Application of Film-Casting Technique to Investigate Drug–Polymer Miscibility in Solid Dispersion and Hot-Melt Extrudate

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ABSTRACT: Determination of drug–polymer miscibility is critical for successful development of solid dispersions. This report details a practical method to predict miscibility and physical stability of drug with various polymers in solid dispersion and, especially, in melt extrudates by applying a film-casting technique. Mixtures of itraconazole (ITZ) with hydroxypropylmethylcellulose phthalate (HPMCP), Kollidon® VA 64, Eudragit® E PO, and Soluplus® were film-casted, exposed to 40°C/75% RH for 1 month and then analyzed using differential scanning calorimetry (DSC), powder X-ray diffractometry, and polarized light microscopy (PLM). ITZ had the highest miscibility with HPMCP, being miscible at drug to polymer ratio of 6:4 (w/w). There was a downward trend of lower miscibility with Soluplus® (miscible at 3:7, w/w, and a few microcrystals present at 4:6, w/w), Kollidon® VA 64 (2:8, w/w) and Eudragit® E PO (<1:9, w/w). PLM was found more sensitive to detect drug crystallization than DSC and powder X-ray diffractometry. There was general correlation between results of film casting and hot-melt extrusion (HME) using a twin screw extruder. For ITZ–Soluplus® mixtures, HME at 4:6 (w/w) resulted in a single phase, whereas drug crystallization was observed at higher drug load. HME of ITZ–Kollidon® VA 64 mixtures also correlated well with the miscibility predicted by film casting. J Pharm Sci 104:2142–2152, 2015

Keywords: solid dispersion; hot-melt extrusion; polymer; itraconazole; drug–polymer miscibility; film casting; amorphous; crystallization; polarized light microscopy; thermal analysis

INTRODUCTION

Amorphous drugs are high-energy materials having higher kinetic solubility and dissolution rates than their crystalline counterparts and, therefore, preferred in the dosage form development of poorly water-soluble drugs. However, the high-energy solids may relax with time resulting in the elimination of microstructure and the growth of local crystalline domains, which ultimately result in crystallization of materials.[1–4] Thus, amorphous drugs are often physically unstable in solid dosage forms. One contributing factor to the physical instability is moisture sorption as the amorphous form is also highly susceptible to moisture uptake.[5] Andronis et al.[3] observed that moisture sorption was higher in amorphous indomethacin relative to its crystalline form, which led to faster nucleation and crystal growth of drug by affecting molecular mobility.

One way of enhancing physical stability of amorphous drugs in solid dosage forms is by solid dispersion. In solid dispersions, drugs are usually dispersed in solid polymeric matrices either molecularly or in their amorphous forms.[6–8] In general, the homogenous dispersions of drugs in suitable polymers increases glass transition temperature (T_g) of the systems as compared with amorphous drugs alone and the resulting increase in viscosity and possible drug–polymer interaction restrict molecular mobility of drugs, thus preventing nucleation of crystalline form and retarding crystal growth.

Although solid dispersions may be kinetically stable for a certain period of time, amorphous drugs may eventually phase separate from solid dispersions depending on their miscibility with polymers and other materials used as carriers and convert to more stable crystalline forms. This leads to reduced product performance, decreased shelf-lives, and lower bioavailability.[9] Many different factors, including chemical nature, molecular weight, viscosity, and T_g of polymers as well as possible molecular interactions between drug and polymer can influence the drug–polymer miscibility. Thus, the selection of appropriate polymeric carriers is critically important for the successful development of solid dispersions. Earlier, we characterized thermal and rheological properties of PVP[10], cellulose[11], and methacrylate-based polymers[12] to help in the selection of appropriate polymers for the preparation of solid dispersion by melt extrusion. Apart from understanding the physicochemical properties of polymers used, it is also important for the successful development of solid dispersions to understand the miscibility between drugs and polymers used. It is, therefore, essential that appropriate polymeric carriers are selected by conducting drug–polymer miscibility screening. The present investigation focuses on the development of a practical method for studying drug–polymer miscibility by using a model drug, itraconazole (ITZ), and representative polymers from the three above-mentioned classes.

The drug–polymer miscibility may be defined as the ability of drug to disperse in a polymer matrix and form a single phase

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without phase separation and drug crystallization. The final concentration of the solubilized drug is dictated by its miscibility with polymer.[13] A review of literature indicates that the drug–polymer miscibility is often determined using theoretical models based on thermodynamic principles.[14] Among the theoretical models, the Hildebrand–Scott model utilizes thermodynamic principles that were originally developed to predict the miscibility of nonpolar solvents.[15] In this model, the cohesive energy density using molar volume and heat of vaporization are used to obtain a constant known as the solubility parameter (δ). It is likely that materials with similar δ values will be miscible with each other. This theory was modified by other researchers in their attempts to predict the miscibility of drugs with polar solvents and with carriers in dry solids.[16–20] However, the predictive value of the theory in selecting polymers for solid dispersion is rather limited.[21]

Another method based on thermodynamic principles, known as the Flory–Huggins method, has also been used to predict drug–polymer miscibility. It is based on a model that considers the system as a hypothetical "lattice" in space.[17] The major limitation of this lattice-based model was the uncertainty in relative contributions of enthalpy and entropy to the process and, as a result, deviations were found between experimental results and theoretical predictions.[21]

One major limitation of studying drug–polymer miscibility in solid dispersion is that drug molecules exhibit low-molecular mobility at temperatures below T_g, which makes it difficult to ascertain whether the drug–polymer miscibility predicted by theoretical calculations are actually valid or not and whether the solid dispersion would be physically stable upon prolonged storage. It is important that reliable drug–polymer miscibility results are obtained within a relatively short time available during preformulation testing of drug candidates. Several researchers stored samples at high temperatures (i.e., near their T_g) to increase molecular mobility and facilitate any drug crystallization.[22,23] Other researchers have used differential scanning calorimetry (DSC) technique to determine drug–polymer miscibility at glass transition temperatures. For example, Forster et al.[24] used this approach to predict the formation of glassy solutions upon melt extrusion of two model drugs with different excipients. However, there are numerous reports[25–27] indicating that when the data obtained at high temperature or near T_g are extrapolated to lower room temperature, the results often deviate from the experimentally observed values. Johari and Shanker[28] also showed the inaccuracy of such methods. They observed that the heat capacity measured using analytical methods, such as DSC, includes specific heat data originating from configurational entropy as well as from the nonconfigurational source. According to them, the nonconfigurational entropy does not contribute to structural relaxation necessary for phase separation, and hence the results deviate from actual miscibility when extrapolated from a high temperature to a low temperature. Thus, the drug–polymer miscibility results are affected by temperature as well as by the analytical technique used.

