Pharmaceutical Research, Vol. 23, No. 8, August 2006 (© 2006)
DOI: 10.1007/s11095-006-9034-1

Research Paper

Use of Surfactants as Plasticizers in Preparing Solid Dispersions of Poorly Soluble API: Stability Testing of Selected Solid Dispersions

Alazar N. Ghebremeskel,[1,2] Chandra Vemavarapu,[1] and Mayur Lodaya[1]

Received January 3, 2006; accepted April 10, 2006

Purpose. The purpose of the study is to evaluate the effect of surfactant-plasticizers on the physical stability of amorphous drug in polymer matrices formed by hot melt extrusion.
Method. Solid dispersions of a poorly soluble drug were prepared using PVP-K30, Plasdone-S630, and HPMC-E5 as the polymeric carriers and surfactants as plasticizers. The solid dispersions were produced by hot melt extrusion at temperatures 10°C above and below the glass transition temperature (Tg) of the carrier polymers using a 16 mm-Haake Extruder. The surfactants tested in this study included Tween-80 and Docusate Sodium. The particle size of the extrudate was reduced to have mean of 100–200 micron. The physical stability of the solid dispersions produced was monitored at 30°C/60% for six-months and at 60°C/85% for two-months in open HDPE bottles. Modulated differential scanning calorimetry, polarized light microscopy, powder X-ray diffraction and dissolution testing was performed to assess the physical stability of solid dispersions upon stress testing.
Results. The dispersions containing HPMC-E5 were observed especially to be susceptible to physical instability under an accelerated stress conditions (60°C/85%RH) of the solid dispersion. About 6% conversion of amorphous drug to crystalline form was observed. Consequently, the system exhibits similar degree of re-crystallization upon addition of the surfactant. However, under 30°C/60%RH condition, the otherwise amorphous Drug-HPMC-E5 system has been destabilized by the addition of the surfactant. This effect is much more reduced in the extruded solid dispersions where polymeric carriers such as Plasdone S-603 and PVP-K30 (in addition to surfactants) are present. Furthermore, the drug release from the solid dispersions was unaffected at the stress conditions reported above.
Conclusions. Possible reasons for the enhanced stability of the dispersions are due to the surfactants ability to lower the viscosity of the melt, increase the API solubility and homogeneity in the carrier polymer. In contrast, while it is possible for the surfactants to destabilize the system by lowering the Tg and increasing the water uptake, the study confirms that this effect is minimal. By and large, the surfactants appear to be promising plasticizers to produce solid dispersions by hot melt extrusion, in so doing improving dissolution rate without compromising the physical stability of the systems.

KEY WORDS: hot melt extrusion; physical stability; plasticizer; solid dispersion; surfactant.

INTRODUCTION

Formation of a homogenous molecular dispersion and the subsequent physical stability of the glassy matrices largely depend on the degree of interaction between the pharmaceutical active (API) and the polymer. Non-covalent interactions in relation to material properties that frequently come into play include hydrogen bonds, van der Waals, k-k stacking, and electrostatic interactions (1–4). Other physical effects such as size (diffusion) of API and free volume (rigidity) of the polymer may also play a role, although to a lesser degree. Selection of polymeric carriers therefore entails matching the properties of polymer with the API, allowing for greater interaction between them (5). Given that the solubility characteristics of a hydrophilic polymer and a poorly soluble API are different, bringing these two components together frequently requires intensive mixing at molecular level (e.g., in a molten state) in the presence of components (e.g., plasticizers and cosolvents) that aid in the interaction between API and polymer.

In an earlier publication evaluating the selection of surfactants for various polymer systems, we reported that (6) that surfactants caused solubilization and plasticization of the API and polymers, reflected in the reduction of (a) Tm and Tg of API, (b) Tg of the polymers, and (c) the combined Tg of the solid dispersion formed from API-polymer composites. The selection of plasticizers (surfactants) for various polymer dispersions containing 50% drug load was evaluated based on the experimental data on the plasticization capability of surfactants, as well as empirical predictions involving solubility parameters (6). It was shown that surfactants such as Tween-80 and Docusate sodium could be used to plasticize various carrier polymers when a hot melt extrusion technique is employed. When incorporated into a polymeric material, these surfactants were shown to improve the workability and

[1] Pfizer Global Research and Development, 2800 Plymouth Rd., Ann Arbor, Michigan 48105, USA.
[2] To whom correspondence should be addressed. (e-mail: firstone_ang@yahoo.com)

flexibility of the polymer, allowing for lower temperature processing than otherwise warranted. While the use of surfactant systems in aiding the processeability of various API-polymer dispersions was well demonstrated (7–12), the secondary effects of the same on the performance of the solid dispersions needed to be studied further. This manuscript thus evaluates the overall performance of the solid dispersions processed using surfactants as plasticizers. On one hand, the solubilization and plasticization capabilities of surfactants have positive implications on the physical stability & dissolution performance of the solid dispersions. Negative consequences from the use of surfactants in this manner can potentially arise from lowered Tg and increased the water uptake by the surfactant containing dispersion (affecting physical stability), as well as thermal denaturation of surfactant during Hot Melt Extrusion (HME) processing (affecting dissolution performance). The significance of each of these mechanisms on the overall performance of the solid dispersions is studied in this manuscript.

MATERIALS AND METHODS

Materials

Plasdone S-630 was obtained from ISP Technologies Inc., (Wayne, NJ). Hydroxypropyl methylcellulose (HPMC-E5); Polyvinylpyrrolidone K30 (PVP K30); Polysorbate-80 (Tween-80, HLB value of 15.0) and sulfobutanedioic acid bis[2-ethylhexyl ester] Dioctyl sulfosuccinate (Docusate Sodium, HLB value of 10) were supplied by Sigma Chemicals (St. Louis, MO). Physical properties of API is shown in Table I. All chemicals were of laboratory reagent grades.

Sample Preparation

A series of binary physical mixtures of mass ratios 1:1 of API and hydrophilic polymers such as PVP-K30, Plasdone-S630, and HPMC-E5 were prepared by gently mixing accurately weighed quantities using a mortar and pestle for 2 min, followed by 15 min of mixing in a turbula mixer. Then the liquid and semisolid surfactants (Tween-80 and Docusate sodium) were first mixed using spatula in a weigh boat for 5 min followed by mortar and pestle for additional 10 min. Blends were considered uniform when three separate DSC thermograms were similar when superimposed. The final mass ratio of all samples tested contained 45:45:10 for the API/polymer/surfactant mixture and 50:50 for the API/polymer mixture by weight.

