AAPS PharmSciTech **2004; 5 (1) Article 8 (http://www.aapspharmscitech.org).**

Influence of Processing-Induced Phase Transformations on the Dissolution of Theophylline Tablets

Submitted: July 16, 2003; Accepted: November 20, 2003

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ABSTRACT

The object of this investigation was to evaluate the influence of (1) processing-induced decrease in drug crystallinity and (2) phase transformations during dissolution, on the performance of theophylline tablet formulations. Anhydrous theophylline underwent multiple transformations (anhydrate → hydrate → anhydrate) during processing. Although the crystallinity of the anhydrate obtained finally was lower than that of the unprocessed drug, it dissolved at a slower rate. This decrease in dissolution rate was attributed to the accelerated anhydrate to hydrate transformation *during* the dissolution run. Water vapor sorption studies proved to be a good predictor of powder dissolution behavior. While a decrease in crystallinity was brought about either by milling or by granulation, the effect on tablet dissolution was pronounced only in the latter. Tablet formulations prepared from the granules exhibited higher hardness, longer disintegration time, and slower dissolution than those containing the milled drug. The granules underwent plastic deformation during compression resulting in harder tablets, with delayed disintegration. The high hardness coupled with rapid anhydrate → hydrate transformation *during* dissolution resulted in the formation of a hydrate layer on the tablet surface, which further delayed tablet disintegration and, consequently, dissolution. Phase transformations during processing and, more importantly, during dissolution influenced the observed dissolution rates. Product performance was a complex function of the physical state of the active and the processing conditions.

KEYWORDS: anhydrous theophylline, crystallinity, dissolution, tablet, hardness

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INTRODUCTION

The physicochemical properties of pharmaceuticals, including solubility and dissolution rate, can be influenced by the degree of crystallinity, solvation state, and crystal form. At room temperature, the anhydrate forms of ampicillin, theophylline, and glutethimide have a higher dissolution rate than their corresponding hydrates.[1] This difference in dissolution rate can be attributed to the difference in the free energy of hydration.[1] Similarly, metastable forms, because of their higher free energy, are expected to dissolve more rapidly than their corresponding stable forms. This effect was observed with the metastable polymorphs of acetazolamide, carbamazepine, and indomethacin.[2] However, this free energy difference between the stable and metastable forms can also provide the driving force for metastable → stable transformation in the dissolution medium. As a result, the observed difference in dissolution rate can be much lower than the predicted values.[3]

Although the physical form of a drug substance is carefully selected for dosage form manufacture, the processing conditions will determine the solid state of the drug in the final product. During tablet manufacture, processing steps may include milling, granulation, drying, and compression. Particle size as well as degree of crystallinity can be profoundly affected by milling as has been observed in case of griseofulvin.[4] The use of a binder solution for wet granulation can cause solvent-mediated phase transformations,[5] and, finally, tablet compression has been reported to cause polymorphic conversions in hyoscine N-butyl bromide, piroxicam, caffeine, carbamazepine dihydrate, and chlorpropamide.[6] Drugs may also undergo multiple transformations during processing. For example, during aqueous wet granulation, the stable theophylline anhydrate polymorph was converted to the hydrate, which dehydrated to the metastable anhydrate when the granules were dried.[7]

In addition to the active ingredient, the excipients in a dosage form can influence product performance.[8] Thus, product performance will be influenced by the solid state of the drug and excipients, as well as the processing conditions. These effects are of particular concern in case of drugs with low

aqueous solubility, since their absorption may be dissolution-rate limited.

The influence of pharmaceutical processing on the physical form (ie solid state) of the drug, and thus its dissolution rate, has received considerable attention in the literature.[4,7,9-11] However, few studies have evaluated the effect of processing-induced phase transformations on tablet performance. For example, it was observed that the polymorphic form of the drug substance as well as the granulating solvent affected the properties of granules and tablets.[12,13] Our goal was to comprehensively evaluate the influence of both the physical form of the active ingredient and the processing conditions on the performance of tablet formulations, using theophylline as the model drug. To achieve this, we first assessed the effect of the solid state of theophylline on its dissolution rate and then, the influence of various pharmaceutical processing steps on the dissolution behavior of theophylline tablets.

The study was divided into the following 3 stages with an increasing number of components in the system, enabling us to comprehensively evaluate the effect of processing-induced transformations on tablet dissolution:

1. First, the effect of the physical form of the drug on its dissolution rate was evaluated. These studies were conducted before and after the drug was subjected to pharmaceutical processing steps.
2. Next, the drug was processed with an excipient and subjected to powder-dissolution studies. These studies were performed to determine the combined effect of the excipient and the physical form of the drug.
3. Finally, the dissolution profiles of several tablet formulations were evaluated. The active ingredient in these formulations had been processed under different conditions.

Theophylline has a low aqueous solubility (8 mg/mL at 25°C) and can exist as an anhydrate or as a monohydrate. Two polymorphic forms of anhydrous theophylline have been characterized.[7] The effect of compression pressure on the hydration as well as dissolution behavior of anhydrous theophylline tablets has been investigated.[14,15] During pharmaceutical processing (aqueous wet granulation followed by drying), the stable anhydrous polymorph underwent multiple transformations (stable anhydrate → hydrate → metastable anhydrate). Tablets prepared using the metastable form dissolved at a slower rate than those containing the stable polymorph. This difference was attributed to rapid metastable anhydrate → theophylline monohydrate conversion *during* dissolution.[7] Thus, processing-induced phase transformations significantly influenced the dissolution behavior of theophylline tablets.

