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Research Article

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Investigation of Polymer-Surfactant and Polymer-Drug-Surfactant Miscibility for Solid Dispersion

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Abstract. In a solid dispersion (SD), the drug is generally dispersed either molecularly or in the amorphous state in polymeric carriers, and the addition of a surfactant is often important to ensure drug release from such a system. The objective of this investigation was to screen systematically polymer-surfactant and polymer-drug-surfactant miscibility by using the film casting method. Miscibility of the crystalline solid surfactant, poloxamer 188, with two commonly used amorphous polymeric carriers, Soluplus® and HPMCAS, was first studied. Then, polymer-drug-surfactant miscibility was determined using itraconazole as the model drug, and ternary phase diagrams were constructed. The casted films were examined by DSC, PXRD and polarized light microscopy for any crystallization or phase separation of surfactant, drug or both in freshly prepared films and after exposure to 40°C/75% RH for 7, 14, and 30 days. The miscibility of poloxamer 188 with Soluplus® was <10% *w*/*w*, while its miscibility with HPMCAS was at least 30% *w*/*w*. Although itraconazole by itself was miscible with Soluplus® up to 40% *w*/*w*, the presence of poloxamer drastically reduced its miscibility to <10%. In contrast, poloxamer 188 had minimal impact on HPMCAS-itraconazole miscibility. For example, the phase diagram showed amorphous miscibility of HPMCAS, itraconazole, and poloxamer 188 at 54, 23, and 23% *w*/*w*, respectively, even after exposure to 40°C/75% RH for 1 month. Thus, a relatively simple and practical method of screening miscibility of different components and ultimately physical stability of SD is provided. The results also identify the HPMCAS-poloxamer 188 mixture as an optimal surface-active carrier system for SD.

KEY WORDS: film casting; HPMCAS; itraconazole; poloxamer 188; polymer-drug-surfactant miscibility; polymer-surfactant miscibility; solid dispersion; Soluplus®.

INTRODUCTION

Low aqueous solubility is one of the most difficult issues facing the development of new chemical entities (NCE) into orally bioavailable drug products (1). Among various strategies to resolve the issue, solid dispersion (SD) has been investigated for over half a century to enhance dissolution rate and improve bioavailability of poorly water-soluble drugs (2–5). Although the drug may exist in SD in the crystalline form, as eutectic mixtures with the carrier or as microfine particles dispersed in the carrier matrix (2, 5), the focus of research in recent years has been on amorphous solid dispersion (ASD), where the drug is dispersed in the amorphous state in polymeric carriers that are also amorphous. Recently, Baghel *et al.* (6) has further defined ASD into three categories: (a) solid solution, where the solute (drug) replaces a solvent molecule, (b) interstitial solid solution, where the solute molecule is present in the interstices, and (c) amorphous solid solution, where the solute is randomly distributed in amorphous

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Abbreviations: ASD, amorphous solid dispersions; DSC, differential scanning calorimetry; HPMCAS, hydroxypropylmethylcellulose acetate succinate;ITZ, itraconazole; PEO, polyethylene oxide; PLM, polarized light microscopy; PVP, polyvinyl pyrrolidone; PXRD, powder X-ray diffraction; SLS, sodium lauryl sulfate; SD, solid dispersion; Soluplus®, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; Tg, glass transition temperature; TPGS, D-α-tocopherol polyethylene glycol 1000 succinate

carriers. Depending on the drug load, the drug may exist in any or all of these three states. It is usually desirable that the drug exists as solid solution. Otherwise, there is the potential that it may phase separate and ultimately crystallize out upon storage.

Despite early promises and much research in the field, various challenges related to processing, physical stability and drug release impeded widespread application of the SD technology in drug product development (3). To be successful, a SD formulation (i) should be processable, i.e., it can be easily developed into drug products and does not require complex manufacturing methods, (ii) it must be physically stable, i.e., it exhibits drug-carrier miscibility and the drug does not crystallize out or phase separate from the carrier, and (iii) it should be able to release drug either in a solution or as an aqueous dispersion once it comes in contact with aqueous media of the gastrointestinal tract (5). In recent years, there has been considerable progress with respect to all these factors responsible for the successful development of solid dispersion. The introduction of the melt extrusion technology for the manufacture of SD during the past 10 to 15 years has greatly simplified the processing issues and increased the interest in a SD formulation as a viable dosage form development option (7, 8). In particular, the need for large volumes of organic solvents to dissolve both the water-insoluble drug and the water-soluble polymer in a common medium for the preparation of SDs by other common techniques, such as spray drying, and solvent evaporation (9), can be avoided by applying melt extrusion. There have also been considerable studies on drug-polymer miscibility in SD (10–13). Parikh *et al.* (14) has recently published a relatively simple and practical film-casting method that was able to predict drug-polymer miscibility and the absence of drug crystallization in SD. Physically stable drug-carrier mixtures for SD and melt extrudate may be identified by using the method. Incomplete release of poorly water-soluble drugs from a formulation was another difficult issue hindering the development of SD (3). During dissolution, the drug may phase separate from SD in the metastable liquid form (15), which may coat the surface of the dissolving solid and, being poorly water-soluble, limit further dissolution of drug from SDs. Serajuddin (3, 16) showed that the incorporation of surfactant may be necessary in a SD formulation to ensure dispersion of such a liquid phase of drug in dissolution media as very fine globules so that the drug release may continue. Numerous other reports have exhibited improvement in dissolution of SD by incorporating surfactants or the lack of complete dissolution due to absence of surfactants (17–20). Moreover, surfactants have been reported to induce drug supersaturation which has helped to enhance intestinal absorption and thus improve bioavailability (21). Mitra *et al.* (22) reported dipyridamole supersaturation ratios of up to 11-fold with poloxamer 188, while Gao *et al.* (23) showed the importance of Tween® 80 along with polymeric precipitation inhibitors in drug solubilization and degree of supersaturation. For these purposes, surfactants could either be used by themselves as SD carriers (24) or be admixed with other carriers (25).

The SD formulations containing high levels of surfactants developed prior to the recent introduction of the melt extrusion process were mostly semisolid in nature that were usually filled in hard gelatin capsules (26). They were not amenable for development into tablets and dry powder-filled hard gelatin capsules, which are often preferred by the patients. In melt extrusion, mixtures of drugs and amorphous polymeric carriers are passed through twin-screw extruders at high temperature, which allows the use of solid polymers having relatively high glass transition temperatures (T_g) in SDs (27). As a result, there is no need for relatively low-melting and waxy carriers that were commonly used to dissolve drug by heating prior to the introduction of this technology in the pharmaceutical field. The melt extrudates may be easily pulverized and converted into tablets or powder-filled hard gelatin capsules. In recent years, there has been much research in the identification of suitable polymers and the physicochemical characterization of such polymers for the preparation of SD by melt extrusion (28–32). There are also several reports on the use of plasticizers to reduce melt viscosity of certain polymers having rigid structures or very high T_g values and facilitate their extrusion at relatively lower temperatures that would not degrade the polymer or drug during melt extrusion (17, 33–35). However, despite the critical importance of surfactants to ensure drug release from SDs with poor inherent dispersibility (3), there are only very limited studies reported in the literature on the use of surfactants in the development of SDs by melt extrusion. Ghembremeskel *et al.* (17) used up to 10% liquid and semisolid surfactants, such as polysorbate 80 and sodium dioctylsulfosuccinate, as plasticizers during melt extrusion. Granules produced from the extrudates were then mixed extragranularly with crystalline solid surfactants, namely, sodium lauryl sulfate (SLS), poloxamer 188 and Myrj 52, before filling them into hard gelatin capsules. Since the melt extrudates contained only liquid or semisolid surfactants, it is not known up to what concentration of a liquid surfactant may be added without impairing the processability of extrudates and what impacts they may have on the processing of extrudates into tablets. Lakshman *et al.* (36) also added a solid surfactant, poloxamer 188, extragranularly with melt extrudates. It was reported earlier that surfactants must be intimately mixed with solid dispersions for their effect on drug release (16, 25, 37). Since the solid surfactants in both of the above-mentioned studies with melt extrusion (17, 36) were added extragranularly, it is also not known what would be the effect if the solid surfactants were intimately mixed with the drug and the polymer within the extrudates instead of being added extragranularly. In one study where drug, polymer, and surfactant were intimately mixed during melt extrusion, Lang *et al.* (19) observed faster release and supersaturation of the drug, itraconazole (ITZ), in aqueous media from solid dispersions in polymeric carriers (HPMCAS and PEO) containing poloxamer 407 and Cremophor RH40. There was, however, a limit how much Cremophor RH40 could be incorporated in the formulation as, being a liquid, it could negatively impact the rigidity of the solid extrudates. For this reason, the authors favored the use of solid or semisolid surfactant like a poloxamer.

