Pharmaceutical Research, Vol. 25, No. 4, April 2008 (© 2007)
DOI: 10.1007/s11095-007-9450-x

Research Paper

Manipulating Theophylline Monohydrate Formation During High-Shear Wet Granulation Through Improved Understanding of the Role of Pharmaceutical Excipients

Håkan Wikström,[1] William J. Carroll,[1] and Lynne S. Taylor[1,2]

Received June 8, 2007; accepted August 29, 2007; published online September 26, 2007

Purpose. To investigate the effect of common pharmaceutical excipients on the kinetics of theophylline monohydrate formation during high-shear wet granulation.
Materials and methods. A mixture of anhydrous theophylline and the excipient was granulated in a high-shear granulator, using water as the granulation liquid. Non-contact Raman spectroscopy was used to monitor the rate of transformation of anhydrate to hydrate during the granulation process. The kinetics of conversion was also monitored in slurries of theophylline whereby the excipients were added to the aqueous phase. Optical microscopy was used to visualize the transformation and to measure the linear growth rates of hydrate crystals in the presence and absence of the excipients.
Results. At pharmaceutically relevant amounts of excipient, the transformation kinetics of theophylline was unchanged for the majority of excipients tested. However, when granulating with low concentrations of some commonly used polymeric binders, the transformation kinetics could be significantly retarded. For example, methylcellulose polymers delayed both the onset of hydrate formation as well as retarding the transformation rate. When 0.3% (*w*/*w*) of hydroxypropyl methylcellulose was added to a model formulation containing 30% (*w*/*w*) theophylline anhydrous, the formation of the monohydrate could be completely prevented over the time period of the granulation experiment, without significantly affecting the granular properties. Microscopic observations of hydrate formation in the presence of the polymer revealed that the polymers that inhibited hydrate formation reduced the hydrate crystal growth rates and influenced hydrate morphology.
Conclusions. Raman spectroscopy is a useful technique to monitor hydrate formation during wet granulation. Some commonly used polymeric pharmaceutical excipients can be used to manipulate theophylline hydrate formation in aqueous pharmaceutical environments. These excipients may affect either the nucleation and/or the growth of the hydrate phase.

KEY WORDS: additive; crystal growth; excipients; high-shear wet granulation; hydrate formation; Raman spectroscopy.

INTRODUCTION

Wet granulation is currently the most widely used technique to improve homogeneity, flowability and compactability of formulations in the production of pharmaceutical solid dosage forms (1). During high-shear wet granulation, the drug and the excipients are blended by intense mechanical agitation via an impeller and a chopper followed by the addition of a granulating liquid. The agitation continues throughout wet massing, which is when granule formation and growth occurs as a result of mobile-liquid bonds formed between primary particles (2). The quantity of water needed to achieve good granules varies with formulation and processing parameters and can be up to 50% by weight of the dry powders. It is well known that moisture affects both the physical and chemical properties of pharmaceutical solids (3). Due to the nature of the process and the stresses involved, there is a high risk for susceptible drugs to experience changes in crystal form during wet granulation. One such processing-induced transformation is the conversion of anhydrous drug to it hydrate form (4).

There is currently a great deal of interest in applying modern process analytical technologies to improve the understanding and control of pharmaceutical unit operations. Raman spectroscopy has been shown to have a high

[1] Department of Industrial and Physical Pharmacy, School of Pharmacy, Purdue University, West Lafayette, Indiana 47907, USA.
[2] To whom correspondence should be addressed. (e-mail: ltaylor@pharmacy.purdue.edu)

ABBREVIATIONS: a_W, water activity; EC, Ethylcellulose; HPC, hydroxypropyl cellulose; HPLC, high-performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; HPMC-AS, hydroxypropyl methylcellulose acetate succinate; MC, methylcellulose; MCC, microcrystalline cellulose; MT, theophylline monohydrate; Na-CMC, sodium carboxy methylcellulose; NIST, National Institute of Standards and Technology; PAA, cross-linked polyacrylic acid; PVP, polyvinyl pyrrolidone; SDS, sodium dodecyl sulfate; SEM, scanning electron microscopy; SMT, solvent-mediated transformation; TP, Theophylline; USP, United States Pharmacopeia; UV, ultraviolet; XRPD, powder X-ray diffractometry.

0724-8741/08/0400-0923/0 © 2007 Springer Science + Business Media, LLC

discriminating power for solid-state forms (5). Additionally, Raman spectroscopy can be coupled to fiber optics, enabling remote sampling (6), which makes it an ideal technique for monitoring of solid state form changes during pharmaceutical processes such as high-shear wet granulation (7).

Hydrate formation will occur during wet granulation as a solvent-mediated transformation (8). This means that the anhydrous form will begin to dissolve and that the hydrate is grown from solution. Because of this transformation route, the morphology of the hydrate will not be the same as that of the anhydrate and is frequently observed to be needle-like (9). Hence, not only will the transformation to the hydrate form potentially lower the solubility of the drug, but the change in morphology may also impose problems later in the manufacturing process chain. Thus, it is important that such transformations can be predicted, detected and either controlled or prevented (10).

Over the last decade, several studies have shown that some excipients can affect the hydrate formation of various pharmaceutical compounds. The inhibiting effect of excipients on transformation kinetics was first discussed by Katzhendler *et al*. (11). The authors noted that the transformation of carbamazepine anhydrous to its dihydrate form in aqueous solution was inhibited when using hydroxypropyl methylcellulose (HPMC) in a sustained release tablet. It was suggested that the inhibition was related to hydrogen bonding between HPMC and carbamazepine (12). In a subsequent study, the authors noticed changes in transformation kinetics when using egg albumin in sustained release matrix tablets (13). Otsuka *et al.* noted that a commonly used binder, hydroxypropyl cellulose (HPC), also affected the transformation of carbamazepine (14). They suggested that HPC altered the nucleation kinetics, and that this effect varied based on the grade and concentration of HPC. Rodríguez-Hornedo *et al.* discussed the impact of adding surfactants on the transformation of carbamazepine (15). Sodium dodecylsulfate (SDS) was found to promote surface-nucleation of the dihydrate on the anhydrous surfaces, whereas sodium taurocholate affected the growth morphology of the dihydrate through interaction with specific crystal faces. Recently, Tian *et al.* studied the influence of various excipients on carbamazepine dihydrate formation in aqueous slurries (16). They concluded that matching both hydrophobicity and hydrogen bonding potential could explain the effect that the different excipients had on the transformation kinetics. Finally, Qu *et al.* observed that HPMC altered the solubility of carbamazepine dihydrate, without affecting the solubility of the anhydrous form, thus changing the thermodynamic driving force for conversion, and retarding the transformation kinetics (17).

Airaksinen *et al.* investigated the effect of two different excipients on the transformation of theophylline anhydrous to its monohydrate form (18) during wet granulation. It was noted that α-lactose had a somewhat promoting effect on the transformation, whereas the water absorbing excipient, silicified microcrystalline cellulose, did not affect the transformation, except when very a low amount of water was used. In a study with nitrofurantoin, the same authors concluded that the mechanism of the retardation of hydrate formation kinetics was water absorption by the excipient, whereby amorphous excipients had the largest effect, followed by microcrystalline cellulose with crystalline excipients, such as α-lactose having no effect (19).

As is evident from the literature review presented above, only limited work has been performed to study the effect of excipients on hydrate formation during wet granulation and that most studies have investigated transformations in slurries. The overall goal of the present study was therefore to better understand the role of additives in influencing the kinetics of hydrate formation during high-shear wet granulation as well as to determine similarities and differences between a wet granulation and a slurry environment. Using theophylline as the model hydrate former, transformation kinetics was monitored for various excipients in both slurry and granulation experiments using Raman spectroscopy to monitor the transformation.

MATERIALS AND METHODS

Materials

Theophylline anhydrous (TP, CAS 58-55-4) was purchased from Rhodia (Cranbury, NJ, USA). Theophylline monohydrate (MT) was prepared by placing anhydrate in a desiccator with 100% relative humidity for at least 2 weeks prior to use to ensure that no anhydrate was present. Raman spectroscopy and X-ray powder diffractometry were used to verify the purity of the theophylline phase. Avicel-PH-101 microcrystalline cellulose (MCC) was obtained from FMC Corporation (Newark, DE, USA). Mannitol (Mannogem) was received from Ruger Chemical Company (Irvington, NJ, USA) and screened through a 20-mesh screen to reduce agglomeration before use. Polyvinyl pyrrolidone K-29/32 (PVP) was obtained from ISP Technologies, Inc. (Wayne, NJ, USA), whereas other PVP grades were a gift from BASF (Ludwigshafen, Germany). Methylcellulose (MC), hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) were gifts from the Dow Chemical Company (Midland, MI, USA), whereas hydroxypropyl methylcellulose acetate succinate (HPMC-AS) was obtained from Shin-Etsu Chemical Co, Ltd., Tokyo, Japan). Hydroxypropyl cellulose (HPC) and sodium carboxymethyl cellulose (Na-CMC) was obtained from Hercules (Wilmington, DE, USA). The cross-linked polyacrylic acid (PAA) used was Carbopol 934P (BF Goodrich Chemical Co, Cleveland, OH, USA). Double-distilled water was used for all experiments.

