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Research Article

Effectiveness of Spray Congealing to Obtain Physically Stabilized Amorphous Dispersions of a Poorly Soluble Thermosensitive API

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Abstract. An amorphous phase produced by micronization up to the molecular or colloidal level of a poorly soluble drug having low lipophilicity can distinctly enhance its solubility characteristics. However, though dispersing the molten mass of a poorly water-soluble drug within polymeric matrix has been found to be most effective in formation of molecular dispersions, the drug molecules which melt at high temperature also accompanied by decomposition, such as acetazolamide, are difficult to formulate as molecular dispersions. Hence, a method is proposed to obtain molecular dispersions of acetazolamide with poloxamer-237 by spray congealing under optimal heat treatment. Uniform molecular and/or colloidal dispersions of the drug were achieved with instantaneous solvent evaporation by mixing a drug solution with molten mass of the plasticizer matrix. Immobilization of dispersed drug molecules was effected subsequently through rapid solidification by spray congealing. Initial characterization of 1:1, 1:1.5, and 1:2 ratios of solid dispersions and devitrification study of an optimized (1:2) ratio ensured efficacy of the proposed method in formation of physically stabilized amorphous systems without thermal degradation and hence resulted in more than ninefold rise in solubility and more than 90% dissolution within initial 10 min. With 1:2 ratio, molecular dispersions could be achieved by initial solvent evaporation stage, which when subjected to spray congealing produced physically stable amorphous systems, without signs of thermal degradation. This study also proposes an opportunity for selection of those polymers with which the drug is immiscible in their fluid state, yet obtaining molecular dispersions.

KEY WORDS: low molecular lipophilicity; melt with decomposition; rapid solidification; solid solutions.

INTRODUCTION

Acetazolamide, *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) acetamide belonging to BCS class IV category has high melting point (≈264°C) indicative of strong crystal lattice (1). It has been reported that the configuration of a molecule and the kind of arrangement in the crystal influences its solubility (1,2). It shall also be noted that when the molecule is highly lipophilic (log P>10), altering the solid state may have little effect on its solubility, since poor aqueous solubility is because of inherent high molecular lipophilicity. On the contrary, when a drug has low lipophilicity (log P<5), it is likely that disruption of the lattice forces within a crystal is needed to increase the effective solubility (1). This can be achieved by altering the crystal form (polymorph, hydrates/solvates) or by producing the amorphous form. The most common technique for producing an amorphous phase in pharmaceutical systems is mechanical activation (energization) of a crystalline mass by micronization (particle size reduction) (3), and the habit effects on solubility are transient and are influenced directly by particle size (1). Thus, solid dispersion systems existing as amorphous phase due to particle size reduction up to molecular or colloidal level could have maximum effect on solubility enhancement and hence, it was focused to obtain amorphous molecular dispersions of the drug, acetazolamide having poor lipophilicity (log P=0.14) in the present study. Historically, spray drying (4,5), freeze-drying (6,7), hot melt extrusion (8,9), and spray congealing (10–13) have been employed in disruption of crystal lattice within drug particles (energization) and subsequently inhibiting spontaneous recrystallization by reducing molecular mobility within polymeric matrix (deenergization) in order to enhance solubility and solid-state stability.

However, several APIs such as didanosine (14), tenoxicam (14), acetazolamide (14,15), hydrocortisone (14,15) melt at high temperature followed by decomposition, which limits use of heat treatment in formation of molecular dispersions. Also, a restricted choice of solvents common for both, the drug and polymer, limits their miscibility in fluid state. Thus, the proposed method combines partial benefits of both the approaches to obtain amorphous molecular dispersions of such thermosensitive APIs to enhance their solubility characteristics.

Poloxamer, a hydrophilic non-ionic surfactant of polyoxypropylene (POP) and polyoxyethylene (POE) with a HLB value >15 has a proven potential to increase solubility of poorly soluble drugs. It exhibits low pour/melt point about

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49°C and viscosity about 700 cps and shows thermoreversible behavior without being influenced by repeated heating and/or cooling. Acetazolamide is dissolved in ethanol (b.p. 78°C), and the solution is added under continuous mechanical stirring to a molten mass of poloxamer-237 maintained between 60 and 65°C. This is likely to evaporate the solvent instantaneously followed by molecular and/or colloidal dispersions of the drug within localized semi-viscous, molten mass of POL developed at evaporation front. Such homogeneous molten mass is then subjected to rapid solidification by way of spray congealing to minimize molecular mobility, crystal nucleation, crystal growth, and crystal habit transitions and hence to ensure physical stability of the amorphous character of acetazolamide within poloxamer-237 matrix. It should be noted that the solvent though flammable can be used safely in the process, as the heating treatment strictly does not make use of a flame. The temperature gradient of molten mass removes the solvent almost completely by evaporation, making the solid dispersions safe to administer.