For melt extrusion of drug formulations, Fule *et al.* (38, 39) incorporated PEG 400, poloxamer 188 (Lutrol® F68) and

poloxamer 407 as plasticizing agents with the polymer Soluplus®. In addition to serving as plasticizers, poloxamer 188 and poloxamer 407 had surface activity. However, relatively low levels of surfactants were used in these studies, having a concentration of 0.6% *w*/*w* in one study (38) and 5 to 10% in the other (39). The drugs used appeared to be miscible with the polymer and the low levels of surfactants used. It is not known what would be the miscibility among polymer, drug and surfactant or whether there would be physical stability issues in formulations if surfactant concentrations >10% were necessary to ensure drug release. There are several reports in the literature indicating that surfactants may negatively impact physical stability of drugs in solid dispersions. Mosquera-Giraldo *et al.* (40) observed by melting a drug substance on microscope glass slides that the presence of surfactants, such as SLS, D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), and sucrose palmitate, had detrimental effect on the physical stability of amorphous celecoxib as they increased crystal growth. The addition of a polymer, polyvinylpyrrolidone (PVP), to the system helped to mitigate the increase in crystal growth. However, the authors observed that the drug-polymer-surfactant ternary systems were highly complex, and they cautioned that the impact of any added surfactant on the stability of amorphous forms of drugs should be carefully investigated during the development of SDs. Medarevic *et al.* (41, 42) studied the effect of poloxamer 188 on carbamazepine-Soluplus-poloxamer solid dispersions prepared by the solvent casting method. Although the surfactant increased the dissolution rate of the formulations, it had a negative impact on the physical stability of amorphous carbamazepine as the drug crystallized out upon storage. Moreover, poloxamer 188 phase separated from the solid dispersion as evident by the presence of a separate melting endotherm of the surfactant during differential scanning calorimetric (DSC) analysis. In their study with the melt extrusion of ITZ-HPMCAS-PEO-poloxamer 407 mixtures, Lang *et al.* (19) observed phase separation between HPMCAS and PEO or poloxamer 407 immediately after preparation, but there was no longer-term stability testing to determine the impact of such phase separation on the miscibility of ITZ.

In our laboratory, we have undertaken various studies on factors influencing the development of SDs by melt extrusion, including the effect of surfactants on physical stability of and drug release from melt extrudates. In the present article, we are reporting the results of systematic screening studies on polymer-surfactant and polymer-drug-surfactant miscibility by using the film casting method. First, the miscibility of the surfactant poloxamer 188 with two commonly used polymeric carriers, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) and HPMCAS (hydroxypropylmethylcellulose acetate succinate) was investigated. It was then followed by a study of the effect of poloxamer 188 on the miscibility of a model drug itraconazole (ITZ) with the two polymers.

Both Soluplus® and HPMCAS are commonly used in SDs as polymeric carriers for drugs. They belong to two different classes of polymers; while Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, HPMCAS is a semi-synthetic cellulosic polymer. In addition to structural differences, the two polymers also differ in their physical properties having T_g values of 72 and 122°C, respectively (28, 29), thus giving different rigidities to SDs produced, with potential impacts on physical stability of drugs. Indeed, because of its relatively lower T_g, Soluplus® was specifically marketed by its manufacturer for its potential use as a carrier for SD by melt extrusion (43), while HPMCAS is commonly used for solid dispersion by spray drying or other solvent evaporation methods. One more reason for using Soluplus® and HPMCAS as polymers in the present investigation is their high miscibility with the model drug ITZ. It was reported by Parikh *et al.* (14) that ITZ was miscible with Soluplus up to 40% *w*/*w* (6:4 polymer-drug ratio), and, in a separate study in our laboratory, it was observed that ITZ was miscible with HPMCAS to the extent of 50% *w*/*w* (S. Gumaste, Personal communication. Manuscript under preparation). By knowing the drug-polymer miscibility, it was convenient to study what influence a surfactant would have by constructing drug-polymer-surfactant phase diagrams. Most of the solid surfactants used in pharmaceutical dosage forms are crystalline or semi-crystalline. Poloxamer 188, a solid surfactant with the melting point around 52°C, was selected because of its previous history of use in solid dispersion (17, 36, 44, 45). It also has a good safety profile after oral administration (46).

MATERIALS AND METHODS

Materials

Itraconazole of the pharmaceutical manufacturing grade was donated by a major generic pharmaceutical company located in the USA. Soluplus® and poloxamer 188 (Kolliphor® P 188) were received as donations from BASF Corporation (Tarrytown, NY, USA). There are several grades of HPMCAS available from their manufacturers. The HPMCAS MG grade of material used in the present study was donated by Shin-Etsu Chemical Co. (SE Tylose USA, Inc., Totowa, NJ). All materials were used as received. The organic solvents used for film casting were of the HPLC grade and purchased from Sigma Aldrich Co. (St. Louis, MO, USA).

Methods

Film Casting

Polymer-surfactant and polymer-drug-surfactant miscibility studies were conducted by a film casting method described earlier by Parikh *et al.* (14). Miscibility of each of the two polymers (Soluplus® and HPMCAS) in the binary mixtures with poloxamer 188 was studied at ratios of 9:1, 8:2, 7:3, 6:4, and 5:5 *w*/*w* between them. Table I shows ratios of polymer, drug, and surfactant used for the miscibility testing in the ternary polymer-drug-surfactant mixtures. Previously, polymer-to-drug ratios of 9:1, 8:2, 7:3, 6:4, and 5:5 *w*/*w* were used to study the miscibility of Soluplus® and HPMCAS with ITZ (14). The same ratios between the polymer and ITZ were maintained in Table I and then poloxamer 188 was added to them. For example, sample 911 contains nine parts of polymer, one part of ITZ, and one part of poloxamer 188,

Table I. Sample Name, Ratio of Polymer-Drug-Surfactant, and Corresponding Percentage Content (*w*/*w*) of Mixtures Prepared for Film Casting

