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Comparison of HPMCAS Chemical Grades (L, M, and H) for Amorphous Solid Dispersion by Hot-Melt Extrusion. II: Polymer-Drug-Surfactant Miscibility and Drug Release with Itraconazole as a Model Drug

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ABSTRACT

Original Article

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is commonly used to develop amorphous solid dispersions (ASDs), but its use is mostly limited to spray-dried preparations. Although hot-melt extrusion (HME) is a simpler, continuous method for preparing ASDs, it is rarely used with HPMCAS. To assess the application of the polymer in HME, we compared physicochemical attributes of three HPMCAS grades (L, M, and H) and, in Part I of the study, found no significant differences in complex viscosity or hot-melt extrudability among the three grades, with or without added drug and surfactants. In the current Part II of the study, the miscibility of the three HPMCAS grades with itraconazole (ITZ) and two surfactants, poloxamer 407 and TPGS, was evaluated, and drug release from melt extrudates of drug-polymer binary mixtures and drug-polymer-surfactant ternary mixtures with all three HPMCAS grades was compared. All HPMCAS grades exhibited similar miscibility with itraconazole and surfactants, and their ASDs showed comparable physical stability, with no evidence of crystallization after storage at 40C°/75% RH for 30 days. The ASDs of drug-polymer binary mixtures with the three HPMCAS grades, however, showed different drug release profiles in a two-step dissolution test conducted initially at pH 1, followed by a change in pH to 6.8; the L grade showed complete release of ITZ from ASDs, whereas the M grade showed ~70% and the H grade only ~10% drug release at the end of the test. Incorporation of surfactants to produce ternary mixtures improved drug release compared to their binary counterparts. At pH 6.8, there was complete drug release (~100%) from the HPMCAS-ITZ-surfactant (65:20:15 w/w) ASDs of L and M grades with poloxamer 407 and TPGS as surfactants, but the drug release was still incomplete (<40%) from the H grade. These results show that while L and M grades of HPMCAS could be suitable for developing ASDs for poorly water-soluble drugs like itraconazole by HME with satisfactory drug release, HPMCAS-H did not provide complete drug release; therefore, the use of H grade for developing ASDs by HME for dissolution improvement of poorly water-soluble drugs should be considered on a case-by-case basis.

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INTRODUCTION

Amorphous solid dispersion is a commonly used formulation strategy to improve the dissolution rate and bioavailability of poorly water-soluble drugs (1–4). Among various polymers available as carriers for ASDs, hydroxypropyl methylcellulose acetate succinate (HPMCAS) has gained popularity in recent years, as it has been demonstrated that HPMCAS is capable of maintaining the drug in a supersaturated state and inhibiting precipitation in aqueous media after dissolution (5–10). However, most marketed products with HPMCAS have been prepared using spray-drying (11,12), which presents manufacturing challenges due to the large volumes of organic solvent required to dissolve both the hydrophobic drug and the hydrophilic polymer in a single solvent system. In addition, after processing, all organic solvents must be collected and disposed of in an environmentally friendly manner, and testing is needed to confirm that any residual solvents in the ASD product meet specifications (13). Although hot melt extrusion (HME) can be used as a solvent-free, one-step, and continuous process for manufacturing ASDs (14), there has been limited use of HPMCAS in HME due to the polymer's high complex viscosity, which makes it difficult to extrude at relatively low temperatures (15). It requires >170ºC to extrude the neat HPMCAS, but it may undergo degradation at such high temperatures, liberating acetic and succinic acids (16,17). These issues are probably responsible for the paucity of HPMCAS-based commercial ASD products manufactured using HME. Only one marketed product, posaconazole delayed-release tablet (Noxafil® Delayed-release Tablet, Merck), was produced by HME using HPMCAS as the polymeric matrix (11); however, this product was discontinued from marketing by its manufacturer in 2024 due to business reasons, although its generic versions manufactured by others remain available.

HPMCAS is a cellulosic polymer produced by adding various neutral, hydrophilic, and acidic substituents to the chain structure of cellulose. A detailed description of the structures of different grades of HPMCAS was given in Part I of this series of papers. HPMCAS comes in three chemical grades, L, M, and H, with differences in their succinoyl and acetyl contents. The succinoyl contents of the L, M, and H grades are 14-18%, 10-14%, and 4-8%, respectively, while their respective acetyl contents are 5-9%, 7-11%, and 10-14%, respectively. Thus, the L grade has the highest succinoyl-to-acetyl ratio, while the H grade has the lowest. HPMCAS is a pH-sensitive enteric polymer that dissolves at different intestinal pH conditions. The highest succinoyl-to-acetyl ratio in the L grade makes it the most hydrophilic among the three grades after ionization and enables it to dissolve at a relatively lower intestinal pH of 5.5. In contrast, M and H grades dissolve at pH 6.0 and 6.8, respectively, or higher.

While different HPMCAS grades have been used for decades as pH-sensitive enteric coating materials for oral dosage forms, there is no clear guidance in the literature regarding which grades of HPMCAS to select for the development of ASDs. Although there are a few reports on the use of different grades of HPMCAS to prepare ASDs by spray drying (18,19) and rotary evaporation from organic solutions (20,21), there are very limited studies on how the differences in chemical grades would influence the melt extrusion of ASDs and drug release from the ASDs produced (22).

The successful development of ASDs by HME depends on several factors: (a) the complex viscosity of the polymers used must be such that they can be extruded at a temperature where both the polymer and drug are stable and the polymer should be fluid enough to dissolve the drug and/or additives during extrusion, (b) the polymer must be miscible with drug and any other additives, such as surfactants, plasticizers, etc., used, and (c) there must be relatively rapid and complete drug release from the extrudates under the desired pH conditions. In Part I of the study, we reported the comparative complex viscosity and extrudability of L, M, and H grades of HPMCAS by using itraconazole (ITZ) as the model drug and two different surfactants, poloxamer 407 (P407) and tocopheryl polyethylene glycol succinate (TPGS). Since the drug-polymer and drug-polymer-surfactant miscibility, as well as drug release, are critically important for developing ASDs with HPMCAS (23–25), the following are the specific objectives of Part II of the study:

- Compare the miscibility of L, M, and H grades of HPMCAS with the model drug, itraconazole (ITZ), alone and in combination with two different surfactants, poloxamer 407 (P407) and TPGS.