MATERIALS AND METHODS

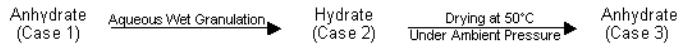
Materials

Anhydrous theophylline, anhydrous magnesium stearate (Sigma Chemical Company, St Louis, MO), sodium starch glycolate (Explotab, Penwest Pharmaceutical Co, Patterson, NY), and microcrystalline cellulose (Avicel PH 200, FMC Corporation, Philadelphia, PA) were sieved (-80 + 200 sieve fraction corresponding to a particle size range of 75-180 μm) before use.

Methods

The processing of theophylline with water is described in Scheme 1. The "neat" anhydrate was granulated with water (no other excipient added) using a glass mortar and pestle. The wet granules were sieved (mesh no. 18) and air dried for a few hours. The granules were then stored in chambers maintained at 75% relative humidity (RH) until the sorbed water was removed and the water content corresponded to that of theophylline monohydrate (~9% wt/wt) monitored by thermogravimetric analysis (TGA) and Karl Fischer Titrimetry (KFT). These granules were then dried to ~0% wt/wt water at 50°C under ambient pressure (Case 3) and sieved (-80 + 200 sieve fraction) before use. Intrinsic and powder dissolution profiles of the 3 samples were obtained. Scheme 1 shows the processing of theophylline with water.

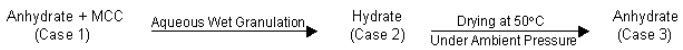
Scheme 1. Processing of theophylline with water.



The "neat" drug was also processed under several other conditions, the details of which are provided in Table 1 in the column entitled, "Processing Conditions."

The "neat" drug was next processed with microcrystalline cellulose (MCC). A 1:1 (percentage wt/wt) physical mixture of anhydrous theophylline and MCC was prepared (Case 1 in Scheme 2) and then granulated with water as detailed above. This granulated mixture (Case 2) was then dried to ~0% wt/wt water at ~50ºC in an oven (Case 3). Scheme 2 shows the processing of (theophylline + MCC), with water.

Scheme 2. Processing of (theophylline + MCC) with water.



After each processing step, the samples were characterized by conventional x-ray diffractometry (XRD), differential scanning calorimetry (DSC), TGA, and KFT.

Table 1. Influence of Processing Conditions on Crystallinity of Anhydrous Theophylline and the Kinetics of Anhydrate → Hydrate Transformation Rate

Sample ID	Processing Conditions	% Decrease in Crystallinity†	Anhydrate → Hydrate Transformation Rate Constant‡ (min^{-1})	Specific Surface Area (m^2/g)
	Unprocessed "neat" crystalline theophylline anhydrate (substantially crystalline, stable polymorph)	NA	0.9	0.2 (± 0.1)
A30	Anhydrate milled for 30 minutes§	39	1.8	1.2 (± 0.2)
AMA	Anhydrate $\xrightarrow[\text{Granulation}]{\text{Aqueous Wet}}$ M‖ $\xrightarrow[\text{Oven at 50°C}]{\text{Drying}}$ Anhydrate¶	25	4.7	1.6 (± 0.1)
AMAV50	Granules dried under vacuum at 50°C	-#	6.1	1.6 (± 0.2)
AMAV90	Granules dried under vacuum at 90°C	~0%	1.7	1.1 (± 0.1)
AMA10	AMA was ground for 10 minutes in a ball mill	32	5.5	1.4 (± 0.1)

†Determined by XRD.
‡Based on water vapor sorption (Figure 6).
§Ground in a ball mill with a paint shaker action (Spex Mixer/Mill, Spex Industries, Metuchen, NJ)
‖Theophylline monohydrate.
¶This processing condition has also been described in Scheme 1.
#The % decrease in crystallinity was comparable to that of AMA. However, this could not be quantified due to the presence of the metastable anhydrate.

Preparation of Tablets

Tablet formulations containing the processed theophylline-MCC mixtures (Cases 1, 2, and 3 in Scheme 2) were prepared. The formulations consisted of the processed or unprocessed drug (48.8% wt/wt), MCC (48.8% wt/wt), sodium starch glycolate (2.0% wt/wt), and magnesium stearate (0.5% wt/wt). The individual powders were sieved (–80 + 200 sieve fraction), weighed, and mixed by the geometric dilution method. To prepare tablets, 300 mg of the physical blend was weighed and compressed in a hydraulic press (Carver model C laboratory press, Menomonee, WI) to a pressure of 140 MPa and held for 1 minute.

X-Ray Powder Diffractometry

Approximately 200 mg of sample was exposed to CuKα radiation (45 kV × 40 mA) in a wide-angle powder XRD (model D5005, Siemens, Madison, WI). The instrument was operated in the step-scan mode, in increments of 0.05°2θ over 5 to 40°2θ, and the counts were accumulated for 1 second at each step. The data collection and analyses were performed with commercially available software (Jade, version 5.0, Materials Data Inc, Livermore, CA).

Glancing Angle X-Ray Diffractometry

The glancing angle studies were carried out in a wide-angle powder XRD (model Dmax B, Rigaku, Tokyo, Japan). The experimental setup was described in an earlier publication.[16]

Thermal Analysis

A DSC (model 910, TA Instruments, New Castle, DE) and a TGA (model 951, TA Instruments) were connected to a thermal analysis operating system (Thermal Analyst 2000, TA Instruments). Approximately 4 mg of the sample was weighed into an aluminum pan, which was crimped non-hermetically and heated in the DSC from room temperature to ~300°C. In the TGA, the samples were heated in an open aluminum pan from room temperature to ~300°C. For both techniques, the samples were heated at 10°C/min, under nitrogen purge.

