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Commentary:

Towards Physico-Relevant Dissolution Testing: The Importance of Solid-State Analysis in Dissolution

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ABSTRACT

Polymorphism and other solid-state phenomena can have effects on many physicochemical properties of pharmaceuticals. In this commentary, some aspects of solid-state pharmaceutics that are important to dissolution testing are highlighted. Examples of how solid-state analysis can be used to aid interpretation of dissolution results are also reviewed. We suggest the term *physico-relevant dissolution testing* to describe the combination of dissolution testing with solid-state analysis.

INTRODUCTION

Polymorphism, in a general sense, is defined as the ability of solid materials, such as pharmaceutical compounds, to exist in different solid forms including crystalline, amorphous, and hydrate or solvate forms. It can have implications on various physicochemical properties, of which solubility and dissolution rate are the most important for therapeutic efficacy (*1*). The effect on solubility and dissolution rate is particularly important if the active pharmaceutical ingredient (API) belongs to Biopharmaceutics Classification System (BCS) (*2*) Class II or IV, where solubility is the rate-limiting step for bioavailability. Polymorphism can also affect processing characteristics, such as powder flow or compaction properties, and intellectual property considerations. In this paper, however, the focus is on the effect of polymorphism on solubility and dissolution rate.

The solid form of an API for consideration as the commercial form is chosen at an early stage of the drug development process. Conventionally, the most stable solid form is the typical candidate. However, new APIs tend to be poorly water soluble, which has forced the industry to seek out methods to increase the solubility. One approach is to use high-energy forms such as metastable polymorphs or amorphous forms. In a recent review, Pudipeddi and Serajuddin (*3*) gathered the solubility data of 55 polymorphic compounds and calculated solubility ratios of different polymorphs. They found that as a general trend, the ratio of polymorph solubility is typically less than two; however, higher ratios were also observed. In another study by Hancock and Parks (*4*), the solubility advantage (i.e., better solubility) of amorphous APIs compared with crystalline counterparts was investigated. The solubility advantage of amorphous forms was a lot greater than that of metastable crystalline forms, and it was concluded that even partially amorphous systems are likely to show clinically relevant solubility increases. Based on these results, it is evident that manipulation of the solid state characteristics of APIs is an attractive option to enhance their solubility. A metastable solid form may also be chosen for development unintentionally. The metastable form may work well for some time, but there is always the possibility that it converts to a previously unknown, late-appearing, more stable form, leading to dissolution test failure. Such an occasion can have serious consequences, as exemplified by the ritonavir case (*5*).

Based on thermodynamics, high-energy forms have greater solubility but, on the other hand, lower physical stability; they tend to convert to the more stable lower energy states. Thermodynamics, however, is not the sole stability-determining factor. In addition to thermodynamics, kinetics plays a role, and the final stability is the result of the interplay between these two factors. Hence, it is possible to stabilize metastable and amorphous forms to exploit their higher solubilities. In addition to shelf-life physical stability studies, we argue that the stability should be investigated during dissolution, since the stability can decrease radically upon immersion in a solvent or dissolution medium. A solid-state change during dissolution can be a direct solid–solid transformation or a solution-mediated transformation. The former encompasses nucleation and growth of the stable form in the solid state (*6*), whereas the latter consists of dissolution of the metastable form with subsequent nucleation and growth of the stable form (*7*). The driving force for a solution-mediated transformation is the supersaturation of the solution with respect to the stable form. The greater the solubility

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difference between the solid-state forms, the higher the possibility for a solution-mediated solid-state transformation. In other words, maximizing the solubility advantage also raises the risk of a solid-state transformation. It is well known that amorphous (*8*) and metastable crystalline (*9*) forms can convert to forms with higher stability (lower solubility) during dissolution. However, the consequences of such transformations are not obvious, and different solid forms of an API can show unexpected and unpredictable dissolution behavior (*10–13*).

IS THE AMOUNT OF RELEASED DRUG ALL WE WANT TO KNOW?