- Compare ITZ release from melt extrudates produced with the three different grades of HPMCAS by two-step dissolution testing, where dissolution was first conducted at

pH 1 to mimic the gastric pH condition, followed by a change to the intestinal pH condition of 6.8.

■ Compare the effect of added surfactants on drug release from ASDs produced by HME with the three grades of HPMCAS.

MATERIALS

Itraconazole (ITZ) was purchased from Attix Pharmaceuticals (Toronto, Canada). Hydroxypropyl methylcellulose acetate succinate (HPMCAS, L, M, and H grades; trade name: AquaSolve®) was donated by Ashland Chemical (Delaware, USA). Each chemical grade of HPMCAS is available in two physical forms: fine (F) and granular (G). Since the polymers melted during HME, it was assumed that their particle size would not affect the extrudate's performance; therefore, only the granular (G) materials were used in the present investigation, given their better powder flow and physical mixing with other formulation components before extrusion. Poloxamer 407 (Kolliphor® P407) and D-α-tocopherol polyethylene glycol succinate (Kolliphor® TPGS) were donated by BASF Corporation (Tarrytown, New York, USA).

METHODOLOGY

Miscibility studies

The miscibility testing of polymer-drug binary mixtures and polymer-drug-surfactant ternary mixtures was performed using the film-casting method reported earlier (23,24,26). Briefly, 1 g each of polymer-drug mixtures (80:20 w/w) and polymer-drug-surfactant mixtures (70:20:10, 65:20:15, or 60:20:20 w/w) were dissolved in 6 mL of methanol-dichloromethane mixture (1:1 v/v). The mixtures were then shaken for 1 hour in closed scintillation vials using a wrist-action shaker (Burrell Scientific, Pennsylvania, USA) to dissolve all components in the solvent. One mL of each prepared solution was poured on a glass plate, and the film was cast using an Elcometer 3540 bird film applicator (Elcometer Inc., Michigan, USA) at the 200-micron setting. The cast films were air-dried at room temperature for 7-8 hours, during which the films' thickness decreased as the solvent evaporated. The final thickness of each film was not measured, but it would decrease to <200 microns due to solvent drying. The dried films were analyzed for physical stability by examining evidence of crystallinity, or its absence, using DSC and PXRD on Day 1 and after exposure to 40ºC/75% RH for 30 days, with the samples stored in a VWR 1545 benchtop incubator (Pennsylvania, USA).

Differential scanning calorimetry (DSC)

A Q-200 differential scanning calorimeter (TA Instruments, Delaware, USA) equipped with a refrigerated cooling assembly was used to record DSC scans to determine melting points and glass transition temperatures, or to confirm the lack of them, for the different formulation components and the ASDs formed. Initially, a 5 mg sample, either a cast film or an extrudate, was crimped in the hermetic Tzero pan using a pinhole. The prepared samples were equilibrated at 5ºC. The samples were then heated to 200ºC at a rate of 5ºC/min, with a modulation of 1ºC/min. Finally, the results were analyzed using Universal Analysis software version 2000 (TA Instruments, Delaware, USA).

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded using a powder X-ray diffractometer XRD 6000 (Shimadzu, Kyoto, Japan) to determine any possible crystallinity in cast films or crushed extrudates. The diffractometer, equipped with a copper anode tube, was operated at a generator voltage of 40 kV and a current of 30 mA. A rate of 2° two-theta (2ºθ)/min was used to scan samples over the range of 10 to 35° two-theta.

Preparation of ASDs by hot-melt extrusion

A co-rotating twin screw extruder (Process 11, Thermo Fisher Scientific, Massachusetts, USA) was used to extrude polymer-drug physical mixtures with or without surfactants (P407 or TPGS). The composition of polymer-drug and polymer-drug-surfactant mixtures used for the purpose of hot-melt extrusion is provided in Table 1. Prior to HME, the various blends were prepared by premixing the samples for 10 minutes using a model WAB T2F Turbula mixer (New Jersey, USA). After premixing the physical blends, all melt extrusions studies were conducted at 160ºC to maintain a consistent processing temperature and minimize any temperature-dependent variations in their properties. The first two zones in the HME barrel, located near the feeder, were, however, set to 50ºC to allow additional powder mixing before the temperature rose to 160ºC. A screw speed of 200 RPM, a feed rate of 1.8 g/min, and a die diameter of 1.5 mm were used for hot-melt extrusion. The screw configurations used were the same as those described in Part I. The torque values generated during the melt extrusion of the mixtures at 160ºC are also provided (Table 1).

After extrusion, the filaments were cooled to room temperature and then converted into powders by soaking them in liquid nitrogen, followed by milling using a Scienceware micro-

Table 1: Composition of extruded mixtures (% w/w) and torque values for HME performed at 160 °C (N=3)[a].

Sr. No.	ITZ	HPMCAS-L	HPMCAS-M	HPMCAS-H	P407	TPGS	% Torque
1	20%	80%					60 ± 4%
2	20%		80%				61 ± 2%
3	20%			80%			57 ± 5%
4	20%	65%			15%		46 ± 5%
5	20%		65%		15%		45 ± 2%
6	20%			65%	15%		42 ± 4%
7	20%	65%				15%	45 ± 3%
8	20%		65%			15%	42± 5%
9	20%			65%		15%	42± 2%

[a] Table adapted from Part I of the manuscripts.

mill (H-B Instruments Company, Pennsylvania, USA). The powders were sieved to collect particles in the 45-212 μm range, which were considered sufficiently fine to provide a high surface area but granular enough for acceptable flow.

