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In Vitro Monitoring of Dissolution of an Immediate Release Tablet by Focused Beam Reflectance Measurement

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Abstract: Changes in in vitro drug release profiles of oral dosage forms are commonly observed due to storage of drug product at elevated temperature and humidity. An example is presented of an immediate release drug product which underwent changes to both release profile and crystal form on storage at elevated humidity. The dissolution rate for unstressed tablets was comparable regardless of the crystal form present. Decreased release rate was only observed for stressed tablets that exhibited crystal form conversion. The cause of the dissolution change was determined by evaluating tablets manufactured with three drug substance crystal forms by fiber optic ultraviolet detection and focused beam reflectance measurement (FBRM). Tablets were also analyzed by near-infrared spectroscopy for crystal form determination. The observed change in dissolution rate correlated with detection of a greater number of larger particles by FBRM. FBRM results indicate increased aggregation of the tablet material due to crystal form conversion, resulting in the presence of slowly disintegrating and dissolving granules during the dissolution process. The improved understanding of the dissolution process allows evaluation of the potential in vivo impact of the stability changes.

Keywords: Tablet dissolution; focused beam reflectance measurement; near-infrared spectroscopy; crystal form; dissolution mechanism

Introduction

In vitro dissolution testing is commonly performed to characterize drug product performance during the development of new pharmaceutical dosage forms.[1] There are many reports of observed changes in drug release profile due to storage of the drug product at elevated temperature and humidity conditions.[2−4] While it is desirable to select dissolution method conditions that are indicators for changes in product performance, the in vivo relevance of the observed changes is often unknown.[1] For example, slow release due to active ingredient change to a less soluble form may affect in vivo exposure, while coning of the excipients at the bottom of the vessel may not be relevant in vivo. To better understand the risk of in vivo exposure change related to changes in the in vitro drug release profile, an improved understanding of the tablet dissolution process is needed.

Multiple models have been proposed for dissolution of immediate release tablets.[1,5−7] Qualitatively, the steps required for dissolution of a tablet can be described as (1)

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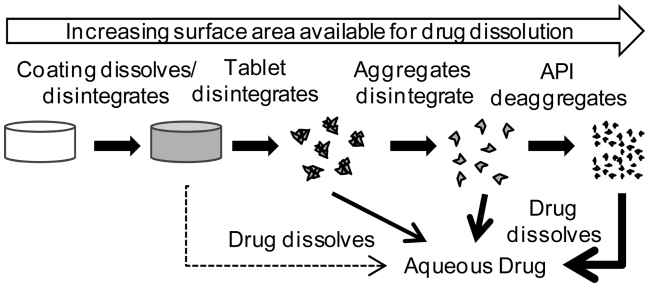

Figure 1. Schematic of immediate release tablet dissolution model.

dissolution of the tablet coating from the surface of the tablet, (2) disintegration of the tablet into aggregate particles of drug and excipient, and (3) deaggregation and dissolution of the aggregates to progressively smaller particles, as illustrated in Figure 1. The dissolution rate of the drug is proportional to the solubility in the medium and the surface area of the material.[6] As disintegration and deaggregation progress, the surface area of drug available to the medium for dissolution increases. If tablet or aggregate disintegration is the rate limiting step in the dissolution process, the overall dissolution rate will be slower than would be predicted based on the drug substance dissolution rate alone. This is because aggregates can effectively behave like larger particles of drug due to the low accessibility of the medium to the drug surface.

In the case of immediate release disintegrating tablets, changes in dissolution have been attributed to changes in excipients due to thermal stress or moisture ingress, changes to the active ingredient such as degradation or form conversion, or a combination of factors.[2−4,8,9] Standard dissolution end points, such as liquid chromatography or ultraviolet (UV) spectroscopy testing, quantify only the amount of dissolved drug. This approach does not allow observation of changes in the tablet and granule disintegration events, providing little insight into the underlying dissolution process.

Focused beam reflectance measurement (FBRM) is an in situ particle characterization technique that has been used for monitoring of particle formation and dissolution in reaction vessels and process streams.[10−13] The FBRM instrument consists of a probe which is placed into the reaction vessel or process stream. Within the probe, a laser is focused on the surface of a sapphire window by a set of rotating optics. When the laser encounters a particle, the light is reflected back to the sensor. The reflected beam signal provides information on the number of particles present and one-dimensional information on the size of the particles, referred to as chord lengths, as a function of time.