Karl Fischer Titrimetry

The water content was determined coulometrically, using a KFT (model CA-05 moisture meter, Mitsubishi Chemical Corp, Kashima, Japan).

Scanning Electron Microscopy

Theophylline tablets before and after exposure to the dissolution medium were mounted on scanning electron microscope (SEM) stubs with double-sided carbon tape. Platinum-coated tablets (50 Å) were observed under an SEM (Hitachi S-800, Hitachi, Tokyo, Japan).

Automated Water Vapor Sorption

Anhydrous theophylline (6-10 mg) was placed in the sample pan of an automated vapor sorption balance (DVS 1000, Surface Measurement Systems, London, UK) and dried at 0% RH under dry nitrogen purge (flow rate of 200 mL/min) for 2 hours. Thereafter, the RH of the sample chamber was set to 90% (25°C), and the weight change was monitored as a function of time.

Surface Area Analysis

Specific surface area was determined by the multipoint (5 points) Brunauer-Emmett-Teller (BET) method using a surface area analyzer (Gemini, Micromeritics, Norcross, GA). Accurately weighed samples were degassed under vacuum at room temperature for at least 12 hours, and measurements were made using nitrogen as the adsorbate and helium as the carrier gas.

Tablet Hardness

The tablet hardness was determined using a hardness tester (Schleuniger, Manchester, NH).

Disintegration Time

The average disintegration time of at least 3 tablets was determined in 900 mL of distilled water at 25°C (Vankel Technology Group, Cary, NC).

Dissolution Rate

Intrinsic dissolution rate. The intrinsic dissolution rates (IDRs) were obtained in a modified Wood's apparatus.[17,18] The samples were placed in a stainless steel holder and compressed in a hydraulic press to 140 MPa. The sample holder with the compacted powder was screwed into the base of a poly(methylmethacrylate) cylinder such that only a single face of the compact (area 0.79 cm^2) was exposed to the medium (distilled water). The cylinder was then placed in a water bath (24°C ± 1°C). Nine hundred milliliters of the dissolution medium was stirred (50 rpm) with a 3-bladed paddle rotated using a synchronous motor (Slo Syn, Superior Electric Co, Rockford, IL) placed directly above the compact. Samples were withdrawn at specific intervals and filtered, and the drug concentration in solution was monitored by UV spectrophotometry at 272 nm (Beckmann DU 7400, Fullerton, CA).

Powder and tablet dissolution. The powder and tablet dissolution profiles were obtained in a 6-station *United States Pharmacopeia (USP)* type II dissolution apparatus (model 6454, Hanson Research, Chatsworth, CA) using ~300 mg of sample. The stirring speed, medium, and sampling methods used were the same as in the intrinsic dissolution experiments.

The intrinsic, powder, and tablet dissolution profiles were compared by the one-way analysis of variance (ANOVA) test ($p \leq 0.05$). When dissolution rates could not be obtained due to nonlinearity of the profiles (discussed later), the amounts dissolved at individual time points were compared.

RESULTS AND DISCUSSION

Characterization of Theophylline Phases

The XRD pattern of the unprocessed drug (Case 1 in Scheme 1) matched that of the stable anhydrate[7] and indicated that it was substantially crystalline.[19] Therefore, the unprocessed drug was considered to be 100% crystalline, and all subsequent crystallinity determinations were performed based on this assumption. When the unprocessed drug was granulated with water (Case 1 in Scheme 1), the observed XRD pattern matched that of theophylline monohydrate.[19] Drying at 50°C under ambient pressure resulted in dehydration (Case 3) to the stable anhydrate with lower crystallinity. Comparison of peak heights (peak at ~12.6°2θ) with that of the unprocessed drug revealed a ~25% decrease in crystallinity.

Effect of Processing on Drug Dissolution

The unprocessed drug (Case 1) had a significantly (ANOVA; $p \leq 0.05$) higher intrinsic dissolution rate than the processed samples (Cases 2 and 3, Figure 1A). The dissolution rates of the 2 processed samples were not significantly different. Because of its lower crystallinity, the processed anhydrate was expected to dissolve at a faster rate than the unprocessed drug. Since theophylline monohydrate is the stable form in aqueous medium at the experimental temperature, it was expected to have the lowest dissolution rate. Thus, the expected rank order of dissolution rates was as follows: Case 3 > Case 1 > Case 2.

When the compacts were placed in contact with the dissolution medium, theophylline anhydrate transformed to the monohydrate. Because of intimate contact with the medium, maximum transformation was expected to be at the tablet surface and to decrease as a function of depth. Since x-rays can penetrate up to a depth of several hundred micrometers, the information obtained is an average over this entire depth of penetration. Therefore, glancing angle XRD, a technique described elsewhere, was used to quantify the anhydrate → hydrate transition as a function of tablet depth.[16] On exposure to the dissolution medium for ~30 seconds, there was ~78% and 90% conversion to theophylline monohydrate at