Sample	Parts			Content (% *w*/*w*)		
	Polymer	Drug	Surfactant	Polymer	Drug	Surfactant
911	9	1	1	82	9	9
913	9	1	3	69	8	23
915	9	1	5	60	7	33
821	8	2	1	73	18	9
823	8	2	3	62	15	23
825	8	2	5	53	13	33
731	7	3	1	64	27	9
733	7	3	3	54	23	23
735	7	3	5	47	20	33
641	6	4	1	55	36	9
643	6	4	3	46	31	23
645	6	4	5	40	27	33
551	5	5	1	45	45	9
553	5	5	3	38	38	23
555	5	5	5	33	33	33

and similarly sample 913 contains nine parts of polymer, one part of ITZ, and three parts of poloxamer 188. The percentages of each individual component in the mixtures are also given in Table I, where the polymer content in the mixtures ranged from 33 to 82% *w*/*w*, the drug content ranged from 7 to 45% *w*/*w*, and the surfactant content ranges from 9 to 33% *w*/*w*. For film casting, 1 g each of binary or ternary mixtures were dissolved in 6 mL of a common solvent (dichloromethane:methanol, 1:1 *v*/*v*) by shaking for 30 min in a tightly closed scintillation vial using a wrist action shaker. Multiple films from each solution were prepared, where, for the preparation of each film, 1 mL of the solution was poured towards the end of a glass plate and then the film was casted at the thickness of 200 μm using a film applicator (14). The films were air-dried at room temperature and humidity for 30 min and then analyzed by polarized light microscopy (PLM), differential scanning calorimetry (DSC), and powder X-ray diffraction (XRD) on the day of preparation (day 1) and after storage at 40°C/75% RH for 7, 14, and 30 days.

Polarized Light Microscopy (PLM)

Glass plates with films still attached to them were placed under Nikon eclipse 50i microscope (Nikon Inc., Tokyo, Japan), and the films were analyzed under 10× cross-polarized lens for any birefringence due to the presence of drug and/or surfactant crystals.

Differential Scanning Calorimetry (DSC)

Samples were analyzed for their thermal patterns using a Q200 DSC equipped with a refrigerated cooling accessory (TA instruments, DE, USA). Approximately 5 mg of a sample was sealed in an aluminum pan (Tzero standard pans and lids with pinhole; TA instruments) and equilibrated at 5°C for 1 min. The sample was then heated to 200°C at the ramp rate of 5°C/min and the modulation of 1°C every min. The results were analyzed using Universal Analysis software version 2000 (TA Instruments), where reversing heat flow data from the modulated DSC were used to obtain the glass transition or melting temperature of the materials. Most of the casted films were tested only once prior to data analysis. Replicate samples were tested only when small amounts of phase separation was observed, in order to verify the obtained data.

Powder X-ray Diffraction (PXRD)

A powder X-ray diffractometer, XRD 6000 (Shimadzu, Japan), was used to obtain powder XRD patterns, using a monochromatic CuKa radiation source operated at 40 kV and 30 mA and the scanning rate of 2°θ/min over the range of 10–60° 2θ. Results were analyzed for the presence of characteristic crystalline peaks of surfactant, drug or both in the films.

RESULTS

Polymer-Surfactant Miscibility

Soluplus-Poloxamer 188

The miscibility between a polymer and a surfactant was tested by casting films of their mixtures on glass slides and then exposing the slides to the accelerated stability testing conditions of 40°C/75% RH to observe any physical instability. DSC scans and powder XRD patterns of the films were recorded to determine whether there were any DSC endotherms or XRD peaks formed due to the possible phase separation of poloxamer 188. Figure 1 shows the DSC scans of Soluplus-poloxamer 188 mixtures with 9:1, 8:2, and 7:3 *w*/*w* ratios recorded on the day of their preparation (day 1) and after exposure to 40°C/75% RH for 7 days (day 7). The DSC scan of one of the mixtures (9:1 *w*/*w*) on day 30 is also given. Distinct endotherms with peaks at ~50°C were observed at 8:2 and 7:3 *w*/*w* ratios on day 1 due to the phase separation of the surfactant in its crystalline form, but not for the 9:1 *w*/*w* mixture. The results were essentially similar on day 7, with only differences that there was indication of a slight endotherm of possible phase separation of poloxamer 188 from the 9:1 *w*/*w* mixture and the endotherms for the other two mixtures grew. The phase separation poloxamer 188 from the 9:1 *w*/*w* gradually became more pronounced with the increase in storage time and distinct endotherm for its crystallization was observed on day 30 (Fig. 1g). Although DSC scans of films with 6:4 and 5:5 *w*/*w* ratios were also recorded at all time points, they are not shown in the figure as the scans were similar to those with higher polymer to surfactant ratios (e.g., 8:2 and 7:3 *w*/*w*), except that the areas of the endotherms were larger due to the presence of higher amounts of poloxamer 188. These results demonstrated that Soluplus® and poloxamer 188 exhibit certain miscibility only at the low level of 9:1 *w*/*w* or 10% *w*/*w* poloxamer 188. However, phase separation due to crystallization of the surfactant may occur after storage of the mixture under the accelerated stability testing condition for a prolonged period of time. It may also be pointed out in Fig. 1 that there was no apparent T_g that could be attributed to the polymer itself.

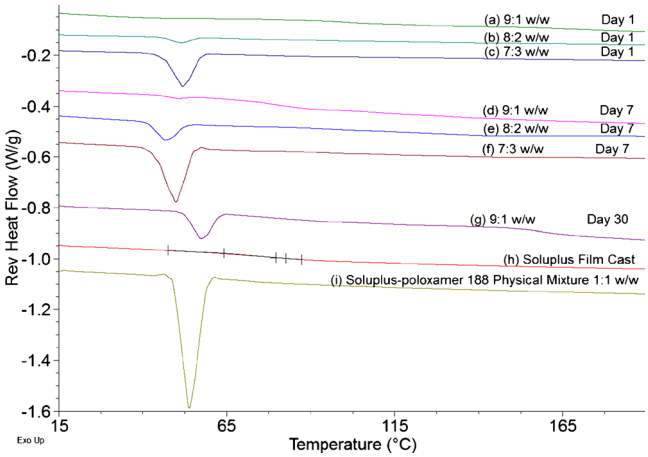

Fig. 1. Differential scanning calorimetry (*DSC*) scans of the films of binary mixtures with different ratios of Soluplus® and poloxamer 188 freshly prepared (day 1) and after exposure to 40°C/75% RH for 7 and 30 days. DSC scans of the film cast of Soluplus® itself and physical mixture of Soluplus® and poloxamer 188 1:1 *w/w* are also shown

Although the T_g of Soluplus® is reported to be 72°C (28), and also shown in Fig. 1h, it possibly decreased and was masked by the melting endotherms of poloxamer 188 in polymer-surfactant mixtures in Fig. 1.

The PXRD studies of the films with different ratios of Soluplus® to poloxamer 188 at various time intervals confirm the phase separation between the two components observed in the DSC scans in Fig. 1. PXRD patterns of all Soluplus-poloxamer 188 mixtures ranging from 8:2 to 5:5 *w/w* ratios showed characteristics peaks of crystalline poloxamer 188 at all time points (data not shown). The PXRD patterns of the 9:1 *w/w* Soluplus-poloxamer 188 mixture on day 1 and after exposure to 40°C/75% RH for 7 and 30 days are shown in Figure A of the Supplementary Section. In agreement with the DSC scans in Fig. 1, clear peaks for the crystalline surfactant indicating phase separation were observed only on day 30.