Dissolution testing

The comparative dissolution testing of milled ASD extrudates containing 20% w/w ITZ with all three grades of HPMCAS (HPMCAS: ITZ, 80:20 w/w) was performed using the USP dissolution apparatus 2 (Distek Inc, New Jersey, USA) at 75 RPM and 37ºC ± 0.5ºC. Dissolution rates were also determined for milled extrudates of ternary mixtures with an additional 15% w/w of either poloxamer P407 or TPGS in the ASDs (HPMCAS:ITZ:surfactant, 65:20:15 w/w). Each dissolution test was conducted with 500 mg of milled extrudate powder (45-212 μm) containing 100 mg of ITZ. During dissolution testing in round-bottom flasks, the milled filaments formed cones at the bottom of the vessels. Therefore, flat-bottom dissolution vessels (1000 mL; Distek Inc., North Brunswick, NJ, USA) were used to minimize coning. It should be noted that, to simulate the gastrointestinal tract environment, dissolution testing was first conducted in 250 mL of a pH 1 dissolution medium (0.1M HCl) (pH ~1) for 2 hours at 37ºC. Then, approximately 70 mL of preheated 0.2 M trisodium phosphate ($Na_3PO_4.12H_2O$) solution was added to adjust the pH to 6.8, and the dissolution testing was continued for an additional 2 hours. A 3-mL aliquot was collected at each time point, and an equal volume of dissolution medium was added to replace it. The aliquots were filtered using 13-mm PVDF syringe filters with a 0.45-μm pore size, in accordance with USP guidelines (27). The filtrates were then appropriately diluted with the HPLC mobile phase before analyzing drug concentrations.

Particle size analysis during dissolution testing

Concurrently with the dissolution testing, particle size analysis was performed for any colloidal drug nanoparticles formed at pH 6.8. For particle size determination, approximately 3-mL volumes of unfiltered aliquots were withdrawn at different time points during the dissolution testing at pH 6.8, and dynamic light scattering analysis was simultaneously conducted using a DelsaNano C particle size analyzer (Beckman Coulter Counter Inc., California, USA). The aliquots were returned to the dissolution vessels after particle size analysis.

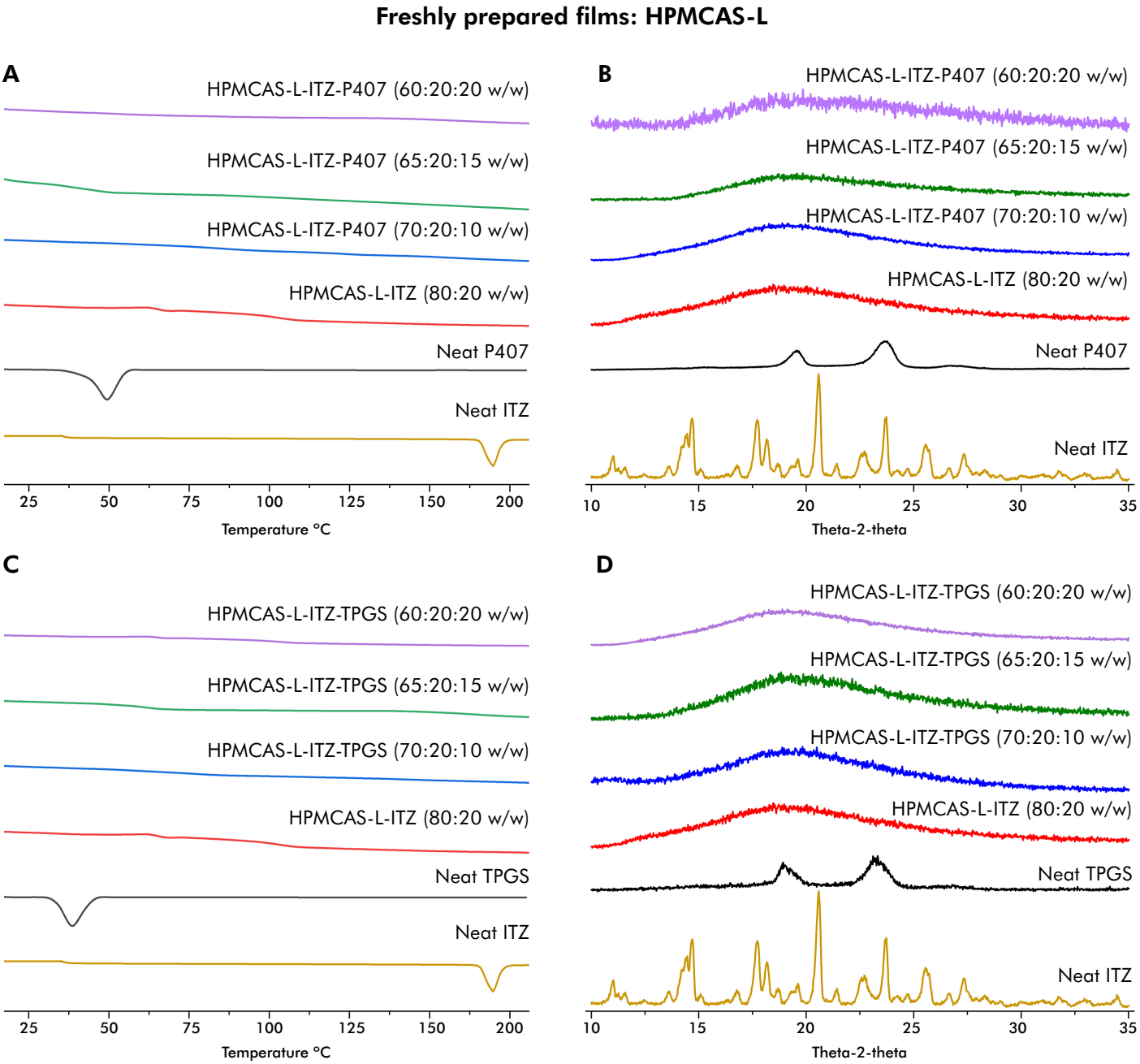
HPLC analysis

An Agilent HPLC (Agilent Technologies, California, USA) with an Agilent HC-C18 column (5 μm, 4.6x150mm) was used to analyze the ITZ content. The mobile phase was a 75:25 (v/v) mixture of acetonitrile and a 0.04 M aqueous solution of sodium acetate, containing 0.2% (v/v) triethylamine, with the pH adjusted to 4.5 with glacial acetic acid. The mobile phase flow rate was 1 mL/min, and the detection wavelength was 265 nm. For preparing a standard graph for HPLC analysis of ITZ, a stock solution was prepared by dissolving neat ITZ in the mobile phase at a concentration of 100 μg/mL. The solution was then further diluted with the mobile phase in a stepwise manner to a concentration of 0.5 μg/mL. There was linearity in the AUC of HPLC peaks between 0.5 and 100 μg/mL (data not shown).