Solubility and Dissolution Rate Experiments

The solubility of theophylline in different solutions was determined in triplicate by dissolving an excess amount of drug in 20 ml of solution that was equilibrated for at least 24 h. The solutions were kept under constant agitation using a Variomag magnetic stirrer (H+P Labortechnik GmbH, Munich, Germany) and at a constant temperature of 25°C using a RM 20 water bath (LAUDA Dr. R. Wobser GmbH & Co. KG, Lauda-Königshofen, Germany). After equilibrium had been reached, the solution was filtered through a 0.45 μm Pall GHP Acrodisc filter (Pall Corporation, East Hill, NY, USA) using a 20-ml plastic syringe (CODAN Medizinische Geräte GmbH & Co KG, Lensahn, Germany). The filtrate was then diluted to an appropriate theoretical

concentration and injected onto a HPLC system. A USP analytical procedure was used to assay the theophylline solutions (20). The chromatographic system comprised of a Waters 600 quaternary pump, a Waters 717+ autoinjector and a Waters 486 variable single wavelength detector (all Waters Corp., Milford, MA, USA). The column used for analysis of TP was a Waters μBondapak C18, 125 Å, 10 μm, 3.9×300 mm column (Waters Corp., Milford, MA, USA).

Intrinsic dissolution rates of theophylline in different solutions were determined by measuring the amount of drug dissolved at different time points using a rotating disk approach. The disks were 10 mm in diameter and 1.5 mm thick weighing about 170 mg and prepared using a Specac IR press (Grasby Specac, Kent, UK) with a 10 mm die (Grasby Specac, Kent, UK) and an applied force of 3 tons with a dwell time of 20 s. The compacts were fitted to a stainless steel holder, exposing only one side to the medium. The holder was then attached to a Stuart Scientific SS20 overhead stirrer (Barloworld Scientific Ltd., Stone, Staffordshire, UK) and lowered into a jacketed glass beaker filled with 100 ml water maintained at 25°C using a RM 20 water bath (LAUDA Dr. R. Wobser GmbH & Co. KG, Lauda-Königshofen, Germany). A rotational speed of 300 rpm was used for all experiments. The solution concentrations were determined using high-performance liquid chromatography ultraviolet detection (HPLC-UV) analysis with an appropriate USP analytical procedure using the HPLC system described above.

Raman Spectroscopy

Raman spectra were collected using two different Raman spectrometers. During the slurry experiments a RamanRxn1-785 Raman spectrometer (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) was used and for the wet granulation experiments a prototype PhAT System (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) was used. Both systems were equipped with a 785-nm excitation laser and fiber optics was used to interface the spectrometer to the sampling device enabling remote measurements. The RamanRxn1 was equipped with a 1/4″ diameter immersion optic (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) attached to a MR Probe (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) yielding a sampling area at the sample of 60 μm in diameter. The prototype PhAT System possessed a non-contact optic sampling device (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) with an optimal working distance of about 18 cm from the probe head, and an illumination area of about 3 mm in diameter.

Each spectrum was the sum of 4 scans, each with an integration time of 5 and 1 s per scan for the RamanRXN1 and PhAT System, respectively. Spectra were collected every 30 s (slurry experiments) or every 10 s (wet granulation experiments).

The calibration procedures used for theophylline quantitation have been published previously (21). Calibration samples were prepared as binary mixtures of the anhydrous and hydrate form using geometric dilution. Samples were prepared at 5% intervals from 0% monohydrate to 20% monohydrate and from 80% monohydrate to 100% monohydrate. Between 20% and 80% monohydrate, the samples were prepared at 10% intervals. All concentrations were prepared in triplicate and samples were randomly divided into a calibration set and independent test set. For the immersion optics system, the probe was placed into the vial, which was then rotated during measurement at a constant speed of about 43 rpm using a custom built tablet rotator utilizing a electrical motor (Micro motors, Inc., Santa Ana, CA, USA) connected to a LPS-151 power supply (Leader Electronics Corp., Yokohama, Japan). A mixing blade was attached to the immersion probe, which lifted material from the bottom of the vial and continuously replaced the material under the probe. Additionally, one spatula was used to clear the edges of the scintillation vial. For the PhAT System, the spectra of the samples were collected from the from the powder surface as the sample vial was rotated at a constant speed of about 43 rpm.

A bivariate calibration was used, utilizing a characteristic peak of anhydrous theophylline at 1707 cm^{-1} and a characteristic peak of theophylline monohydrate at 1664 cm^{-1}. Neither of the excipients used were found to influence the Raman signal in the region used for the calibration. The accuracy of the calibration when using the immersion optics Raman was approximately 10%, whereas the accuracy of the calibration of PhAT System was 5%, with the quantitation limit of monohydrate theophylline being 5–10% for both systems. This was deemed sufficient for the purpose of determining transformation kinetics.

X-Ray Powder Diffraction

Crystal forms in select granulations were verified by measuring the powder X-ray diffraction pattern of the wet granules using the equipment described below and comparing to the pattern of the reference hydrate powder. Powder X-ray diffractometry (XRPD) was performed with Shimadzu XRD 6000 (Kratos Analytical, Chestnut Ridge, NY, USA) using Cu Kα radiation, voltage of 40 kV and current of 40 mA. Measurements were performed with a scan speed of 4° 2θ/min and a step size of 0.04° 2θ/min between 6° and 30° 2θ.

Scanning Electron Microscopy

Particle morphology of raw and processed material was evaluated with scanning electron microscopy (SEM) using a FEI Quanta 200 scanning electron microscope (FEI Company, Hillsboro, OR, USA). Samples were prepared for analysis by placing a small amount on carbon double-stick tape fixed to an aluminum mount. Then, samples were sputter coated using a 108auto sputter coater (Cressington Scientific Instruments, Inc., Cranberry Twp., PA, USA) at ~20 mA and ~0.13 mbar (Ar) with Au/Pd for 90 s. Under high vacuum mode, an Everhart Thornley detector was used with a beam voltage was 5.0 kV. The instrument was calibrated for magnification using NIST standards and the magnification reported on the SEM images were calculated upon the initial data acquisition.

Optical Microscopy

The morphology and growth rate of theophylline monohydrate in various solutions was determined by using a Nikon

E600 Pol microscope (Nikon Corp., Tokyo, Japan) equipped with a Photometrics CoolSnap cf digital camera (Roper Scientific, Inc., Tucson, AZ, USA). Pictures were captured at regular intervals for later analysis of growth rate of different crystals within the field of view. Only crystals that stayed in sharp focus were used in order to limit errors from growth occurring out of the plane of focus. The monohydrate form of all crystals was confirmed using a Ramascope LS50 Raman microscope (Renishaw, Gloucestershire, UK).

Water Activity Measurements

The water activity of polymer solutions was tested using an AquaLab (Decagon Devices, Inc., Pullman, WA, USA) water activity tester. Solutions of drug in water and drug in polymer solution, as well as polymer solution without drug were prepared using ratios similar to those prepared for the slurry experiments described in Table 1.

Slurry Experiments

Dry material was weighed and placed in a 150 ml glass beaker dressed in aluminum foil that was placed on a magnetic stirrer unit. The immersion optic was placed in the beaker just above the magnetic stirrer bar and angled towards the movement of the flow. Either water or aqueous polymer solution was added to the beaker as the magnetic stirrer was activated. The amount of each additive used is shown in Table 1. Raman spectra were collected every 30 s by averaging 4 scans each with an integration time of 5 s. The experiment was halted when no visible change in the spectra could be seen.

Small-Scale Wet Granulation

An in-house built small-scale granulator was designed and constructed to enable high-shear wet granulation at a 30-g scale (Fig. 1). This enabled granulation of only drug and a realistic amount of excipient, without needing to add a diluent or waste excess amounts of drug. The granulator was built from a stainless steel block with a polycarbonate lid. The chopper was controlled by a HP E3610A voltage regulator (Hewlett Packard, Palo Alto, CA, USA) and the impeller was rotated using a Lightnin L5U08F overhead mixer (Lightnin, Dublin, Ireland). The formulation consisted of pure drug with addition of one excipient at a time, either dry mixed or dissolved in the granulation liquid. The amount of each additive used is shown in Table 1. The impeller was rotated with a constant speed of about 200 rpm, which delivered a tip speed identical to that used for the lab-scale Diosna experiments described below, where the mixing speed was 100 rpm. The chopper speed was set at about 1000 rpm and the granulation liquid was added at a constant rate of 20 ml/min using a 10-ml plastic syringe (CODAN Medizinische Geräte GmbH & Co KG, Lensahn, Germany).

Lab-Scale Wet Granulation

Dry material was weighed and placed in a Diosna P 1/6 high-shear mixer-granulator (Dierks and Söhne GmbH, Osnabrück, Germany) equipped with a 2 l stainless steel bowl. The binder solution was sprayed onto the mix using a Masterflex Quick Load Model 7021-24 pump (Cole-Palmer Instrument Co., IL, USA) and the amount of binder solution added was determined gravimetrically using a Mettler PC 8000 balance (Mettler Toledo, Inc., Hightstown, NJ, USA).