Because of the complexity of the theoretical methods and their limitations in predicting drug–polymer miscibility, there is a need for a practical method that may be used during the preformulation testing of drugs to screen different polymers for their miscibility with polymers and to ascertain the extent of miscibility in the selected polymer. In one such method, the drug solubility was determined in dilute solutions of monomers and dimers related to the polymer used and the results were then used to predict drug–polymer miscibility.[29] However, such a method overlooks the structural aspects of solids, such as limitation on molecular motion and orientation in a solid matrix structure. Other experimental approaches, such as preparing solid dispersions in small scale by hot-melt extrusion (HME),[30] have also been explored to prescreen polymers. As mentioned earlier, any recrystallization of drug in such a method becomes very slow because of high viscosity of polymers in solid state, and, in most cases, the solid dispersions do not reach thermodynamic equilibrium state in a relatively short period of time available for preformulation screening.[31] The lack of adequate amounts of drugs to prepare melt extrudates with many different polymers for preformulation screening may also be an issue.

In an attempt to develop a predictive tool that may be used in the preformulation setting, Kolter et al.[32] developed a film-casting method in which drug–polymer films prepared by using polyvinyl-based polymers were cast on glass plates, stored at 23°C/54% RH for 7 days and analyzed microscopically. The authors concluded that the film casting was a useful technique to rank-order polymers for their solubilization capacity of various drugs. Although not used specifically for the purpose of prescreening different polymers, Janssens et al.[33] compared physical stability of ITZ by casting films of ITZ–Eudragit® E 100 mixture and compared the results with those obtained after spray drying of mixtures. The results suggested that a thermodynamic equilibrium between drug and polymer may be ascertained more rapidly in films than observing the physical stability of spray-dried products. Similarly, Weuts et al.[34] applied the method to investigate the miscibility of etravirine with hydroxypropylmethylcellulose. Thus, the film-casting technique could prove to be a useful tool to systematically assess the miscibility of drugs with various polymers during preformulation testing. However, all of the studies mentioned above were rather limited in their scopes, and more in-depth studies to explore the value of film casting for drug–polymer miscibility screening are needed. In the absence of such studies, the film-casting technique has not yet been widely adopted by the pharmaceutical industry during preformulation studies for the development of solid dispersion formulations.

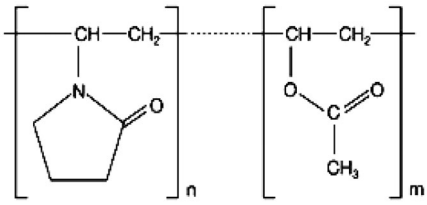
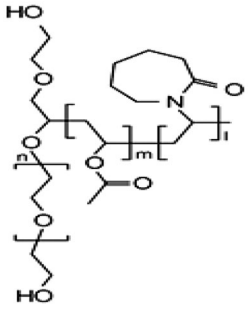
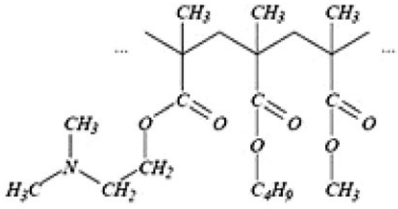
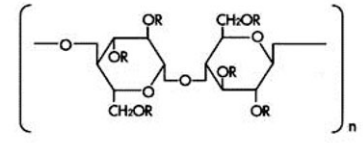
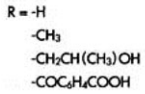
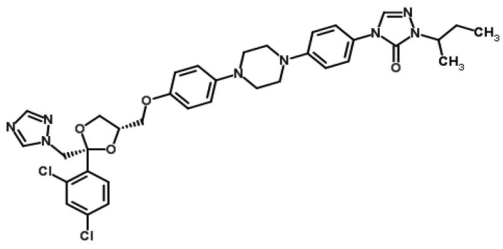
In recent years, the interest in solid dispersion of poorly water-soluble drugs has increased greatly in the pharmaceutical field after introduction of the HME technology to prepare such formulations.[35–37] The primary objective of the present study was to investigate the capability of film-casting technique to predict drug-polymer miscibility and to rank-order different polymers such as cellulose ether, polyvinylpyrrolidone, polymethacrylate, and polyvinyl acetate-polyvinyl capralactone graft copolymers for miscibility with a poorly water-soluble drug, ITZ. The results obtained from film casting were then correlated with the physical stability of solid dispersions prepared by the HME process.

MATERIALS AND METHODS

Materials

Names, structures, and selected physicochemical properties of the polymers and drug used are given in Table 1. Kollidon® VA 64 (polyvinylpyrrolidone vinyl acetate copolymer) and Soluplus® (polyvinyl caprolactam–polyvinyl

Table 1. Names, Structures, and Selected Physicochemical Properties of Polymers and Drug Used

Components	Chemical Structure	Glass Transition Temperature	Molecular Weight (Da)
Kollidon® VA 64 (polyvinylpyrrolid-one vinyl acetate copolymer)		106°C	45,000–60,000
Soluplus® (polyvinyl caprolactam–polyvinyl acetate–polyethyleneglycol copolymer)		77°C	90,000–140,000
Eudragit® EPO (dimethylaminoethyl methacrylate–butyl methacrylate–methyl methacrylate copolymer)		45°C	47,000
HPMCP/HP-50 (hydroxypropylmethyl cellulose phthalate)	 	143°C	37,900
Itraconazole		T_m: 166°C T_g: 59°C	705

acetate–polyethylene glycol copolymer) were donated by BASF Corporation (Tarrytown, New York). Eudragit® E PO (dimethylaminoethyl methacrylate-butyl methacrylate–methyl methacrylate copolymer) was donated by Evonik Corporation (Parsippany, New Jersey), and hydroxypropylmethylcellulose phthalate (HPMCP)/HP 50 was donated by Shin-Etsu Chemicals (Tokyo, Japan). ITZ of the pharmaceutical grade was obtained from a major generic pharmaceutical company in the USA. Amorphous ITZ was prepared by melting the crystalline ITZ at 175°C, followed by quench-cooling using liquid nitrogen. The amorphous nature of drug was confirmed by using powder X-ray diffractometry.

Methods

Preparation of Films

A schematic representation of the film-casting technique is shown in Figure 1. Binary mixtures of ITZ with Eudragit®

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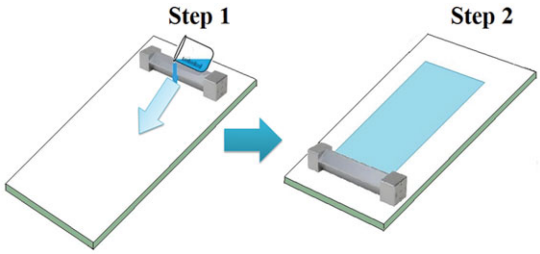

Figure 1. Schematic representation of the film casting process. Step 1: drug–polymer mixture was placed on the glass plate. Step 2: film caster with uniform gap was swiped across the glass plate to obtain a film of uniform thickness, after which it was dried at room temperature.

