Tablet Disintegration Performance: Effect of Compression Pressure and Storage Conditions on Surface Liquid Absorption and Swelling Kinetics

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Abstract

The disintegration process of pharmaceutical tablets is a crucial step in the oral delivery of a drug. Tablet disintegration does not only refer to the break up of the interparticle bonds, but also relates to the liquid absorption and swelling behaviour of the tablet. This study demonstrates the use of the sessile drop method coupled with image processing and models to analyse the surface liquid absorption and swelling kinetics of four filler combinations (microcrystalline cellulose (MCC)/mannitol, MCC/lactose, MCC/dibasic calcium phosphate anhydrous (DCPA) and DCPA/lactose) with croscarmellose sodium as a disintegrant. Changes in the disintegration performance of these formulations were analysed by quantifying the effect of compression pressure and storage condition on characteristic liquid absorption and swelling parameters. The results indicate that the disintegration performance of the MCC/mannitol and MCC/lactose formulations are driven by the liquid absorption behaviour. For the MCC/DCPA formulation, both liquid absorption and swelling characteristics affect the disintegration time, whereas DCPA/lactose tablets is primarily controlled by swelling characteristics of the various excipients. The approach discussed in this study enables a rapid (< 1 min) assessment of characteristic properties that are related to tablet disintegration to inform the design of the formulation, process settings and storage conditions.

Keywords: disintegration, tablet, stability, liquid absorption, swelling

1. Introduction

Tablet disintegration is an essential, and in many cases a performance-controlling, process for immediate release formulations. The disintegration process typically consists of several interconnected mechanisms: liquid uptake, swelling (uni- and omni-directional), dissolution of excipient particles and the break-up of interparticle bonds (Quodbach and Kleinebudde, 2015a; Desai et al., 2016; Markl and Zeitler, 2017). Each of these disintegration mechanisms is influenced by the raw material properties (e.g. particle size, surface energy, swelling ability), formulation (e.g. disintegrant concentration, choice of binder) as well as the selected manufacturing route (e.g. direction compression, granulation) and process conditions (e.g. compression pressure, liquid/binder ratio). Understanding the relationship between these factors and the tablet performance in terms of its disintegration and dissolution behaviour is crucial for

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selecting a robust formulation, design space and control strategy. For example, a disintegration process which is primarily influenced by its liquid uptake rate is highly sensitive to changes in tablet porosity (e.g. a MCC/lactose-based formulation) (Maclean et al., 2020), which should thus be tightly controlled during manufacturing.

To develop a deeper understanding of tablet disintegration, new methods in addition to the traditional disintegration testing are required. Several research groups have developed new approaches to quantify the fundamental disintegration mechanisms using high-speed imaging (Berardi et al., 2018; Basaleh et al., 2020), terahertz pulsed imaging (Markl et al., 2018, 2017; Al-Sharabi et al., 2020), magnetic resonance imaging (Quodbach et al., 2014a,b; Dvořák et al., 2020; Catellani et al., 1989), and water uptake and (swelling) force measurements (Caramella et al., 1986; Peppas and Colombo, 1989; Tomas et al., 2018). The liquid uptake and wettability of powder and pharmaceutical compacts were also investigated using the sessile drop method, where several groups observed a correlation between the wettability characteristics and the disintegration/dissolution performance of tablets for a range of different formulations (Yang et al., 2016, 2018; Liu et al., 2018; Yang et al., 2019).

These studies focused on the investigation of the disintegration behaviour of a tablet after compaction and to date, only a few studies have assessed the impact of storage conditions on the disintegration behaviour. The effect of each disintegration mechanism on the overall performance may evolve during storage due to changes in microstructure (e.g. particle swelling affecting wettability and swelling) and surface characteristics (e.g. surface energy affecting wettability and particle dissolution). Both physical and chemical stability can be assessed using an accelerated stability assessment protocol (ASAP) approach, although it is currently more commonly applied for chemical stability analysis (Waterman, 2011). This assessment approach uses five to eight storage conditions that combine temperatures in the range of 25–80°C with relative humidities (RH) in the range of 10–75% and samples are stored for up to 8 weeks (Scrivens et al., 2018; Scrivens, 2019).

Rudnic et al. (1979) studied the change of disintegration time as a function of storage time and conditions, i.e. varying the storage temperature and relative humidty. The results indicated a shortening of the disintegration time for lactose formulations across all studied conditions (25°C/45% RH, 35°C/60% RH, 45°C/75% RH). The same behaviour was also observed for the dibasic calcium phosphate formulations except for the 25°C/45% RH condition, where the disintegration time increased after storage. Chowhan (1980) also observed an increase in disintegration time when dibasic calcium phosphate dihydrate-based tablets were stored in a high humidity (93% RH) environment. Marshall et al. (1991) studied the change in water uptake and swelling force of tablets with different disintegrants when stored for 1 year at elevated temperatures and relative humidities. The authors highlighted that the results indicated a lag time before a swelling force was generated, which was attributed to the time it takes the liquid to be absorbed by the compact. Quodbach and Kleinebudde (2015b) investigated the effect of relative humidity on the liquid uptake, swelling force, and disintegration time for various disintegrants in a dibasic calcium phosphate-based formulation. They observed the strongest impact of the change in RH on the disintegration time for sodium starch glycolate tablets, which is attributed to decreased water uptake and force development kinetics. Scrivens (2019) showed a slowdown of the drug release from tablets stored at elevated temperates and relative humidities and they were able to model this using a modified Arrhenius equation. Tsunematsu et al. (2020) successfully used the available surface area of tablets stored at varying temperatures and 75% RH for 2, 4 and 8 weeks to predict the long-term change of the drug release. Both Scrivens (2019) and Tsunematsu et al. (2020) highlighted that the changes on the release kinetics are caused by physical rather than chemical processes. These studies indicate that the extent of the effect of the storage condition and whether it causes an acceleration or slowing down of the disintegration and dissolution process highly depends on the used formulation, manufacturing settings, storage condition and storage time.

This study demonstrates a method based on the

sessile drop technique to rapidly quantify surface liquid absorption and swelling kinetics. The reproducibility of this method is discussed for four formulations compacted at a low and high pressure. This technique is then used to identify the performance-controlling mechanisms (liquid absorption or swelling) of the four formulations stored at five different conditions (relative humidity and temperature).

