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Solid-state properties and crystallization behavior of PHA-739521 polymorphs

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Abstract

PHA-739521 is an experimental compound that exhibits polymorphism. The two anhydrous crystal forms, I and II, are characterized using powder X-ray diffractometry, thermal analyses, moisture sorption gravimetry. Both Forms I and II are non-hygroscopic and are stable to compaction pressure. The melting temperature is about 152 °C for Form I and 168 °C for Form II. Forms I and II are enantiotropically related where Form I is more stable below a transition temperature of approximately 70 °C. Crystallization behavior of this compound from solutions and during heating is also studied. Information obtained is used to design an appropriate crystallization process to successfully manufacture desired polymorph at large scale.

Keywords: Polymorph; PHA-739521; Transition temperature; Crystals; Thermal analysis; Physical characterization; Solid state

1. Introduction

PHA-739521 ($C_{16}H_{11}F_4N_3O_2S$, MW = 385.34) is an experimental compound with a molecular structure shown in Fig. 1. Its chemical name is 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide. It is a weak acid with a $pK_a = 9.58 \pm 0.11$.

Polymorphism has common occurrences in organic molecular crystals. The conformational flexibility of PHA-739521 due to the single bond connection of benzene rings (Fig. 1) makes it easier to achieve an energy minimum in different crystal lattice structures, thus offering a higher chance for exhibiting polymorphism. In fact, two anhydrous crystal forms and some solvated crystal forms have been isolated and characterized. We focus our discussion on the two anhydrous crystal forms, I and II, in this report.

The importance of identifying and characterizing different crystal forms of a drug has been well documented in the literature (Haleblian and McCrone, 1969; Threlfall, 1995). The differences in solubility and dissolution rate (Grant and Higuchi, 1990; Grant and Brittain, 1995; Brittain and Grant, 1999), morphology and color (Yu et al., 2000), mechanical properties (Sun and Grant, 2001, 2004), physico-chemical stability (Yuan et al., 2004; Chen et al., 2002) of different crystal forms warrant a detailed study of polymorphism of any new drug molecules. In addition, patenting new solid forms is an important part of modern life-cycle management of innovative pharmaceutical compounds (Bernstein, 2002). We report here solid-state properties and crystallization behavior of PHA-739521 polymorphs characterized with an aim of developing an appropriate crystallization process for large scale manufacturing of desired crystal form.

2. Materials and methods

2.1. Materials

A batch of crystalline PHA-739521 is obtained from Early Process R&D of legacy Pharmacia. The chemical purity of this lot is 99.6% by HPLC. Synthesis of PHA-739521 follows the procedures described previously (Sun and O'Connor, 2005).

2.2. Crystallization methods

The most common polymorph screening methods are crystallization from solutions by evaporating solvent, cooling a supersaturated solution, or adding a poor solvent to a solution. In these methods, drug molecules that are dispersed in solvents

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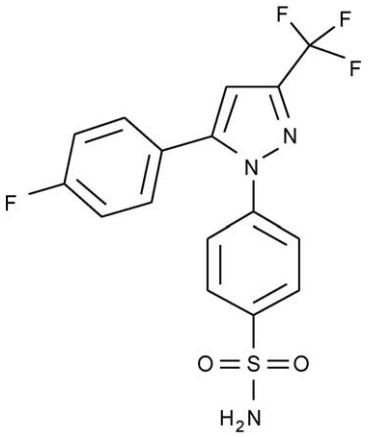

Fig. 1. Molecular structure of PHA-739521.