E PO (1:9, 2:8, 3:7, 4:6, w/w), Kollidon® VA 64 (1:9, 2:8, 3:7, 4:6, 5:5, w/w), Soluplus® (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, w/w), and HPMCP/HP 50 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, w/w) were prepared and then dissolved in the 1:1 mixtures of dichloromethane and methanol such that the final concentrations of the solids ranged from 0.2 to 0.5 g/mL. The solutions were poured onto 10 × 10 cm^2 glass plates and then cast into films using Elcometer® model no. 3540 bird film applicator (Rochester Hills, Michigan). A fixed gap of 200 μm in the film applicator was used, which resulted in uniform film application on the plates. Transparent to translucent films were produced when the plates were dried at room temperature to remove the organic solvent. Preliminary studies using thermogravimetric analysis showed that a drying period of 6 h was sufficient to remove the residual solvent to below 2% (w/w) of the solid content. Therefore, the films were dried for at least 6 h at room temperature.

Powder X-ray Diffraction Analysis

Powder X-ray diffraction (XRD) studies of films were performed using Shimadzu 6000 X-ray diffractometer (Shimadzu Corporation, Kyoto, Japan). Samples for the powder XRD analysis were prepared by placing the films peeled or scraped from glass plates on glass sample holders with cavities and pressing them to obtain smooth and uniform surfaces. For analysis, a CuKa, monochromatic radiation source emitting X-ray radiation at 60 kV and 55 mA was used and the sample was scanned at a scanning rate of 2θ/min over the range of 10°–60°. The presence or absence of peaks corresponding to ITZ was considered as evidence of the drug present in, respectively, crystalline or amorphous forms.

Differential Scanning Calorimetry

Samples were analyzed for their thermal patterns as a function of temperature using a Q200 modulated DSC instrument (TA Instruments, New Castle, Delaware). The instrument was calibrated using indium as the standard for heat flow and temperature and sapphire as the standard for heat capacity. Films were scraped or peeled from glass plates and 2-6 mg of each sample was sealed in an aluminum pan with pinhole. The samples were equilibrated at 35°C for 5 min, which was then followed by heating from 35°C to 200°C at the heating rate of 3°C/min and the modulation rate of 1°C/min. During DSC studies, certain samples were also heated at a rate of 10°C/min instead of 3°C/min and similar results were obtained, which confirmed that heating rate did not significantly affect any solublization of crystalline drug in polymer during the DSC run. The results were analyzed using Universal Analysis software version 2000 (TA Instruments) and reversing heat flow data from the modulated DSC were used to obtain the glass transition or melting temperature of the materials. The presence of a drug melting endotherm was considered to be an indication of the presence of crystalline drug.

Polarized Light Microscopy Analysis

Films adhered to glass plates were directly observed at 10 X magnification under the polarized light microscope (Eclipse 50i; Nikon Inc., Tokyo, Japan). The presence of birefringence, which is a characteristic property of crystalline substances to refract light from a polarized light source, was considered as an indication of crystallization from films. In some cases, polarized light microscopy (PLM) studies were also performed for films scraped from the glass plates, which in most cases were broken into small pieces.

Physical Stability Testing

Intact films adhering to glass plates were stored under controlled environmental conditions in desiccators at 40°C/75% RH. The humidity in desiccators was maintained by using a saturated solution of NaCl. The relative humidity and temperature were 40 ± 2°C and 75 ± 5% RH and were monitored continuously by using a hygrometer (Daigger Scientific, Vernon Hills, Illinois) for 4 weeks of testing. Samples were analyzed using modulated DSC and PLM as described in the earlier sections to detect any drug crystallization.

HME Study

The HME experiments were conducted using the Process 11 twin screw extruder (Thermo Scientific, Waltham, Massachusetts). Uniform mixtures of ITZ and polymer were added to the melt extruder at a feeding rate of 1 g/min through a hopper and were extruded at a screw speed of 300 rpm. Mixtures with Kollidon® VA 64 were extruded at 150°C and that with Soluplus® was extruded at both 150°C and 170°C. Samples with HPMCP were very stiff and not suitable for melt extrusion.

RESULTS AND DISCUSSION

Films of uniform thickness were obtained following solvent evaporation. The appearance and consistency of the dried films varied from transparent and plastic-like for drug–polymer miscibility to white opaque for phase separation. Preliminary studies were conducted to identify optimal gap setting for film casting. The film applicator used in this study had four different gap settings of 50, 100, 150, and 200 μm. It was observed that the films obtained by using gap settings of 150 μm and lower resulted in thin and uneven films on glass plates. To cast even and uniform films for all different concentrations of drug and polymer mixtures used, it was necessary to use the 200 μm gap setting. The thickness of the film decreased further when the films dried, which depended on the solid content of the solutions used, and, therefore, the effective thickness of the dried films could be much less than 200 μm. Gap settings higher than 200 μm were not explored as Kolter et al.[32] observed that higher film thickness resulted in slow and sometimes incomplete drying that may result in drug recrystallization.

Characterization of Films

Powder XRD

The films were scraped from glass plates to study their powder XRD patterns. It was observed for certain drug–polymer mixtures that even when the films were translucent and indicated phase separation, they were devoid of characteristic XRD peaks for any crystalline drug (results not shown). It could be possible that the drug phase separated in the amorphous form or the concentration of any crystalline drug present was below the detection limit. On the basis of these results, it was concluded that powder XRD method might not be sensitive enough to detect low levels of drug crystallization and, therefore, it was not considered to be a primary analytical method to characterize films (Suppl. Material Fig. 1).

PLM Studies

During PLM studies, the presence of birefringence was considered to be an indication of drug crystallization from polymeric matrices. The drug–polymer miscibility was established by determining the ratio of drug to polymer above which birefringence was observed in the sample. The polarized microscopic images of the films of different drug–polymer mixtures recorded within 24 h of film casting and after exposure to 40°C/75% RH for 1 month are shown in Figure 2. In Figure 2-I, the image a gives the PLM image of the neat polymeric film of Eudragit® E PO indicating that no crystalline drug was present, whereas images b and c give the PLM images of films with 1:9 and 2:8 (w/w) drug–polymer mixtures. Birefringence because of the presence of crystalline drugs was observed for both ratios (Figs. 2-Ib and 2-Ic), indicating that the miscibility of ITZ with Eudragit® E PO is less than 1:9 (w/w). The results were in agreement with the literature value that indicated that the theoretical miscibility of ITZ in Eudragit® E 100 was below 7%, that is, less than 1:9 (w/w).[33] As the presence of the crystalline drug was observed in fresh samples, the ITZ–Eudragit® E PO mixtures corresponding to Figures 2-Ib and 2-Ic after storage at 40°C/75% RH for 1 month are not shown as they were similar.