Out of 1:1, 1:1.5, and 1:2 ratios of spray congealed solid dispersions, 1:2 ratio was found to be suitable through ease to process, complete amorphization and maximum enhancement in solubility aspects and hence optimized. Devitrification study ensured solid-state stability of an amorphous form of acetazolamide in an optimized ratio and unaltered solubility characteristics over the period of 6 months. Hence, the present study proposes a strategic approach to obtain solubility enhanced, physically stabilized amorphous molecular dispersions of a thermosensitive API at optimal processing conditions. Simple, but effective initial stage of mixing the drug solution with the molten mass of a polymer and subsequent ease of processing by spray congealing also ensures scale-up of the proposed method to commercial production of solid dispersions of such drug molecules.

MATERIALS AND METHODS

Materials

Acetazolamide (ACT) was a kind gift from D. K. Pharma Chem Pvt. Ltd. (Mumbai, India). Poloxamer-237 USP/NF (POL) was supplied as a gift sample by BASF Corporation (Washington, USA) as Lutrol® F-87. All other chemicals and solvents used were of analytical reagent grade.

Preparation of Solid Dispersions by Spray Congealing

Ten grams of ACT was dissolved in ethanol so as to obtain 35% *w*/*v* solution. This ethanolic solution of ACT was added in 1:1, 1:1.5, and 1:2 ratios to a molten mass of POL maintained between 60 and 65°C, under continuous stirring using a mechanical stirrer in a jacketed kettle. This ensured uniform dispersion of ACT on molecular and/or colloidal level. The source of heat energy supplied during mixing should be strictly an ultrasound, microwave, or steam due to flammable nature of the solvent. The molten mass was then fed to a thermostatically controlled (with water heated up to 80–85°C, circulated by a peristaltic pump) feed cup and a two-fluid nozzle. This molten mass was sprayed using a laboratory scale spray dryer (B-290, Buchi Labortechnik AG, Switzerland) under the following set of conditions—(liquefying medium) inlet 80°C, aspirator 100%, feed pump 20%, nozzle cleaner 5 pulse. Instantaneous solidification of the atomized droplets of molten mass was achieved with an increased temperature gradient by circulating an inlet gas as N2 in a closed mode using an inert loop (B-295, Buchi Labortechnik AG, Switzerland). External walls of a spray cylinder were lined with ice packs, which further enhanced the performance for cooling a few coarse droplets lodging onto the inner walls of the spray cylinders. The solidified powder was stored in a desiccated environment until further study.

The ratios higher than 1:2 were processed; however, the outcomes based on ease of processing, enhancement in solubility characteristics, conversion to amorphous form were found to be comparable to those of 1:2 ratio. Thus, through economic point of view, i.e., least utilization of the carrier, yet attaining comparable effectiveness and minimum bulk of dose in final dosage form were given consideration and hence 1:2 ratio was optimized and the results for the higher ratios are not included.

Initial Characterization

ACT and all the ratios of solid dispersions of ACT with POL (ACTL) were subjected to initial characterization, which included the following:

Morphological Appearance

Samples were mounted on double-faced adhesive tape and sputtered with thin gold layer using sputter coater unit. Surface morphology was studied with a scanning electron microscope (Jeol 5400, Japan).

FT-IR Study

FT-IR spectra of ACT and all the ratios of ACTL were obtained using a FT-IR spectrometer (8,400 S, Shimadzu Corporation, Japan). About 2–3 mg of the samples was finely ground with dry KBr and mounted on the sample cell. The spectra were scanned over wavenumber range of 4,000−450 cm^{-1}.

Thermal Analysis

DSC measured curves of ACT and its solid dispersions were obtained using differential scanning calorimeter (Mettler Toledo 821^e, Mettler Toledo, Switzerland) operated with Star^e software (version 9.01). The instrument was equipped with an intra cooler. An inert atmosphere was maintained by purging nitrogen gas at flow rate of 40 mL/min. Accurately weighed quantities of samples (3–5 mg) were analyzed in hermetically sealed, pin holed aluminum crucibles. The samples were heated at a constant rate at 10°C/min over a temperature range of 30–300°C. The instrument was calibrated for temperature and heat flow using Indium and Zinc standards, respectively. The percent crystallinity was then determined using the following equation (16):

$$\text{Percent crystallinity} = \left[(\Delta H_m - \Delta H_c)/\Delta H_{\mathring{A}_m}\right] \times 100\% \qquad (1)$$

In Eq. (1), the heat of melting (ΔH_m) and heat of cold crystallization (ΔH_c) were determined by integrating the areas under the endotherm and represented in terms of J/g. Depending upon the thermal history of a sample, a cold crystallization exothermic peak may or may not be observed during thermal characterization. ΔH_{m° is a reference value and represents the heat of melting derived from thermal characterization of the pure, unprocessed drug.

Crystallographic Study

XRPD profiles of ACT and all the ratios of ACTL were recorded on X-ray diffractometer (Bruker AXS-D8 Advance, Germany). The samples were irradiated with monochromatic Cu K radiation (1.542 A°) and analyzed between 2 and 50° 2θ. The voltage and current of 40 kV and 40 mA were used, respectively. The range and scan speed was 5×10^3 CPS and 10 mm/° 2θ, respectively.

Drug Content

Fifty milligrams each of solid dispersions was dissolved in 100 mL of methanol, in triplicate. After appropriate dilution with methanol, the absorbance was measured at λ_{max}=264 nm.