Table I. Physical Properties of the API

MW = ~400
Tm/Tg = 1.3
Moderate glass former
Aq. solubility ~5 μg/ml
pKa = 11; not ionized at pH < 10
Log *P* > 3.5
Dissolution limited absorption

Hot Melt Extrusion (HME)

The extrusion process was performed using the 16 mm Haake Rheomix co-rotating intermeshing twin screw extruder in a controlled environment at process conditions for each of the selected systems (Table II). The screw speed was adjusted to 100 rpm, resulting in a residence time in the extruder of approximately 2–3 min. The powder blends were manually fed into the melt extruder (10 g/min). Extrudate collection began 3 min after the run was initiated to allow any material from the previous runs to be extruded prior to sample collection. The melt extrudate was air cooled on a conveyor belt. All extrudate samples were stored in a controlled temperature cabinet at 25°C (25%RH).

Stability Study

A 3-gram sample size of each of the solid dispersion was transferred to HDPE bottles and placed open-dish inside humidity chambers pre-equilibrated to 30°C/60%RH and 60°C/85%RH, respectively. At specific time interval during the course of study, the bottles were removed and inspected for any physical changes while in the bottle. A small amount of sample was then withdrawn from each bottle for characterization by pXRD, mDSC, polarized microscopy and dissolution testing, before putting the whole bottle back into the chamber.

Powder X-Ray Diffraction Studies (pXRD)

All samples were characterized for X-ray pattern using a KD-2660-N X-ray diffractometer controlled by the D-Max B controller and Datascan MDI software (Rigaku Ultima-plus, Tokyo, Japan) with CuKα radiation (λ = 1.54 Å) generated from a copper source operating at a power level of 40 KV and 40 mA. The test samples were packed into 0.5 mm deep graphite sample holders. The samples were scanned over the range of 3–50° 2-theta at a scan rate of 1°/min with slit configuration 0.5°, 0.5°, 0.3 mm and 0.6 mm for divergence, scatter, receiving and monochromator slit, respectively.

Modulated Differential Scanning Calorimetry (DSC)

DSC measurements were carried out using a TA Instruments Q1000 modulated differential scanning calorimetry (TA Instruments Inc., New Castel, DE). About 5–7 mg sample was accurately weighed and placed in a hermetic aluminum pan with a pinhole lid and crimp sealed. The measurement was made in two cycles. In first cycle, the samples were heated from 20 to 200°C at rate of 5°C/min with a modulation amplitude and period of ± 0.796°C every 60 s, respectively. The sample was quench cooled to 20°C and then reheated (second cycle) at 5°C/min to 200°C at the same ramp rate, modulation amplitude, and period.

Water Uptake

Water sorption studies of the milled solid dispersions were performed using a VTI Vapor Sorption Analyzer

Table II. Increased Water-Uptake by the Surfactant Containing Dispersions had Minimal Effect on the Recrystallization of API when Tested Under both Stability Conditions

Materials	Process Temperature (°C)	Extrudate Tg (°C)		Water Uptake (%)		Percentage of Crystallinity	
		Cycle #1	Cycle #2	30°C/60%RH	60°C/85%RH	30°C/60%RH (6-months)	60°C/85%RH (2-months)
API/Plasdone	100	77.21	79.30	1.8	5.0	0.90	0.82
	120	79.95	82.13			0.82	
API/Plasdone/Tween-80	100	55.89	54.68	2.0	5.5	1.38	0.79
	120	55.74	53.46			1.48	
API/HPMC-E5	135	67.09	70.06	1.7	5.6	1.24	5.74
	155	68.20	71.83			1.14	
API/HPMC-E5/Tween-80	135	50.87	48.39	1.9	6.0	4.44	6.22
	155	51.04	47.96			4.47	
API/PVP-K30	158	96.73	96.59	3.3	9.0	1.16	1.35
	178	99.47	99.52			1.45	
API/PVP-K30/Tween-80	158	83.72	80.68	3.5	10.0	2.14	2.35
	178	81.32	80.76			1.93	
API/PVP-K30/Docusate	158	83.19	83.24	3.6	11.0	1.80	2.51
	178	83.86	83.91			1.45	

Upon 2-months of accelerated stability test at 60°C/85%RH condition, about 6% of the API was found to recrystallize in both API/HPMC-E5 and API/HPMC-E5/Tween-80 systems. For the 6 months of stability test at 30°C/60%RH condition, while 4.5% of re-crystallization was observed for API/HPMC-E5/Tween-80 system, the API/HPMC-E5 remained mostly stable.

(SGA-100, VTI Corporation, Hialeah, FL). The vapor sorption analyzer was programmed to acquire weight data at 30 and 60°C in the relative humidity range of 10–90% every 2 min., after the sample has been loaded onto the microbalance.

Polarized Optical Microscopy

Sample morphology and crystalline birefringence behavior of the samples were investigated using a polarizing optical microscope (Leitz Lab 12 Pol S, Wild Leitz, Heerbrugg,

