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Effects of Surfactants on Itraconazole-HPMCAS Solid Dispersion Prepared by Hot-Melt Extrusion I: Miscibility and Drug Release

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ABSTRACT

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) has been widely investigated as a carrier for amorphous solid dispersion (ASD) of poorly water-soluble drugs. However, its use has mostly been limited to ASDs prepared by spray drying using organic solvents, and the solvent-free method, hot-melt extrusion (HME), has only limited use because it requires high processing temperature where the polymer and drug may degrade. In this investigation, surfactants were used as plasticizers to reduce the processing temperature. Their effects on drug release were also determined. To determine suitability of using surfactants, the miscibility of HPMCAS with 3 surfactants (poloxamer 188, poloxamer 407, and d-alpha tocopheryl polyethylene glycol 1000 succinate) and a model drug, itraconazole (ITZ), was studied by film casting. HPMCAS was miscible with ITZ (>30%) and each surfactant (>20%), and in ternary HPMCAS-ITZ-surfactant (60:20:20) system. ASDs prepared by HME of HPMCAS-ITZ-surfactant mixtures (70:20:10 and 65:20:15) at 160°C were physically stable after exposure to 40°C and 75% relative humidity for 1 month. The presence of 15% w/w surfactant provided up to 50% drug release at pH 1 as compared to only 8% from ASDs with HPMCAS alone. On changing the pH of the dissolution medium from 1 to 6.8 in a step-dissolution process, complete drug release (90%-100%) and extremely high apparent supersaturation (~75,000 times) of ITZ were observed when the solutions were filtered through 0.45 μm filters. The apparently supersaturated solutions consisted of colloidal particles of ~300 nm size. The present study demonstrates that stable ASDs with improved processability and drug release may be prepared by HME.

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Introduction

Over two-thirds of the compounds in the drug discovery pipeline exhibit very poor water solubility,[1-3] and, according to the United States Pharmacopeia (USP) definitions, they may be called insoluble or practically insoluble.[4] They also fall into the Biopharmaceutical Classification System II or IV as the highest dose strengths do not dissolve in 250 mL or less of the buffer over the pH range of 1 to 7.5 at 37°C.[5] As a consequence, such compounds exhibit variable and erratic bioavailability depending on their dissolution rate in gastrointestinal fluids. Various formulation strategies, such as pro-drug formation,[6] micronization,[7] salt formation,[8] self-emulsifying drug delivery systems,[9] solubilization in concentrated aqueous solutions of weak acid and base,[10,11] amorphous solid dispersion (ASD)[12-14] and others, were applied to improve the dissolution rate and, thereby, bioavailability of poorly water-soluble drugs. Among them, the ASD, where the drug may be molecularly distributed in the amorphous carrier as solid solution or randomly distributed in the carrier as the amorphous form, has in recent years emerged as the most widely investigated strategy to improve dissolution rates of a poorly water-soluble drug.[15] When a water-soluble carrier is used and the matrix dissolves in the aqueous medium, the amorphous drug saturates or supersaturates the medium and the excess drug precipitates out as fine particles in presence of polymer, and these fine particles redissolve rapidly during dissolution testing.[12,16] Thus, high dissolution rates are expected from ASDs.

As pointed out by Serajuddin[12] in 1999, the difficulty in manufacturing and the incomplete drug release were major challenges in the widespread application of the solid dispersion technology in drug development. Since then, there has been considerable progress in both areas. As evident from several excellent review articles published in recent years, spray drying has become an established method for the preparation of ASD.[17-20] In addition, hot-melt extrusion (HME) has emerged as a newer and important technology in the pharmaceutical field for the preparation of ASD.[21,22] Drug products developed by using both spray drying and HME have successfully been marketed.[20,23] With respect to drug release, there were many reports where dissolution of ASD was either incomplete or retarded, because the poorly soluble drugs coated the ASD particles during dissolution testing, thus preventing further drug release, and, in many cases, drugs did not diffuse out from polymeric matrices due to the nature of drugs and polymers used. The incorporation of surfactants in formulations improved drug dissolution.[24-26] However, for the successful formulation of ASD, it is necessary to select a surfactant that is miscible with the polymer used and does not lead to any physical instability issue during shelf-life, for example, drug crystallization.

Between the 2 methods of preparing ASD mentioned previously, namely, spray drying and HME, the primary challenge with spray drying is the need for large volumes of organic solvents to dissolve water-insoluble drugs and water-soluble polymeric carriers in the common solvent. For example, Curatolo et al.[27] used 10 g of acetone to dissolve 133 mg of an experimental drug candidate and 67 mg of HPMCAS, which gave the drug to solvent ratio of 1:75 w/v for spray drying at the laboratory scale. Thus, if the same ratio of solids to acetone is used for scaling up the manufacturing process, it would require 9480 L of acetone (density of acetone = 791 g/L at 20°C) to manufacture solid dispersion for 100 kg of the drug. High volumes of organic solvents were also used by other investigators to prepare solid dispersions of drugs with HPMCAS by spray drying at laboratory scale: 1 L of acetone-ethanol (10:40) mixture for 10 g of curcumin and 10 g of HPMCAS[28]; 1 L of acetone for 20 g of celecoxib and 40 g of HPMCAS[29]; 1L of acetone-ethanol (10:40) mixture for 20 g of quercetin and 20 g of HPMCAS[30]; 1L of acetone or methanol for 25 g mixture of felodipine and polyvinylpyrrolidone or HPMCAS[31]; and 185 mL of acetone plus 85 mL of water to dissolve 2.5 g of griseofulvin and 2.5 g of HPMCAS.[32] In all of these cases, the drug to organic solvent ratios ranged from 1:75 to 1:40 w/v. Because there are 3 ASD products marketed by Vertex Pharmaceuticals (ivacaftor, Kalydeco®; lumacaftor/ivacaftor, Orkambi®; telaprevir, Incivek™) that contain HPMCAS as the polymeric matrix and are prepared by spray drying; it was of interest to also evaluate compositions of these products and determine the amount of organic solvent was used to manufacture them. However, all such information is not readily available in the literature. The review of the patent literature indicates that the ASD in one of the products, Kalydeco®, contains 80% w/w drug, 19.5% HPMCAS HG, and 0.5% sodium lauryl sulfate, and it was prepared by dissolving 87.5 g of total solids (contains 70 g drug) in a mixture of 671g of methylethyl ketone and 74.6 g of water (10.5% w/w solids).[33] Although the ratio of drug to organic solvent was reduced to about 1:10 w/v for the manufacture of this product, the spray-dried material does not appear to be true ASD because the amount of HPMCAS used was less than one-fourth of the drug and, as mentioned in the patent, the solid dispersion was only "substantially amorphous" with the crystalline drug present.[33] A fully ASD could possibly be prepared using larger amounts of HPMCAS; however, it would have possibly required larger volumes of organic solvent. The second marketed product mentioned previously, Orkambi®, is apparently a fixed combination product of ivacaftor (same as in Kalydeco®) with another drug lumacaftor, which has also been manufactured as

spray-dried solid dispersion by dissolving the drug in methanol at the ratio of 1:100 w/v.[34] No detailed manufacturing process for the third marketed product, telaprevir (Incivek™), containing HPMCAS and manufactured by spray drying is readily available. However, according to Connelly et al.,[35] this product may not also exist as a true ASD because its differential scanning calorimetry (DSC) scans showed multiple glass transition temperatures and the melting endotherm of drug, indicating 2 distinct amorphous phases and a crystalline phase. In addition to increasing solubility of drug and polymer, relatively large volumes of organic solvents are also needed to reduce viscosity of solutions for enabling spray drying as it is known that concentrated solutions of HPMCAS are viscous and difficult to spray dry. The aforementioned examples and description indicate that the preparation of HPMCAS-based ASDs by spray-drying may require relatively large volumes of organic solvents, and the solvent requirement may be reduced only by reducing amount of HPMCAS in the formulation, which may not be desirable in consideration of physical stability of products. The recovery of organic solvents after spray-drying to prevent environmental exposure also becomes a major development issue.[18] In addition, it is necessary to ensure that there are no residual organic solvents present in drug products as they could be toxic. Connelly et al.[35] reported that telaprevir (Incivek™) solid dispersion contained 7%-13% w/w residual solvent after spray-drying, which required further secondary drying for 24 h at 50°C in a jacketed biconical dryer to remove all the solvent. Thus, although spray drying is a viable option for the development of drug products, it has many complexities and, according to Li et al.,[20] spray-drying may be more suitable for the early stage of pharmaceutical development, where relatively small amounts of materials are produced and, therefore, the need of organic solvent is relatively small. They suggested that alternative product development strategies could be necessary at later stages.

