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Research Article

Theme: Develop Enabling Technologies for Delivering Poorly Water Soluble Drugs: Current Status and Future Perspectives
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In Vitro Characterization of a Novel Polymeric System for Preparation of Amorphous Solid Drug Dispersions

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Abstract. Preparation of amorphous solid dispersions using polymers is a commonly used formulation strategy for enhancing the solubility of poorly water-soluble drugs. However, often a single polymer may not bring about a significant enhancement in solubility or amorphous stability of a poorly water-soluble drug. This study describes application of a unique and novel binary polymeric blend in preparation of solid dispersions. The objective of this study was to investigate amorphous solid dispersions of glipizide, a BCS class II model drug, in a binary polymeric system of polyvinyl acetate phthalate (PVAP) and hypromellose (hydroxypropyl methylcellulose, HPMC). The solid dispersions were prepared using two different solvent methods: rotary evaporation (rotavap) and fluid bed drug layering on sugar spheres. The performance and physical stability of the dispersions were evaluated with non-sink dissolution testing, powder X-ray diffraction (PXRD), and modulated differential scanning calorimetry (mDSC). PXRD analysis demonstrated an amorphous state for glipizide, and mDSC showed no evidence of phase separation. Non-sink dissolution testing in pH 7.5 phosphate buffer indicated more than twofold increase in apparent solubility of the drug with PVAP–HPMC system. The glipizide solid dispersions demonstrated a high glass transition temperature (T_g) and acceptable chemical and physical stability during the stability period irrespective of the manufacturing process. In conclusion, the polymeric blend of PVAP–HPMC offers a unique formulation approach for developing amorphous solid dispersions with the flexibility towards the use of these polymers in different ratios and combined quantities depending on drug properties.

KEY WORDS: amorphous solid dispersions; fluid bed drug layering; hypromellose (hydroxypropyl methylcellulose, HPMC); polyvinyl acetate phthalate (PVAP); solubility enhancement; sugar spheres (Suglets).

INTRODUCTION

Amorphous solid dispersions have great potential to improve the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs (1, 2). To improve amorphous stability, solid dispersions of drugs with hydrophilic or amphiphilic polymers are prepared, in which the polymeric carrier acts as a crystallization inhibitor and amorphous stabilizer (3). Solid dispersions are commonly prepared by solvent evaporation and melt extrusion. Solid dispersions by solvent evaporation are achieved by co-precipitation or spray drying of drug and polymeric carrier from a common solvent. While spray drying is one of the most common manufacturing methods, it creates low bulk density powder with poor flow properties and challenging formulation development. Alternative technique for preparing solid dispersion is spraying a solution of drug and polymer on inert small spherical substrates such as Suglets® using a Würster column in a fluid bed coater (4–6). The advantage of this method is the ease of manufacturing of drug-layered pellets as compared to spray-dried powder. This technique has been used for manufacturing solid dispersions of itraconazole (ITZ) which is marketed as drug-layered pellets in capsules (Sporanox®) (7). For lab scale screening, a rotary evaporator (rotavap) is used for solvent evaporation to prepare small batches of solid dispersions, as a feasibility assessment tool.

Polymeric excipients are an important component of solid dispersions that may improve the physical stability of amorphous solids by inhibiting the crystallization of the amorphous form. The ability of these polymeric excipients to maintain the drug in supersaturated state in gastrointestinal (GI) tract upon dissolution into GI fluids makes them more desirable than the other solubilizing strategies. A variety of polymers have been reported in literature as enabling and stabilizing excipients for amorphous solid dispersions including but not limited to hydroxypropyl methylcellulose acetate succinate (HPMCAS),

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hypromellose (HPMC), hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), povidone, crospovidone, and polymethacrylates (8–13). DiNunzio and coworkers reported the incorporation of amorphous ITZ in dispersions made with enteric polymers CAP and PVAP (10). They demonstrated that amorphous compositions of ITZ with these polymers provided improved bioavailability due to the increased period of time in the supersaturated state of ITZ in rat small intestine. Miller *et al.* demonstrated that METHOCEL™ E50 and Eudragit L100-55 produced substantially greater *in vivo* absorption than immediate release formulations owing to improved supersaturation of ITZ in the small intestine (14). The absorption variability with Eudragit L 100-55 was 140% which reduced to 32% by addition of 20% Carbopol 974P to the Eudragit L 100-55 matrix, although both formulations had equivalent area under the dissolution curve (15).

Cellulose derivatives especially HPMC and HPMCAS serve as particularly successful carriers for amorphous material. Konno and coworkers demonstrated that HPMC and HPMCAS were more effective than polyvinylpyrrolidone (PVP) for inhibiting crystallization growth of felodipine in amorphous dispersions (16). In another study, Kennedy and coworkers also reported improved amorphous physical stability and oral bioavailability for a poorly soluble development-stage VR1 antagonist AMG 517 by generating amorphous solid dispersions of HPMCAS and HPMC (17). AMG 517 was incorporated at 15 or 50 wt% into polymeric microparticles of HPMCAS and HPMC by spray drying. Amorphous solid dispersion samples containing HPMCAS showed superior dissolution profile with higher supersaturation compared to HPMC at 15%, but the trend was reversed for 50% HPMC content. Collectively, *in vitro* dissolution and a comparative PK evaluation against an Ora-Plus suspension suggested rapid dissolution and a more complete absorption of AMG 517 via the amorphous solid dispersion approach. The amorphous solid dispersion approach thus significantly improved oral bioavailability for a poorly soluble VR1 antagonist while stabilizing the amorphous form of the molecule.

Several mechanisms for stabilization of amorphous solids in the presence of polymers have been proposed in the literature. In most cases, polymers will have more than one type of interaction with drugs, for example hydrogen bonding, aromatic (π–π interaction) and hydrophobic/hydrophilic interactions (13,18). There is a limited flexibility with using a single polymer for developing amorphous solid dispersions for variety of water-insoluble drugs with various physicochemical characteristics. There are also limited number of polymers that provides both stable amorphous dispersion and improved solubility; therefore, the aim of this study was to develop a binary polymeric blend in order to meet these requirements. HPMC, a nonionic polymer, was selected for its hydrogen bonding potential and its stabilizing ability to prevent crystallization while PVAP an acidic polymer was selected due to its ionic properties and potential aromatic (π–π) and hydrophobic/hydrophilic interactions. This work describes a synergistic combination of binary polymeric components and a poorly water-soluble model drug, glipizide, with enhanced solubility and stability of the amorphous form of the drug. The glipizide solid dispersions were manufactured by two processes: rotary evaporation (rotavap) and fluid bed drug layering on Suglets. The amorphous solid dispersions generated were evaluated for their enhanced solubility and stability using *in vitro* techniques such as supersaturated dissolution studies, powder X-ray diffraction (PXRD), glancing angle (incidence) X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR).

MATERIALS

Dichloromethane (HPLC grade) and methanol (HPLC grade) were obtained from VWR International, Inc. USA. Glipizide was obtained from Medilom, Belgium. HPMC (United States Pharmacopeia substitution type 2910; METHOCEL E3, Dow Chemical Company, USA), PVAP, and Suglets (710–850 μm; sphericity >0.95, friability <1%), Colorcon Inc., USA were used in the study. HPMCAS (MF, Shin-Etsu, Japan) was used for comparative studies.