RESULTS AND DISCUSSION

In amorphous solid dispersions, drugs, polymers, and other added components must be miscible with each other. According to Zografi and Newman (28), the polymer must form a single-phase, amorphous "miscible" system with a drug in an ASD, where the polymer-drug miscibility is governed by the same general thermodynamic principles that govern the mixing of liquids. Furthermore, these authors stated that, "the concentration of components, their molecular size and shape, and their degree of polarity and ability to interact are all critical characteristics that must be evaluated in choosing an appropriate API-polymer combination." Essentially, miscibility is taken as the components' mutual equilibrium solubility, which can be determined

Figure 1. (A) DSC scans and **(B)** PXRD patterns of freshly prepared HPMCAS-L-ITZ-P407 films, and **(C)** DSC scans and **(D)** PXRD patterns of freshly prepared HPMCAS-L-ITZ-TPGS films, at surfactant concentrations of 0, 10, 15, and 20% w/w. The DSC scans and PXRD patterns of neat ITZ, P407, and TPGS are also shown as references.



experimentally in terms of concentration and temperature by determining phase diagrams (28). Indeed, Gumaste et al. (23) previously confirmed the use of miscibility testing by film casting to construct phase diagrams of HPMCAS (M)-itraconazole-poloxamer 188 and Soluplus®-itraconazole-poloxamer 188 systems. Since the three grades of HPMCAS used in the present investigation differ chemically, we investigated whether the differences would affect their miscibility with the model drug, itraconazole, and the two surfactants, poloxamer 407 and TPGS. Instead of constructing complete phase diagrams with all three polymer grades, miscibility was compared at only a few selected concentration levels. Then, dissolution testing of ASDs produced by HME was conducted to compare their performance. The results of these studies are presented below:

Miscibility studies

The cast films of HPMCAS-ITZ binary mixtures and HPMCAS-ITZ-surfactant ternary mixtures were characterized by DSC and PXRD to assess ITZ crystallization. Although the amorphous form of the drug could initially be miscible in the films, the ASD could still be metastable relative to its crystalline forms, and eventually undergo phase transformation. To study this, the films were exposed to accelerated stability testing at 40°C/75% RH for 30 days, followed by assessment of crystallinity using DSC and PXRD. A detailed description of the results of the miscibility testing is given below:

Miscibility of freshly prepared films

It has previously been reported that HPMCAS-M and ITZ were miscible at a 50:50 w/w ratio, and that a HPMCAS-M:ITZ:poloxamer 188 mixture with a 54:23:23 w/w ratio was also miscible (23). Based on this information, the miscibility testing in the present investigation was conducted for HPMCAS-ITZ binary mixtures at an 80:20 w/w ratio and the HPMCAS-ITZ-surfactant ternary mixtures with 20% w/w ITZ and poloxamer 407 (P407) or TPGS at concentrations of 10, 15, or 20% w/w. Although miscibility testing was conducted with all three chemical grades of HPMCAS, the results of the freshly prepared samples with the L grade only are shown in Figure 1, because results for the M and H grades were very similar to those for the L grade (data for M and H grades can be provided by the authors upon request).