Solubility and Dissolution Characteristics

The solubility of ACT itself and in the three ratios in 0.1 N HCl were measured in triplicate. The known excess of ACT and solid dispersions (depending upon drug content) was added to 10 mL of 0.1 N HCl solution. The samples were rotated at 80 r.p.m. for 72 h at 37.0±0.5°C using an Orbital Shaking Incubator (RIS-24BL, Remi, India). The samples were then filtered, suitably diluted with methanol, and analyzed spectrophotometrically at λ_{max}=264 nm. Dissolution rate of pure drug and ACT from all the ratios of solid dispersions was performed, in triplicate using US Pharmacopoeia XXXII, Type II Dissolution Test Apparatus (DA-6D, Electrolab, India). ACT in spite of being a high dose, low potency drug, the dissolution test was performed on the samples equivalent to 10 mg of ACT to form a saturated solution of drug substance in a given volume of dissolution medium to maintain sink condition. Samples were placed in the dissolution vessels containing 500 mL of 0.1 N HCl solution maintained at 37.0±0.5°C and stirred at 75 r.p.m.±4%. Selection of 0.1 N HCl as dissolution medium signifies simulation of gastric condition in terms of pH where the drug is predominantly expected to dissolve. The aliquots of suitable volume (i.e., 5 mL) were collected at predetermined intervals of time and replaced immediately with equal volumes of fresh dissolution medium, maintained at the same temperature. After filtration, each of the collected aliquots was suitably diluted with methanol and analyzed spectrophotometrically at λ_{max}=264 nm. The data was studied using PCP-Disso v2.08 software. Physical mixtures of an optimized ratio of ACTL was also studied for solubility and dissolution characteristics to demonstrate that ACT dissolution is significantly enhanced *via* solid dispersions and not *via* interfacial wettability assisted by POL.

Devitrification Study

Devitrification tendency of amorphous system was studied by subjecting the optimized ratio of ACTL to elevated temperature (40±2°C) and humidity (75±5% RH) conditions to accelerate its devitrification during its storage in Alu-Alu blister packs over the period of 6 months and after 24 months. Samples were evaluated for molecular interactions, solid-state characterization, solubility, and dissolution characteristics of ACT on completion of 6 months of storage.

RESULTS

A plasticizer, such as POL in an increasing amount, was found to have lowered the melt viscosity of the molten mass, thus facilitating the feeding and atomization process. The solidified particles of ACTL in 1:2 ratio were found to have a glossy, translucent appearance over other two ratios.

Initial Characterization

Morphological Appearance

SEM images (Fig. 1) of ACT and POL are shown at 1,500, 2,000, 3,500, and 750, 1,000, 1,500 magnifications, respectively, and ACTL are shown at 500, 1,000, and 2,000 magnifications. ACT was observed as flake-like and short rod-like crystal structures. In contrast, ACTL appeared as a discrete, dense and microporous particles having poor sphericity. 1:1 and 1:1.5 ratio of ACTL though showed microfine particles dispersed uniformly within polymeric matrix, coarse flake-like ACT crystals were absent as an entity. On the other hand, ACTL (1:2) showed complete absence of crystalline nature of the dispersed phase, and their surface morphology appeared as a matrix of very fine spherical structures. Surface morphology of all the ratio of ACTL showed fine irregularities as crests and folds.

FT-IR Study

FT-IR spectrum of ACT (Fig. 2) showed a strong band at 3,302.5 cm^{-1}, a doublet at 3,180.0 and 3,096.2 cm^{-1}, a medium intensity band at 1,681.7 cm^{-1}, a medium intensity band at 1,402 cm^{-1} and a broad, medium intensity band in the range 800–666 cm^{-1}. In FT-IR spectrum of POL (Fig. 2), the characteristic bands were observed at 2,976.6, 1,964.1, 1,158.0, and 968.1 cm^{-1}. A shift in band at 1,681.7 cm^{-1} to lower wavenumber in FT-IR spectrum of all the ratios of solid dispersions (Fig. 2) was observed. Also the principal bands typically at 3,180.0, 3,096.2, 2,976.6, 1,964.1, 1,158.0, and 968.1 cm^{-1} were reduced in intensity and broadened.

Thermal Analysis

DSC measured curve of ACT (Fig. 3) showed a sharp endotherm of enthalpy 511 J/g between narrow melting range (Tm) of 258–262°C, which was followed by an exothermic peak. DSC measured curve of POL (Fig. 3) also showed a sharp melting endotherm between 49.1 and 58.6°C. DSC measured curve of ACTL(1:1) and ACTL(1:1.5) showed presence of broadened endothermic peaks corresponding to the melting of POL and ACT with decreased enthalpy value 134.3 J/g and