Table 1. Summary of the Results from Screening Experiments in Slurries and Small-Scale Granulations

Excipient	Amount (*w*/*w* drug)	Effect	
		Slurry	Granulation
PVP K-12	1.0%	NE	LE
PVP K-17	1.0%	NE	LE
PVP K-25	1.0%	NE	LE
PVP K-29/32	1.0%	NE	LE
PVP K-30	1.0%	NE	LE
PVP K-90	1.0%	NE	LE
PVP-VA	1.0%	NE	LE
XL-PVP	1.0%	NT	SE
MC A15	1.0%	VE	VE
MC A4C	1.0%	VE	VE
MC A15C	1.0%	VE	VE
MC A4M	1.0%	VE	VE
HPMC F50	1.0%	VE	QE
HPMC F4M	1.0%	VE	QE
HPMC K3	1.0%	QE	VE
HPMC K4M	1.0%	QE	QE
HPMC K15M	1.0%	QE	QE
HPMC K100M	1.0%	QE	QE
HPMC E3	1.0%	QE	VE
HPMC E5	1.0%	QE	VE
HPMC E50	1.0%	QE	QE
HPMC E4M	1.0%	QE	QE
HPMC-AS	1.0%	SE	SE
HPC	1.0%	SE	SE
HEC	1.0%	NT	LE
EC 7	1.0%	NE	NE
PEG 2000	1.0%	NT	NE
PMA	1.0%	NT	NE
PAA	1.0%	SE	VE
Na Al Si	1.0%	NT	NE
Na-CMC	5.0%	LE	QE
Na Starch Glycolate	5.0%	NT	SE
MCC	10%	NT	SE
Ca_2PO_4	10%	NT	LE
Lactose	10%	NT	SE
Lactose H_2O	10%	NT	NE
Corn starch	10%	NT	LE
Mannitol	10%	LE	LE
Phosphate	1.0%	NE	NE
Citric acid	1.0%	NT	NE
NaCl	1.0%	NE	NE
Mg Stearate	0.5%	NT	NE
Talc	0.5%	NT	NE
SDS	1.0%	NE	NE
Tween 20	1.0%	NT	LE
CTAB	1.0%	NT	PE
β-CD	1.0%	NT	NE
Na Ascorbate	1.0%	NT	LE
Na Benzoate	1.0%	NT	NE

The amount of additive is stated based on the weight ratio of additive to anhydrous drug
NE no effect; *PE* promoting effect; *LE* little retarding effect; *SE* somewhat effective retarder; *QE* quite effective retarder; *VE* very effective retarder; *NT* not tested

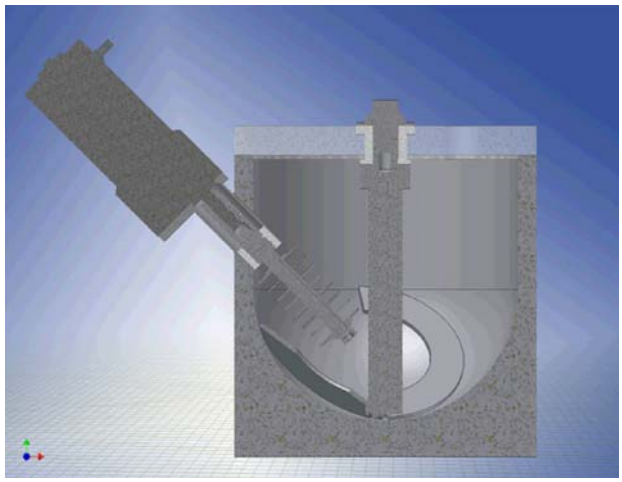

Fig. 1. Schematic of the small-scale high-shear wet granulator used in this study. The batch size used for all experiments was 30 g of starting material. For each experiment the mixing speed was 200 rpm and the chopper was rotated at a speed of approximately 1,000 rpm. The granulation liquid was added at a radial position 90° before the chopper using a liquid addition rate of 20 ml/min, and the spectrometer detecting the conversion was situated at a radial position 180° from the chopper.

Three model formulation granulations were carried out according to the parameters listed in Table 2, without adding HPMC. A fourth granulation was undertaken that was identical to the previous three, but with the addition of HPMC. The granular properties were comparable for all four batches in terms of particle size distribution, Carr's index and loss on drying.

Software

HoloGRAMS software (version 4.0, Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) was used to control the Raman spectrometers. The XRD-6000 V 4.1 for NT/98 software (Kratos Analytical, Chestnut Ridge, NY, USA) was used to control the X-ray diffractometer. The scanning electron microscope was controlled by the xTm software (v. 2.01, FEI Company, Hillsboro, OR, USA) and analyzed using XT Docu software (v. 3.2, Soft Imaging System GmbH, Münster, Germany). The CoolSnap cf digital camera was controlled by MetaVue software (version 6.1r6, Universal Imaging Corp., West Chester, PA, USA). An in-house LabView (version 6.1, National Instruments, Inc., Austin, TX, USA) program was used to control the AquaLab. Excel 2000 (build 9.0.2720, Microsoft Corporation, Seattle, WA, USA) and PowerPoint 2000 (build 9.0.2716, Microsoft Corporation, Seattle, WA, USA) were used for growth rate calculations, with the former also being used for the Raman calibration calculations and quantitation. Sigma Plot (version 8.02, SSPS, Inc., Chicago, IL, USA) was used for curve fitting and graph plotting.

Table 2. Batch Information and Experimental Parameters for the Lab-Scale Wet Granulation Experiments

Parameters	Values
Formulation	
Theophylline anhydrous	90 g
Microcrystalline cellulose	105 g
Mannitol	105 g
Polyvinyl pyrrolidone K-29/32[a]	14.5 g
Water[a]	115 g
Hydroxypropyl methylcellulose E5	1.0 g[b]
Process parameters	
Bowl volume	2 l
Mixing speed (Tip speed)	100 rpm (0.9 m/s)
Chopper speed	1200 rpm
Experiment parameters	
Dry mixing time	2 min
Binder solution addition time	37 s
Wet massing time	10 min

[a] Added as the granulating liquid
[b] Excluded in standard granulation

RESULTS

Granulation Screening Experiments

Using the small-scale granulator described above, the transformation of theophylline anhydrous to the monohydrate in the presence of a wide variety of excipients was monitored using in-line Raman spectroscopy. Numerous excipients were screened in an effort to determine which excipients could be used to manipulate the kinetics of hydrate formation. The excipients tested included commonly used diluents (e.g., MCC), binders (e.g., PVP K-29/32), disintegrants (e.g., Na-CMC), solubilizers (e.g., SDS) and buffers (e.g., citric acid). A summary of the results is shown in Table 1. Most of these excipients proved to have little or no effect on the transformation kinetics of theophylline, with the exception of some commonly used binders, especially methylcelluloses. In Fig. 2, theophylline transformation kinetics with no additive (called Water) is compared with the transformation kinetics in the presence of PVP, HPC, HPMC (grades E, K and F), and MC (grade A). The transformation profiles are all characterized by an induction period where no transformation is observed following the addition of water (at time zero), followed by conversion of the anhydrous material to the monohydrate, whereby a

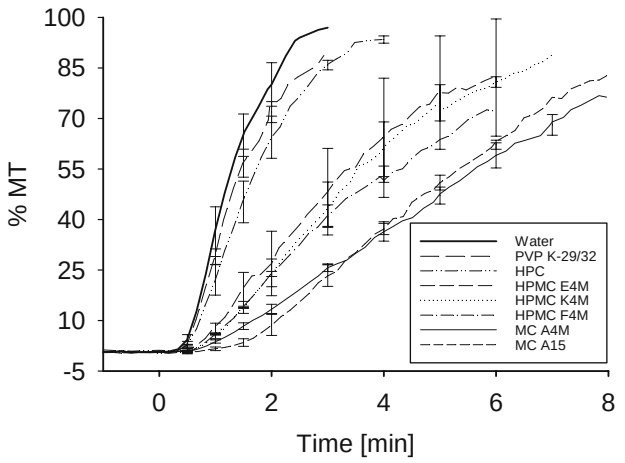

Fig. 2. Transformation profiles for the conversion of anhydrous theophylline to the monohydrate form when using different polymers as additives during wet granulation.

steeper slope indicates a faster transformation rate. From Fig. 2 it can be observed that PVP does not significantly affect the transformation kinetics, and that HPC only has a small retarding effect. In contrast, MC and HPMC were found to have a much larger effect, increasing the onset time and reducing the transformation rate. Within the different grades of methylcelluloses tested, the trend observed was that the less hydrophobic the polymer, the greater the effect on the transformation profile (Fig. 2).

Following identification of excipients with the best retarding effects, the influence of excipient addition methodology was investigated. Polymers were either dry blended with the drug or dissolved in the granulation liquid, maintaining the same drug/polymer ratio. The latter methodology also served to eliminate any particle size differences between the various polymers tested. The method of excipient addition was found to be unimportant, and the transformation kinetics when using a dissolved binder was comparable to the kinetics seen when adding the binder dry.

In order to better compare the results obtained from the different excipients, select data were fitted by linear regression. Only the linear portion of the transformation profile was used; the onset time and slope were then estimated from the regression coefficients. Figure 3 shows how these values differ when using a range of different polymers. In general, it can be observed that those polymers which result in an increase in the onset time also decreased the transformation rate as evident by a decrease in the value of the slope.