of various properties, e.g., polarity, polarizability, and hydrogen bonding propensity, undergo different molecular interactions with the solvent molecules. Consequently, different nuclei may be formed during the process of de-saturation. If the different nuclei are given the opportunity to grow, we obtain different crystal forms. Although crystallization conditions such as stirring rate and rate of de-saturation may also affect the final crystal form obtained, solvent alone provides the most profound impact. Solvents used in this study are dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, ethyl acetate (EtOAc), methyl ethyl ketone (MEK), tetrahydrofuran (THF), acetone, methanol (MeOH), ethanol (EtOH), *iso*-propyl alcohol (IPA), methyl *tert*-butyl ether (MtBE), acetonitril (ACN), methylene chloride (CH_2Cl_2), polyethylene glycol (average MW = 400, PEG400), *n*-butanol, *n*-propanol, *t*-pentanol, toluent, chloroform ($CHCl_3$), propylene glycol (PG), water, hexane, cyclohexane. They are listed in Table 1 along with estimated solubility data at 23 °C. Generally the following steps are used to estimate solubility. Accurately weighed solid ~1 mg is added to a 10 mL glass vial. Solvent of known volume is added to the vial. The vial is intermittently shaken by hand for ~5 min. If solid remains, the procedure is repeated until the solid is completely dissolved. Solubility is then bracketed using the total volumes after the last two additions. If solid is completely dissolved after the first addition, the solubility is expressed as greater than the weight of solid divided by volume of the solvent. In some solvents, e.g., acetone, ethanol, solubilities are determined gravimetrically. Excess solid is equilibrated in the solvents for more than 2 weeks at ambient temperature. A known volume of supernatant is withdrawn using a micro-syringe, dried, and weighed. Solubility is calculated from the weight of the remaining solid and volume of the solution. They are reported as a single number rather than a range. We also study crystallization behavior of PHA-739521 under different thermal treatments in a search of as many polymorphs as possible.

2.2.1. Solvent evaporation

Solvents in which solubility of PHA-739521 is greater than 1 mg/mL are used for this part of the work. An appropriate amount of the chosen solvent is used to dissolve about 20–100 mg of PHA-739521 in a glass vial. When the dissolution is slow, the vial is place in the path of a steam while gently shaken to facilitate complete dissolution of solids. If particles still do not dissolve completely, the solution is then passed through a 0.45 μm membrane to yield a clear solution. These clear solutions are slightly heated and then put in a fume hood to allow complete evaporation of the solvent. If the evaporation of solvent is slow, e.g., DMF, DMSO, the evaporation process is facilitated by introducing a continuous flow of dry nitrogen to the vial. The remaining dry solids are subsequently characterized.

2.2.2. Precipitation induced by adding miscible poor solvent

Water is chosen as the anti-solvent because of the low aqueous solubility of this compound (<0.001 mg/mL). About 200 mg of compound is dissolved in an appropriate amount (1–4 mL) of selected organic solvents that are miscible with water. Each solution is filtered through a 0.45 μm membrane to remove any particles. Water (10 mL) is then added quickly to the solution. If precipitation occurs, the suspension is filtered in 10 min. If no precipitation takes place immediately, the solution is set on a bench for weeks or months to allow spontaneous crystallization. Once initiated, precipitation often happens within a short period of time. Therefore, this method favors the formation of metastable forms if they exist. It has been frequently observed that the metastable form crystallizes out of solution first and subsequently converts to a more stable form in accord with Ostwald's rule of stage (Ostwald, 1897). As demonstrated later in this report, the rate of conversion to the more stable form is influenced, among other factors, by the solubility in the final solvent mixture.

Table 1
Solubility of PHA-739521 in various solvents

Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)
DMF	>1800	MeOH	312	*n*-Butanol	3.2–4.1	Water	<0.001
DMSO	>1200	EtOH	157.6	*n*-Propanol	5.0–4.2	Hexane	Insoluble
Dioxane	>781	IPA	58	*t*-Pentanol	<4.9	Cyclo-hexane	Insoluble
EtOAc	68–1000	MtBE	>106	Toluene	1.1–15.7		
MEK	>591	ACN	446	$CHCl_3$	<24		
THF	712	CH_2Cl_2	>39	PEG 400 + H_2O (2:1, v/v)	2.0–4.0		
Acetone	658	PEG 400	>27	PG + H_2O (4:1, v/v)	2.4–8.5		

2.2.3. Suspension crystallization

In a search for the room temperature stable polymorph early in development, excess PHA-739521 powder is suspended in various solvents in which PHA-739521 exhibits solubility greater than 2 mg/mL. Because metastable forms exhibit higher solubilities in a given solvent, it tends to convert to the most stable form through a solution-mediated process. To enhance the mass transfer rate thus the conversion kinetics, suspensions are stirred using magnetic bars. To ensure complete conversion, an aliquot of the suspension is withdrawn, filtered, and analyzed using powder X-ray diffractometry (PXRD) at 1 week and 1 month time point. The polymorphic nature of the solids can be easily identified since PXRD patterns of the two polymorphs are different. When thermodynamic equilibrium is achieved, this method should yield the thermodynamically most stable solid form in the given solvent at the chosen temperature and pressure. In contrast to the precipitation method, suspension crystallization often produces the most stable anhydrous solid form provided a solvate does not form.