In this work, the FBRM instrument was utilized to monitor the progress of tablet and aggregate disintegration throughout the dissolution process in the dissolution vessel.[14−16] The FBRM instrument provided nonspecific detection of any particles suspended in the dissolution medium. Additionally, fiber optic UV detection was used to determine the drug release profile of the tablets. These techniques were applied to an immediate release tablet formulation that had undergone changes in release profile and crystal form after storage at high humidity. The preferred crystal form, referred to as form A, was observed to undergo recrystallization to yield either form B or C, both of which are relatively stable nonstoichiometric hydrates. Slurry and annealing experiments carried out using drug substance forms B and C identified no conditions that caused interconversion of the two forms. Forms B and C have similar solubility, and both were slightly less soluble than form A. The relative amount of forms B and C present in the tablets was dependent upon water activity during storage. Conversion was relatively rapid, and was observed to approach steady state after one month of storage at high humidity. In the drug product, form B predominated when the water activity is above about 0.39, while below that level, form C predominated.

Experimental Section

Materials. Tablets were prepared by a high shear wet-granulation process using each of the three crystal forms of the active ingredient (Eli Lilly, Indianapolis, IN). The unit

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Table 1. Test Sample Composition

ingredient name	active tablet[a] (mg)	placebo tablet[a] (mg)
Granulation		
drug substance	21.53	0
lactose anhydrous granular	61.68	83.21
lactose spray dried special	15.42	15.42
crospovidone XL-10	3.125	3.125
Granulation Solution		
povidone	6.25	6.25
polysorbate 80	0.625	0.625
Outside Powders		
microcrystalline cellulose granular -102	12.50	12.50
crospovidone XL-10	3.125	3.125
magnesium stearate	0.75	0.75
Film Coating		
lactose based color mixture	5.00	5.00

[a] Total tablet weight: 130.0 mg.

formulas for the test materials are summarized in Table 1. A granulation liquid containing binder and a wetting agent was granulated with a dry powder blend containing the drug substance using a 10 L or 65 L Powrex granulator (Glatt, Binzen, Germany). The wet granulation was milled with a 197S Comil equipped with a 0.500 in. square mill screen (Quadro Engineering, Ontario, Canada) and then dried by a MP-1 or MP-2/3 fluid bed dryer (GEA Niro, Soborg, Denmark). The dried granulation was then milled with a 197S Comil equipped with a 0.040 in. grated mill screen. The milled granulation was then mixed with additional excipients and compressed using a XL200 tablet press (Korsch, South Easton, MA) equipped with 7 mm round tooling to yield the core tablets. The core tablets were subsequently color-coated using a Compu-Lab 24 equipped with a 15 in. drum (Thomas Engineering, Hoffman Estates, IL). Placebo tablets were also prepared by substituting an equivalent quantity of diluent for the active ingredient in the tablet. In process samples of granulation, final blend, uncoated, and coated tablets were collected for one lot of placebo and form A tablets.

Material characteristics of the drug substance and formulated material are summarized in Table 2. Particle size distribution for the drug substance used in each of the active lots was determined by laser light diffraction with the Mie optical model using the particle size distribution analyzer LA-920 (Horiba Instruments, Ann Arbor, MI). The drug substance was dispersed in analyte-saturated hexane (Mallinckrodt, Phillipsburg, NJ) containing 0.2% or 0.25% sorbitan monooleate (Span 80, Sigma Aldrich, St. Louis, MO) for analysis, and results were the average of two replicates. Particle size distributions for the granulated material from the placebo and active form A lots were determined by laser diffraction using a Malvern Mastersizer 2000 with Scirocco 2000 dry powder feeder (Malvern Instruments, Worcestershire, U.K.), with results showing the average of 3 replicates. Tablet breaking strength was measured by a Key hardness tester (Key International, Englishtown, NJ), and tablet thickness was measured by a digital thickness gauge (Mitutoyo, Aurora, IL). Theoretical porosity was calculated by dividing the apparent tablet density by the final blend true density. Final blend true density was measured using a Micromeritics AccuPyc 1330 helium pycnometer (Micromeritics, Norcoss, GA). Apparent tablet density was calculated by dividing the tablet weight by its volume, and tablet volume was estimated based on tablet thickness and tooling geometry.

