starch glycolate. This is also supported by examinations of van Kamp et al. who measured the water uptake of disintegrant powders[23]. They found a much higher water absorption of sodium starch glycolate (2300 mg of water per 100 mg of disintegrant) compared to croscarmellose sodium (500 mg of water per 100 mg of disintegrant) and crospovidone (450 mg of water per 100 mg of disintegrant), which is an indicator for the swelling capacity of the substances. This shows that even after two wet granulation steps, disintegrants maintain properties that make one more preferable over others.

Contrary to the findings of Shotton and Leonard, Gould and Tan observed longer disintegration times when the disintegrant was added extragranularly. The reason for the different findings might be the use of other filler materials. Gould and Tan used a combination of a soluble API and MCC whereas Shotton and Leonard employed sulfadiazine. It can be assumed that the wicking capabilities of the base materials vary. It is known that MCC is a potent wicking agent[49], which can cause a rapid water penetration into the tablet matrix to the intragranular disintegrant. If the disintegrant had worse wicking abilities than MCC, it might slow down the water penetration when added extragranularly and thereby delay disintegration. This hypothesis would only be valid if sulfadiazine was less hydrophilic and wettable than the used disintegrant. Even though it was not examined in the present work, the observations hint towards the importance of the applied filler material (see section 1.2.1.3).

Gordon et al. measured the dissolution rates of p-aminobenzoic acid from wet granulated tablets containing intra- and extragranular disintegrants based on different filler materials[38]. Unfortunately, the disintegration times of tablets are not reported. The dissolution rates increased in the following order: no disintegrant < intragranular < intra- and extragranular < extragranular. This does not support the findings of Shotton and Leonard since higher dissolution rates are expected from smaller particles, i.e. intragranularly added disintegrant. It can only be hypothesized about the cause of the observed variations. An approach similar to the one mentioned in the section above, deviating wettability of the used base materials, could be possible.

1.2.2.5 Melt granulation

In melt granulation, the binder is not initially a fluid as in wet granulation, but a low melting solid[50]. After melting, the binder acts like a binding liquid and causes the agglomeration of the powder. Compared to wet granulation, usually less heat energy is required because the lengthy spraying and drying phases are not necessary. Additionally, no solvents are required to prepare the binder, which is frequently based on polyethylene glycols or waxes. Melt granulation can be performed via high shear mixing, fluidized bed granulation, and extrusion[51,52]. Perissutti et al. produced carbamazepine containing melt granules in a high shear mixer based on polyethylene glycol 4000[53]. The incorporation of crospovidone into the granules did not influence the dissolution rate but decreased the disintegration time below the limits of the European Pharmacopoeia. When crospovidone was added to the external phase, the disintegration time further decreased but the time point at which 90 % of the drug was released was not changed. Until now, no studies have been conducted to further investigate the impact of melt extrusion in general and different melt extrusion processes on the efficacy of different disintegrants.

1.2.3 Storage conditions

Parameters affecting the disintegrant as well as all other excipients are relative humidity and temperature, i.e. the storage conditions. Disintegrants are hydrophilic polymers and especially the modified natural ones contain extensive numbers of hydroxyl groups with hydrogen bonding capabilities.

Chowhan described increased disintegration times after storage at a relative humidity (rh) of 93 %[24]. Expansion or contraction of the incorporated starch grains was mentioned as possible reason for the findings. Ten years later, Gordon and Chowhan stored tablet formulations of various hygroscopicity and solubility at 30 °C for 14 months[54]. Relative humidity was not controlled during this period. Generally, dissolution was slightly improved by 8 % after storage, but the effect could not be ascribed to changes of the disintegrants. On the other hand, formulation hygroscopicity directly influenced the dissolution. The dissolution increase was less pronounced for hygroscopic formulations compared to non-hygroscopic formulations.

In another study, Gordon et al. examined the impact of elevated storage temperature and relative humidity[37]. Tablets with disintegrants were stored either at room temperature or at 37 °C and 80 % rh. Depending on both, type of filler/binder and disintegrant, the dissolution rate decreased after storage. At all storage conditions and time points, the highest amount of drug was released from croscarmellose sodium containing tablets. At the same time, croscarmellose sodium was also affected most at elevated conditions. Crospovidone and sodium starch glycolate released similar amounts of API and were affected less. Storage at room temperature for 8 months did not affect dissolution as much as storage at elevated conditions for 2 weeks. As shown by Gordon and Chowhan[54], storage at higher temperature for 14 months actually increased dissolution. In consequence, the relative humidity should be the dominating influence on disintegration.

Marais et al. stored tablets based on different fillers at the climatic conditions according to the four climatic zones defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[55]. She confirmed that storage at elevated rh decreases the disintegration times of tablets whereas higher temperatures hardly affect disintegration. A softening of the tablets was observed and interpreted as reason for the findings. When formulations contained > 2.5 % croscarmellose sodium, tablets disintegrated within 3 months in the storage cabinets at 60 % and 70 % rh.

These results can be explained with changes in the polymer structure during storage. Faroongsarng and Peck determined the glass transition temperatures (T_gs) of corn starch, croscarmellose sodium, and sodium starch glycolate before and after storage at elevated rh[26]. After 24 h exposure to 100 % rh, T_gs decreased by at least 25 °C for croscarmellose sodium and sodium starch glycolate and by 10 °C for corn starch. A

decrease of the T_g is accompanied with a higher molecular mobility also below the T_g. This should cause a slow release of the stored energy of the disintegrant particles, as the polymer chains slowly detangle during storage. In consequence, the amount of energy released during disintegration is decreased and the disintegration potentially delayed. It seems reasonable that these results can be extrapolated to other disintegrants but experimental data is lacking.