Next, the effect of polymer concentration was investigated by adding different amount of MC A15, one of the best retarding polymers (Fig. 4a). It appears that, once a threshold concentration of MC was reached at about 0.25% (*w*/*w* drug), there was little to be gained by adding more polymer. The effect of polymer molecular weight was also investigated (Fig. 4b) and was found to have a minimal effect, with the onset time increasing somewhat with decreasing molecular weight. Finally, the effect of methylcellulose substitution grade was tested using three different HPMC grades of the same viscosity (E4M, K4M and F4M) and comparing to MC of the same viscosity (A4M). These results are shown in Fig. 4c. As is evident from these results, the more the hydrophilic the polymer, the better the inhibitory effect.

Slurry Experiments

Slurry experiments were also carried out to determine if the same excipients could also alter the transformation kinetics in a water-rich, low-shear environment. As shown in Table 1, and in good agreement with the granulation experiments, the vast majority of excipients investigated did not show any effect on the transformation profile of theophylline. However, with a few exceptions that are discussed below, polymers that demonstrated a retarding effect in granulation experiments also functioned as retarding agents during the slurry experiments. The transformation profiles when using select additives are shown in Fig. 5. Essentially, the trends are identical to those seen for the granulation experiments presented in Fig. 2, with the transformation rates being slightly slower for a given additive in the slurries at similar drug/additive ratio. However, it can be noted that the onset time for the transformation was significantly longer for slurry experiments, as exemplified by methylcellulose (10.0±1.7 min onset time in slurry compared to 0.8±0.2 min during granulation experiments).

As is apparent from Table 1, excipients that can be described as "water scavenging" due to their ability to absorb large quantities of water, e.g. PAA and Na-CMC, showed little effect on the transformation kinetics in slurries despite the fact that some effect was observed in granulation experiments. For the slurry experiments, these types of excipients were also added in two different ways, i.e. either dissolved in water or dry mixed with the drug. In all but one case there was no notable difference between the two addition methodologies. However, when using dissolved cross-linked poly-

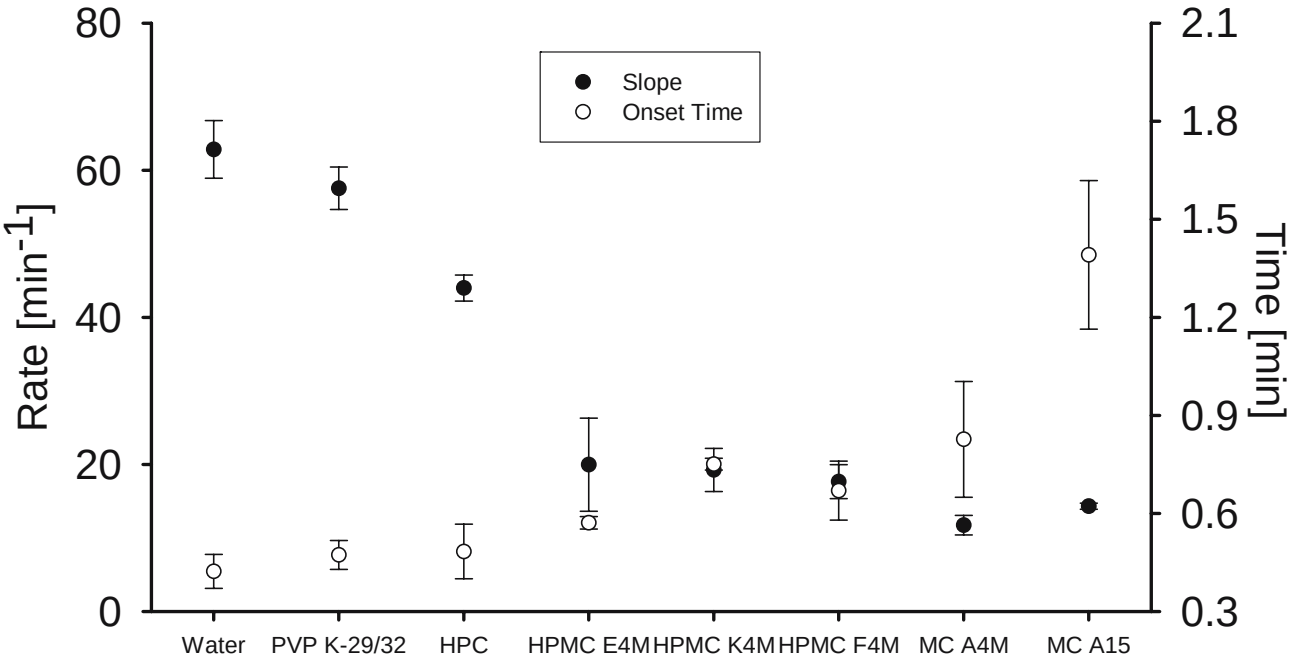

Fig. 3. Rate constants and onset times of hydrate formation of theophylline during wet granulation experiments when using various additives.

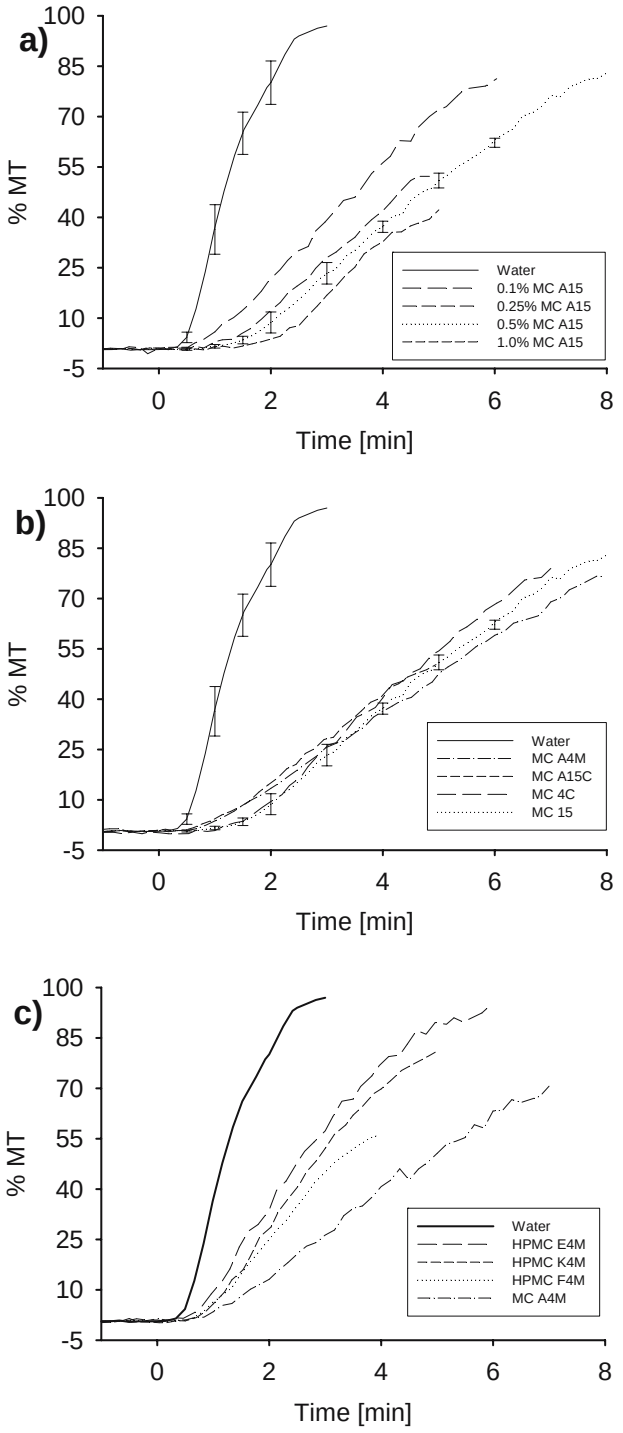

Fig. 4. Influence of concentration, molecular weight and substitution chemistry of methylcellulose polymers. **a** transformation profiles when using solutions of different concentration of MC A15 as the granulation liquid; **b** transformation profiles when using methylcellulose of different molecular weights, **c** transformation profiles when using different grades of methylcelluloses.

acrylic acid there was an extended onset time relative to when PAA was added dry. These results are compared with those obtained from the granulation experiment in Fig. 6, where it can be seen that PAA pre-dissolved in water in the slurry has a similar retarding effect as for the granulation experiment.

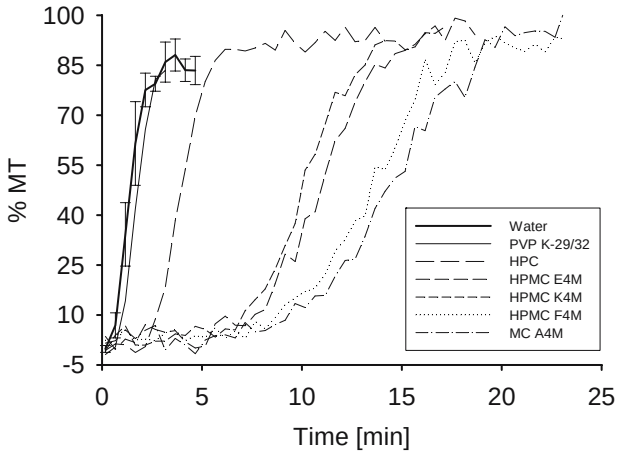

Fig. 5. Transformation profiles of theophylline anhydrous to its monohydrate form in the presence of various polymers during slurry experiments.