Controlled Humidity Storage. Controlled humidity storage chambers were prepared using saturated salt solutions. Saturated solutions of lithium chloride (Sigma Aldrich, St. Louis, MO), potassium carbonate (Fisher Scientific, Fair Lawn, NJ), and sodium chloride (Fisher Scientific, Fair Lawn, NJ) in water were placed at the bottom of sealed containers. These salt solutions result in relative humidity conditions of approximately 11%, 43%, and 75% respectively. A plastic spacer was placed in each container to prevent sample contact with the saturated solution. Samples were placed on the plastic spacer in open sample cups as indicated in Table 3. The sealed humidity containers were stored in a Thermolyne series 9000 oven (Thermo Scientific, Waltham, MA) for one month at 30 °C.

Water activity of the tablets was tested before and after controlled humidity storage using a Novasina ms1 water activity meter (Lanchen, Switzerland).

Crystal Form Characterization. Near infrared (NIR) spectroscopy was utilized for crystal form determination.[17−20] Five tablets from each lot were analyzed in the transmittance mode ($n = 1$ analysis per tablet) using a Bruker MPA FT-NIR (Ettlingen, Germany). A multivariate quantitative model was built using a statistical mixture design with 12 lots of tablets with differing quantities of each of the three drug substance crystal forms. OPUS software version 5.5 (Bruker, Ettlingen, Germany) was used to build the multivariate quantitative model, which had 36 spectra in the calibration set and 24 in the validation set. Several unique spectral differences between the three forms were seen in the region between 9000 and 8400 cm^{-1} when vector normalization and first derivative spectral pretreatment were applied, as shown in Figure 2. The spectra were truncated to the 8397.4 to 9006.8 cm^{-1} range and preprocessed with a first derivative plus vector normalization to obtain a three-factor partial least-

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Table 2. Tablet Processing Conditions and Material Properties

	lot 1 (placebo)	lot 2	lot 3	lot 4	lot 5
drug substance form	na[a]	A	A	B	C
drug substance particle size (μm) d_{10}, d_{50}, d_{90}	na	1, 6, 13	2, 8, 14	1, 6, 16	1, 4, 9
granulation scale (kg)	22	22	22	2.5	2.5
granulation particle size (μm) d_{10}, d_{50}, d_{90}	121, 232, 1050	121, 526, 1146	66, 463, 1147	na	na
compression force (kN)	11.7	9.5	9.3	9.9	9.5
breaking force (kP)	7.5	6.8	6.8	6.5	8.2
tablet thickness (mm)	3.24	3.31	3.31	3.31	3.3
theor porosity (%)	0.13	0.13	0.14	0.13	0.13

[a] Not available.

Table 3. Summary of Material Storage Conditions

material name	process stage	crystal form	storage conditions (% RH)
lot 1 (placebo)	coated tablet	none	11, 43, 75
lot 2	final blend	form a	75
lot 2	granulation	form a	75
lot 2	uncoated tablet	form a	75
lot 2	coated tablet	form a	75
lot 3	coated tablet	form a	11, 43, 75
lot 4	coated tablet	form b	11, 43, 75
lot 5	coated tablet	form c	11, 43, 75

squares model. The limits of quantitation were estimated to be 4%, 12%, and 3% for forms A, B, and C, respectively.

Dissolution Testing. Tablet dissolution was determined using a Distek Evolution 6100 (North Brunswick, NJ) equipped with USP Apparatus 2 (paddles). The paddle speed was set to 75 rpm for the first 60 min of testing, and then was increased to 250 rpm for an additional 30 min. The 75 rpm paddle speed was selected in order to suspend a majority of the particles in the vessel while minimizing turbulent mixing which could cause changes in the tablet dissolution profiles. Medium was added to the vessels by preheating and degassing 950 mL of deionized water using a Distek ezfill 4500 (North Brunswick, NJ) and adding 50 mL of 2.0% polysorbate 80 (Fisher Scientific, Fair Lawn, NJ) solution, resulting in 1000 mL of 0.1% polysorbate 80 as the dissolution medium. Typically, dissolution tests are conducted on single dosage units; however, in this case two tablets or an equivalent amount of powder was used for each test. The amount of material in the vessel was increased in order to increase the FBRM signal, and did not have a significant impact on the UV profile. Tablets and powder were introduced to the vessel by adding them directly to the medium surface approximately halfway between the paddle shaft and the wall of the vessel. No sinkers or baskets were utilized for this study as the tablets immediately sank to the bottom of the vessel, and powders were observed to quickly disperse into the medium during mixing.