The results of Marshal, Chowhan, and Gordon et al., can be explained with changes of the T_g, but not the findings of Marais. It is possible that the matrices softened so much due to absorbed water that the cohesive force mostly vanished during storage, in this case. This could potentially cause decreased disintegration times.

1.3 Aims of the thesis

When reading these studies, one might get the impression that most of the mechanisms behind the parameters described in section 1.2 are not thoroughly understood, yet. The large number of applied excipients, the deviations in disintegrants or lubricant concentrations, the variety of investigation techniques – it appears that, until now, only few parts of a much larger puzzle have been found and that they could not even be placed in the right order. Most of the conducted studies are coherent and well executed, but the results can only rarely be connected to findings of other working groups.

The aim of this study was the establishment of new methods and the introduction of new classification systems for disintegrants based on the experimental data. The new methods should be able to acquire comprehensive data of the investigated systems to structure the findings. A model tablet system should be investigated and thoroughly understood.

In detail the aims were:

- To construct an apparatus capable of simultaneously measuring water uptake and force development of disintegrating tablets and to establish a measurement protocol for reproducible measurements.

- To investigate the influence of relative humidity during storage and relative tablet density depending on the applied disintegrant with the new apparatus. Additionally, a classification based on the water uptake properties should be introduced.

- To introduce a new measurement technique to visualize and quantitatively analyze rapidly disintegrating tablets to elucidate the mechanisms of actions and underlying processes.

- To implement an image analysis algorithm for the acquired real-time magnetic resonance imaging data capable of quantifying the surface roughness of the disintegrating tablets as surrogate for the available surface area during disintegration.

- To establish an apparatus based on a new measurement principle for the continuous measurement of the particle size distribution of disintegrating tablets and to classify disintegrants upon their abilities to decrease the particle size over time.

1.4 Outline of the thesis

Different aspects of the disintegration process have to be considered and investigated to improve the understanding of disintegration mechanisms and processes. It is not sufficient to describe a single aspect of tablet disintegration but necessary to create a comprehensive picture of the events.

In section 2, an apparatus capable of simultaneously measuring the water uptake and force development of a single tablet is introduced. The apparatus allows a detailed analysis of the interplay between these two factors. It will be shown that disintegrants acting by different mechanisms show distinct behaviors and the underlying processes are explained. By compressing tablets to different relative densities, it is demonstrated that different brands of polacrilin potassium act by different mechanisms.

The force development and water uptake studies are extended in section 3. The impact of the relative humidity during storage will be examined. Data of tablets containing a swelling and a shape memory polymer is obtained and thoroughly discussed. Based on the water uptake behavior of tablets, a classification system of disintegrants is introduced.

To gain further insights into tablet disintegration, high resolution, real-time magnetic resonance imaging (MRI) is introduced as analytical technique in section 4. MRI is able to visualize the inside of tablets during disintegration. The histograms of acquired images are analyzed and interpreted in terms of water uptake and distribution within the tablets.

The application of different disintegrants in a tablet may result in different dissolution profiles, likely due to diverse particle sizes generated during dissolution. An image analysis algorithm for the MRI data is therefore proposed in section 5 to quantify the

surface roughness of the disintegrating tablets as surrogate for the surface area during disintegration.

A new method to directly and continuously determine the particle size distribution of disintegrating tablets is presented in section 6. Investigations of tablets prepared with several disintegrants reveal their impact on the generated particle sizes. A new ranking system based on the efficacy of disintegrants is introduced.

In section 7 the work is summarized and a conclusion of all published papers is given.

1.5 Perspective of the own work

In order to introduce new or improved measurement principles and techniques, only direct compressed tablets based on DCP were manufactured for this work. None of the tablets contained an API, they consisted solely of DCP, disintegrant, and lubricant. The system was chosen because of its simplicity and because it has been extensively investigated in literature before. Accordingly, the feasibility of obtained results could be evaluated by comparison with published data. This is necessary as most of the applied techniques are new and no comparable approaches exist. This approach covers only a fraction of the parameters introduced in section 1.2 and it is likely, that some, if not most of the findings will be different when these parameters are taken into account. However, the newly introduced methods and principles can be applied to investigate and further understand these factors in the future in order to help the formulation scientist to choose the right disintegrant according to the requirements of the dosage form.

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2 Systematic classification of tablet disintegrants by water uptake and force development kinetics

2.1 Pretext

In literature, a measurement principle has been introduced, to simultaneously detect water uptake and force development during disintegration (see section 2.2). In the following work, an apparatus based on this principle is presented. The analysis of these factors and their interdependency is essential to understand the disintegration process as a whole.

Systematic classification of tablet disintegrants by water uptake and force development kinetics

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http://onlinelibrary.wiley.com/doi/10.1111/jphp.12276/abstract

3 Performance of tablet disintegrants: Impact of storage conditions and relative tablet density

3.1 Pretext

According to literature, the storage conditions greatly influence the disintegration ability of disintegrants (see section 1.2.3). Therefore, the apparatus described in section 2 is employed to quantify this influence. Is will also be investigated, whether the relative tablet density changes the disintegration behavior and if the acquired data allows mechanistic interpretations.

