Formulation-dependent stability mechanisms affecting dissolution performance of directly compressed griseofulvin tablets

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ABSTRACT

During drug product development, stability studies are used to ensure that the safety and efficacy of a product are not affected during storage. Any change in the dissolution performance of a product must be investigated, as this may indicate a change in the bioavailability. In this study, three different griseofulvin formulations were prepared containing microcrystalline cellulose (MCC) with either mannitol, lactose monohydrate, or dibasic calcium phosphate anhydrous (DCPA). The tensile strength, porosity, contact angle, disintegration time, and dissolution rate were measured after storage under five different accelerated temperature and humidity conditions for 1, 2, and 4 weeks. The dissolution rate was found to decrease after storage for all three batches, with the change in dissolution rate strongly correlating with the storage humidity. The changes in physical properties of each formulation were found to relate to either the premature swelling (MCC/DCPA, MCC/lactose) or dissolution (MCC/mannitol) of particles during storage. These results are also discussed with consideration of the performance- and stability-controlling mechanisms of placebo tablets of the same formulations (Maclean et al., 2021; Maclean et al., 2022).

1. Introduction

In the pharmaceutical industry, stability studies are performed throughout the drug product development process, and the data collected is used to optimise the formulation and manufacturing settings; assign the retest period or shelf life; determine the packaging configuration and storage instructions; and support regulatory submissions. Stability studies will typically assess both the chemical and physical stability of the product to ensure that it remains both safe and effective throughout its shelf life. Chemical stability focuses on identifying and quantifying the formation of chemical degradants, as well as identifying the potential degradation pathways. The physical stability of a product encompasses changes in the physical properties, for example, the dissolution behaviour of a product. Changes in the dissolution performance of a product during stability must be investigated, as this could indicate a change in the bioavailability of the product.

The dissolution process begins when a tablet comes into contact with liquid, typically dissolution media (*in vitro*) or physiological fluids (*in vivo*). Liquid will penetrate the tablet through pores in the microstructure and particle wetting occurs. Particles with swelling

capacity (for example, tablet disintegrants) will swell as the dissolution medium is absorbed, exerting a force on the surrounding matrix to encourage the disintegration of the tablet. If soluble excipients such as lactose or mannitol are present, these materials can dissolve and leave greater pore space for liquid penetration. Depending on the composition of the tablet, these processes may occur simultaneously to different rates and extents. As the tablet disintegrates, the surface area exposed to the dissolution medium increases, allowing faster dissolution of the active pharmaceutical ingredient (API) (Markl and Zeitler, 2017; Quodbach and Kleinebudde, 2015a).

The mechanisms of change in dissolution performance of a tablet during storage are not well defined in the literature, however several studies have investigated these changes using different formulations, manufacturing routes, and storage conditions.

Given that tablets often contain high concentrations of excipients, it follows that the properties of these materials will influence the physical stability of the product. Molokhia et al. (1982) found that the use of mannitol and lactose resulted in increased tensile strength, slower disintegration and slower dissolution after storage at 40 °C/90%

relative humidity (RH). This was attributed to the partial dissolution of soluble materials in the moisture contained in the tablet. Upon removal from storage, these materials may recrystallise due to the reduction in available moisture at lower humidity, resulting in the formation of new solid bridges. In contrast, tablets composed of tricalcium phosphate, an insoluble filler, showed no significant changes in tensile strength, disintegration or dissolution performance (Molokhia et al., 1982). This was further supported by Gordon et al. (1993), in a study which demonstrated that tablets composed of lactose were more susceptible to changes in physical stability than those containing less soluble fillers. Aside from the composite solubility of the formulation, Sacchetti et al. (2017) found that the effects of moisture uptake under high humidity varied between plastically-deforming fillers, such as microcrystalline cellulose (MCC), compared to elastic or brittle fracture fillers, such as lactose or dibasic calcium phosphate dihydrate (DCPD).

In addition to the major tablet components, tablet disintegrants can also affect the dissolution performance of a product during storage. Due to the highly hygroscopic nature of disintegrants, they are susceptible to moisture uptake during storage under high humidity which can result in premature swelling (Quodbach and Kleinebudde, 2015a). Premature swelling of the disintegrant can result in a reduction in tensile strength (Marais et al., 2003) and changes to the pore structure of the tablet, due to gradual expansion of these particles as moisture is absorbed from the air during storage (Khan and Rhodes, 1975). After storage under high humidity, Chowhan (1980) found that DCPD-based tablets containing croscarmellose sodium (CCS) no longer disintegrated upon contact with liquid. Instead, dissolution occurred via diffusion from the intact tablet. Similarly, Li et al. (2004) investigated the reduction in dissolution rate of benazepril hydrochloride tablets after storage under accelerated conditions. The slowdown in dissolution of these tablets was attributed to premature activation of crospovidone. This was supported by increases in surface roughness and the formation of microscopic cracks on the tablet surface, which was observed by scanning electron microscopy (SEM) (Li et al., 2004). This mechanism was further confirmed by Quodbach and Kleinebudde (2015b), who demonstrated that the maximum swelling force generated for tablets containing CCS and crospovidone was lowered for tablets stored above 58%RH for 1 month. In general, it is expected that the gradual expansion of disintegrants during storage at high humidity results in reduced efficiency. This loss in efficiency is likely to be a permanent, and therefore high humidity excursions during storage could result in reduced product performance.

Changes in dissolution performance during storage can also be caused by chemical interactions or degradation. For example, Rohrs et al. (1999) demonstrated that a decrease in dissolution rate of delavirdine mesylate upon exposure to high humidity was the result of a moisture-mediated interaction between croscarmellose sodium and the API. In the case of capsule products, a study by Desai et al. (1994) found that hydrolysis of hydrochlorothiazide during storage under accelerated conditions resulted in the formation of formaldehyde, which subsequently caused cross-linking of the gelatin capsule shell. Cross-linking of gelatin capsules results in a decrease in dissolution rate due to delayed rupture of the capsule, however, this is typically an *in vitro* phenomenon as enzymes present in the gastrointestinal tract can digest the capsule *in vivo* (Meyer et al., 2000).