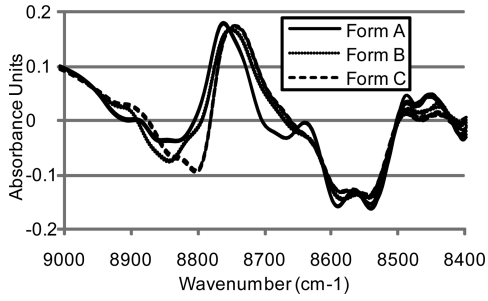

Figure 2. NIR overlay of first derivative and vector normalized spectra for five tablets of each of three drug products (100% form A, 100% form B, 100% form C).

Drug release profiles were determined by fiber optic UV at 275 nm using the Leap Technologies Opt-Diss UV fiber optic instrument equipped with 1 cm path length probes (Distek, North Brunswick, NJ). Dissolution was assumed to be complete after 80 min of total run time (60 min at 75 rpm plus 20 min at 250 rpm). The average response between 80 and 90 min (from 20 to 30 min at 250 rpm) for each run was utilized as a reference to calculate the relative extent of drug release during the first 60 min of each run. Placebo materials were not monitored by UV.

Particle monitoring was performed with the Lasentec FBRM model S400A with probe model PI-14/206 (Mettler Toledo, Columbus, OH), with a scanning speed of 2 m/s, particle size range of 1 to 1000 μm, and logarithmic 90 channel grouping. Data acquisition and processing were performed using Lasentec FBRM Data Acquisition Control Interface V 6.7.0 software. Data were recorded every 5 s during the dissolution runs. Prior to each run, the absence of particle contamination on the surface of the sensor was confirmed by testing the FBRM probe in deionized water. If needed, the probe surface was cleaned using deionized water and methanol. The probe was then placed into the dissolution vessel as shown in Figure 3, using a ring stand to position the probe. The ring stand was marked with graduations to ensure consistent placement of the probe from run to run. The dissolution medium in the vessel was confirmed to be free of particulates by testing with the FBRM probe prior to starting the dissolution run.

Raw chord length distribution data is characterized by the FBRM software into bins, referred to as channels, with specific upper and lower limits. The particle size range A to B is divided into N logarithmic channels of equal ratio, r, between the left and right channel boundary as defined by

$$r = \left(\frac{B}{A}\right)^{1/N}$$

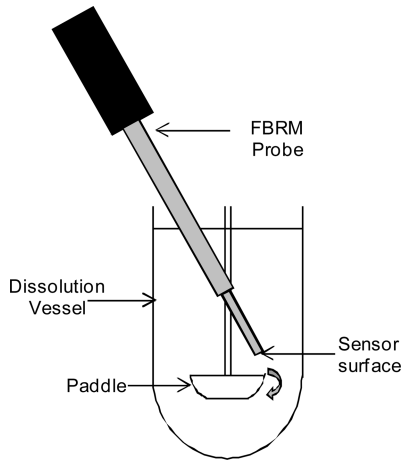

Figure 3. Schematic of FBRM probe position in the dissolution vessel. The probe is placed halfway between the paddle and the side of the vessel, approximately 3 cm above the top of the paddle, and angled such that the flow of medium in the vessel is directed onto the sensor surface.

The channel midpoint M_i is defined as

$$M_i = A\sqrt{r^{2i-1}}$$

for channels $i = 1, 2, \ldots N + 1$. Square weighting of the signal was performed using FBRM software version 6.7.0 using the following equation:

$$y_i = \frac{M_i^2}{\sum_{j=1}^{N} M_j^2} \cdot Nn_i$$

where y_i is the weighted counts in channel i, M_i is the channel midpoint, N is the number of channels, and n_i is the unweighted counts in channel i.[21]

Square-weighting of the FBRM signal was applied in order to emphasize larger chords in the chord length distribution. Unweighted FBRM signal of dissolved tablets is dominated by the large number of small particles in the tablet coating. This makes comparisons of coated and uncoated materials problematic. In addition, the small coating particles have a tendency to stick to the surface of the FBRM probe due to the relatively low fluid flow, causing spikes in the signal. Square weighting the signal minimizes these interferences, and provides the ability to follow the progression of tablet and aggregate disintegration.

A nine point boxcar moving average was applied to the square weighted FBRM signal, in order to filter high frequency noise from the data. Quantitative metrics for comparison of FBRM dissolution results are not well established in the literature. In this work, changes in FBRM dissolution results were evaluated by qualitative comparison of the square weighted mean chord length and total square

(21) *Mettler Toledo iC FBRM User's Guide*; Mettler Toledo: 2007; PN 0031605 Rev A, pp 146−150.