Performance of tablet disintegrants: impact of storage conditions and relative tablet density

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4 Tablet disintegration studied by high-resolution real-time MRI

4.1 Pretext

The data in sections 2 and 3 reflects only parts of the processes during disintegration. The apparatus does neither consider the expansion behavior of the tablets, nor the distribution of water in the tablets. Therefore, high resolution, real-time MRI is employed to visualize the events within the tablets during disintegration. The data is analyzed qualitatively as well as quantitatively in terms of image-wise histogram analysis. The influence of disintegrants, disintegrant concentration, and different relative densities is examined

Tablet Disintegration Studied by High-Resolution Real-Time Magnetic Resonance Imaging

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Article available online at:

http://onlinelibrary.wiley.com/doi/10.1002/jps.23789/abstract

5 Assessment of disintegrant efficacy with fractal dimensions from real-time MRI

5.1 Pretext

This study is based on the measurements in section 4. The concept of fractal dimension is used to describe the surface roughness of disintegrating tablets. The approach is based on the assumption that the surface roughness correlates with the available surface area during disintegration and, thus, also with dissolution rates.

No link to the online supplementary material can be provided as the work is currently in the submission status.

Assessment of disintegrant efficacy with fractal dimensions from real-time MRI

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6 A new apparatus for real-time assessment of the particle size distribution of disintegrating tablets

6.1 Pretext

The following work introduces a novel measurement principle and apparatus to continuously measure the particle size distribution of disintegrating tablets. Unlike the use of fractal dimensions described in section 5, it is a direct measurement of the particle size distribution. It is investigated according to which kinetic the generated particles further disintegrate and how different disintegrants influence the measurement.

A New Apparatus for Real-Time Assessment of the Particle Size Distribution of Disintegrating Tablets

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http://onlinelibrary.wiley.com/doi/10.1002/jps.24168/abstract

7 Summary and future outlook

The presented work greatly contributes to the understanding of the tablet disintegration process and the mechanisms of action of tablet disintegrants. A new apparatus based on a previously published measurement principle has been developed and improved to perform static measurements on disintegrating tablets. As tablet disintegration is an active process, which cannot be covered in entirety by measurements with the new apparatus, real-time MRI was employed for the first time and innovative methodologies based on these measurement were established. For dynamic inline particle size measurements, a second apparatus has been invented. The conducted experiments covered basic research topics, yet, also focused on application in pharmaceutical development. Based on the obtained data, two classification systems for tablet disintegrants could be introduced to structure the findings.

As first step, a new apparatus was developed based on a principle adapted from literature and introduced to analyze the water uptake and force development of disintegrating tablets. The obtained data allowed a detailed description of the interplay of the changes of water uptake and the resulting force development depending on the employed disintegrant and relative tablet density. Water uptake ratios of limited or unlimited water uptake allowed discrimination between swelling and shape recovery disintegrants. Tablets with swelling disintegrants absorbed at least 4 times as much water when the water uptake was not limited. Shape recovery disintegrants absorbed less than 2.5 times the amount of water. The data hinted towards two polacrilin potassium disintegrant brands acting via different mechanisms. One absorbed only 1.5 times as much water, indicating a shape recovery mechanism, whereas the other one absorbed 3 times the amount of water, which points towards a swelling mechanism. This was confirmed by compressing tablets with different compression forces. The swelling polacrilin potassium disintegrated within only 31.3 s at the lowest compression force, whereas the shape recover disintegrant did not disintegrate within 180 s but in 5.0 s, when the compression force was highest. This confirmed the results of the water uptake experiments, as shape recovery requires a minimum amount of energy input to be able to cause disintegration. Therefore, it seems feasible that depending on the polymer synthesis, different mechanisms of action can result for substances complying with the same pharmacopoeial monograph. This further demonstrates that the disintegration behavior of disintegrants directly depends on the employed disintegrant. By fitting the obtained data with a modified Hill equation, the disintegrants are classified according to the amount of absorbed water and velocity of water uptake. This classification can help formulation scientists to choose the correct disintegrant based on the requirements of the tablet. When only little liquid is available, e.g. in the oral cavity, disintegrants that absorb only little water should be chosen. Amberlite IRP88, a polacrilin potassium disintegrant, would

be the disintegrant of choice, as it absorbed only 252 mg of water, requiring as little as 32 s to absorb half of it. This is in contrast to an absorbed amount of 639 mg with a half-maximum value of 125 s by Primojel, a sodium starch glycolate. The other sodium starch glycolate, Explotab, performs only slightly better, requiring 79 s to absorb half of the maximum amount of 525 mg of water.

Analysis of tablets stored at different relative humidities reveal a large impact on water uptake and force development. The maximal produced forces by the disintegrating tablets decreased with increasing relative humidity, whereas especially in the case of sodium starch glycolates, the disintegrants that absorb the highest amount of water, the speed of the disintegration process is decreased at increased relative humidity (from 27.3 s at 0 % rh to 148.4 s at 80 % rh). Storage at a relative humidity between 40 % and 58 % was found to influence the disintegration process to the least extent.

The second step provided a new look on tablet disintegration by application of high resolution, real-time MRI. For the first time, the dynamic water uptake and disintegration of rapidly disintegrating tablets were visualized. Qualitative analysis of the videos clearly indicates a swelling mechanisms for sodium starch glycolate and croscarmellose sodium and a shape memory mechanism for crospovidone. The quantitative, image-wise analysis of the histograms demonstrates the capability of this technique to distinguish between tablets with different disintegrants and its sensitivity to investigate the influence of relative tablet density and disintegrant concentration. The innovative application of real-time MRI allows the analysis of different factors from a single experiment for which different experiments had to be performed before.