There is no question that dissolution testing is a powerful performance test for APIs and dosage forms. Nevertheless, a conventional dissolution test (i.e., one in which the concentration of API in the dissolution medium is the only parameter measured) provides information-poor data. A deviation from a 'normal' dissolution curve can, of course, be detected, but the underlying reasons for anomalous dissolution behavior cannot be directly attributed to any physicochemical phenomena taking place in the sample under investigation. Traditionally, a change in the dissolution rate has been considered as an indication of a possible solid-state transformation. However, different wetting characteristics, burst effects, and changes in the specific surface area, to name but a few possibilities, can also cause changes in the dissolution rate and complicate the analysis. Furthermore, several of these phenomena may occur simultaneously, therefore making it difficult to determine the exact cause of the "uncharacteristic" profile.

In addition to the dissolution medium, an important part of solid dosage form dissolution testing is the dissolving solid sample itself. Dissolution media have been the subject of extensive research, and important progress has been achieved, such as the development of biorelevant dissolution media (*14*). However, analysis of only the drug in solution reveals just a part of the occurring phenomena. We argue that it is important to gain a deeper understanding of the dissolution process by directly analyzing not only the drug in the liquid dissolution medium, but also the solid state of the dissolving sample. This is especially important whenever an API is used in a nonthermodynamically stable state. Such an approach makes dissolution testing physico-relevant and provides a more complete picture of the dissolution behavior.

HOW TO EXTRACT SOLID-STATE INFORMATION FROM THE DISSOLUTION PROCESS

With respect to monitoring of the process, crystallization from solution is not far from a conventional dissolution test. They both encompass solid samples that are in contact with a solvent, and similar methods of analysis are applicable for both. Sophisticated methods are used for in situ analysis during crystallization. For example, Schöll et al. (*15*) used a combination of different fiber-optic measurement techniques to determine solution concentration, the morphology of the solid particles, and the solid state of the compound being crystallized. With similar approaches, many times more information could be extracted from a dissolution test as well. Various fiber-optic systems for monitoring concentration during dissolution testing are already available (*16*), so successful application of additional solid-state analytical techniques would not require giant steps to be taken. Of course, such additional instrumentation is not essential for all compendial dissolution testing but for developmental and troubleshooting purposes, and whenever the API is used in a non-thermodynamically stable state, such an approach would be beneficial.

A straightforward approach to monitor the solid-state properties during dissolution has recently been introduced and is shown in Figure 1 (*17*). The experimental setup comprised a channel flow dissolution vessel coupled to a UV-vis spectrometer with a flow-through cuvette. Drug released from a constant surface area exposed to the dissolution medium was measured simultaneously with the solid-state properties of the drug remaining in the solid sample. Additionally, a Raman spectrometer with a fiber-optic probe was used to monitor the solid state of the dissolving sample in situ simultaneously with the measurement of the drug released from a constant surface area. Raman spectroscopy was chosen because of it is relatively easy to use, and can be applied to aqueous environments. Recent developments in spectrometer design have made Raman spectroscopy one of the basic solid-state analytical techniques and it is readily available in pharmaceutical laboratories in industry and academia. With Raman spectroscopy even small physicochemical changes occurring in the solid sample upon dissolution can be detected as it is a high resolution technique.

EXAMPLES OF SOLID-STATE TRANSFORMATIONS THAT CAN OCCUR DURING DISSOLUTION TESTING

Hydrate Formation

Many APIs and excipients undergo hydrate formation in aqueous surroundings. In the study by Aaltonen et al. (*17*), the dissolution of two pure anhydrous APIs, theophylline and nitrofurantoin, was examined in purified water. Both APIs underwent solid-state transformations to the hydrate form during dissolution, and the changes were quantitatively analyzed using Raman spectroscopy. Also, the dissolution of a compacted 50:50 mixture of theophylline anhydrate and microcrystalline cellulose was studied, and the method was suitable for detecting the solid-state changes of the API in the presence of the excipient. Since all transformations were direct