Figure 2-II shows the microscopic images of the pyrrolidone-based copolymer, Kollidon® VA 64, films at 0:1, 2:8, and 3:7 (w/w) drug to polymer ratios (images a, b, and c for freshly prepared films, and images d, e, and f for films after exposure to 40°C/75% RH for 1 month). Birefringence was observed for 3:7 (w/w) drug to polymer ratio after exposure to 40°C/75% RH for 1 month (Fig. 2-IIf). From these results, it was concluded that ITZ was miscible with Kollidon® VA 64 up to 2:8 (w/w) drug to polymer ratio. As mentioned earlier, the powder XRD could not detect the presence of ITZ in any of the films prepared with Eudragit® E PO and Kollidon® VA 64. Thus, this result shows that PLM proved to be much more sensitive than the powder XRD in studying drug–polymer miscibility. It should, however, be mentioned here that the results represent drug–polymer miscibility at 40°C/75% RH upon storage for 1 month, which is a relatively harsh condition considering that both the amorphous drug and the polymer would adsorb considerable amounts of moisture at the high humidity of 75% RH, the molecular mobility of the drug 40°C would be higher than that at room temperature, and 1 month of storage is a relatively long time for the nucleation of drug under such a condition. As mentioned earlier, Kolter et al.[32] used 23°C/54% RH for 7 days for the storage of drug–polymer films. Therefore,

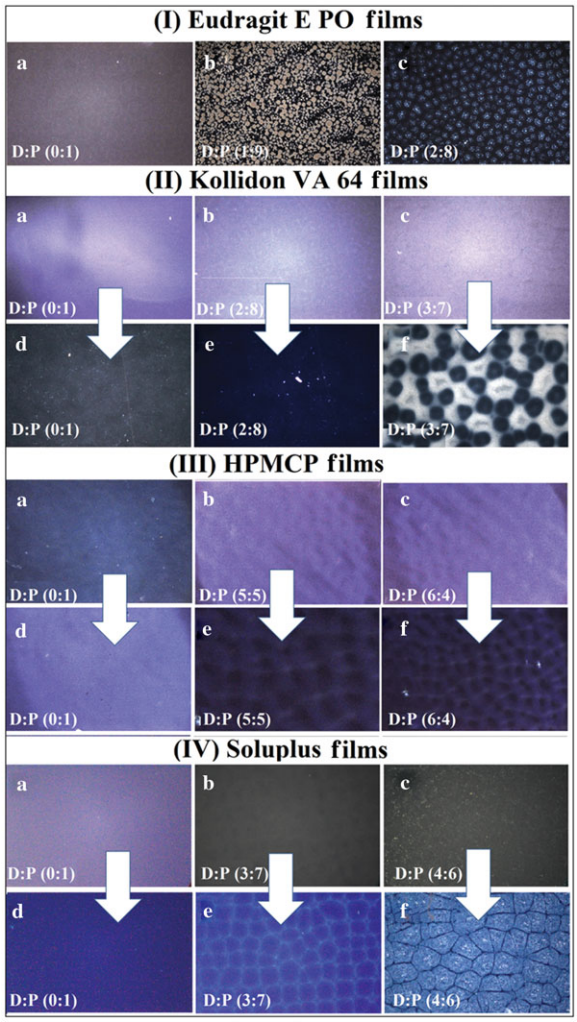

Figure 2. Polarized light microscopic images (10x) of the films of (I) Eudragit® E PO, (II) Kollidon® VA 64, (III) HPMCP, and (IV) Soluplus® without and with drug present, where a, b, and c represent fresh films, and d, e, and f represent films after their exposure to 40°C/75% RH for 1 month. Drug to polymer ratios (D:P) are given as w/w. Illumination and brightness of the images differed as they were recorded at different times and they also depended on how the lenses were crossed to observe birefringence. The primary focus was on the detection of any crystals formed.

if desired, alternative conditions may be used for the storage of films during the drug–polymer miscibility screening. We believe that the storage of the thin films at 40°C/75% RH for 1 month would provide a conservative estimate of the physical stability of solid dispersion prepared. If no crystallization of drug is observed under such a condition, the solid dispersion dosage forms would be physically stable during their shelf lives as they are generally packaged under protective conditions and stored at lower temperature and humidity conditions.

The cellulose-based polymer, HPMCP, had the highest miscibility with ITZ. The microscopic images of the films for neat polymer and of 5:5 and 6:4 (w/w) drug to polymer mixtures are shown in Figure 2-III. Drug to polymer ratios of 6:4 (w/w) and lower did not exhibit birefringence after exposure to 40°C/75% RH for 1 month (Figs. 2-IIIe and 2-IIIf), indicating drug–polymer miscibility. The crystallization of drug was

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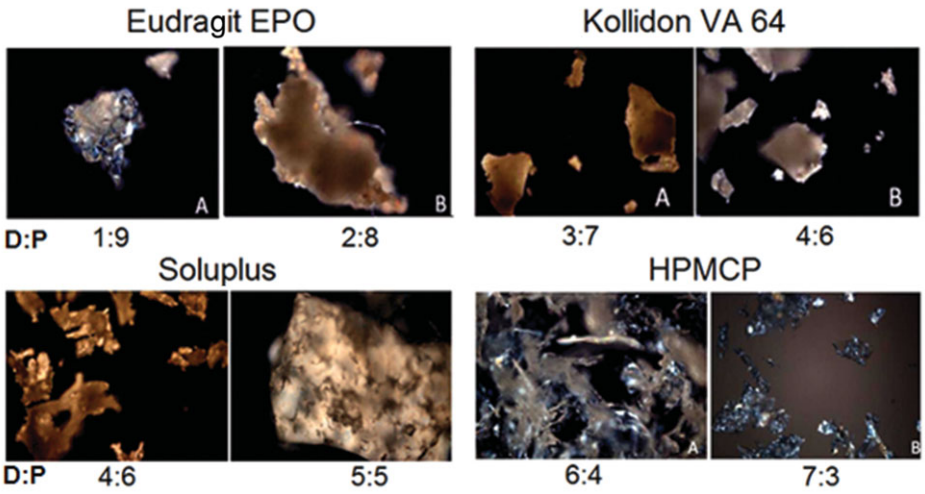

Figure 3. Polarized light microscopic images (10×) of ITZ–polymer films scrapped from the glass surface. Images of various drug to polymer (D:P, w/w) ratios are shown.

detected at 7:3 (w/w) and higher drug–polymer ratios (images not shown).