Within the third step, a new concept to quantify the efficacy of tablet disintegrants was introduced by means of fractal dimensions of obtained MRI data. The fractal dimensions, determined after surface geometry extraction according to a proposed algorithm, describe the roughness of the tablet surface. The available surface area during disintegration and, thereby, dissolution rate from the particles is expected to correlate with the surface roughness of the disintegrating tablets. The fractal dimensions of tablets containing croscarmellose sodium were only slightly influenced by relative tablet density and remained around 1.45. However, increasing amounts of polacrilin potassium strongly increased the detected absolute fractal dimension of the disintegrating tablet and the velocity at which the maximum is reached. When 0.5 % of polacrilin potassium were employed, reaching the maximum fractal dimension of 1.4 lasted 11 s, when 4 % were added, reaching 1.5 lasted only 3.5 s. Only small differences, mainly concerning the rate at which the fractal dimensions change, are found between tablets containing different disintegrants. Analog to the water uptake measurements, sodium starch glycolate disintegrants act much slower (> 22 s to maximum fractal dimension) compared to polacrilin potassium disintegrants (2.6 s

and 11.6 s to maximum fractal dimension), crospovidone (4.1 s to maximum fractal dimension), and croscarmellose sodium (6.6 s to maximum fractal dimension).

The fourth step resolves the formerly unsanswered question of particle size distribution during disintegration. The data obtained from dynamic inline measurements can be applied to rationally select disintegrants in pharmaceutical development. To directly determine the particle size distribution of tablets during disintegration, a new measurement principle and apparatus were invented. The developed apparatus enables the continuous inline measurement of the particle sizes and their change rate. Comparative measurements with dynamic image analysis reveal strong alterations of the particle sizes by the employed impeller pump. This alteration is minimized by separating the commonly integrated propelling / measurement ciruit into two separate circuits. Thereby, the passage of particles through the pump is prevented and in consequence a greater number of larger particles as well as lower particle size change rates are detected throughout the measurement. The detected particle sizes during disintegration but also the change rate of the particle size greatly depend on the incorporated disintegrant. The sodium starch glycolate disintegrants performed worst, generating particles sizes > 460 µm after 280 s with half-lifes of 57.9 s and 104.7 s. Crospovidone showed the best results in term of final particle size (Kollidon CL-SF: $x_{50} = 178$ µm) and in terms of half-life (Polypasldone XL-10: $t_{1/2} = 16.8$ s). These results are contrary to the analysis of the MRI data with fractal dimensions, where only little differences between disintegrants are found. The discrepancy is most likely due to the negligible energy input during disintegration of the MRI measurements. In the newly constructed particle size analyzer, the particles are actively dispersed by the movement of the medium, whereas the tablet rests passively in the MRI reaction cavity. Future investigations are required to asses which measurement technique, MRI in conjunction with fractal dimensions or the direct determination of the PSD, complies better with dissolution data.

The particle size data allowed the definition of disintegrant efficiency (the half-life of particle size) and effectiveness (the final generated particle size). The product of efficiency and effectiveness is defined as *e value* and represents a simple measure to classify disintegrants. The disintegrant with the lowest e value of 3.9 and therefore the one with the best efficacy in the investigated forumlation is Polyplasdone XL-10, followed by Kollidon CL-SF with an e value of 5.5, whereas Polyplasdone XL and Primojel have the lowest efficacy (e values of 44.7 and 49.2). The e value will likely depend on the main tablet component and can therfore be used to select the best disintegrant for a given matrix substance, once more experiments are conducted. When superior disintegration performance is required, for example when a poorly soluble API is incorporated, the e value facilitates the selection of the right disintegrants.

The newly introduced techniques either facilitate data acqusition or permit the determination of completely new data, which allows a detailed analysis of the disintegration process. In future, the newly introduced methods can be applied to systematically improve the understanding of disintegration and interactions of influencing factors.

8 Zusammenfassung und Ausblick

Ziel der Arbeit waren neue Erkenntnisse zum Verständnis des Tablettenzerfalls und der grundlegenden Mechanismen verschiedener Zerfallhilfsmittel. Auf Grundlage eines veröffentlichten Messprinzips wurde eine Apparatur für statische Messungen zerfallender Tabletten konstruiert und verbessert. Diese Messungen können die aktive Natur des Tablettenzerfalls jedoch nicht vollständig abbilden. Daher wurde erstmalig zeitlich hochaufgelöste Magnetresonanztomographie (Echtzeit-MRT) zur Bildgebung eingesetzt. Zur Auswertung der gewonnen Bildinformationen wurden neue Methodiken entwickelt. Zudem wurde eine weitere Apparatur entwickelt, mit dem Ziel, die Partikelgröße zerfallender Tabletten kontinuierlich zu bestimmen. Bei den durchgeführten Experimenten handelt es sich in erster Linie um Grundlagenforschung, jedoch immer auch mit Fokus auf die Anwendbarkeit der gewonnenen Erkenntnisse für die pharmazeutische Entwicklung. Des Weiteren wurden zwei Klassifizierungssysteme für Zerfallhilfsmittel, basierend auf den Ergebnissen dieser Arbeit, eingeführt.