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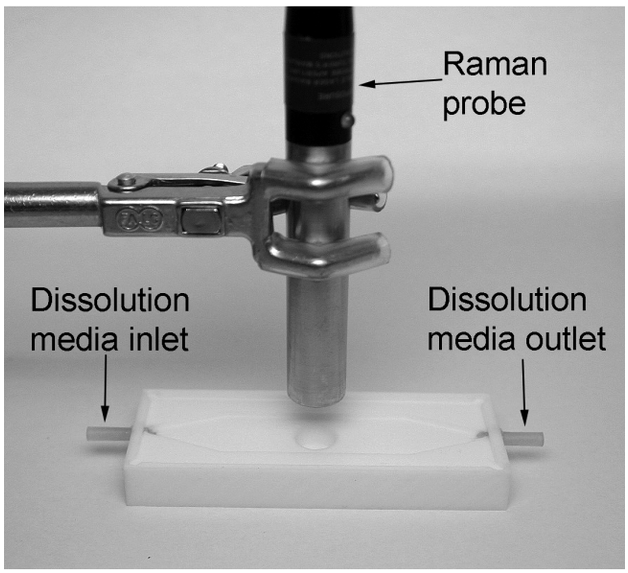

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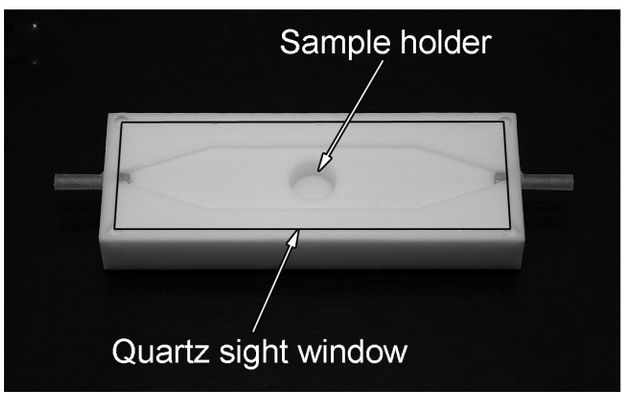

Figure 1. Experimental setup used to combine solid-state analysis with dissolution testing. (A) Raman probe assembly and (B) the channel-flow dissolution apparatus. (Reprinted with permission from ref 17. Copyright 2006 Wiley-Liss, Inc.)

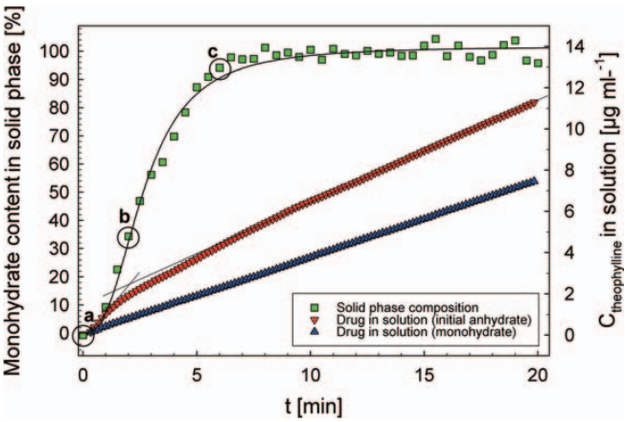

Figure 2. Dissolution of (initially) anhydrous theophylline (▼) combined with simultaneous Raman spectroscopic solid-state analysis (■). The constant dissolution rate of theophylline monohydrate is shown for comparison (▲). (Adapted from ref. 17. Copyright 2006 Wiley-Liss, Inc.)

transformations between two solid forms (involving no intermediate solid forms), they could be quantified with a classic calibration model using intensities of characteristic peaks of the solid forms identified in the Raman spectra.