Several recent publications have proposed novel approaches to the prediction of changes in dissolution performance during storage. The commercial software ASAP*prime*® was used to study the slowdown in dissolution rate for two different products in a study by Li et al. (2016). Whilst this software was originally developed for the prediction of chemical stability (Waterman, 2011), it was able to accurately predict the change in dissolution for two tablet formulations. This study found that for two different products, the relative impact of temperature and humidity varied based on the API. Scrivens (2019) proposed the use of an 'acceleration factor' (AF) which adjusts the timescale (*x*-axis) of the dissolution profile to enable the overlap of profiles across different storage conditions. By determining the AF at multiple conditions and timepoints, multiple linear regression was used to determine coefficients for the effects of temperature and humidity on the dissolution performance, enabling long-term predictions. Using long-term stability data spanning an 18-month study, the AF-based predictions were validated for an immediate-release tablet formulation containing MCC and DCPA, demonstrating that this technique can offer reliable predictions of long-term stability. In another approach, Tsunematsu et al. (2020) calculated the available surface area to predict changes in the dissolution performance on stability. This approach aimed to bridge the gap between empirical and mechanistic predictions of dissolution stability by basing long-term dissolution predictions on the change in available surface area for the API. This approach was demonstrated to produce accurate predictions of the dissolution profile of ebastine tablets after 6 months of storage at 40 °C/75%RH.

Previously, the change in physical properties and disintegration performance of 16 different placebo formulations was investigated before and after storage under five different temperature and humidity conditions (Maclean et al., 2021, 2022). It was found that the changes in disintegration could be related to the performance-controlling disintegration mechanism of the tablets prior to storage, for example, whether tablet disintegration was driven by swelling, dissolution of soluble fillers, or wettability and liquid-uptake. The correlations observed between the change in disintegration time and the physical tablet properties of the 16 formulations suggested that the mechanisms varied between the different filler combinations.

The objective of this study is to assess the dissolution performance of tablets composed of three different formulations using griseofulvin as a model drug. Each batch was stored under five different accelerated temperature and humidity conditions in order to characterise any physical changes in the tablet properties after 1, 2, and 4 weeks of storage. The relationship between environmental conditions (temperature and humidity), storage time, and the dissolution performance of different batches was investigated with consideration of the mechanisms of change during storage.

2. Materials

Griseofulvin ((+)-Griseofulvin (>97%), VWR International Ltd., UK) was used as a model drug in each tablet formulation. Griseofulvin is a non-hygroscopic and poorly soluble drug. Due to its low solubility, surfactant was added to the dissolution media to enable dissolution testing under sink conditions. In this study, dissolution testing was performed using 0.4% w/v sodium dodecyl sulphate (SDS) in water, in which the solubility of griseofulvin is 0.30 mg/mL. Griseofulvin can be detected by UV–Vis spectroscopy, with a λ_{max} of 291 nm. Griseofulvin was also selected as it does not contain a primary amine, and therefore cannot undergo the Maillard reaction with lactose which could result in the discolouration of tablets after storage.

The formulations also contained a combination of two of the following fillers — microcrystalline cellulose (MCC) (Avicel® PH-102, FMC International), mannitol (Pearlitol® 200 SD, Roquette), lactose (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 added to each formulation as a disintegrant and a lubricant, respectively.

Magnesium chloride and sodium chloride (Merck Life Science UK Ltd., UK) were used to make saturated salt solutions for humidity control at 30%RH and 75%RH, respectively. The dissolution media was prepared using SDS Micro Pellets (>99%) (Fisher Scientific Ltd., UK).
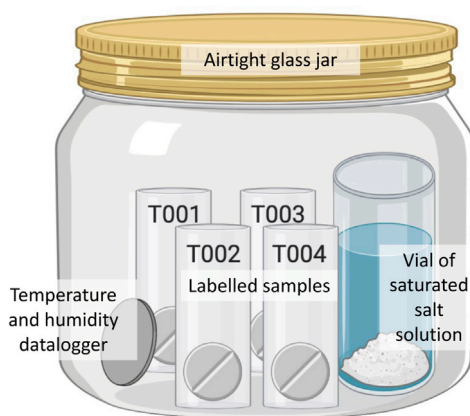
Fig. 1. Storage of samples during accelerated stability studies.

Table 1
Accelerated stability storage conditions.

Temperature (°C)	Humidity (% RH)	Storage time (weeks)
37	30	1, 2, 4
37	75	1, 2, 4
50	75	1, 2, 4
60	30	1, 2, 4
60	75	1, 2, 4

Table 2
Sampling plan with the number of tablets used for physical characterisation at the initial timepoint ($n_{initial}$) and the number of tablets at subsequent stability timepoints (n_t).

Physical property	$n_{initial}$	n_t
Weight & dimensions	All	14
Tensile strength	10	4
Porosity	All	14
Terahertz spectroscopy	6	6
Dynamic contact angle	4	4
Disintegration	3	3
Dissolution	3	3

Tablets were stored at five different temperature and humidity conditions, as listed in Table 1. For each condition, tablets were stored for 1, 2 and 4 weeks.

After storage, samples were allowed to equilibrate to ambient conditions for 2 weeks before any characterisation was performed. This enabled the measurement of tablet weight without fluctuations due to the gradual loss of absorbed moisture during storage.

3. Methods

3.1. Tablet manufacture

Three formulations were prepared, each containing griseofulvin (30% wt.), croscarmellose sodium (5% wt.) and magnesium stearate (1% wt). The remaining 64% wt. was composed of a 1:1 ratio of two different fillers — MCC/mannitol, MCC/lactose, or MCC/DCPA. These formulations were selected to mimic the formulations of placebo tablets which were previously characterised with respect to their disintegration mechanism and physical stability (Maclean et al., 2021, 2022). Blends were prepared by mixing the fillers, disintegrant and griseofulvin in a bin blender (AB-015 bin blender, Pharmatech, UK) for 20 min with a blend speed of 20 rpm and agitator speed of 200 rpm. After 20 min, the lubricant was added and the powder was blended for a further 5 min. Round flat-faced tablets were then compressed using an automated single-punch tablet press (FlexiTab, Bosch Packaging Technology Ltd., UK) with a 9 mm die and a compression force of 10 kN (equivalent to a compression pressure of 157.2 MPa).

3.2. Sample storage

Tablets were stored in airtight glass jars, each containing a vial of saturated salt solution to control the humidity within the jars as shown in Fig. 1.

Saturated solutions of magnesium chloride and sodium chloride were used to simulate 30% and 70%RH, respectively. Within each glass jar, tablets were labelled in order to track weight and dimension changes for each individual tablet. To ensure constant temperature and humidity throughout the study, a DS1923 Hygrochron iButton Temperature/Humidity logger (Measurement Systems Ltd, Berkshire, UK) was added to one sample jar per condition for each batch. The datalogger was set to record the temperature at intervals of 10 min to ensure that conditions were constant throughout the study. After storage, the temperature and humidity values recorded by the dataloggers were found to be suitably close to the nominal conditions.

3.3. Physical characterisation

The sampling plan for the stability study is outlined in Table 2 with details of each of the methods given below.