METHODS

Rotary Evaporation

The evaporated solid dispersions were prepared by the following process: Glipizide (20% *w*/*w*) and the combination of HPMC–PVAP (80% *w*/*w* in the ratio of 3:1) were dissolved in 1:1 (*v*/*v*) mixture of dichloromethane and methanol. All mixtures were visually inspected to confirm that the glipizide and the polymers were fully dissolved, and one-phase solutions were formed. The solvent was quickly removed using a rotary evaporator (Buchi RotaVapor, RII, Buchi, USA) in a water bath maintained at 60°C. Each precipitate was transferred to a Teflon-coated Petri dish. The residual solvent was then removed under vacuum at 40°C for at least 12 h. The dried precipitates were then pulverized in a grinder (Waring grinder, USA) followed by sieving through a 40-mesh (425 μm) screen. Solid dispersions were stored at 5°C in sealed containers until analysis. Solid dispersions containing PVAP, HPMC, and HPMCAS as single polymeric carriers in a drug-polymer ratio of 1:4 were prepared using the above method.

Fluid Bed Drug Layering

The solid dispersion of glipizide was also manufactured by a fluid bed drug layering method. Deposition of glipizide solid dispersion on Suglets was performed in a fluid bed coater (GPCG2 lab system equipped with a 4-in. Würster column, Glatt, Germany). Glipizide (20% *w*/*w*) and the combination of HPMC–PVAP (80% *w*/*w* in the ratio 3:1) were dissolved in a 1:1 (*v*/*v*) mixture of dichloromethane and methanol. The drug–polymer solution was then sprayed onto Suglets to achieve a 20% *w*/*w* theoretical weight gain.

The operating conditions are shown in Table I for batch size of 0.5–1.0 kg. Drug-layered pellets were stored in sealed plastic bags at 5°C until further analysis.

Table I. Drug Layering Process Parameters

Parameter	Average value
Inlet air temperature (°C)	45.3
Product temperature (°C)	31.1
Exhaust air temperature (°C)	29.6
Air flow (m^3/h)	69.4
Atomizing air pressure (bar)	1.2
Spray rate (g/min)	14.8

Preparation of Physical Mixtures

Physical mixtures (PM) of glipizide with the polymers were prepared by thoroughly mixing the accurately weighed quantity of drug and polymers. These mixtures were subsequently passed through a 40-mesh screen (425 μm) and stored in a desiccator at room temperature until further analysis.

Solubility Determination of Crystalline Glipizide in Phosphate Buffer

Excess amount of glipizide was added to phosphate buffer (pH 7.5) in a stoppered conical flask and stirred for 24 h at 37°C to achieve equilibrium. The dispersion was centrifuged at 4,000 rpm, and 2 mL of supernatant was withdrawn and diluted in 100 mL of the medium. Concentration of glipizide in the supernatant was determined in triplicate by an ultraviolet (UV) spectrophotometer (Agilent 8453 UV–vis spectrophotometer, USA) through a 1.0-cm cell at 275 nm, with three-point drop corrections at 256 to 296 nm.

Assay Evaluation

Each sample was dissolved in methanol and precisely diluted with a solution of 1:1 ratio of pH 6.0 phosphate buffer/methanol. The content of glipizide was determined with HPLC based on a calibration line of standards of known concentrations. HPLC analysis was performed with a C_{18} Column (150 mm×4.6 mm, 5 μm Phenomenex Luna, USA) a UV detector (Agilent 8453 UV–vis spectrophotometer, USA). Phosphate buffer (pH 6.0)/methanol (55:45; *v*/*v*) was used as mobile phase at a flow rate of 1.0 mL/min. The injection volume was 20 μL and UV detection was used at a wavelength of 225 nm; the retention time for glipizide was 15 min. All experiments were done in triplicates.

Supersaturated Dissolution Testing

For supersaturated dissolution testing, the dissolution profiles of amorphous glipizide were obtained by non-sink dissolution tests in 500 mL pH 7.5 phosphate buffer without enzyme maintained at 37±0.5°C using USP 35 apparatus II (paddle) at 50 rpm (VK 7000, USA). An excess amount of amorphous sample (3× of equilibrium solubility of glipizide in water) was added to 500 mL of media. Dissolution tests were performed for at least 4 h which is equivalent to the intestinal transit time in human (19). The samples were withdrawn at determined time points and filtered through a 0.45-μm filter. The filtrate was immediately diluted and concentration of glipizide was analyzed using ultra performance liquid chromatography (UPLC)/UV. UPLC analysis was performed with a C_{18} Column (50 mm×2.1 mm, 1.8 μm, Acquity HSS T3, USA) a UV detector (Agilent 8453 UV–vis spectrophotometer, USA). Phosphate buffer (pH 6.0)/methanol (45:55; *v*/*v*) was used as mobile phase at a flow rate of 0.5 mL/min. All solvents used were of HPLC grade. The injection volume was 5 μL and UV detection was used at a wavelength of 276 nm; the retention time for glipizide was 0.9 min.

PXRD

PXRD patterns for amorphous solid dispersions as well as physical mixtures of drug and polymer were recorded at room temperature with a Bruker D8 Advance diffractometer to determine the crystalline state of the drug in solid dispersions. The samples were not subjected to grinding or other pretreatment prior to analysis. The samples were scanned over the range of 2–45° 2–θ. Stability powder samples were characterized for X-ray using a Shimadzu, Lab X, XRD-6000 (Shimadzu, Japan). Powder X-ray diffraction patterns were traced for crystalline glipizide, various carriers, and solid dispersions. The position and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug.

Glancing Angle X-ray Diffraction

For drug-layered pellets, X-ray pattern was recorded using glancing (grazing) incidence method. Pure glipizide was tested using the same method as reference. Each sample was tested without modification. A small portion of each sample was placed onto a zero background holder and run in a Panalytical X'pert MPD diffractometer using Cu radiation at 45 KV/40 ma. An incident angle of 1° was used for scanning through the range of 5–70° with a step size of 0.0167° and a counting time of 500 s/step. Once the diffraction patterns were obtained, the phases were identified with the aid of the Powder Diffraction File published by the International Centre for Diffraction Data.

Scanning Electron Microscopy

The morphology of pure drug, physical mixture, and amorphous solid dispersions was examined under a scanning electron microscope (FEI Phenom SEM). The samples were gold sputter coated before being subjected to scanning electron microscopy.

Fourier Transform Infrared Spectroscopy

FTIR spectra of samples were recorded using a Nicolet iS10 FTIR Spectrometer (Thermo Scientific, USA). The technique of attenuated total reflectance (ATR) was applied over the wave number range of 4,000–400 cm^{-1} with a resolution of 4/cm. Averages of 16 spectra (scans) were recorded as final results.

Differential Scanning Calorimetry

DSC and modulated temperature differential scanning calorimetry (mDSC) studies were carried out on a DSC Q200 (TA Instruments, USA) equipped with nitrogen as a purge gas for the refrigerated cooling system. Powder samples, approximately 8–10 mg, were accurately weighed, placed in an aluminum pan, and crimped with an aluminum lid. The DSC data were analyzed by using the Universal Analysis 2000 software.

Accelerated Stability Testing

The purpose of this study was to evaluate the physical and chemical stability of the glipizide solid dispersions manufactured via two methods of rotary evaporation and fluid bed drug layering as described above. The stability studies were conducted on the solid dispersions powders as well as pellets at 40°C/75% relative humidity (RH) open (open dish) and closed (HDPE bottles) conditions for 1 month. Samples were withdrawn at 2 and 4 weeks and retested for drug content, supersaturated dissolution testing, mDSC, PXRD, and FTIR studies.

RESULTS AND DISCUSSION

Solubility of Crystalline Glipizide and Assay

The crystalline solubility of glipizide was 278±0.04 (μg/mL). HPLC potency analysis indicated that potencies of all solid dispersions were within desired range of 99%± 1%.