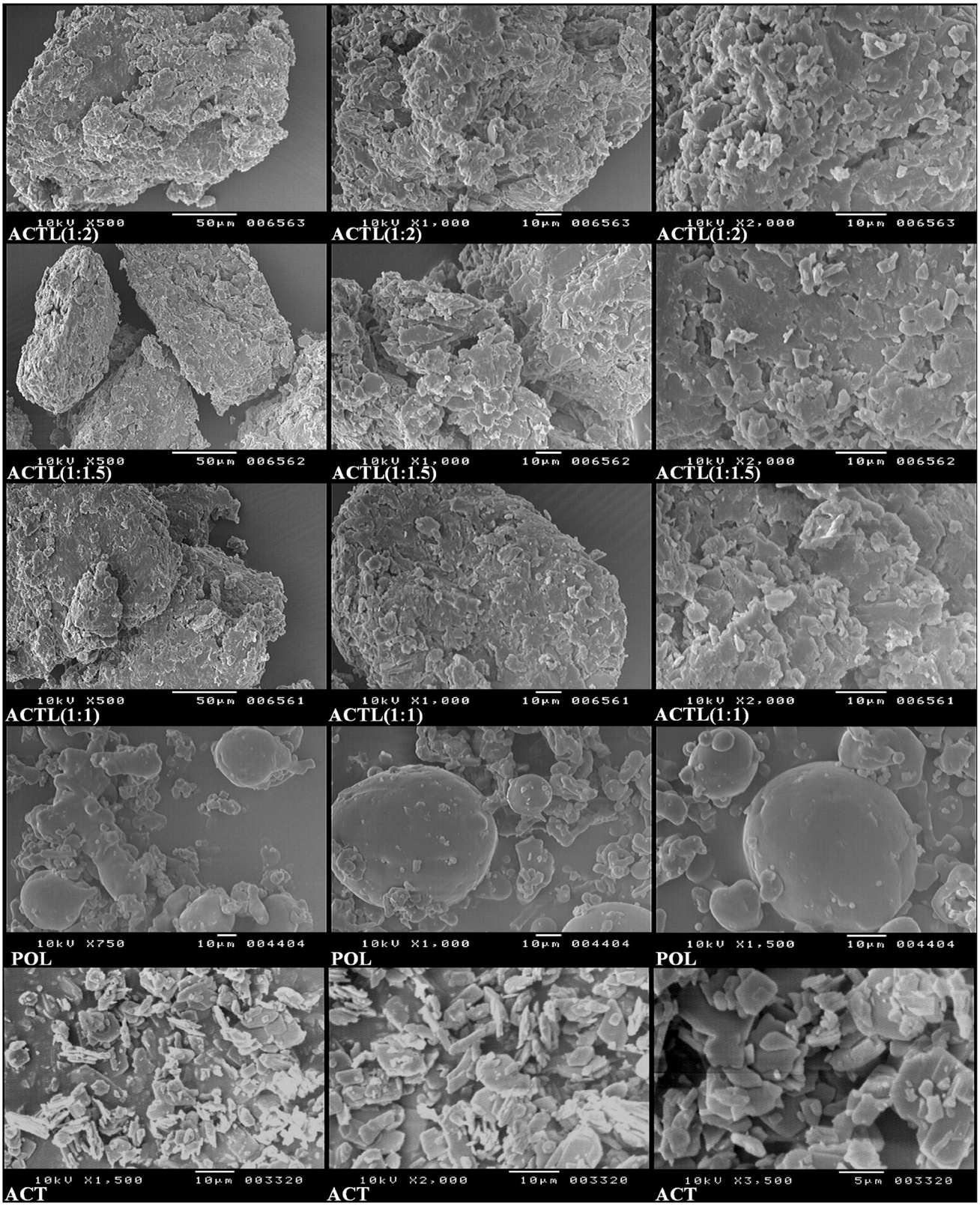

Fig. 1. SEM images of acetazolamide (ACT), poloxamer-237 (POL) and solid dispersions of acetazolamide with poloxamer-237 (ACTL) at suitable magnifications

160.8 J/g, respectively, for ACT. Interestingly, DSC measured curve of ACTL(1:2) showed occurrence of a glass transition (Tg) without enthalpy relaxation (13) at reduced onset temperature of 218.7°C and a change in heat capacity. Also an exotherm corresponding to ACT degradation was found to be absent in ACTL(1:1.5) and ACTL(1:2).