3.3.1. Weight and dimensions

The weight and dimensions of each tablet were recorded before storage. At each stability timepoint, the weight and dimensions were measured again for tablets used for tensile strength measurements, disintegration testing, and dissolution testing. Tablet weight was measured to the nearest 0.1 mg using an analytical balance, and the thickness and diameter were measured to the nearest 0.1 mm using a pair of digital calipers.

3.3.2. Tensile strength

The hardness of each tablet was measured using a hardness tester (Copley TBF 1000, Copley Scientific Ltd, Nottingham, UK). The tensile strength, σ_t, of tablets was calculated using the tablet hardness, F, diameter, d, and height, h, based on the equation by Fell and Newton (1970) for round, flat-faced tablets:

$$\sigma_t = \frac{2 \cdot F}{\pi \cdot d \cdot h}. \tag{1}$$

3.3.3. Porosity

The true density of each material, $\varrho_{t,i}$, was measured in triplicate by gas pycnometry (MicroUltrapyc 1200e, Quantachrome, Graz, Austria) using nitrogen gas. The true density values of the excipients have previously been published by Maclean et al. (2021), and the true density of griseofulvin was measured as 1.4710 g cm^{-3}.

The true density of the formulation, $\varrho_{t,mix}$, was calculated as the weighted harmonic mean using the true density and the weight fraction, c_i, of each tablet component (Sun et al., 2018):

$$\varrho_{t,\mathrm{mix}} = \left(\sum_i^N \frac{c_i}{\varrho_{t,i}} \right)^{-1} \tag{2}$$

with $N = 5$ tablet components in each batch. The porosity, ϵ, can then be calculated using:

$$\epsilon = 1 - \frac{\frac{m}{\pi \cdot (d/2)^2 \cdot h}}{\varrho_{t,\mathrm{mix}}}, \tag{3}$$

where m is the tablet weight, d is the tablet diameter, and h is the tablet thickness.

3.3.4. Terahertz spectroscopy

Terahertz time-domain spectroscopy was performed using a Tera-Pulse Lx Spectrometer (TeraView Ltd). The sample chamber was purged with nitrogen to remove moisture from the air during analysis. Samples were analysed using an optical delay of 200 ps and 30 averages. From the terahertz measurements, the refractive index and loss coefficient were obtained. Based on the spectra obtained, a frequency of 0.8 THz was selected for comparing the change in refractive index and loss coefficient across different conditions and timepoints. This frequency was selected as this point was free from peaks (caused by the tablet components) for all formulations. Example spectra from a tablet of each formulation are shown in Figure S1 in the Supporting Information.

3.3.5. Contact angle

Dynamic contact angle measurements were performed using a drop shape analyser (Krüss DSA30, Krüss GmbH) as previously described by Maclean et al. (2021). Briefly, video recordings were taken at a rate of 30 frames per second as a single droplet of water was dispensed on to the surface of the tablet. Videos were analysed using MATLAB (R2019a, MathWorks) to determine the contact angle between the droplet and the tablet surface at each frame. Further details on the processing of contact angle measurements are also provided by Markl et al. (2021).

3.3.6. Disintegration

Disintegration testing was performed using an Erweka ZT 233 (Total Laboratory Services Ltd) disintegration tester. The time taken for tablets to disintegrate in 800 mL of water at 37 °C was recorded to the nearest second for each tablet tested.

3.3.7. Dissolution

Dissolution testing was performed using a USP II (paddle) apparatus (Copley DIS6000 Dissolution Tester, Copley Scientific Ltd). Dissolution testing was performed using 900 mL of 0.4% w/v SDS in water at 37 °C, with paddle speed of 75 rpm. One tablet was tested per dissolution vessel. Samples were manually collected at 3, 7, 10, 15, 20, 25, 30, 45, and 60 min. After the 60 min timepoint, the paddle speed was increased from 75 to 200 rpm for a 30 min infinity spin, after which point a final sample was collected. At each sampling timepoint, 10 mL was removed from the vessel and filtered through a 0.2 μm PTFE syringe filter, with a discard volume of 5 mL. Samples were analysed by high-performance liquid chromatography (HPLC). Full details of the dissolution media selection, paddle speed selection, and the HPLC method are given in Section 1 of the Supporting Information.

The dissolution profiles collected for each batch, condition and timepoint were fitted to a Weibull curve using Python 3.9:

$$D_t = 100 \cdot (1 - \exp[-k_d \cdot t_d]^b) \tag{4}$$

where D_t is the percentage of griseofulvin dissolved (relative to the final dissolution after the 30 min infinity spin), t_d is the time in minutes, k_d and b are the dissolution rate and shape parameters, respectively.

For the purposes of comparing the change in dissolution performance of each formulation after storage, the dissolution shape parameter, b, was fixed based on the initial dissolution profiles, as per Scrivens (2019). This is based on the assumption that the curve shape is not affected by storage, and allows changes in dissolution performance to be clearly distinguished.

3.4. Statistical analysis

Pearson correlation coefficients were calculated using GraphPad Prism 9 (version 9.0.2, GraphPad Software LLC) to identify correlations between the different physical properties of the tablets during storage. Correlations were considered significant if $p < 0.05$.

4. Results

4.1. Tablet weight and dimensions

The initial weight and dimensions of all tablets are listed in Table S2 of the Supporting Information. The change in weight and dimensions after storage of the tablets used for terahertz spectroscopy for each batch are given in Tables S3, S4, and S5 in the Supporting Information.

4.2. Tensile strength

The tensile strength of each batch after storage is shown in Fig. 2. For all three formulations, the tensile strength decreased after storage for the first week under each condition. At subsequent timepoints, tensile strength remained relatively constant or showed only small changes. There are a few exceptions, specifically, MCC/mannitol tablets stored at 60 °C/75%RH which continued to decrease throughout the duration of the study, and 50 °C/75%RH tablets which increased slightly between the 1 and 2 week timepoints. In some cases, there was a slight increase in tensile strength after the 1 week timepoint, for example, MCC/DCPA tablets stored at 30%RH and MCC/lactose tablets stored at 37 °C/30%RH.

4.3. Porosity

The porosity of each batch is shown in Fig. 3. At the initial timepoint, MCC/lactose and MCC/mannitol tablets have a starting porosity of approximately 11 and 13%, respectively. Tablets composed of MCC/DCPA have a much higher porosity of around 20%, due to the high intra-particle porosity of DCPA.