2. Materials and Methods

2.1. Materials

Four fillers were used for the tablet formulations: microcrystalline cellulose (MCC) (Avicel®PH-102, FMC International), spray-dried mannitol (Pearlitol®200 SD, Roquette), spray-dried lactose monohydrate (FastFlo®316, Foremost Farms USA) and dibasic calcium phosphate anhydrous (DCPA) (Anhydrous Emcompress®, JRS Pharma). Croscarmellose sodium (CCS) (FMC International) and magnesium stearate (Mallinckrodt) were used as a disintegrant and a lubricant, respectively. True density, particle size and shape values for all excipients are summarised in Section S1 and Table S1 in the Supporting Information. Dynamic vapour sorption isotherms and single particle dissolution rates (mannitol and lactose only) can also be found in Maclean et al. (2020).

2.2. Formulations and Tableting

The impact of the formulation on the surface absorption and swelling kinetics were investigated for four filler combinations (47% w/w each): MCC/mannitol, MCC/lactose, MCC/DCPA, DCPA/lactose. These fillers were mixed with CCS (5% w/w) for 20 min in a blender (Pharmatech AB-015, Pharmatech, Warwickshire, UK) with a blend speed of 20 rpm and an agitator speed of 200 rpm. The lubricant (magnesium stearate, 1% w/w) was added and further blended for 5 min. The selected excipients and the respective concentrations result in common formulations selected for immediate release tablets within the industry (Reynolds et al., 2017), where the addition of an API would primarily impact the filler concentrations.

The blend was then compacted to round flat-faced tablets with a diameter of 9 mm using a single punch automated tablet press (FlexiTab, Bosch Packaging Technology Ltd, Merseyside, UK). The weight was kept constant at 350 mg and a tensile strength of >2.5 MPa was targeted. The difference in tensile strength between the various formulations is attributed to the different fundamental compression behaviours of MCC compared to lactose and DCPA. MCC is a soft and ductile material that undergoes plastic deformation under pressure, whereas lactose and DCPA are both brittle materials (Reynolds et al., 2017). The formulation with these two brittle fillers thus resulted in a tensile strength <2.5 MPa even though the compression pressure was increased significantly. The compression pressures used are shown in Table 1 for each formulation. More details about the tensile strength and the porosity measurements can be found in Maclean et al. (2020).

2.3. Accelerated Stability Testing

Accelerated stability testing was performed for the four formulations compacted at high pressure (Table 1). Table 2 lists the storage conditions and time points used in this study. Five storage conditions have been chosen to align closely with a more traditional ASAP protocol (Waterman et al., 2007; Waterman, 2011; Scrivens et al., 2018) while taking into consideration the equipment available to generate elevated temperatures. The temperature and humidity ranged from 37 – 70°C and 30 – 75% RH, respectively. Tablets were stored in airtight glass jars with an open vial of saturated salt solution using magnesium (approximately 30% RH) or sodium chloride (approximately 75% RH). The relative humidity of a saturated salt solution changes with temperature (Greenspan, 1977) and therefore the %RH were not constant for the three different temperature settings. The jars were then stored within ovens to control the temperature. Prior to testing, jars were opened to equilibrate to ambient temperature and humidity for three days. Testing was performed for samples stored for 2 and 4 weeks.

Table 1: Compression pressure, tensile strength and porosity listed for the four formulations. In the following the two different compression settings are referred to as the low pressure and high pressure studies.

	Low pressure			High pressure		
	Compression pressure (MPa)	Tensile strength (MPa)	Porosity (%)	Compression pressure (MPa)	Tensile strength (MPa)	Porosity (%)
MCC/mannitol	126	2.9 ± 0.1	15.6 ± 0.2	157	3.4 ± 0.0	13.1 ± 0,3
MCC/lactose	126	2.9 ± 0.1	15.9 ± 0.3	157	3.6 ± 0.1	14.0 ± 0,2
MCC/DCPA	126	2.9 ± 0.0	26.6 ± 0.2	157	3.8 ± 0.2	24.6 ± 0,4
DCPA/lactose	189	2.3 ± 0.1	22.8 ± 0.3	252	3.0 ± 0.1	20.3 ± 0.3

Table 2: Accelerated stability storage conditions.

Temperature (°C)	Humidity (%RH)	Timepoints (weeks)
∼	∼	0 (initial)
37	30	2, 4
37	75	2, 4
50	75	2, 4
70	30	2, 4
70	75	2, 4

2.4. Disintegration Testing

A Copley DTG 2000 Disintegration Tester (Copley Scientific Ltd, Nottingham, UK) was used to determine the disintegration time in 800 mL of distilled water at 37°C. The disintegration time was measured for six tablets per formulation.

2.5. Sessile Drop Technique

Sessile drop images were recorded at a rate of 30 frames per second using Krüss DSA30 drop shape analyser (Krüss GmbH, Hamburg, Germany). A single droplet of MilliQ® Ultra-pure water was dispensed on to the surface of the tablet. The recorded video was analysed using MATLAB (R2019a, MathWorks, Massachusetts, USA) and the steps involved in the data processing are outlined in Figure 1. The primary task of the image processing was to separate the droplet and swelling material (both highlighted in blue in Figure 3) from the tablet in each frame, which is described in detail in Section S2 and Figure S1 in the Supporting Information.

Characteristic parameters of the liquid absorption and swelling profiles are determined from the measured surface area, $S(t)$, of the identified droplet as a function of time. The liquid absorption ratio, $y(t)$, is determined by

$$y(t) = \frac{S(t) - S(0)}{S(0)}. \tag{1}$$

$y(t)$ is an estimate of the liquid absorbed by the tablet relative to the initial droplet size, $S(0)$, at $t = 0$. A power law is then used to extract characteristic parameters about the liquid absorption as a function of time:

$$y(t) = kt^m. \tag{2}$$

with k and m as two fitting parameters.

