articles

molecular pharmaceutics

Application of Melt Extrusion in the Development of a Physically and Chemically Stable High-Energy Amorphous Solid Dispersion of a Poorly Water-Soluble Drug

Jay P. Lakshman,[†] Yu Cao,[†] James Kowalski,[†] and Abu T. M. Serajuddin*[,‡]

Pharmaceutical and Analytical Development Department, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, and Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Queens, New York 11439

Received July 25, 2008; Revised Manuscript Received September 4, 2008; Accepted September 11, 2008

Abstract: Formulation of active pharmaceutical ingredients (API) in high-energy amorphous forms is a common strategy to enhance solubility, dissolution rate and, consequently, oral bioavailability of poorly water-soluble drugs. Amorphous APIs are, however, susceptible to recrystallization and, therefore, there is a need to physically stabilize them as solid dispersions in polymeric carriers. Hot melt extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. There is a potential that the API, the polymer or both may degrade if excessively high temperature is needed in the melt extrusion process, especially when the melting point of the API is high. This report details a novel method where the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w. By this means, melt extrusion could be performed much below the melting temperature of the drug substance. Since the glass transition temperature of the amorphous drug was lower than that of the polymer used, the drug substance itself served as the plasticizer for the polymer. The addition of surfactants in the matrix enhanced dispersion and subsequent dissolution of the drug in aqueous media. The amorphous melt extrusion formulations showed higher bioavailability than formulations containing the crystalline API. There was no conversion of amorphous solid to its crystalline form during accelerated stability testing of dosage forms.

Keywords: Amorphous solid; high-energy solid; poorly soluble drug; melt extrusion; stability; dissolution; bioavailability

Introduction

Aqueous solubility is a limiting factor in the oral bioavailability of poorly water-soluble compounds.[1] Formulation of such compounds in amorphous high-energy forms can provide improved solubility and dissolution rate and the consequent improvement in bioavailability.[2] Amorphous states for pharmaceuticals can have as much as 10−1600-fold higher solubility than their crystalline forms.[3] While the strategy of using drugs in their high-energy amorphous state can be effective in bioavailability enhancement, the approach is fraught with difficulties from a stability perspective as amorphous drugs, because of the lower free energy of crystalline forms, tend to transform to their crystalline forms over time.[4−7] Therefore, the common approach of retaining the bioavailability enhancement of a particular high-energy solid dosage form is to kinetically stabilize the drug substance in the amorphous state for the duration of desired shelf life.[8]

* Corresponding author. Mailing address: College of Pharmacy and Allied Health Professions, St. John's University, 8000 Utopia Parkway, Queens, NY 11439. Tel: 718-990-7822. Fax: 718-445-7926. E-mail: serajuda@stjohns.edu.

[†] Novartis Pharmaceuticals Corporation.

[‡] St. John's University.

(1) Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. Theoretical basis for a biopharmaceutical drug classification: correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* **1995**, *12*, 413–420.

(2) Serajuddin, A. T. M. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* **1990**, *88*, 1058–1066.

(3) Hancock, B. C.; Parks, M. What is the true solubility advantage for amorphous pharmaceuticals? *Pharm. Res.* **2000**, *17*, 397–404.

10.1021/mp8001073 CCC: $40.75
Published on Web 10/07/2008

The kinetic stability of high-energy solid dosage forms can be achieved for over a reasonable duration of time by better understanding and taking advantage of the factors influencing it. The amorphous to crystalline transformation can be exacerbated in general by supersaturation and higher molecular mobility.[9] Factors such as glass transition temperature, viscosity, plasticization and storage temperature play an important role in determining the kinetic stability of as well as the development of high-energy amorphous solid dosage forms. Among these factors, storage temperature, for example, plays a role on accelerated stability testing and, therefore, on predicting shelf life of drug product.

Transformation from amorphous to crystalline state can be accelerated by atmospheric moisture sorbed during storage of high-energy solid dosage forms unless moisture sorption is controlled by choice of formulation ingredients or packaging materials. Trace amounts of crystalline drug substance left behind from an imperfect manufacturing process can also accelerate recrystallization of amorphous drug substance by acting as seed crystals.

One common approach to physically stabilize amorphous solids from their propensity to recrystallize is to protect them in the form of solid dispersion where the amorphous material is dispersed in polymeric carriers.[10] Various manufacturing processes to produce solid dispersions of drugs in polymeric matrices have been reported in the literature.[10,11] The solvent evaporation method, where both the drug substance and the polymer used to form the matrix are required to be dissolved in a common solvent, has traditionally been used to prepare solid dispersions. However, it is difficult to identify solvents where both the hydrophobic drug substance and the hydrophilic polymer would have good solubility. The handling of organic solvents in the manufacturing facilities of pharmaceutical dosage forms also poses occupational safety and environmental concerns.[2] For these reasons, melt extrusion has gained popularity in recent year since no organic solvents are used.[12−14] The pharmaceutical application of melt extrusion was reported as early as in 1971;[15] it is a continuous process that is carried out using a twin screw extruder where the drug, polymer and optional plasticizers are mixed intimately under controlled conditions of temperature and shear. Heating of the drug−polymer mixture to a temperature higher than the melting point of the drug substance is necessary to convert the crystalline material into its amorphous state. The processing temperature has also to be significantly higher than the glass transition temperature of the polymer to induce plasticity to it during the extrusion process. It is usually necessary to heat the drug substance to a temperature 15−30 °C above the melting point of the drug substance, depending on the drug load, to ensure complete conversion to amorphous form and intimate mixing with the polymeric matrix. The processing temperature could thus be quite high for a high-melting drug substance. One major limitation of the melt extrusion process to prepare solid dispersion is the degradation of drug substance or polymer. Since the drug substance or the polymer or both may undergo degradation at high temperature, an alternative strategy to produce solid dispersion at a relatively lower melt extrusion temperature is necessary.