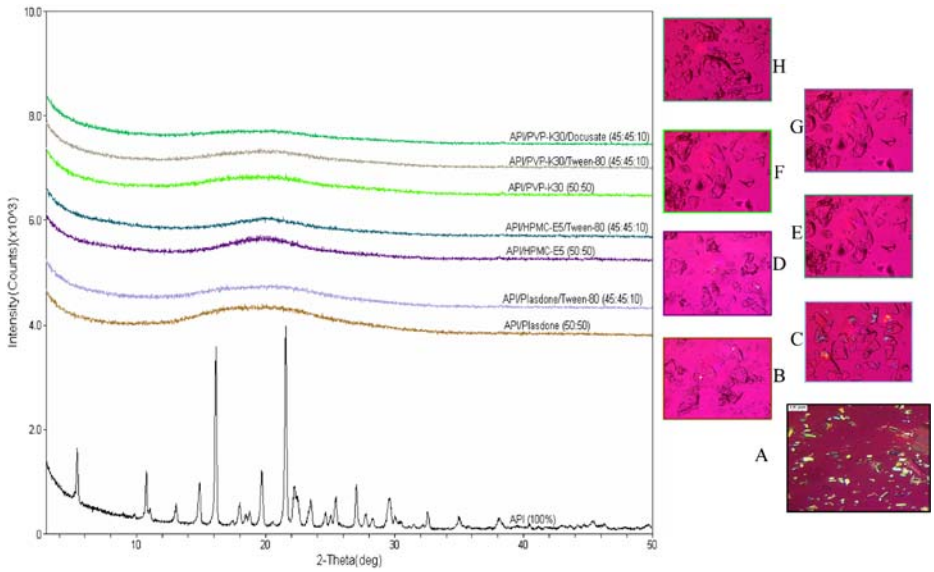

Fig. 1. pXRD and photomicrographs of initial extrudates produced at 10°C below the Tg of the carrier polymer. (A) Crystalline-API; (B) API/Plasdone; (C) API/Plasdone/Tween-80; (D) API/HPMC-E5; (E) API/HPMC-E5/Tween-80; (F) API/PVP-K30; (G) API/PVP-K30/Tween-80; (H) API/PVP-K30/Docusate.

Switzerland) with a tungsten lamp as the light source. Milled extrudates from the stability chambers were pulled at specified time intervals and crushed to powders, if pelletized upon moisture uptake. The powders were then dispersed in mineral oil and viewed under a magnification of 100× with the polarizers perfectly crossed. Recrystallization of API during the stability test was monitored by following the birefringence from any newly formed crystals.

Dissolution Test

Dissolution testing of capsules containing various solid dispersions was performed using apparatus II on a Van Kel VK7010 Dissolution Tester (VanKel Industries, Edison, NJ) equipped with a fiber optic spectrophotometer (C Technologie Inc-VERIFY). The capsules were placed into the dissolution medium (50 mM Phosphate buffer pH 12.0), which was maintained at 37°C by a circulating bath and agitated at 100 rpm. The amount of drug release into the 900 ml dissolution medium was determined at 263 nm at specific time intervals and analyzed spectrophotometrically. All dissolution tests were performed in triplicates. The percent dissolved API was plotted as a function of time for each of the stress conditions.

RESULTS AND DISCUSSION

Hot Melt Extrusion

The Tgs for Plasdone S-630, HPMC-E5, and PVP-K30 are ~111, ~146, and ~168°C, respectively, while the melting temperature of API is 161–165°C. The melt viscosities of API and polymers vary significantly (10 *versus* > 1,000 cps). Mixing these two components therefore requires optimal conditions of temperature and screw design. For comparison, extrudates were prepared with and without the surfactants. Both blends contained the same API to polymer ratio and were processed at the same temperatures 10°C above and below the glass transition temperature of the carrier polymers as shown in Table II.

As discussed in the previous paper (6), the API-polymer mixtures without the plasticizing surfactant became more flexible, more transparent and changed from a light green to a darker yellow as the temperature increased above Tg of the carrier polymer. In addition, the load and torque decreased as the extrusion temperature increased. The extrudate was milled using a Fitzmill (Model L1A, Fitzpatrick Co., Elmhurst, IL) in three stages. First, coarse milling with knives forward at high speed, second, intermediate with hammers