A modified version of the Schott model (Schott, 1992) was deployed to extract characteristic parameters about the surface swelling. The Schott model describes first-order swelling kinetics in terms of the weight ratio of the absorbed liquid to the sample. The swelling, $s(t)$, as a function of time in this study is described as an absolute change in the measured surface area, S:

$$s(t) = S\left(t - t_{s,0}\right) - S\left(t_{s,0}\right) \tag{3}$$

with $t_{s,0}$ as the time when the swelling was clearly observed. Figure 2 depicts an example of the measured surface area indicating three different phases, i.e. a liquid absorption, a transition and a swelling phase. The initiation of the swelling phase was identified and recorded as $t_{s,0}$. $t_{s,0}$ was defined as the time

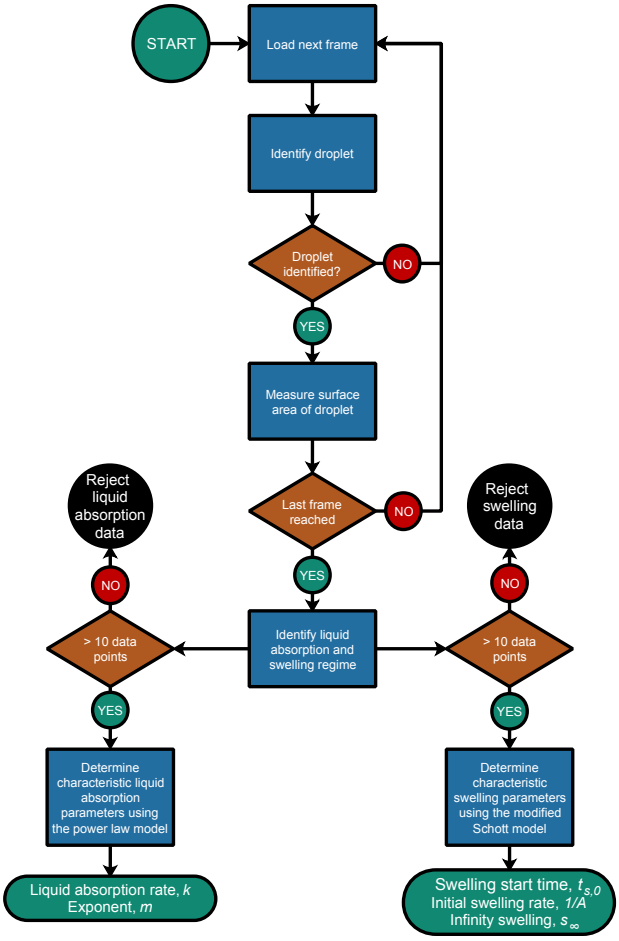

Figure 1: Data analysis workflow outlining the image processing, extraction of the liquid absorption and swelling profiles and the determination of the characteristic parameters using Eqs. 2 and 4.

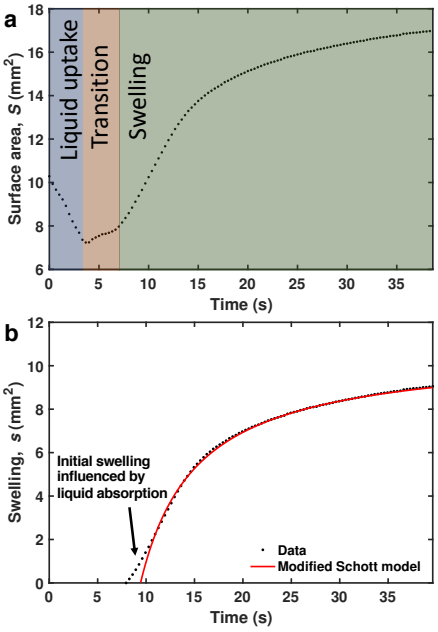

Figure 2: Example data of the a) surface area, S, and the b) swelling profile, s, as a function of time determined from the sessile drop images. a) indicates the three phases observed in the images: liquid absorption, transition, swelling. b) highlights the initial swelling that is influenced by the droplet. The modified Schott model was fitted to the swelling data excluding the initial swelling phase. For clarity, only every 10th data point is displayed.

at the point of inflection $\left(\frac{d^2S(t)}{dt^2} \approx 0\right)$, where $S(t)$ undergoes a steep positive rise $\left(\frac{dS(t)}{dt} > 0\right)$ afterwards. $t_{s,0}$ was verified manually for each measurement and corrected in case it was wrongly selected in the transition phase (due to high variations of $S(t)$ in the transition phase).

Figure 2b also shows that the initial swelling does not follow the Schott model. This is attributed to the fact that the initial swelling is non-uniform and influenced by the liquid absorption, i.e. the swelling at the centre of the droplet was delayed compared to the outward region of the droplet. Consequently, uniform swelling was delayed by a certain time, t_r, in the majority of cases. After t_r, the swelling can be well described by the Schott model:

$$s(t) = \frac{t - t_r}{A + \frac{t - t_r}{s_\infty}}. \tag{4}$$

t_r was determined by finding the time delay that minimises the root mean squared error (RMSE) between the fitted model and the data. This was implemented by varying t_r from 0 to 75% of the total swelling time and identifying the t_r that resulted in the smallest RMSE between the model and the data for all cases tested. The fitting parameters A and s_∞ represent the reciprocal of the initial swelling rate and

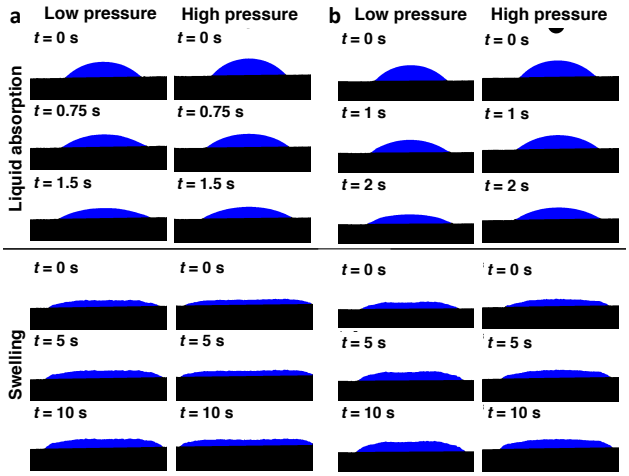

Figure 3: Sessile drop images of the a) MCC/Mannitol and b) MCC/DCPA formulations as a function of time. The low and high compression pressures are given in Table 1 for each formulation. The blue area indicates the droplet and the swelling material. The time for the swelling is given as the time starting after the transition phase (see Figure 2).

the swelling at infinite time, respectively:

$$\begin{aligned} \lim_{s(t)\to 0} &= \frac{1}{A}, \\ \lim_{s(t)\to \infty} &= s_\infty. \end{aligned} \tag{5}$$

Four repeats were conducted for the samples used to study the effect of compression pressure and the initial time point for the stability testing. Two repeats were performed for samples stored for 2 and 4 weeks.