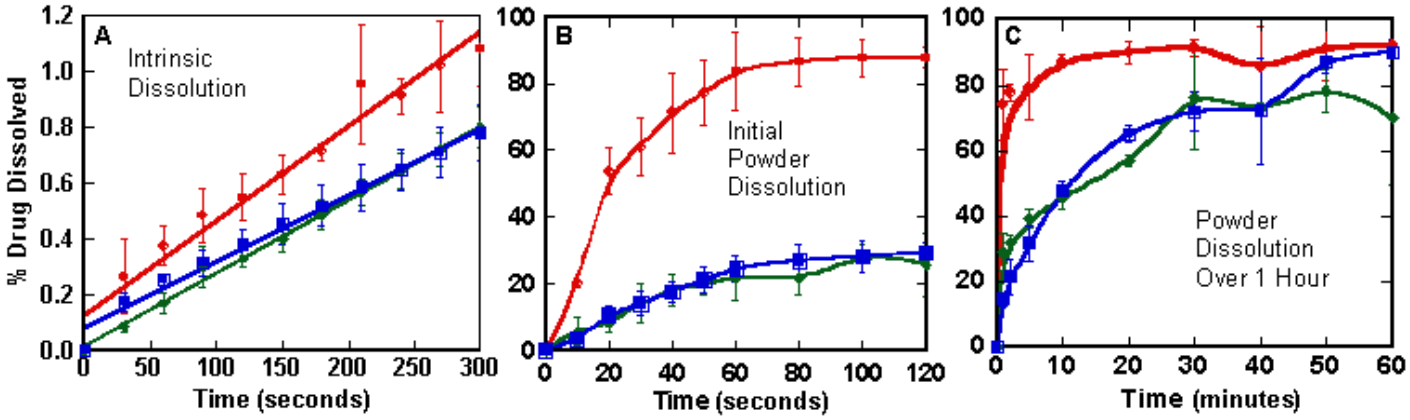


Figure 1. Dissolution profiles of unprocessed and processed anhydrous theophylline samples: Case 1 (●), Case 2 (♦), and Case 3 (■). These are described in Scheme 1.

the surface of the compacts prepared using the unprocessed and processed drug, respectively (Figure 2). Because of its lower crystallinity, the processed anhydrate (Case 3) dissolved at a faster rate, resulting in more rapid supersaturation at the compact surface followed by a higher rate of hydrate crystallization. As a result of this rapid conversion, the dissolution profile of the processed anhydrate (Case 3) was similar to that of the hydrate. Since the unprocessed drug did not convert as readily to the hydrate, the observed profile in this case substantially reflected the dissolution rate of the anhydrate.

Because of the nonlinearity of profiles, dissolution rates could not be obtained (Figure 1B). The amounts of drug dissolved at the individual time points were compared. The unprocessed drug dissolved to a significantly (ANOVA; $p \leq 0.05$) greater extent than the processed samples (Cases 2 and 3) in the first 20 minutes (Figures 1B and 1C). As in the case of intrinsic dissolution studies, the rank ordering of powder dissolution was as follows: Case 1 > Case 2 ≈ Case 3. Because the anhydrate → hydrate transformation rate of the processed anhydrate (Case 3) was higher than the unprocessed drug (Case 1), the powder dissolution of Case 3 is lower than that of Case 1. Thus, the processing-induced loss in the degree of crystallinity accelerated the anhydrate → monohydrate conversion rate *in the medium* and lowered its dissolution. Anhydrous carbamazepine is reported to behave similarly.[20]

Effect of Processing with Microcrystalline Cellulose

When the theophylline anhydrate-microcrystalline cellulose (MCC) physical blend (Case 1 in Scheme 2) was subjected

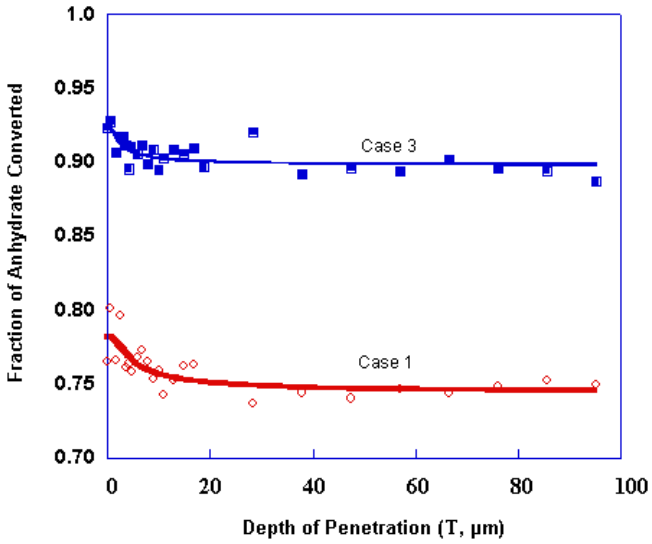


Figure 2. Fraction of anhydrous theophylline converted to theophylline monohydrate as a function of tablet depth following exposure to the dissolution medium for 30 seconds. The open circles (○) and the filled squares (■) are the experimental data points for unprocessed anhydrous theophylline (Case 1) and the anhydrate formed by dehydration of the monohydrate (Case 3), respectively. The τ profile (solid curve) is a fitting to the experimental data points. The complete details are provided elsewhere.

to aqueous wet granulation with water, the drug transformed to the monohydrate (Case 2; XRD results not shown). As before, dehydration during drying resulted in the formation of the stable anhydrate with lower crystallinity. The extent of dissolution can be rank ordered as follows: Case 1 > Case 2 > Case 3 (Figures 3A and 3B). While MCC did not seem to influence the dissolution of the unprocessed drug, it facili-