In a production environment, binder solutions may be prepared up to 24 h prior to use to ensure complete hydration of the polymer. To investigate the effect of hydration, freshly prepared solutions of methylcellulose were compared to solutions that had been aged for up to 2 days. While the rate of the transformation remained the same regardless of the age of the solution, as indicated by the slope of the transformation profile, the onset time changed over time. For solutions used within 6 h of preparation, the onset time was constant at around 10 min, while after 24 h it increased to 16 min and after 48 h it was over 22 min.

Lab-Scale Granulations

A lab-scale experiment was carried out whereby 0.3% (*w*/*w*) HPMC E5 was added to the model formulation listed in Table 2. Results shown in Table 1 indicate that PVP, MCC and mannitol, added as individual components, had a minimal effect on the transformation kinetics either during slurry or during small-scale wet granulation experiments. The results shown in Table 3 of these excipients also indicate that the growth rate is unaffected by their presence. Furthermore, as shown in Fig. 7a, when

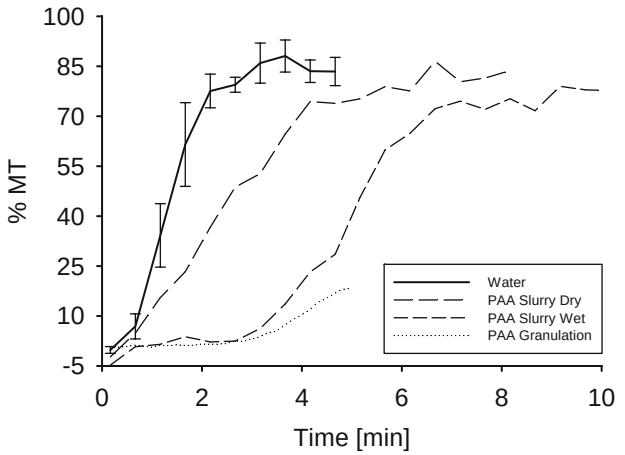

Fig. 6. Transformation profile of theophylline anhydrous to its monohydrate form when using cross-linked polyacrylic acid as an additive in different types of experiments.

Table 3. Growth Rate of Theophylline Monohydrate Crystals When Using Different Polymers as Solution Additives (n=3–6)

Additive	Growth rate	
	(μm/min)	SD
None	35.5	2.6
PAA	39.6	19.3
Mannitol	38.2	3.6
EC 7	33.8	6.0
PVP K-12	24.7	15.8
PVP K-29/32	27.0	8.7
PVP K-90	27.3	10.0
HPC	5.5	2.0
HPMC E4M	6.9	2.6
HPMC E5	3.8	0.4
MC A4M	1.8	0.6
MC A15C	1.3	0.8
MC A4C	1.1	0.2
MC A15	1.1	0.2

Each additive was added at a level of 0.5% (*w*/*w*), with the exception of mannitol, which was added at 10% (*w*/*w*).

adding HPMC E5 during the small-scale granulation experiments, the onset time was approximately 1 min, and the transformation was complete after 7–8 min. However, when HPMC E5 was added to the model formulation in the lab scale granulation, at the same drug/polymer ratio used in the small-scale granulation, the transformation was completely inhibited over the timescale of the granulation experiment, as seen in Fig. 7b. Hence, it appears as if there might be a cooperative effect between the excipients, which results in an extended onset time. The granule properties of the formulation containing HPMC were compared with those of the standard formulation, and no major differences were seen for the flowability, particle size distribution or water content.

Optical Microscopy

The growth rates of theophylline monohydrate crystals in water and aqueous solutions of select polymers were estimated using an optical microscope equipped with a digital camera. Results are shown in Table 3. The growth rates are based on the average of three to six repeat determinations. The variability between repeat experiments is quite large, however, significant differences can be seen between the various excipients. For example, methylcellulose retarded the growth rate of theophylline monohydrate by a factor of approximately 30 relative to the growth rate in water. Additionally, some excipients resulted in very noticeable differences in crystal morphology, although the crystal form that grew was unaltered, as confirmed by Raman microscopy and XRPD. Optical micrographs showing the hydrate crystals are presented in Fig. 8. Excipients that did not affect the transformation kinetics, such as PVP, had no influence on morphology (Fig. 8b compared with Fig. 8a). Excipients that had an intermediate effect on transformation kinetics, for example HPC, resulted in a moderate change in hydrate morphology, as shown in Fig. 8f. Here it can be seen that the needle-like morphology of theophylline monohydrate grown from water is altered to a more rod-like morphology in the presence of HPC. For the methylcelluloses, which slowed the crystal growth rates considerably, the hydrate morphology was quite altered with polygonal crystals resulting (Fig. 8i and Fig. 8l for HPMC E4M and MC A15, respectively). These changes in morphology indicate that the relative areas of the various crystal faces are significantly different for crystals grown in the presence of certain additives, and this observation may offer some insight into the mechanism of the inhibitory effect.

Solubility and Dissolution Rate Experiments

In order to determine any changes in solubility, intrinsic dissolution rate experiments and equilibrium solubility experiments were performed in pure water, as well as in select polymer solutions. The solubility of theophylline monohydrate was found to be the same in the polymer solutions as in water even when the polymer concentrations were ten times greater than those used to manipulate hydrate formation kinetics. Additionally, the solubility ratio between the anhydrous form and theophylline monohydrate, as determined from the intrinsic dissolution data, remained the same in pure water and in polymer solutions. Thus, it appears

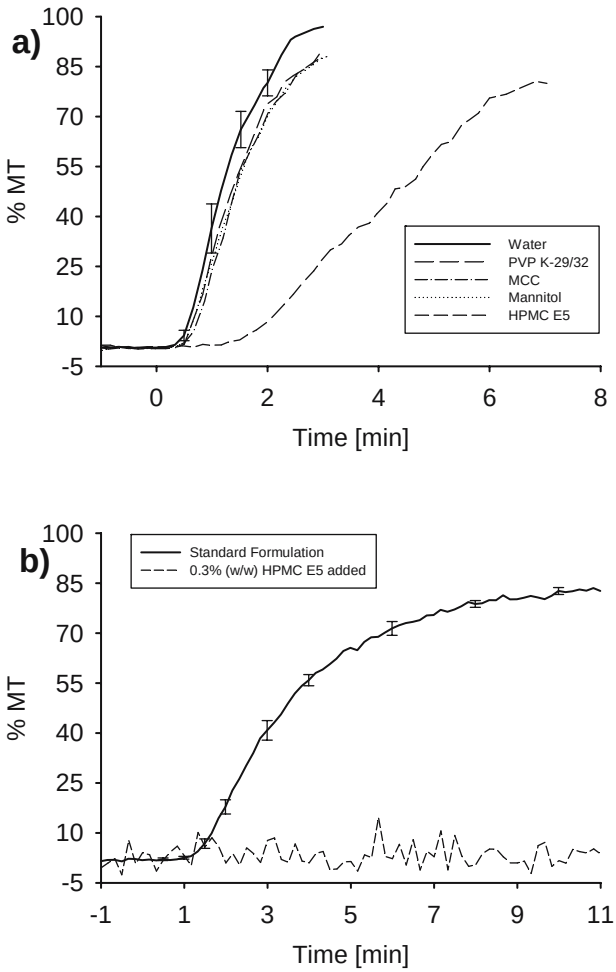

Fig. 7. Transformation kinetics during various granulation experiments. **a** Transformation profiles of individual components during small-scale granulation experiments. **b** Transformation profiles of three standard batches compared to a batch with 0.3% (*w*/*w*) HPMC E5 added to the dry mixture.