Unlike spray drying, HME is a solvent-free method of producing ASD; however, it has its own limitations. There could be degradation of drug, polymer, or both at the high temperature usually necessary for melt extrusion. For example, Meena et al.[36] reported that HPMCAS has a glass transition temperature (Tg) of 122°C, and a temperature considerably higher than 160°C is necessary to extrude it, where the polymer itself may degrade. No practical method of extruding HPMCAS at a relatively lower temperatures is currently available, and, therefore, 4 of the 5 products containing HPMCAS as the carrier that are currently available in the market for drug therapy have been prepared by spray-drying or solvent-controlled precipitation.[23,37-39] Only 1 marketed product, posaconazole (Noxafil®), has been prepared by HME of drug-HPMCAS mixtures, where a 1:3:0.08 w/w mixture of posaconazole, HPMCAS, and ascorbic acid was extruded.[23,40] No processing temperature for the product has, however, been reported.

The heightened interest in the development of HPMCAS-based solid dispersions during the past decade is due to the reported ability of the polymer to keep poorly water-soluble basic drugs supersaturated in the dissolution media by weak acid-base interaction.[27,28,41] The present investigation deals with the development of solid dispersion formulations using HPMCAS as the polymeric carrier by HME as alternative to spray-drying so that such formulations can be more widely used in the pharmaceutical field. According to Sarode et al.,[37] the Tg of HPMCAS must be reduced using drugs or other additives as plasticizers for its successful processing by HME. Therefore, we explored the feasibility of lowering the processing temperature of HPMCAS by using several surfactants as plasticizers. For the physical stability of ASDs, it is, however, necessary that the surfactants used are miscible with the polymer and the drug-polymer mixture.[42] In addition, surfactants should not have any negative impact on drug dissolution and

supersaturation from ASDs. Rather, they should ideally increase them both. Therefore, there were 2 primary objectives of the present investigation: first, to study the miscibility of different polymer-surfactant and polymer-drug-surfactant mixtures and, second, to study effects of surfactants on the drug release from the HPMCAS-based solid dispersion. Solid surfactants such as poloxamer 188, poloxamer 407, and d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) were used over liquid surfactants because solid surfactants are easy to blend with the polymer and drug and exhibit better flow from feeder to extruder during HME.[43] With respect to drug release, it should be noted that HPMCAS is insoluble at low acidic pH conditions of the stomach, and it is soluble only in intestinal pH conditions at pH > 5.5. Therefore, there is the potential for delayed onset of drug action from HPMCAS-based ASDs and, depending on gastric-emptying time, food effect, and so forth, the bioavailability of drug may also vary.[23] For this reason, we explored the possibility of increasing drug release under gastric pH conditions by adding surfactants to the formulations. Itraconazole (ITZ), which is a weakly basic drug with the extremely low intrinsic solubility of ~4 ng/mL and the pK_a value of 3.7, was used as a model drug.[44,45]

Materials and Methods

Materials

ITZ was purchased from Fisher Scientific International, Inc. (Pittsburg, PA). Hydroxypropyl methylcellulose acetate succinate of the MG grade (HPMCAS-MG; AQOAT AS-MG) was kindly donated by Shin-Etsu Chemicals (Totowa, NJ). Kolliphor P188 (poloxamer 188; P188), Kolliphor P407 (poloxamer 407; P407), and Kolliphor TPGS were donated by BASF Corp. (Tarrytown, NY). All materials were used as received.

Miscibility Testing

The polymer-surfactant and polymer-drug-surfactant miscibility testing was performed using the film casting method described previously.[46,47] Briefly, 1 g of each polymer-surfactant mixture (90:10, 80:20, and 70:30 w/w) and polymer-drug-surfactant mixture (80:10:10, 70:20:10, 65:20:15, 60:20:20 and 50:30:20 w/w) was dissolved in 6 mL of methanol-dichloromethane mixture (1:1 v/v) by shaking for 1 h in a closed scintillation vial using a wrist action shaker. To cast film, 1 mL of the solution was poured on a glass plate, and the 200-micron film was casted using Elcometer 3540 bird film applicator (Elcometer Inc., Rochester Hills, MI). The casted films were dried by placing them in fume hoods at room temperature for an hour. The films were analyzed on day 1 and day 30 for possible phase separation or the presence of any crystals (crystallization) using DSC and powder X-ray diffraction (PXRD). Before analysis on day 30, the films were exposed to 40°C and 75% relative humidity (RH) for 30 days to accelerate phase separation and crystallization, if any.

Apart from film casting, crushed extrudates of polymer-drug (80:20 w/w) and polymer-drug-surfactant (70:20:10 and 65:20:15 w/w) mixtures were also evaluated for physical stability and possible phase separation and/or crystallization by DSC and PXRD on day 1 and after exposure to 40°C and 75% RH for 30 days.

Differential Scanning Calorimetry

DSC scans were recorded using a Q200 DSC equipped with a refrigerated cooling assembly (TA Instruments, New Castle, DE). For this purpose, 5 mg of a sample was crimped in the hermetic Tzero pan with a pinhole and equilibrated at 5°C. The sample was then heated to 200°C at the rate of 5°C/min with a modulation of 1°C/min.

The results were analyzed using Universal Analysis software version 2000 (TA Instruments), where the reversible heat flow, deconvoluted from total heat flow, was used to obtain the glass transition temperature (T_g) and melting temperature of the samples.

Powder X-Ray Diffraction

A powder X-ray diffractometer (XRD 6000; Shimadzu, Kyoto, Japan) was used to record PXRD patterns and determine any crystallinity of casted films and crushed extrudates. The diffractometer was operated with a copper anode tube at the generator voltage and the current of 40 kV and 30 mA, respectively. The samples were scanned at the rate of 2°θ/min over the range of 10°-35° 2θ. The polymer-drug and polymer-surfactant physical mixtures (97:3, 95:5, 93:7 and 90:10 w/w) were evaluated to determine the limit of detection for crystals. The characteristic peaks were distinctly observed in physical mixtures containing 95% polymer and 5% drug or surfactant.

Polarized Light Microscopy

Glass plates with casted films were analyzed under 10× cross-polarized lens using Nikon eclipse 50i microscope (Nikon Inc., Tokyo, Japan) for any birefringence due to the presence of drug, surfactant, or both as crystals.

Hot-Melt Extrusion

Polymer-drug and polymer-drug-surfactant physical mixtures, prepared according to Table 1, were blended together using the TURBULA® mixer (Glen Mills, NJ). Melt extrusion of the physical mixtures was then conducted using Process 11 co-rotating twin-screw extruder (Thermo Scientific, Bridgewater, NJ) at the barrel temperature of 160°C, which is above the glass transition temperature (T_g) of polymer and close to the melting point of ITZ (165°C). Feed rate and screw speed during melt extrusion were kept constant at, respectively, 2 g/min and 200 RPM. The screw configuration used was described previously by Solanki et al.[48] which included 3 kneading zones containing forward kneading elements and a series of conveying elements. The first kneading zone near the feeder consisted of 7 kneading elements with the offset angle of 30°, which were then followed by 7 kneading elements with the offset angle of 60°. In the second kneading zone, there were 6 kneading elements with the offset angle of 60°, and, in the third kneading zone, 4 kneading elements with the offset angle of 60°, followed by 7 kneading elements with the offset angle of 90° were used. Torque generated during melt extrusion was recorded to determine the effect of drug and surfactants on the extrudability of HPMCAS. Filaments of extrudates were produced using a 1.5-mm die, and they were cooled down to room temperature on a conveyer belt. The filaments were milled using a Scienceware® micro-mill (H-B Instruments Company, Collegeville, PA). To facilitate milling, the filaments were soaked in liquid nitrogen before milling. The powders

Table 1
Compositions of Polymer-Drug and Polymer-Drug-Surfactant Blends Used for Hot-Melt Extrusion

Mixture Code	HPMCAS (% w/w)	ITZ (% w/w)	P188 (% w/w)	P407 (% w/w)	TPGS (% w/w)
20% ITZ	80	20	—	—	—
10% P188	70	20	10	—	—
10% P407	70	20	—	10	—
10% TPGS	70	20	—	—	10
15% P188	65	20	15	—	—
15% P407	65	20	—	15	—
15% TPGS	65	20	—	—	15

were then screened through the ASTM sieve no. 70 (aperture of 212 μm) and used for dissolution testing and stability study.