HPMCAS-Poloxamer 188

In contrast to Soluplus®, the DSC study showed that poloxamer 188 is highly miscible with HPMCAS. For freshly prepared films (day 1) with 9:1, 8:2, 7:3, 6:4, and 5:5 *w/w* ratios of HPMCAS to poloxamer 188, an endothermic peak due to the phase separation of poloxamer 188 was observed only at 5:5 *w/w* (Fig. 2; the scan of only 5:5 *w/w* mixture day 1 is shown, and there were no endotherms at higher polymer to surfactant ratios). As shown in Fig. 2, when the films were exposed to 40°C/75% RH for 7 days, the phase separation of the surfactant was also observed at 6:4 *w/w*, and the films with other polymer to surfactant ratios (9:1, 8:2, and 7:3 *w/w*) remained miscible at 7 days as well as at 30 days. The DSC scans of 5:5 *w/w* mixture showed phase separation at all other time points (data not shown). These results thus demonstrate

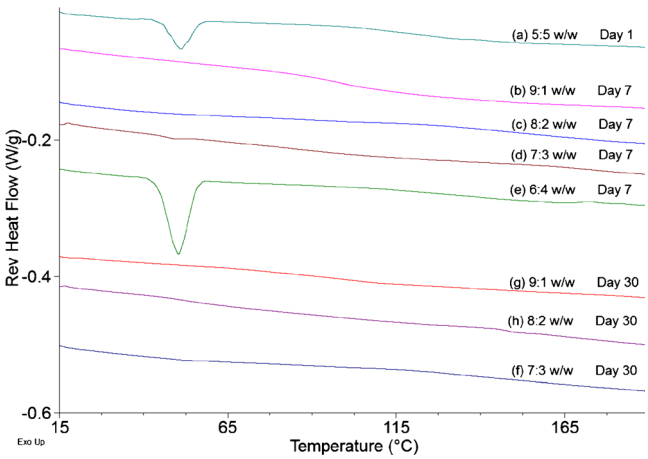

Fig. 2. Differential scanning calorimetry scans of the films of binary mixtures with different ratios of HPMCAS and poloxamer 188 on day 1 (freshly prepared) and after exposure at 40°C/75% RH for 7 and 30 days. The DSC scans of physical mixtures are shown in Figure B of the Supplementary Material for reference

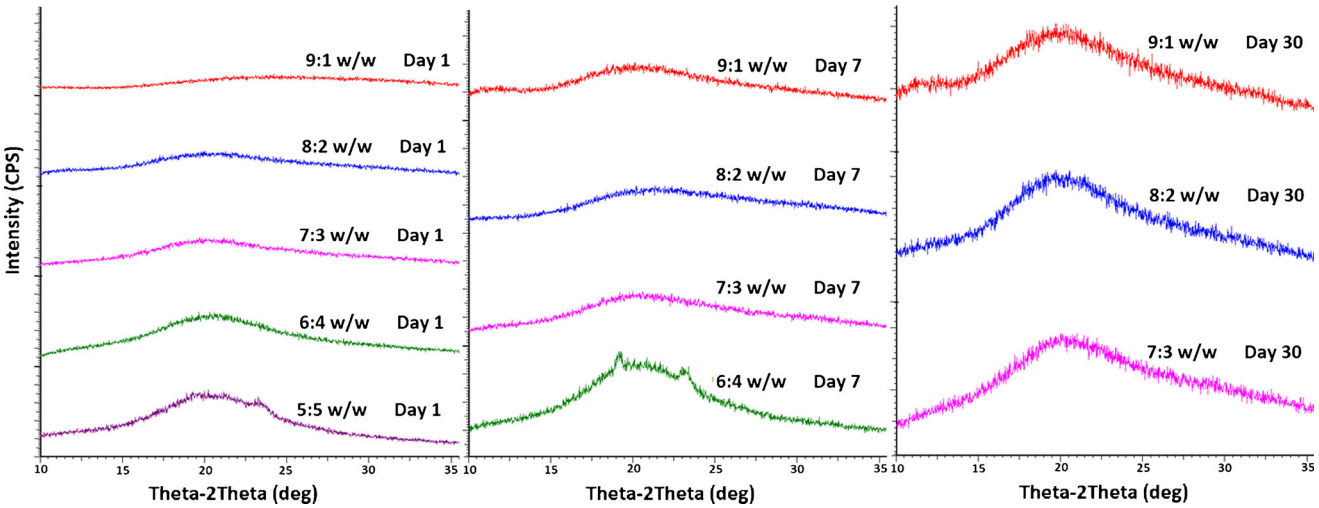

Fig. 3. PXRD patterns of the films of binary mixtures with different ratios of HPMCAS and poloxamer 188 on day 1 (freshly prepared) and after exposure to 40°C/75% RH for 7 (day 7) and 30 (day 30) days

that poloxamer 188 is miscible with HPMCAS to the extent of at least 30% *w/w*.

The PXRD scans of the HPMCAS-poloxamer 188 films presented in Fig. 3 are in agreement with the DSC scans given in Fig. 2. Figure 3 shows that the film with 6:4 *w/w* polymer to surfactant ratio was amorphous on day 1 and there were peaks due to the phase separation of poloxamer 188 on day 7. The films with the 7:3 *w/w* ratio did not show any PXRD peaks initially and even after exposure to 40°C/75% RH for 7 and 30 days, again confirming that poloxamer 188 was miscible with HPMCAS at 30% *w/w*.

Polymer-Drug-Surfactant Miscibility

Soluplus-ITZ-Poloxamer 188

As shown in Table I, the polymer to drug ratios used in this study were 9:1, 8:2, 7:3, 6:4, and 5:5 *w/w*. It was reported earlier that Soluplus® and ITZ were miscible with each other up to 6:4 *w/w* polymer to drug ratios (40% drug load) (14). It was also observed that up to 50% *w/w* ITZ was miscible with HPMCAS (S. Gumaste, personal communication). In addition to their relative ratios, concentrations of polymer, drug, and surfactant in the mixtures are also given in Table I. They differed depending on the ratios of the components. For example, when their ratios were 9:1:1 *w/w* (sample 911), concentrations of Soluplus®, ITZ, and poloxamer 188 in the mixture were, respectively, 82, 9, and 9% *w/w*, while for the 7:3:5 *w/w* ratio (sample 735), the concentrations were, respectively, 47, 20, and 33% *w/w*.

DSC scans and PXRD patterns of selected Soluplus-ITZ-poloxamer 188 mixtures in freshly prepared films and after storage under accelerated stability testing conditions (40°C/75% RH) for different intervals of time are shown in Figs. 4 and 5, respectively. To illustrate the results of DSC studies, the scans of freshly prepared films (day 1) of 9:1:1, 9:1:3, 9:1:5,

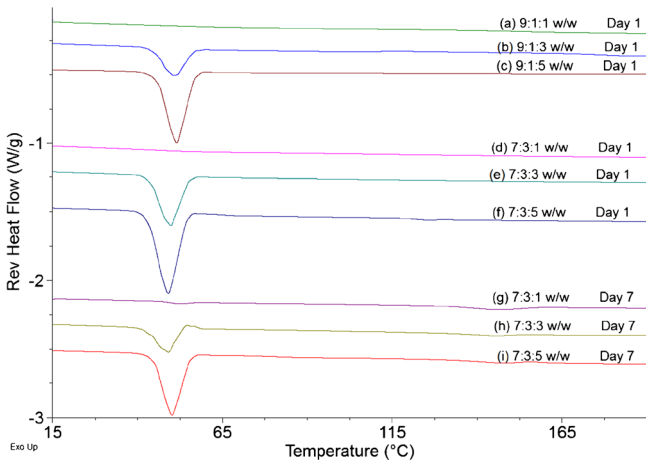

Fig. 4. Differential scanning calorimetry scans of the films of ternary mixtures of Soluplus®, itraconazole, and poloxamer 188 on day 1 (freshly prepared) and after exposure to 40°C/75% RH for 7 days (day 7)