After storage, the porosity generally increased for all batches, however, the increases in porosity are much lower than those observed for placebo tablets of the same formulations (Maclean et al., 2021). This is expected, as changes in the tablet porosity are caused by the premature expansion of MCC and CCS. The difference in extent of porosity change may be due to the reduced MCC content (32% wt. in griseofulvin tablets, compared to 47% wt. in placebo tablets reported by Maclean et al., 2021). The porosity values shown in Fig. 3 are also calculated based on changes in tablet volume using the true density of the original mixture, and therefore these calculations do not account for potential changes in the true density of the materials due to the uptake of moisture. For MCC and CCS, which undergo disintegrant preactivation during storage and then subsequently lose the additional moisture after removal from storage, a reduction in particle density is expected, which would contribute towards increased porosity.

4.4. Terahertz spectroscopy

The change in refractive index and loss coefficient extracted from the terahertz spectroscopy measurements are shown in Fig. 4.

Changes in refractive index are caused by variations in the sample material or porosity. In this study, the tablet materials were not changed during the course of the stability study, and only negligible quantities of moisture are present at the time of analysis as the tablets were conditioned at room temperature for a minimum of two weeks after removal from storage. The moisture content of samples at the time of analysis is shown in Figure S4 in the Supporting Information, with <1% of moisture present at the time of analysis. On this basis, any changes observed in the refractive index are attributed to changes in the intra- and/or inter-particle porosity. For all formulations, the refractive index tends to decrease slightly during storage (Fig. 4A), indicating an increase in porosity.

The loss coefficient relates to the absorption and scattering of radiation as it passes through the sample. As the material was not altered and the quantity of moisture present at the time of analysis is negligible, an increase in the loss coefficient is attributed to an increase in scattering
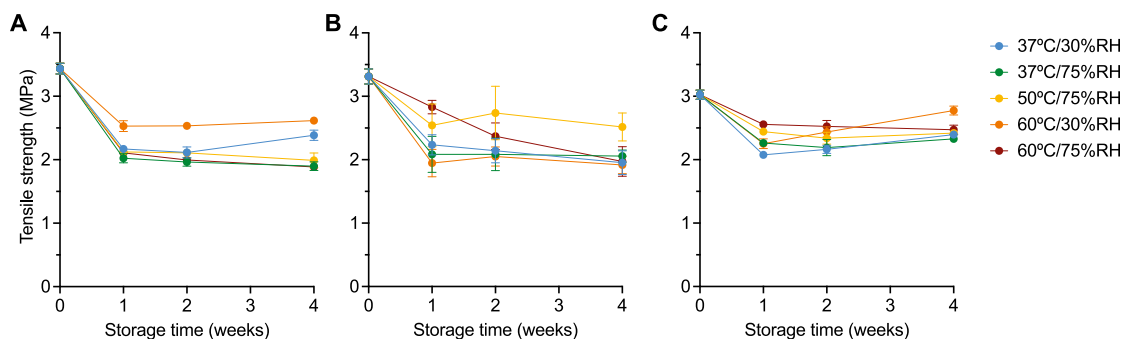
Fig. 2. The tensile strength of tablets composed of (A) MCC/lactose, (B) MCC/mannitol, and (C) MCC/DCPA tablets after storage under accelerated temperature and humidity conditions (mean ± standard deviation, $n = 10$ at 0 weeks and $n = 4$ at subsequent timepoints).
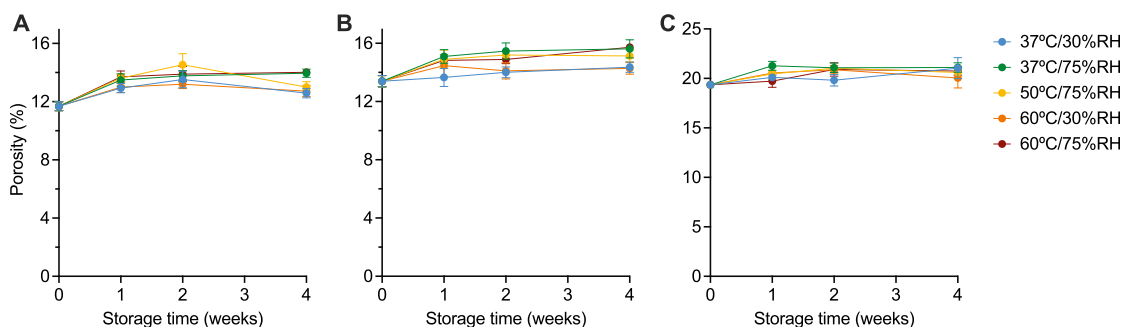

Fig. 3. The porosity of tablets composed of (A) MCC/lactose, (B) MCC/mannitol, and (C) MCC/DCPA after storage under accelerated temperature and humidity conditions (mean ± standard deviation, $n = 210$ at 0 weeks, and $n = 14$ at subsequent timepoints).

caused by growth of domain sizes in the tablets. The loss coefficient (Fig. 4B) shows different behaviour across each formulation, which suggests that different mechanisms of change are occurring across each formulation.

4.5. Contact angle

The change in initial contact angle of each batch during storage is shown in Fig. 5. The contact angle generally increased during the first 1 or 2 weeks of storage under most conditions. Increases in the contact angle suggest decreases in the wettability of the tablets. The contact angle is influenced by the surface chemistry, porosity and roughness, which all may be affected by storage under accelerated temperatures and humidity.

4.6. Disintegration time

The disintegration times of each batch before and after storage are shown in Fig. 6. In general, tablets composed of MCC/mannitol and MCC/lactose showed little change during storage, with the exception of tablets stored at 60 °C/75%RH, which resulted in significantly slower disintegration after storage for 4 weeks. Interestingly, the disintegration times of MCC/mannitol tablets showed little change in the first 2 weeks of storage at this condition, and MCC/lactose tablets also showed only slight increases prior to the 4 week timepoint. In the case of MCC/DCPA-based tablets, disintegration was generally much faster (approximately 20 s at initial compared to 55 s for MCC/mannitol and 92 s for MCC/lactose). For this formulation, there was no clear trend observed for changes in disintegration time, however the disintegration time remained under 30 s even after storage for 4 weeks.

4.7. Dissolution

Dissolution profiles of tablets after 4 weeks storage under different conditions are shown in Fig. 7. To compare the dissolution performance, profiles are plotted using the percentage of the final mass of griseofulvin dissolved, i.e the final mass dissolved after the infinity spin.