In the beginning of the dissolution test, when the theophylline sample was still anhydrous, the dissolution rate was fast, but after the solid-state transformation was initiated, the dissolution rate started to decrease (red triangles, 0–6 min; Figure 2). When the solid-state transformation was complete, the dissolution rate reached a steady state (after 6 min). With scanning electron microscopy (SEM), micrographs taken off-line at time points 0, 2, and 6 min show the formation of the hydrate phase on the surface of the sample (Figure 3A–C). The micrographs also revealed the change in specific surface area due to the growth of a new phase. This resulted in a slightly higher dissolution rate for the initially anhydrous sample than for a sample compressed of theophylline monohydrate even after full anhydrate to monohydrate conversion had occurred. The solid state can also be verified before and after the dissolution test with X-ray powder diffraction (XRPD). XRPD confirmed that the initially anhydrous theophylline sample (Figure 4A) was fully converted to the monohydrate after the dissolution test (Figure 4B). Off-line XRPD, however, has several disadvantages compared with in situ Raman monitoring. Using off-line XRPD, one cannot gain information about the paths of the sometimes-complicated transformations that may involve several solid forms (as reviewed later in this paper). Further, it requires removal of the sample from the dissolution vessel which, in its own right, could induce solid-state transformations. Unlike in situ analysis, the off-line XRPD measurements also add to the time spent on the overall sample analysis.

Crystallization of an Amorphous Form

Crystallization of the amorphous form of an API is another common solid-state transformation occurring in wet conditions. Savolainen et al. (*18*) investigated the solid-state behavior during dissolution of two amorphous APIs, indomethacin and carbamazepine, using the same dissolution–Raman spectroscopy setup used above. Indomethacin exists in two crystalline forms, α and γ, and an amorphous form. In the study, all solid-state forms of the API showed different dissolution behavior. In the two dissolution media studied, the amorphous form showed superior dissolution rates compared with the two crystalline forms at the beginning of the tests. However, during the tests, the dissolution rate of the amorphous samples decreased. These changes could be explained by