To probe relative stability of two polymorphs in a broader temperature range, 23–90 °C, mixture of the two polymorphs is suspended in toluene that has been equilibrated at temperatures of interest in a closed glass vial. Toluene was chosen because of its high boiling point, 111 °C, and reasonable solubility (>1 mg/mL at room temperature) of PHA-739521. Excess solid of one polymorph is first added to saturate toluene with stirring in a glass vial at the chosen temperature. The other polymorph is added at least 0.5 h later. The suspension is stirred continuously for at least 3 days. A portion of the suspension is withdrawn and immediately filtered. The filtered solid is analyzed using PXRD to identify the stable crystal form. By repeating the experiment at different temperatures, the transition temperature between the two polymorphs, T_t, is bracketed.

2.2.4. Thermal treatment

Microquantities of dry powders are heated on a hot-stage microscope (HSM) or on a differential scanning calorimeter (DSC) to induce possible phase changes. Phase changes in microsamples are captured by microscopic observation of crystals (morphology, melting, etc.) or by recording heat changes in the samples. Bulk powders are heated in a dry oven and cooled to produce large quantities of new forms if possible. Crystal form of the powders after thermal treatments is identified using PXRD. The formation of solvates or hydrates is excluded in this method since no solvent is present.

2.3. Polymorph characterization methods

2.3.1. Powder X-ray diffractometry (PXRD)

Powder X-ray diffraction is performed using a Scintag X2 Advanced Diffraction System (controlled by Scintag DMS/NT 1.30a and Microsoft Windows NT 4.0 software). The system uses a Copper X-ray source (45 kV and 40 mA) to provide Cu $K\alpha_1$ emission of 1.5406 Å and a solid-state Peltier cooled detector. The beam aperture is controlled using tube divergence and anti-scatter slits of 2 and 4 mm width and detector anti-scatter and receiving slits of 0.5 and 0.2 mm width. Data is collected from 2° to 35° two-theta using a step scan of 0.03°/step with a counting time of 1 s per step. Scintag round, top loading aluminum sample holders with a 12 mm diameter cavity are utilized for the experiments. Powders are packed into the holder and gently pressed by a glass slide to ensure coplanarity between the sample surface and the surface of the sample holder.

2.3.2. Microscopy

The morphology and dimensions of crystals are observed under a microscope (Model BH-2, Olympus Optical Co. Ltd., Japan) using polarized light for imaging. Digital images are captured using imaging software SPOT (V2.2.1, Diagnostic Instruments, Inc.). To prepare slide samples for microscopic observation, a small quantity of powder is dispersed in silicone oil unless specified and is covered by a cover glass. When heating is desired, a Linkam hot stage (Model THMS 600) controlled by a Linkam temperature controller (Model TP92, Scientific Instrument Ltd., UK) is mounted on a microscope. The powder is then heated on the hot stage and changes to crystals are observed through the microscope. The microscope was also connected to a TV monitor, a VCR and a computer. Images may be viewed from TV monitor and recorded on videotape for more detailed examination.

2.3.3. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) data is obtained using a DSC calorimeter (TA Instruments 2920). Powder (1–5 mg) is packed in an aluminum DSC pan. An aluminum lid is place on top of the pan and is crimped. The crimped pan is placed in the sample cell along with an empty pan as a reference. Temperature is increased to 250 °C from 30 °C at a rate of 10 °C/min. The thermal cell is purged with dry nitrogen at 50 mL/min. The TA Instruments Thermal Solutions™ for NT (version 1.3L) is used for data collection and Universal Analysis™ for NT (version 2.4F) is used for data analysis.

2.3.4. Dynamic moisture sorption gravimetry

Moisture sorption isotherm is collected on a home-built temperature controlled atmospheric microbalance (Bergren, 1994). Approximately 10 mg sample is placed in the sample pan of the balance. The humidity is sequentially varied from room relative humidity (RH) to 0% RH and is then ramped to 90% RH followed by a decrease of RH to 0% again in 3% RH steps. The mass is measured every 2 min. The RH is changed to the next step value when the mass change of the sample is less than 0.5 μg in 10 min. Data is collected and exported to an Excel spreadsheet for graphing.