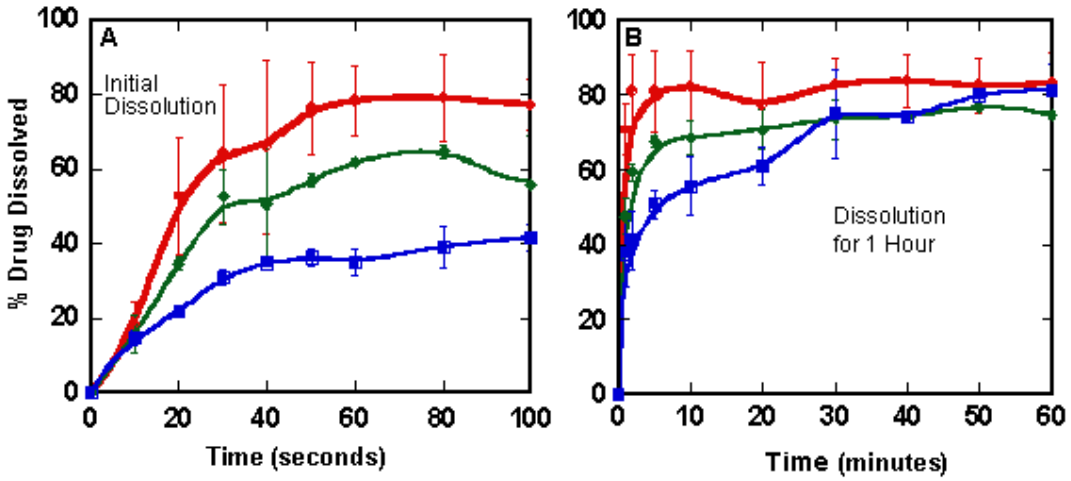


Figure 3. Powder dissolution profiles of anhydrous theophylline processed with MCC. Case 1 (●), Case 2 (♦), and Case 3 (■) are described in Scheme 2.

tated theophylline dissolution in the processed samples (compare Figures 1B and 3A). Interestingly, the kinetics of the anhydrate → hydrate transformation in the dissolution medium was unaffected by MCC (conclusion based on XRD; results not shown). MCC is known to cause deaggregation of powders, increasing the effective surface area in contact with the medium (Scheme 2; Cases 2 and 3).[8] Therefore, the dissolution rate enhancement is attributed to particle deaggregation in the dissolution medium. Microscopic examination revealed that the theophylline monohydrate particles formed during the dissolution run (Case 3 in Scheme 2) were much larger than the theophylline monohydrate in the granules (Case 2 in Scheme 2). Therefore, the difference in dissolution profiles of the processed samples (Cases 2 and 3; Figure 3A) is attributed to particle size differences, as has been reported in case of carbamazepine.[20]

Dissolution of Tablets

Finally, tablet formulations prepared with theophylline-MCC mixtures at various stages of processing (Scheme 2) were subjected to dissolution studies (Figure 4). During the first 20 minutes, the extent of dissolution of the unprocessed drug tablet (Case 1) was higher than that of theophylline hydrate (Case 2). The processed anhydrate (Case 3) tablets exhibited the slowest dissolution (Scheme 2; Figure 4). Case 3 tablets were significantly harder (28 ± 4 kP) than the unprocessed drug (11 ± 1 kP) and the hydrate (10 ± 3 kP) tablets. The disintegration times of Case 3 tablets were also significantly longer (Table 2).

During compression, the powder particles undergo rearrangement, brittle fracture, and deformation. The deformations can be elastic, plastic, and viscoelastic. In numerous

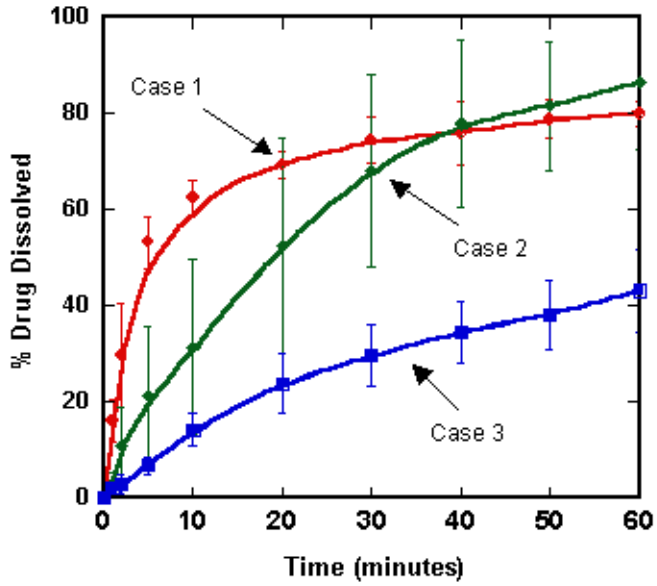


Figure 4. Tablet dissolution profiles of Cases 1, 2, and 3. Scheme 2 contains the processing details and Table 1 describes the formulation composition.

amorphous pharmaceuticals, including partially crystalline lactose and microcrystalline cellulose, the formation of hard compacts has been attributed to plastic deformation during compression.[21,22] Amorphous indomethacin,[23] partially crystalline lactose,[21] and amorphous β-cyclodextrin[24] yielded harder tablets than did their crystalline counterparts.[21] Thus, plastic deformation during compression of the processed anhydrate (Case 3 in Scheme 2) may be responsible for the higher tablet hardness and the longer disintegration time (compare formulation no. 3 with formulation no. 1 in Table

Table 2. Relevant Properties of Tablet Formulations

Formulation No.[†]	Processing Conditions[‡]	Comparison of Dissolution Rates	Hardness (kP)	Disintegration Time (seconds)
1	Unprocessed drug ("neat")		11 (±1)[§]	40 (±2)
2	A30	1 ≈ 2	14 (±2)	80 (±1)
3	AMA	1 > 3	28 (±4)	303 (±26)
4	AMAV90	1 ≈ 4	9.0 (+3)	148 (+2)
5	AMA10	1>5>3	14 (±2)	86 (±31)

[†]Formulation contains 48.8% wt/wt microcrystalline cellulose, 0.5% wt/wt magnesium stearate, and 2% wt/wt sodium starch glycolate.