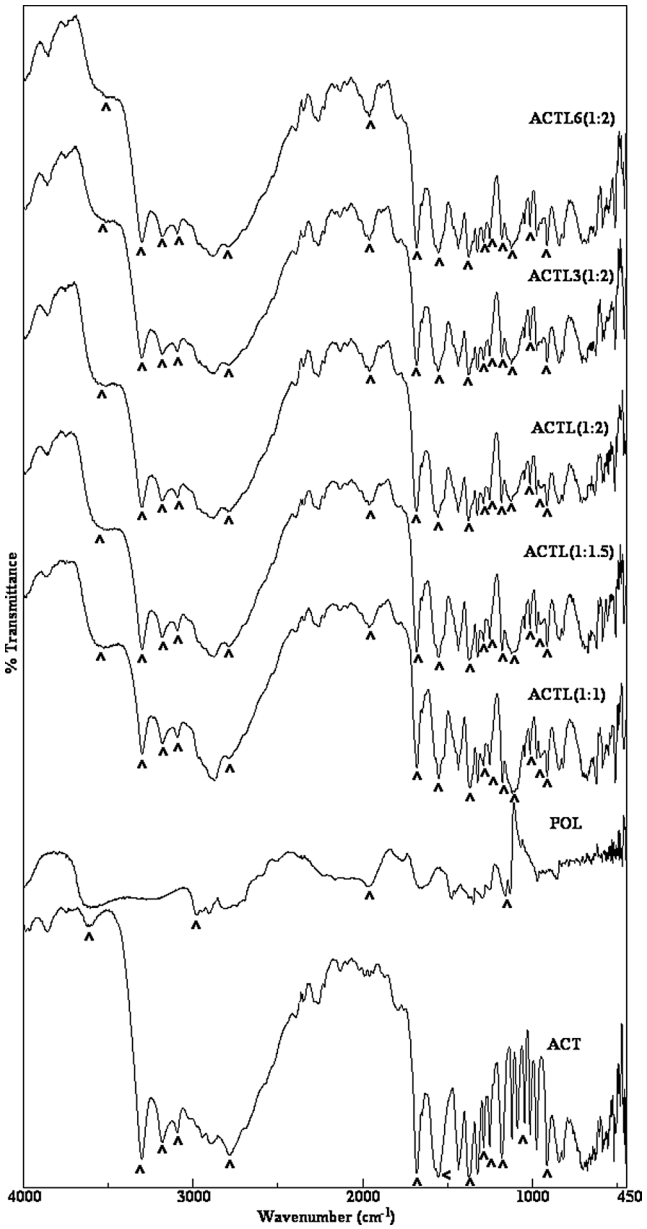

Fig. 2. FT-IR spectrum of acetazolamide (ACT), poloxamer-237 (POL) and solid dispersions of acetazolamide with poloxamer-237 (ACTL) during initial characterization and of optimized ratio after 3 months (ACTL3) and 6 months (ACTL6)

Crystallographic Study

XRPD profiles of ACT and POL (Fig. 4) showed sharp and intense diffraction peaks. XRPD profiles of ACTL(1:1) and ACTL(1:1.5) though showed presence of characteristic diffraction peaks, the peak height was reduced and broadened significantly. XRPD profile of ACTL(1:2) distinctly showed a halo diffraction pattern and absence of all the principal peaks corresponding to crystalline ACT and POL.

Drug Content

Percent content of ACT in ACTL was found to be in the range of 96.4±0.52% to 101.3±0.17% (n=3) of theoretical ratio of the drug in the respective solid dispersions.

Solubility and Dissolution Characteristics

Spray congealed solid dispersions of ACT with POL showed enhanced solubility (Table I) and dissolution (Fig. 5) compared to solubility and dissolution rate of pure drug, which was reported to be 0.891 mg/mL±0.821% and 58.09% dissolution within initial 60 min. Out of the three ratios of ACTL, 1:2 ratio distinctly showed about ninefold rise in solubility and more than 95% dissolution within initial 10 min in the dissolution medium. Whereas ACTL(1:2) PM reported only a marginal improvement in solubility and dissolution of ACT.

Devitrification Study

The results obtained from devitrification study of an optimized ratio of ACTL provided an insight into influence of environmental conditions on solid-state stability of the amorphous form of ACT in its molecular dispersions and hence on solubility characteristics. FT-IR spectrum (Fig. 2) of the optimized ratio of ACTL during storage for 3 months (ACTL3) and 6 months (ACTL6) revealed insignificant change in position and intensity of the principal peaks. Thermal events reported by the DSC scans of ACTL3 and ACTL6 (Fig. 3) were similar to those of its initial run in terms of an onset temperature and change in heat capacity of an endothermic peak at 218.7°C and were without recurrence of melting endotherm corresponding to crystalline ACT and a degradation exotherm. A halo diffraction pattern of ACTL3 and ACTL6 did not show reappearance of diffraction peaks (Fig. 4). ACTL3(1:2) and ACTL6(1:2) showed an insignificant alteration in dissolution pattern (Fig. 5) and indifferent intrinsic solubility (Table I).

DISCUSSION

A glossy, translucent appearance of the particles of ACTL(1:2) gave an impression of effective size reduction of ACT at molecular or colloidal level following the proposed method.

The presence of short flake-like and long rod-like crystals indicated crystalline nature of ACT. Whereas, the absence of long rod-like crystals and reduced particle size of short flake-like crystals in photomicrographs of ACTL(1:1) and ACTL(1:1.5) indicated reduced crystallinity of the dispersed drug. Morphological characteristics of the particles in ACTL(1:2) such as very fine near-spherical structures dispersed uniformly within plasticizer matrix could be correlated with crystal habit modification of the drug by the plasticization effect (17) of POL. Fine irregularities at the surface of the particles such as crests and folds also were supposed to contribute to an enhanced apparent surface area of the solid dispersions and subsequently to an improved solubility characteristics.

Characteristic bands in FT-IR spectrum of ACT at 3,180.0 and 3,096.2 cm^{-1} correspond to N-H stretching doublet of N-H bands resulting from symmetrical and asymmetrical stretching, 3,302.5 cm^{-1} corresponds to C-H stretching vibration, 1,681.7 cm^{-1} corresponds to free C=O stretching, 1,402.0 cm^{-1} corresponds to C-N stretching vibration and in the range of 800–666 cm^{-1} corresponds to plane N-H wagging.