3. Results

3.1. Effect of Compression Pressure

This initial study discusses the effect of the compression pressure on the surface liquid absorption and swelling kinetics determined by the sessile drop method. Sessile drop images were recorded continuously and the droplet was identified in each image (Figures 3 and S2 in the Supporting Information). The change in liquid absorption and swelling behaviour is not clearly visible in the images, but it becomes apparent in the extracted profiles (Figure 4) when applying the data analysis procedure as outlined in Figure 1. The liquid absorption profiles highlight that a lower pressure accelerated the absorption process. This is attributed to the fact that a lower compression pressure yields tablets with a higher porosity. The porosity directly impacts the wettability and hence the liquid absorption rate, where typically an increase in porosity results in a shorter disintegration time (Yassin et al., 2015; Markl et al., 2017; Al-Sharabi et al., 2020). The fastest liquid absorption was observed for the low pressure MCC/DCPA formulation (higher porosity), whereas the high pressure MCC/lactose formulation showed the slowest liquid absorption behaviour. The liquid absorption behaviour of the formulations containing MCC, DCPA and lactose is primarily driven by the surface energy of the excipients and the pore structure of the compact. The mannitol based formulation is also influenced by the rapid dissolution of the mannitol that increases the available pore space and hence accelerates the liquid absorption process (Maclean et al., 2020).

The characteristic parameters indicate that the liquid absorption changes are primarily reflected by the parameter k (Figure 5), which is related to the slope of the profile. The liquid absorption rate (k) increased with decreasing pressure for all formulations. The parameter m is close to 1 for the low pressure formulations, which indicates that the absorbed liquid increases linearly with time. In case of MCC/mannitol, MCC/lactose and DCPA/lactose, m decreases and is < 1 (positive curvature in profile) for tablets compacted at a higher pressure. On the contrary, m increased for MCC/DCPA, which can also be observed in the negative curvature of the swelling profile in Figure 4. Besides wettability, the liquid absorption process is also influenced by the swelling of the particles (Markl et al., 2017). The enlargement of the particles that swell causes a decrease in the pore space, which affects the liquid absorption process and in turn causes changes in k and m.

The liquid absorption process ends within a few seconds, whereas the swelling process continues for > 30 s (Figure 4). In the case of MCC/DCPA, the material rapidly reaches its maximum swelling capac-

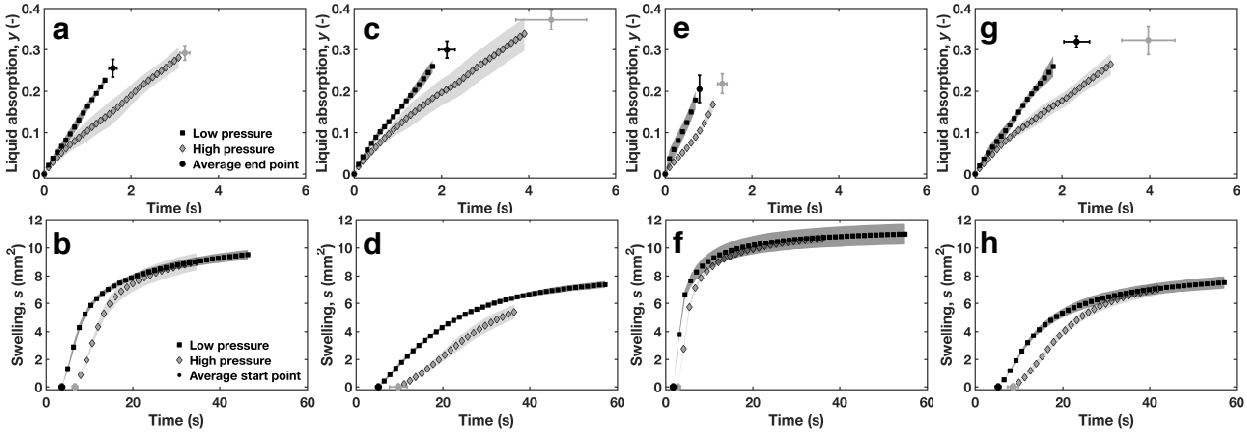

Figure 4: Liquid absorption and swelling as a function of time for (a,b) MCC/mannitol, (c,d) MCC/lactose, (e,f) MCC/DCPA, and (g,h) DCPA/lactose formulations. The top row (a,c,e,g) shows the liquid absorption profiles and the bottom row (b,d,f,h) displays the swelling profiles. The solid line indicates the average profile and the shaded area represents the standard deviation of four measurements. The solid line and shaded area ends at the shortest individual profile of the respective batch. The average end point for the liquid absorptions and the average start point for the swelling, $t_{s,0}$, are indicated by a marker (filled circle). Time $t = 0$ is the start of the sessile drop measurement (start of liquid absorption). The compression pressures used for each formulation are given in Table 1. For the sake of clarity, only every 3rd and 40th data point are shown in (a,c,e,g) and (b,d,f,h), respectively.

ity, whereas the other formulations require significantly longer with the lactose-based tablets having the slowest swelling behaviour.

The swelling behaviour differs between the four formulations and is driven by the swelling capacity of the individual components. There are only two components used in the studied formulations which swell when they come into contact with liquid: MCC and CCS (Soundaranathan et al., 2020). The swelling observed on the tablet surface is a superposition of the swelling of individual particles and the swelling of particles is only initiated once they are wetted. The swelling process therefore strongly depends on the liquid absorption kinetics. The fastest swelling ($1/A$ in Figure 5) was observed for the MCC/DCPA formulation, which also has the highest liquid absorption rate (k in Figure 5). The combination of high liquid absorption rate, i.e. large number of particles are wetted within a short period of time, and the high swelling capacity of this formulation (MCC and CCS are swelling) makes this formulation the fastest disintegrating tablets as indicated by the shortest disintegration time (Figure 6). The swelling is also impacted by the pore space as particles in the compact will partially swell into the pore space, which will not be observed as swelling on the tablet surface. Therefore, even though the three MCC-based formulations all have the same swelling components (MCC and CCS), the observed swelling is impacted by the liquid absorption process and pore space which varies for each formulation.