3. Results and discussion

3.1. Solid-state properties of Forms I and II

The PXRD patterns of Forms I and II are distinctively different and can be easily distinguished (Fig. 2). When Form II is heated in a DSC pan, only a melting peak at ∼170 °C with a leading edge of 167.7 °C is observed (Fig. 3). Therefore, the melting temperature of Form II is ∼168 °C. However, when

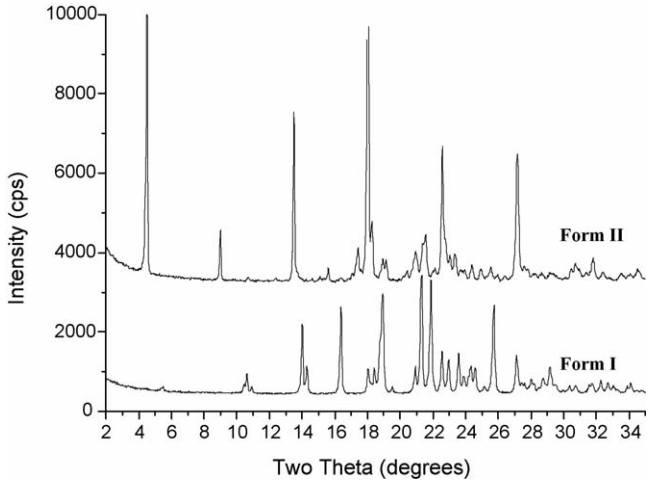

Fig. 2. PXRD patterns of Forms I and II of PHA-739521.

Form I is heated, an endotherm, at about 145 °C, is observed before an endotherm corresponding to melting of Form II at ~170 °C (Fig. 3). Although melting point of Form I cannot be easily measured using DSC because of the conversion to Form I, melting of some well formed Form I crystals that are isolated from other crystals is observed at 151–153 °C using HSM. The melting temperature of Form I is thus ~152 °C.

Using the HSM at a 10 °C/min heating rate, it is observed that the endothermal event at 145 °C corresponded to a solid-state conversion as characterized by changes in crystal morphology. The *Heat of Transition* rule states in part that "If an endothermal transition is observed at some temperature it may be assumed that there is a transition point below it, i.e., the two forms are related enantiotropically" (Burger and Ramberger, 1979). According to this rule, the two polymorphs are enantiotropically related since the solid–solid transition is endothermal. That means that one polymorph is thermodynamically more stable at temperatures below a critical transition temperature, T_t, but becomes metastable when temperature exceeds T_t. The results from suspension crystallization in toluene show that at >71.5 °C, a mixture of I and II always converts to II, but at <71.0 °C, the mixture always converts to Form I. Therefore, Form I is thermodynamically more stable at <71.0 °C and II is more stable at >71.5 °C. The T_t lies between 71.0 and 71.5 °C.

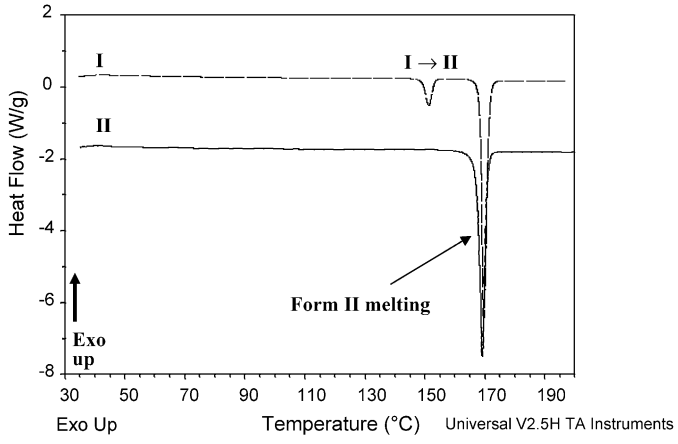

Fig. 3. DSC plots of Forms I and II.