In einem ersten Schritt wurde, begründet auf einem publizierten Messprinzip, eine neue Messapparatur entwickelt, die simultan die Wasseraufnahme und die Kraftentwicklung zerfallender Tabletten erfassen kann. Die so gewonnenen Daten ermöglichen eine detaillierte Beschreibung der Wechselwirkungen zwischen Wasseraufnahme und Kraftentwicklung in Abhängigkeit vom verwendeten Zerfallhilfsmittel und der relativen Tablettendichte. Die Verhältnisse von unbegrenzter und begrenzter Wasseraufnahme der Tabletten erlauben die Unterscheidung zwischen quellenden Zerfallhilfsmitteln und solchen, die mittels eines Formgedächtniseffektes wirken. Tabletten mit quellenden Zerfallhilfsmitteln absorbierten mindestens die vierfache Menge, wenn die Wasseraufnahme nicht begrenzt wurde. Zerfallhilfsmittel mit Formgedächtniseffekt hingegen nahmen weniger als die zweieinhalbfache Wassermenge auf. Die Daten deuteten darauf hin, dass die Wirkung von zwei verschiedenen Polacrilin-Kalium-Zerfallhilfsmitteln auf unterschiedlichen Mechanismen beruht. Eines absorbierte weniger als eineinhalbmal so viel Wasser, wenn die Wasseraufnahme nicht begrenzt wurde, was einen Formgedächtniseffekt vermuten lässt. Das andere absorbierte mehr als dreimal so viel Wasser, was auf einen Quellungsmechanismus hindeuten könnte. Diese Vermutungen konnten bestätigt werden, indem Tabletten mit unterschiedlichen Tablettierkräften hergestellt wurden. Tabletten der geringsten Tablettierkraft, welche das quellende Polacrilin-Kalium enthielten, zerfielen innerhalb von 31,1 s. Tabletten mit dem durch einen Formgedächtniseffekt wirkenden Polacrilin-Kalium zerfielen allerdings nicht innerhalb von 180 s, wenn sie mit der geringsten Tablettierkraft hergestellt wurden. Bei Verwendung der höchsten Tablettierkraft wurde ein Zerfall innerhalb von 5.0 s erreicht. Dies untermauert die Ergebnisse der Wasseraufnahmeuntersuchungen, da Formgedächtniszerfallhilfsmittel eine gewisse Minimalkraft während des

Pressvorganges benötigen, um ausreichend Energie für den Tablettenzerfall zu speichern. Es scheint folglich plausibel, dass Zerfallhilfsmittel, die der gleichen Arzneibuchmonographie angehören, je nach Synthese unterschiedliche Zerfallsmechanismen aufweisen können. Darüber hinaus zeigt diese Entdeckung, dass das Zerfallsverhalten direkt vom verwendeten Zerfallhilfsmittel abhängt.

Die Modellierung der Wasseraufnahmedaten mit einer modifizierten Hill-Gleichung erlaubte die Klassifizierung der Zerfallhilfsmittel nach Wasseraufnahmemenge und Wasseraufnahmegeschwindigkeit. Das kann Formulierungsentwicklern bei der Wahl des bestmöglichen Zerfallhilfsmittels, je nach Anwendungszweck, helfen. Sollte nur wenig Wasser für den Zerfall zur Verfügung stehen, wie z.B. in der Mundhöhle, sollte ein Zerfallhilfsmittel gewählt werden, welches nur eine geringe Wassermenge benötigt, um seine Wirkung zu entfalten. In diesem Fall wäre Amberlite IRP88, ein Polacrilin-Kalium-Zerfallhilfsmittel, die Substanz der Wahl. Es benötigte im untersuchten Fall nur 252 mg Wasser, um den Zerfall herbeizuführen, und nahm die Hälfte dieser Wassermenge in nur 32 s auf. Im Gegensatz dazu steht Primojel, ein Natriumstärkeglykolat, welches 132 s benötigte um die Hälfte der maximalen Wassermenge von 639 mg aufzunehmen. Explotab, das andere untersuchte Natriumstärkeglykolat, war nur geringfügig besser, da es 79 s benötigte um die Hälfte von 525 mg Wasser zu absorbieren.

Bei weiteren Untersuchungen wurde gezeigt, dass unterschiedliche relative Lagerungsluftfeuchten einen großen Einfluss auf die Kraftentwicklung und Wasseraufnahme haben. Die maximal durch die Zerfallhilfsmittel erzeugten Kräfte nahmen mit steigender relativer Luftfeuchte ab. Insbesondere die Zerfallszeiten der beiden Natriumstärkeglykolate, der beiden Zerfallhilfsmittel, die am meisten Wasser absorbierten, wurden durch hohe Luftfeuchten beeinflusst (die Zerfallszeiten stiegen von 27.3 s bei 0 % relativer Feuchte auf 148.4 s bei 80 % relativer Feuchte). Abschließend konnte gezeigt werden, dass relative Lagerungsluftfeuchten zwischen 40 % und 58 % den Zerfallsprozess am geringsten beeinflussten.

Die Anwendung hochaufgelöster Echtzeit-MRT erlaubte im zweiten Schritt eine neue Sichtweise auf den Tablettenzerfall. Zum ersten Mal wurden die im Tabletteninneren ablaufenden Prozesse während des Auseinanderbrechens schnell zerfallender Tabletten visualisiert. Die qualitative Analyse der Bilder erlaubt eine klare Unterscheidung zwischen einem Quellungsmechanismus für Natriumstärkeglykolat und Croscarmellose-Natrium und einem Formgedächtnismechanismus für Crospovidon. Die quantitative Auswertung aller Bildhistogramme beweist die Fähigkeit der Methode, Aussagen über die grundlegenden Prozesse während des Zerfalls zu treffen. Die Methode ist sensitiv genug, um den Einfluss der relativen Tablettendichte, aber auch unterschiedlicher Zerfallhilfsmittelmengen zu untersuchen. Mittels Echtzeit-MRT können Daten in nur einem Experiment erhoben

werden, für die bisher eine Vielzahl verschiedener Experimente durchgeführt werden mussten.