The compression pressure has only a marginal effect on the starting point of the swelling ($t_{s,0}$) of all formulations, but it does affect the profiles of the swelling. Even though the liquid absorption rate increased for the low pressure MCC/mannitol formulation relative to the high compression pressure compact, the initial swelling rate ($1/A$) decreased significantly. This is also the driving factor in increasing the disintegration time (Figure 6) for the low pressure tablets of this formulation. This is primarily attributed to a decrease in pore space in the lower pressure compacts, where the swelling of particles is more rapidly observed on the tablet surface due to the limited swelling of these particles into the pore space. On the contrary, an increase in $1/A$ could be

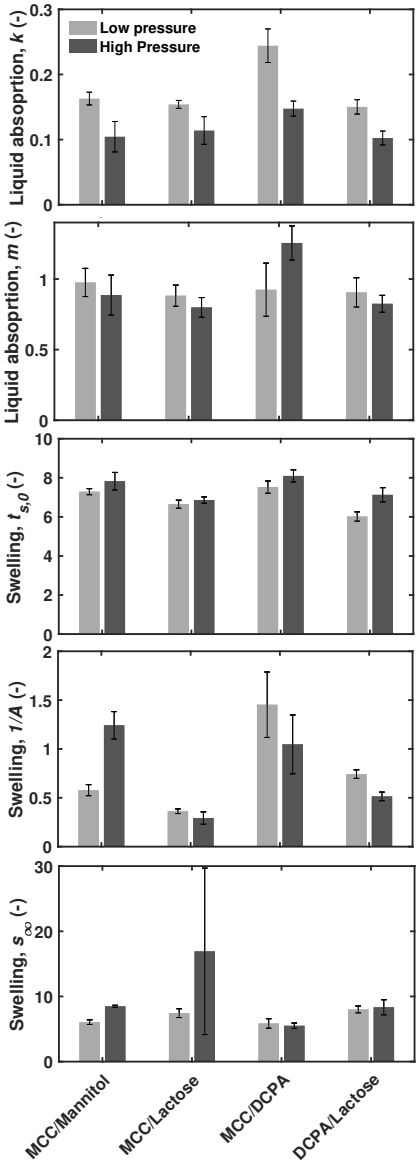

Figure 5: Characteristic parameters of the liquid absorption and swelling profiles extracted from the profiles shown in Figure 4 using Eqs. 2 and 4, respectively. The standard deviation is calculated from four repeats.

observed for the other three low pressure formulations. A change in the maximum swelling (s_∞) was observed for MCC/lactose. This, however, did not impact the disintegration time as this formulation is controlled by the liquid absorption process (Maclean et al., 2020). The disintegration performance of such a formulation is mainly influenced by changes that affect the liquid absorption (e.g. porosity) rather than the swelling process.

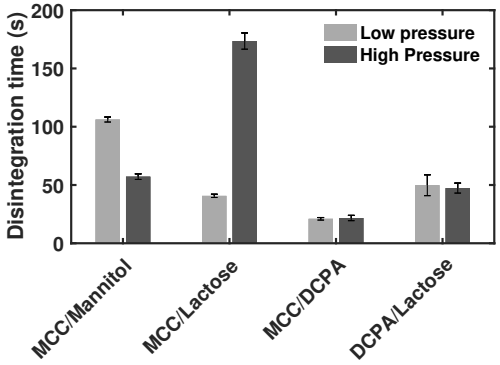

Figure 6: Disintegration time for the different formulations. More details about this data can be found in Maclean et al. (2020).

The low standard deviation in Figure 4 (shaded area) indicates a high consistency between the samples and an excellent reproducibility of the sessile drop measurements including the data analysis. The extraction of the characteristic parameters is also very reproducible for all parameters except s_∞, which strongly depends on whether the sessile drop measurement captured the swelling plateau. For some samples (e.g. MCC/lactose) the changes observed in the sessile drop images were minimal and therefore the measurement was stopped. This particularly effected the high pressure MCC/lactose samples, which is also reflected in its large error bar of s_∞. The accuracy of s_∞ can be improved by extending the measurement time.

3.2. Effect of Stability Testing

The effect of accelerated stability testing on the liquid absorption and swelling kinetics was studied for five storage conditions, two time points and four formulations.

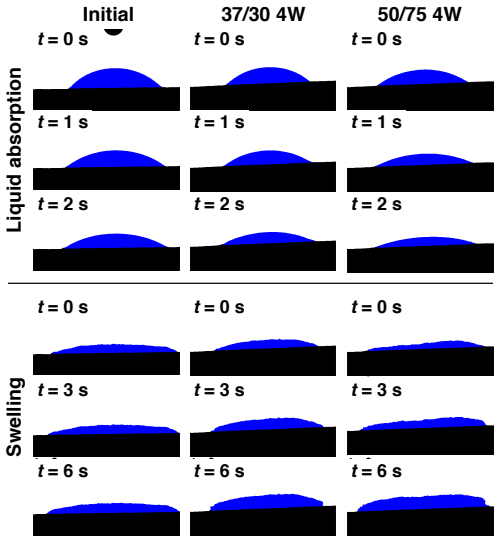

Figure 7: Sessile drop images of the DCPA/lactose tablets after compaction and after storage at 37°C/30%RH and 50°C/75%RH for 4 weeks.

3.2.1. Sessile drop measurements

Tablets were analysed using the sessile drop method after storing them at the given condition for 2 and 4 weeks. A change in both liquid absorption and swelling behaviour can be observed from the sessile drop images (Figure 7 and S3 – S5 in the supporting information). The position of the tablet and the droplet in the image changed for some of the samples, which is attributed to a small change in the sessile drop setup between measurements and a change in thickness of the samples. A change of the sample thickness is attributed to elastic relaxation of the tablet as well as swelling of particles initiated by the moisture taken up during storage. These changes, however, did not influence the extracted profiles and characteristics parameters.