As shown in Figure 2-IV, ITZ was miscible with Soluplus® up to 5:5 (w/w) ratio in the freshly prepared films. After exposure to 40°C/75% RH for 1 month, the film with 3:7 (w/w) ITZ–polymer ratio showed visible cracks but no birefringence and the 4:6 (w/w) ratio displayed, in addition to visible cracks, slight birefringence, possibly because of the presence of microcrystalline drug. It was, therefore, concluded that the systems had reached equilibrium at the 3:7 (w/w) drug–polymer ratio and there is a potential for the crystallization of ITZ at a higher ratio (Suppl. Material Figs. 2 and 3). In a separate set of experiments, films were scraped from the glass plate, ground into small pieces, and then stored in open glass bottles at 40°C/75% RH for 1 month to facilitate rapid equilibrium and the results were in agreement with those obtained with intact films on glass plates. Thus, there is no difference in stability whether the film or the ground powder of solid dispersion is used for testing.

It was observed in the present investigation that it is easier to visualize crystals formed during the PLM study if intact films are used rather than the ground drug–polymer film or solid dispersion. Figure 3 shows the PLM images of several samples prepared by scraping films from glass slides, ground lightly, and then visualized under the microscope for birefringence. Although birefringence because of the presence of crystalline drug could be observed, the results might not be able to distinguish small differences in crystallization. It was also observed during the PLM analysis that broken films and the ground extrudates refract lights at the edges that could appear birefringent and thus may provide a wrong impression of the presence of crystals. For example, the ground melt extrudate of Soluplus® prepared without any drug showed some light refraction under the polarized light microscope that could falsely be interpreted as birefringence. Thus, for the development of a reproducible method devoid of inherent measuring errors, the PLM results of intact films were considered to be more reliable as compared with those of powdered or broken fragments of films. It is, therefore, recommended that intact films should be used for PLM studies during preformulation testing of drug–polymer miscibility.

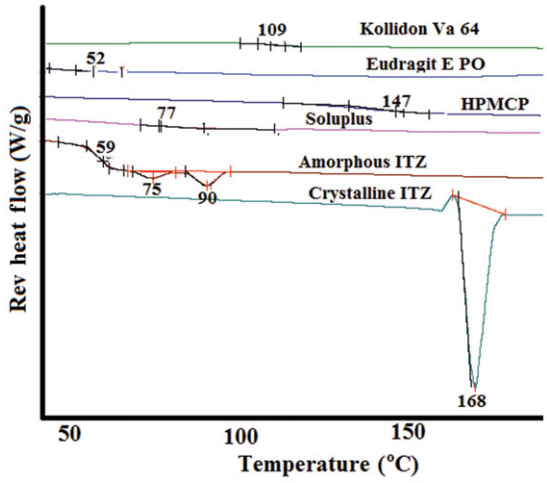

Figure 4. Differential scanning calorimetry scans of different polymers, amorphous ITZ, and crystalline ITZ. From top to bottom: Kollidon® VA 64 (T_g 109°C), Eudragit® E PO (T_g 52°C), HPMCP (T_g 147°C), Soluplus® (T_g 77°C), amorphous ITZ (T_g 59°C, along with minor endotherms at 75°C and 90°C that are attributed to the formation of mesophases), and crystalline ITZ (T_m = 168°C).

DSC Studies

The DSC scans of neat Eudragit® E PO, Kollidon® VA 64, HPMCP, and Soluplus®, without the presence of any drug, are shown in Figure 4. In agreement with earlier reports,[10–12] the polymers were amorphous and their T_g values corresponded approximately to those reported earlier. DSC scans of amorphous and crystalline ITZ are also shown in Figure 4. As expected, the amorphous ITZ did not have the peak at 168°C that was observed for the crystalline ITZ. Separately, the PLM and powder XRD studies also confirmed that the material was amorphous. However, in addition to the T_g at 59°C, the DSC scan of amorphous ITZ demonstrated endothermic peaks at 75°C and 90°C. Similar endothermic transformations for amorphous or glassy ITZ at 74°C and 90°C were reported earlier in the literature by Six et al.,[38] which they attributed to the formation of

mesophases and not to any crystallization of drug. The effect of the presence of such mesophases is reflected in the DSC scans of ITZ–polymer films conducted in the present investigation, as shown later in Figure 5.

Results of DSC analysis for the scraped or peeled films of drug–polymer mixtures exposed to 40°C/75% RH for 1 month are shown in Figure 5. The DSC scans of the films prior to their exposure to high temperature and humidity are not shown as they were either similar to those in Figure 5 or, in some cases, did not show any endotherm because of the crystallization of ITZ, whereas the samples exposed to 40°C/75% RH did. As shown in Figure 5a, the 1:9 (w/w) ITZ–Eudragit® E PO mixture was devoid of any endothermic event for the melting of crystalline drug and hence indicated drug–polymer miscibility. The sample displayed a T_g at 44°C, which corresponded to that of the polymer. ITZ was not miscible at higher ratios (2:8 and 4:6, w/w), as apparent from endothermic peaks observed between 145°C and 160°C because of the melting of crystalline drug. Although no drug endotherm was observed in the DSC scan at the 1:9 (w/w) drug–polymer ratio, as mentioned earlier the PLM study showed the presence of crystalline drug both before and after exposure to elevated temperature and humidity conditions. Thus, PLM was found to be more sensitive to determine drug–polymer miscibility than the DSC. It is possible that the crystalline drug was solubilized in the molten polymer during heating of the 1:9 (w/w) drug–polymer mixtures and, therefore, no endothermic peak was observed. As shown in Figure 5a, endothermic peaks were observed at 152°C and 160°C for 2:8 and 3:7 (w/w) mixtures, respectively, indicating drug crystallization. The melting peaks of the mixtures were, however, below the melting temperature of the pure crystalline drug (167°C), which is possibly because of the presence of polymer in the mixture that resulted in the depression drug melting point.