7:3:1, 7:3:3, and 7:3:5 *w/w* Soluplus®-ITZ-poloxamer 188 ratios (samples 911, 913, 915, 731, 733, and 735, respectively) and 7-day films with 7:3:1, 7:3:3, and 7:3:5 *w/w* are given in Fig. 4. There were no further changes when samples 911, 913, and 915 were stored for 7, 14, and 30 days and samples 731, 733, and 735 were stored for 14 and 30 days. It may be observed in Fig. 4 that poloxamer 188 was miscible in samples 911 and 731 (poloxamer 188 concentration of 9% *w/w*) as there were no endothermic peaks for the surfactant on day 1 as well as after storage under accelerated stability testing conditions. The phase separation of the surfactant was observed when concentrations of the surfactant were increased to higher levels (samples 913, 915, 733 and 735). These results are in general agreement with the results of Soluplus-ploxamer miscibility testing in absence of drug shown in Fig. 1. It may be observed in Fig. 4 that there were no significant endothermic peaks near the melting point of ITZ (166°C) in any of the freshly prepared films as well as in those exposed to high temperature and humidity for 7 days. In films with higher drug loads (i.e., 7:3 polymer-drug ratio) with different levels of surfactant, there were some very minor, shallow, and broad peaks in the temperature range of 140 to 150°C. It appeared that the crystallized drug in the films, if any, redissolved in the polymer or surfactant inside the DSC pans during heating and, therefore, the DSC results were not conclusive for any crystallization of drug.

The PXRD patterns of the films in Fig. 5 show that the powder X-ray diffraction is much more suitable for studying any crystallization of ITZ. The semi-crystalline poloxamer 188 has prominent peaks at 19 and 23° 2θ, while ITZ exhibits a characteristic peak at 21° 2θ. While no ITZ peak was evident in day 1 films, there were ITZ peaks in all samples on day 7, even when the drug concentration was <10% *w/w* and the surfactant concentration was 9% *w/w*. Although ITZ was miscible with Soluplus® up to 40% *w/w* (14), these results demonstrate that the presence of poloxamer 188 had a detrimental effect on the drug-polymer miscibility by decreasing the drug load to <10% *w/w*.

The results of the microscopic examination of films were in agreement with the PXRD results, although the crystallization of both poloxamer and ITZ could sometime interfere in distinguishing between their birefringence. For illustration, polarized light microscopic (PLM) images of 7:3:1, 7:3:3, and 7:3:5 *w/w* Soluplus-ITZ-poloxamer 188 films on day 1, day 7, and day 14 are shown in Fig. 6. On day 1, there was no apparent phase separation of drug or surfactant in the sample 731, while the phase separation surfactant in the crystalline form showed birefringence in sample 733 and sample 735. However, on day 7 and day 14, ITZ crystals were observed in sample 731 and both the drug and the surfactant crystallized in the other two samples. These results are in agreement with the corresponding PXRD results in Fig. 5. Thus, PLM may also serve as a rapid and convenient tool for screening polymer-drug-surfactant miscibility in films.

HPMCAS-ITZ-Poloxamer 188

The DSC analysis was found to be inconclusive for the HPMCAS-ITZ-poloxamer 188 miscibility testing, because, as mentioned earlier, there could be a potential that any drug crystallizing out of the film might redissolve in the polymer-

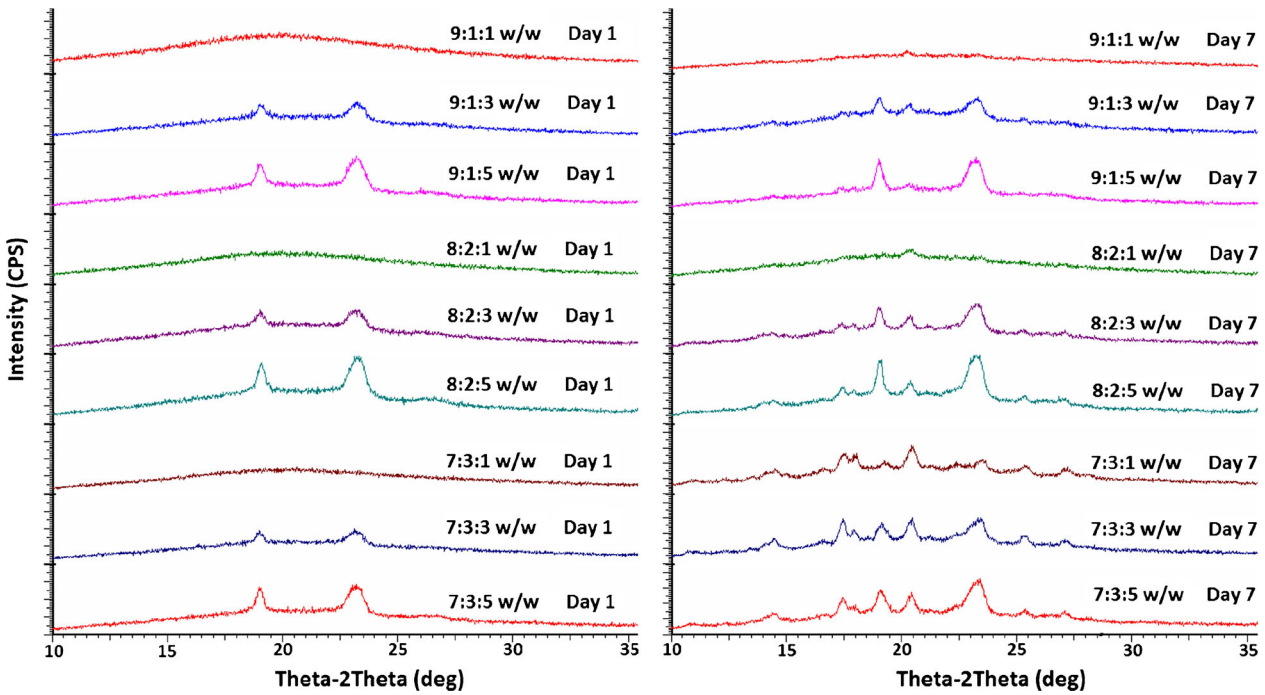

Fig. 5. PXRD patterns of the films of ternary mixtures of Soluplus®, itraconazole, and poloxamer 188 on day 1 (freshly prepared) and after exposure to 40°C/75% RH for 7 days (day 7)