The extracted profiles (Figure 8 and S6 – S8 in the Supporting Information) reveal a considerable effect of the storage conditions on the liquid absorption and swelling behaviour. Swelling could not be observed for several extreme storage conditions, i.e. storage at high temperature/high relative humidity (e.g. 50°C/75% RH and 70°C/75% RH in Figure 8b and d). This also depended on the time point as exemplified for the MCC/lactose formulation in Figure 8: swelling could be observed for the 50°C/75% RH at the 2 weeks time point (Figure 8b), but it could not be detected after a storage time of 4 weeks (Figure 8d). The characteristic liquid absorption and swelling parameters were extracted from each profile using the power law (Eq. 2) and modified Schott model (Eq. 4). The model and the experimental data are in excellent agreement as shown for several examples in Figure S9 in the Supporting Information.

3.2.2. Correlation with storage conditions

The effect of the storage condition on the liquid absorption and swelling behaviour was studied by determining the Pearson correlation coefficient (Figure 9). This coefficient indicates whether a characteristic parameter is negatively or positively correlated with the temperature or the relative humidity. The correlation coefficient in Figure 9 is only shown for cases where the correlation is considered significant.

MCC/mannitol, MCC/lactose and DCPA/lactose formulations are strongly impacted by the storage temperature (Figure 9a), whereas the MCC/DCPA formulation is primarily influenced by the relative humidity (Figure 9b). A strong negative correlation was observed between the temperature and the liquid absorption characteristics of the MCC/mannitol and MCC/lactose formulations. This means that the higher the temperature, the slower the liquid is absorbed by the tablet. This also results in a lag time of $t_{s,0}$ in the case of MCC/lactose as suggested by a strong positive correlation coefficient with temperature. In general, a slowing down of the liquid absorption process (negative correlation coefficient) delays the start of the swelling (positive correlation coefficient).

The liquid absorption characteristic k is positively correlated with the relative humidity for the MCC/DCPA tablets. An increasing relative humidity thus resulted in an acceleration of the liquid absorption process. This faster liquid absorption then caused an earlier start of the swelling, i.e. decrease of $t_{s,0}$ as shown by the negative correlation coefficient in Figure 9b. The correlation coefficients in

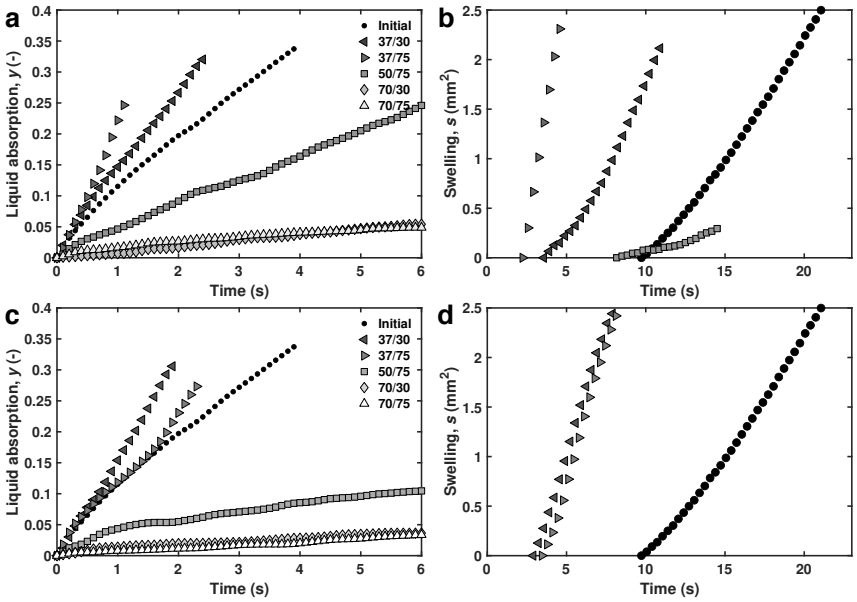

Figure 8: Liquid absorption and swelling profiles for the MCC/lactose formulation. (a,b) and (c,d) show the profiles of the tablets stored for 2 and 4 weeks, respectively. $t = 0$ is the same for the liquid absorption and swelling profile. Each swelling profile starts at $t_{s,0}$, which differs for each formulation. Some tablets did not show any swelling. Each profile is the average of 2 – 4 measurements. For the sake of clarity, only every 2nd and 5th data point are shown in (a,c) and (b,d), respectively.

Figure 9 also suggest that the swelling characteristics ($1/A$ and s_∞) are only influenced by the temperature for the DCPA/lactose formulation.

3.3. Temporal change of liquid absorption and swelling

The temporal change of two characteristic liquid absorption and swelling parameters was analysed by calculating the percentage change of the characteristic parameter at 2 and 4 weeks in relation to the initial (time point 0) value (Figure 10). Overall, the liquid absorption characteristic k is particularly influenced in the first two weeks, whereas the swelling behaviour also changes from 2 to 4 weeks. In the majority of cases of the DCPA-based formulations, the liquid absorption and swelling characteristics undergo a significant change in the first 2 weeks of the testing and only a minimal change in the following two weeks. In case of MCC/mannitol, the swelling is more significantly impacted by the storage condition than the liquid absorption and the swelling parameter A also changes considerably from 2 to 4 weeks. The temperature has a strong negative influence on the liquid absorption (smaller k value results in slower liquid absorption) in the first two weeks of the storage testing.

3.3.1. Correlation with disintegration time

The effect of storage conditions on the liquid absorption and swelling characteristics also impacts the overall disintegration time. In the following this is discussed on the basis of the correlation coefficient between the disintegration time and the characteristic parameters of the liquid absorption and swelling kinetics (Figure 11). A significant negative correlation is observed for MCC/mannitol and MCC/lactose with the exponent m from the power law (Eq. 2). This indicates that a decrease in m results in an increase of the disintegration time, i.e. the smaller m, the faster the initial liquid absorption.