The DSC analysis of films with Kollidon® VA 64 (Fig. 5b) showed a single T_g for mixtures with 3:7 (w/w) and lower drug load after exposure to 40°C/75% RH for 1 month. During PLM analysis, the 3:7 (w/w) sample showed some phase separation and possibly slight birefringence in the film after exposure to 40°C/75% RH for 1 month (Fig. 2-II), which were not apparent in the DSC scan. As explained above in case of Eudragit® E PO, it is possible that the crystallized drug either dissolved in the polymer during heating by the DSC or the concentration of crystallized drug was below the detection limit of the DSC. In either scenario, the result again confirms that PLM was a more effective method as compared with DSC. Films with 4:6 (w/w) ratio of ITZ and Kollidon® VA 64 displayed T_g values at 55°C and 105°C corresponding to the drug and the polymer. As discussed earlier, other characteristic features, such as the endothermic transition of amorphous drug at 90°C because of the formation of mesophase, was also observed at 4:6 and 5:5 (w/w) ITZ–Kollidon® VA 64 ratios. Additionally, an endotherm at 162°C was observed for 4:6 (w/w) ratio because of the melting of drug. Similar results were also obtained for the 5:5 (w/w) ratio of drug to polymer, where the melting peak for ITZ was more prominent. On the basis of the DSC analysis, it was concluded that ITZ was immiscible with Kollidon® VA 64 at 4:6 (w/w) and higher drug load.

Figure 5c shows that the ITZ was miscible with HPMCP at 4:6, 5:5, and 6:4 (w/w) ratios, as indicated by single T_g values of 101°, 91°, and 87°C, respectively, which fell in between the T_g

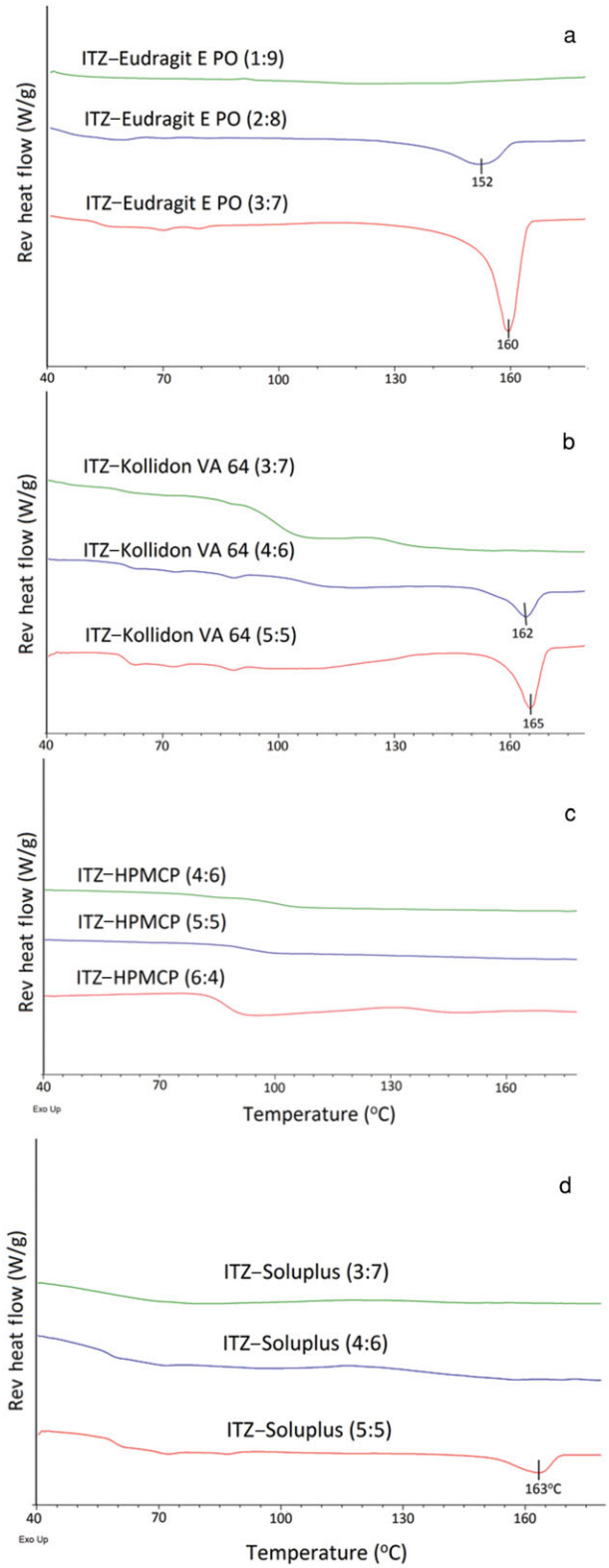

Figure 5. Differential scanning calorimetry scans of the films of (a) ITZ–Eudragit® E PO, (b) ITZ–Kollidon® VA 64, (c) ITZ–HPMCP, and (d) ITZ–Soluplus® mixtures after exposure to 40°C/75% RH for 1 month. Drug to polymer ratios are shown in parentheses, which were 1:9, 2:8, and 3:7 (w/w) for Eudragit® E PO, 3:7, 4:6, and 5:5 (w/w) for Kollidon® VA 64, 4:6, 5:5, and 6:4 (w/w) for HPMCP, and 3:7, 4:6, and 5:5 (w/w) for Soluplus®.

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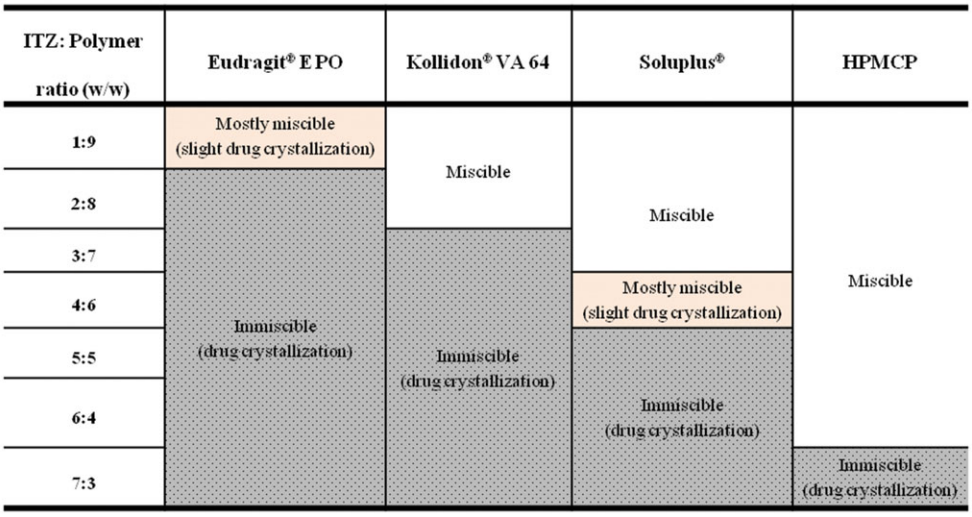

Figure 6. Relative miscibility of itraconazole with different polymers as observed by polarized light microscopy after exposure of casted films to 40°C/75% RH for 1 month.

values of the amorphous drug (59°C) and the polymer (143°C). Films at 7:3 (w/w) and above drug load indicated immiscibility between the drug and the polymer as the drug peak was observed (data not shown). On the basis of above observations, it was concluded that ITZ and HPMCP would be highly miscible (up to 6:4, w/w) at room temperature for an extended period of time.