This report details the development of a bioavailable oral dosage form for a poorly water-soluble API where the drug substance was first converted to an amorphous form and the amorphous material was then melt-extruded with a suitable polymer. In this way, the melt extrusion could be carried out much below the melting temperature of the drug substance, and since the glass transition temperature of the amorphous drug in this case was lower than that of the polymer used, the drug substance itself served as the plasticizer for the polymer and the addition of plasticizer to facilitate melt extrusion could be either avoided or minimized. Preliminary studies showed that the drug substance by itself is susceptible to conversion to its crystalline form during accelerated stability testing, especially in presence of moisture. The solid dispersion by melt extrusion physically stabilized the amorphous form. The report also details the in vitro and in vivo evaluation of the product.

(4) Yoshioka, S.; Stella, V. J. *Stability of drugs and dosage forms*; Kluwer Academic/Plenum Publishers: New York, 2000; pp 139−150.
(5) Bhugra, C.; Pikal, M. J. Role of thermodynamic, molecular, and kinetic factors in crystallization from the amorphous state. *J. Pharm. Sci.* **2000**, *97*, 1329–49.
(6) Yu, L. Amorphous pharmaceutical solids: Preparation, characterization and stabilization. *Adv. Drug Delivery Rev.* **2001**, *48*, 27–42.
(7) Zhou, D.; Grant, J. W.; Zhang, G. G. Z.; Law, D.; Schmitt, E. A. A calorimetric investigation of thermodynamic and molecular mobility contributions to the physical stability of two pharmaceutical glasses. *J. Pharm. Sci.* **2007**, *96*, 71–83.
(8) Shibata, Y.; Fujii, M.; Kokudai, M.; Noda, S.; Okada, H.; Kondoh, M.; Watanabe, Y. Effect of characteristics of compounds on maintenance of an amorphous state in solid dispersion with crospovidone. *J. Pharm. Sci.* **2007**, *96*, 1537–47.
(9) Glynn, P. D.; Reardon, E. J. Solid-solution aqueous-solution equilibria: thermodynamic theory and representation. *Am. J. Sci.* **1990**, *290*, 164–201.
(10) Vasanthavada, M.; Tong, W. Q.; Serajuddin, A. T. M. Development of Solid Dispersions for Poorly Water-Soluble Drug. In *Water-Insoluble Drug Formulations*; Liu, R., Ed.; Informa Healthcare: New York, 2008; pp 149−184.
(11) Karanth, H.; Shenoy, V. S.; Murthy, R. R. Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report. *AAPS PharmSciTech* **2006**, *7*, Article 87.
(12) Choksi, R.; Zia, H. Hot-melt extrusion technique: A review. *Iran J. Pharm. Res.* **2004**, *3*, 107–117.
(13) Chokshi, R J.; Sandhu, H. K.; Iyer, R. M.; Shah, N. H.; Malick, A. W.; Zia, H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion process as a means to manufacture solid dispersion/solution. *J. Pharm. Sci.* **2005**, *94*, 2463–74.
(14) Dong, Z.; Chatterji, A.; Sandhu, H.; Choi, D. S.; Chokshi, H.; Shah, N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. *Int. J. Pharm.* **2008**, *335*, 141–149.
(15) El-Egakey, M. A.; Soliva, M.; Speiser, P. Hot extruded dosage forms. 4. Technology and dissolution kinetics of polymer matrices. *Pharm. Acta Helv.* **1971**, *46*, 31–52.

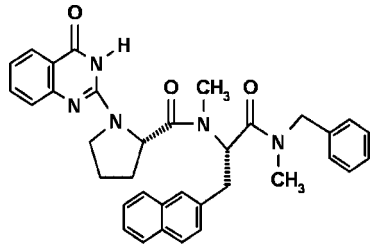

Figure 1. Chemical structure of compound **I**. Molecular formula: $C_{35}H_{35}N_5O_3$. Molecular weight: 573.7.

Experimental Section

Materials. The drug substance, compound **I**, was manufactured by Novartis Pharmaceuticals Corp., Basel, Switzerland. The chemical structure of **I** is given in Figure 1. The compound has pK_a values of 2.9 and 10.0, with room temperature aqueous solubility of 0.03 mg/mL at pH 1 and <0.003 mg/mL in the pH range of 3 to 9. The melting point of the drug substance is 170 °C. Polyvinylpyrrolidone K30 (PVP-K30) and poloxamer 188 were obtained from BASF Corp. (Mount Olive, NJ). All other materials used were of analytical grade or better.

Manufacture of Amorphous Drug Substance. Crystalline drug substance was dissolved in methylene chloride. Approximately 500 mL of solvent was needed to dissolve 2.5 g of drug substance. The solution was evaporated using a rotary evaporator at 40 °C and then dried in an oven at about 45 °C overnight to fully remove any residual solvent. The amorphous material thus obtained was tested using a differential scanning calorimeter (DSC) to ensure amorphicity.

Hot-Stage Microscopy. Miscibility of drug substance with polymer was evaluated using a hot-stage microscope (Carl Zeiss Inc., Thornwood, NY). About 5 mg of amorphous **I** was placed on an open glass slide, and a temperature ramp of 1 °C/min was employed. At temperatures above 120 °C, very small amounts of different kinds or amounts of polymers were scattered over the liquefying drug substance and observed for disappearance of solid phase. Results were captured using photomicrography.

Differential Scanning Calorimetry (DSC). A differential scanning calorimeter (Mettler Toledo, Columbus, OH) equipped with a liquid nitrogen cooling accessory was used to evaluate the miscibility of drug substance with polymer. A physical mixture of crystalline drug substance and polymer was heated to 190 °C at 10 °C/min, then cooled to −20 °C at 10 °C/min and then reheated back to 190 °C at 1 °C/min.