The disintegration performance of MCC/DCPA is impacted by both the liquid absorption and the

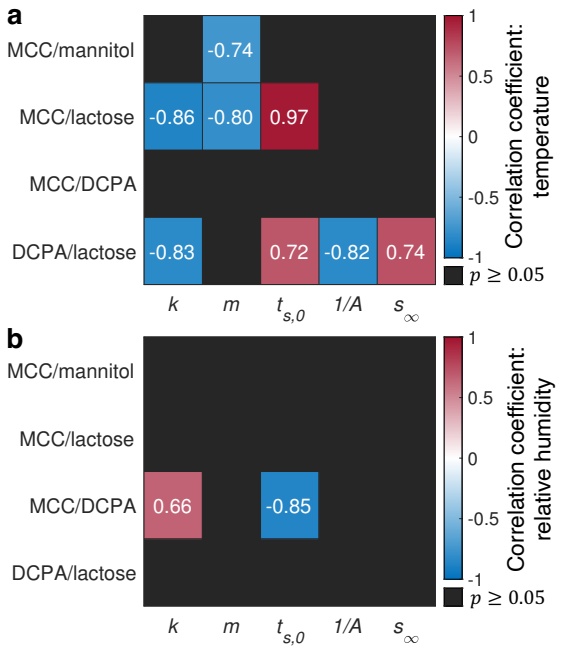

Figure 9: Pearson correlation coefficient between the storage conditions and the characteristic parameters of the liquid absorption (k, m) and swelling ($t_{s,0}$, $1/A$, s_∞). a) Correlation with temperature. b) Correlation with the relative humidity (RH). This correlation coefficient is calculated for a data set that includes the 2 weeks and 4 weeks time points but not the initial (0 weeks) tablets. Results are only shown for $p < 0.05$ indicating that the correlation is considered significant.

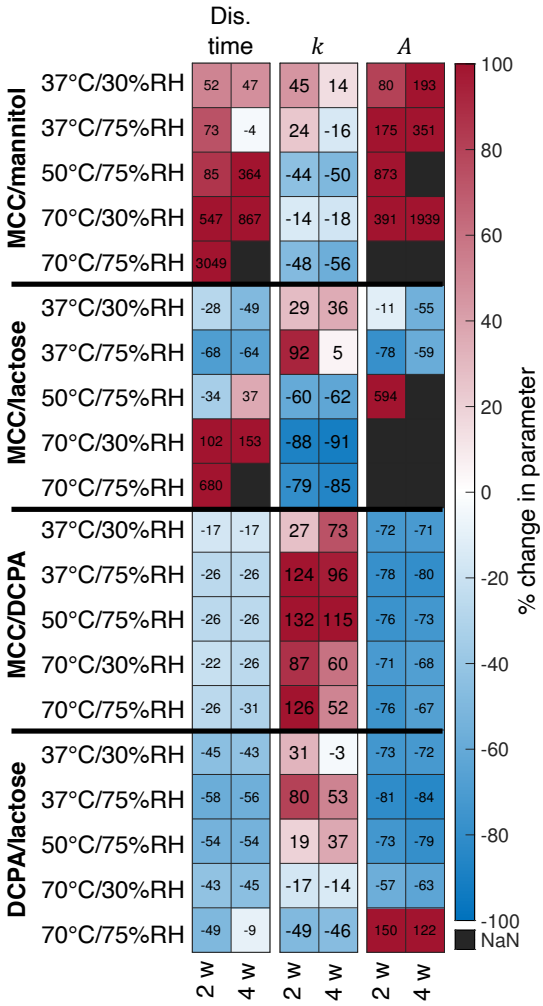

Figure 10: Percentage change of the disintegration time (dis. time), a liquid absorption parameter (k) and a swelling parameter (A) for each storage condition, formulation and the two time points (2 and 4 weeks). The percentage change was calculated for each value at 2 and 4 weeks in relation to the respective parameter at time point 0 (initial). A negative value indicates a decrease of the parameter at the specified time point with respect to time point 0, whereas a positive value reflects an increase of that parameter. NaN denote cases in which the tablet did not disintegrate (in case of the disintegration time) or no swelling was observed (in case of A).

swelling behaviour. The results also show that m is in the case of MCC/DCPA positively correlated with the disintegration time, which is in contrast to the negative correlation for the other MCC-based formulations (Figure 11). The disintegration performance of DCPA/lactose is primarily impacted by the swelling characteristics ($1/A$). This is also in line with the observations made in Maclean et al. (2020), where the DCPA/lactose formulations were classified as swelling-controlled.

The start of the swelling is positively correlated with the disintegration time for all formulations, which means that the shorter the lag time $t_{s,0}$, the faster the tablet disintegrates. $t_{s,0}$ is strongly influenced by the liquid absorption process (as discussed above), but it also depends on the swelling ability of the specific formulation.

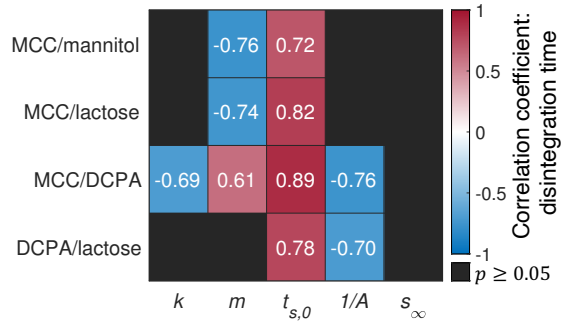

Figure 11: Pearson correlation coefficient between the disintegration time and the characteristic parameters of the liquid absorption (k, m) and swelling ($t_{s,0}$, $1/A$, s_∞). This correlation coefficient is calculated for a data set that includes the initial (0 weeks) as well as the 2 weeks and 4 weeks time points. Results are only shown for $p < 0.05$ indicating that the correlation is considered significant.

4. Discussion

It has been demonstrated in the literature that changes in the liquid absorption and swelling directly impact the dissolution performance (Al-Sharabi et al., 2020). The liquid absorption and swelling are fundamental disintegration mechanisms that link the raw material properties and process settings to the dissolution performance. Having a deep understanding about these fundamental mechanisms is thus needed to inform formulation and process development.

The liquid absorption and swelling results enable the assessment of changes of these processes in response to variations in the formulation, process setting and storage condition. The absolute liquid absorption and swelling values extracted from this technique cannot be directly compared to other methods such as water uptake and swelling force measurements, terahertz pulsed imaging or magnetic resonance imaging. This is primarily due to the fact that the sessile drop method evaluates only one single droplet instead of exposing the entire tablet to the liquid as it is the case for the other techniques. However, general conclusions such as identifying the formulation with the fastest liquid absorption (MCC/DCPA) or slowest swelling rate (MCC/lactose) are comparable to other methods. Since minor changes in the formulation and process conditions can have a considerable impact on the liquid absorption and swelling behaviour, comparisons of the results from this study with the literature should be done with caution.