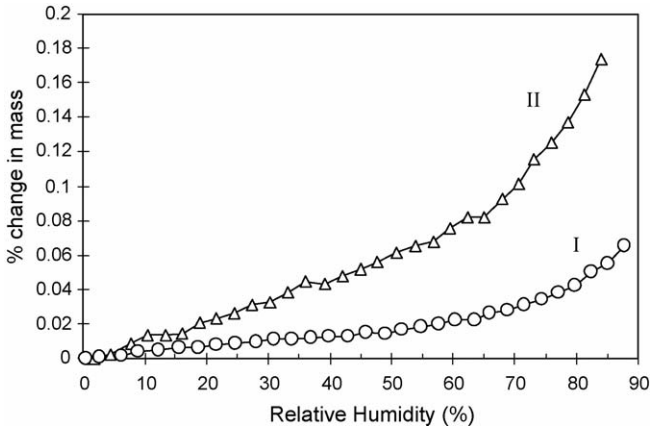

Fig. 4. Moisture sorption plots of Forms I and II of PHA-739521.

DMSG data show that both Forms I and II are non-hygroscopic. At 90% RH, less than 0.2% water is absorbed (Fig. 4). Form II appears to take up slightly more water than Form I. In general, the low water uptake of PHA-739521 suggests good stability of the drug to moisture during storage. In addition, it suggests that aqueous-based wet-granulation processes would be a possible option for the tablet formulation development.

Both polymorphs are compressed at 400 MPa for 1 min using a hydraulic Carver press. The tablets are analyzed using PXRD. No conversion to a different crystal form is observed. Therefore, both polymorphs are stable to compaction pressure. Undesired crystal form conversion during tablet manufacturing is unlikely.

3.2. Crystallization behavior

3.2.1. Crystallization by evaporation of solvent from solution

The results of crystallization using this method are listed in Table 2. Because of very high solubility in MeOH, acetone, ACN, MEK, THF, and dioxane (>312 mg/mL, Table 1) and because these solvents are also very volatile, evaporation of small amount of them results in growth of large amount of crystals on the air–solution interface. Therefore, during the evaporation experiments, a hard crust is formed on the top of

Table 2
Solid forms obtained from evaporation of solvents

Solvent	Solid obtained	Solvent	Solid obtained
EtOH	I	IPA	II
Acetone	I	*n*-Butanol	II
ACN	I	*n*-Propanol	II
MEK	I	*t*-Pentanol	II
THF	I	EtOAc	I + II
Dioxane	I	MtBE	I + II
$CHCl_3$	I	MeOH	Methanol solvate
CH_2Cl_2	I	Hexane	Solubility is too low
Toluene	I	Cyclodexane	Solubility is too low
DMF	I	DMSO	Did not crystallize

Table 3
Solid forms obtained from precipitation of PHA-739521 from organic solvents by adding water

Solvent	Immediately after precipitation	One day after precipitation
MeOH	II	II
EtOH	II	II
IPA	II	II
Acetone	II	II
ACN	II	II
DMSO	I	I
MEK	No precipitation	I
THF	No precipitation	No precipitation

the solution, which slowed further evaporation of the remaining solvent. In those cases, crusts are broken using a clean spatula to allow complete evaporation of the solvent. Evaporation of EtOAc, EtOH, IPA, DMF, and DMSO is relatively slow. Therefore, they are purged by dry nitrogen gas to facilitate complete evaporation of solvents. Because PHA-739521 is not soluble in hexane and cyclohexane, no crystal was obtained from the two solvents. On the other hand, no crystal is obtained from DMSO even under vigorous nitrogen purge for extended period of time, perhaps due to very high solubility in DMSO and low volatility of this solvent. In other solvents, evaporation under ambient conditions achieves complete removal of solvent.

Form I is obtained from evaporation of EtOH, acetone, ACN, MEK, THF, Dioxane, $CHCl_3$, CH_2Cl_2, toluene, and DMF. Form II is obtained from evaporation of IPA, *n*-butanol, *n*-propanol, and *t*-pentanol. A mixture of Forms I and II are obtained from MtBE and EtOAc. It appears that IPA favors the formation of Form II over Form I, but ethanol does the opposite. As it will be mentioned later, a MeOH solvate is formed when PHA-739521 crystallizes from pure MeOH. Desolvation of the MeOH solvate yields Form II when air-dried.