Der dritte Beitrag der Arbeit ist das Konzept, die Wirksamkeit von Zerfallhilfsmitteln mit Hilfe der fraktalen Dimensionen der Tablettenoberflächen aus den Echtzeit-MRT Experimenten zu beurteilen. Fraktale Dimensionen beschreiben in diesem Fall die Rauigkeit der Tablettenoberflächen. Die grundlegende Vermutung ist, dass die während des Zerfalls zur Verfügung stehende Oberfläche, und damit auch die Freisetzungsrate, von der Rauigkeit der Tabletten abhängt. Die fraktale Dimension Croscarmellose-Natriumhaltiger Tabletten wurde nur minimal durch die relative Tablettendichte beeinflusst und schwankte um 1,45. Ein zunehmender Gehalt an Polacrilin-Kalium führte allerdings zu einer deutlichen Steigerung der fraktalen Dimension und der Geschwindigkeit, mit der diese ihren Maximalwert erreichte. Bei einer Konzentration von 0,5 % Polacrilin-Kalium wurde die maximale fraktale Dimension von 1,4 innerhalb von 11 s erreicht. Wurden 4 % Zerfallhilfsmittel verwendet, genügten 3,5 s um die fraktale Dimension von 1.5 zu erreichen. Die fraktalen Dimensionen von Tabletten die verschiedene Zerfallhilfsmittel beinhalteten, unterschieden sich nur unwesentlich. Die Zeiten, in denen die maximalen fraktalen Dimensionen erreicht wurden, waren jedoch verschieden. Analog zu den Messungen der Wasseraufnahme benötigten die Natriumstärkeglykolate die längste Zeit (> 22 s), verglichen zu den Polacrilin-Kalium-Zerfallhilfsmitteln (2,6 s und 11,6 s), Crospovidon (4,1 s) und Croscarmellose-Natrium (6,6 s).

Im vierten Schritt konnte die Frage nach der Partikelgrößenverteilung zerfallender Tabletten beantwortet werden. Die Erkenntnisse aus den durchgeführten Inline-Messungen können für die rationale Auswahl des passenden Zerfallhilfsmittels in der pharmazeutischen Entwicklung verwendet werden. Um die Partikelgrößenverteilung und deren Änderungsrate direkt und kontinuierlich zu erfassen, wurden ein neues Messprinzip und eine dazugehörige Apparatur entwickelt. Bei Vergleichsmessungen mit dynamischer Bilderanalyse wurde gezeigt, dass sich die Größe der Tablettenpartikel beim Durchgang durch die Antriebspumpe stark verändert. Diese Änderung konnte bei der neuen Apparatur minimiert werden, indem der gewöhnliche, kombinierte Antriebs- und Messkreislauf in zwei separate Kreisläufe getrennt wurde. In der neuen Apparatur müssen die Tablettenpartikel nicht die Pumpe passieren, um in Bewegung gehalten zu werden. So wird mit der neuen Apparatur, im Vergleich zur dynamischen Bildanalyse, eine größere Anzahl großer Partikel gemessen, wobei die Partikelgrößenänderungsrate deutlich langsamer ist. Zudem konnte gezeigt werden, dass diese beiden Parameter in hohem Maße von den verwendeten Zerfallhilfsmitteln abhängen. Die Natriumstärkeglykolate schnitten erneut am schlechtesten ab, da sie die Partikelgrößen im besten Fall lediglich auf 460 μm reduzierten und Halbwertszeiten von 57,9 s und 104,7 s aufwiesen. Crospovidon zeigte sowohl bei der generierten Partikelgröße die besten Ergebnisse (Kollidon CL-SF: $x_{50} = 178$ μm), als auch bei der Halbwertszeit (Polyplasdone XL-10: $t_{1/2} = 16,8$ s). Die gefundenen

Unterschiede widersprechen den Ergebnissen der Berechnungen der fraktalen Dimensionen aus den MRT-Daten, bei denen nur marginale Diskrepanzen zwischen den Zerfallhilfsmitteln gefunden wurden. Diese Ungleichheiten sind vermutlich in den unterschiedlichen Messbedingungen begründet. Während bei den Echtzeit-MRT-Messungen nur minimale Wasserbewegungen auftreten, werden die Partikel in der neuentwickelten Apparatur durch die Hydrodynamik aktiv dispergiert. Zukünftige Untersuchungen müssen klären, welche der beiden Messmethoden, MRT mit Berechnung der fraktalen Dimensionen oder die direkte Bestimmung der Partikelgrößenverteilung, Ergebnisse generiert, die am ehesten mit Freisetzungsdaten korrelieren.

Auf Grundlage der gewonnenen Erkenntnisse konnten die Begriffe der Effektivität und Effizienz auf Tablettenzerfallhilfsmittel übertragen werden. In diesem Fall steht die Effektivität für die generierte Partikelgröße am Ende einer Messung und die Effizienz für die Halbwertszeit der Partikelgrößenreduktion. Zum Klassifizieren von Zerfallhilfsmitteln wurde das Produkt und Effektivität und Effizienz, der sogenannte *e-Wert*, eingeführt. Das Zerfallhilfsmittel mit dem geringsten e-Wert von 3,9, und damit mit der höchsten Wirksamkeit, ist Polyplasdone XL-10, gefolgt von Kollidon CL-SF mit einem e-Wert von 5,5. Polyplasdone XL und Primojel haben insgesamt die höchsten e-Werte und damit die geringste Wirksamkeit (44,7 und 49,2). Der e-Wert hängt aller Wahrscheinlichkeit nach von den jeweils verwendeten Tablettenkomponenten ab und kann deswegen verwendet werden, um das beste Zerfallhilfsmittel für eine bestimmte Tablettenmatrix zu wählen. Voraussetzung dafür ist eine größere Anzahl Messungen verschieden zusammengesetzter Tabletten mit der neuen Apparatur. Wenn die bestmögliche Zerfallsleistung nötig ist, z.B. im Falle von schwerlöslichen Arzneistoffen, kann der e-Wert als Entscheidungsgrundlage herangezogen werden.

Die neu entwickelten Methoden vereinfachen die Datenerhebung entweder stark oder ermöglichen die Erhebung völlig neuer Daten. Dies erlaubt eine detaillierte Analyse des Tablettenzerfallsprozesses. Diese Methoden können künftig dafür verwendet werden, das Verständnis um Zerfallhilfsmittel, die grundlegenden Prozesse und um die Wechselwirkungen verschiedener Einflussfaktoren systematisch zu erweitern.