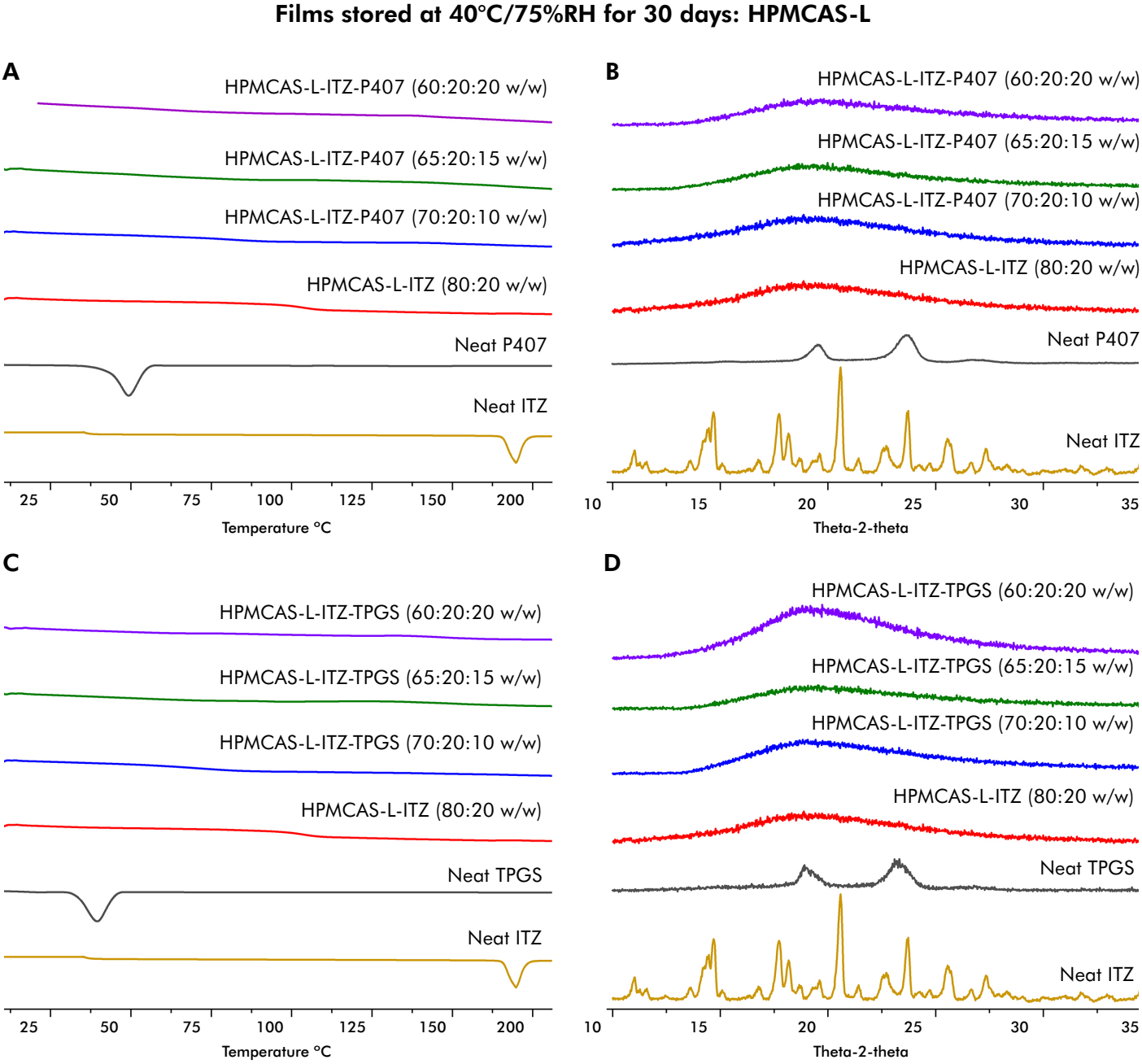
Figure 1 gives the DSC scans and PXRD patterns of freshly prepared films of 80:20 w/w binary mixtures of HPMCAS-L and ITZ and of ternary mixtures containing 20% w/w ITZ and 10, 15, or 20% w/w of either of the two surfactants used (P407 and TPGS). As indicated in Figure 1, ITZ, P407, and TPGS by themselves show evidence of crystallinity, with DSC melting peaks at 167°C, 50°C, and 37°C, respectively, and exhibit individual PXRD patterns with characteristic peaks. Additionally, it has been reported that amorphous ITZ and HPMCAS exhibit baseline shifts due to glass transition temperatures (Tg) at 59°C (29) and 121°C - 123°C (30), respectively. However, the absence of any melting peaks in the DSC scans, the absence of any characteristic peaks in PXRD patterns, and any baseline shift due to possible Tg of ITZ and HPMCAS in drug-polymer and drug-polymer-surfactant mixtures in Figure 1 demonstrate that ITZ is completely miscible with HPMCAS-L in binary mixtures and when combined with a surfactant (P407 or TPGS) in ternary mixtures with HPMCAS-L. Similar results were obtained with HPMCAS-H and HPMCAS-M (data not provided but available on request). In summary, all three grades of HPMCAS were completely miscible in polymer-ITZ binary mixtures of 80:20 w/w ratio and in ternary mixtures up to 60:20:20 w/w polymer-ITZ-surfactant ratio.

Keeping the 20% w/w drug loading constant, the surfactant concentration (P407 or TPGS) was varied at 10%, 15%, and 20% w/w, as shown in Figure 1, to investigate whether there were any differences in the miscibility of surfactants with the three grades of HPMCAS depending on their concentrations. As demonstrated by the absence of endotherms for crystalline ITZ and surfactants, and the amorphous nature in PXRD patterns in Figure 1, the ternary mixtures were miscible in freshly prepared samples (Day 1) at all surfactant concentrations up to 20% w/w with the three grades of HPMCAS (Figure 1).

Miscibility testing after exposure to accelerated stability testing conditions

Figure 2 gives the results of the miscibility testing of HPMCAS-ITZ binary mixtures and HPMCAS-ITZ-surfactant ternary mixtures using HPMCAS-L after exposure to 40°C/75% RH for 30 days. All DSC scans and PXRD patterns (Figure 2) are like those for the freshly prepared (Day 1) films in Figure 1. Similar results were also obtained with M and H grades of HPMCAS (data not shown, but available upon request). These results demonstrate that at a 20% w/w concentration of ITZ and with the addition of either P407 or TPGS at 10, 15, and 20% w/w, ITZ and surfactants are miscible with all three grades of HPMCAS. They indicate that any tri-component ASDs prepared would likely remain amorphous and be stable at 40°C/75% RH for at least 30

Figure 2. (A) DSC scans and **(B)** PXRD patterns of HPMCAS-L-ITZ-P407 films, and **(C)** DSC scans and **(D)** PXRD patterns of HPMCAS-L-ITZ-TPGS films at surfactant concentrations of 0, 10, 15, or 20% w/w, after exposure to 40°C/75% RH for 30 days. The DSC scans and PXRD patterns of neat ITZ, P407, and TPGS are also shown as references.