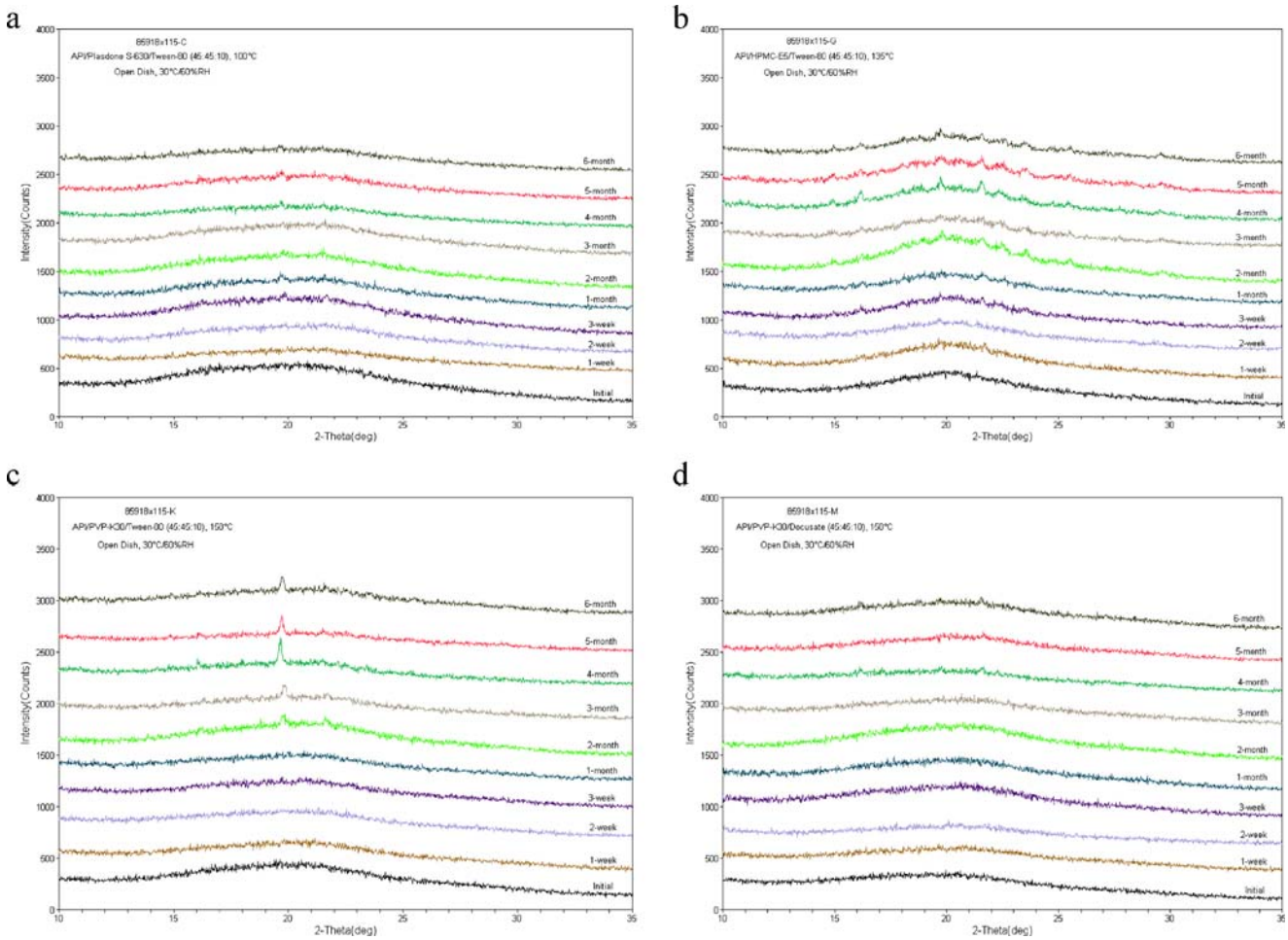

Fig. 2. pXRD of solid dispersion: initial sample and samples stored for 1, 2, 3-weeks, 1, 2, 3, 4, 5, and 6-months at 30°C/60%RH. (a) API/Plasdone/Tween-80; (b) API/HPMC-E5/Tween-80; (c) API/PVP-K30/Tween-80; (d) API/PVP-K30/Docusate sodium.

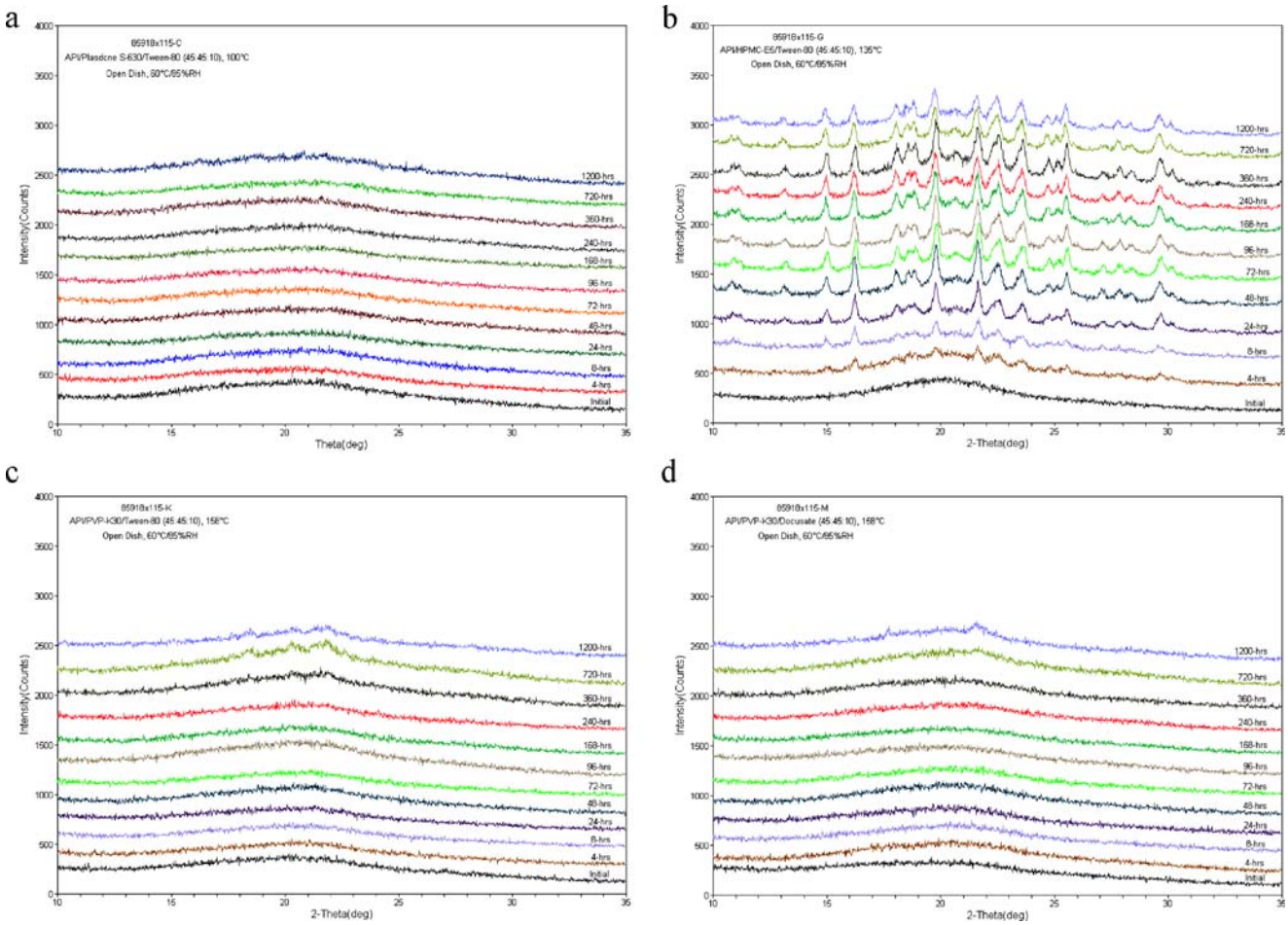

Fig. 3. pXRD of solid dispersion: initial sample and samples stored for 4, 8, 24, 48, 72, 96, 168, 240, 360, 720, and 1,200-h at 60°C/85%RH. (a) API/Plasdone/Tween-80; (b) API/HPMC-E5/Tween-80; (c) API/PVP-K30/Tween-80; (d) API/PVP-K30/Docusate sodium.

forward at high speed, and lastly, fine milling with hammers forward at high speed. The resulted milled dispersion (particle size range of 25 to 200 μm) was then used for analysis.