Preparation of Solid Dispersions. Physical blends of amorphous drug substance and PVP-K30 were prepared using a Turbula mixer (Wiley A. Bachofen, Basel, Switzerland). Melt extrusion of the mixture was then carried out using a small scale ThermoScientific Haake MiniLab twin screw extruder (Newington, NH) at 20%, 30% and 40% drug loads and temperatures of 178−184 °C. A water-chilled force feeder was used to maintain consistent feed rate and to prevent heat migration and premelting of the blends in the feeder assembly. PVP-K30 was used as a matrix material and sorbitol was added as a plasticizer at 10% and 5% levels to the 20% and 30% drug-loaded extrusions, respectively. The extrudates obtained were chilled in a freezer for about one hour.

Preparation of Solid Dosage Form. The chilled extrudates were milled using a Glen mill (Clifton, NJ) or mortar and pestle, and powders were screened through a 35-mesh (0.5 mm) screen prior to mixing with microcrystalline cellulose (Avicel PH102) and poloxamer 188 in the external phase. The mixture was filled in size 0 hard gelatin capsules at an appropriate weight so that each capsule contained 50 mg of drug substance.

In Vitro Evaluation. Dissolution of melt extruded formulations was tested in different media using a Vanderkamp 600 USP method 2 dissolution apparatus (medium volume, 1000 mL; rotation speed, 50 RPM). All samples were analyzed by HPLC. One of the media, pH 2 buffer, was used as a non-sink medium to distinguish dissolution rates among different formulations.

In Vivo Evaluation in Dog Models. Three different formulations of **I** were evaluated for their oral bioavailability using a randomized crossover pharmacokinetic study. Two of these formulations containing melt extrudates in PVP-K30 containing 20% (formulation A) and 30% (formulation B) drug loads were tested for relative bioavailability using a fasted beagle dog as the animal model. A separate formulation containing triturates of the crystalline drug substance along with poloxamer 188 (formulation C) served as a control. No attempt was made to determine absolute bioavailability since an acceptable intravenous formulation was not available. Four dogs were used per arm. The dogs were fasted for about 12 h before dosing, and three to five days was allowed between the arms of the study to ensure wash out of the previous treatment.

Stability Evaluation. Melt extrudates with 20% and 30% drug loads and their formulations (with Avicel and poloxmer added externally) used for the dog study were stored in amber glass bottles at 25 °C/60% RH open and 40 °C/75% RH open for 1 to 12 months. The samples were tested before the study (initial analysis), and certain samples were selected and tested using powder X-ray diffraction, modulated DSC, TGA, HPLC assay and dissolution at the end of the study.

Results and Discussion

Characterization of Drug Substance. The crystalline drug substance could be converted to its amorphous form by the solvent evaporation technique. It was, however, recognized that a large volume of methylene chloride was necessary to dissolve a relatively small amount of drug substance for conversion to the amorphous form. Alternative methods for more efficient manufacture of the amorphous API as well as to avoid organic solvents were subsequently explored by the Chemical Development division of Novartis; however, they were not a part of the present investigation. The amorphous material was characterized by various analytical techniques, including powder X-ray diffraction, microscopy and differential scanning calorimetry (DSC). The glass transition temperature of the material was established

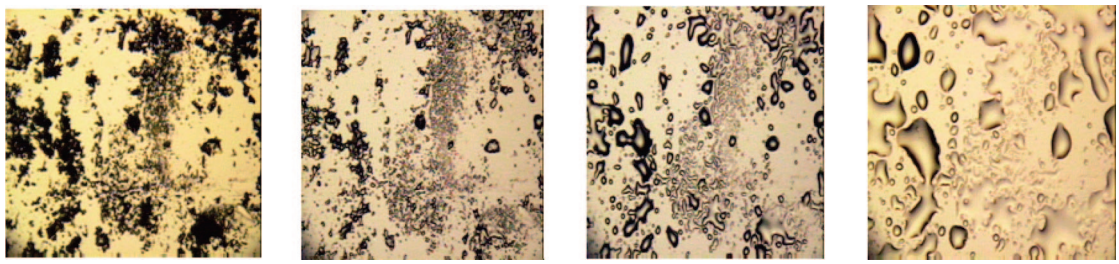

Figure 2. Appearance of amorphous compound **I** under hot-stage microscope at 25 °C, 120 °C, 126 °C, 140 °C (from left to right).

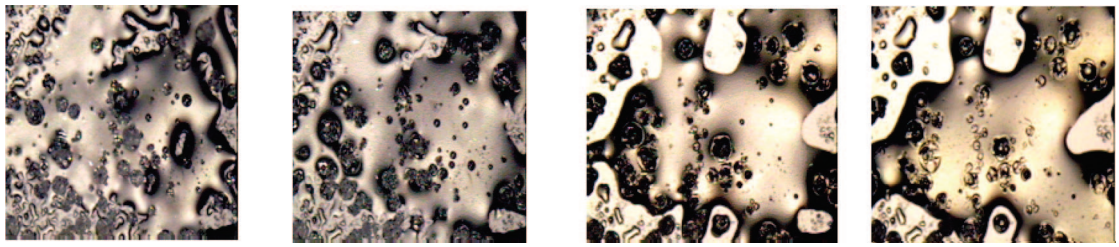

Figure 3. Appearance of physical mixtures of compound **I** and PVP K-30 under hot-stage microscope at 120 °C, 140 °C, 155 °C, 170 °C (from left to right) when powders of PVP-K30 are added to amorphous **I** on the glass slide.

to be around 125 °C. Since the primary objective of the present study was to develop a solid dispersion formulation of the amorphous material, various polymers were screened for their miscibility with the drug substance by using hot-stage microscopy and differential scanning calorimetry.