Solid-State Characteristics of Glipizide Amorphous Solid Dispersions

Powder X-ray patterns of glipizide amorphous solid dispersions and glancing incidence X-ray diffraction of drug-layered pellets are shown in Figs. 1 and 2, respectively. The

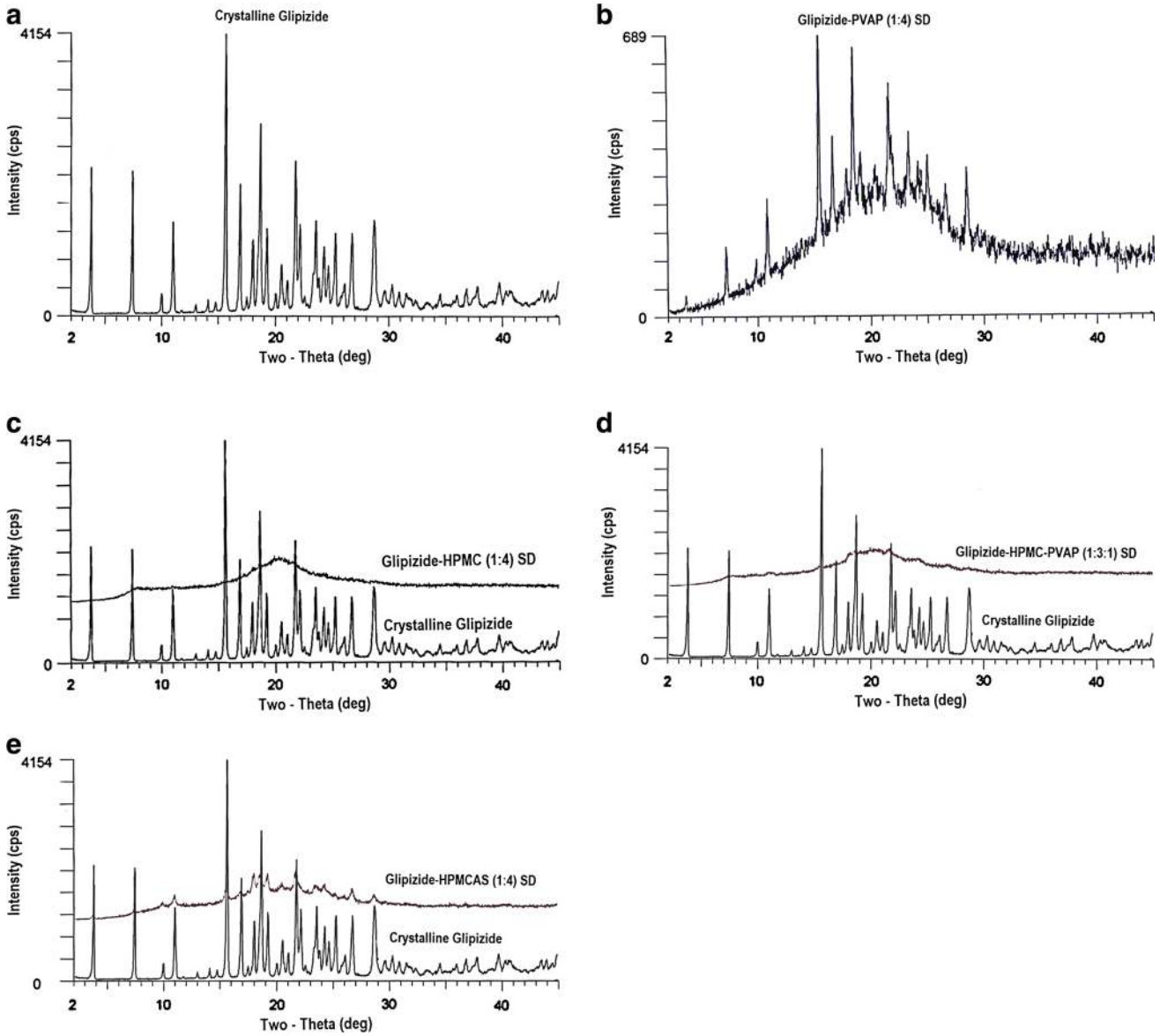

Fig. 1. X-ray diffraction patterns of neat glipizide (**a**), glipizide-PVAP (1:4) SD (**b**), glipizide–HPMC (1:4) SD (**c**), glipizide–HPMC–PVAP (1:3:1) SD (**d**), glipizide–HPMCAS (1:4) SD (**e**)

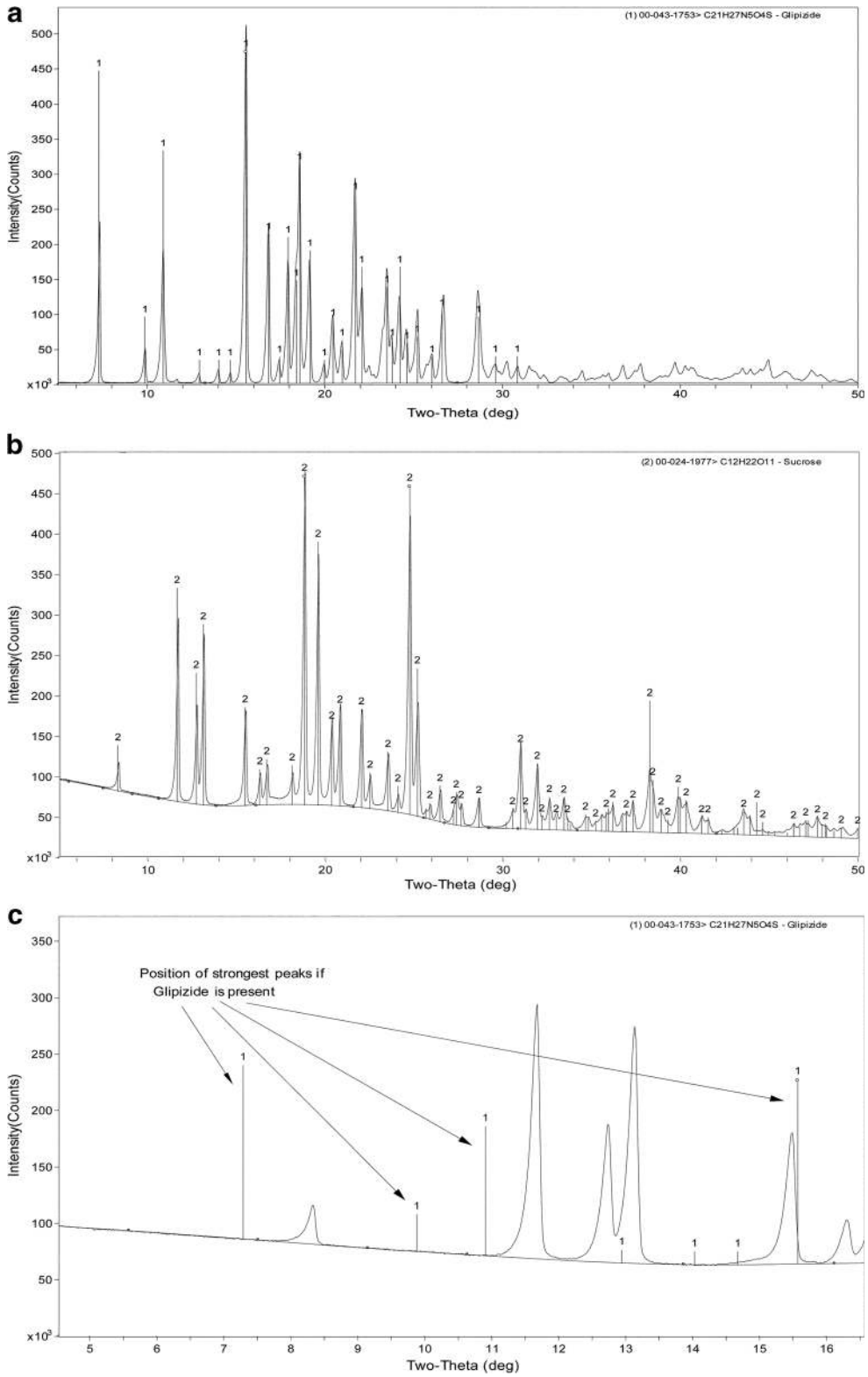

Fig. 2. Glancing incidence x-ray diffraction patterns of neat glipizide (**a**), glipizide pellets (**b**), and comparative patterns (**c**)

crystalline nature of glipizide is depicted by sharp diffraction peaks as shown in Fig. 1a.