As shown in Figs. 7 and 8, the dissolution rate of each batch is affected by storage. In particular, storage at 60 °C/75%RH appears to result in the greatest slowdown in dissolution rate for MCC/mannitol and MCC/lactose. The dissolution profile of MCC/DCPA-based tablets stored at 60 °C/30%RH appears distorted in shape and has increased variability compared to the other conditions. For this condition, additional testing was performed using 3 spare tablets stored under the same conditions, which confirmed that these results were not caused by a measurement error. Instead, this may be caused by chemical degradation or a polymorphic change in griseofulvin after storage under these conditions. Further investigation of this effect was considered out of scope for this study.

5. Discussion

5.1. Characterisation of tablet properties

The griseofulvin tablets were formulated to correspond to previous work on placebo tablets (Maclean et al., 2021, 2022; Markl et al., 2021), which investigated the performance- and stability-controlling disintegration mechanisms of placebo tablets. The formulations selected maintained the same concentrations of disintegrant and lubricant (5% and 1% wt., respectively) and a filler ratio of 1:1, however, the total concentration of filler was reduced to allow 30% wt. drug loading of griseofulvin. The initial properties of the griseofulvin tablets are compared to the properties of their equivalent placebo batches from Maclean et al. (2021) in Fig. 9.

The disintegration of tablets composed of MCC/lactose was classified as wettability-controlled during the placebo studies (Maclean
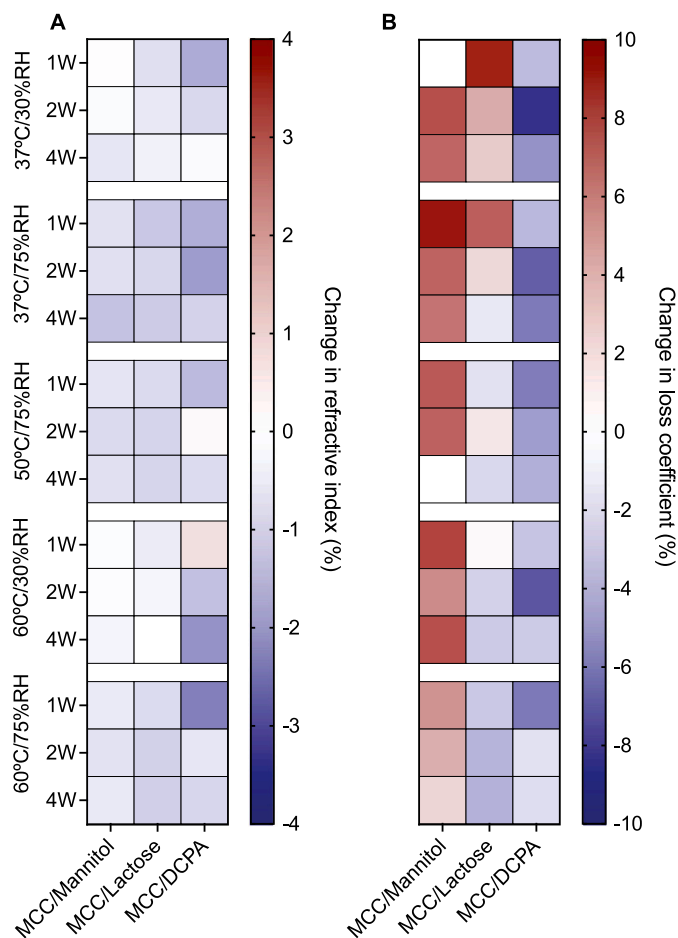
Fig. 4. The relative change in (A) refractive index and (B) loss coefficient at 0.8 THz for samples stored under different temperature and humidity conditions, based on *n* = 6 samples per timepoint and condition.

et al., 2021). The disintegration of these tablets was primarily limited by its porosity that controlled the liquid penetration. The substitution of 15% wt. each of MCC and lactose with griseofulvin resulted in reduced porosity and wettability, however the disintegration time was found to decrease. This suggests that at this drug loading of griseofulvin, the properties of the API may cause a change in the performance-controlling mechanism of the formulation, i.e. the disintegration process is no longer limited by low porosity and slow liquid penetration but by the dissolution of the API.

In terms of porosity, the greatest difference between placebo and griseofulvin tablets is observed for tablets containing MCC/DCPA. Tablets containing DCPA have a high porosity due to the high intra-particle porosity of DCPA. As a result, the substitution of 15% wt. DCPA with griseofuvlin results in a significant decrease in porosity for this batch. Despite the decrease in porosity, the disintegration time of MCC/DCPA tablets did not significantly change when griseofulvin is added to the formulation. The placebo tablets were previously classified as swelling-controlled (Maclean et al., 2021), whereby the porosity is sufficiently high that disintegration is not limited by liquid penetration and is primarily controlled by the swelling of MCC and the disintegrant.

Similarly to MCC/DCPA tablets, tablets containing MCC/mannitol also showed no change in disintegration time with the addition of griseofulvin to the formulation, despite decreases in both wettability (as indicated by an increase in the initial contact angle) and porosity. This

suggests a change in the performance-controlling mechanisms with the addition of 30% wt. griseofulvin as the disintegration of placebo tablets of this formulation was found to be sensitive to changes in porosity and wettability (Maclean et al., 2021).

5.2. Correlations between temperature and humidity

The correlations between the change in physical tablet properties and the storage temperature and humidity are shown in Fig. 10. There are very few correlations between the storage temperature and any of the tablet properties. For MCC/DCPA, a correlation is found between the temperature and the tensile strength, and for MCC/lactose a correlation is found between the temperature and the loss coefficient.

Several correlations are found between the storage humidity and the physical tablet properties. Firstly, all batches show a strong negative correlation between the storage humidity and the dissolution rate, k_d, indicating that increased storage humidity results in slower dissolution. This suggests that during storage, changes in dissolution performance are primarily driven by storage humidity rather than temperature.

The correlations between the physical tablet properties and the humidity suggest different mechanisms of change in each formulation. For example, both MCC/lactose and MCC/mannitol show positive correlations between humidity and porosity, indicating that high humidity leads to increased porosity after storage. This is further supported by strong correlations with the refractive index, which is also related to the porosity. These correlations with porosity are attributed to the premature swelling of MCC and CCS upon exposure to high humidity, and the subsequent loss of moisture after removal. Overall, expansion of the particles results in a permanent change in the microstructure. These results are in agreement with the previous study of placebo tablets, where strong correlations between the porosity and humidity for all formulations containing MCC were attributed to premature swelling (Maclean et al., 2022).