Powder X-ray Diffraction

Initially, pXRD and polarized microscopy tests demonstrated that the solid dispersions prepared by the melt

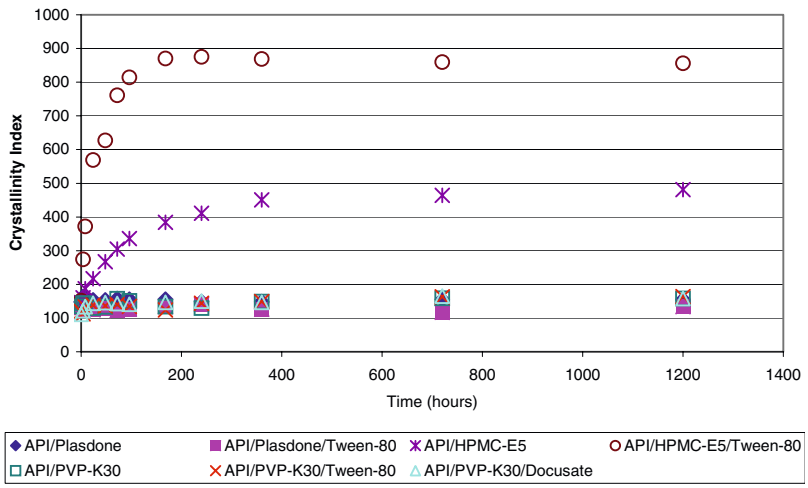

Fig. 4. The time dependence of the crystallization of the solid dispersions at 60°C/85%RH.

extrusion were all amorphous, Fig. 1. The stability of these solid dispersions was then assessed by storing the samples in open HDPE bottles at 30°C/60%RH and 60°C/85%RH (accelerated stability test) and following the physical changes as a function of time. For the most part, the samples stored at 30°C/60%RH were free flowing powders. Some of the samples stored at 60°C/85%RH formed soft-cake that easily got dispersed, but the formulations containing Plasdone S-630 and PVP K-30 solidified such that the samples have to be broken into pieces with a spatula before a small piece can be removed. Most of these samples tested largely remain amorphous after 6-month storage at 30°C/60%RH as shown in Fig. 2. However, both Powder X-ray Diffraction and Optical Microscopy studies showed some minor conversion of the API from amorphous to crystalline with time in certain samples.

Conversely, the powder X-ray diffraction and microscopy studies of solid dispersions stored at 60°C/85%RH (accelerated stability test) for up to 50-days is shown in Fig. 3. The temperature and RH conditions for accelerated stability testing were chosen such that crystallization can be induced and assessed (by PXRD) within a period of 7 days. The solid dispersions of the API/Plasdone S-630/Tween-80 and API/PVP-K30/(Tween-80 or Docusate sodium) remained stable in conformity with the 30°C/60%RH condition. The API/HPMC-E-5/Tween 80 solid dispersion stored at 60°C/85%RH, however, shows some conversion to crystalline form in the first 24-h as shown in Fig. 3b. In fact, the optical micrograph image of the API/HPMC-E5 with and without Tween-80 showed that the re-crystallization of the API stored in an open dish at 60°C/85%RH started in the first 4-h. Likewise, the powder diffraction of the API/HPMC-E5 system stored for one or more days at 60°C/85%RH reveal some conversion of the API from amorphous to crystalline (less than 6% by peak height). On the other hand, the same sample stored for 6-month at 30°C/60%RH did not show any change from that stored in desiccators.

The time dependence of the crystallization solid dispersions at 60°C/85%RH was evaluated either (a) qualitatively by comparing the PXRD patterns or (b) quantitatively by measuring the intensity of reflections from 3–4 (14.8, 16.1, 19.7 and 21.5° 2θ) prominent peaks seen in the API. The intensity of the four significant reflections for the API were then measured and summed for each sample. The total of these reflections was considered to be a measure of crystallinity, here, it is termed the crystallinity index, and was plotted as a function of time for each sample in Fig. 4. The data suggests that solid dispersions containing HPMC-E5