Soluplus® with T_g of 72°C was the last polymer studied. It was found that samples with 4:6 (w/w) and lower drug load were devoid of any drug endotherm and displayed miscibility with polymer after exposure to 40°C/75% RH for 1 month (Fig. 5d). An increased drug load resulted in drug crystallization, characterized by the endothermic peak at 163°C for the 5:5 (w/w) mixture. However, according to PLM studies, birefringence was observed in the 4:6 (w/w) mixture, indicating partial crystallization of drug (Fig. 2-IV). When the PLM image was observed with an expanded scale, it was clearly observed that only microcrystals of the drug were formed at the 4:6 (w/w) ratio (Suppl. Material Figs. 2 and 3). The discrepancy between PLM and DSC results could be because of the presence of low amount of crystallized drug that possibly dissolved in the molten polymer during the DSC analysis and hence the melting endotherm was absent. On the basis of DSC and PLM studies, it was concluded that ITZ was miscible with Soluplus® up to 3:7 (w/w) ratio and the 4:6 (w/w) ratio may still be acceptable because of very low level of drug crystallization.

Comparison of Analytical Methods

The differences in results obtained from PLM, modulated DSC, and powder XRD analyses indicate that the latter two techniques were not as sensitive to detect a low level of crystalline drug as the PLM analysis. As PLM utilizes the principle of birefringence, it provides detectable results at very low drug concentrations from films of uniform thickness. It is, therefore, suggested that the PLM be used to detect any drug crystallization, with the DSC being the close second. Although the DSC may miss some drug crystallization as the drug may resolubilize in the polymer during heating, it still provides a good indication of the miscibility of drug with the polymer.

Miscibility of Different Polymers with ITZ

A summary of film-casting experiments based on the visual observation, PLM analysis, and the modulated DSC analysis of films is presented in Figure 6. The ITZ–polymer miscibility was found in the following order: HPMCP > Soluplus® > Kollidon® VA 64 > Eudragit® E PO. It should be noted here that this rank order represents polymers after their exposure to the high humidity of 75% RH at 40°C, and, therefore, the polymers contain certain amounts of water depending on their hygroscopicity. The amount of water adsorbed at 40°C/75% RH was not quantitated in the present study. The physical stability results obtained are, however, very relevant to the development of stable dosage forms of solid dispersions as the products are expected to be exposed to humidity and high temperatures during their shelf lives.

It was of interest to know how the experimental data generated in the present investigation compare with the theoretical prediction based on solubility parameters. Soluplus®, which had similar δ value (δ = 19.4) to Eudragit® E PO (δ = 19.6), showed much better miscibility with ITZ (δ = 26.5) than Eudragit® E PO. It had even higher miscibility than Kollidon® VA 64 (δ = 21.2), which has a closer δ value to ITZ.[32,39,40] The observed discrepancy highlights the drawback of theoretical models that, as mentioned earlier, do not consider weak interactions between drugs such as ITZ with graft polymers such as Soluplus®.[32] As reported by Marsac et al.,[41] the experimental solubility of a drug in a polymer, that is, miscibility with each other, may be much different from values predicted theoretically based on solubility parameters. This is because polar drugs and polymers may have chemical interactions, such as adhesive and cohesive bonding, which may lead to a deviation from the predicted difference in solubility parameters.[21] Another limitation of the theoretical methods is that they often show only the rank order of miscibility and do not indicate the extent of miscibility. A practical method such as the one presented in this report provides the extent of miscibility, which is very important for the development of drug products.

Melt Extrusion Study

In recent years, HME has extensively been used in the preparation of solid dispersions of drugs.[35–37] The technology was applied in the present investigation to verify the applicability of the film-casting method as a screening tool to predict drug–polymer miscibility in solid dispersion. Preliminary melt extrusion studies showed that mixtures of ITZ with Soluplus® and Kollidon® VA 64 could be extruded at 150°C, which is 18°C below the melting point of ITZ (168°C). However, some of the extrudates of ITZ–Soluplus® mixtures at 150°C appeared slightly hazy, possibly because of nonuniform mixing at the screw configuration used for melt extrusion. For this reason, the ITZ–Soluplus® mixtures were also extruded at 170°C. Strands of ITZ–Soluplus® melt extrudates were approximately 2-4 mm in diameter. As the thickness of the strands were much higher than the 0.2 mm films produced by film casting, it hindered the PLM measurement and, therefore, only the DSC results were used to assess drug–polymer miscibility in melt extrudates. The drug–polymer ratios for melt extrusion were selected based on the DSC results of film casting experiments in which 4:6 (w/w) ratio was found to be miscible with Soluplus®, whereas 5:5 (w/w) and higher drug load remained immiscible (Fig. 5d). Thus, ITZ–Soluplus® ratios of 4:6 and 5:5 (w/w) were selected for comparing the physical stability of melt extrudates.

As shown in Figures 7c and 7g, clear extrudates were obtained at both ITZ–Soluplus® ratios of 4:6 (w/w) and 5:5 (w/w) at 170°C, indicating drug–polymer miscibility in fresh samples. Storage of samples at 40°C/75% RH for 1 month resulted in phase separation of sample at the 5:5 (w/w) drug load, as observed by the conversion of clear extrudates into opaque mass (Fig. 7h), whereas at the lower drug load of 4:6 (w/w), no visible phase separation was observed (Fig. 7d). The results were further confirmed by performing DSC on stress-tested extrudates. As shown by the DSC scans in Figure 8, extrudates with

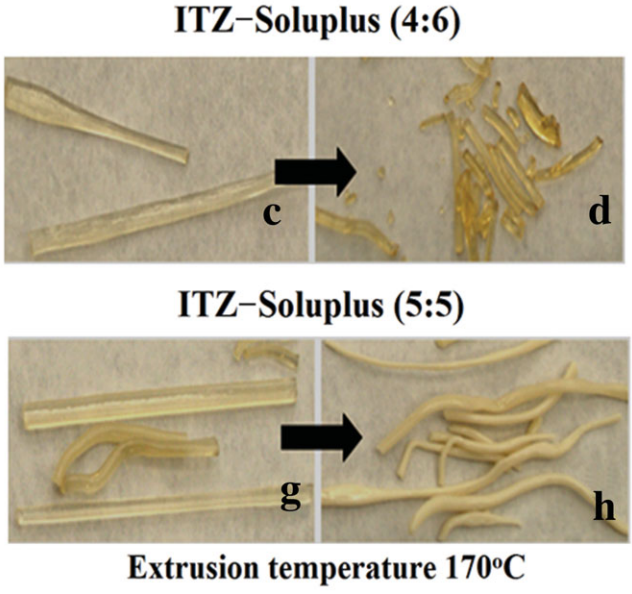

Figure 7. Images of melt-e xtruded strands of ITZ–Soluplus® mixtures at 4:6 and 5:5 (w/w) ratios, where c and g are for fresh extrudates, and d and h are for extrudates exposed to 40°C/75% RH for 1 month. HME was conducted at 170°C.