In addition to the correlations with porosity, storage humidity is also correlated with tensile strength for both MCC/lactose and MCC/mannitol tablets. However, unlike the porosity, the correlations differ between the two formulations. For MCC/lactose, a negative correlation suggests that higher humidity conditions are associated with decreased tensile strength. This is consistent with the behaviour of MCC/lactose placebo tablets, as the decreases in tensile strength may be attributed to the increased porosity resulting in reduced bonding area, and so weaker inter-particle bonds. In contrast, tablets composed of MCC/mannitol showed a positive correlation between tensile strength and humidity, indicating that storage at high humidity results in stronger inter-particle bonds. This is not in agreement with the results from the placebo tablets, however increased tensile strength after storage has been observed in the literature, where it is attributed to the partial dissolution and recrystallisation of soluble components allowing the formation of new solid bridges (Chowhan, 1980; Molokhia et al., 1982). Overall, tablets composed of MCC/mannitol show decreases in tensile strength despite this positive correlation. This suggests that there may be competing mechanisms occurring for this formulation, where swelling of the MCC and disintegrant may be occurring prematurely during storage, whilst mannitol may be susceptible to partial dissolution and recrystallisation.

5.3. Correlations between physical tablet properties

The correlation coefficients for each physical tablet property with the dissolution rate, k_d, is shown in Fig. 11.

The dissolution rate parameter, k_d, shows several significant correlations across each formulation tested. Firstly, the dissolution rate is strongly correlated with humidity for all three formulations, as discussed above. This is in agreement with the general trend observed in the literature, where samples stored at high humidity demonstrate slower dissolution. MCC/lactose-based tablets also show correlations
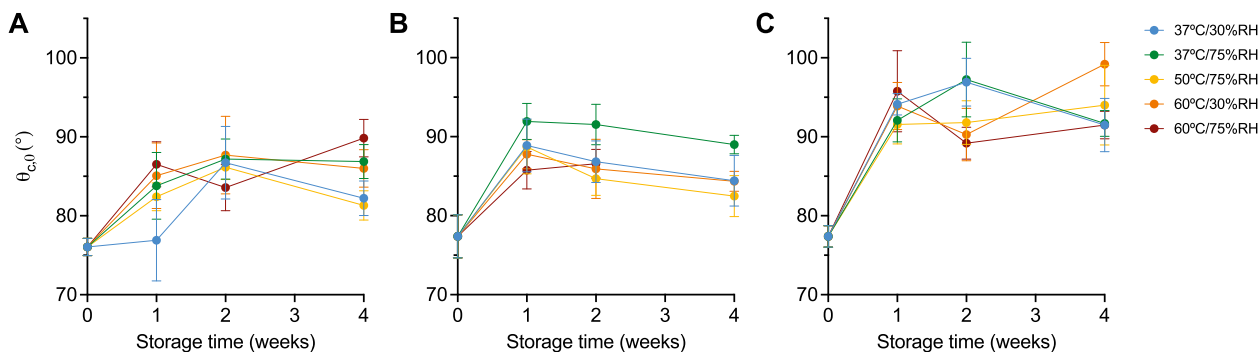
Fig. 5. The initial contact angle ($\theta_{c,0}$) of tablets composed of (A) MCC/lactose, (B) MCC/mannitol, and (C) MCC/DCPA after storage under accelerated conditions (mean ± standard deviation, $n = 4$).
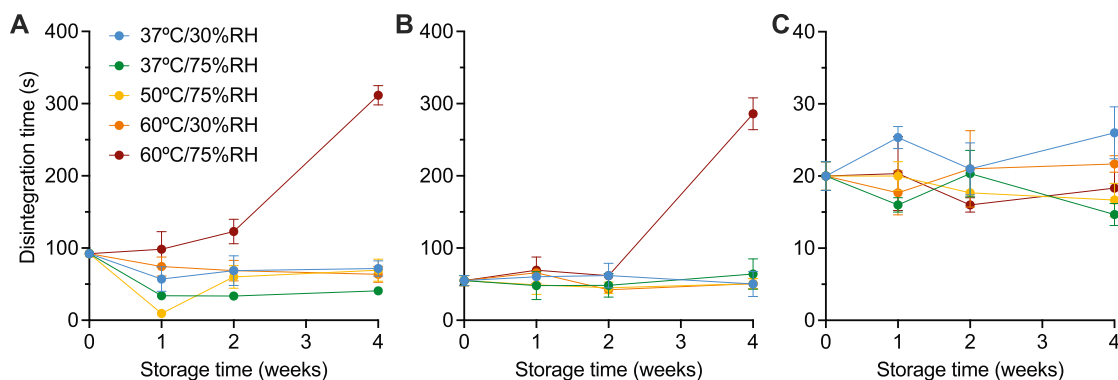

Fig. 6. The disintegration time of (A) MCC/lactose, (B) MCC/mannitol, (C) MCC/DCPA tablets after storage under accelerated temperature and humidity (mean ± standard deviation, $n = 3$).
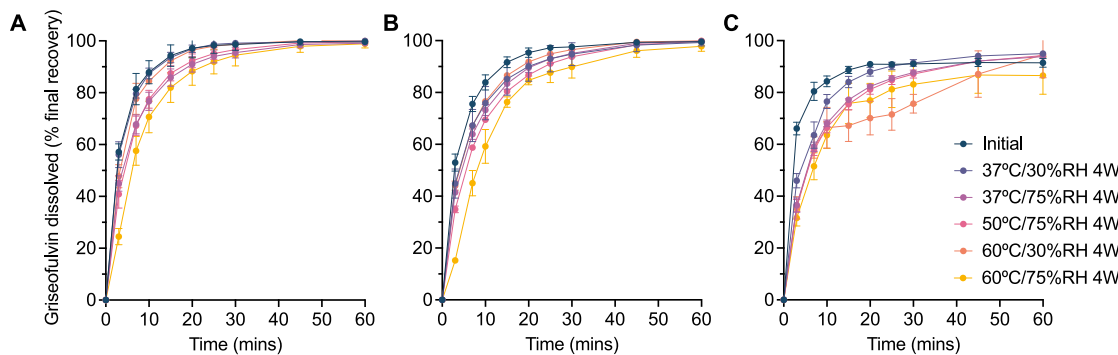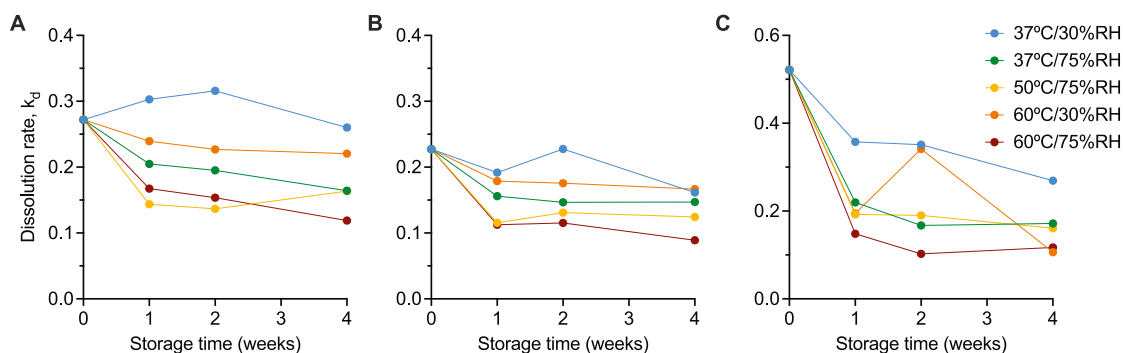

Fig. 7. The dissolution profiles of (A) MCC/lactose, (B) MCC/mannitol, and (C) MCC/DCPA for tablets stored for 4 weeks under accelerated temperature and humidity conditions (mean ± standard deviation, $n = 3$ for all batches except MCC/DCPA 60 °C/30%RH at 4 weeks, for which $n = 6$).