Figures 1b and 1e show the PXRD patterns of glipizide-PVAP and glipizide-HPMCAS solid dispersions where the peaks of glipizide are still observed but with less intensity. However, the X-ray pattern of solid dispersions of glipizide–HPMC (Fig. 1c) and glipizide–HPMC–PVAP (Fig. 1d) shows that the crystalline peaks of glipizide were replaced with amorphous halos. This suggests that glipizide was present in an amorphous form in these samples.

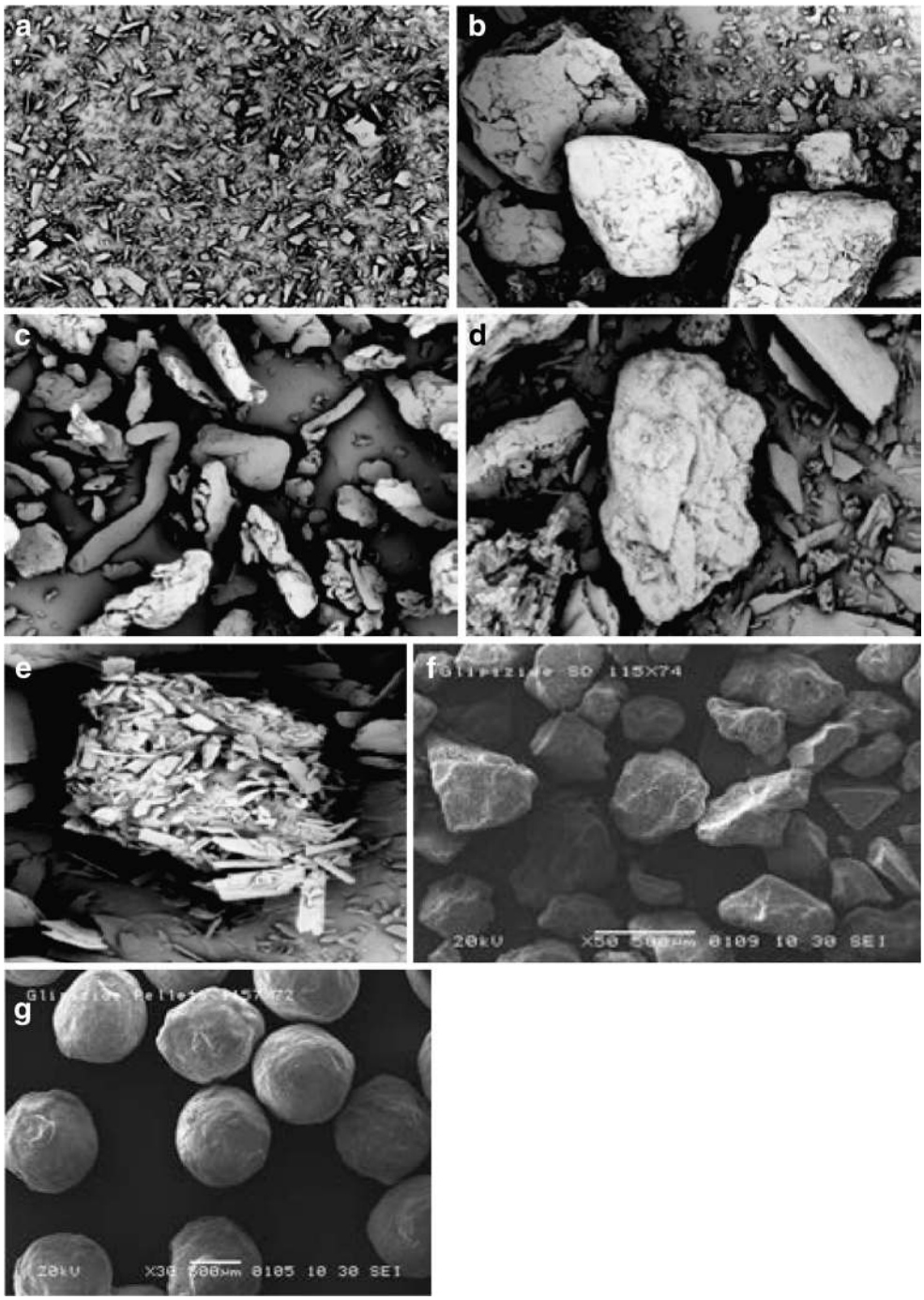

Fig. 3. Scanning electron micrographs of neat glipizide (**a**), PVAP (**b**), HPMC (**c**), glipizide–PVAP (1:4) physical mixture (**d**), glipizide–HPMC (1:4) physical mixture (**e**), glipizide–HPMC–PVAP (1:3:1) solid dispersions (**f**), and glipizide–HPMC–PVAP (1:3:1) drug-layered pellets (**g**)

The experimental patterns of glipizide, and the pellets layered with glipizide–HPMC–PVAP (1:3:1) are shown in Fig. 2a, b at full scale along with stick patterns representing the identified phases. It is shown that the glipizide sample was phase-pure glipizide, while the pellet sample was crystalline sucrose mixed with amorphous material. The presence of the amorphous content was represented by the broad hump in the pattern centered at $2\theta = 22°$. Figure 2c shows an expanded view of the XRD pattern from the pellets with the stick pattern of glipizide superimposed to show where the strongest peaks would appear if glipizide were present. There were no peaks representing glipizide at these locations indicating that that glipizide was present in amorphous form in the drug-layered pellets.

Scanning Electron Microscopy (SEM)

SEM images of glipizide, PVAP, HPMC, physical mixtures, and ternary solid dispersion of glipizide–HPMC–PVAP