In Vitro Step Dissolution

Dissolution of crushed extrudates (<212 μm) containing 100-mg equivalent of ITZ per dissolution vessel was conducted using the USP dissolution apparatus II (Distek Inc., North Brunswick, NJ) at 75 RPM and 37°C ± 0.5°C. Crushed extrudates formed cones at the bottom of flasks when the dissolution testing was carried out in round bottom dissolution vessel. Peak dissolution vessels (Distek Inc.) were, therefore, used to avoid cone formation and facilitate drug release.[49,50] The dissolution test was conducted in 250 mL of 0.1 N HCl (pH 1) for 2 h. The pH was then adjusted to 6.8 by adding ~80 mL of preheated 0.2 M trisodium phosphate (Na_3PO_4) solution, and the dissolution test was then continued for additional 5 h. Aliquots of the dissolution media were withdrawn periodically and filtered through 25-mm polyvinylidene fluoride (PVDF) syringe filters having the pore size of 0.45 μm. The filter pore size was selected according to the USP general method for dissolution,[51] where 0.45 μm was the lowest recommended size; it is commonly used to filter solutions for solubility and dissolution testing. For selecting the type of filter material, different fractions of drug solutions (1, 3, and 5 mL) were filtered through PVDF, poly-tetrafluoroethylene, and polypropylene filter materials, and the collected filtrates were analyzed for drug content. Among the tested filter materials, no significant difference in the drug concentration was found with the PVDF syringe filter among various fractions of filtrate, and, therefore, it was selected to filter the dissolution media aliquots. The similar syringe filter was used earlier by DiNunzio et al.,[52] for filtration of HPMCAS-ITZ solutions. Filtrates were diluted with the high-performance liquid chromatography (HPLC) mobile phase before the analysis according to the method described later. Unfiltered aliquots were also analyzed to determine whether there is any difference in drug concentrations between filtered and unfiltered aliquots that could indicate the possibility of drug precipitation or crystallization during dissolution.

Solubility of ITZ in Surfactants

To elucidate the possible mechanism of the drug release from ASDs, solubility of crystalline ITZ in surfactant solutions was determined. The study was carried out in 0.1 N HCl at surfactant (P188, P407, TPGS) concentrations of 0.1, 2, 5, and 10% w/w at 37°C. Excess amount of ITZ was added to the pre-dissolved surfactant solutions, and the dispersions were then shaken using mechanical shaker at 37°C for 24 h. Aliquots of suspensions were passed through 0.45 μm PVDF filters before the analysis by HPLC.

Drug Analysis

ITZ concentration in aliquots withdrawn from the dissolution media was quantified using the Waters HPLC system and the Agilent HC-C18 (2) column (5 μm, 4.6 × 150 mm). The mobile phase consisted of a 75:25 v/v mixture of acetonitrile and 0.04 M sodium acetate trihydrate aqueous solution containing 0.2% v/v triethylamine (pH adjusted to 4.5 using glacial acetic acid). The flow rate of 1 mL/min and the detection wavelength of 265 nm were used for analysis.

Particle Size Determination

Aliquots of dissolution media collected after the change in pH to 6.8 were analyzed to determine the possible presence of any colloidal nanoparticles. Approximately 3-4 mL of the unfiltered aliquot was filled in a disposable plastic cuvette for each analysis by dynamic light scattering using a DelsaNano C particle size analyzer (Beckman Coulter Inc., Brea, CA).

Results and Discussion

Miscibility Testing

In ASD, the drug is usually dispersed in amorphous polymers either in the molecular or amorphous state. Often, the ASD is not a thermodynamically stable system as the amount of drug present could be in excess of its solubility or miscibility in the carrier. As a consequence, drugs may crystallize out from ASD, which is undesirable as it defeats the purpose of preparing ASDs, that is, to enhance dissolution rate and bioavailability.[14,53] Such recrystallization of drugs is accelerated by the presence of moisture and the exposure to high temperature during storage. For the successful development of ASD, it is essential that the drug remains miscible with the carrier, and, when more than 1 carriers are used in the same formulation, carriers themselves should also be miscible with each other. Qian et al.[54] defined drug-carrier miscibility as the ability of drug to stay amorphously or molecularly dispersed in the polymeric matrix without any crystallization of drug during shelf-lives of drug products. In the present investigation, the film casting technique developed previously in our laboratory was used to study polymer-surfactant and polymer-drug-surfactant miscibilities.[46,47] Although there are certain theoretical models available to calculate drug-polymer miscibility, they were not used in the present investigation because of their limited predictive values. In this regard, Anderson[55] has recently reported that "the vast majority of publications to date have used mathematical models based on regular solution theory such as Flory-Huggins theory to predict drug-polymer miscibility, despite the fact that they were never intended to be applied to hydrogen-bonded systems."

Earlier, Gumaste et al.[47] reported that ITZ was miscible with HPMCAS up to 50% w/w. Because in the present investigation the ITZ loading was kept at 20% w/w, it was expected that it would be fully miscible with the polymer in binary systems. When a crystalline surfactant, such as poloxamer 188 (P188), is added to the formulation, it is essential that the surfactant is also miscible with the formulation, that is, it does not crystallize out, and it should not adversely affect the miscibility of drug with the polymer. Gumaste et al.[47] also reported that P188 was miscible with HPMCAS-MG up to 30% w/w. Moreover, in the ternary polymer-drug-surfactant mixtures, 23% w/w of each of ITZ and P188 and 54% w/w of HPMCAS were miscible. Because the melt extrudates prepared in the present investigation contained 20% w/w ITZ and 10% or 15% w/w of P188, both of these components would be miscible forming a homogeneous solid dispersion with HPMCAS.

In addition to P188, poloxamer 407 (P407), another block copolymer, and TPGS were used in the present investigation as surfactants and plasticizers. Because these surfactants were not previously tested for their miscibility with HPMCAS or the HPMCAS-ITZ mixture, their miscibility tests were conducted in the present study and the results are described below:

HPMCAS-P407 and HPMCAS-ITZ-P407 Miscibility

DSC scans and PXRD patterns of freshly prepared films (day 1) of HPMCAS-P407 mixtures (90:10, 80:20, and 70:30 w/w) and after exposing them to 40°C and 75% RH for 30 days (day 30) are shown, respectively, in Figures 1a and 1b. P407 is a crystalline material that melts at 57°C,[56] while HPMCAS is an amorphous material that exhibits the T_g of 122°C.[37] On both day 1 and day 30, DSC scans of the binary mixtures of HPMCAS and P407 did not reveal any endotherm
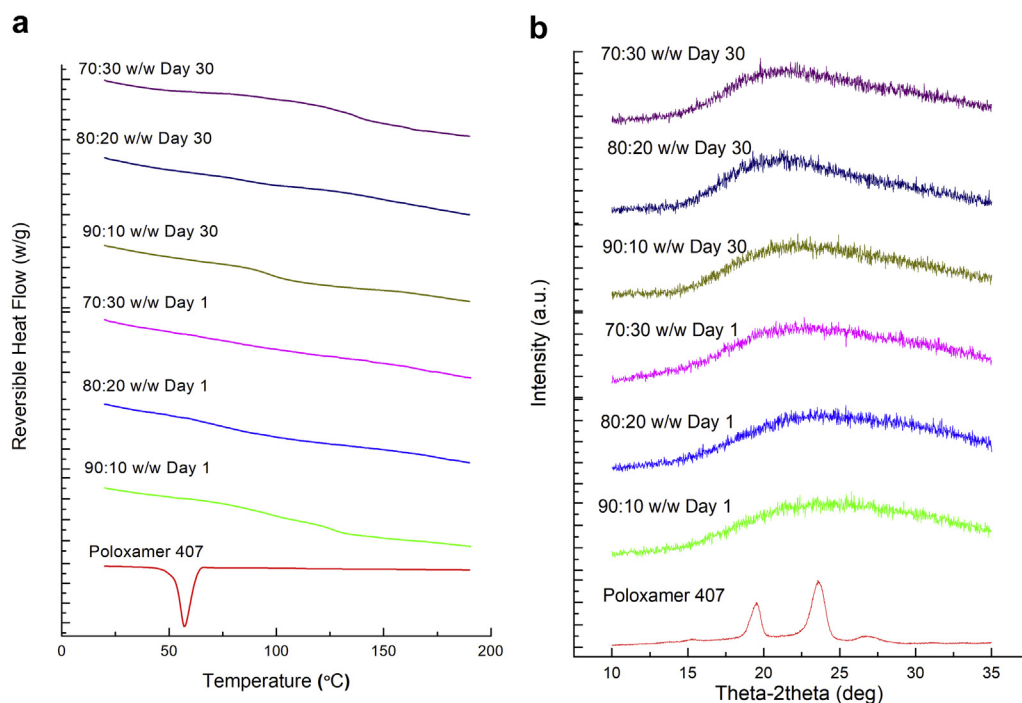
Figure 1. (a) DSC and (b) PXRD scans of freshly prepared films (day 1) of HPMCAS-P407 binary mixtures and after their exposure to 40°C and 75% RH for 30 d (day 30). The HPMCAS to poloxamer 407 (P407) ratio is noted along with each scan.

corresponding to the melting of P407, and there was only a single T_g conforming to a miscible system. The PXRD patterns in Figure 1b also did not show any peaks corresponding to those of P407. These results, therefore, indicate that P407 was miscible with HPMCAS at concentrations up to 30% w/w. In the previous study by Gumaste et al.[47] (2016), it was observed that P188 was also miscible with HPMCAS up to 30% w/w. Any P407 concentration higher than 30% w/w was not tested in the present investigation as such a high concentration of surfactant was not expected to be used.