Hot-Stage Microscopy (HSM). When heated in a steadily rising temperature ramp of 1 °C/min over the range of 120 to170 °C, it was observed that amorphous **I** liquefied around its glass transition temperature (T_g) of 125 °C (Figure 2). Different polymers at room temperature were added in small amounts to the liquefying **I** starting at about 120 °C and observed under microscope for the disappearance of the solid phase as the temperature was ramped. PVP-K30 showed good miscibility with liquefied **I** (Figure 3). Accordingly, larger amounts of PVP-K30 were tested with liquefying **I** under HSM over the temperature range of 120 to170 °C and as much as 10% w/w PVP-K30 appeared to dissolve in the amorphous drug substance. Such liquefaction of drug substance and the miscibility with PVP-K30 helped in lowering the glass transition temperature of the polymer and, thereby, reducing the processing temperature of the melt extrudate.

Differential Scanning Calorimetry (DSC). DSC was used to characterize mixtures of **I** and PVP-K30 and to identify the drug load that PVP-K30 can carry without phase separation. About 5−10 mg samples of the mixture of crystalline **I** and PVP-K30 at different ratios were prepared in aluminum pans crimp-sealed with a pinhole. The samples were individually subjected to a heat−cool−heat cycle involving heating to 190 at 10 °C/min, then cooling to −20 at 10 °C/min and then reheating to 190 at 1 °C/min. This heat−cool−reheat cycle was used to remove the thermal history of the samples. Data obtained from the final reheating cycle alone is summarized in Figure 4. It can be seen that all samples with drug loads of 15 to 40% showed a single T_g indicating that **I** was miscible with PVP-K30 to large extents at elevated temperatures.[16] It is also clearly seen that the T_g of the drug−polymer mixture decreased from 140 to 127 °C as the drug load increased from 15 to 40%. For the purpose of physical stability, it is recommended that a solid dispersion should ideally have a T_g of at least 50 °C higher than the room temperature;[3] the T_g of greater than 125 °C for the mixture of drug and PVP-K30 in the present case was at least 100 °C higher than the room temperature and thus favorable to the stability of the product.

Manufacture of Solid Dispersions. Physical blends of the amorphous drug substance and PVP-K30 prepared by using a Turbula mixer (Wiley A. Bachofen, Basel, Switzerland) were fed in to the ThermoScientific Haake Minilab twin screw extruder (Newington, NH) set at a temperature of 150 °C. Feed rates of 50 RPM and extrusion speed at 100 RPM were used as the initial starting conditions. However, it was soon realized that a higher temperature of about 175 °C was required to process the material without exceeding the maximum torque of 500 N cm. Feed rate and extrusion speed also needed to be reduced to 40 RPM and 75 RPM, respectively, to enable processing at a reasonable torque. The higher temperature of 175 °C caused slight browning of the clear extrudates at 20 and 30% drug loads, accompanied by, respectively, ∼15% and ∼10% drug degradation. No degradation was seen for the 40% drug-loaded solid dispersion. Consequently, sorbitol was chosen as a plasticizer and blended to the drug−polymer physical mixture to reduce the torque (Table 1). It is interesting to note that the higher the drug load, the less was the need for plasticizer as the amorphous drug itself served as the plasticizer. At 40% drug load, no plasticizer was needed as

(16) Vasanthavada, M.; Tong, W. Q.; Joshi, Y.; Kislalioglu, M. S. Phase behavior of amorphous molecular dispersions I: Role of hydrogen bonding in solid solubility and phase separation kinetics. *Pharm. Res.* **2005**, *22*, 440–48.

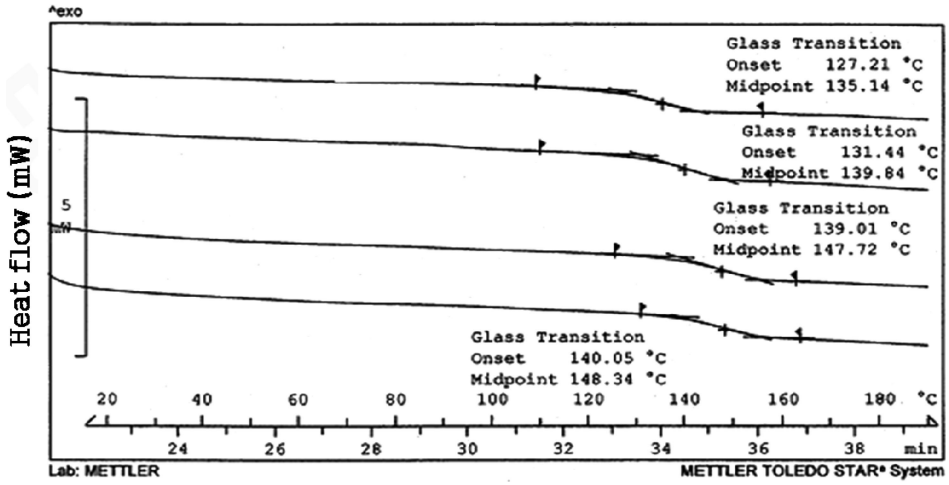

Figure 4. Differential scanning calorimetry (DSC) scans of mixtures of compound **I** and PVP-K30. The drug contents from top to bottom are 40%, 30%, 20% and 15% w/w, and their respective glass transition onset temperatures are 127, 131, 139 and 140 °C. The glass transition midpoints are about 8 °C higher than their respective onsets.