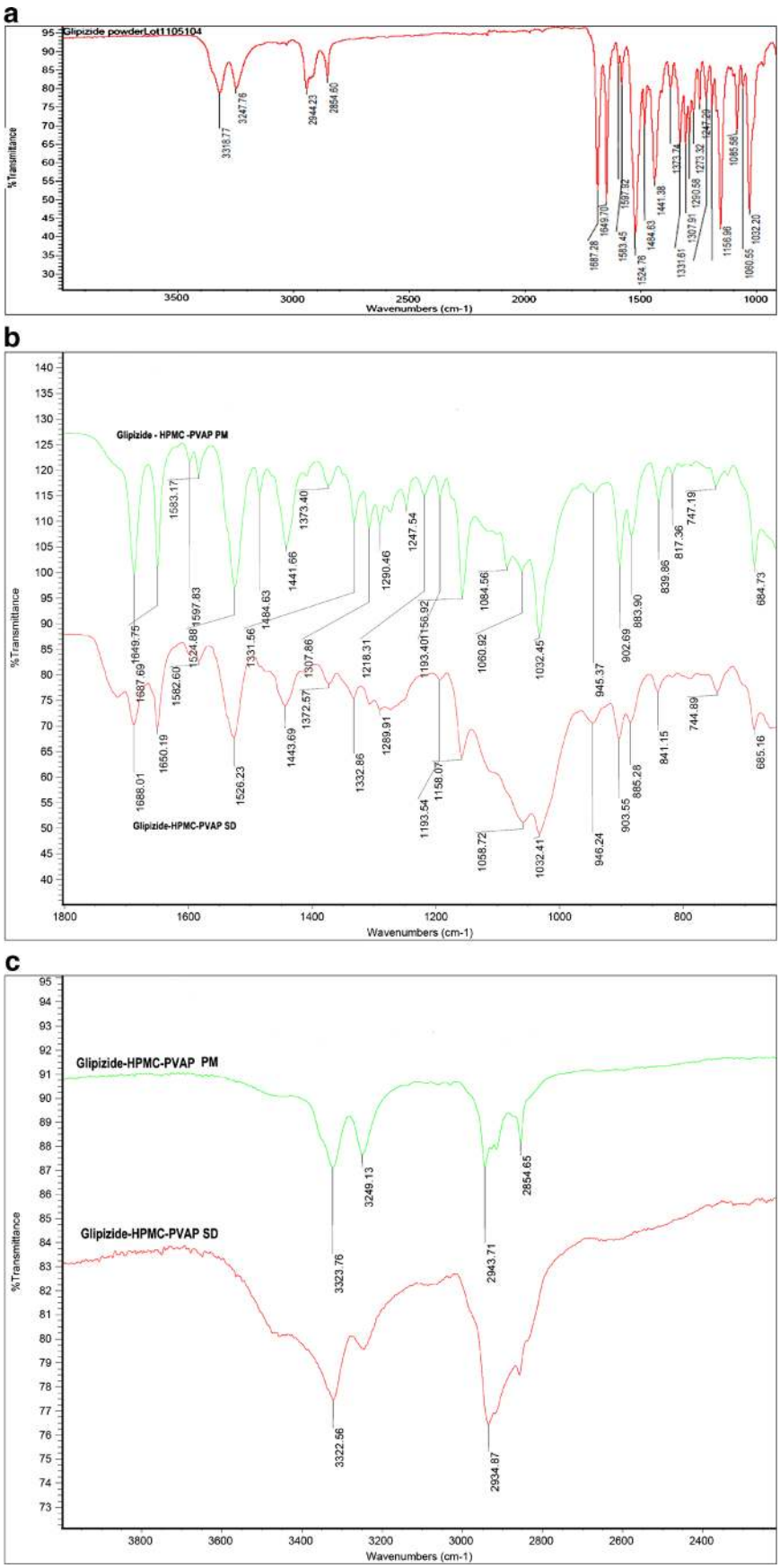

Fig. 4. FTIR spectra of crystalline glipizide (**a**) and glipizide–HPMC–PVAP amorphous solid dispersions and physical mixture (**b, c**)

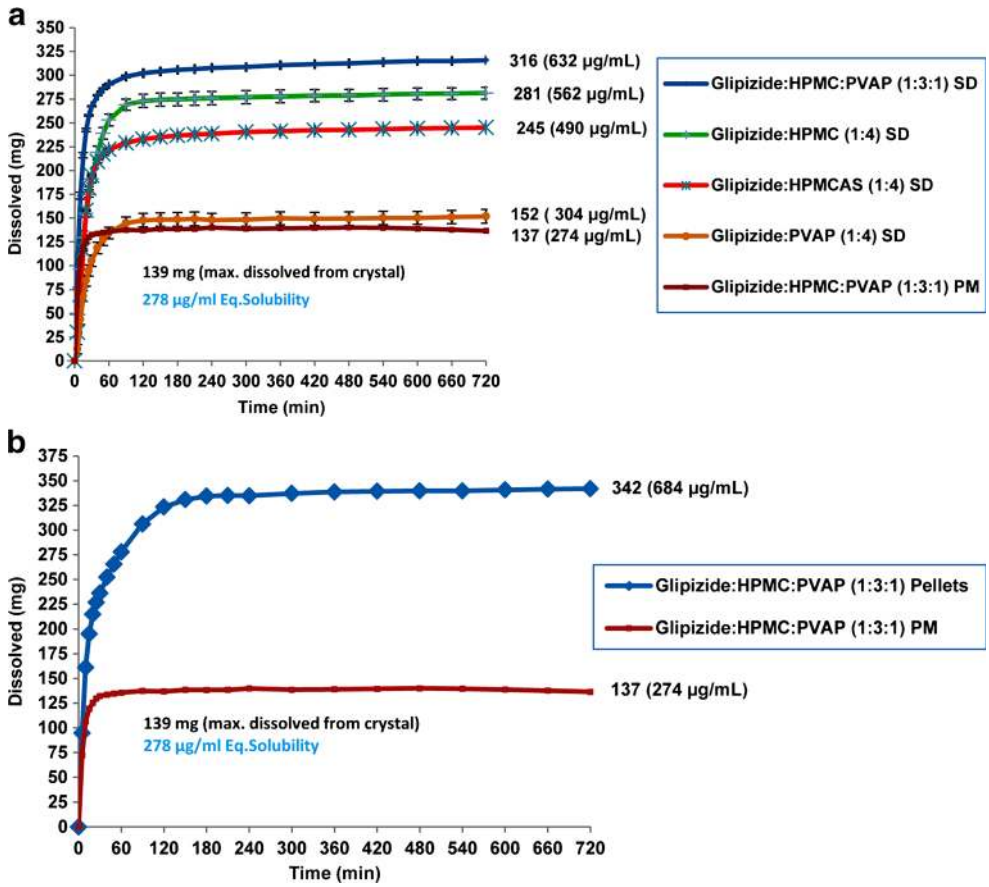

Fig. 5. Release profiles of glipizide solid dispersions powder and physical mixture in non-sink condition pH 7.5 phosphate buffer, 500 mL, dose 420 mg (**a**), and release profiles of glipizide drug-layered pellets and physical mixture (**b**)

(1:3:1) powder- and drug-layered pellet are shown in Fig. 3. Glipizide appeared as needle-like crystals and both polymers PVAP and HPMC appeared as plate-like particles. In the physical mixtures, the presence of glipizide crystals can be detected on the surface of HPMC and PVAP particles. In case of amorphous solid dispersions, the original morphology of the glipizide and polymers was significantly modified. This change in shape and appearance may indicate a new single solid phase hence supporting XRD observations.

Thermal Analysis

Pure glipizide exhibited a sharp melting endotherm peak at 214°C, corresponding to melting temperature (T_m) of glipizide. The melting endotherm peak shifted to lower temperature of 183°C for glipizide physical mixtures. But for amorphous solid dispersions, no melting endotherm was observed indicating no glipizide crystals observed in the solid dispersions. The glass transition temperature (T_g) of solid dispersion of glipizide–PVAP–HPMC was found to be between 110°C and 114°C.

FTIR Spectroscopy

The potential interactions between glipizide and the polymeric system comprising PVAP and HPMC were investigated using FTIR. Absence or shifting of characteristic peaks, in infrared spectrum of the drug after processing, would indicate changes in the drug characteristics or possibilities of drug–carrier interactions. FTIR spectra of glipizide, physical mixture, and solid dispersions of glipizide–HPMC–PVAP (1:3:1) are illustrated in Fig. 4. In FTIR analysis, the spectrum of pure glipizide shows well-defined peak characteristics at 3,248 cm^{-1} (aromatic C–H stretching), 3,319 cm^{-1} (N–H stretching), 1,687 cm^{-1} (C=O stretching), and 2,939 cm^{-1} (C–H aliphatic stretching). Spectra of physical mixtures and solid dispersions of glipizide–polymer show the same peaks with an exception on the methyl shift from 2,944 to 2,933 cm^{-1} which might indicate an aromatic π–π interaction with phenyl group in PVAP. There was no significant difference among the spectra of amorphous solid dispersions and physical mixtures of glipizide which indicated no chemical interactions between the drug and carriers in the solid dispersion.