3.2.2. *Precipitation induced by adding miscible poor solvent*

Eight solvents, including EtOH, MeOH, IPA, acetone, ACN, MEK, DMSO, and THF are used to prepare solutions of high concentrations. Water is then added to induce precipitation as described in the method section. Immediate precipitation occurs from EtOH, MeOH, IPA, acetone, and ACN. The solids are identified as Form II using PXRD (Table 3). It is observed that Form II converts to Form I in less than one hour at room temperature in IPA. However, Form II precipitated from above-mentioned solvent systems does not convert to Form I after 1 day. This is likely due to the fact that solubility of drug in the final crystallization medium drops significantly after water is added as shown for water + ethanol system (Fig. 5). Solubility of Form I PHA-739521 increases log-linearly with increasing volume fraction of EtOH up to 90% EtOH. This is typical of solubility profile of organic crystals in solvent and water mixtures (Yalkowsky, 2000). This low solubility in final medium results in low mass transfer rates and therefore very slow solvent-mediated form conversion. This is consistent with the previous work that highlights the need of adequate solubility for reasonable conversion kinetics from a metastable crystal form to a stable one (Gu et al., 2001; Miller et al., 2005). Therefore, when Form I is preferred, the rate of water addition should be kept slow while the suspension being stirred to allow sufficient time for complete conversion of Form II to I during precipitation. During the manufacturing process of the drug, water is added to an alcoholic solution to induce precipitation. If the rate of water addition is too fast during earlier batches, mixtures of Forms I and II are always obtained even with extended stirring after water addition.

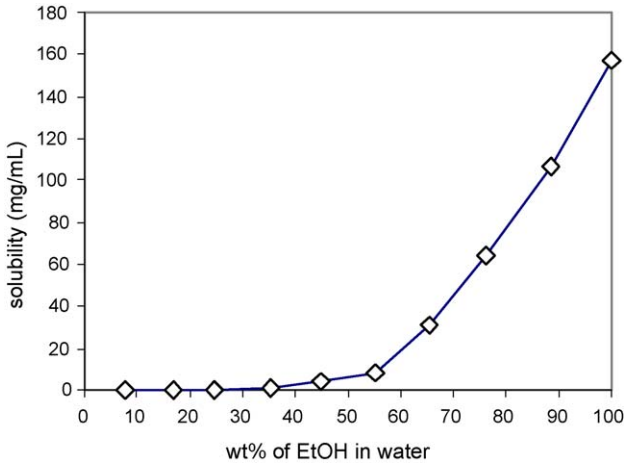

Fig. 5. Solubility of PHA-739521 Form I in ethanol and water mixtures at 23 °C.

When water is added to DMSO solution, Form I is obtained immediately after precipitation. This result suggests that DMSO interacts with PHA-739521 in a unique way to promote the nucleation and growth of the more stable Form I even when the de-saturation rate is very high. This intriguing observation deserves more detailed investigation in the future. However, it is not further explored in this report because DMSO will not be a suitable solvent for commercial manufacturing of bulk PHA-739521 Form I.

PHA-739521 molecules interact with both MEK and THF so strongly that the miscibility with water is significantly reduced. When water is added to MEK solution, two liquid phases are obtained and immediate precipitation does not occur. However, after a few hours or days (varied from trial to trial) rod-shaped Form I crystals grow from the oil phase as shown by PXRD. When water is added to THF solution, two liquid phases are also obtained but no crystallization occurred even after 4 months of storage at room temperature. Thus, neither MEK nor THF is a good solvent in the commercial manufacturing of bulk PHA-739521 crystals.

3.2.3. *Suspension crystallization for the stable polymorph*

Suspension crystallization is carried out using a 1:1 mixture of Forms II and I in MeOH, MeOH + water (1:1, v/v), EtOH, IPA, acetone, ACN, THF, and PEG 400 + water (2:1, v/v). The results are listed in Table 4. Solvated crystals are obtained from PEG 400 + water (2:1, v/v) and pure methanol. Both solvates have been thoroughly characterized and crystal structures obtained but a discussion of their physical properties is out of the scope of this report. In all other solvents, Form I is obtained, i.e., Form II converts to Form I in those solutions. Since Form I instead

Table 4
Solid forms obtained from suspension crystallization experiments at 23 °C