Table 1. Preparation of Solid Dispersions of Compound **I** in PVP-K30[a]

process variables	expt 1	expt 2	expt 3	expt 4
drug load, % w/w	20%	20%	30%	30%
plastisizer (sorbitol), % w/w	none	10%	none	5%
process temp, °C	178−184	180	180−184	178
torque, N cm	200−500	27−43	130−450	51−70

[a] Process conditions of 40 RPM feed rate and 75 RPM extrusion rate were used for all four experiments summarized.

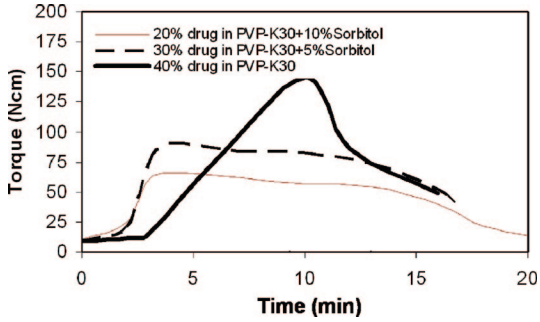

Figure 5. Torque profile during melt extrusion at about 180 °C.

the plasticization from the liquefied amorphous drug was adequate to allow processing at the same conditions as those of the 20 and 30% drug-loaded formulations (Figure 5). Use of sorbitol as a plasticizer effectively reduced the drug degradation to less than 1.5% for all drug loads tested. This is because the lower torque as a result of the use of a plasticizer reduced any localized heat that could be generated within the extruder during the extrusion process. Extrudates in the first 5 min and last 5 min of a run were discarded as equilibrium conditions or steady-state torque could not be achieved. Visually transparent extrudates obtained over every 2 min duration between 5 and12 min of processing time were collected in separate glass bottles and cooled in a freezer. As seen from Figure 5, the torque equilibrium could not be obtained for the 40% drug-loaded sample over the melt extrusion period of 5 to 12 min. The obtained material was collected regardless for characterization. DSC and powder XRD studies of all melt extrudate samples reconfirmed that no crystallinity existed in any of the samples.

Table 2. Compositions of Capsule Formulations

	drug load in melt extrudate		
materials	20% w/w	30% w/w	40% w/w
Melt Extrudate Composition			
compound **I**, mg	50.0	50.0	50.0
PVP K30, mg	175.0	108.4	75.0
sorbitol, mg	25.0	8.4	0.0
External Phase Composition			
microcrystalline cellulose (PH102), mg	100.0	100.0	100.0
Pluronic F68, mg	56.0	56.0	56.0
total capsule content, mg	406.0	322.8	281.0

Solid Dosage Form. All capsules were prepared at 50 mg doses and contained 100 mg of microcrystalline cellulose (Avicel PH 102) as the diluent and 56 mg of poloxamer 188 (Pluronic F68) as the surfactant to enable wetting, and amounts of PVP-K30 and sorbitol varied as shown in Table 2. They were evaluated for assay and content uniformity by using HPLC; both the assay (95−105%) and the content uniformity (<6%RSD) were found to be acceptable.

In Vitro Dissolution. The dissolution of the 50 mg capsules was evaluated using USP type 2 apparatus with 1000 mL of 0.01 N HCl at the paddle speed of 50 RPM. Although it was a non-sink condition, it could delineate differences in dissolution of different formulations being evaluated. It was seen that all high-energy solid dispersions at 20−40% drug loads performed better than the control formulation made by triturating crystalline **I** with poloxamer 188 and microcrystalline cellulose (Figure 6).

Based on the dissolution results in 0.01 M HCl, the 40% drug-loaded formulation was dropped from further evaluation. Evaluation of the remaining formulations in a pH 6.8 USP buffer with 0.1% sodium lauryl sulfate, which provided higher drug solubility, showed minimal difference between

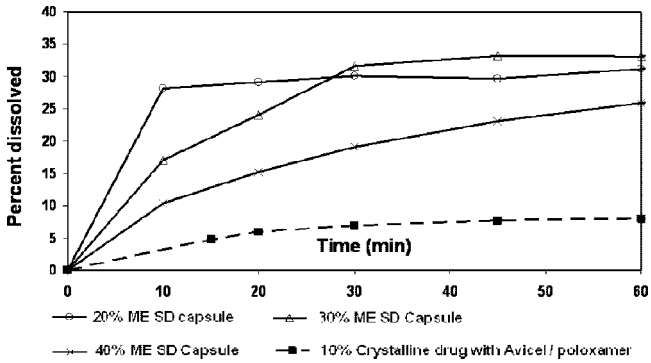

Figure 6. In vitro dissolution of high-energy solid dispersion (SD) formulations prepared by melt extrusion (ME) with 20−40% drug load. The dissolution profile of a 10% mixture of crystalline drug with microcrystalline cellulose and poloxamer 188 served as the control.

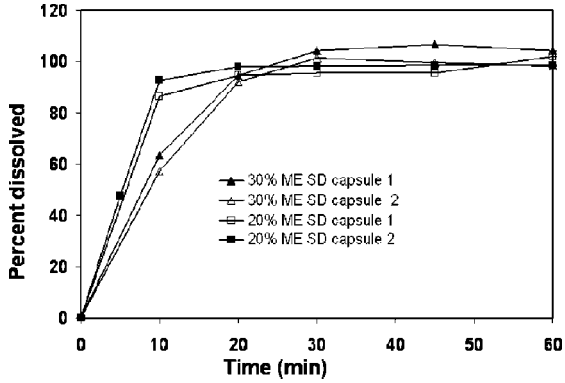

Figure 7. In vitro dissolution of high-energy solid dispersion formulations with 20 and 30% drug loads in the pH 6.8 buffer containing 0.1% sodium lauryl sulfate. Individual profiles for the dissolution of two capsules are provided.

20 and 30% drug-loaded solid dispersions, with over 80% drug dissolving in 20 min; only the initial rates at <20 min differed (Figure 7).