9 List of original publications

1. Julian Quodbach, Peter Kleinebudde
   Systematic classification of tablet disintegrants by water uptake and force
   development kinetics
   J Pharm Pharmacol 66 (2014) 1429-1438

2. Julian Quodbach, Peter Kleinebudde
   Performance of tablet disintegrants: Impact of storage conditions and relative
   tablet density
   Pharm Dev Technol (2014) in press, DOI: 10.3109/10837450.2014.920357

3. Julian Quodbach, Amir Moussavi, Roland Tammer, Jens Frahm, Peter
   Kleinebudde
   Tablet disintegration studied by high-resolution real-time magnetic resonance
   imaging
   J Pharm Sci 103 (2014) 249-255

4. Julian Quodbach, Amir Moussavi, Roland Tammer, Jens Frahm, Peter
   Kleinebudde
   Assessment of disintegrant efficacy with fractal dimensions from real-time
   MRI
   Int J Pharm 475 (2014) 605-612

5. Julian Quodbach, Peter Kleinebudde
   A New Apparatus for Real-Time Assessment of the Particle Size Distribution
   of Disintegrating Tablets
   J Pharm Sci (2014) 3657-3665

6. Julian Quodbach, Johanna Mosig, Peter Kleinebudde
   Compaction behavior of isomalt after roll compaction
   Pharmaceutics (2012) 494-500, DOI: 10.3390/pharmaceutics4040494

10 Contributions to meetings

10.1 Oral presentations

1. Julian Quodbach, Peter Kleinebudde
   Novel approaches towards understanding disintegration – invesitgation of
   superdisintegrants
   6th Annual PSSRC Symposium, Lisbon, Portugal, 28.08.2012

2. Julian Quodbach, Peter Kleinebudde
   Tablet disintegration – water uptake rate and force development
   PARTEC 2013, Nürnberg, 24.04.2013

3. Julian Quodbach, Amir Moussavi, Roland Tammer, Jens Frahm, Peter
   Kleinebudde
   Beurteilung von Tablettensprengmitteln mittels Echtzeit-MRT und fraktaler
   Dimensionen
   *Jahrestreffen ProcessNet-Fachgruppe Agglomerations- und Schüttguttechnik,
   Magdeburg, 11.03.2014*

4. Julian Quodbach, Peter Kleinebudde
   The particle size progression of disintegrating tablets
   *6th International Congress on Pharmaceutical Engineering, Graz, Österreich,
   17.06.2014*

10.2 Poster presentations

1. Julian Quodbach, Peter Kleinebudde
   Impact of the porous network on the disintegration behavior of tablets
   containing super disintegrants
   *8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical
   Technology, Istanbul, Türkei, 21.03.2012*

2. Julian Quodbach, Peter Kleinebudde
Design of an apparatus to measure the disintegration force and water uptake of tablets
DPhG Jahrestagung, Greifswald, 11.10.2012

3. Amir Moussavi, Julian Quodbach, Jens Frahm, Roland Tammer
Real-time MRI of tablet disintegration: Visualization and quantification
21ˢᵗ ISMRM Meeting & Exhibition, Salt Lake City, UT, USA, 20.-26.04.2013

4. Julian Quodbach, Amir Moussavi, Roland Tammer, Jens Frahm, Peter Kleinebudde
Fractal dimensions of disintegrating tablets derived from real-time MRI
AAPS Annual Meeting and Exposition, San Antonio, TX, USA, 13.09.2013

5. Julian Quodbach, Amir Moussavi, Roland Tammer, Jens Frahm, Peter Kleinebudde
Quantifying Tablet Disintegration with High-Resolution Real-Time MRI
9ᵗʰ World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lissabon, Protugal, 03.04.2014

6. Josefine Pott, Olivia Polinard, Julian Quodbach, Elena Reitz, Markus Thommes
Residence time evaluation in hot melt extrusion using image analysis
9ᵗʰ World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lissabon, Protugal, 02.04.2014

7. Julian Quodbach, Peter Kleinebudde
The particle sizes progression of disintegrating tablets containing superdisintegrants
AAPS Annual Meeting and Exposition, San Diego, CA, USA (submitted)