Supersaturated Dissolution Studies

The dissolution studies reported in the literature and as recommended by US FDA are generally conducted under sink conditions wherein drug concentrations are maintained at least three to five times below equilibrium solubility (19,20). However, the ability of amorphous solid dispersions to supersaturate the dissolution media *in vitro* as well as *in vivo* necessitates the testing of these formulation systems under non-sink conditions for better *in vitro*/*in vivo* correlation. Figure 5 shows the dissolution profiles of glipizide solid dispersions compared with that of the crystalline drug.

Table II. Assay Results—Stability Samples

	Assay% (±SD)				
		40°C/75% RH			
Sample ID	Initial	2 weeks closed	4 weeks closed	2 weeks open	4 weeks open
Glipizide solid dispersion powder	100 (0.3)	104 (0.9)	102 (0.6)	102 (3.2)	100 (0.6)
Glipizide drug-layered pellets	100 (0.3)	97 (0.8)	105 (1.3)	92 (1.8)	104 (2.7)

RH relative humidity, *SD* standard deviation

As shown in Fig. 5, the amorphous solid dispersion of glipizide with PVAP and HPMC polymeric system achieves a higher amount of supersaturation as compared to the amorphous solid dispersion with single polymers. The amorphous solubility of glipizide in PVAP–HPMC system is slightly higher than that observed with HPMCAS system. The amorphous solubility of glipizide is also enhanced nearly 2.5 times its crystalline solubility as shown in Fig. 5. The synergistic advantage provided by the polymeric blend of PVAP–HPMC (1:3) is clearly indicated from Fig. 5. It may be postulated that when HPMC, PVAP, and poorly soluble drug are dissolved in a common solvent and the solvent is evaporated, the drug transforms from a crystalline to an amorphous state, which is stabilized by hydrophilic and hydrophobic interactions within HPMC and PVAP backbone. Since an amorphous form of a drug has higher apparent solubility than a crystalline form, the solubility of the poorly soluble drug in the polymeric composition is enhanced, and the solubility-enhanced form is stabilized from recrystallization both as a solid dispersion and when dissolved in an aqueous medium. The thermodynamic analysis of high-energy forms reported by Murdande et al. (21) indicated that nucleation is the critical step that determines the supersaturated concentration of a drug. HPMC has been reported as an effective nucleation inhibitor for amorphous molecules (16,22,23). Ilevbare and coworkers (24) studied the effect of many polymers including a series of cellulose derivatives, on the solution crystal growth of ritonavir. They have attributed the rate inhibition of crystal growth to three key polymer properties: (1) hydrophobicity, the effective polymers had a moderate level of hydrophobicity; (2) rigidity of polymer structure, the semirigid cellulose polymers were more effective than the semiflexible synthetic polymers of similar hydrophobicity; and (3) amphiphilicity of the cellulose-based polymers. The cellulosic polymers containing more ionizable carboxylic acids groups were better crystal growth inhibitors relative to nonionic cellulose polymers. The binary polymeric systems of PVAP–HPMC used in this study exhibited supersaturation stability for glipizide. The hydroxyl groups of HPMC and PVAP can form hydrogen bonds with electronegative groups on drug molecules such as oxygen or nitrogen atoms. Furthermore, the phenyl groups on PVAP may form π–π interactions with other aromatic groups on drug molecules to further stabilize the molecular associations. The combination of these potential stabilizing interactions from both HPMC and PVAP leads to a synergistic stabilization of the drug molecule i.e., the polymers when used in combination more effectively stabilize the amorphous form of a poorly soluble drug than either polymer alone. PVAP is an enteric polymer with a high T_g (130°C) that dissolves above pH 5, creating a negatively charged surface on the polymer which might result in separation of the large amorphous aggregates of drug/polymer.

The preferential dissolution of PVAP at intestinal pH as well as recrystallization inhibition potential of HPMC may translate into a highly efficient polymeric system for amorphous solid dispersions and enhance solubility and stability of supersaturated solid dispersions. This is evident from the release profiles in Fig. 5a, where the glipizide dissolution is faster and higher from PVAP–HPMC (1:3) dispersions as compared to dispersions based on single polymers: HPMC, PVAP, or HPMCAS. The enhancement of the drug dissolution rate can also be related to several other factors such as the improvement of wetting and solubilization by a hydrophilic carrier and the reduction of the drug particle size as well as reduced particle aggregation. A similar solubility and dissolution rate enhancement was observed for glipizide–HPMC–PVAP pellets on non-sink dissolution testing (Fig. 5b). The supersaturated solution was maintained for at least 720 min (12 h) similar to the powder solid dispersion. The dissolution of glipizide is somewhat faster and to a greater extent from pellets as compared to amorphous solid dispersion powder which may be due to a large surface area of drug-layered pellets and the solubility of the sugar spheres. On the other hand, since powder solid dispersions are often agglomerated in the media and the effective surface area is smaller than the actual surface area, the release might be reduced. In addition, many times powders are floating on top of the media due to poor wettability which also can cause less exposure to the dissolution media. Generally, an amorphous form of drug is thermodynamically unstable and has a tendency to revert to the equilibrium state via recrystallization of drug. Precipitation inhibitors such as polymers are known to inhibit the recrystallization of drugs and thus maintain the supersaturation of the drug in the dissolution fluid. In this case, it has been shown that the blend of PVAP–HPMC is successful in enhancing and maintaining the supersaturation of amorphous form of glipizide.

Stability Studies

Physical and chemical stability of glipizide solid dispersion containing amorphous glipizide, HPMC, and PVAP in 1:3:1 ratio was evaluated by subjecting the amorphous solid dispersions to accelerated stability testing conditions at 40°C/75% RH. The results of dissolution profile (dose 3×, i.e., 2.2 g of solid dispersion powder and 12 g of drug-layered pellets; non-sink conditions,

simulated intestinal fluid, SIF, pH 7.5) and the potency assay evaluation of solid dispersion and drug-layered pellets for 1 month at 40°C/75% RH open and closed conditions are shown in Table II and Fig. 6.

There was no significant change in assay and dissolution profile of the glipizide–HPMC–PVAP solid dispersions upon storage at accelerated stability conditions. Solid-state characterization indicated no change in amorphous state of glipizide. Friesen et al. (9) described the ratio of T_m/T_g (°K/°K) as an indication of the propensity for the compound to crystallize from the amorphous state and explained that as the T_m/T_g ratio of the compound increases, the physical stability of the spray-dried solid dispersion decreases. They categorized the tested materials into three groups based on this ratio. First group consisted of compounds with relatively low T_m/T_g ratios (<1.25), the second group had somewhat higher T_m/T_g ratios (1.25–1.40), and the compounds in third group had even higher T_m/T_g values (greater than 1.4). The solid dispersions in third group are compounds that normally require drug loadings between 10% and 35% *w*/*w* and often require special packaging to avoid ingress of water or storage under reduced humidity conditions to maintain physical stability. Glipizide demonstrates a melting temperature (T_m) of 471.5 K and T_g of 331.3 K which results in a high ratio of T_m/T_g 1.4, indicating high propensity of glipizide to crystallize from the amorphous state. The polymer blend of PVAP–HPMC prevented crystallization of glipizide in dissolution media for at least 12 h and stabilized the amorphous form of glipizide.