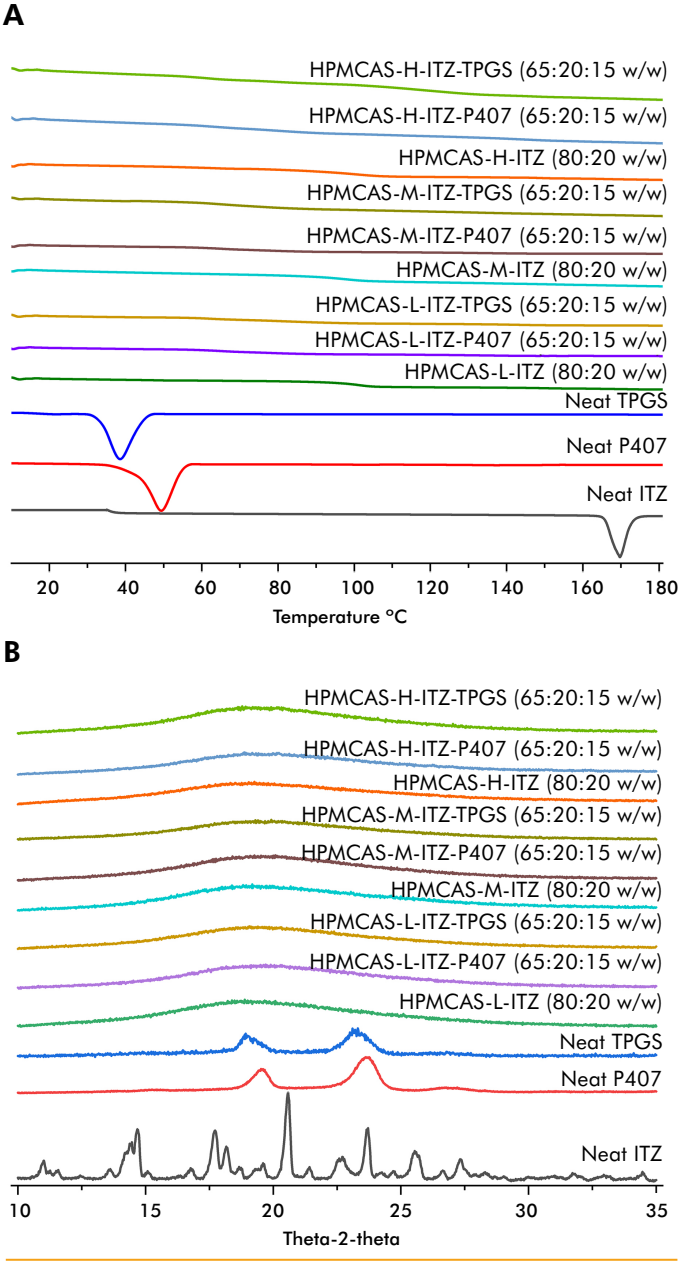
days, and all three HPMCAS grades would behave similarly. Although no long-term stability testing was conducted in the present investigation, it is likely that such systems will remain stable for much longer in ambient conditions with lower temperatures and lower humidity.

Characterization of ASDs prepared by HME

Based on the results of the HPMCAS-ITZ-surfactant miscibility testing described above, the mixtures of the three HPMCAS grades with ITZ were prepared at the 80:20 w/w ratio, and those with ITZ and surfactant (poloxamer 407 or TPGS) were prepared at 65:20:15 w/w HPMCAS:ITZ:

surfactant ratio (Table 1). These mixtures were selected based on their torque values, which all fell within an acceptable range. The drug-polymer mixtures with all three grades of HPMCAS produced torque in the range of 57-61% at 160ºC. With the plasticizing effects of surfactants on HPMCAS, the ternary mixtures produced much lower torque in the 42-45% range.

Figure 3. (A) DSC scans and **(B)** PXRD patterns of milled extrudates of HPMCAS-ITZ, HPMCAS-ITZ-P407, and HPMCAS-ITZ-TPGS mixtures containing 20% w/w ITZ and 15% w/w surfactant (P407 or TPGS) with all three grades of HPMCAS. The DSC scans and PXRD patterns of neat itraconazole, P407, and TPGS are also shown as references.



The results of the DSC and PXRD analyses of the extrudates are given in Figure 3. In agreement with the miscibility testing by film casting (Figures 1 and 2), none of the prepared ASDs showed a crystalline drug peak around 167°C (the melting point of ITZ), confirming that ITZ was completely amorphized in the prepared ASDs. Additionally, no peak was noticed at 37ºC or 50ºC (melting points of TPGS and P407, respectively) (Figure 3A), indicating that the surfactants also turned completely amorphous. The PXRD patterns (Figure 3B) show only amorphous halos and no crystalline peaks, confirming that both the API and surfactants are in an amorphous state after HME processing.

Overall, the results demonstrate good agreement between miscibility results for the binary and ternary mixtures in cast films and melt-extruded ASDs, and that there are no differences among the three grades of HPMCAS with respect to their miscibility with itraconazole and either of the two surfactants.