[‡]Processing conditions described in Table 1.

[§]Mean ± SD (n = 3).

2). The lower crystallinity also accelerated the anhydrate → hydrate transformation *during* dissolution, possibly resulting in a hydrate layer on the intact compact surface. This could impede penetration of the dissolution medium into the tablet, further increasing tablet disintegration time. Such surface transformations inhibited medium penetration in amorphous lactose[25] and sodium phenobarbital tablets.[26]

Therefore, it is postulated that the decrease in degree of crystallinity resulted in harder tablets, and disintegration was delayed by the rapid surface crystallization of the monohydrate. This hypothesis was supported by SEM of the unprocessed and processed (Case 1 and 3, respectively, Scheme 2) tablet surfaces after exposure to the medium for 30 seconds (Figure 5). The Case 3 tablet surface was intact and hydrate crystallization was evident, while the tablet containing the unprocessed anhydrate seemed to have disintegrated. During dissolution studies, Case 1 formulations disintegrated rapidly, while Case 3 tablets showed no discernible disintegration (visual observation). Therefore, consistent with literature reports, the tablet properties (hardness, disintegration, and dissolution) seem to be substantially influenced by the crystallinity of the drug.[21,23] The various stresses encountered during pharmaceutical processing can bring about a decrease in drug crystallinity. For example, both milling and compression are known to cause a decrease in the degree of crystallinity.[6] In addition, there is an added complication in case of anhydrous theophylline. While aqueous wet granulation causes its transformation to theophylline monohydrate, it reverts back to the anhydrate during subsequent drying. The solid state of the final anhydrous phase is strongly influenced by the dehydration conditions. In order to comprehensively understand the effect of processing on product performance, it is necessary to evaluate the effect of each of these processing steps on drug crystallinity. For example, the milling-induced decrease in crystallinity may have occurred predominantly on the particle surface, as has been postulated by Huettenrauch,[27] while dehydration is expected to affect both the surface and the bulk.

Anhydrous theophylline was either milled or granulated (Table 1). Milling caused a decrease in the degree of crystal

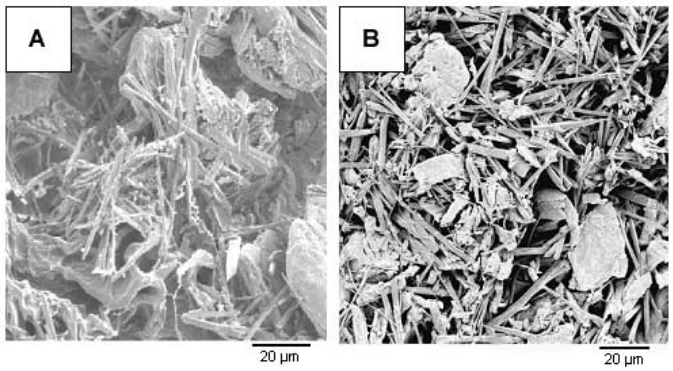


Figure 5. SEM photomicrographs of anhydrous theophylline tablets after exposure to the dissolution medium for 30 seconds: (A) Case 1 tablets (original magnification × 1200) and (B) Case 3 tablets (original magnification × 1000). These cases are described in Scheme 2.

linity (sample A30, Table 1). The unprocessed anhydrate was also granulated with water and dried to ~0% wt/wt water under the following conditions:

1. AMA. Sample prepared by aqueous granulation of "neat" anhydrate (A) resulting in the monohydrate (M), followed by drying of the granules under ambient pressure at 50°C to finally yield the anhydrate (A) causing ~25% decrease in crystallinity compared with the unprocessed drug (referred to as Case 3 in Scheme 1).
2. AMAV90. Sample prepared by aqueous granulation of "neat" anhydrate (A) resulting in the monohydrate (M), followed by drying of the granules (under reduced pressure at 90°C) to finally yield the anhydrate (A). There was no measurable change in crystallinity. Although partially crystalline anhydrate may have been formed on dehydration, the crystallinity was regained during annealing at 90°C.
3. AMAV50. At 50°C under reduced pressure, resulting in a mixture of the metastable and stable anhy-

drates with lower crystallinity. Since the dissolution behavior will be influenced not only by the degree of crystallinity but also by the polymorphic composition of the system, comparison with samples containing only a single polymorph may not be valid. Hence, the effects of dehydration under reduced pressure at 50°C have not been discussed further.