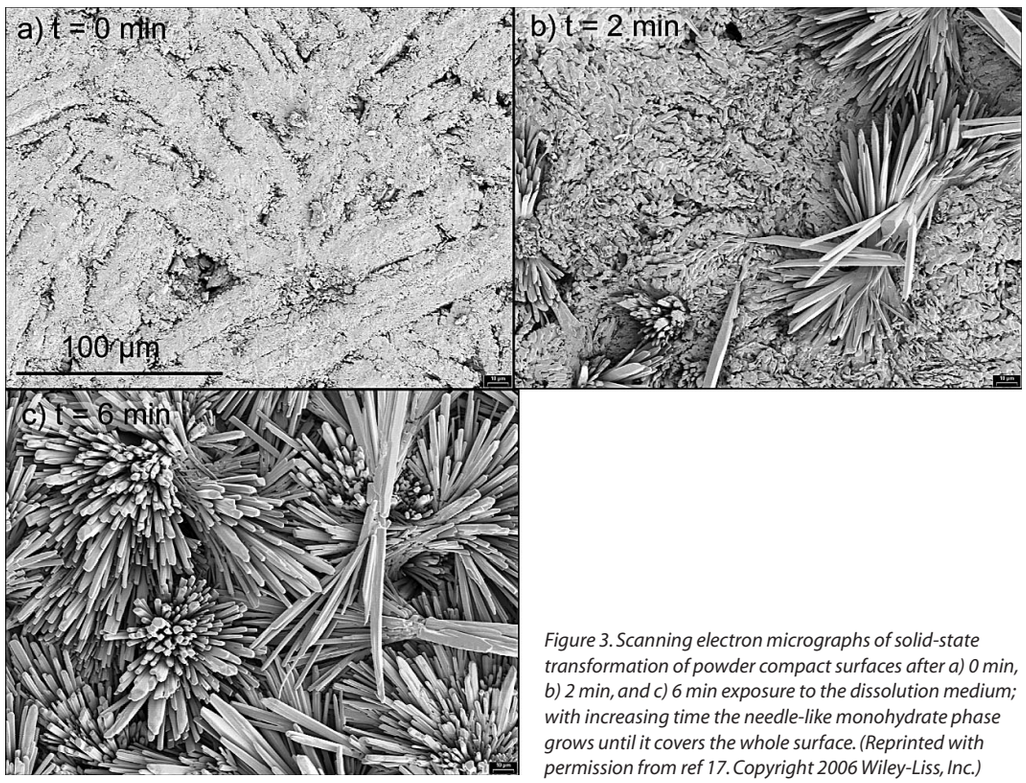

Figure 3. Scanning electron micrographs of solid-state transformation of powder compact surfaces after a) 0 min, b) 2 min, and c) 6 min exposure to the dissolution medium; with increasing time the needle-like monohydrate phase grows until it covers the whole surface. (Reprinted with permission from ref 17. Copyright 2006 Wiley-Liss, Inc.)

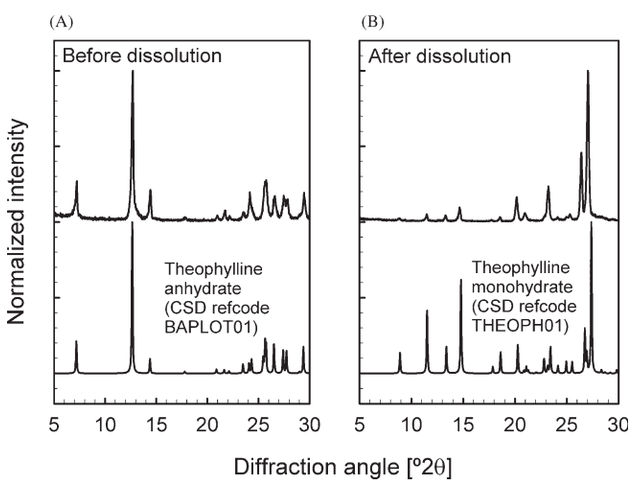

Figure 4. XRPD patterns of theophylline anhydrate tablet surfaces (above) and corresponding reference structures from Cambridge Structural Database (CSD) (below) (A) before and (B) after dissolution testing.

analyzing the Raman data recorded in situ. The Raman spectra of the different solid forms of indomethacin are unique but still very similar and exhibit overlapping bands. Multivariate analysis was used in the analysis, as it is able to cope with such data. A semi-quantitative classification method, partial least-squares discriminant analysis (PLS-DA), where the spectra of the three pure solid forms (amorphous, α, and γ) were used for calibration, was employed to analyze the Raman data. Results show that the recrystallization tendency of amorphous indomethacin is dissolution-media dependent, and even though the recrystallization could not be completely blocked, the dissolution rate of indomethacin could be kept higher by slowing down the recrystallization rate. During the course of the experiments, the amorphous form partly crystallized to the metastable form α but not to form γ, which is the thermodynamically stable form. Raman spectroscopy was sensitive to even small amounts of the recrystallized API species.

Crystallization of an Amorphous Form Followed by Hydrate Formation

In the same study, the dissolution behavior of amorphous carbamazepine was more complicated than the dissolution behavior of amorphous indomethacin (*18*). A pH 7.2 phosphate buffer solution was used as the dissolution medium, and the dissolution rate of amorphous carbamazepine was compared with that of the stable form in aqueous surroundings, the dihydrate. The in situ Raman data were analyzed with the same method (PLS-DA) as in the indomethacin example, but this time, four solid forms (the amorphous form, crystalline forms I and III, and the dihydrate) were used for calibration purposes. The multivariate analysis of Raman data

revealed the complicated nature of solid-state transformations taking place during dissolution of carbamazepine. First, the amorphous form crystallizes to anhydrous forms I and III, and subsequently, the formation of carbamazepine dihydrate occurs. Amorphous carbamazepine showed varying dissolution behavior; with some samples dissolving faster while others had slower dissolution rates than those for the dihydrate. The dissolution rate was dependent on the ratio of the various solid forms present during the tests, and according to Raman spectroscopy and XRPD, the solid state of the initially amorphous sample was always a mixture of three crystalline forms (forms I, III, and the dihydrate) at the end of the experiments. The in situ solid-state analysis was an indispensable tool for clarifying the path of multiple solid-state transformations that occur during dissolution of amorphous carbamazepine.