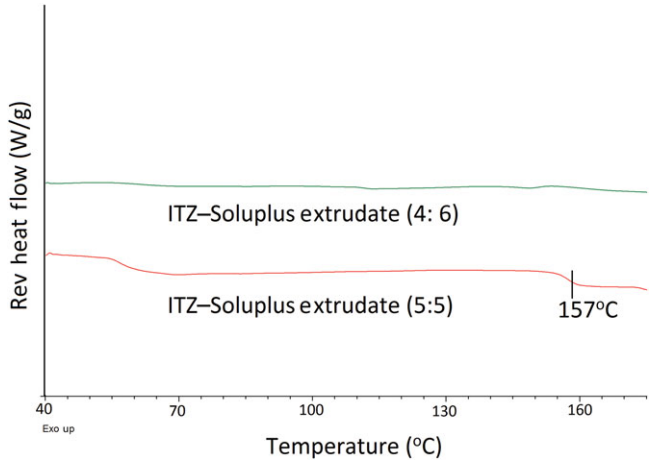

Figure 8. Differential scanning calorimetry scans of ITZ–Soluplus® extrudates at 4:6 and 5:5 (w/w) ratios after exposure to 40°C/75% RH for 1 month. Extrudate with the 5:5 (w/w) ratio displayed melting endoderm at 157°C, which was followed by degradation.

the 4:6 (w/w) drug to polymer ratio remained miscible after exposure to accelerated conditions for 1 month, whereas extrudates with the ratio of 5:5 (w/w) showed phase separation, as indicated by the presence of endotherm with onset at 157°C. The T_g of ITZ–Soluplus extrudates for 4:6 and 5:5 (w/w) was observed to be between 60°C and 65°C. These results are in agreement with the DSC analysis of ITZ–Soluplus® films presented in Figure 5d. As noted earlier, the PLM analysis of films, however, showed some birefringence at the 4:6 (w/w) ratio because of the presence of microcrystalline drug. Thus, the PLM analysis of 3:7 (w/w) ITZ–Soluplus® mixture provided a conservative indication of the drug–polymer miscibility. If no phase separation in the film was observed by PLM, it could reasonably be assured that there would be no phase separation upon long-term storage of solid dispersions. As discussed earlier, it could also be possible that the formulation at the 4:6 (w/w) ratio may also have acceptable physical stability. As mentioned earlier, the ITZ–Soluplus® mixture was also extruded at 150°C. As shown in Figures 4 and 5 of the Supplementary Material, the physical stability results are similar whether the extrusion was conducted at 150°C or 170°C.

Melt extrusion of the ITZ–Kollidon® VA 64 (2:8, w/w) mixture resulted in transparent extrudates, which when analyzed using DSC were devoid of drug melting endotherm. It was found that an exposure to accelerated conditions resulted in phase separation as observed by discoloration of the extrudates (from transparent to pale white extrudates). DSC analysis of the extrudates exposed to 40°C/75% RH for 1 month (Fig. 9) showed that the phase separation could be because of the conversion of drug–polymer mixtures into two separate amorphous phases of drug and polymer as apparent by two T_g values at 61°C and 107°C corresponding to ITZ and Kollidon® VA 64, respectively. Drug crystallization was not observed in the melt extrudates during the experimental time period. This result also correlates with film-casting experiments in which ITZ–Kollidon® VA 64 films (2:8, w/w) displayed visible phase separation (Fig. 2II) but no crystallization of drug, as indicated by the lack of any melting endotherm even after exposure to accelerated stability testing conditions (Fig. 5b).

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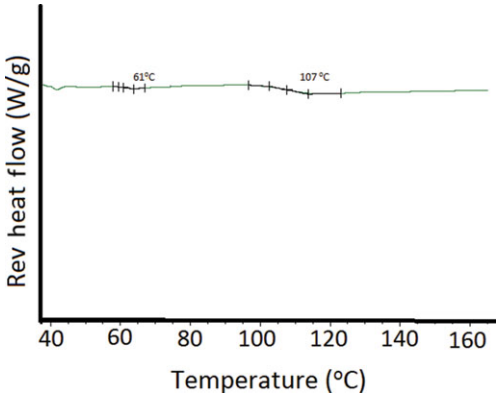

Figure 9. Differential scanning calorimetry scan of ITZ–Kollidon® VA 64 (2:8, w/w) extrudate after exposure to 40°C/75% RH for 1 month, indicating amorphous phase separation as displayed by two T_g values at 61°C and 107°C for, respectively, amorphous ITZ and Kollidon VA 64.

Hydroxypropylmethylcellulose phthalate was an extremely stiff polymer and did not undergo solid to molten state transition at the processing temperature. Melt extrusion for the ITZ-HPMCP mixture (6:4, w/w) at 170°C resulted in nonuniform extrudates with molten drug and stiff solid polymer mixed unevenly in the matrix, and extrusions above 170°C resulted in discoloration of the product. For these reasons, the extrudates were not studied for their physical stability. It might, however, be possible that the mixture of drug with HPMCP could be extruded by adding a plasticizer to the mixture. No such study was, however, conducted as the present film-casting experiments did not include a plasticizer.

This report presents a film-casting method that can serve as a predictive tool to assess drug–polymer miscibility and, therefore, physical stability of solid dispersions. As the films were very thin (<200 μm) and uniform, the film casting created a physical configuration that quickly approached equilibrium conditions and thus it provided an insight into the long-term physical stability. The maximum amount of drug that can be present in a solid dispersion with a particular polymer can be easily determined by using this method. In this way, suitable polymers or different mixtures of polymers may be identified for solid dispersions. The effect of the addition of any plasticizer or surfactant in the solid dispersion may also be ascertained by incorporating such components in solid dispersions.

CONCLUSIONS

The film-casting method described in this report provides practical estimation of the miscible drug concentration in a drug–polymer matrix within a relatively short period of time (<4 weeks). Looking at it in another way, the method can determine when the drug and the polymer are not miscible. Furthermore, the results obtained can be correlated with the physical stability of solid dispersions, especially those prepared by melt extrusion. Among various techniques used to visualize the presence of crystalline drug in the film, the PLM was found to be most sensitive, followed by DSC as the close second.

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