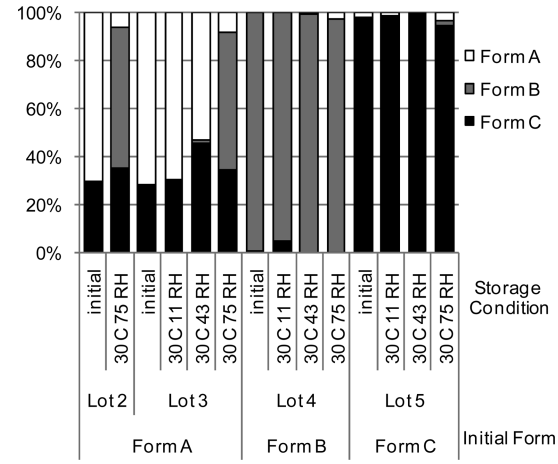

Figure 4. Crystal form composition of coated tablets as determined by NIR spectroscopy at initial and 1-month stressed conditions.

weighted particle counts plotted as a function of dissolution time. The square weighted chord length provided a measure of the mean size of the particles susupended in the medium, while the total square weighted particle count provided a measure of the relative amount of material suspended in the medium as a function of time. In the systems studied here, the mean size of the particles, the shape of the particle count profile, and the number of particles counted were found to be useful parameters to describe differences between profiles.

Results and Discussion

Initial water activity results were approximately 0.17 for the placebo to 0.24 for the active tablets. The initial results reflect the moisture level present in the bulk material after processing and storage. Water activity results for stressed materials were consistent with the expected moisture levels in the controlled humidity chambers, and verified equilibration of the tablets to the storage conditions.

Crystal form composition of the active tablets, as determined by NIR, is illustrated in Figure 4. Initial samples of form A tablets contained approximately 30% of form C due to ambient moisture exposure during bulk storage. Hydration was not reversed after 1-month storage of the form A tablets at 11% humidity, and no significant conversion was observed for the form B and C tablets at any of the stressed storage conditions. The form A tablets showed nearly complete conversion to forms B and C after storage at 75% humidity, with formation of intermediate levels of form C after storage at 43% humidity.

Square-weighted FBRM mean chord length and particle counts per second as a function of dissolution time are shown in Figures 5a and 5c for unstressed placebo materials. For the coated and uncoated tablets, an increase in particle counts was observed in the first 10 min, coinciding with the disintegration of the tablet. Dissolution of soluble excipients was rapid relative to the tablet disintegration rate, and only the particles due to insoluble excipients were observed in suspension throughout the dissolution run. The larger number

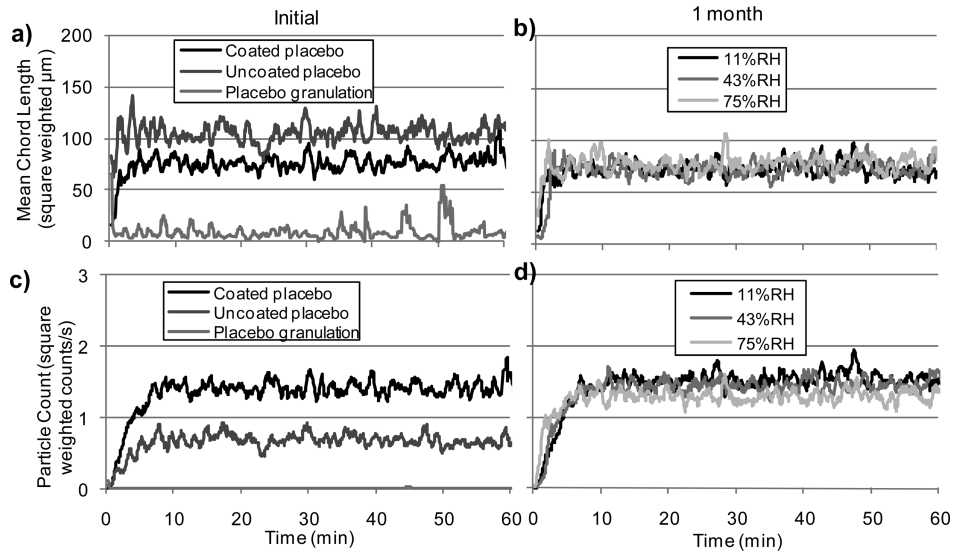

Figure 5. Square weighted mean chord length (a and b) and square weighted particle counts per second (c and d) as a function of dissolution time for unstressed samples of coated and uncoated placebo tablets and placebo granulation (a and c), and coated placebo tablets stressed at 30 C for one month at 11, 43, and 75% humidity (b and d).