11 Appendix

11.1 MATLAB code for MRI histogram analysis (section 4)

Parts of the code are based on proprietary code of the Biomedizinische NMR Forschungs GmbH at the Max-Planck-Institut für biophysikalische Chemie in Goettingen, Germany.

```matlab
clc
clear
close all

%% User Inputs

StudyCode = 'fs5';

recnum = [1];

PhanNum = 599;

tic

for i = 1:1

AcqNum  = recnum(i);

%% Read Data

Data = PrepareData(PhanNum,StudyCode,AcqNum);

OrigData = Data;

%% Norm Data

Data = NormData(Data);

%% Mask Data

Data = MaskData(Data);

%% Surface Coil Correction

Data = SurfCoilCorr2(Data);

%% Make Histogram

 HistData = HistAnal_try(Data);
 GFHistData = GaussFilter(HistData);
 surf (GFHistData)

% select the last 20 Frames
```

```matlab
% AnalData = mean(GFHistData(:,end-20:end)');                    %%
mean of either gauss filtered data or only normal histdat

for j = 1:size(GFHistData, 2);

AnalData = GFHistData(:,j)';

%% find Waterpeak and Tabletpeak
[Peak PeakPos] = findpeaks(AnalData,'minpeakdistance',50,
'minpeakheight', 150, 'npeaks', 2);
%% der abstand zwischen den peaks muss mindestens 50 sein

TabletPeakValue = Peak(1);

TabletPeakPos = PeakPos(1);

if numel(Peak)== 2

WaterPeakValue = Peak(2);

WaterPeakPos = PeakPos(2);

[Mini MiniPos] = min(AnalData(TabletPeakPos:WaterPeakPos));

MiniPos = MiniPos + TabletPeakPos -1;

PeakHeightMin(AcqNum) = AnalData(MiniPos);

else
end


PeakPos1 (AcqNum) = PeakPos(1);

if numel (Peak) == 2

PeakPos2 (AcqNum) = PeakPos(2);

PeakMax2(AcqNum) = AnalData(PeakPos(2));

PeakData (5,j) = AnalData(PeakPos(2));
%Height of Peak 2

PeakData (6,j) = PeakPos(2);
%Position of Peak 2

PeakData (1,j) = AnalData(MiniPos);
%Height of Minimum

PeakData (2,j) = MiniPos;
%Position of Minimum

else
end

if PeakPos(1) <= 40
%if peak position below 40 units, write 0

PeakData (4,j) = PeakPos(1);
%Position of Peak 1
else
    PeakData (4,j) = 0;
```

```matlab
end


PeakMax1(AcqNum) = AnalData(PeakPos(1));

if PeakPos (1) <= 40                                    %if peak
position below 40 units, write a peak height of 0
PeakData (3,j) = AnalData(PeakPos(1));                  %Height of Peak
1
else
    PeakData (3,j) = 0;
end


PeakDataFin = PeakData';

PeakDataMA = NaN(size (PeakDataFin,1), size (PeakDataFin,2));
%create matrix to write

%apply moving average with 9 av. points
for k = 1:size (PeakDataFin,2)
PeakDataMA (:,k) = smooth (PeakDataFin (:,k),'moving',9);
end

xlswrite ('Kollidon CL_6.xls', PeakDataMA);
%write xls-file

end
PixelNo = length(nonzeros(Data(:,:,1)))
toc
```

11.2 MATLAB code for image processing (section 5)

Copyright for the box counting code belongs to Frederic Moisy and can be found at: http://www.mathworks.com/matlabcentral/fileexchange/13063-boxcount/content/boxcount/html/demo.html

```matlab
clear
clc
tic
jpegFiles = dir('*.jpg');
%select jpgs from current folder

Blank = imread('Explotab_1 001.jpg');
%load img which will be subtracted from background

White = 255*ones(320,320,3);
%create matrix with maximum intensity
white_uint8 = uint8(white);
%convert into uint8

Negative = white_uint8-blank;
%create negative of blank to subtract from background

numfiles = length(jpegFiles);
%sets numfiles equals the number of jpgs

mydata = cell(1, numfiles);
%creates cell array

white_2 = ones(320,320);
%build matrix to create negative images of binaries

Se = strel('square',3);
%structuring element for erosion

se2 = strel('square',6);
% '' for dilation

for k = 1:numfiles;
  mydata{1,k} = imread(jpegFiles(k).name);
%load all jpgs into the cell arry

  mydata_crop{1,k} = imcrop(mydata{1,k},[78 65 185 110]);
%crop original image


  cleaned{1,k} = mydata{1,k}+negative;
%subtract blank image (why do I actualy create a negative? Doesn't make
sense)

  cleaned_crop{1,k} = imcrop (cleaned{1,k},[78 65 185 110]);
%crop greyscale image

  gray_level{1,k} = graythresh(cleaned{1,k});
%calculates thresholds for each image with the Otsu method

  bin{1,k} = im2bw(cleaned{1,k},gray_level{1,k});
%create binary image w/ gray_level
```

```matlab
  bin_single{1,k} = single(bin{1,k});
%convert matrices in cell to single

  bin_negative{1,k} = white_2-bin{1,k};
%erosion&dilation consider black background, white foreground; inversed
images are created

  bin_er{1,k} = imerode(bin_negative{1,k},se);                    %erosion

  bin_er_dil{1,k} = imdilate(bin_er{1,k},se2);                    %dilation

  bin_clean{1,k} = bin_negative{1,k}.*bin_er_dil{1,k};
%multiplication of matrices to obtain surface information ob original
image

  bin_clean_crop{1,k} = imcrop(bin_clean{1,k},[78 65 185 110]);
%crop binarised image

  bin_edge{1,k} = edge(bin_clean{1,k});
%detect edges of tablets

  bin_edge_si{1,k} = single(bin_edge{1,k});

  bin_edge_crop{1,k} = imcrop(bin_edge{1,k},[78 65 185 110]);
%crops images

  bin_edge_crop_si{1,k} = single(bin_edge_crop{1,k});

  bin_edge_crop_lo{1,k} = logical(bin_edge_crop{1,k});

  [n r s] = boxcount(bin_edge_crop_lo{1,k},'slope');

  frac2(:,k) = log(n);

  frac3 (:,k)= log(r);

  p (k,:) = polyfit(frac3(2:8,k),frac2(2:8,k),1);
%calculate linear (1st order polynomal) fit of N and R, w/out boxes of
size 1 and 256

  ppos = -1 * p;
for i=1:numfiles
  plot(log(frac3(:,i)),log(frac2(:,i)));

  plot(frac3(:,i),frac2(:,i))

  p (i,:) = polyfit(frac3(:,i),frac2(:,i),1);

  ylim([0 9])

  xlim([0 10000])

  title(i)

  pause(0.075)
end

tab_edge = VideoWriter('tab_edge.avi');

tab_edge.FrameRate = 13;

open (tab_edge)
```

```matlab
for k = 1:numfiles;

    writeVideo(tab_edge,bin_edge_crop_si{1,k});
end
close (tab_edge);
```

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