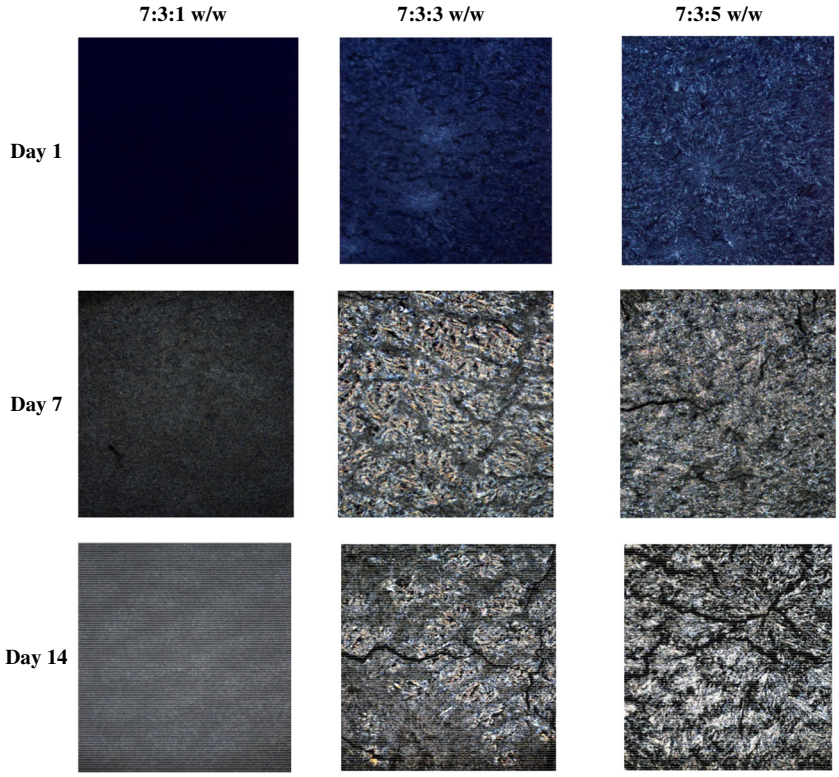

Fig. 6. Polarized light microscopic images (10×) of the films with different ratios of Soluplus®, itraconazole, and poloxamer 188 freshly prepared on day 1 (row 1) and after exposure to 40°C/75% RH on day 7 (row 2) and day 14 (row 3)

surfactant mixture upon heating. For illustration, the DSC scans on day 1 and day 14 for samples with HPMCAS-ITZ-poloxamer 188 ratios of 7:3:1, 7:3:3, and 7:3:5 *w/w* (samples 731, 733, and 735, respectively) are given in Fig. 7. The results were essentially similar when the storage time was increased up to 30 days. The phase separation of poloxamer 188 from the film could be clearly distinguished by the DSC analysis as observed by the presence of endotherms at the high surfactant load (sample 735). However, it is not certain whether shallow endotherms observed in the region around 145°C was due to crystalline ITZ or for any other event in the complex polymer-drug-surfactant system.

Unlike the films containing Soluplus®, the PXRD analysis revealed that poloxamer 188 had only minimal adverse effect on the miscibility between HPMCAS and ITZ. The PXRD patterns of 8:2, 7:3, and 6:4 *w/w* parts of HPMCAS and ITZ with additional 1, 3, and 5 parts of poloxamer 188 are shown in Fig. 8 as representative examples of the results obtained. For comparison, the PXRD patterns of physical mixtures are given in Fig. C of the Supplementary Material. In Fig. 8, amorphous halos were observed in all PXRD patterns and there were no indication of the presence of any peaks due to the crystallization of drug or surfactant on day 1. Samples 821, 823 and 825, which contained 8:2 *w/w* ratios HPMCAS to ITZ with increasing amounts of the surfactant, did not indicate any crystallization of drug or surfactant after exposure of the films to 40°C/75% RH for 1 month. Even when the HPMCAS to ITZ ratio was increased to 7:3 or 6:4 *w/w*, there was no crystallization of drug or surfactant in samples with the two lower levels of surfactant (samples 731, 733, 641, and 643). The crystallization of drug and surfactant were observed in samples 735 and 645, which had the highest level of surfactant. As noted in Table I, the concentration of poloxamer 188 in sample 733 was 23% *w/w*, along with 23% *w/w* ITZ and 54% *w/w* HPMCAS, and these results, therefore, show that up to this concentration of the surfactant may be incorporated in a HPMCAS-based solid dispersion, where the surfactant would remain in the amorphous state and would not induce crystallization of drug like ITZ from polymer-drug-surfactant films.

In addition to DSC and PXRD, the films were also analyzed by the polarized light microscopy (PLM) for any drug crystallization. The results were in general agreement with that of PXRD. As mentioned above, samples 731, 733, 641, and 643 did not show any PXRD peaks upon storage of films under accelerated stability testing conditions for up to 30 days. None of these films exhibited any birefringence in the PLM (data not shown). In contrast, PXRD peaks were observed in samples 735 and 645. For illustration, PLM images of sample 735 (7:3:5 *w/w* polymer-drug-surfactant ratio) are shown in Fig. D of the Supplementary Material, where, in agreement with the PXRD patterns in Fig. 8, the films exhibited birefringence on day 14 and day 30 due to the

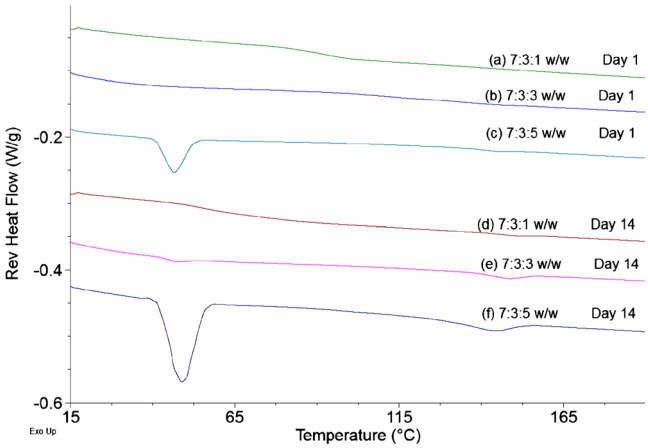

Fig. 7. Differential scanning calorimetry scans of the films of ternary mixtures of HPMCAS, itraconazole, and poloxamer 188 on day 1 (freshly prepared) and after exposure at 40°C/75% RH for 14 days (day 14)

presence of drug, surfactant or both. However, it was difficult to distinguish whether the birefringence was due to the drug or the surfactant. Although PLM was found to be a robust and reliable technique to identify stability issues with the SD films, more importance was given in the present investigation to DSC for identification of any phase separation of poloxamer 188 and to PXRD for any crystallization of ITZ.

Phase Diagrams

Soluplus-ITZ-Poloxamer 188 Miscibility

Ternary phase diagrams of the miscibility of each of the two polymers, Soluplus® and HPMCAS, with itraconazole and polaxamer 188 on the day of preparation and upon exposure to 40°C/75% RH for different periods of time were constructed. Results of the examination of films for any crystallization of surfactant or drug by DSC, PXRD, and PLM were considered in constructing the phase diagrams. Figure 9a–c shows phase diagrams of the Soluplus-based formulations on day 1, day 7, and day 14. It may be observed that, on day 1, poloxamer 188 phase separated from all films, except those containing 9% *w/w* surfactant, and both ITZ and poloxamer 188 phase separated from only two films containing high concentrations drug and surfactant. However, upon exposure to high temperature and humidity for 7 and 14 days, ITZ crystallized out from all the films, and the surfactant also phase separated from all films, except for two on day 7 and one on day 14. These results demonstrated that although ITZ could be miscible with Soluplus® itself up to 40% *w/w*, the presence of poloxamer 188 had a detrimental effect on the drug-polymer miscibility.