of particles counted for the coated tablets was due to insoluble coating ingredients that result in a large number of small particles in the 1−20 μm size range. These small coating particles also bring the mean size of the particles in the coated tablet sample to approximately 75 μm compared to about 100 μm for the uncoated tablets. Placebo granulation, which is primarily made up of lactose, disperses and dissolves very rapidly such that few particles are counted by the FBRM.

Square weighted mean chord length and particle counts for coated placebo tablets exposed to varying moisture levels are shown in Figures 5b and 5d. No change in the mean size of the particles, the shape of the particle count profile, or the number of particles counted was observed as a function of storage humidity. The lack of change in the placebo tablet after storage at varying humidities indicates that any changes in the active tablets were due to the active ingredient or an interaction of the active ingredient with the excipients, and not due to a change in the excipients alone.

Dissolution results for active materials from different process stages are shown in Figure 6. Figures 6a and 6c show the square weighted FBRM results for dissolution of unstressed materials. The uncoated and coated tablets have similar particle count profiles, with an increase in particle counts over the first 10 min, which correlates with the tablet disintegration time. After 10 min, a decrease in particle counts occurred until a steady state was reached. The granulation and final blend materials dispersed rapidly in the vessel, with initial particle counts similar to the maxima observed for the intact tablets. For the final blend, the particle counts decreased to a steady state comparable to the intact tablets, which is consistent with the equivalent quantity of insoluble excipients in the materials. The granulation, which contains primarily soluble materials, decreased to around zero counts after approximately 20 min.

The tablet disintegration time was similar for the active and placebo tablets, indicating that the presence of active ingredient was not impacting tablet disintegration. After the tablet disintegrated, the mean particle size was larger, and a larger number of particle counts was observed for the active tablets compared to the placebo tablets (Figures 5a and 5c). The higher particle counts were due to slower dissolution of the particles formed by disintegration of the active tablets. This resulted in the formation of a maximum in the particle count profiles for the active tablets that was not observed for the placebo tablets. The slower decrease in chord counts for the active granulation compared to the placebo granulation suggested that the granule disintegration and dissolution rate was driven by the presence of the active ingredient. Slower granule disintegration may also be caused by differences in the granule size, density, or porosity due to the presence of greater quantities of soluble excipients during the granulation process.

FBRM signals for dissolution of 1 month 30 °C 75% humidity stressed samples from different process stages are shown in Figures 6b and 6d. The coated and uncoated tablets disintegrated in approximately 10 min, which was comparable to the unstressed tablets. An increase in the mean particle size and the number of particles counted was observed for all stressed materials, as was a reduction in the rate of decrease in the particle counts. This indicated the presence of larger, slower dissolving aggregate particles. The mean size of the particles was larger for the granulation and final blend compared to the tablets, while the change in the rate of decrease in particle counts did not appear to be dependent on the process stage of the material.

The rate of decrease in FBRM counts for both unstressed and stressed samples was visually comparable to the rate of increase of drug in solution by UV as shown in Figure 6e and 6f. The point at which the FBRM counts reach steady state correlated well with complete drug release as measured by UV.