The results of X-ray, and DSC of SD powder and the results of X-ray of drug-layered pellets are shown in Figs. 7 and 8. The stability results indicated that solid dispersions of glipizide in the polymer blend were stable for at least 1 month. These results also indicated that irrespective of the manufacturing process, the performance and the stability of amorphous glipizide were maintained throughout the duration of the accelerated stability testing.

Analyses of solid dispersion formulations manufactured using solvent evaporation (rotavap) method demonstrated amorphous solid dispersions by PXRD and no evidence of phase separation by mDSC. The glipizide–HPMC–PVAP solid dispersion demonstrated a relatively high T_g of 110–114°C (383–387 K).

The polymeric blend of PVAP–HPMC has been demonstrated to possess superior supersaturation potential as compared to individual polymers, namely PVAP, HPMC, and HPMCAS. Considering the complicated intellectual property scenario surrounding HPMCAS, this can be considered as a viable alternative for preparing stable amorphous solid dispersions. The blend also imparts flexibility in the

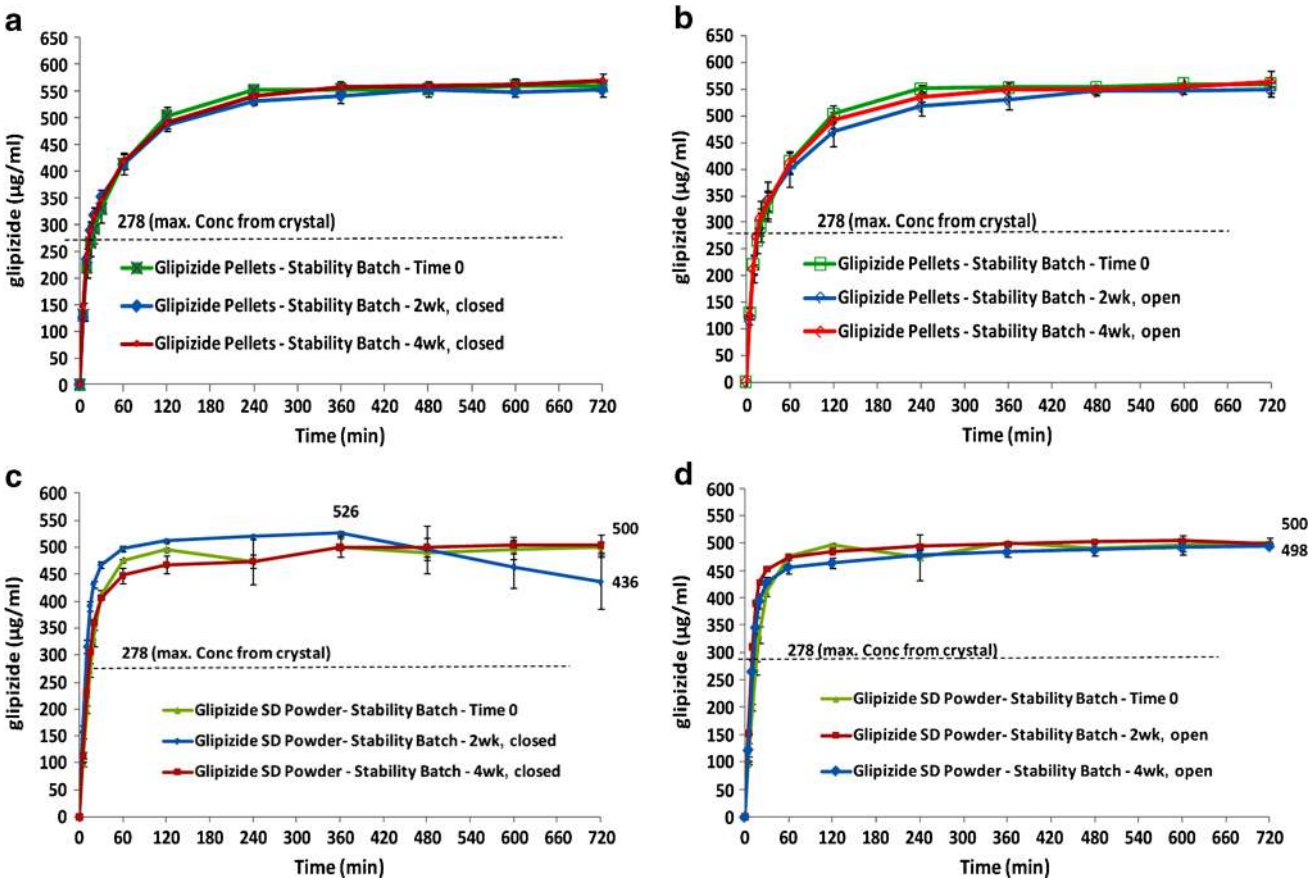

Fig. 6. Non-sink dissolution: stability samples, 40°C/75% RH; glipizide drug-layered pellets, *closed* (**a**); glipizide drug-layered pellets, *open* (**b**); glipizide solid dispersion powder, *closed* (**c**); glipizide solid dispersion powder, *open* (**d**)