The miscibility testing of ternary mixtures was performed with 10, 20, and 30% w/w P407 along with 10% and 20% w/w ITZ as these concentrations were found to be individually miscible with HPMCAS. DSC and PXRD scans of freshly prepared films (day 1) of the ternary mixtures of HPMCAS, ITZ, and P407 (80:10:10, 70:20:10, 65:20:15, 60:20:20, 50:20:30 w/w) are shown, respectively, in Figures 2a and 2b, and the scans after exposure of the films to 40°C and 75% RH for 30 days (day 30) are shown, respectively, in Figures 2c and 2d. Based on these results, there was no indication of the crystallization of ITZ and the phase separation of P407, except in the mixture containing 30% w/w of P407. The DSC scan of the freshly prepared film containing 30% w/w P407 (day 1) exhibited 2 distinct T_g at around 56°C and 96°C (Fig. 2a), indicating an amorphous-amorphous phase separation. Six et al.[57] reported the T_g of ITZ to be 58°C, and, therefore, the first T_g in the DSC scan could be due to the presence of amorphous ITZ. No endotherm in the DSC scans corresponding to the melting of P407 was observed, indicating that P407 still remained amorphous in the ternary system containing 30% P407. The second T_g at 96°C could, therefore, be attributed to the amorphous components of the ternary system that are miscible with each other. After exposure to 40°C and 75% RH for 30 days, the DSC scan of the film containing 30% P407 also showed an endotherm at 155°C (Fig. 2c). Although the melting point of ITZ is 166°C, the endotherm at 155°C could still be due to the crystallization of ITZ as the presence of amorphous polymer and surfactant is known to lower the melting point of drug.[58] Unlike the

DSC scans, the absence of any characteristic peaks for ITZ in PXRD may be attributed to low detection limit of the analytical technique.[59] The results of the PLM analysis were in general agreement with those by DSC and PXRD, with the possible difference from the DSC scan that there was no significant birefringence in the film observed under the cross-polarized light in the microscope when the 60:20:20 w/w HPMCAS-ITZ-P407 film was exposed to 40°C and 75% RH for 30 days. The films containing 50:30:20 and 50:20:30 w/w HPMCAS-ITZ-P407 showed birefringence under cross-polarized light indicating possible crystallization of the drug or surfactant. No birefringence due to possible crystallization of the drug or surfactant was observed in any other films. It may be concluded from these results that HPMCAS, ITZ, and P407 are miscible in ternary mixtures at 10% and 20% w/w ITZ as well as 10% and 20% w/w P407.

HPMCAS-TPGS and HPMCAS-ITZ-TPGS Miscibility

Polymer-surfactant and polymer-drug-surfactant miscibility testing similar to those with P407 was also conducted using TPGS as the surfactant. DSC scans and PXRD patterns of HPMCAS-TPGS mixtures (90:10, 80:20, 70:30 w/w) are shown, respectively, in Figures 3a and 3b. TPGS is a crystalline material with the melting endotherm at 38°C in the DSC scan (Fig. 3a) and characteristic peaks at 19° and 23° in PXRD patterns (Fig. 3b). Because none of these characteristic peaks were present in the binary mixtures in Figure 3 on day 1 and day 30, the results confirmed that TPGS was miscible with HPMCAS up to 30% w/w concentration.

Similarly, DSC scans and PXRD patterns in Figure 4 show that ternary mixtures of HPMCAS, ITZ, and TPGS were also miscible at 80:10:10, 70:20:10, 65:20:15, and 60:20:20 w/w ratios as no characteristic peaks of ITZ and TPGS in both freshly prepared and aged films were observed in Figures 4a-4d. The ternary mixtures containing TPGS showed miscibility similar to that of P407. Fresh and aged films containing ternary mixtures, except the mixture containing 30% w/w TPGS, showed no melting endotherm. In both
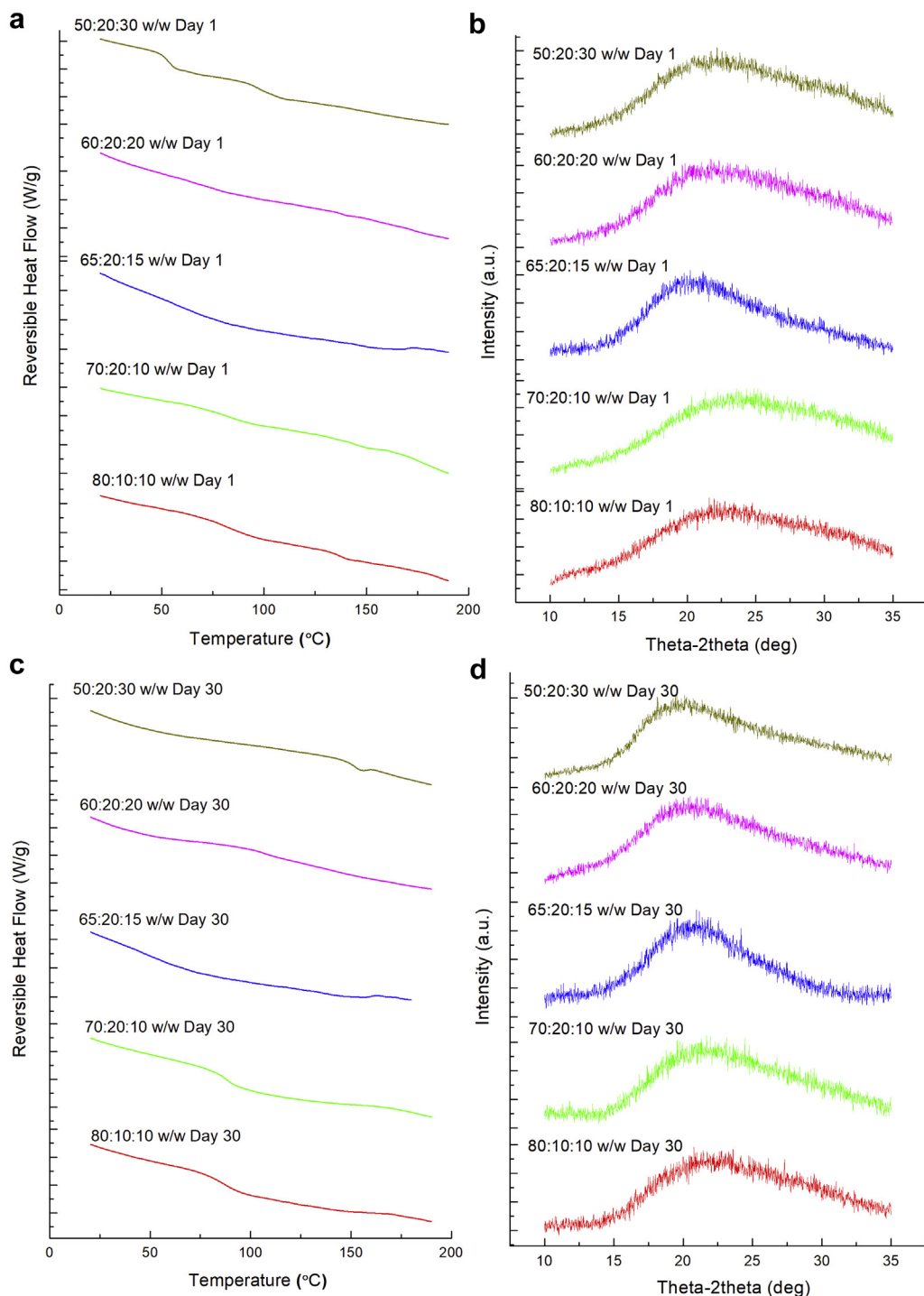
Figure 2. (a) DSC and (b) PXRD scans of freshly prepared films of HPMCAS-ITZ-P407 ternary mixtures on day 1, and (c) DSC and (d) PXRD of the same films after exposure to 40°C and 75% RH for 30 d (day 30). The polymer-drug-surfactant ratio is noted along with each scan.

fresh and aged films containing 50% HPMCAS, 20% ITZ and 30% P407, there were melting endotherms at 152°C that may possibly be attributed to the crystalline ITZ or some other phase transformation (Figs. 4a and 4c). The PLM analysis also indicates slight birefringence when the 50:20:30 w/w HPMCAS-ITZ-TPGS films on day 30 and no such birefringence was observed in any other films. Thus, the results demonstrate that up to 20% ITZ was miscible in the ternary mixture containing up to 20% TPGS.