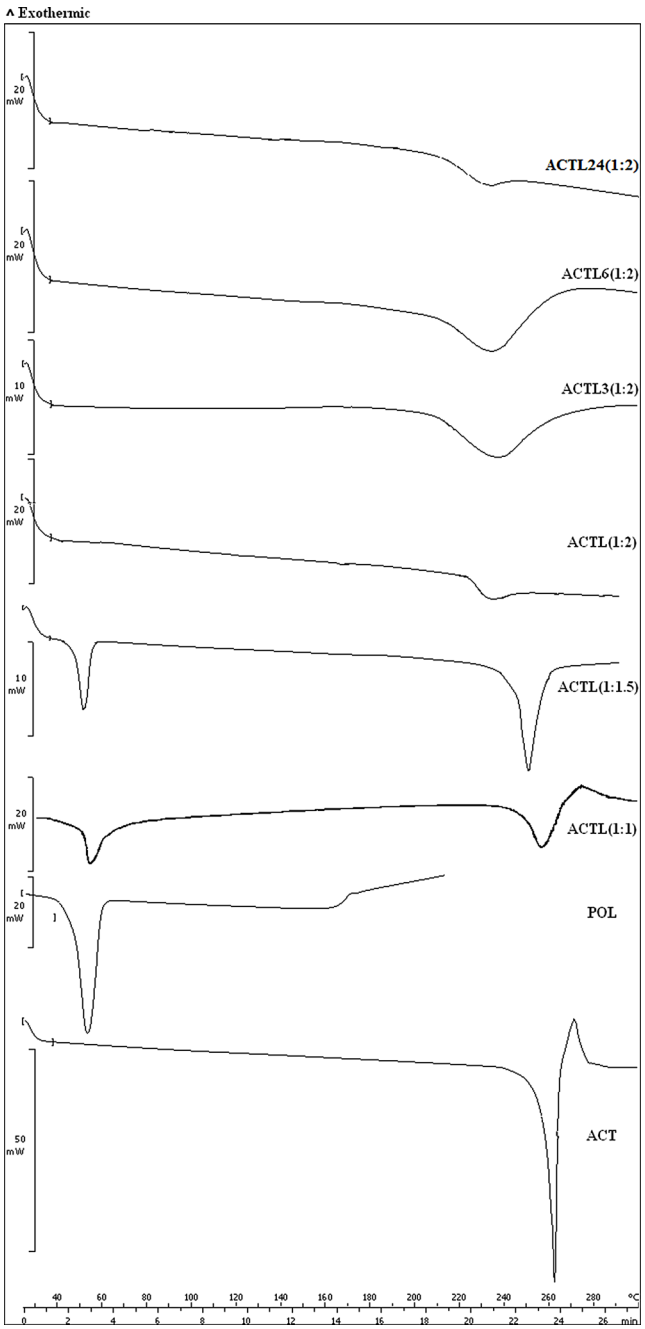

Fig. 3. DSC thermograms of acetazolamide (ACT), poloxamer-237 (POL) and solid dispersions of acetazolamide with poloxamer-237 (ACTL) during initial characterization and of optimized ratio after 3 months (ACTL3), 6 months (ACTL6), and 24 months (ACTL24)