Fig. 8. The dissolution rate constant, k_d, of (A) MCC/lactose, (B) MCC/mannitol, and (C) MCC/DCPA tablets after storage under accelerated temperature and humidity ($n = 3$ except MCC/DCPA 60 °C/30%RH at 4 weeks, for which $n = 6$).
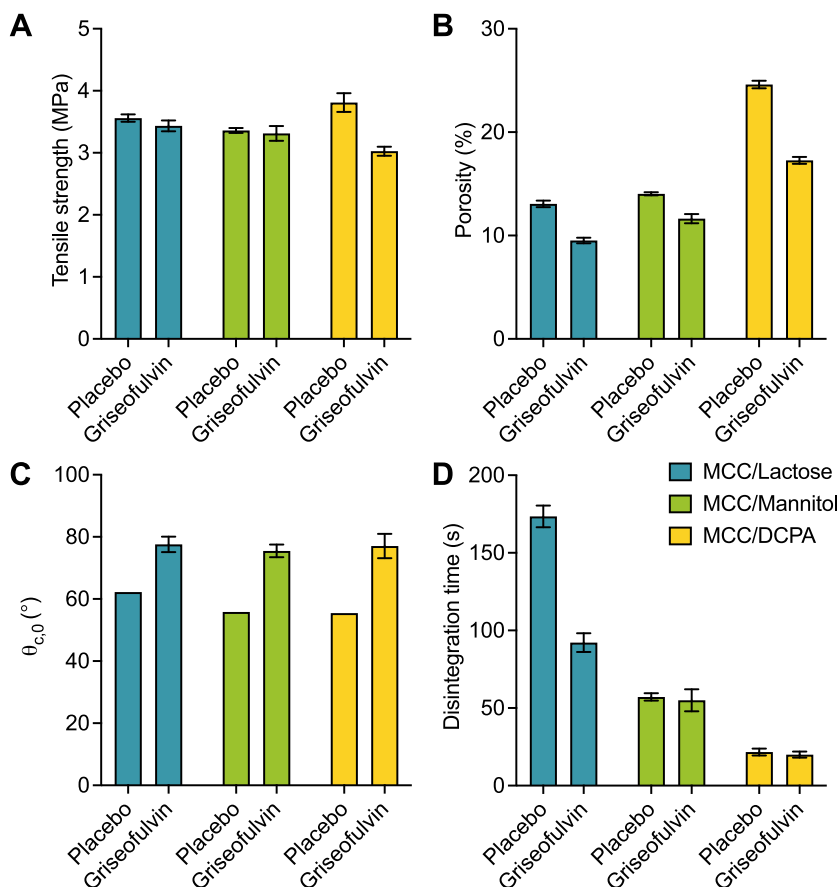
Fig. 9. The (A) tensile strength, (B) porosity, (C) initial contact angle ($\theta_{c,0}$), and (D) disintegration time of griseofulvin tablets compared to the equivalent placebo tablets discussed by Maclean et al. (2021). Results shown as mean ± standard deviation, except placebo tablets in (C) for which $n = 2$.
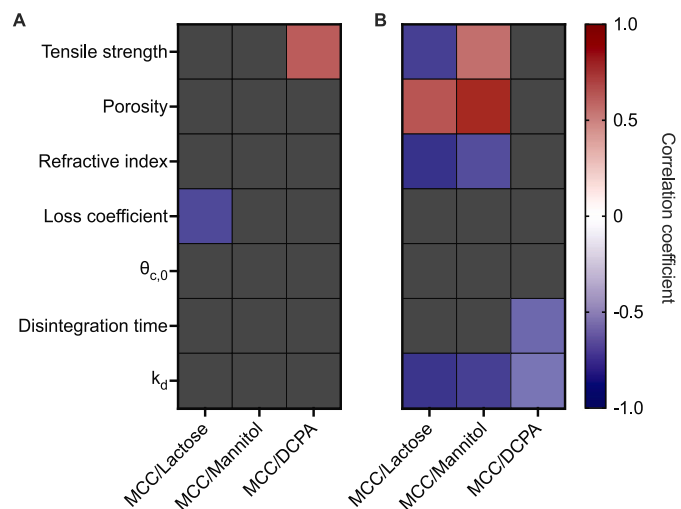

Fig. 10. The correlation coefficients of the relative change in each physical property with (A) the storage temperature, and (B) the storage humidity. Only significant correlations where $p < 0.05$ are shown.