Physical Stability of Crushed Extrudates

Melt extrudates of ITZ in HPMCAS were prepared by using 20% ITZ and 0, 10, and 15% of each of the 3 surfactants. The extrudates were composed of the following ratios of different components: HPMCAS-ITZ, 80:20 w/w; HPMCAS-ITZ-P188, 70:20:10 and 65:20:15 w/w; HPMCAS-ITZ-P407, 70:20:10 and 65:20:15 w/w; and HPMCAS-ITZ-TPGS, 70:20:10 and 65:20:15 w/w. Filaments
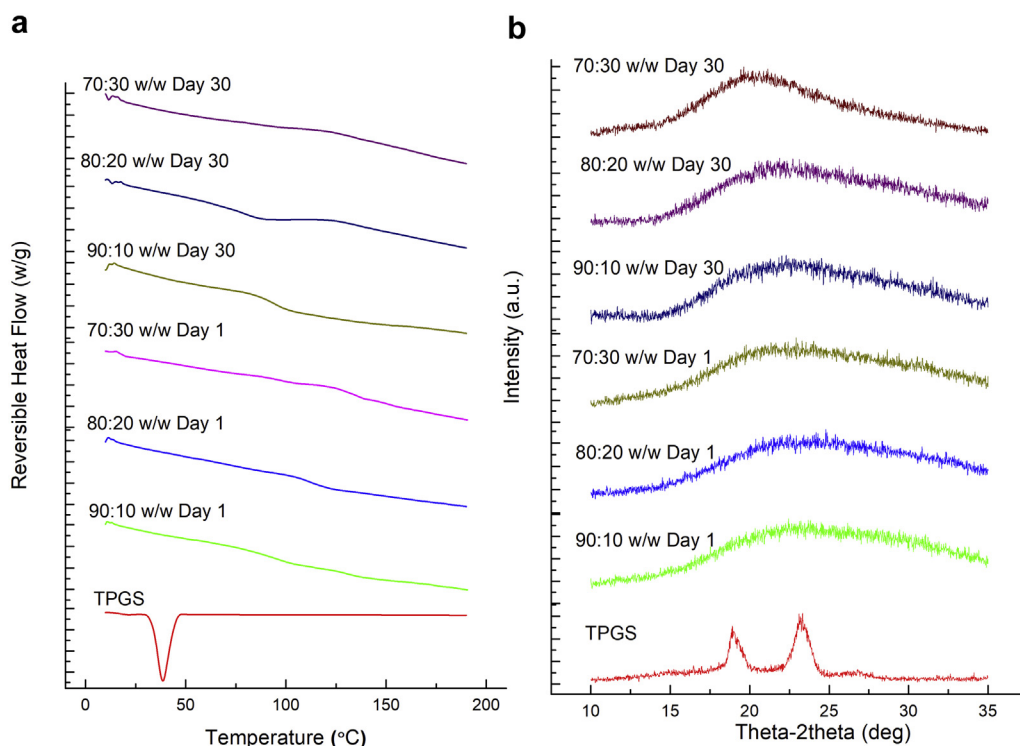
Figure 3. (a) DSC and (b) PXRD scans of freshly prepared films (day 1) of HPMCAS-TPGS binary mixtures and after exposing them to 40°C and 75% RH for 30 d (day 30). The HPMCAS to TPGS ratio is noted along with each scan.

obtained from the extruder were crushed and exposed to 40°C and 75% RH for up to 30 days. Physical stability of the crushed extrudates as compared to the freshly prepared samples was evaluated by DSC (reversible heat flow vs. temp) and PXRD, and the results are given in Figure 5. The freshly crushed filaments of the HPMCAS-ITZ mixture (80:20 w/w) exhibited a single T_g at around 100°C indicating the formation of ASD, which was in agreement with the value reported by Lang et al.[26] On exposure to 40°C and 75% RH, the T_g decreased to 65°C, indicating plasticization of the polymer in presence of moisture.[42] Nonetheless, there was no ITZ melting peak observed, thus confirming miscibility of the system and physical stability of ASD formed. The freshly crushed extrudates of ternary mixtures containing 10% and 15% w/w surfactants exhibited single T_g values at ~58 and ~48°C, respectively, indicating the formation of a single-phase solid dispersion system. On exposure of the ternary mixtures to 40°C and 75% RH, the systems remained amorphous as there were no endotherms observed; however, there were also no clearly distinguishable T_g observed, possibly because of the complexity of the quaternary systems formed after the absorption of moisture.

In addition to reversible heat flow versus temperature as determined by modulated DSC and shown in Figure 5, DSC scans of total heat flow versus temperature of freshly crushed extrudates and after exposing them to 40°C and 75% RH for 1 month were recorded to further corroborate the absence of drug or surfactant endotherm, and the results are shown in Figure 6. There were no endotherms in any of the scans, indicating the formation of ASD. Interestingly, on exposure to 40°C and 75% RH, crushed extrudates showed a broad endotherm from 50°C to 125°C, which might be due to the removal of moisture during heating. As shown in Figures 5 and 6, all extrudates were amorphous as indicated by the lack of any DSC melting endotherms and the absence of PXRD crystalline peaks of ITZ. There were no changes in the DSC scans and PXRD patterns on exposure to 40°C and 75% RH for 30 days,

indicating physical stability of ASD. The results of the stability testing of the crushed extrudates are also in agreement with that of the miscibility testing by film casting.

Dissolution Studies

HPMCAS is an enteric coating polymer that remains unionized at pH < 5.5. It dissolves in the intestinal pH range of 6 to 7.5 to form solutions or colloidal dispersions.[27,41] However, drug release in the acidic pH condition of stomach is desirable for the rapid absorption and onset of action. If dosage forms contain HPMCAS that dissolves only in the intestine, the transit time from the stomach to the intestine will considerably delay the drug release, and, hence, the onset of action. Such transit time may also be variable depending on whether the drug is taken with food or not, thus leading to the variation in drug action.[23] Therefore, as mentioned earlier, one of the objectives of the present investigation was to study whether the addition of surfactant to the formulation would increase drug release at the low gastric pH condition. For these reasons, to study the impact of surfactant on drug release, dissolution tests of crushed extrudates were carried out with the USP dissolution apparatus II, using 500 mg of the extrudate containing 100 mg of ITZ in each test. Each test was conducted for 2 h in 0.1 N HCl (pH 1), followed by additional 5 h after adjusting the pH to 6.8. In addition, the effect of surfactant on possible supersaturation and precipitation of drug in the intestinal pH condition was studied.