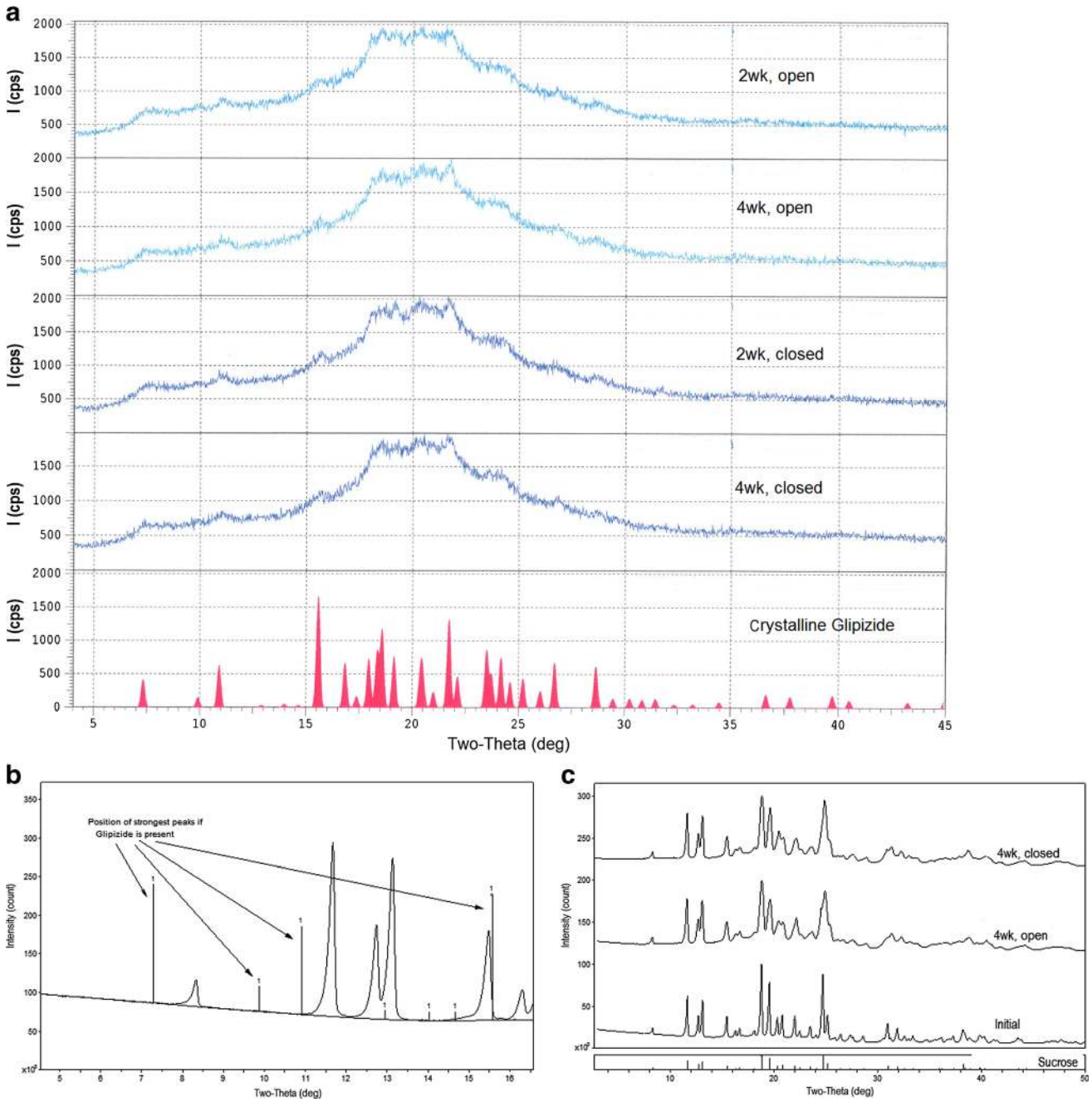

Fig. 7. X-ray diffraction—stability samples, 40°C/75% RH, SD powder (**a**), drug-layered pellets (**b** and **c**)

ratios of PVAP–HPMC combination depending on a particular drug.

Generally, amorphous solid dispersion powders have been difficult to formulate into oral solid dosage forms due to low bulk density and poor flow properties. This work was planned to demonstrate the supersaturation potential of novel polymeric blend of PVAP–HPMC as well as its unique application in manufacturing of amorphous solid dispersions by drug layering of pellets. In this work, the drug layering process is carried out in a fluid bed dryer with Würster attachment. It represents the ubiquitous nature of the equipment in formulation labs and ease of manufacturing of drug-layered pellets as compared to spray drying process followed by compaction of amorphous powders. The drug layering process is also easily scalable on various levels. The drug-layered pellets have superior dissolution properties as compared to amorphous powders due to high surface area and reduced potential of aggregation of nanoparticles generated by dissolution of amorphous solid dispersions.

This work demonstrated the use of a polymeric blend of PVAP–HPMC for generating stable amorphous solid dispersions and the ease of manufacturing of PVAP–HPMC solid dispersions via drug layering on pellets.

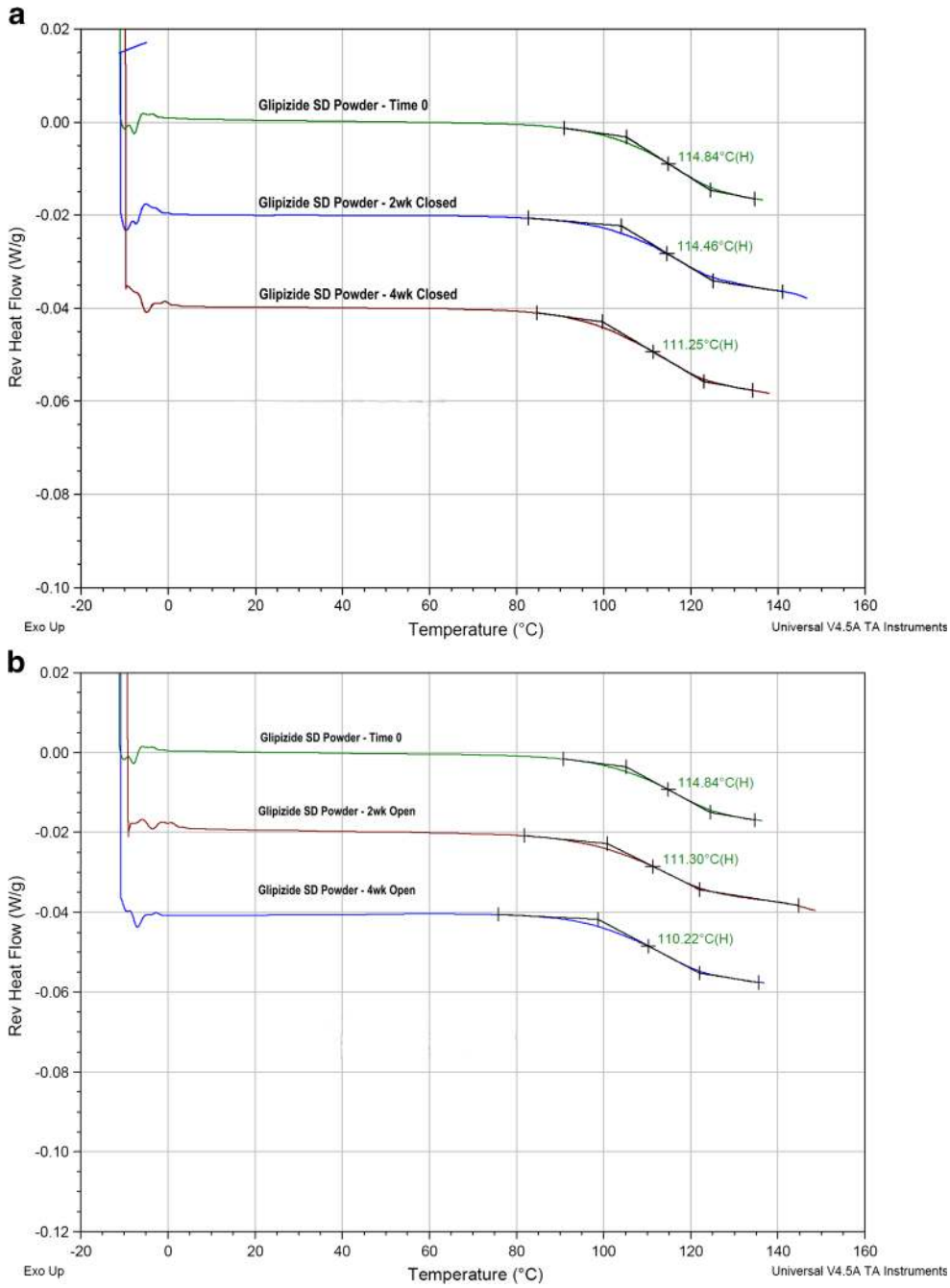

Fig. 8. Differential scanning calorimetry: stability samples, 40°C/75% RH, SD powder *closed* (**a**), *open* (**b**)

CONCLUSIONS

PVAP is an enteric polymer that was successfully used in combination with HPMC to produce solid dispersions of poorly soluble drug glipizide. The amorphous solid dispersions of glipizide-HPMC-PVAP were prepared using two solvent evaporation methods including rotary evaporation and fluid bed drug layering of Suglets. Amorphous solid dispersions were characterized using thermal analysis, PXRD, and FTIR techniques. The PVAP–HPMC polymeric blend sustained the supersaturation of amorphous form of glipizide in the non-sink dissolution medium. Irrespective of the manufacturing process, the solid dispersion of blends demonstrated superior supersaturation of the drug as compared to the individual polymers. Non-sink dissolution results indicated approximately 2.3-fold increase in apparent solubility and maintained for at least 12 h. The amorphous solid dispersions of glipizide–HPMC–PVAP were stable on accelerated stability testing for 1 month at 40°C/75% RH. The blend of HPMC–PVAP allows flexibility to manipulate the ratios of the polymers in the blend to suit the needs of the individual drug depending on its physicochemical properties.

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