Influence of Processing on Water Vapor Sorption Kinetics

In addition to the effect on crystallinity, processing also increased the specific surface area of the drug (Table 1). This difference was persistent even on sieving. The effect of crystallinity as well as particle size, on the anhydrate → hydrate transformation rate, was evaluated by water vapor sorption studies. While the total water uptake was ~10% wt/wt, indicating transition to theophylline monohydrate, processing accelerated the anhydrate → hydrate transition (Figure 6, Table 1). When the data were fitted to various solid-state kinetic models, the best fit was obtained with the 3-dimensional nucleation and growth (Avrami-Erofeev) model.[28] Since dehydration and milling were the 2 major processing steps, their effects were individually considered.

1. Milled sample (A30). The transformation rate was higher than in the unprocessed drug due to both a decrease in crystallinity as well as an increase in surface area.
2. Dehydrated samples (AMAV90, AMA). Since the crystallinity of AMAV90 was similar to that of the unprocessed drug, the higher transformation rate and the shorter lag time (see inset, Figure 6) were attributed to an increase in surface area.

The transformation rate of AMA was considerably higher than that of the unprocessed drug due to decreased crystallinity and an increased surface area. Although the mechanism of anhydrate → hydrate transformation in the solid state (water vapor sorption studies) is likely to be different from that in solution (during dissolution), these studies indicate that processing facilitated the anhydrate → hydrate transformation.

Effect of Processing on Powder and Tablet Dissolution

The powder as well as the tablet dissolution behavior of the various processed samples were compared. Initially (at the 1 minute time point), the unprocessed drug exhibited a more rapid powder dissolution than all the processed samples (Figure 7). As indicated by the water vapor sorption studies, processing facilitated the anhydrate → hydrate transformation, consequently decreasing drug dissolution. Therefore, water vapor sorption can be used to predict the kinetics of solution-mediated phase transitions. Such an approach has also been used with carbamazepine.[11,29] This initial difference in dissolution was not evident at longer time points (30 minutes, Figure 7). The powder dissolution studies provide insight into the dissolution behavior of the drug before tablet compression. It is evident that while the initial (1 minute)

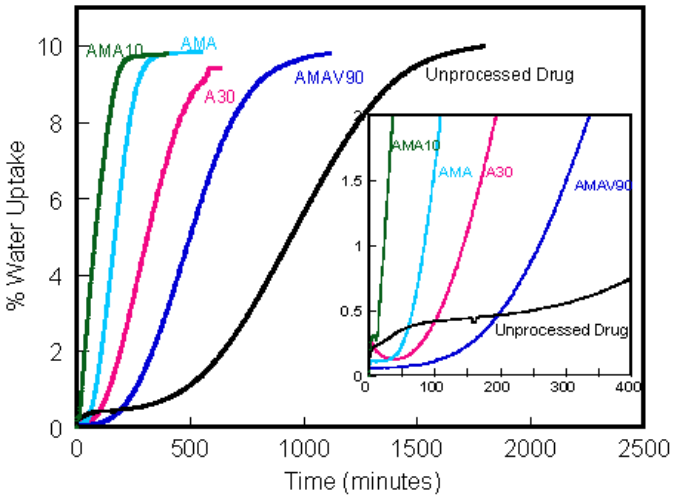


Figure 6. Water vapor sorption isotherms (at 25°C and 90% RH) of theophylline samples (-80 +200 sieve fraction) obtained on processing. Inset shows initial water vapor sorption isotherms.

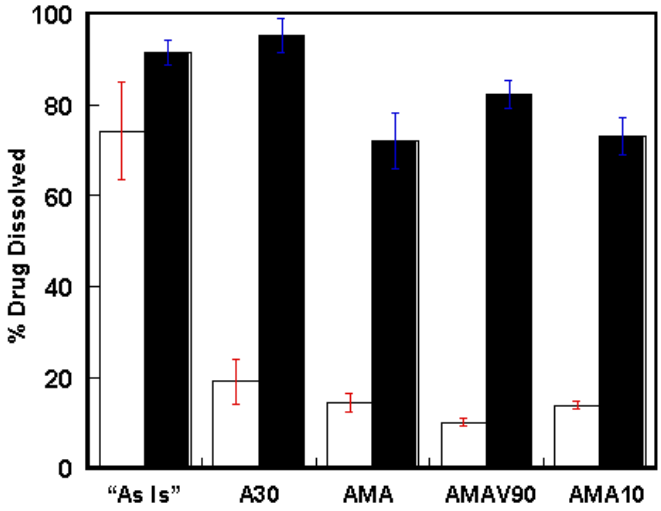


Figure 7. Powder dissolution of anhydrous theophylline processed under different conditions. The percentage drug dissolved was determined at 1 minute (clear bar) and at 30 minutes (shaded bars). The processing conditions are described in Table 1.

powder dissolution behavior was influenced by processing, drug dissolution at longer intervals (30 and 50 minutes) remained unaffected (Figures 7 and 8). Since all the processed anhydrate samples exhibited similar powder dissolution behavior, the observed differences in tablet dissolution could be attributed to the effect of compression with the most significant effect occurring in the samples subjected to granulation and drying.

Figure 8 presents the effects of processing on the dissolution behavior of anhydrous theophylline tablets. The least amount of drug was in solution in the AMA formulation. The decrease in anhydrate crystallinity was brought about by dehydration during drying and resulted in hard tablets. The formation of hard tablets coupled with the rapid conversion to theophylline monohydrate, particularly on the tablet surface, effectively impeded medium penetration into the tablet interior. As a result, the disintegration time is considerably longer (Table 2).