Comparative *in vitro* dissolution of ASDs

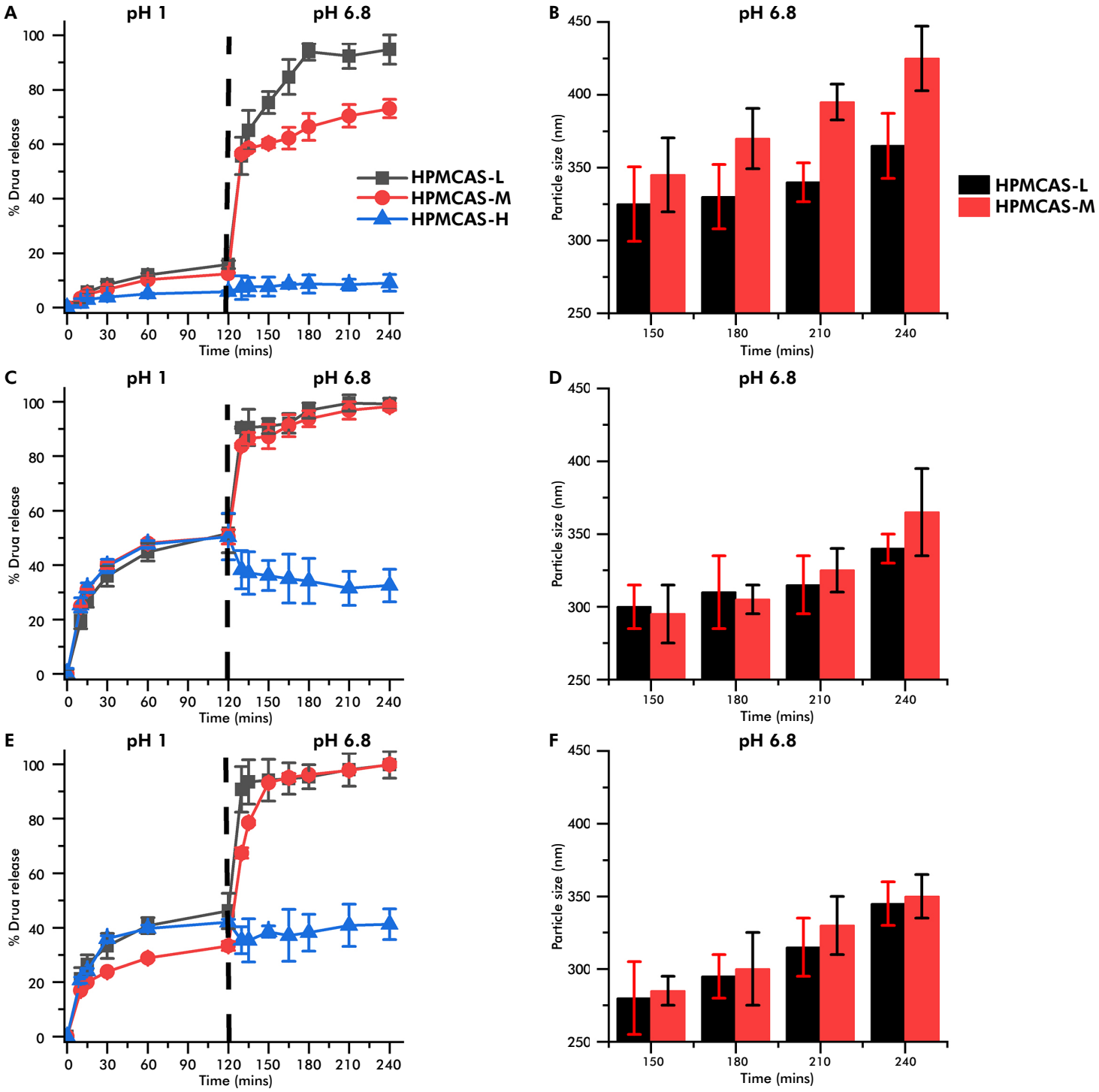
The results of the dissolution testing of ASDs containing three grades of HPMCAS in binary mixtures with ITZ (80:20 w/w HPMCAS: ITZ) are shown in Figure 4A, and ternary mixtures containing 15% w/w poloxamer 407 or TPGS (HPMCAS:ITZ:surfactant ratio, 65:20:15 w/w) are given in Figures 4C and 4E, respectively. The corresponding particle sizes of the aqueous dispersions in dissolution media collected during dissolution testing of extrudates containing L and M polymer grades in pH 6.8 media are shown in Figures 4B, 4D, and 4F, respectively. No particle size was determined in pH 1 media since the ASDs did not disperse at this pH, and, similarly, no particle size determination for the HPMCAS-H ASDs at pH 6.8 was made, as the materials did not disperse in this medium either.

The interpretation of the drug release profiles and particle size analysis data from dissolution testing presented in different sub-figures of Figure 4 is provided in the following two sections:

Dissolution of binary ASDs (HPMCAS and ITZ)

Dissolution profiles of 80:20 w/w HPMCAS-ITZ ASDs with all three HPMCAS grades without any surfactants present in the formulations (Formulations 1, 2, and 3 in Table 1 are shown in Figure 4A. As enteric polymers with acidic groups that ionize at relatively high intestinal pH, all HPMCAS grades remain practically insoluble at pH 1, and any drug release from ASDs at this pH would be by diffusion

Figure 4. *In vitro* dissolution (**A**, **C**, and **E**) and particle size analysis in dissolution media (**B**, **D**, and **F**) of milled extrudates (ASDs), where **4A**: *in vitro* dissolution of ASDs containing binary mixtures of HPMCAS-L, M, and H with ITZ (80:20 w/w); **4B**: particle size analysis during dissolution testing of ASDs containing binary mixtures HPMCAS-L and M with ITZ (80:20 w/w); **4C**: *in vitro* dissolution of ASDs containing ternary mixtures of HPMCAS-L, M, or H with ITZ and poloxamer 407 (65:20:15 w/w); **4D**: particle size analysis during dissolution testing of ASDs containing ternary mixtures of HPMCAS-L and M with ITZ and poloxamer 407 (65:20:15 w/w); **4E**: *in vitro* dissolution of ASDs containing ternary mixtures of HPMCAS-L, M, or H with ITZ and TPGS (65:20:15 w/w); and **4F**: particle size analysis during dissolution testing of ASDs containing ternary mixtures of HPMCAS-L and M with ITZ and TPGS (65:20:15 w/w).



only (31). Therefore, the release of ITZ from L, M, and H grades of HPMCAS at pH 1 over a 2-hour period was incomplete, with the amounts released being, respectively, ~15%, 12%, and 6% of the total drug (100 mg) present in the extrudate powders added. There were, however, major differences in drug release rates from the three grades of HPMCAS after a pH change to 6.8 at 2 hours: the L and M grades released rapidly, whereas the H grade did not. The total amounts of ITZ released after 240 min were 94, 73, and <10%, for ASDs made with the L, M, and H grades, respectively. Sarabu et al. (22) also obtained similar results during *in vitro* dissolution of a model drug, nifedipine, from ASDs prepared by HME using the three HPMCAS grades. They observed almost complete drug release from L and M grades in 900 mL of pH 6.8 phosphate buffer within 60 minutes from ASDs containing 101 mg equivalent of nifedipine, but only 23% drug release from HPMCAS-H ASDs at 2 hours.

ITZ is a weakly basic drug having a pKa value of 3.7 and poor aqueous solubility of ~4 ng/mL at pH 7.0 (32), and, therefore, in the present investigation, only ~1.3 mg of ITZ would be expected to dissolve in approximately 320 mL of dissolution media present after the change in pH to 6.8. This represents approximately 1.3% of the total ITZ equivalent (100 mg) of ASD added to the dissolution medium. Therefore, in the absence of any supersaturation and its maintenance by the ASD, most of the ITZ would be expected to precipitate from the dissolution media. However, as mentioned above, there were, respectively, 94 and 73 percent drug dissolution at pH 6.8 from ASDs with L and M grades of HPMCAS, and only the H grade gave <10% drug release.