Drug Release From ASDs Without and With 10% w/w Surfactants

Dissolution profiles of ASDs consisting of HPMCAS-ITZ (20:80 w/w) and HPMCAS-ITZ-surfactant (70:20:10 w/w) mixtures are shown Figure 7a. Three different surfactants, namely poloxamer 188 (P188), poloxamer 407 (P407), and TPGS, were used separately in the mixtures. The ASD containing the HPMCAS-ITZ mixture
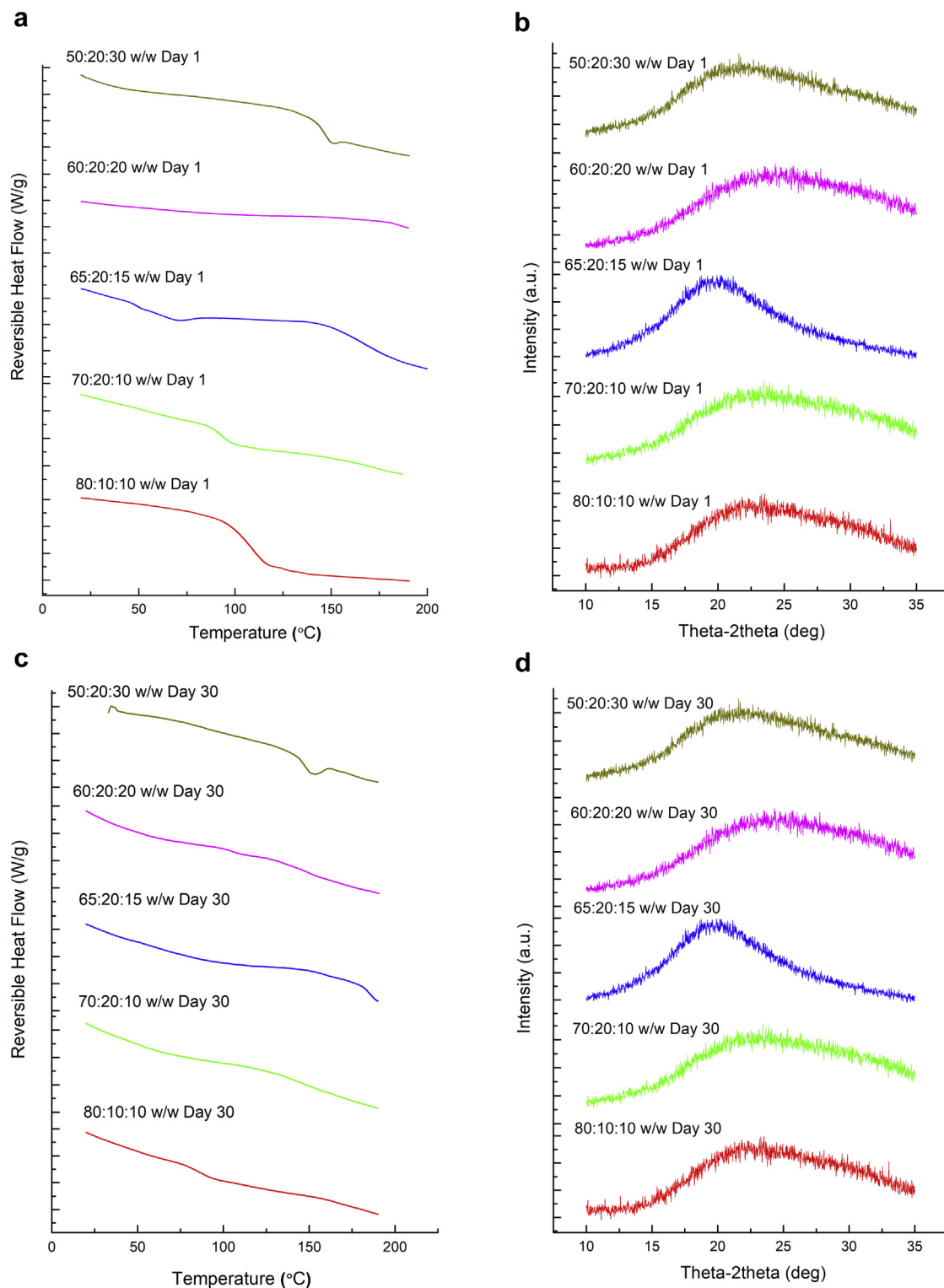
Figure 4. (a) DSC and (b) PXRD scans of the freshly prepared films (day 1) of ternary mixtures of HPMCAS-ITZ-TPGS, and (c) DSC and (d) PXRD of the same films on day 30 after exposure to 40°C and 75% RH. The polymer-drug-surfactant ratio is noted along with each scan.

without added surfactant showed only 8% drug release at pH 1, followed by up to 80% drug release when the pH was changed to 6.8. It takes ~60 min at pH 6.8 to reach the 80% of drug concentration in the dissolution medium, which remains practically unchanged for another 4 h, indicating the absence of any drug precipitation. As mentioned earlier, ITZ is a weakly basic drug with the pK$_a$ value of 3.7 and having the solubility of ~4 ng/mL for the

unionized species at pH 6.8. Thus, having 80% of the drug (out of 100 mg) being present in ~330 mL of the dissolution medium (after pH adjustment) when filtered through the 0.45-μm filter represents apparent supersaturation of almost 60,000 times. Such extreme supersaturation and the lack of drug precipitation may be attributed to the interaction between the basic ITZ and acidic HPMCAS containing acetyl and succinyl groups.
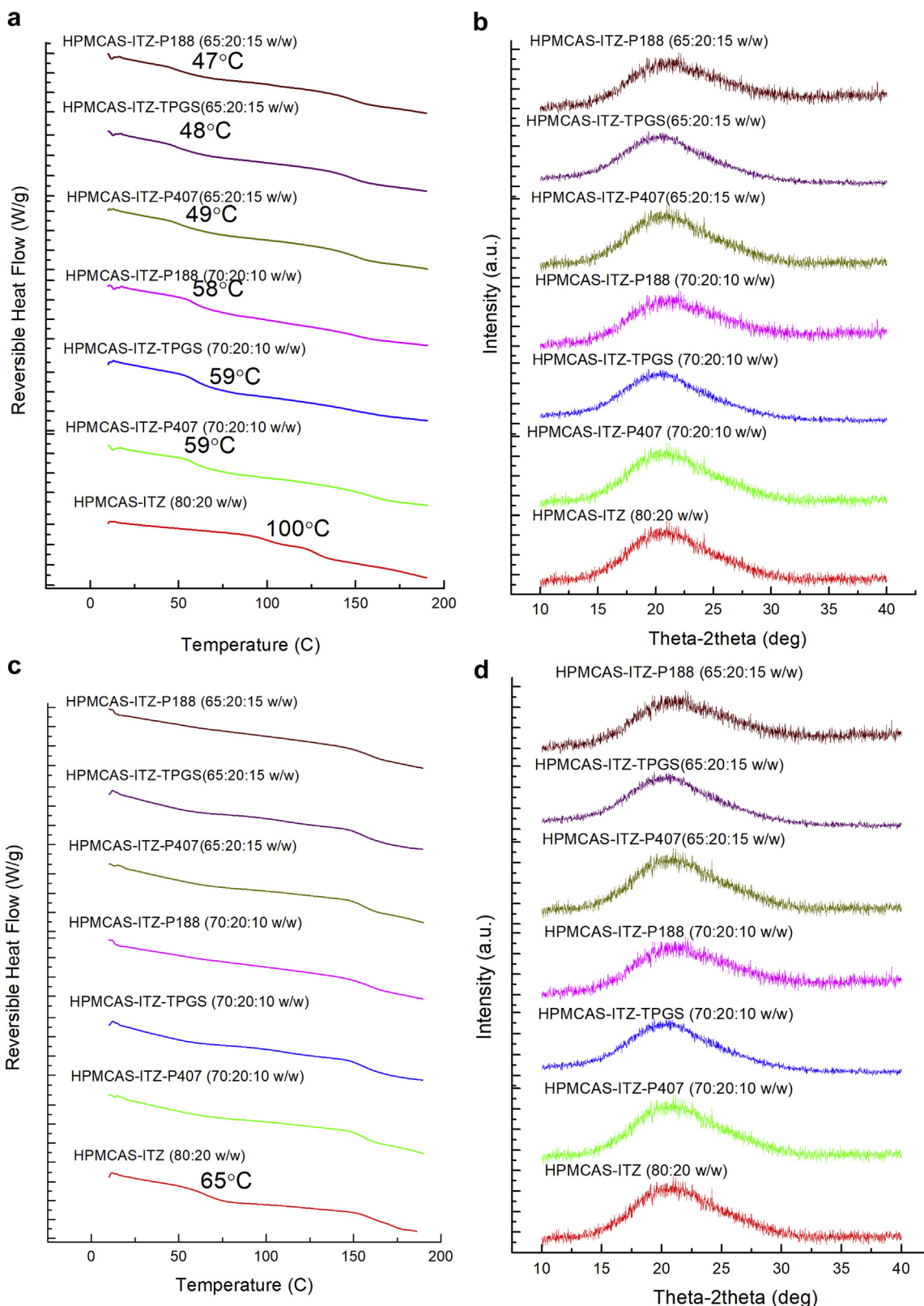
Figure 5. (a) DSC and (b) PXRD scans of freshly crushed extrudates of ternary mixtures containing HPMCAS-ITZ-surfactant on day 1, and (c) DSC and (d) PXRD scans of the same after exposure to 40°C and 75% RH for 30 d (day 30). The distinct glass transition temperatures (Tg) are indicated for DSC scans.