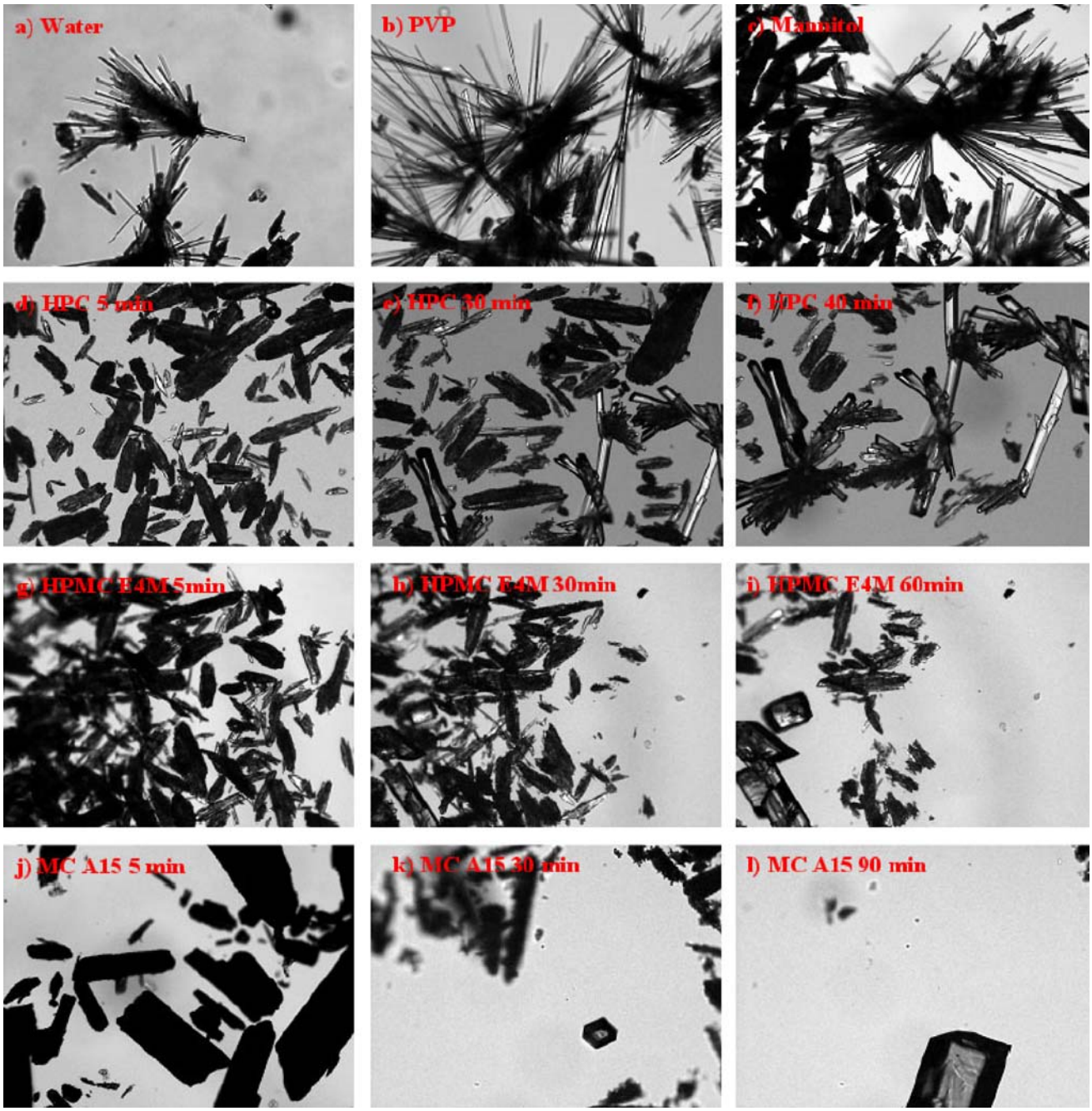

Fig. 8. Micrographs illustrating the difference in growth and morphology for hydrate formation in water with that in three different solutions. **a** TP in water after 10 min; **b** TP in PVP K-29/32 solution after 10 minutes; **c** TP in mannitol solution after 10 min; **d–f** TP in HPC solution; **g–i** TP in HPMC E4M solution; **j–l** TP in MC A15 solution.

that, at the concentrations used, the polymers do not alter the solubility or dissolution rate of either the anhydrous or monohydrate form of theophylline.

Water Activity Measurements

From a thermodynamic perspective, it is know that for a hydrate to be stable, the water activity (a_w) must be maintained above a certain critical value that is characteristic for a given hydrate (22). For theophylline, this value has been estimated to be between 0.5–0.6 (23). It is also known that additives can influence a_w, and that transformation kinetics depend on a_w (17). At the concentrations employed in the granulation and slurry experiments, it was found that the polymers that inhibited hydrate formation did not have a very dramatic influence on a_w with all solutions producing a_w values of 0.99 or greater.

DISCUSSION

Hydrate formation in an aqueous environment would be expected to occur through a solvent-mediated transformation (SMT), which is a three-stage process (24). Firstly the meta-

stable form dissolves, making the solution supersaturated with respect to the stable form. Secondly, once supersaturation has been established, nucleation of the stable form may occur. Finally, once nuclei of the stable form are present in the solution, growth of that form will continue until all of the meta-stable phase has dissolved and the drug concentration of the solution has decreased to the solubility of the stable form. A simulated transformation profile of a solvent-mediated transformation is shown in Fig. 9. The schematic illustrates how the transformation might appear under an optical microscope. It is useful to consider how the polymeric inhibitors might influence each of three stages of the SMT.

During the first stage of the SMT, that is dissolution of anhydrous theophylline, the driving force is the degree of undersaturation (25), as shown in Equation 1. Essentially, as long as the solution concentration is less than the solubility of theophylline anhydrous, anhydrous drug will continue to dissolve.

$$\frac{dc}{dt} = k_D \sigma \tag{1}$$

where c is the solution concentration, t is time, k_D is the dissolution rate constant and σ is the degree of undersaturation. At constant temperature, the dissolution rate constant is a function of drug diffusivity, particle size distribution and hydrodynamics (26).

The presence of a polymer could potentially affect diffusivity and hydrodynamics through a change in viscosity, however, at the levels added in this study (typically 0.5 mg/ml or less for the slurry experiments), such effects would be anticipated to be very minor. Additionally, strong interactions between drug and polymer in solution could increase the amount of drug solubilized, however, no changes in solubility or dissolution rate were observed in the presence of the polymers. Hence, it is apparent that the polymers must influence either or both of the later two stages of the SMT.

The second stage of transformation is the formation of stable nuclei of theophylline monohydrate. In the simulated hydrate formation profile shown in Fig. 9, this would occur sometime prior to the point marked with the arrow. Equation 2 shows a generalized equation for the rate of nucleation.

$$\frac{dN}{dt} = N_0 e^{-\frac{\Delta G^*}{k_B T}} \tag{2}$$

where N is the number of nuclei in solution, t is time, N_0 is the pre-exponential term, ΔG^* is the critical Gibbs free energy for the formation of a nucleus, k_B is the Boltzman constant and T is the temperature. Classic nucleation theory argues that the energy needed to overcome the energy barrier for nucleation is proportional to the cube of the surface energy, the square of the molecular volume and inversely proportional to the square of the supersaturation

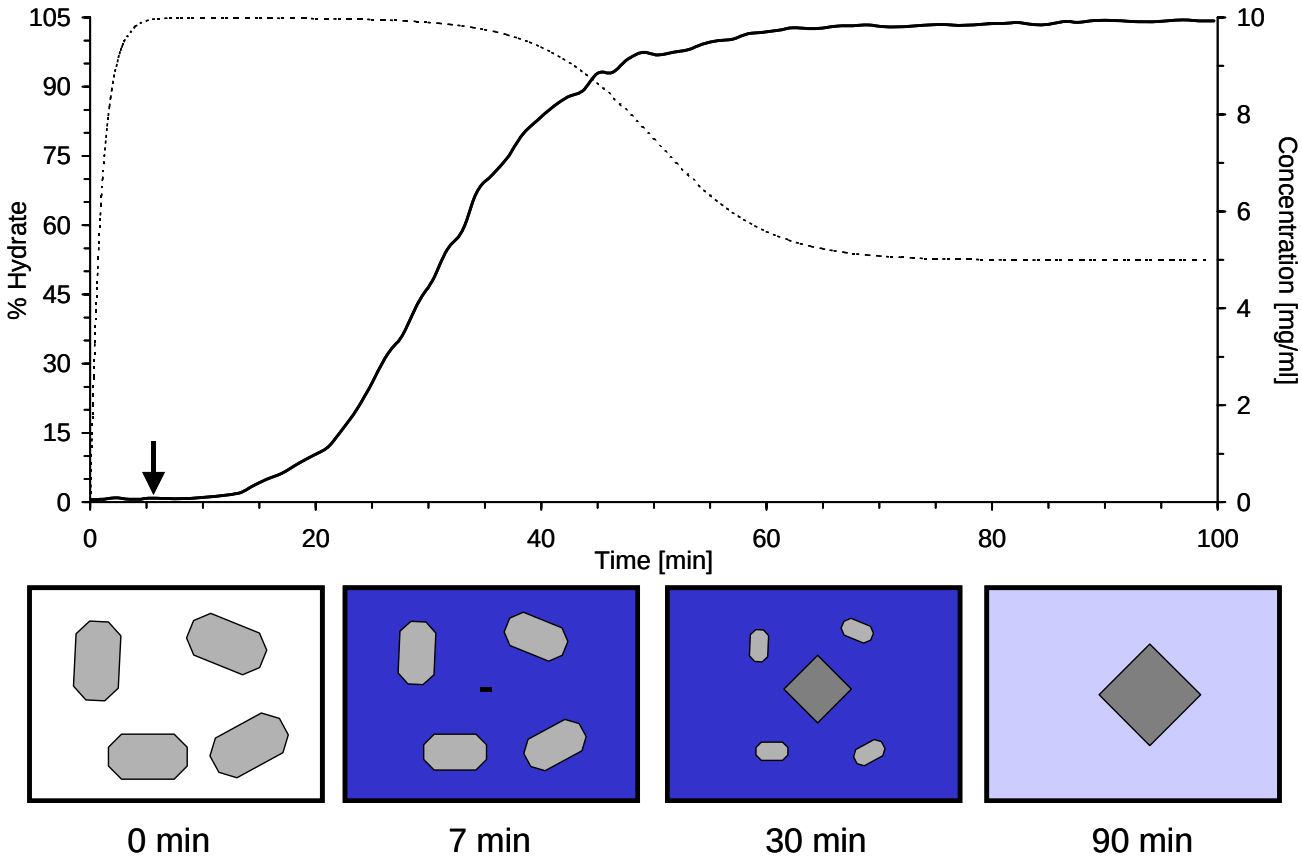

Fig. 9. Overview of a solvent-mediated transformation. The graph depicts a simulated transformation profile of the hydrate formation (*solid line*), as well as a solution concentration profile (*dotted line*). Below the chart, the schematic depicts how the different stages of the transformation might appear under a microscope.