Pharmacokinetic Study. Melt-extruded solid dispersions containing 20% and 30% drug loads were chosen for the PK study in dog model. A control formulation comprising 20% crystalline **I** and 80% poloxamer triturated together in a mortar and pestle was also used. A randomized crossover design was considered essential to obtain definitive conclusions despite the use of only four dogs in the study. Results form the study expressed as mean plasma concentrations are shown in Figure 8. The mean bioavailability obtained for the three formulations was in the order of 20% solid dispersion >30% solid dispersion ≫ 20% crystalline drug triturate with poloxamer.

Stability Study. Melt extrudates with 20% and 30% drug loads and capsules prepared by using them (with Avicel PH102 and poloxmer 188 added externally) were subjected to accelerated stability testing. As the final T_g of the extrudates were high (>125 °C) and as no substantial tendency for recrystallization was exhibited by the drug during the heat−cool−reheat DSC cycles of the extrudates, it was not considered necessary to take any special precau-

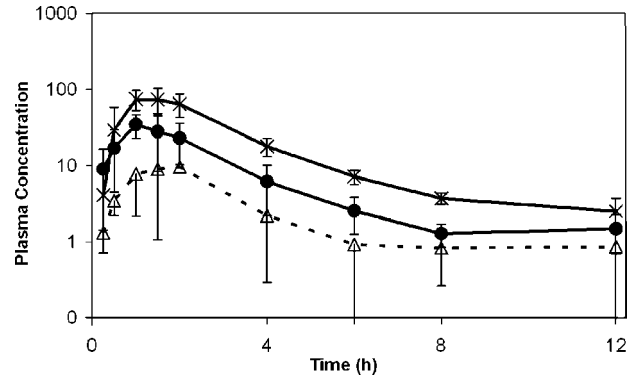

Figure 8. Mean plasma concentrations in dogs ($n = 4$) after oral administration of 50 mg capsules. The samples from top to bottom are 20% melt-extruded solid dispersion (ME SD) capsules, 30% ME SD capsules and 20% crystalline drug triturated with 80% poloxamer 188 that served as the control.

tions to avoid moisture sorption during accelerated stability studies. The samples were simply stored in glass amber bottles at 25 °C/60% RH open and 40 °C/75% RH in open state and without capsule shells for 1 to 12 months.

Samples after storage under accelerated storage conditions that were evaluated for dissolution employed 1000 mL of pH 2 (0.01N HCl) medium at 50 RPM in a type 2 USP apparatus. As discussed earlier, although the pH 2 medium provided a non-sink dissolution condition, it had better discrimination ability than the pH 6.8 medium containing a surfactant. For this reason, the pH 2 medium was used for the stability testing of samples. Another reason for not using the pH 6.8 medium was that the surfactant used to enhance drug solubility could mask differences in drug release and dispersion from samples. Samples were collected using disposable syringes with nylon filters of 0.20 μm pore size and analyzed by HPLC. Results summarized in Table 3 indicate that there was no impact on dissolution for 6 months for samples stored at 25 °C/60% RH under open conditions. However, samples stored at 40 °C/75% RH under open conditions showed a dissolution slow-down at the 6 month time point. As it will be presented later, there was no phase conversion from amorphous to the crystalline form of the drug substance that could reduce the dissolution rate of samples stored at 40 °C/75% RH for a prolonged period of time. Therefore, the slow-down in dissolution rate upon storage at this condition for 6 months was attributed to the change in consistency of samples from loose powder to sticky gel, which decreased the surface area of drug substance and retarded disintegration and dispersion of sample in an aqueous medium. Protection from moisture would be warranted for both formulations to minimize or avoid such a dissolution slow-down.

Modulate differential scanning calorimeter (MDSC), equipped with a liquid nitrogen cooling accessory, was used to determine the T_g of the stability samples. Samples (5−10 mg) sealed in aluminum pans with a pinhole were individually ramped to 190 at 1 °C/minute (amplitude, ±1 °C; period,

Table 3. Dissolution Evaluation of Capsule Compositions Containing 20% and 30% Melt-Extruded Solid Dispersions after Storage in Glass Bottles (without Capsule Shells) under Accelerated Stability Conditions

		% dissolved	
melt extrudates	storage conditions	30 min	60 min
compound **I**, 20% + PVP-K30, 70% + sorbitol, 10%	initial	32	34
	25 °C/60% RH open, 1 month	33	34
	25 °C/60% RH open, 6 months	35	35
	40 °C/75% RH open, 1 month	32	31
	40 °C/75% RH open, 6 months	13	12
compound **I**, 30% + PVP-K30, 65% + sorbitol, 5%	initial	32	33
	25 °C/60% RH open, 6 months	35	35
	40 °C/75% RH open, 6 months	8	8

30 s). The results are summarized in Figure 9 and Figure 10 for 20% and 30% melt extrudates, respectively. It is seen that at 25 °C/65% RH, both samples retained the single T_g for the drug−polymer mixture for about 3 months. However,