Although it is customary to measure drug concentration during dissolution testing after filtration through 0.45 μm filters, which is the pore size recommended by the USP,[51] it was of interest to determine whether ITZ was molecularly distributed in the dissolution medium or it was dispersed as extremely fine colloidal particles that would pass through the 0.45 μm filters. There were 2
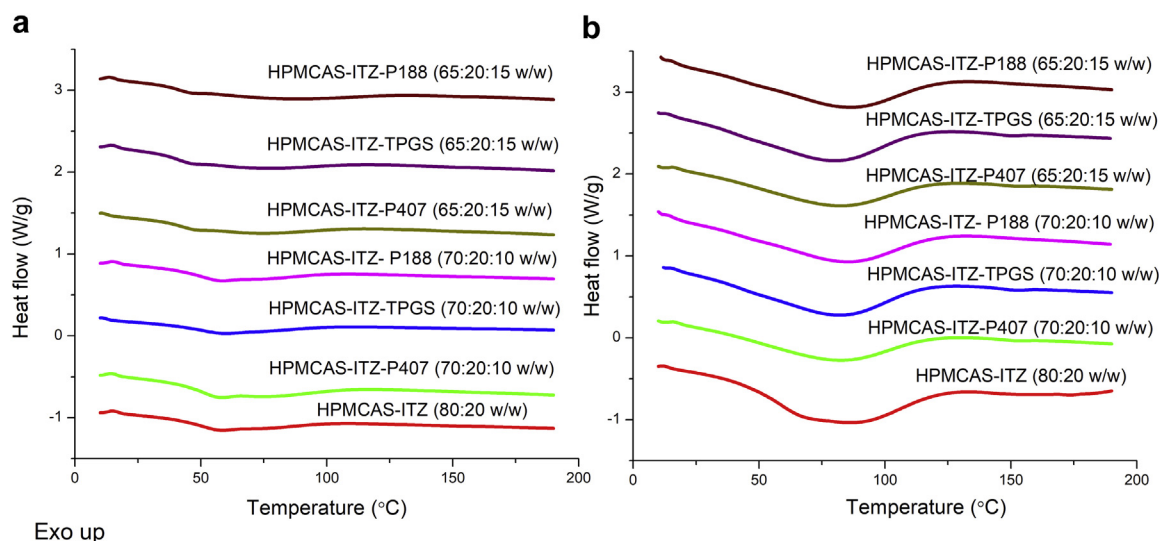
Figure 6. DSC scans (total heat flow vs. temperature) of (a) freshly prepared crushed extrudates (day 1) and (b) after exposure to 40°C and 75% RH for 30 d (day 30). Y-axis scale for (a) and (b) are kept the same to compare thermal events. After exposure of crushed extrudates to 40°C and 75% RH, DSC scans show broad endotherm until about 125°C, which indicates the presence of moisture. The absence of ITZ endotherm at 166°C indicates the physical stability of ASD.

reasons for such an interest: first, both unfiltered and filtered dissolution media after the dissolution of drug appeared slightly translucent and, second, there was a discrepancy between concentrations of ITZ in unfiltered and filtered solutions during dissolution testing of the ITZ-HPMCAS solid dispersion at pH 6.8 (100% in unfiltered solution vs. 80% in filtered solution). The results of the particle size analysis of the filtrates during dissolution testing of the HPMCS-ITZ (80:20 w/w) ASD at pH 6.8 is given in Figure 7b. It was found that the ASD indeed formed a colloidal suspension in the dissolution medium at pH 6.8. The average particle size of the colloidal dispersion of ITZ at pH 6.8 at 180 min was ~350 nm, which increased with time to ~400 nm at 420 min. Only about 80% of ITZ passed through the 0.45-μm filter possibly because a certain fraction of the dispersed particles in the dissolution medium was >450 nm and did not pass through the filters.

Figure 7a also shows the dissolution profiles HPMCAS-ITZ-surfactant ASDs containing 20% ITZ and 10% of each surfactant used. While the drug release from the solid dispersion at pH 1 in absence of any surfactant was only 8%, the presence of 10% P407 in the ASD increased the drug release to 40% in 2 h. The ASD containing 10% TPGS exhibited ~20% drug release at 2 h. In contrast, no significant improvement in drug release at 2 h was observed when 10% P188 was present in the formulation. During all these tests at pH 1, substantial amounts of crushed extrudates were observed to be either settled at the bottom of the dissolution vessels or floating around in the dissolution media. The materials rapidly dissolved when the pH was changed to 6.8, where almost complete drug dissolution (90%-100%) was observed when the filtered aliquots were analyzed for the drug content. The particle size analysis of the filtrates, however, showed that the drug was present in the filtrates as colloidal dispersions with particle sizes in the vicinity of ~300 nm. The presence of surfactants decreased the particle size of colloidal dispersions as compared to that without any surfactant. The reduction in particle size enabled passage of the particles through the 0.45-μm filter, and, as a consequence, the dissolution profiles showed close to 100% drug concentrations.

Drug Release From ASDs With 15% w/w Surfactants

The results of drug release and particle size analyses of ASDs containing 15% w/w of surfactants are, respectively, shown in

Figure 7. (a) *In vitro* step dissolution of crushed extrudates of polymer-drug (80:20 w/w) and polymer-drug-surfactant (70:20:10 w/w) mixtures at pH 1 for 2 h, followed by additional 5 h after changing pH to 6.8. Aliquots were filtered through 0.45 μm pore size filters. (b) Particle size analyses of unfiltered aliquots withdrawn from pH 6.8 media, indicating *in situ* nanoparticle formation. Each data point represents the average of 3 determinations.

Figure 9. Solubility of ITZ at 0.1, 2, 5, and 10% w/w surfactant concentration in the 0.1 N HCl (pH 1) medium at 37°C after equilibration for 24 h. Each data point represents the average of 3 determinations.

solvation of the system and, thereby, facilitated diffusion of the drug from the polymeric matrix.[60] However, in the present investigation, there were distinct differences in the effect of 3 different surfactants on the release of ITZ from ASDs at pH 1 (Figs. 7 and 8). For this reason, any possible effects of the physicochemical properties of surfactants on drug release were further explored. Several physicochemical attributes of the surfactants are listed in Table 2. Chemically, poloxamers are ABA type of block copolymers containing hydrophilic ethylene oxide (A) and hydrophobic propylene oxide (B) chains, where the difference among different grades of poloxamers lies in the number of A and B chains present and their molecular weights. Because of such differences, P188 has higher hydrophilic lipophilic balance (HLB) value and higher critical micellar concentration (CMC) than that of P407. TPGS is also an amphiphilic surfactant chemically comprised of hydrophobic α-tocopheryl (vitamin E) succinate and hydrophilic polyethylene glycol 1000, and it has the lowest HLB value among the 3 surfactants and the CMC close to that of P407.[61-63]