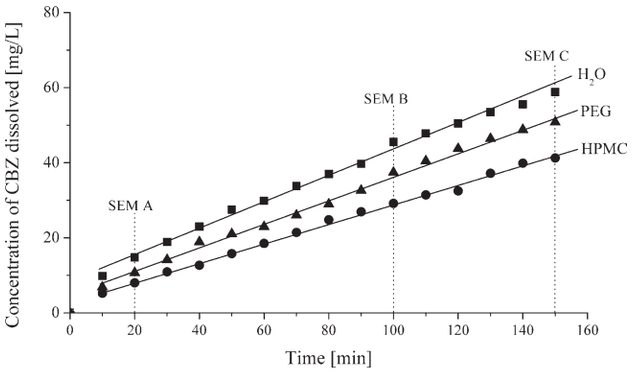

Figure 5. Dissolution profiles of CBZ form III compacts in three different dissolution media; water (■); PEG solution (▲); and HPMC solution (●). The dashed lines (SEM A–C) indicate the time points for SEM images shown in Figure 6. (Reprinted with permission from ref 19. Copyright 2006 Wiley-Liss, Inc.).

FACTORS AFFECTING SOLID-STATE BEHAVIOR DURING DISSOLUTION OR ADMINISTRATION

There are several factors that can promote or prevent solid-state transformations during dissolution testing and in the GI tract. For example, the presence of various excipients in the final dosage form can alter the performance of the API by acting as promoters or blockers for solid-state transformations. This can result in unpredictable solid-state behavior different from what one would expect based on intrinsic dissolution of pure solid forms of the API. To be able to achieve in vitro–in vivo correlation (IVIVC), dissolution media that are representative of actual physical conditions should be used. From the solid-state viewpoint, it is also very important to use biorelevant media, since their components can have an effect similar to that of excipients on the solid-state transformation tendency of APIs. Some examples of the effect of excipients and biorelevant dissolution media on the solid-state behavior of an API during dissolution are given below.

Effect of Formulation Excipients

In another study involving carbamazepine, Tian et al. (*19*) examined the effect of the presence of two common excipients, hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG), on the dissolution of carbamazepine anhydrate form III and carbamazepine dihydrate. Disks were compressed of both solid forms and their dissolution tested in 200 mL of distilled water and 0.1% aqueous solutions of HPMC and PEG in a paddle apparatus. The solid state of the disks recovered at various time points was investigated with SEM and XRPD. It was found that even at such small concentrations, the presence of excipients can have an effect on the dissolution behavior. The anhydrous form III had the highest dissolution in water; the second highest was in the PEG solution, and the lowest in the HPMC solution (Figure 5). Because the dihydrate is the thermodynamically stable form in aqueous media, it was growing on the compact surface during dissolution in water as seen in the scanning electron micrographs (Figure 6). In the PEG solution, the growth of the dihydrate form was noticed as well, but to a lesser extent and with a slightly different morphology. The interaction between PEG and carbamazepine molecules interfered with the solid-state transformation in PEG solution and resulted in formation of fan-shaped dihydrate clusters, whereas in water, the dihydrate existed as randomly oriented needle-like crystals. HPMC blocked the hydrate formation completely, and no dihydrate growth could be seen with either SEM or XRPD. Although the dihydrate is the stable form that has the lowest thermodynamic solubility, the dissolution medium that promoted the largest dihydrate growth (water) resulted in the highest dissolution. The highest dissolution in water was attributed to the largest increase in specific surface area available for dissolution. In the HPMC solution, the disk remained anhydrous, but its thermodynamic solubility advantage was overridden by the lack of surface area growth due to the interaction between the excipient and the API.