Solvent	Starting solid	Solid at equilibrium
MeOH	I + II	Solvate
MeOH + water (1:1, v/v)	I + II	I
EtOH	I + II	I
IPA	I + II	I
Acetone	I + II	I
ACN	I + II	I
THF	I + II	I
PEG 400 + water (2:1, v/v)	I + II	Solvate

of the methanol solvate is formed in methanol + water mixture (1:1, v/v), it may be concluded that the activity of methanol in the methanol + water mixture (1:1, v/v) is below that required to stabilize the methanol solvate at room temperature. Overall, the results confirm the previous conclusion that Form I is the room temperature more stable solid form of PHA-739521. This is also consistent with the observation that dissolution rate ratio of the two polymorphs is II/I = 1.26 in ethanol + water (2:1, v/v) at 25 °C.

As mentioned in the earlier discussion, the results from suspension crystallization in toluene at different temperatures show that Form II is more stable at >71.5 °C, and Form I is more stable at <71.0 °C. The T_t lies at ~71 °C.

3.2.4. Thermal treatment

The starting material of PHA-739521 is heated in a drying oven at 180 °C until completely melted. The hot melt is then removed from the oven and stored in a refrigerator for about 30 min. A glassy solid is obtained. PXRD shows no intensive diffraction peak therefore, no long-range order of molecules in this solid, i.e., the solid is amorphous in nature. DSC thermogram of this amorphous solid shows a glass-transition event at 44 °C and an exothermal crystallization peak at 80.6 °C (Fig. 6). The crystals then melt at 169.1 °C corresponding to the melting temperature of Form II. This indicates that crystallization of the amorphous solid in the DSC pan yields Form II not Form I.

When bulk Form I crystals (18 g) are put in a drying oven at 150 °C for about 30 min. A small fraction of Form I converts to Form II. When the same bulk Form I is heated further at 155 °C for 3 days, all Form I converts to Form II. When compared to DSC data, higher temperature and longer time are required for complete conversion from Form I to II for bulk powder. Because the same lot of Form I is used in both DSC and the oven heating studies, the different conversion kinetics likely reflects thermal lag in the bulk powder caused by poor heat conductivity of the crystals and poor contact in the bulk powder. No detectable chemical degradation of the compound occurs after the heat treatment. Therefore, this method appears viable for preparing bulk Form II if desired. On the other hand, bulk Form I can be obtained by suspending Form II or mixtures of Forms I and II in appropriate solvents at room temperature.

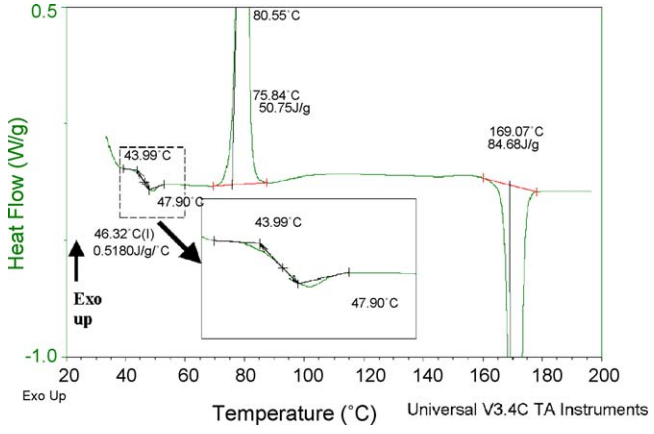

Fig. 6. DSC thermogram of the amorphous solid.

4. Conclusions

Crystallization properties and solid-state properties of two crystalline anhydrous forms of PHA-739521 are studied. The two forms are an enantiotropic pair with Form I more stable at temperatures below ~71 °C. Both Forms I and II are stable to compaction pressure and are non-hygroscopic. Due to its expected thermodynamic stability under conditions of normal unit operations, Form I is a preferred crystal form for formulation development. Low aqueous solubility and low hygroscopicity of the crystals suggest good stability of this compound to wet granulation process and in finished dosage form. Fast precipitation at room temperature by adding water to miscible solvents results in the crystallization of metastable Form II. Suspension crystallization in a number of solvents results in the stable Form I except PEG 400 + water mixture and MeOH where solvates are obtained.

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