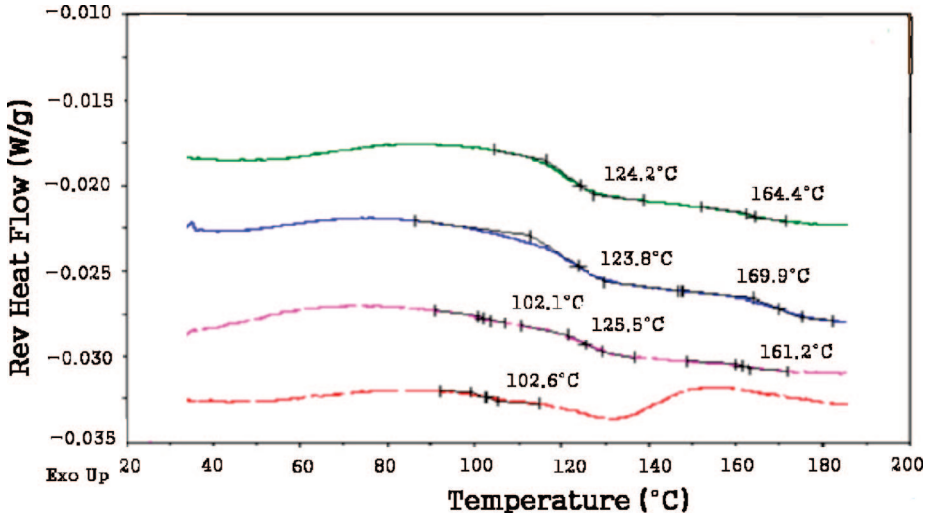

Figure 9. MDSC of 20% compound **I** melt extrudates stored over 12 months at various conditions. The storage conditions from top to bottom are 25 °C/60% RH, 3 months; 25 °C/60% RH, 12 months; 40 °C/75% RH, 6 months; and 40 °C/75% RH, 12 months.

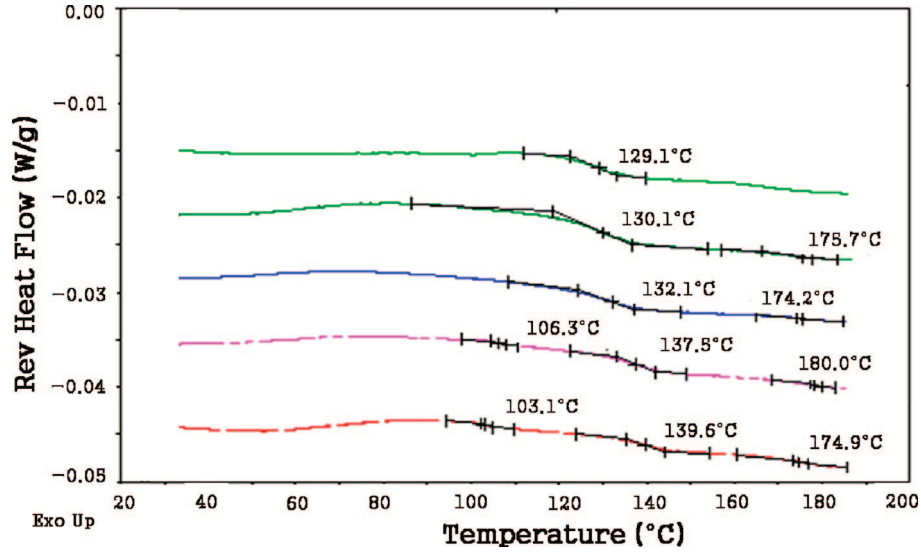

Figure 10. MDSC of 30% compound **I** melt extrudates stored over 12 months at various conditions. The storage conditions from top to bottom are 25 °C/60% RH, 1 month; 25 °C/60% RH, 3 months; 25 °C/60% RH, 12 months; 40 °C/75% RH, 6 months; and 40 °C/75% RH, 12 months.

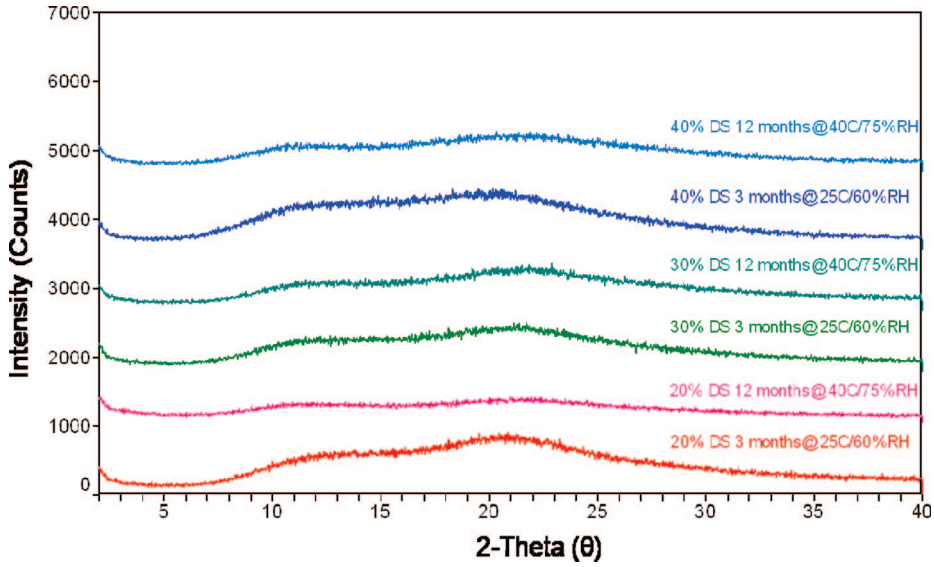

Figure 11. Powder X-ray diffraction of 20%, 30% and 40% melt extrudates stored over 12 months at various conditions.