While the crystallinity of AMAV90 is comparable to that of the unprocessed drug (Table 1), only the AMAV90 had undergone anhydrate → hydrate → anhydrate transition. This sample "history" seems to be responsible for the higher water affinity (transformation rate constants in Table 1) and, as a consequence, the longer disintegration time (Table 2). While the difference in disintegration times translated to small differences in the initial dissolution profiles (data not shown), the percentage drug dissolved from the AMAV90 tablets was virtually identical to that of the unprocessed drug tablets at 50 minutes (Figure 8). When compared with AMA, AMAV90 converted to hydrate at a slower rate (Table 1) indicating that tablet disintegration preceded substantial surface hydrate formation.

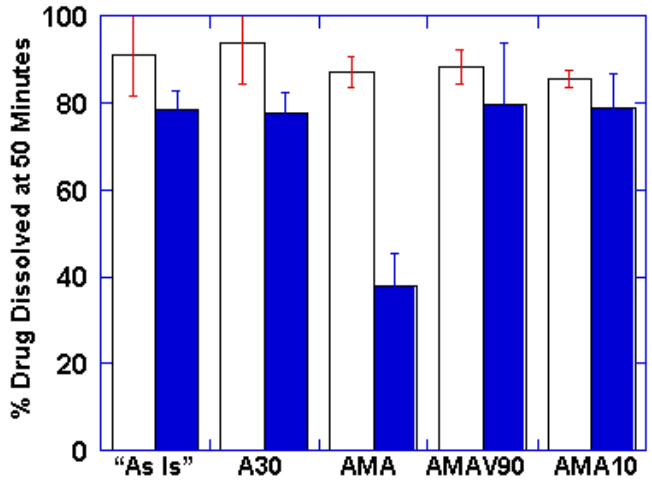


Figure 8 Tablet (filled bars) and powder (clear bars) dissolution of anhydrous theophylline processed under different conditions. The processing conditions are described in Table 1.

When compared with the unprocessed drug, milling for 30 minutes (A30) caused a pronounced decrease in the degree of crystallinity, increase in surface area and consequently, an increase in the anhydrate → hydrate transformation rate constant (Table 1). The increased affinity for water could be responsible for the longer disintegration time (Table 2). Again, a comparison of this milled sample (A30) with the dried granules (AMAV90) provides insight into the effect of sample history. While these 2 samples have nearly the same affinity for water (transformation rate constant; Table 1), the AMAV90 tablets have a longer disintegration time. This is particularly noteworthy because AMAV90 also exhibited no amorphous character. In this context, it is also useful to compare the milled anhydrate (A30) with the granules dried at 50°C (AMA). While both these processing conditions resulted in a loss in crystallinity (Table 1), as postulated earlier, the milling-induced decrease in crystallinity may have occurred predominantly on the particle surface, and dehydration was expected to affect both the surface and the bulk. Their differences in affinity for water (Table 1) might be responsible for the very pronounced differences in disintegration time (Table 2) and dissolution behavior (Figure 8).

While a decrease in the crystallinity of the anhydrate could be brought about either by milling (A30) or by dehydration (AMA), the effect of these processing conditions on tablet hardness showed pronounced differences. While milling seemed to have a small effect on tablet hardness (Table 2), the tablets with the highest hardness were obtained using dried granules (AMA). Earlier, we had postulated that, when compressed, amorphous compounds predominantly undergo plastic deformation, resulting in hard tablets. This postulate does not seem to hold true when the amorphous character is introduced by milling (A30). Mechanical stress is known to result in plastic deformation of anhydrous crystalline theophylline.[30] When this material is again subjected to a mechanical stress (compression), the likelihood of plastic deformation is substantially reduced. As a result, the tablet hardness is comparable with that of the unprocessed anhydrate (Table 1).

If the above reasoning is correct, then subjecting AMA granules to mechanical stress *before* they are compressed should decrease the likelihood of plastic deformation *during* compression and the consequent formation of hard tablets. Hence, AMA granules were milled for 10 minutes and compressed (AMA10; Table 2). The resulting tablets had lower hardness values and shorter disintegration times (Table 2), and consequently more rapid dissolution than the AMA formulation (Figure 8). These results suggest that plastic deformation during compression was unlikely and therefore must have occurred during milling. While a decrease in crystallinity can be brought about either by milling or by granulation, the effect on product performance (meas-

ured by dissolution) was only observed with the granulated product.

Since the studies were carried out in 3 stages, we could comprehensively evaluate the effect of processing-induced transformations on tablet dissolution. Although the crystallinity of the processed anhydrate was lower than that of the unprocessed drug, its intrinsic dissolution rate was lower. This finding could be attributed to rapid anhydrate → hydrate phase transformations during dissolution. As a result, the expected enhancement in dissolution rate was not observed. Although both granulation and milling resulted in a decrease in anhydrate crystallinity, their influence on tablet dissolution was different, revealing the significant influence of the specific processing conditions (ie, sample history).

CONCLUSION

Both milling and aqueous wet granulation caused a decrease in the crystallinity of anhydrous theophylline. This processing-induced decrease in crystallinity accelerated the anhydrate → monohydrate conversion *during* dissolution. The major perceived advantage of the metastable form of a drug is the enhancement in the solubility and dissolution rate. In order to realize this advantage, it is customary to ensure the physical stability of the metastable form during both manufacture and storage. The studies presented here reveal that rapid phase transition *during* dissolution can negate the potential advantage of metastable forms.

ACKNOWLEDGEMENTS

The authors thank Dr. Paul Predecki, University of Denver, Denver, CO, for his contributions to the glancing angle x-ray diffraction studies.

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