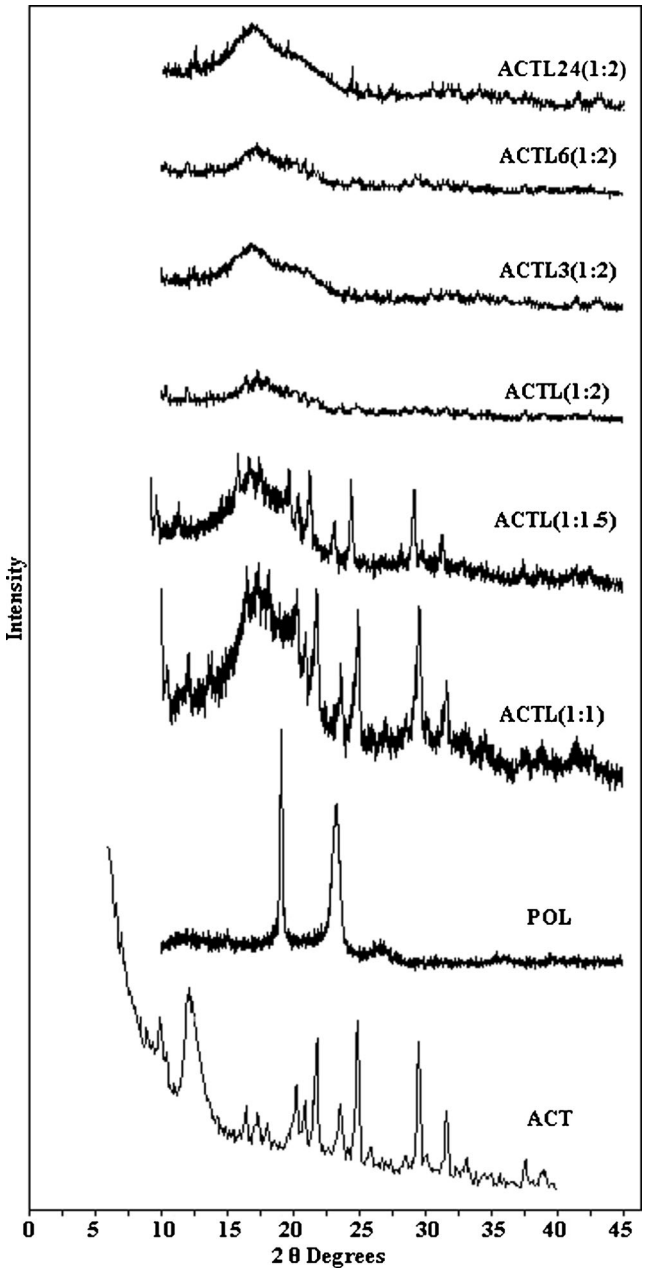

Fig. 4. XRPD profile of acetazolamide (ACT), poloxamer-237 (POL) and solid dispersions of acetazolamide with poloxamer-237 (ACTL) during initial characterization and of optimized ratio after 3 months (ACTL3), 6 months (ACTL6), and 24 months (ACTL24)

Also characteristic bands in the range of 1,100–900 cm^{-1} pointed towards crystalline polymorphic form A of ACT (14). A slight broadening and shift in the position of the free C=O vibration and N-H stretching vibration to lower wavenumber suggested intermolecular hydrogen bonding in solid dispersions.

Sharp melting endotherm at temperatures higher than 200°C is generally correlated with strong crystal lattice forces between drug molecules in a crystal habit (1). ACT was also reported to undergo thermal degradation following melting (14,15). It was revealed in the present study also by an exothermic peak following melting endotherm in DSC measured curve (Fig. 3). Sharp endothermic peak in DSC measured curve of POL (Fig. 3) suggested its crystalline nature. Broadened endothermic peak between 240 and 265°C and its decreased enthalpy value in ACTL(1:1) and ACTL(1:1.5) (Fig. 3) suggested residual crystallinity (18), and it was calculated to be 23.76 and 31.47%, respectively, by using equation 1 (Table II). On the other hand, occurrence of only one Tg at reduced onset temperature of about 218.7°C, and change in heat capacity suggested amorphous molecular dispersions of ACT within POL (18,19). This ratio also reported the least percent crystallinity of 13.95%, among the three ratios.

Table I. Solubility of acetazolamide and solid dispersions of acetazolamide with poloxamer-237 during initial characterization and of optimized ratio after 3 and 6 months (R.S.D.<2, n=3)

Sr no.	Sample	Solubility (mg/mL)±S.D.
1	ACT[a]	0.891±0.821
2	ACTL[b](1:1)	2.228±0.731
3	ACTL[b](1:1.5)	4.010±0.297
4	ACTL[b](1:2)	8.286±0.310
5	ACTL[c](1:2)PM	2.782±0.190
6	ACTL3[d](1:2)	8.275±0.935
7	ACTL6[e](1:2)	8.269±0.984

ACT[a]: Pure, unprocessed acetazolamide
ACTL[b]: Solid dispersions of acetazolamide with poloxamer-237
ACTL[c] PM: Physical mixture of acetazolamide with poloxamer-237
ACTL3[d]: Solid dispersions of acetazolamide with poloxamer-237 after 3 months of storage during devitrification study
ACTL6[e]: Solid dispersions of acetazolamide with poloxamer-237 after 6 months of storage during devitrification study

A characteristic diffraction pattern of ACT confirmed its crystalline polymorphic form A (13) and POL exhibited its crystalline nature. Amorphous character of ACT in ACTL(1:1) and ACTL(1:1.5) obtained by the proposed method was found to be improved significantly by POL and could produce homogeneous, amorphous solid solutions in ACTL(1:2), in which the drug was dispersed molecularly in the plasticizer matrix, as confirmed by the halo diffraction peak (2).

Standard deviation of the determinations of drug content in triplicate suggested that the drug was uniformly distributed throughout the solid dispersions obtained by the proposed method.

Partially amorphous character and reduced particle size at colloidal level and hence enhanced surface area, increased wettability by non-ionic surfactant nature of a plasticizer contributed in enhancement of rate of the dispersed drug in 1:1 and 1:1.5 ratios. Significant improvement in solubility and dissolution rate observed with ACTL(1:2) was attributed mainly to formation of molecular dispersions of ACT with molten POL and minimized molecular mobility during initial mixing step and subsequently inhibition of drug recrystallization due to rapid solidification of the atomized droplets during spray congealing. The absence of strong crystal lattice forces within ACT and weak intermolecular hydrogen bonds between the drug and plasticizer molecules contributed to an enhancement in solubility and dissolution from ACTL(1:2). These observations on partial or complete conversion to amorphous phase were confirmed with the help of XRPD study. Thus, ACTL(1:2) was assigned as an optimized ratio on the grounds of maximum intrinsic solubility, faster dissolution, and complete amorphous character of molecularly dispersed ACT and was subsequently subjected to devitrification study.