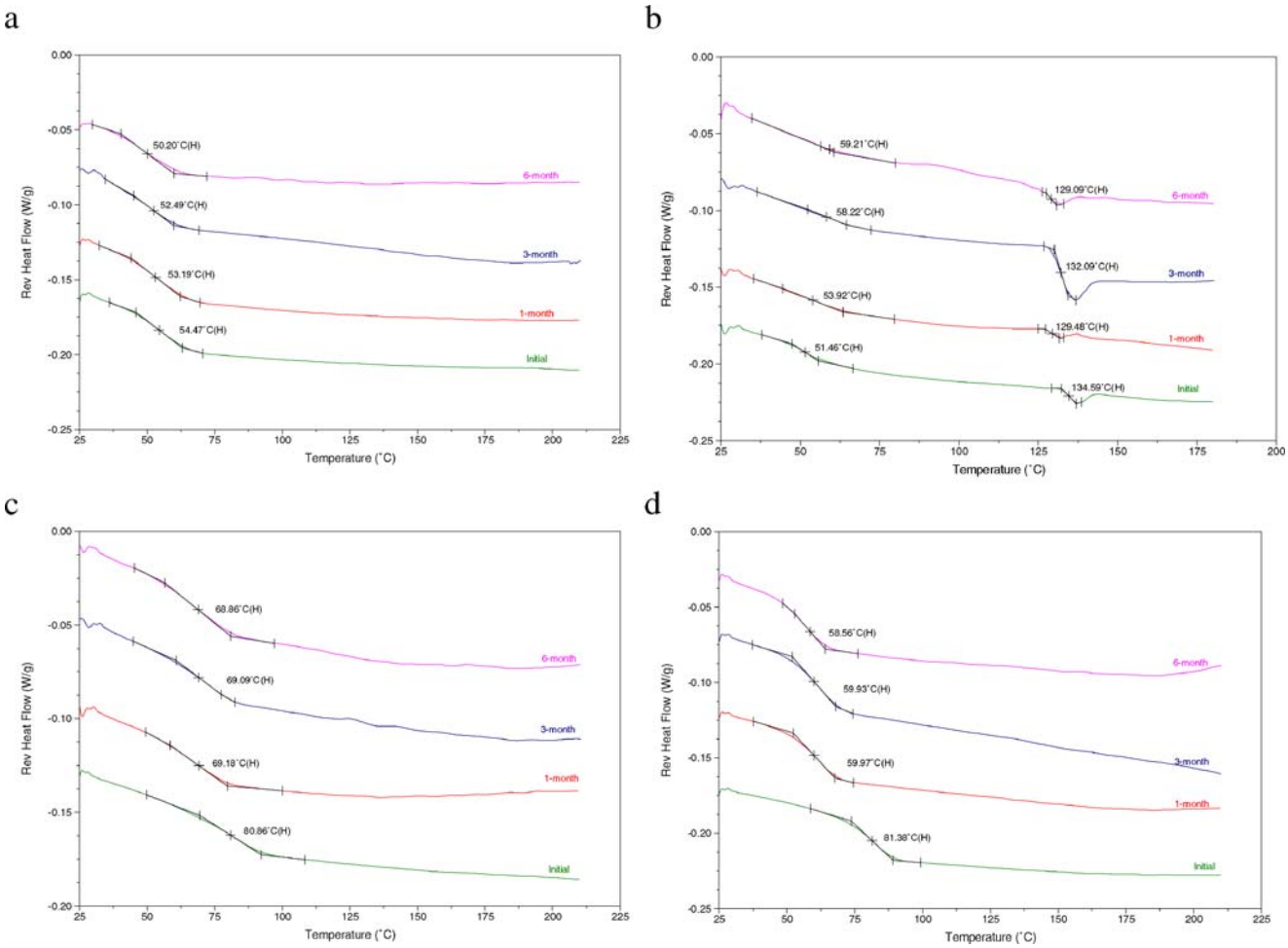

Fig. 5. mDSC reversible heat flow scan of solid dispersions with (a) API/Plasdone/Tween-80; (b) API/HPMC-E5/Tween-80; (c) API/PVP-K30/Tween-80; (d) API/PVP-K30/Docusate sodium Tgs calculated from the first DSC cycle (5°C/min) of the solid dispersions prepared at 10°C below carrier polymer Tg.

(regardless of the additives) allows the most rapid crystallization, while Plasdone S-630 and PVP-K30 appear to inhibit crystallization effectively including for systems containing the plasticization surfactants.

Thermal Analysis

The DSC analysis on the solid dispersions prior to exposing the samples to stress conditions showed single glass transition temperatures above that of amorphous API (58°C). The Tgs calculated from the first cycle of the solid dispersion are listed in Table II. These values are within 1–3°C of the Tgs calculated from the second cycle of the same samples. The absence of any additional transitions, as well as the similarity in the Tg values determined from two cycles indicate that the solid phases of initial milled dispersions are very homogenous. The compositions containing surfactants have not shown any tendency of spontaneous crystallization. These findings are consistent with the results from polarized optical microscopy (Fig. 1).

The uniformity of phases within the solid dispersions produced at 30°C/60%RH and 60°C/85%RH was studied using mDSC. DSC scan of (a) API/Plasdone/Tween-80, (b) API/HPMC-E5/Tween-80, (c) API/PVP-K30/Tween-80, and (d) API/PVP-K30/Docusate sodium, which were stored at 30°C/60%RH for a period of 6-month are shown in Fig. 5. In comparison to the dispersions containing no additive, the differences in the phase uniformity and crystallinity within these samples processed at different conditions were minor and were discernable by mDSC only to a certain extent. However, a second endothermic transition is observed in the first cycle of the measurement for the API/HPMC-E5/Tween-80 solid dispersions, Fig. 5b.

The role of surfactant-based plasticization on the stability of the dispersions was tested at the accelerated 60°C/85%RH. While the effects of plasticization can be ranked from the above mDSC study, no direct correlation was seen in the accelerated stress testing. All the additives used, however, did provide sufficient stabilization to the dispersions when compared to similar API/polymer ratio systems without any additional stabilization (Fig. 6).

The stability testing of the samples stressed at both 30°C/60%RH and 60°C/85%RH did not show any significant differences between the samples processed at various conditions (10°C above or below the Tgs of the carrier polymers). In conclusion, the differences in the crystallinity of samples changed primarily with the type of carrier polymer, but not as pronounced with other process modifications as revealed by mDSC and microscopy. Among the polymer carriers evaluated, the recrystallization of behavior