The excipients also influenced the dissolution of carbamazepine dihydrate disks. As expected, no solid-state transformations were detected because the dihydrate is the stable form in these conditions. However, differences in the dissolution rate and solid-state behavior could still be observed. Initially, dissolution in the excipient solutions was faster than in water. This could be explained by the lower surface tension of the PEG and HPMC solutions, which improved wetting of the disks, compared with water. However, at a later stage, there was a sudden increase in the dissolution in water that did not occur in the excipient solutions. SEM analysis elucidated the reason for the change and indicated differences in the dihydrate crystal morphology generated by the different dissolution

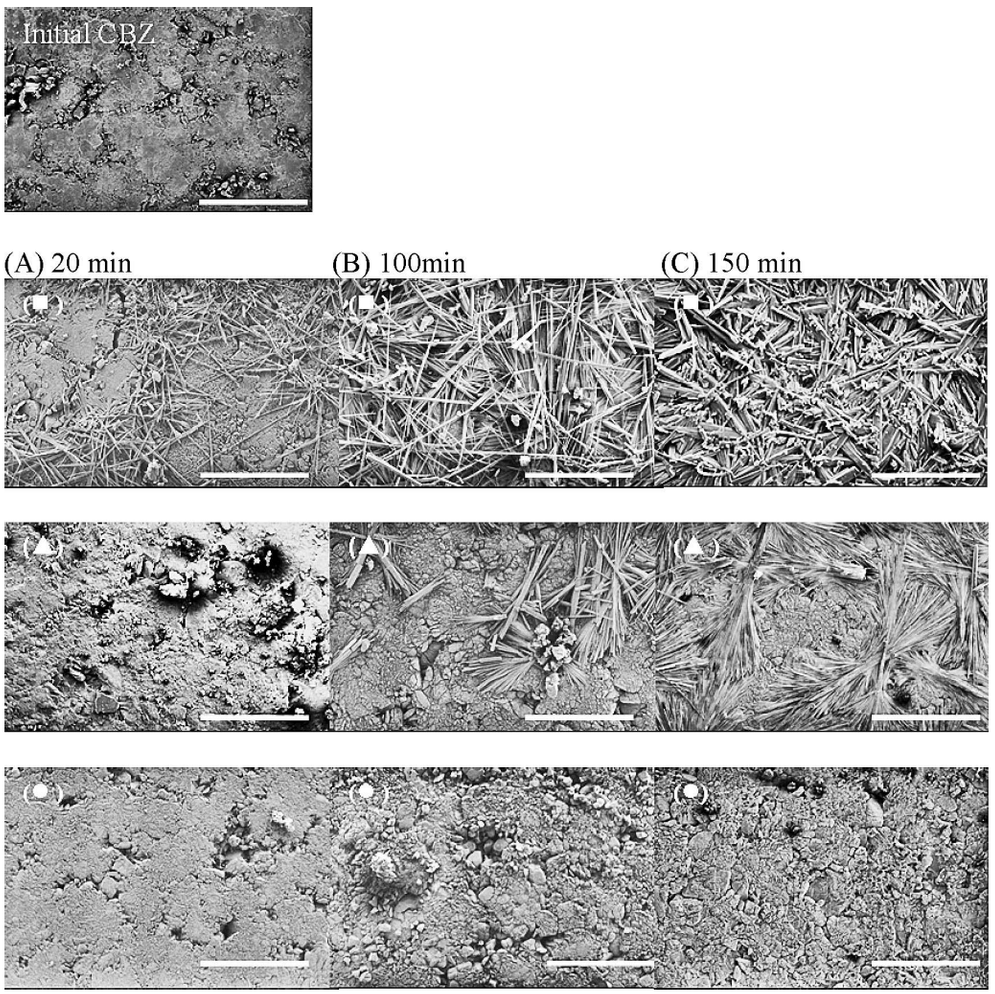

Figure 6. Scanning electron micrographs of initial CBZ compacts and compacts recovered after dissolution in each medium for (A) 20 min, (B) 100 min, and (C) 150 min in (■) water, (▲) PEG solution, and (●) HPMC solution. All micrographs were taken using the same magnification, scale bars: 500 µm. (Reprinted with permission from ref 19. Copyright 2006 Wiley-Liss, Inc.)

media. Dissolution in water resulted in a porous disk surface, while the surface remained smooth in the excipient solutions, again due to interactions between the excipients and the API.