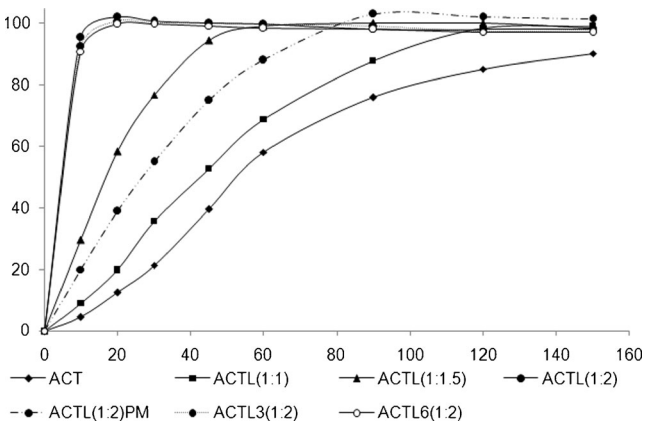

Fig. 5. Dissolution rate of acetazolamide (ACT) and solid dispersions of acetazolamide with poloxamer-237 (ACTL) during initial characterization and of optimized ratio after 3 months (ACTL3), 6 months (ACTL6), and 24 months (ACTL24) (R.S.D.<2, n=3)

Table II. Percent crystallinity of solid dispersions of acetazolamide with poloxamer-237 during initial characterization

	Parameter		
Sample	ΔH_m	$\Delta H_m/\Delta H_{m^\circ}$	Percent crystallinity
ACTL(1:1)	121.54	0.2376	23.76%
ACTL(1:1.5)	160.98	0.3147	31.47%

ΔH_{m°: 511.54 J/g
ΔH_c: Nil

ACTL: Solid dispersions of acetazolamide with poloxamer-237
ΔH_m: Heat of melting of ACTL
ΔH_c: Heat of cold crystallization of ACTL
ΔH_{m°: Heat of melting of pure drug

Unchanged position and intensity of the principal peaks in FT-IR spectrum of optimized ratio showed absence of any further interactions between the drug and plasticizer molecules over the period of devitrification study. Unaltered thermal and diffraction profiles over the period of 24 months confirmed that the drug was stabilized in its amorphous form in 1:2 ratio of ACTL obtained by the proposed method. Such stabilization of physically metastable amorphous form could be attributed to immobilization of drug molecules (20) within plasticizer matrix. The procedural aspects involved were rapid molecular dispersion of ACT within localized semi-viscous POL molten mass, followed by immobilization of the dispersed drug molecules by rapid solidification of the molten mass with spray congealing. Thus unchanged pattern of dissolution (Fig. 5) and solubility (Table I) observed during devitrification study was effected through stabilization of amorphous form of ACT within molecular dispersions.

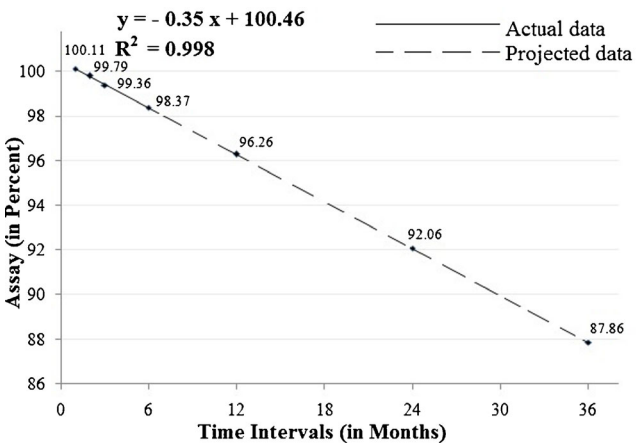

Fig. 6. Projected assay of ACTL(1:2) over 36 months based on the data collected during devitrification study

Projected assay (Fig. 6) for ACTL(1:2) for 12, 24, and 36 months based on the assay data collected during devitrification study for 6 months shown more than 90% assay value during 24 months, and it is not falling below 85% after completion of 36 months. Thus the shelf life of ACTL(1:2) was proposed to be 24 months.

CONCLUSION

The proposed two-step method was found to be suitable in disruption of the crystal lattice forces within acetazolamide, its dispersion on molecular level within a plasticizer, polxamer-237 and hence stabilization of its amorphous form in an optimized ratio of solid dispersions. It is interesting to note that the dispersion of acetazolamide within a plasticizer matrix could be achieved on molecular basis, without the need of melting the drug and avoiding thermal degradation. Marked improvement in solubility characteristics of the drug was reported at 1:2 ratio of solid dispersions, which could be attributed to conversion to amorphous form, size reduction of the drug up to the molecular level and increased wettability of the drug by the surfactant nature of the plasticizer. 1:2 ratio of solid dispersions also reported unaltered amorphous character, solubility and dissolution rate during storage over the period of 6 months under the influence of environmental conditions such as temperature and humidity. Hence, it can be summarized that solubility enhanced physically stable amorphous dispersions of a thermosensitive poorly soluble drug can be obtained by following the proposed method, which can be scaled up to the production level due to its simplicity, effectiveness, and wider scope of applicability.

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