There appears to be a good correlation between HLB values of surfactants and the increase in the dissolution rate at pH 1. The dissolution rate increased in the order of P188 < P407 < TPGS, indicating that higher dissolution rate was observed as the HLB value decreased. The most hydrophilic surfactant P188 provided the lowest dissolution rate. Lesser hydrophilic P407 and TPGS with the low HLB values of 22 and 13, respectively, provided progressively higher dissolution rates. Serajuddin et al.[64,65] reported that water-insoluble liquid or amorphous layers of poorly water-soluble drugs are formed on the surface of solid dispersions during dissolution, thus blocking further release from inside the ASD pellets or particles, and the presence of surfactants in ASDs prevents the formation of such layers by emulsifying or suspending the liberating drug. It is apparent in the present investigation that the lower HLB value of surfactants favors more efficient removal of drug from the dissolving surface.
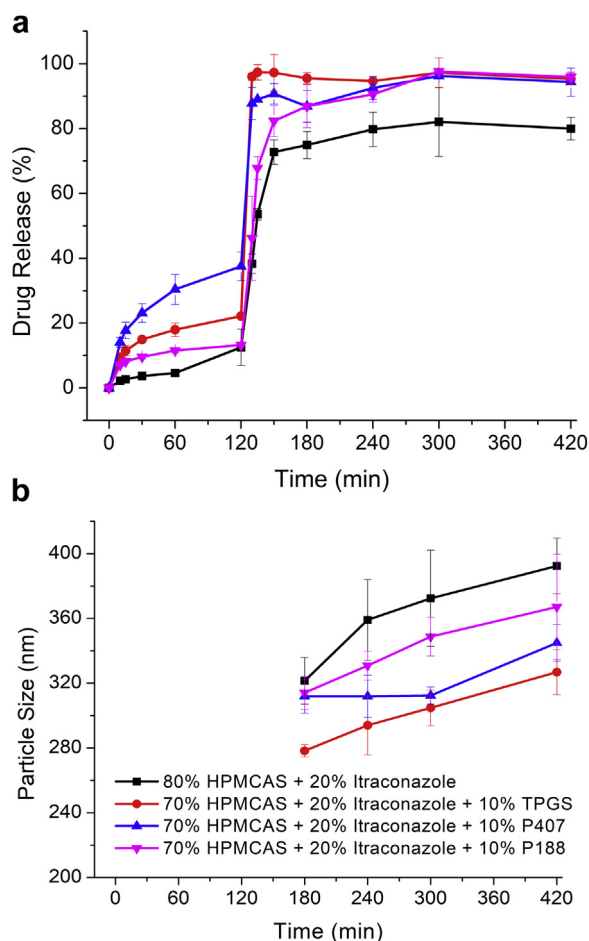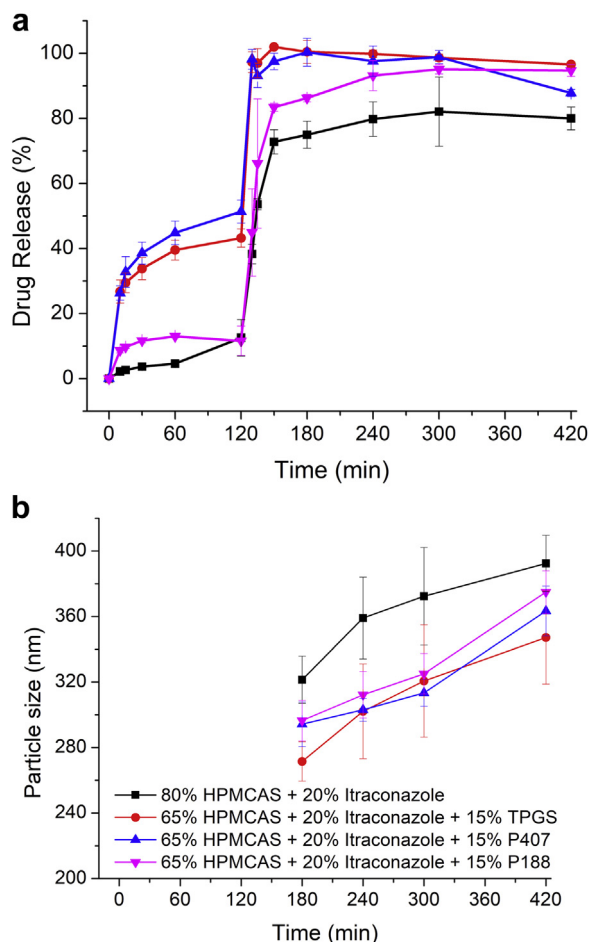
Figure 8. (a) *In vitro* step dissolution of crushed extrudates of polymer-drug (80:20 w/w) and polymer-drug-surfactant (65:20:15 w/w) mixtures at pH 1 for 2 h, followed by additional 5 h after changing pH to 6.8. Aliquots were filtered through 0.45 μm pore size filters. (b) Particle size analyses of unfiltered aliquots withdrawn from pH 6.8 media, indicating *in situ* nanoparticle formation. Each data point represents the average of 3 determinations.

Figures 8a and 8b. At pH 1, solid dispersions containing P407 provided the highest drug release of 50%, which was followed by 40% drug release from the formulation containing 15% TPGS. Poloxamer 188, however, did not provide any significant increase in drug dissolution in 2 h in the pH 1 medium as compared to the solid dispersion that did not contain any surfactant. The dissolution was rapid and almost complete (90%-100%) when the pH was changed to 6.8. Formulations containing 15% surfactants provided similar particle sizes in pH 6.8 dissolution media as those with 10% surfactants.

Possible Mechanism of the Effects of Surfactants on Drug Release and Supersaturation

The enhanced drug release from ASD in the presence of surfactants has previously been reported to be due to improved
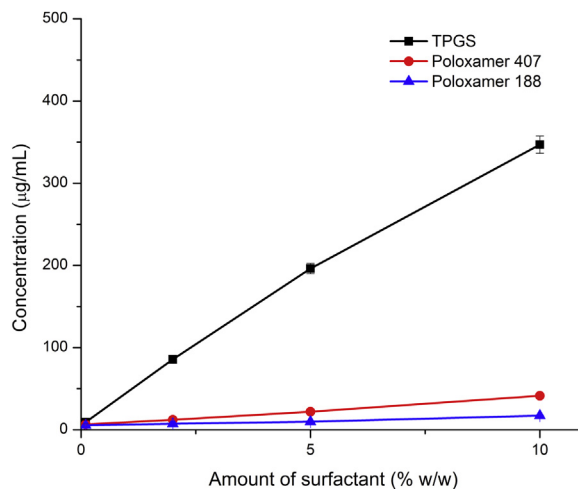
Table 2
Physicochemical Properties of Surfactants and Their Maximum Attainable Concentrations in 250 mL of Dissolution Medium at pH 1 After Dissolution of Amorphous Solid Dispersion Containing 100-mg Equivalent of Itraconazole

Surfactant	Mol Wt (g/mol)	HLB	CMC (mg/mL)	Surfactant Concentration in 250 mL of Dissolution Medium (mg/mL)	
				Polymer-Drug-Surfactant Ratio (70:20:10 w/w)	Polymer-Drug-Surfactant Ratio (65:20:15 w/w)
Poloxamer 188 (P188)	8400	29	65	0.2	0.3
Poloxamer 407 (P407)	12,600	22	0.07	0.2	0.3
TPGS	1500	13	0.15	0.2	—

There also appear to be some effects of the CMC of surfactants on drug release. P188, which has the highest CMC, has the lowest influence on drug release. On the other hand, P407 and TPGS that have closely similar CMCs provided higher drug release, which could be due to greater solubilization of drug in surfactants, hence higher release at pH 1. If all the surfactants from the added ASDs with 10% and 15% w/w surfactants were dissolved in 250 mL of the pH 1 dissolution medium used, the surfactant concentrations in the media would, respectively, be 0.2 and 0.3 mg/mL. These concentrations are higher than the CMCs of P407 and TPGS, which could be responsible for higher drug concentrations in the pH 1 dissolution media as compared to that with P188, especially in formulations containing 15% surfactant.

There could also be another possible mechanism for the difference in drug release from formulations containing different surfactants, which is the local solubilization of drug on the surface of or in the microenvironment of the ASD during dissolution testing. For this reason, the effects of the 3 surfactants on drug solubility in 0.1 N HCl were determined at 37°C, and the results are shown in Figure 9. The drug solubility increased in the order of P188, P407, and TPGS, and this is also the order at which the dissolution rate of drug increased. The drug solubility is about double in P407 than P188, which could be the reason of higher drug release at pH 1 from solid dispersions containing P407 than that with P188. It is also possible that a combination of all 3 mechanisms mentioned previously, namely, HLB, CMC, and drug solubility may participate in drug release from solid dispersions containing surfactants.

With respect to the dissolution of ASD at pH 6.8, there are numerous reports in the literature on the supersaturation of drugs in the dissolution media. The supersaturation is expected to greatly increase drug permeation or flux through intestinal membranes as it provides a much higher concentration gradient.[66,67] When all 100 mg of ITZ dissolves in 330 mL of the pH 6.8 dissolution medium in the present investigation, the degree of supersaturation is ~75,000 times considering that the maximum solubility of the drug at this pH is only 4 ng/mL. The results of the present investigation show that the drug may, however, not be present as molecular solutions in the apparently supersaturated solutions. They may indeed be present as very fine particles which would require further dissolution before the drug may be absorbed. Because the nanoparticles are extremely fine and remain in the dispersed state, it may be expected that they would rapidly dissolve and be absorbed. Surfactants and lipid digestion products present in the gastrointestinal tract may also facilitate redissolution of any precipitated drug. The supersaturation and the formation of very fine nanoparticles could be due to possible hydrogen bonding between the basic moieties of ITZ and acidic moieties of HPMCAS. Such interactions between ITZ with dicarboxylic and tricarboxylic acids have been reported in the literature.[10]

Conclusions

In the present study, HPMCAS-based ASDs with the incorporation of surfactants have been prepared by HME. ITZ, a poorly water-soluble weak base, was used as a model compound. ASDs containing polymer-drug-surfactant mixtures have been found to be miscible by film casting, and crushed extrudates were stable for at least 1 month under accelerated stability testing condition of 40°C and 75% RH. The surfactants worked as plasticizers for HPMCAS and thus enabled processing of ASDs at a relatively lower temperature. ASDs containing surfactants showed higher drug release at the low gastric pH condition as compared to solid dispersions containing polymer and drug only. Surfactants also helped in rapid and complete dissolution of ASDs at pH 6.8. It was, however, observed that the apparently supersaturated solutions formed at pH 6.8 were

indeed colloidal dispersions of very fine particles having a particle size <400 nm. Nonetheless, it is expected that the nanoparticles formed *in situ* would redissolve rapidly and thus provide higher bioavailability of poorly water-soluble drugs.

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