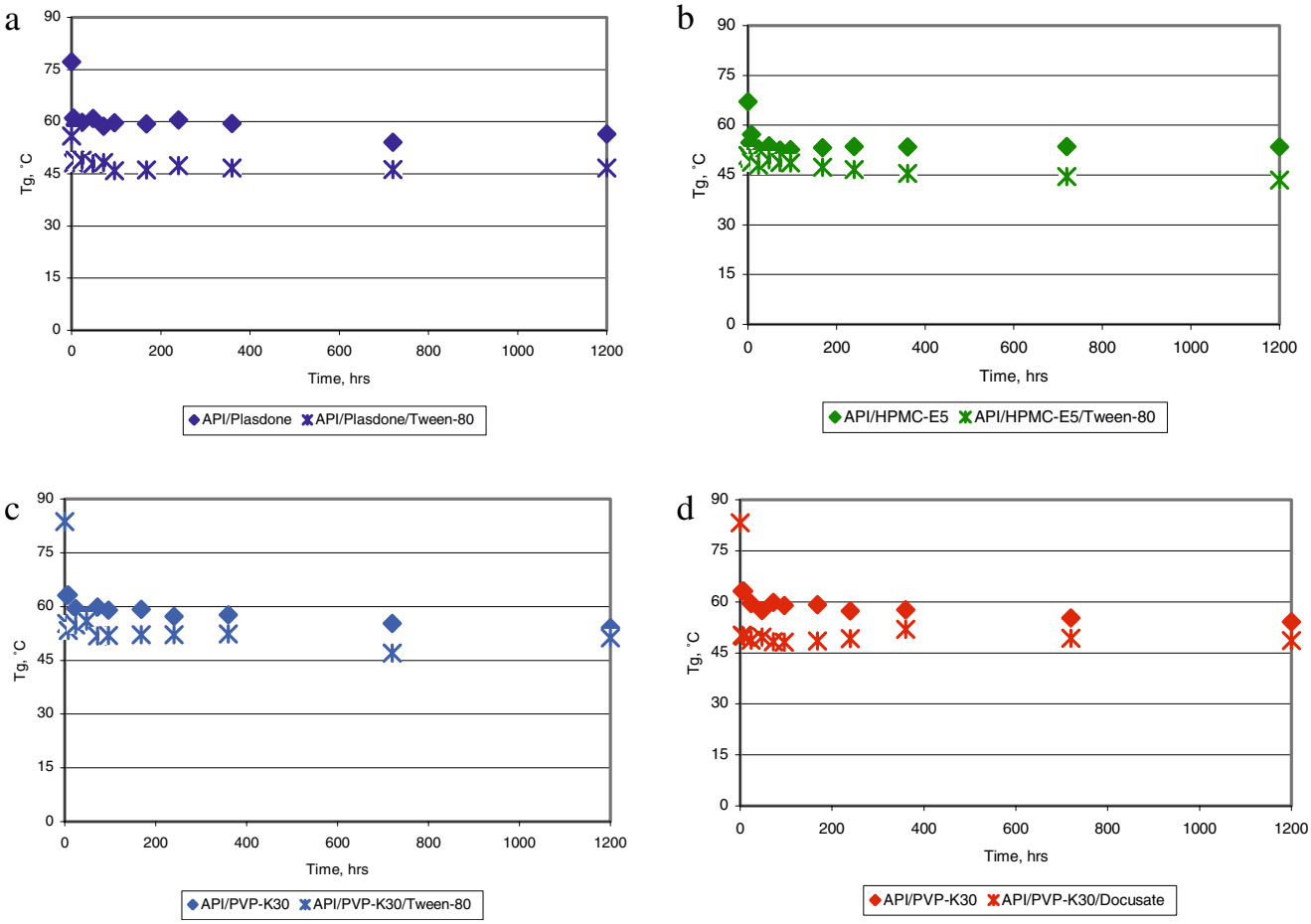

Fig. 6. Solid dispersion Tgs for the initial sample and samples stored for 4, 8, 24, 48, 72, 96, 168, 240, 360, 720, and 1,200-h at 60°C/85%RH. Tgs calculated from the first DSC cycle (5°C/min) of the solid dispersions prepared at 10°C bellow carrier polymer Tg. (a) API/Plasdone/Tween-80; (b) API/HPMC-E5/Tween-80; (c) API/PVP-K30/Tween-80; (d) API/PVP-K30/Docusate sodium.

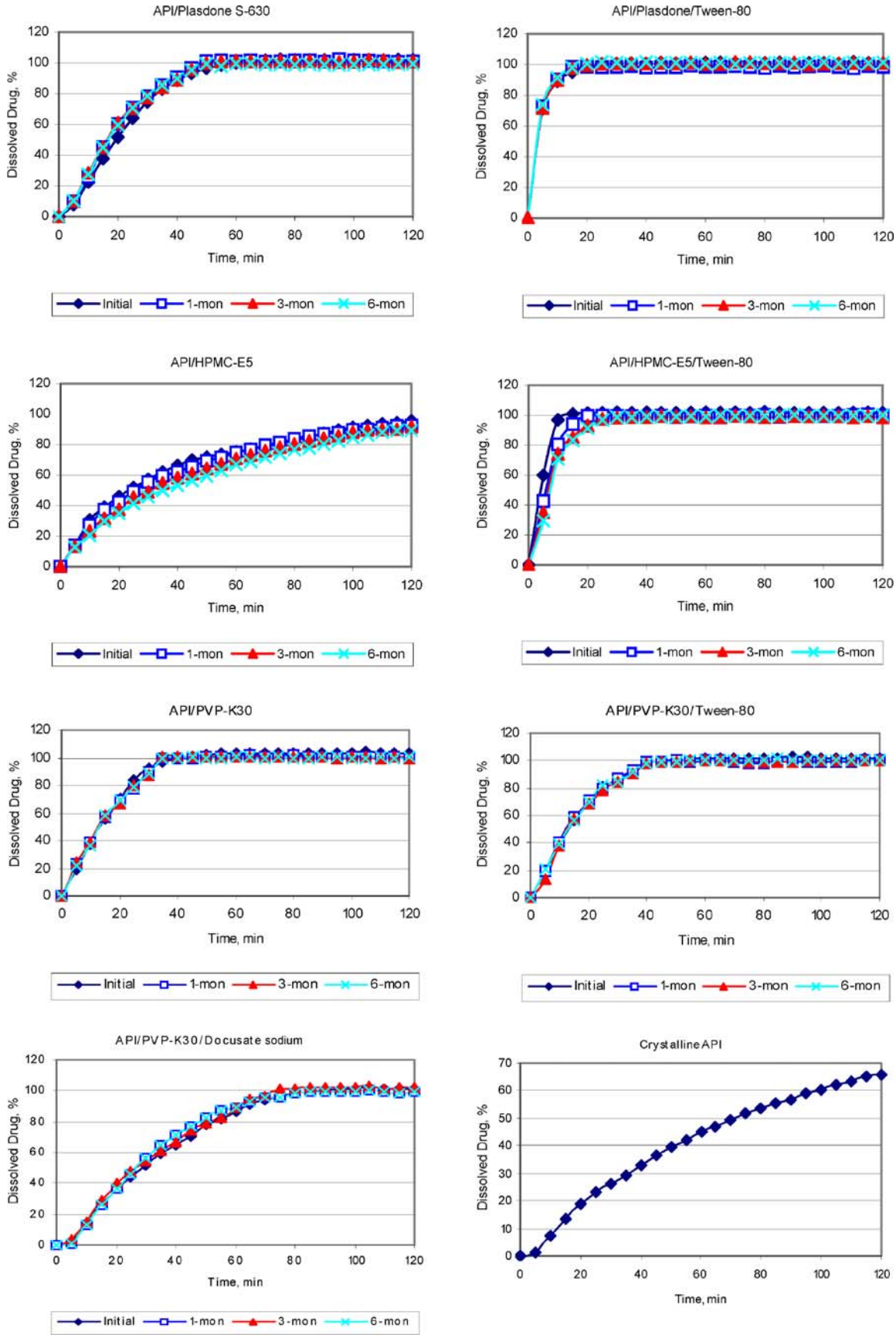

Fig. 7. Dissolution profiles of solid dispersions monitored initial sample and samples stored for 1, 3, and 6-months at 30°C/60%RH. (a) API/Plasdone; (b) API/Plasdone/Tween-80; (c) API/HPMC-E5; (d) API/HPMC-E5/Tween-80; (e) API/PVP-K30; (f) API/PVP-K30/Tween-80; (g) API/PVP-K30/Docusate sodium; (h) Crystalline-API.

of API from the three carrier systems correlated well with the effective Tg of the solid dispersion at the specified relative humidities. Respectively, the difference between the storage temperature and Tg of solid dispersions for HPMC-E5, PVP-K30 and Plasdone S-630 at 60%RH are 7, 23 and 17. Furthermore, increased water-uptake by the surfactant containing dispersions had minimal effect in the re-crystallization of API when tested under both stability conditions as shown in Table II.