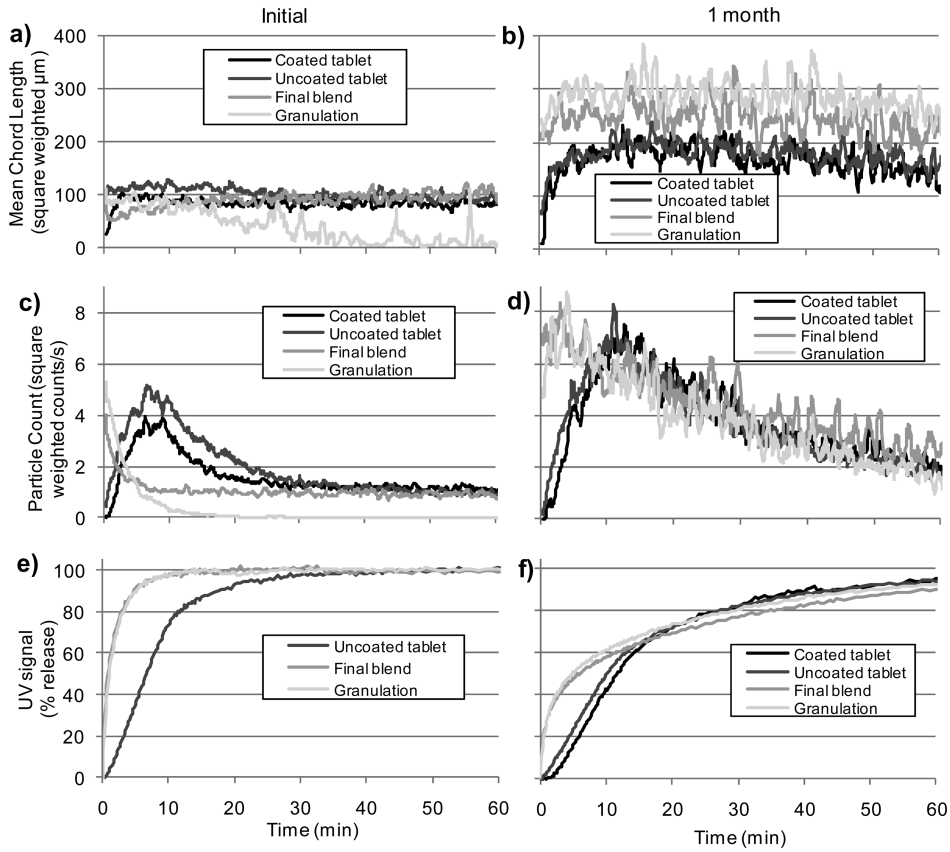

Figure 6. Square weighted mean chord length (a and b), square weighted particle counts per second (c and d), and UV signal (e and f) as a function of dissolution time for unstressed samples of active coated and uncoated tablets, final blend and granulation (a, c, and e) and for the same materials stressed at 30 C and 75% humidity (b, d, and f).

Dissolution results for unstressed and stressed coated tablets manufactured with each of forms A, B, and C are shown in Figure 7. FBRM signals for the form A tablets (Figures 7a and 7d) showed an increase in mean particle size and particle counts during dissolution of the 75% humidity sample, which correlated with slower release of drug as measured by UV (Figure 7g). Little change from initial is observed for the 11% and 43% humidity samples, consistent with the relatively low levels of form conversion observed for these materials. The form B and C tablets did not show a change in FBRM or UV profile after stress storage (Figures 7b, 7c, 7e, 7f, 7h, and 7i). The release profile by UV showed that drug release for forms B and C is rapid, indicating that a change in solubility due to conversion of form A material after high humidity storage was not the cause of the decreased dissolution rate.

Run-to-run variability of the FBRM signal was not evaluated in this study. Hydrodynamic studies of the paddle dissolution apparatus suggest that probe placement within the vessel could be a source of variability.[22,23] Low numbers of large particles are counted by the FBRM, and relatively noisy signal is also observed. However, good agreement in FBRM profiles was observed between the form B and C tablets at all storage conditions and time points (Figure 7). This is consistent with the similarity in the UV dissolution profiles, suggesting that the reproducibility of the FBRM signal is acceptable for the purposes of this study.

In the drug product investigated here, the change in crystal form due to humidity exposure might be expected to impact the dissolution rate because of lower solubility of the form B and C material. However, in this case, the solubility of the crystal forms is similar enough that drug release from the aggregates was rapid compared to the rate of tablet disintegration. Therefore, there is no decrease in the dissolution rate of the form B and C tablets compared to the unstressed form A tablets (Figure 7).

The stressed placebo and form B and C tablets showed no change in dissolution profile as a result of humidity exposure (Figures 5 and 7). This suggests that the change in dissolution of the form A tablets was not due to changes in the tablet excipients nor chemical interaction of the drug with the excipients. Instead, the dissolution change only occurred when the form A material was hydrated in the matrix. The change occurred regardless of the process stage of the material (Figure 6). Although the tablet disintegration time was similar in the stressed and unstressed tablets, the results