(27). Additionally, the pre-exponential term is proportional to the viscosity of the solution.

Thus according to classical nucleation theory, the three main factors controlling the nucleation rate from solution are temperature, degree of supersaturation and the interfacial tension (28). As discussed above, the polymers do not affect supersaturation, since the solubility of both forms remains the same at the polymer concentrations used in this study, and the temperature was kept constant between experiments. The surface energy term is the only remaining factor that the polymer might affect in order to change the nucleation kinetics, although dramatic viscosity changes could affect the pre-exponential term (as has been discussed previously, the amounts of polymer used here are not likely to significantly affect the viscosity). However, classical nucleation theory describes homogeneous nucleation, which is unlikely to occur in this system due to the moderate supersaturation levels generated, and the potential for foreign surfaces that can aid heterogeneous nucleation. Furthermore, in these systems, and especially during the granulation experiments, secondary nucleation will be important due to shear forces (29).

The last stage involved in a SMT is growth of the monohydrate. This is illustrated in Fig. 9 as the increase in size of the newly formed crystal and the increase in the percent transformed. Once growth occurs, the disappearance of the anhydrous material will continue as the solution is depleted of drug molecules due to the formation of the new phase. Once all anhydrous crystals have dissolved, the solution concentration will slowly decrease until it reaches the equilibrium solubility of the hydrate form, as shown in Fig. 9. It has been proposed that theophylline monohydrate grows through screw dislocation growth (9). According to the Burton-Cabrera-Frank crystal growth model (30), the driving force for this growth mechanism is surface diffusion flux, which in turn is related to the supersaturation according to Equation 3 (9).

$$\frac{dG}{dt} = k'c(\ln \rho)^2 \approx k_G \mu^n \tag{3}$$

where c is the solution concentration and ρ is the solubility ratio. In the simplified equation, k_G is the growth rate constant, μ is the supersaturation and n is about 2 at low levels of supersaturation and closer to 1 at high levels of supersaturation (9). The rate constant (k') depends on the diffusivity, the surface energy of the crystal-solution interface and temperature. Analogous to the nucleation situation, the only effect the polymer is anticipated to have is on the surface energy term, since it has been demonstrated that there is no change in supersaturation at the levels of polymer used in this study.

Comparison of Slurry and Wet Granulation Experiments

The results of this study demonstrate that hydrate formation kinetics can be manipulated during both slurry experiments and high-shear wet granulation using various excipients. In general, the differences observed between the two types of systems were manifested as variations in overall transformation rates with the same excipients being effective in both situations. Interestingly, by comparing Figs. 2 and 5, it can be seen that, when identical systems are compared, the overall transformation rates were faster in the granulation experiments than in the water-rich slurries with main contributor to a reduced transformation time being a decreased onset time in the case of the granulations. This result highlights the likely importance of shear forces in influencing the transformation rate. During the slurry experiments the shear forces are much less pronounced compared with those present during the granulation experiments, however the amount of water is significantly greater in the slurry experiments. In theory, the transformation kinetics is independent of the volume of water (24), however, the increase in shear forces and the improved mixing of the granulation experiments will decrease the time to supersaturation, which is a prerequisite for nucleation. In addition, the density of particulates in solution will be far greater during the granulation experiments, which, together with the increased shear forces, is likely to promote secondary nucleation. This promotion of nucleation in the wet granulator explains why the transformation commences so abruptly.

The consistency of inhibitory effects between wet granulation and slurry experiments was not observed for certain types of excipients, classified as "water-scavenging", which typically showed an effect only during the wet granulation experiments. Hence, it appears that when the availability of water is limited, these additives may result in a decrease in the transformation rate, in agreement with previous results (7). The water-scavenging excipient with the most pronounced effect was cross-linked polyacrylic acid. Interestingly, PAA was the most effective excipient at retarding hydrate formation during the granulation experiment, with a transformation rate constant slightly lower than that of MC A15 and an onset time that was more than twice as long. In slurry, when PAA dissolved in water was used as the transformation medium, there was a significant increase in onset time and the rate constant was also less than half that in pure water (Fig. 6), although PAA did not significantly alter the crystal growth rate (Table 3). When PAA was dry blended with the drug and the mixture was added to pure water, the transformation kinetics was more similar to those in water. It thus appears that PAA hydration may be slower than the transformation time and at this point, it is unclear if PAA acts to reduce transformation times during wet granulation/slurry through a specific or non-specific effect, i.e. through its water absorbing capability. For the other polymers, there was no significant difference between dissolving the polymer in water prior to the slurry experiment or mixing the polymer with the drug and adding this mixture to pure water.

Mechanism of Effect of Excipients

Essentially, it was observed that excipients that had little effect on transformation rates in the slurries or wet granulation experiments, also had no effect on growth rate, while those that influenced the transformation kinetics, reduced crystal growth rates and altered crystal morphology (Table 3 and Fig. 8). For example, PVP had only marginal effect on the rate of transformation, and no effect on the onset time, as seen in Fig. 3 and the growth rates were similar to those seen for water (Table 3). The micrograph in Fig. 8b also clearly indicates that the needle-like morphology seen when theophylline monohydrate is formed in pure water, is also maintained when PVP is added to the solution, with the hydrate

needles growing from the surface of anhydrate particles, as reported previously (31). In contrast, the micrograph in Fig. 8f shows that when grown in the presence of HPC, the morphology of theophylline monohydrate is somewhat altered and the crystal growth rate is substantially reduced (Table 3). The monohydrate crystals still nucleate from the surface of the anhydrous crystals, but there appears to be fewer nucleation sites than for water and PVP. While MC and HPMC have similar crystal growth rates to HPC (Table 3), transformation profiles are longer (Fig. 2 and Fig. 5) and hydrate morphology is more altered (Fig. 8i and Fig. 8l). In addition, nucleation from the surface of the anhydrate particles and nucleation in general appears to be very much reduced. This is particularly apparent from Fig. 8j–l where it can be seen that only one hydrate crystal grows within the field of view. While morphology changes could be caused by the crystals growing under different supersaturation levels, intrinsic dissolution rate as well as equilibrium solubility experiments suggest that this is not the explanation for these systems. The morphology change observed in the microscopy experiments (Fig. 8) can also be seen following the granulation experiment. This is demonstrated in Fig. 10 where SEM pictures of the final granules using water and MC A15 solution as the granulation liquid, respectively, are shown. Based on the observed changes in morphology and the number of hydrate crystals produced, polymers with inhibitory effects are believed to adsorb to fast-growing surfaces of the hydrate crystal, thus retarding overall growth rates. The morphological changes arise because the crystal faces where growth has been retarded become more prominent relative to the other faces. In some instances it is believed that the polymer also adsorbs to the surface of the anhydrate particles, inhibiting heterogeneous nucleation.

Preliminary results indicate that MC A15 is not a general solution for all hydrate forming drugs (Gift 2006, personal communication). Out of four drugs tested, no single polymer was the optimum choice for more than one drug. These preliminary results indicate that the mechanism responsible for the change in transformation kinetics of hydrate formation is specific to a drug-polymer combination and supports the hypothesis that specific adsorption to the fast growing faces is an important mechanism of inhibition. In addition, the observation that such small amounts of polymer are required to inhibit hydrate formation, provides support for the proposed adsorption mechanism.

Tian *et al.* suggested that matching hydrophobicity, in the form of solubility parameter, and hydrogen bonding ability with the drug enables prediction of which additives would be effective retarding agents (16). Their conclusions appear to be well supported for the case of carbamazepine, however, this does not seem to be a suitable approach for theophylline. The solubility parameter for theophylline is about 28 $MPa^{1/2}$ (32). According to Tian *et al.* the solubility parameters of HPMC, PVP, MC, HPC and HEC are about 19.5, 22.5, 24, 27 and 30 $MPa^{1/2}$, respectively (16). Hence, the best match between the solubility parameter of the drug and polymer would be for HPC, which did not significantly alter the transformation kinetics.

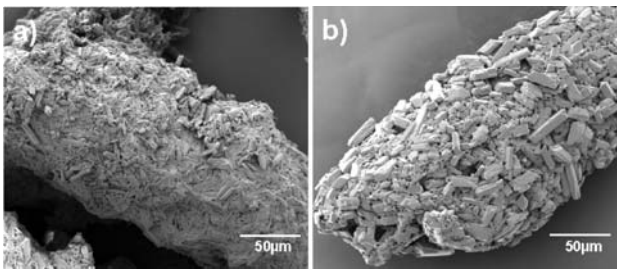

Fig. 10. SEM picture of theophylline monohydrate granules from the small-scale wet granulator. **a** water used as granulation liquid; **b** aqueous MC A15 solution used as granulation liquid.