Dissolution Testing

As previously discussed (6), the primary purpose behind formulating poorly soluble drugs in solid dispersions containing surfactants is to enhance their dissolution rate and saturation solubility. The surfactants contributed significantly to the increased dissolution rate by creating a favorable microenvironment for the drug at the dissolving surface. As shown in Fig. 7, the API/polymer mixture dissolves slowly over the 120 min timeframe, while the extrudates containing surfactants reached a plateau concentration in 10 min or less. For example, API/Plasdone S-630 solid dispersion took 45 min to completely dissolve, while API/Plasdone S-630 containing Tween-80 dissolved completely in 10 min. The same was also true for the system containing HPMC-E5, increasing the dissolution rate from 120 min to less than 10 min. For the API/PVP-K30 system no changes were observed. The plausible reason being, PVP-K30 containing blends were extruded at much higher temperatures (160 to 180°C). These would most likely result in denaturation of the surfactant and compromising their effectiveness to enhance the dissolution rate.

Figure 7 also shows the dissolution profiles of stressed samples (at 30°C/60%RH) pulled at different exposure times (at initial, 1, 3, and 6-month). The results show that hardly any noticeable changes in both the rate and extent of drug release were found as a consequence of exposure to the stress conditions. This is in complete agreement with the pXRD and mDSC results that the solid dispersions remain amorphous throughout the stability study. Even with some localized regions of crystalline API being presented in the extrudates of the API/HPMC-E5 and API/HPMC-E5/Tween-80 systems, the overall contribution of such crystals on dissolution might be limited, as demonstrated by the peaks in pXRD (about 6% re-crystallization of the API by peak height). Furthermore, the difference, if any, between extrudates processed at temperatures 10°C above and below the carrier polymer Tg appeared to be negligible.

CONCLUSIONS

The study shows that practically all of the extruded solid dispersions stored at 30°C/60%RH and 60°C/85%RH are stable for the duration of the stability test. The dispersions containing HPMC-E5 were observed especially to be susceptible to physical instability under an accelerated stress conditions (60°C/85%RH) of the solid dispersion. About 6% conversion of amorphous API to crystalline form was observed. Consequently, the system exhibits similar degree of re-crystallization upon addition of the surfactant. However, under 30°C/60%RH condition, the otherwise amorphous API/HPMC-E5 system has been destabilized by the addition of the surfactant. This effect is much more reduced in the extruded solid dispersions where polymeric carriers such as Plasdone S-603 and PVP-K30 (in addition to surfactants) are present. In summary, the recrystallization of behavior of API from the three carrier systems correlated well with the deviation of effective Tg of the solid dispersion (at specified RH) from the storage condition. On the other hand, the influence of the two surfactants evaluated on API–PVP dispersions was very similar in their plasticization, water uptake and consequently, their physical stability. Possible reasons for the enhanced stability of the dispersions are due to the surfactants ability to lower the viscosity of the melt, increase the API solubility and homogeneity in the carrier polymer. In contrast, while it is possible for the surfactants to destabilize the system by lowering the Tg and increasing the water uptake, the study confirms that this effect is minimal.

ACKNOWLEDGMENTS

A.N. Ghebremeskel greatly appreciates the assistance given by Dr. Zeri Teweldemedhin and Dr. Darshan Parikh.

REFERENCES

1. M. C. Etter, J. C. Macdonald, and J. Bernstein. Graph-set analysis of hydrogen-bond patterns in organic crystals. *Acta Crystallogr. Sect. B, Struct. Commun.* **46**:256–262 (1990).
2. M. C. Etter and S. M. Reutzel. Hydrogen-bond directed cocrystallization and molecular recognition properties of acyclic imides. *J. Am. Chem. Soc.* **113**:2586–2598 (1991).
3. B. Moulton and M. J. Zaworotko. From molecules to crystal engineering: supramolecular isomerism and polymorphism in network solids. *Chem. Rev.* **101**:1629–1658 (2001).
4. B. Rodríguez-Spong, C. P. Price, A. Jayasankar, A. J. Matzger, and N. Rodríguez-Hornedo. General principles of pharmaceutical solid polymorphism: a supramolecular perspective. *Adv. Drug Deliv. Rev.* **56**:241–274 (2004).
5. D. Q. M. Craig. The mechanism of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* **231**:131–144 (2002).
6. A. N. Ghebremeskel, C. Vemavarapu, and M. Lodaya. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer/surfactant combinations using solubility parameters and testing the processability. Accepted July 11, 2006 to *Int. J. Pharm.* (2006).
7. A. Dakkuri, H. G. Schreoeder, and P. P. Deluca. Sustaining release from inert wax matrices. II. Effect of surfactants on tripelennamin hydrochloride release. *J. Pharm. Sci.* **67**:355–357 (1978).
8. N. Najib and M. S. Suleiman. Kinetics of drug release from ethylcellulose solid dispersions. *Drug Dev. Ind. Pharm. Sci.* **11**:2169–2181 (1985).
9. S. Luhtala. Effect of sodium lauryl sulphate and polysorbate 80 on crystal growth and aqueous solubility of carbamazepine. *Acta Pharm Nord.* **4**:85–90 (1992).
10. A. Nokhodchi, P. Khaseh, T. Ghafourian, and M. R. Siahi-Shadbad. The role of various surfactants and fillers in controlling the release rate of theophylline from HPMC matrices. *STP Pharmacol. Sci.* **9**:555–560 (1999).
11. A. Nokhodchi, S. Norouzi-Sani, M. R. Siahi-Shadbad, F. Lotfipoor, and M. Saeedi. The effect of various surfactants on the release rate of propranolol hydrochloride from hydroxypropyl-methlcellulose (HPMC)-Eudragit matrices. *Eur. J. Pharm. and Biopharm.* **54**:349–356 (2002).
12. L. R. Chen, J. A. Wesley, S. Bhattachar, B. Ruiz, K. Bahash, and S. R. Babu. Dissolution behavior of a poorly water soluble compound in the presence of Tween 80. *Pharm. Res.* **20**:797–801 (2003).