Liquid absorption parameters are mainly linked to surface energy and true density of each component and the porosity of the compact. The swelling characteristics are primarily influenced by the swelling ability of the individual components but also by the pore structure (see explanation in Section 3.1). These links can facilitate the formulation and process design. The proposed method has the potential to play a key part in identifying the performance-controlling mechanism (liquid absorption vs swelling) and inform the process and formulation development (Figure 12). For example, the disintegration time of a liquid absorption-controlled formulation can be optimised (accelerated) by increasing the tablet porosity through decreasing the compression pressure of the tablet press. This will effectively increase k as is observed when comparing the high and low pressure formulations of MCC/lactose (k in Figure 5). A higher k reflects a faster liquid absorption process that causes an earlier start of the swelling and leads to a shorter disintegration time. A swelling-controlled formulation may require an increase in the quantity of swellable material, e.g. the MCC/DCPA formulation has MCC as an additional swellable material compared to the DCPA/lactose formulation. This additional swellable material increases the $1/A$ value (MCC/DCPA vs DCPA/lactose in Figure 5) and thus shortens the disintegration time (MCC/DCPA vs MCC/lactose in Figure 6).

The choice of accelerated storage conditions should ensure sufficient independent variation of temperature and relative humidity to build up a design space, which is essential to generate a robust modelling plane. This choice of conditions and also time points can be informed by liquid absorption and swelling characteristics (Figures 9–11). For MCC/mannitol, MCC/lactose and DCPA/lactose the results indicate that it is more important to vary the temperature, whereas for MCC/DCPA variations in the relative humidity affect the characteristic parameters (Figure 9). In terms of time points, it is clear from Figure 10 that considerable variations occur in the

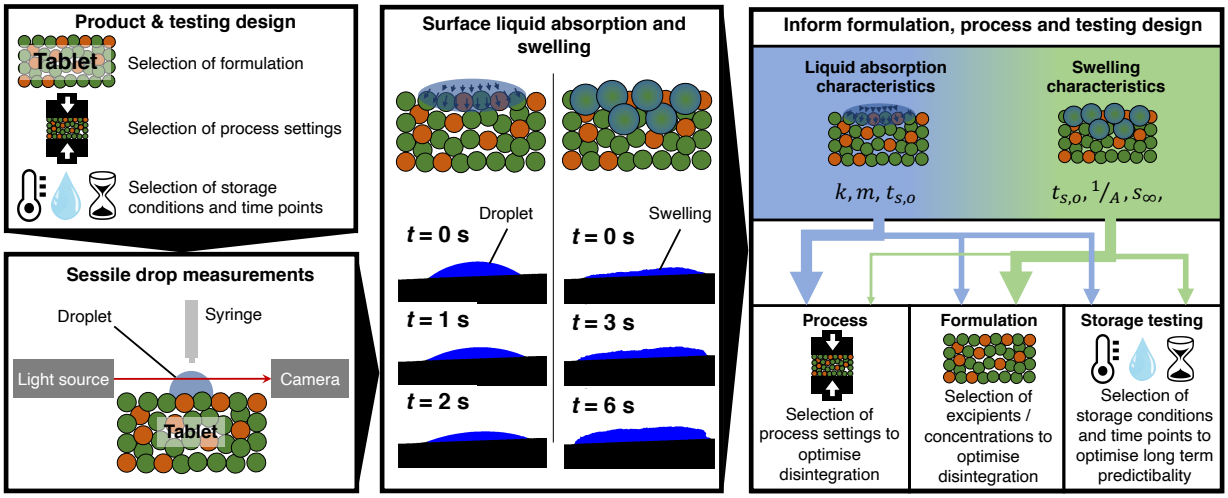

Figure 12: Formulation, process and testing design guide based on the characteristic liquid absorption and swelling characteristics. Three levels of arrow widths (right part of the schematic) indicate a low, medium and high significance for formulation, process and testing design. The characteristic parameter $t_{s,0}$ is considered as both a liquid absorption and swelling characteristic.

first two weeks for most formulations. These outcomes can inform future studies in terms of adding additional time points before 2 weeks and adding more temperature conditions for MCC/mannitol, MCC/lactose and DCPA/lactose as well as more relative humidity conditions for the MCC/DCPA formulations. This will facilitate the generation of a robust modelling plane to maximise the predictability of the long term stability.

5. Conclusion

The approach demonstrated in this study enables a rapid (< 1 min) assessment of characteristic properties that are related to tablet disintegration. This methodology allows formulators, process engineers and analytical scientists to identify fundamental performance mechanisms that are impacted by the formulation, manufacturing settings and storage conditions.

This method was applied to study the effect of compression pressure and storage condition on characteristic liquid absorption and swelling parameters and its relationship to the disintegration time of four formulations. The disintegration performance of the MCC/mannitol and MCC/lactose formulations are driven by the liquid absorption behaviour, which is primarily impacted by the storage temperature. Changes in the liquid absorption and swelling characteristics impacted the disintegration time for the MCC/DCPA formulation, which is mostly influenced by the relative humidity. The disintegration performance of DCPA/lactose tablets are controlled by the swelling behaviour, which is altered by the storage temperature.

The presented approach focused on the assessment of the effect of pressure and accelerated storage conditions on the surface liquid absorption and swelling behaviour using a sessile drop measurements. Future work will be required to also assess the translatability of the outcomes of such an accelerated study to the long term storage behaviour. Rates of chemical or physical changes established within the design space as a function of temperature and/or relative humidity could then be extrapolated to more traditional long term storage conditions, such as 25°C/60% RH or 30°C/75% RH.

It has to be noted that this study focused on placebo tablets and used water at one specific tem-

perature as the disintegration medium. Adding an API and changing the liquid (e.g. a simulated gastric fluid) impact the disintegration behaviour and may alter the performance-controlling mechanism. Studying the impact of API properties on the liquid absorption and swelling behaviour and its link to disintegration and dissolution will be crucial to further inform the formulation and process design. In addition, different compression pressures can also affect the physical changes during storage. A fast assessment of these performance-controlling mechanisms as discussed in this study can allow us to develop a better understanding of the impact of each of these factors on the disintegration and dissolution performance as a function of storage condition and time. The gained understanding will in turn support the design of a formulation and process conditions, the development of a control strategy and also the determination of the shelf life and recommended storage conditions.

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