Polymer Inhibitory Effects in a Multicomponent System

As shown in Fig. 7, it can be seen that addition of HPMC was able to completely inhibit hydrate formation over the timescale of the experiment when combined with the model formulation shown in Table 2. In contrast, the transformation still occurred in slurries and binary wet granulations, even when the ratio of the drug to the polymer was kept constant. It appears that inhibitory excipients may be more effective in formulations than when tested alone. There are likely to be several explanations for these observations. One explanation for the complete inhibition could be the combination of the inhibiting ability of HPMC with the water absorbing capability of MCC, which together leads to much less favorable conditions for nucleation of the monohydrate. Another explanation might be that the presence of the other excipients may reduce the extent of secondary nucleation by altering the shear stress experienced by the drug particles. These results highlight the importance of examining the inhibitory effect of excipients in the final formulation and the complex interplay between formulation ingredients and the wet granulation process.

CONCLUSION

Formation of hydrate drug during pharmaceutical drug product manufacturing may influence both later stages of the manufacturing process, and the product performance. In this study, it has been demonstrated that some commonly used pharmaceutical excipients can be used to retard hydrate drug formation during high-shear wet granulation. This is accomplished by affecting one or two of the three stages of hydrate formation, namely the growth kinetics and/or the nucleation rate. The most effective retarders of theophylline monohydrate formation during wet granulation proved to be some commonly used binders, namely low molecular weight methylcelluloses. The results indicate that the most likely mechanism is selective adsorption of polymer to fast growing crystal surfaces of the hydrate crystal, as the morphology is changed from needle-shaped in the absence of the polymer, to a more polygon-like morphology when methylcellulose was present in the growth medium. Additionally, the onset time of the transformation is significantly increased and the number of hydrate crystals produced is significantly reduced, suggesting that the polymer also may also affect the nucleation stage. Since theophylline monohydrate has been shown to grow from defects on the anhydrate crystal surface, it is speculated that the polymer can preferentially adsorb to those regions. Finally, a small amount of polymer, added to a standard drug formulation, completely inhibited the forma-

tion of hydrate drug throughout the wet granulation process, without affecting the final properties of the granules.

ACKNOWLEDGEMENTS

Dr. Alan Gift, Daniel Sage and Margaret K. Kunkel (all Purdue University) are gratefully acknowledged for assistant with data analysis and experimental support. Jerry J. Sheppard (Purdue University) is acknowledged for his assistance with designing the small-scale granulator, and the general machine shop of Purdue University is thanked for building it. The authors are grateful to Mary A. Albrecht (SSCI, Inc.) for providing the SEM pictures. Sharon Deram (SBI Analytical, Inc.) and Kaiser Optical Systems, Inc., are acknowledged for their assistance with instrumentation. The Dow Chemical Company, BASF and ISP Technologies, Inc. are thanked for supplying the majority of the polymers used for this study. The Dane O. Kildsig Center for Pharmaceutical Processing Research and AstraZeneca R&D Mölndal are acknowledged for funding.

REFERENCES

1. L. L. Augsburger, and M. K. Vuppala. Theory of granulation. In D. M. Parikh (ed.), *Handbook of Pharmaceutical Granulation Technology, Vol. 81*, Marcel Dekker, New York, NY, 1997, pp. 7–23.
2. P. Holm. High shear mixer granulators. In D. M. Parikh (ed.), *Handbook of Pharmaceutical Granulation Technology, Vol. 81*, Marcel Dekker, New York, NY, USA, 1997, pp. 151–203.
3. S. R. Byrn. *Solid State Chemistry of Drugs*, Academic, New York, NY, USA, 1982.
4. K. R. Morris, U. J. Griesser, C. J. Eckhardt, and J. G. Stowell. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. *Adv. Drug Deliv. Rev.* **48**:91–114 (2001).
5. H. G. Brittain. Methods for the characterization of polymorphs and solvates. In H. G. Brittain (ed.), *Polymorphism in Pharmaceutical Solids, Vol. 95*, Marcel Dekker, New York, NY, 1999, pp. 227–278.
6. Y. Qiu, X. Z. Qu, X. Q. Song, J. X. Chen, and F. T. Chau. Construction of a CCD multichannel fiber-optic spectrometer and its application. *Instrum. Sci. Technol.* **24**:143–150 (1996).
7. H. Wikström, P. J. Marsac, and L. S. Taylor. In-line monitoring of hydrate formation during wet granulation using Raman spectroscopy. *J. Pharm. Sci.* **94**:209–219 (2005).
8. E. Räsänen, J. Rantanen, A. Jørgensen, M. Karjalainen, T. Paakkari, and J. Yliruusi. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. *J. Pharm. Sci.* **90**:389–396 (2001).
9. N. Rodríguez-Hornedo, and H. J. Wu. Crystal-growth kinetics of theophylline monohydrate. *Pharm. Res.* **8**:643–648 (1991).
10. Specifications: Test procedures and acceptance critera for new drug substances and new drug products: Chemical substances Q6A, ICH Steering Committee, International Conference on Harmonization, Geneva, Switzerland, 1999, p. 31.
11. I. Katzhendler, R. Azoury, and M. Friedman. Crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets based on hydroxypropyl methylcellulose. *J. Control Release.* **54**:69–85 (1998).
12. I. Katzhendler, K. Mader, R. Azoury, and M. Friedman. Investigating the structure and properties of hydrated hydroxypropyl methylcellulose and egg albumin matrices containing carbamazepine: EPR and NMR study. *Pharm. Res.* **17**:1299–1308 (2000).
13. I. Katzhendler, R. Azoury, and M. Friedman. The effect of egg albumin on the crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets and in aqueous solutions. *J. Control Release.* **65**:331–343 (2000).
14. M. Otsuka, T. Ohfusa, and Y. Matsuda. Effect of binders on polymorphic transformation kinetics of carbamazepine in aqueous solution. *Colloid. Surf. B-Biointerfaces.* **17**:145–152 (2000).
15. N. Rodríguez-Hornedo, and D. Murphy. Surfactant-facilitated crystallization of dihydrate carbamazepine during dissolution of anhydrous polymorph. *J. Pharm. Sci.* **93**:449–460 (2004).
16. F. Tian, D. J. Saville, K. C. Gordon, C. J. Strachan, J. A. Zeitler, N. Sandler, and T. Rades. The influence of various excipients on the conversion kinetics of carbamazepine polymorphs in aqueous suspension. *J. Pharm. Pharmacol.* **59**:193–201 (2007).
17. H. Qu, M. Louhi-Kultanen, and J. Kallas. Additive effects on the solvent-mediated anhydrate/hydrate phase transformation in a mixed solvent. *Cryst. Growth Design.* **7**:724–729 (2007).
18. S. Airaksinen, P. Luukkonen, A. C. Jørgensen, M. Karjalainen, J. Rantanen, and J. Yliruusi. Effects of excipients on hydrate formation in wet masses containing theophylline. *J. Pharm. Sci.* **92**:516–528 (2003).
19. S. Airaksinen, M. Karjalainen, N. Kivikero, S. Westermarck, A. Shevchenko, J. Rantanen, and J. Yliruusi. Excipient selection can significantly affect solid-state phase transformation in formulation during wet granulation. *AAPS PharmSciTech.* **6**: (2005).
20. Theophylline capsules. USP28-NF23, Vol. S2, United States Pharmacopeia, Rockville, MD, USA, 2005.
21. J. Rantanen, H. Wikström, F. E. Rhea, and L. S. Taylor. Improved understanding of factors contributing to quantification of anhydrate/hydrate powder mixtures. *Appl. Spectrosc.* **59**:942–951 (2005).
22. D. J. W. Grant, and T. Higuchi. *Solubility Behavior of Organic Compounds*, Wiley, New York, NY, USA, 1990.
23. M. D. Ticehurst, R. A. Storey, and C. Watt. Application of slurry bridging experiments at controlled water activities to predict the solid-state conversion between anhydrous and hydrated forms using theophylline as a model drug. *Int. J. Pharm.* **247**:1–10 (2002).
24. P. T. Cardew, and R. J. Davey. The kinetics of solvent-mediated phase-transformations. *Proc. R Soc. Lond. A.* **398**:415–428 (1985).
25. A. A. Noyes, and W. R. Whitney. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.* **19**:930–934 (1897).
26. A. W. Hixson, and J. H. Crowell. Dependence of reaction velocity upon surface and agitation I—Theoretical consideration. *Industrial Eng. Chem.* **23**:923–931 (1931).
27. J. W. Gibbs. On the equilibrium of heterogeneous substances. *Trans. Conn. Acad.* **3**:343–524 (1878).
28. J. W. Mullin. *Crystallization*, Elsevier, Oxford, UK, 2001.
29. T. P. Melia, and W. P. Moffitt. Secondary nucleation from aqueous solution. *Industrial Eng. Chem.* **3**:313–317 (1964).
30. W. K. Burton, N. Cabrera, and F. C. Frank. The growth of crystals and the equilibrium structures of their surfaces. *Philosophical Transactions of the Royal Society of London Series A, Mathematical and Physical Sciences.* **243**:299–358 (1951).
31. N. Rodríguez-Hornedo, D. Lechuga-Ballesteros, and H. J. Wu. Phase-transition and heterogeneous epitaxial nucleation of hydrated and anhydrous theophylline crystals. *Int. J. Pharm.* **85**:149–162 (1992).
32. B. C. Hancock, P. York, and R. C. Rowe. The use of solubility parameters in pharmaceutical dosage form design. *Int. J. Pharm.* **148**:1–21 (1997).