HPMCAS-ITZ-Poloxamer 188 Miscibility

Figure 9d–f gives ternary phase diagrams of HPMCAS-ITZ-poloxamer 188 mixtures determined by film casting and then exposure to high temperature and humidity. On day 1, ITZ was miscible in the films at all the combinations studied while poloxamer 188 was miscible only upto 23% *w/w* (Table I). There were no phase separation of drug or surfactant on day 7 at 23% *w/w* poloxamer 188 and up to

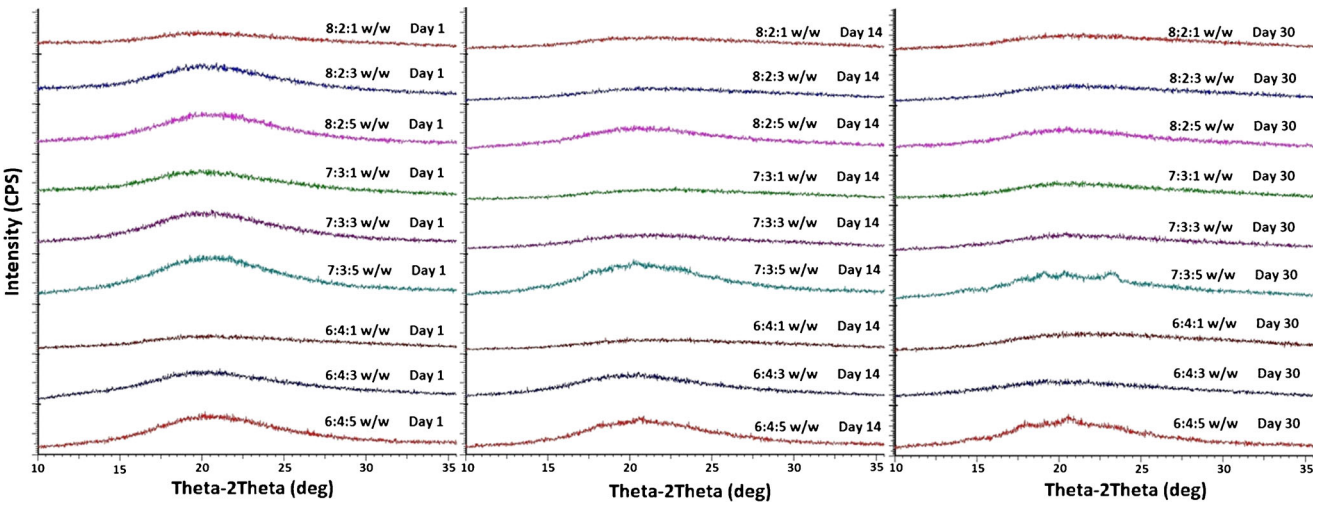

Fig. 8. PXRD patterns of the films of ternary mixtures of HPMCAS, itraconazole, and poloxamer 188 on day 1 (freshly prepared) and after exposure to 40°C/75% RH for 14 (day 14) and 30 (day 30) days

45% *w/w* ITZ; there was some phase separation of drug only in the films containing 33% *w/w* poloxamer 188 and having ITZ concentration of 20% *w/w* and higher. There was increased phase separation of the surfactant and drug after prolonged exposure of the films to the accelerated stability testing conditions. However, even after exposure to 30 days, at least 23% *w/w* each of ITZ and poloxamer 188 was miscible with HPMCAS (54% *w/w*) in the mixture. These results demonstrate that, depending upon the types of polymer and surfactant used, high concentrations of both the drug and the surfactant may be incorporated in a solid dispersion film and the system can still remain amorphous.

DISCUSSION AND CONCLUDING REMARKS

Solid dispersions are complex pharmaceutical drug delivery systems where drugs are dispersed in suitable carriers. Amorphous polymers have emerged as the carriers of choice for SDs, and it is essential that drugs remain in the molecularly mixed or amorphous forms when dispersed in such carriers. Surfactants may also be necessary to ensure complete drug release from SDs upon exposure to gastrointestinal fluids after oral administration. Serajuddin *et al.* (3, 5) discussed extensively the role of surfactant on drug release and dissolution from solid dispersions. There are, however, no general methods for screening of different components for their miscibility in SDs. Most of the theoretical methods for drug-carrier miscibility screening reported in the literature have only very limited practical values (14). Moreover, the methods mostly involve binary drug-polymer mixtures and are not suitable for multi-component SDs. Earlier, Parikh *et al.* (14) presented a practical and relatively simple film casting method for studying miscibility of drugs with polymers in binary systems. In the present investigation, the film casting technique was successfully applied to determine the miscibility of ternary solid dispersion systems containing polymer, drug, and surfactant. First, the miscibility of each of two polymers, Soluplus® and HPMCAS, in binary systems with a common solid surfactant, poloxamer 188, was studied. The study was then extended to polymer-ITZ-poloxamer 188 mixtures. Three analytical methods, namely, differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and polarized light microscopy (PLM) were used to detect any phase separation or crystallization of surfactant and drug from the polymer. Both DSC and PXRD could detect the phase separation of poloxamer 188 from the films. However, employing DSC to detect drug crystallization could be challenging, especially if there is considerable difference between the *Tg* of the polymer and the melting point of the drug. Since DSC is a dynamic testing process, polymers with low *Tg*, such as Soluplus® (72°C) and Eudragit® EPO (57°C) (30), will be liquid with low viscosity prior to reaching the melting temperature of drug like ITZ (166°C), and in such cases any crystalline drug will redissolve before melting which may lead to erroneous conclusion about the drug-carrier miscibility. The inability of the technique in detecting phase separation has been reported in the literature (47, 48). While having one glass transition temperature in DSC for a SD may be indicative of the existence of both drug and polymer as a single phase, Purohit and Taylor (47) demonstrated that discrete drug-rich domains may still be observed when samples were analyzed by high-resolution analytical methodologies, thus indicating that incomplete miscibility may still exist. In contrast, PXRD is a static technique, where phase changes during testing may be rare. In the present study, PXRD was found to be more suitable to detect any crystallization of ITZ. However, the PXRD also has its own limitation; in most PXRD equipment, the limit of detection is around 5% and it may be difficult to detect drug crystallization below this limit. While the PLM may be able to detect drug at <5% (14), the technique may not be suitable when two or more components phase separate and all show birefringence. In the present investigation, it was difficult to distinguish between ITZ and poloxamer 188 when both phase separated from the films as crystalline materials. In such a scenario, PLM may also not be able to identify whether ITZ converts into either of its mesophases. For these reasons, it may be necessary to apply multiple techniques, such as DSC, PXRD, and PLM, in the same study to obtain a clear understanding of the drug-carrier miscibility.

While ITZ was miscible with Soluplus® and HPMCAS to the extent of 40 and 50% *w/w*, respectively, poloxamer 188 was miscible with only HPMCAS and not with Soluplus®. In the ternary systems, ITZ was miscible only with the HPMCAS-poloxamer 188 mixtures. The phase diagrams of the ternary systems show that the drug crystallizes out of the Soluplus®-ITZ-poloxamer 188 SD films even at the low levels of drug (9% *w/w*) and surfactant (9% *w/w*), while in the HPMCAS-ITZ-poloxamer 188 SD films, high concentrations of both the drug and surfactant remained miscible. A completely amorphous system containing 23% *w/w* each of ITZ and poloxamer 188 and 54% *w/w* of HPMCAS could be observed in the phase diagram that remained physically stable upon exposure to 40°C/75% RH for 1 month. It appears that the drug-surfactant miscibility has an influence on the miscibility of ITZ in the solid dispersion; when poloxamer 188 phase separated, the drug also crystallized out.