Effect of Biorelevant Media

Lehto et al. (*20*) also studied the dissolution and solid-state behavior of carbamazepine using in situ Raman spectroscopy, but from a different viewpoint. The dissolution of carbamazepine anhydrate form III was studied and compared with carbamazepine dihydrate in two different dissolution media, namely a simple buffer solution and fasted state simulated intestinal fluid (FaSSIF), both having a pH of 6.8. The solid state of the samples was successfully analyzed with in situ Raman spectroscopy, even though FaSSIF was slightly opaque, which may have complicated the analysis. The dissolution behavior of the API was very different depending on the dissolution medium. In the buffer solution, the dissolution rate of initial form III decreased during the dissolution test and had lower overall dissolution than the dihydrate compact. In contrast, the dissolution behavior of the two carbamazepine forms in FaSSIF was as expected thermodynamically. The anhydrous form III started off with a higher dissolution rate than the dihydrate, and after a while, decreased and reached a steady rate that was the same as that of the dihydrate. The intrinsic dissolution rates of both form III and the dihydrate were higher in FaSSIF than in the buffer. FaSSIF contains surfactants that can increase the dissolution of drugs by improving wetting and facilitating solubilization, but the components of FaSSIF can affect dissolution performance by altering the solid-state behavior as well. In both dissolution media, a partial solid-state transformation

from form III to the dihydrate was noticed. Unlike in the previous study of Tian et al. (*19*), the transformation was not completely blocked using the excipient HPMC. However, according to the in situ Raman analysis, the extent of transformation was higher in the buffer solution than in FaSSIF. When the samples were analyzed with SEM, the crystal morphology was very different depending on the dissolution medium, suggesting an interaction between the drug and FaSSIF components. XRPD also verified the presence of both form III and the dihydrate after dissolution and confirmed the SEM results by showing distinctly different preferred orientation effects due to different crystal habits.

CONCLUSIONS

Several comments pertaining to properties of nonthermodynamically stable APIs are worth considering when interpreting anomalous dissolution profiles.

- Metastable polymorphic and amorphous forms of an API may not be stable during a dissolution study or after administration regardless of their stability over the shelf-life of the dosage form in the dry state.
- Solid-state transformations can and do occur during dissolution testing. These conversions are not always detectable from measuring the API concentration in solution, because there may be overlapping phenomena (such as specific surface-area changes and differences in wettability) that may override solid-state transformation processes.
- The analysis of the concentration of API in the dissolution medium is not always sufficient to explain what is happening in the solid state.
- To understand the sometimes-complicated dissolution behavior of APIs and formulations, it is recommended to directly monitor the solid-state properties during the dissolution process, especially during the developmental stage and for APIs in a non-thermodynamically stable state.
- It is worth mentioning that the solid-state analysis does not have to be quantitative; qualitative or semi-quantitative methods are easier and faster to apply, and are often adequate.

Numerous examples of the use of solid-state manipulation to enhance the dissolution of pharmaceuticals have been reported. This area of pharmaceutical research is constantly growing and will be of increasing importance due to the apparent trend of new APIs becoming ever less soluble. The use of more complex formulation approaches to stabilize the solid state should lead to more complex dissolution behavior as well. This underlines the need for more powerful methods of analysis that enable more information to be extracted from dissolution testing. Inclusion of in situ measurements of solid-state properties of the APIs during dissolution testing may help to pave the way for physico-relevant dissolution testing.

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