Table 4. Physicochemical Characterization of Melt Extrudates without the External Phase or Capsule Shell after Storage under Accelerated Stability Conditions

composition	conditions, time (all in open state)	appearance	% water TGA	X-ray	% impurity (HPLC)
compound **I**, 20% + PVP-K30, 70% + sorbitol, 10%	initial	loose powder	6.6	amorphous	0.51
	25 °C/60% RH, 1 month	loose powder	13	amorphous	ND[a]
	25 °C/60% RH, 3 months	loose powder	9	amorphous	ND
	25 °C/60% RH, 12 months	slightly sticky		amorphous	ND
	40 °C/75% RH, 1 month	sticky gel	14	amorphous	ND
	40 °C/75% RH, 12 months	sticky gel	14	amorphous	0.88
compound **I**, 30% + PVP-K30, 65% + sorbitol, 5%	initial	loose powder	5	amorphous	0.85
	25 °C/60% RH, 1 month	loose powder	7.1	amorphous	0.88
	25 °C/60% RH, 3 months	slightly sticky	9	amorphous	ND
	25 °C/60% RH, 12 months	slightly sticky		amorphous	ND
	40 °C/75% RH, 1 month	sticky gel	13	amorphous	0.80
	40 °C/75% RH, 12 months	sticky gel	12	amorphous	1.0

[a] ND = not determined.

after 12 months of storage, evidence of phase separation was seen wherein a polymer-rich phase with a T_g of approximately 170 °C started to emerge. The evidence of phase separation was stronger at 40 °C/75% RH where both 20% and 30% drug-loaded samples started to exhibit after 6 months a polymer-rich phase with a T_g of about 170 °C and a drug-rich phase with a T_g of about 102−107 °C. Although evidence for phase separation is seen, it is only a precursor to recrystallization of drug substance. Lack of evidence for recrystallization is promising in that better storage conditions such as a moisture barrier packaging (aluminum foil) can be easily employed to further defer the phase separation as well as the recrystallization beyond a potentially reasonable shelf life of 3 years at 25 °C. Figure 11 shows the lack of change in powder X-ray diffraction of melt extrudates over the duration of 12 months after storage under 25 °C/60% RH and 40 °C/75% RH. Table 4 shows the overall summary of stability studies. Samples containing 20% and 30% drug loads continued to retain their amorphocity despite an uptake of up to 13−14% moisture. Chemical degradation was less than 1% throughout the duration of one year even at the worst case condition of 40 °C/75% RH.

Comparison of Different Formulation Principles. At the early stage of the present study, an attempt was made to determine whether other methods of preparing high-energy amorphous forms of the drug substance than the one described in the present report would provide better bioavailability. Techniques such as spray-drying, spray-granulation and solvent evaporation by rotary evaporator were tested. A melt extruded formulation using PVP-K90 was also developed to understand the effect of polymer viscosity on dissolution and bioavailability.

A brief summary of only the PK results of this study are given here, without a detailed description of methods of preparing such alternative formulations. The results shown in Figure 12 indicate that the 20% drug-loaded melt extrudate using PVP-K30 provided a 7-fold greater bioavailability than the control formulation made of crystalline drug triturated with poloxamer 188. The solvent-evaporated solid dispersion

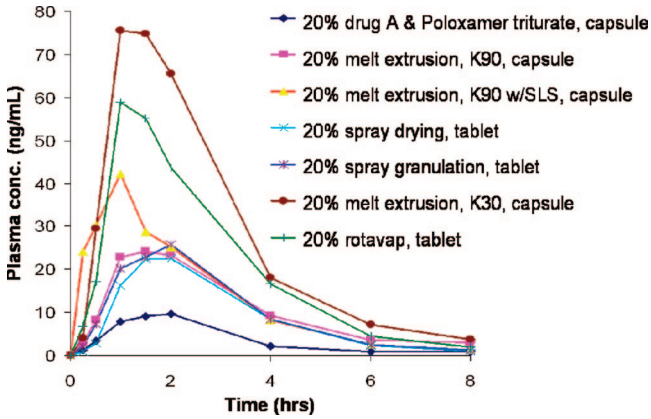

Figure 12. Mean PK profile for 50 mg high energy solid dosage forms compared against the control formulation consisting of crystalline drug triturated with poloxamer. Data pooled from two independent PK studies in dogs.

in PVP-K30 that was processed using a rotary evaporator at the bench scale provided the second best improvement in bioavailability. Among the other formulations, PVP-K30 based spray-dried, spray-granulated and the PVP-K90 based solid dispersion produced relatively lower bioavailability enhancement of 2- to 3-fold, a significant improvement regardless. PVP-K30 was clearly better than PVP-K90. As expected, the use of the surfactant sodium lauryl sulfate (SLS) with PVP-K90 improved the bioavailability further. It was identified early in the development program that the manufacture of dosage forms using various solvent evaporation methods, such as spray-drying, spray-granulation and rotary evaporation, could pose manufacturing and scale up issues due to the need for large volumes of environmentally unfriendly organic solvents to dissolve the drug substance, and, therefore, further activities with these methods were abandoned. No detailed experimental studies were conducted to delineate the mechanism of differences in bioavailability among different formulations. It is, however, hypothesized that spray-dried and spray-granulated formulations were not intimately or molecularly dispersed as with melt extrudates that were exposed to high shear mixing. Further, the rate of dispersion and the degree of supersaturation of drug substance in aqueous media could also be different for samples prepared by different methods. Overall, the results indicate that the PVP-K30-based melt extrusion would be the optimal choice with the most favorable bioavailability as well as the long-term shelf life as demonstrated in the present report.

Conclusion

Amorphous melt extrusion formulations with drug load over 20% to 40% that used PVP-K30 as the solid dispersion matrix were manufactured at small scale and evaluated using DSC, powder X-ray, HPLC assay and dissolution. The melt-extruded amorphous formulations showed higher oral bioavailability than the crystalline formulation. The drug load clearly influenced dissolution and the oral bioavailability, and at a constant drug load, the manufacturing process appears to influence biovailability of high-energy solid dosage forms. The formulation containing amorphous melt extrudates with 20% drug load was selected for further development. It was physically and chemically stable at controlled room temperature for at least one year, and the prognosis for longer-term stability was good.

Acknowledgment. The authors thank Dr. Rama A. Shmeis and Dr. Yatindra M. Joshi for helpful discussion and advice and Dr. Irene Mueller for studies in animal models.

MP8001073