Fig. 11. The correlation coefficients of the relative change in each physical property with the dissolution rate parameter, k_d, as determined by fitting dissolution profiles using the Weibull curve. Only significant correlations where $p < 0.05$ are shown.
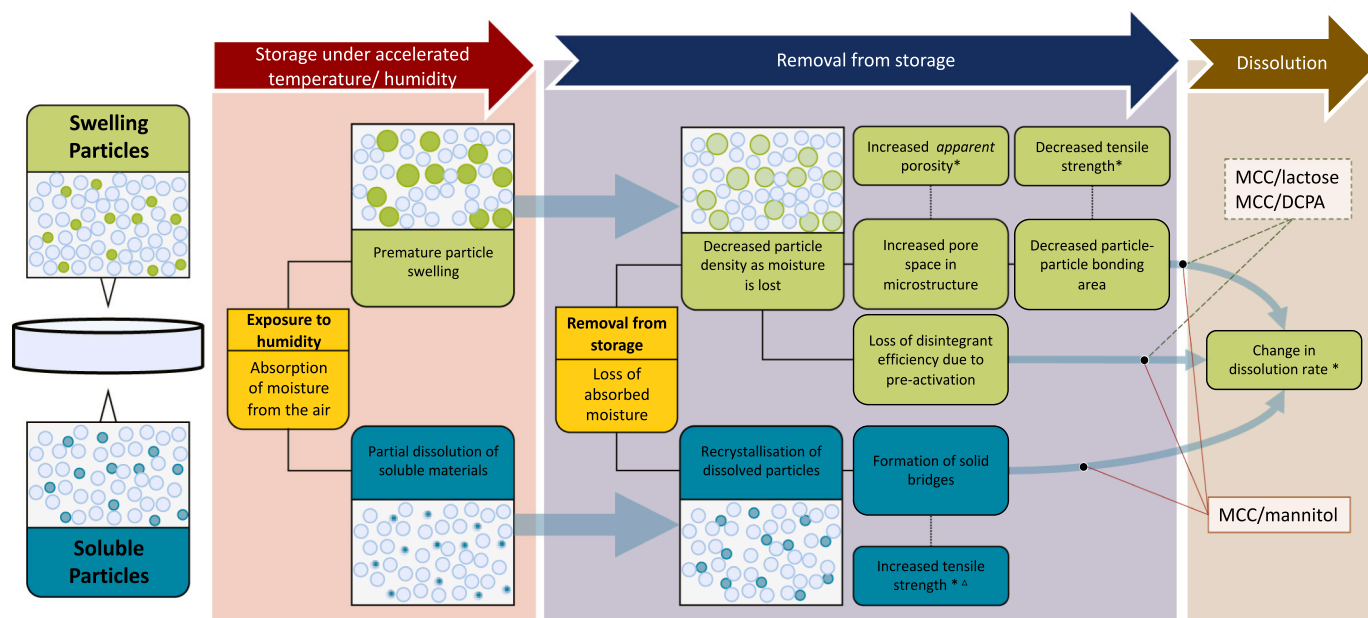
with porosity and refractive index, suggesting that the increases in porosity correlate strongly with decreased dissolution rates. This is also observed in MCC/mannitol tablets, which show strong correlations with tensile strength and porosity.

It is generally expected that increases in tablet porosity would be associated with faster dissolution due to improved liquid penetration through open pores in the tablet. In the case of samples which have

Fig. 12. A schematic summary of the mechanisms of change observed in this study * and in the literature △ by Chowhan (1980), Molokhia et al. (1982).

been stored at high humidity, the changes in the observed porosity are attributed to premature swelling of the disintegrant. Whilst disintegrant preactivation can lead to an increase in tablet dimensions, this also leads to decreased particle density when the absorbed moisture evaporates after removal from the accelerated humidity conditions. In addition to the decreased particle density, premature swelling of the disintegrant is thought to reduce the efficiency of the disintegrant as some of the swelling energy has already been released prior to disintegration and dissolution. For both of these reasons, the dissolution rate can be expected to decrease after storage at high humidity.

In addition to the refractive index and porosity, a correlation exists between the loss coefficient and the dissolution rate for MCC/lactose. In this case, where the materials are the same and the quantity of moisture is negligible, changes in the loss coefficient are driven by changes in the particle size or shape, which may be caused by the recrystallisation of soluble materials (e.g. lactose) in the tablet (Chowhan, 1980; Molokhia et al., 1982).

Tablets composed of MCC/DCPA have a positive correlation between the disintegration time and dissolution rate, indicating that the dissolution rate increases with increased disintegration times. It would generally be expected that dissolution rate would decrease as disintegration slows down, however, it should be noted that the disintegration times of DCPA-based tablets were very fast and there was not a clear trend during storage (Fig. 6), and so this correlation may not be representative of the true mechanisms of change.

5.4. Mechanisms of change in dissolution performance

A schematic summary of the mechanisms of change during storage is shown in Fig. 12. The mechanisms of change in physical properties of tablets can generally be distinguished based on whether the materials are swelling or soluble. During storage under high humidity conditions, swelling particles are likely to absorb moisture from the air and prematurely expand. This is observed primarily in disintegrants, but will also occur for any other swelling materials, for example, MCC. For these materials, removal from storage and the subsequent loss of moisture appears to result in a decrease in particle density. This is observed in the increased tablet porosity after storage, as well as the decreased tensile strength due to less contact points for particle–particle bonding. In addition to these effects, a decrease in disintegrant efficiency is

expected as some of the energy reserved for swelling or shape recovery is gradually lost during storage.

For soluble materials, storage under accelerated humidity can result in partial dissolution and subsequent recrystallisation upon removal from storage. As the soluble material recrystallises, the formation of new solid bridges can result in increased tensile strength. If an increase in tensile strength is observed, the dissolution rate may decrease as the breaking of inter-particle bonds for disintegration and dissolution may be slower.

Considering that most formulations will often contain more than one type of material, it is likely that these mechanisms may occur simultaneously to different rates and extents depending on the relative quantities of each type of material. For this reason, consideration of the whole formulation are required when determining the mechanistic changes in physical tablet properties.

Aside from the material properties, a critical factor in the tablet properties after storage is the equilibration period after tablets are removed from storage. During this time, the tablets undergo a form of relaxation whereby the additional moisture absorbed from the air is subsequently lost by evaporation. This process is not instantaneous, and so additional work is needed to identify the optimal time to test tablets after removal from storage, this may be achieved by monitoring the weight change or using non-destructive techniques like terahertz spectroscopy to identify the time at which no further relaxation effects are observed. The length of this relaxation period is also likely to change based on the material properties or porosity, which could both influence the rate of moisture loss after removal from storage.

6. Conclusions

In this study, the change in dissolution performance of three different griseofulvin formulations was investigated using an accelerated stability study. For all formulations, a decrease in the dissolution rate was observed. This slowdown in dissolution was found to correlate with humidity, whereby storage under high humidity resulted in the greatest decrease in dissolution rate. These changes in dissolution performance were also found to correlate with changes in other physical tablet properties, such as porosity and tensile strength. The correlations between these properties varied based on the formulation, suggesting that the mechanism of change varies based on the material properties, for example, the overall swelling capacity or solubility of the formulation.

Currently, the mechanisms of change in dissolution performance during storage are not well defined in the literature. A systematic approach is required to distinguish the effects of different API and excipient properties on the physical stability of pharmaceutical tablets, and to fully elucidate these mechanisms. With an improved understanding of these mechanisms, mechanistic models could be developed to better predict the physical stability of tablets. Additionally, the equilibration period following the removal of samples from storage should be assessed in order to determine the optimal time between the removal from storage and analysis of samples. This would contribute towards robust stability study designs, with reliable and reproducible results.

Declaration of competing interest

Data availability

Data will be made available on request.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.122473.

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