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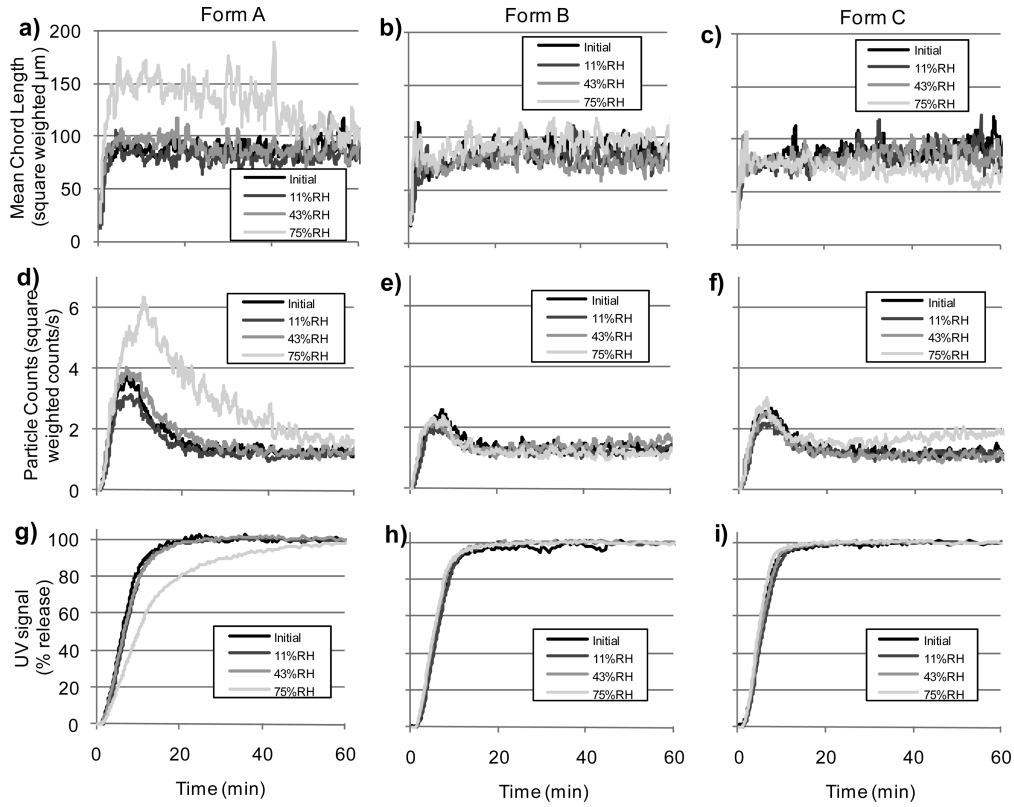

Figure 7. Square weighted mean chord length (a, b and c), square weighted particle counts per second (d, e, and f), and UV signal (g, h, and i) as a function of dissolution time for form A (a, d, and g), form B (b, e, and h) and form C (c, f, and i) coated tablets at initial and after 1 month stressed storage at 30 °C and 11, 43, and 75% humidity conditions.

indicated that humidity exposure resulted in the formation of aggregates which were slow to undergo further disintegration and dissolution. The larger aggregates may have been caused by the formation of larger drug crystals or aggregates during form conversion, or by a physical interaction of the drug with excipients during the recrystallization event.

In the absence of form conversion, the rate limiting step for the dissolution process for this formulation was the disintegration of the tablets. This was demonstrated by the rapid release of drug from the final blend and granulation, which reached 80% released in about 3 min, as compared to about 12 min for the tablet as shown in Figure 6e. When extensive conversion occurred in the form A tablets, granule or aggregate disintegration became the rate limiting steps in the dissolution process, as observed for all of the form A materials stressed at 75% RH (Figures 6 and 7).

Conclusion

FBRM was successfully applied to monitor the disintegration and dissolution of an immediate release tablet formulation. A change in dissolution observed after high humidity exposure was found to be due to changes in the disintegration and dissolution of the aggregates. The changes occur due to form conversion of the form A drug substance, but are not related to lower solubility of the form B and C materials.

Evaluation of the risk of in vivo exposure change was possible with improved understanding of the rate limiting step in the dissolution process. The change in dissolution was evaluated relative to the known pharmacokinetic parameters and existing in vivo results. In this example, a different formulation of the drug product that exhibited slower in vitro release was observed to have an impact on bioavailability. That is, drug substance release was slow and the suppressed release was attributed to the formulation rather than the physical properties of the drug substance. The change in aggregate disintegration and dissolution observed in vitro for the formulation evaluated here is also expected to occur in vivo. Therefore the changes to the in vitro release profile were also believed to have the risk of impacting bioavailability. Consequently, controls were established for drug release and moisture exposure for the drug product. The controls ensured that any changes in the drug product due to moisture exposure did not impact bioavailability of the drug.

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