Further studies are in progress in our laboratory to investigate mechanisms polymer-surfactant and polymer-drug-surfactant miscibility as well as the difference between the roles of Soluplus® and HPMCAS in these systems. There are various reports in the literature on the possible mechanism of the stabilization of drugs in amorphous solid dispersions. Bhardwaj *et al.* (49) studied molecular mobility of ITZ solid dispersions in HPMCAS and PVP by dielectric analysis. They observed that HPMCAS was substantially more effective than PVP in inhibiting ITZ crystallization, which they attributed to the increase in α-relaxation at temperature above T_g for the HPMCAS solid dispersion, with consequent increase in crystallization time and decrease in crystallization rate constant for ITZ. PVP did not have such an effect on α-relaxation and crystallization time. However, the difference in the effects of HPMCAS and Soluplus® observed in the present study does not appear to be due to difference in α-relaxation as, by itself, ITZ is highly miscible with both HPMCAS and Soluplus® (50 and 40% *w/w*, respectively), even after storage at high humidity and temperature for one month. It appears that the miscibility of between HPMCAS and poloxamer 188 could be due to hydrogen bonding between them. HPMCAS is a cellulosic material, and, in general, celluloses contain large number of hydroxyl and ether groups in glucose units of the polymer

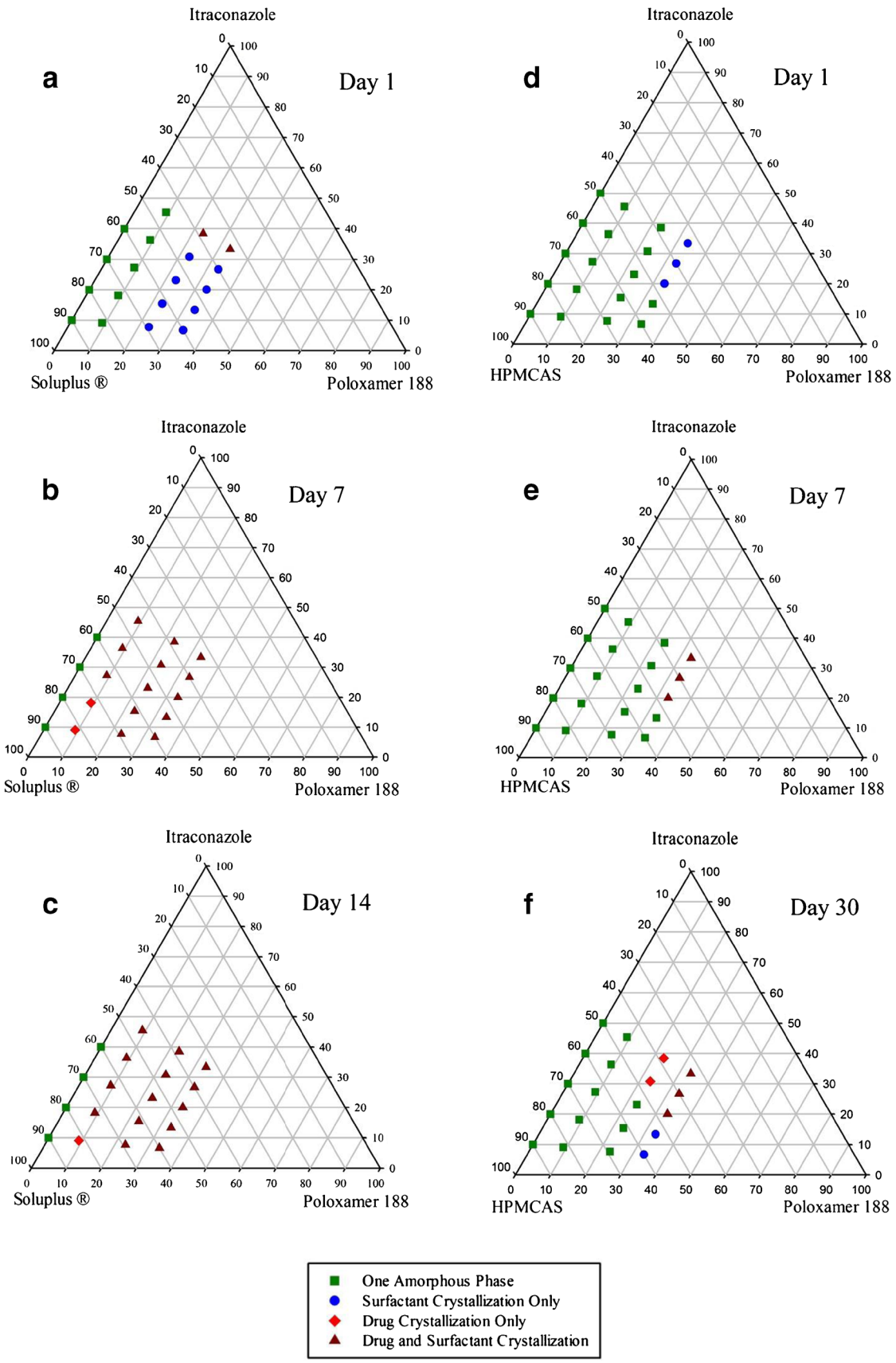

Fig. 9. Ternary phase diagrams for Soluplus®, itraconazole, and poloxamer 188 films, freshly prepared (day 1) and after exposure at 40°C/75% RH for 7 (day 7) and 14 (day 14) days; HPMCAS, itraconazole, and poloxamer 188 films, freshly prepared (day 1) and after exposure at 40°C/75% RH for 7 (day 7) and 30 (day 30) days. Miscibility information of the binary mixtures of Soluplus® and itraconazole obtained from ref. (14)

chain, which render them highly capable of intra- and intermolecular hydrogen bonding. Although some of the –OH groups in HPMCAS are converted to ethers by reacting with other chemicals, the remaining –OH groups are still capable of hydrogen bonding. One of the chemicals used to form ether is succinic acid, which also has a free –OH group capable of hydrogen bonding. Thus, HPMCAS is highly capable of hydrogen bonding with poloxamer 188 to make them miscible. In contrast, Soluplus® is poly(vinyl caprolactam-polyvinyl acetate-polyethylene glycol) block copolymer without much hydrogen bonding capability. This hypothesis is in agreement with the observations of Chen *et al.* (50) where they partially attributed superior stability of the SD of several drugs in HPMCAS over those in PVP-VA (Kollidon® VA64) to molecular interactions, including hydrogen bonding.

Since high miscibility between HPMCAS and poloxamer 188 appears to be due to hydrogen bonding, it is also possible that hydrogen bonding could be responsible for keeping the HPMCAS-ITZ-poloxamer 188 SD together. In a recent report, Parikh *et al.* (51) reported that ITZ forms hydrogen bonds with the –OH groups present in succinic and other weak acids. In case of the Soluplus-ITZ-poloxamer 188 SD, the phase separation of poloxamer 188 somehow interferes with the interaction between Soluplus® and ITZ, the mechanism of which has not been delineated.

It may be pointed out here that harsh stability testing condition of 40°C/75% RH was used in the present investigation. Yet, it is remarkable that HPMCAS-ITZ-poloxamer 188 SD films remained physically stable under such a condition. Thus, the present report provides a practical method of screening various components of SDs for their miscibility and ultimately physical stability during shelf life. Such a screening study may be completed in a month or less. If the stability testing condition is considered too harsh for a particular system, less stringent conditions may be applied.

In conclusion, a practical method for the identification of suitable components, such as polymer and surfactant, is presented in this report. Using the method, it has been identified that HPMCAS is highly miscible with the solid surfactant poloxamer 188. A HPMCAS to poloxamer 188 ratio of 7:3 *w/w* may be used without any crystallization of surfactant. An amorphous solid dispersion system was also formed when the drug ITZ was incorporated with HPMCAS and poloxamer 188 in a solid dispersion. Thus, the HPMCAS-poloxamer 188 mixture appears to be an ideal carrier for the solid dispersion of poorly water-soluble drug that will not only maintain the drug in the amorphous form, it may also enhance drug release and dissolution or aqueous dispersion from the system.

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