Further studies were conducted to determine the cause of the apparently high drug dissolution from ASDs containing HPMCAS-L and HPMCAS-M, despite the low solubility of ITZ. Visually, ASDs containing these two HPMCAS grades dispersed fully in aqueous media at pH 6.8, but the media turned translucent and whitish. In contrast, the media were relatively transparent, with large particles of ASDs swirling around in the media from ASDs with HPMCAS-H, indicating the relative lack of drug release or aqueous dispersion. Therefore, particle size analysis of the dissolution medium was conducted before filtration to determine whether the high ITZ concentrations observed in ASDs containing HPMCAS-L and HPMCAS-M could be due to the formation of any dispersed drug that passed through 0.45-µm pore-size filters during dissolution testing. The results of the particle size analysis of pH 6.8 dissolution media containing ASDs with L and M grades of HPMCAS are given in Figure 4B. For the ASD with HPMCAS-L, the average particle sizes at 150- and 240-minute time points were ~325 and ~365 nm, respectively, and, with HPMCAS-M, they were, respectively, ~345 and ~425 nm, showing that the colloidal nanoparticles of ITZ or ITZ-polymer aggregates were produced during dissolution testing of ASDs with HPMCAS-L and HPMCAS-M. Thus, particle-size analysis of the dissolution media confirms that the high dissolution rates of ITZ observed from ASDs containing HPMCAS-L and M were due to the formation of fine nanoparticles in the dissolution media. Particle sizes were not determined for ASDs with HPMCAS-H during dissolution testing, as most extrudates swirled in aqueous media as large particles, and the particle size was above the detection limit since the ASDs did not disperse into submicron particles.

As mentioned earlier, the major difference among the three grades of HPMCAS is the ratio of their succinoyl to acetyl groups; the higher the ratio, the more acidic the polymer is. Consequently, the three grades of HPMCAS dissolve in aqueous media at different pH ranges as follows: HPMCAS-L at pH ≥ 5.5, HPMCAS-M at pH ≥ 6.0, and HPMCAS-H at pH ≥ 6.8. These differences are reflected in the dissolution of ASDs with the three grades of HPMCAS, as indicated in Figure 4A. Additionally, as reported by Wang et al. (33), the aggregation behavior of the three grades of HPMCAS after dissolution in aqueous media also differs, where the aggregation decreases in the following order: HMPCAS-L>HPMCAS-M>HPMCAS-H, and the lower the aggregation, the less ability of the polymer to maintain supersaturation of the drug in dissolution media. Therefore, such a difference in the aggregation of the three grades of HPMCAS might also have influenced the supersaturation of ITZ during dissolution at pH 6.8, as observed in Figure 4A. In addition, a close examination of Figures 4A and 4B reveals that the difference in total drug release between HPMCAS-L and HPMCAS-M at pH 6.8 may be explained by the particle size analysis of the dissolution media. Since the particle size was larger with HPMCAS-M than with HPMCAS-L, it is possible that some particles were filtered out from the dissolution medium with HPMCAS-M, resulting in a lower drug concentration. A similar observation was also reported by Solanki et al. (24) while preparing ASDs containing HPMCAS-M-ITZ (80:20 w/w).

Dissolution of tri-component ASDs containing surfactants

To study the effects of surfactants on comparative drug release from L, M, and H grades of HPMCAS, ASDs were also prepared by using 15% w/w of either poloxamer 407 (Formulations 4, 5, or 6 in Table 1) or TPGS (Formulations 7, 8, or 9 in Table 1) in the formulations. The results of the dissolution testing of the three grades of HPMCAS containing poloxamer 407 are given in Figure 4C, and the particle sizes for L and M grades in dissolution media after the change in pH to 6.8 are given in Figure 4D. The corresponding results for ASDs containing TPGS as the surfactant are shown in Figures 4E and 4F. The presence of surfactants in Figures 4C and 4E increased the dissolution rates of ITZ at pH 1, as compared to those without surfactants (Figure 4A). Although the polymers themselves were insoluble at this pH, the presence of surfactants in the ASDs increased the diffusion of ITZ out of the polymeric matrices, thereby enhancing drug release at pH 1. After the change in pH from 1 to 6.8, the addition of either surfactant at the 15% w/w level increased the dissolution or dispersion rates of ITZ in aqueous media from HPMCAS-L and HPMCAS-M-based ASDs, as compared to those without the surfactant. There was almost complete drug release from both L and M grades in the presence of surfactants. In contrast, the drug release at pH 6.8 from ASDs with HPMCAS-H was much lower (<40%), indicating that even the presence of surfactants did not ensure complete drug release from HPMCAS-H at pH 6.8. The particle size determination of the unfiltered dissolution media from HPMCAS L and M grade samples demonstrated that the surfactants decreased the particle size in dissolution media to the range of about 300 to 350 nm (Figures 4D and 4F) and produced solutions that were translucent and whitish. In contrast, ASDs with HPMCAS-H did not fully disperse, even with the addition of surfactants, resulting in relatively transparent solutions with large ASD particles that swirled in the dissolution medium and were not amenable to dynamic light scattering analysis.

CONCLUSIONS

This is Part II of a two-part study, in which three grades of HPMCAS (L, M, and H) were compared for their miscibility with the drug itraconazole in binary mixtures and with the drug and surfactant (poloxamer 407 or TPGS) in ternary mixtures, and then for drug release from melt-extruded ASDs developed based on the miscibility testing. It was demonstrated by applying the film-casting technique that there was no difference in the miscibility of the three HPMCAS grades with the drug and surfactants; all were completely miscible with 20% w/w ITZ as well as with 20% w/w ITZ plus up to 20% w/w surfactants. Based on these studies, ASDs were prepared using 80:20 w/w HPMCAS-ITZ mixtures and 65:20:15 w/w HPMCAS-ITZ-surfactant mixtures with either poloxamer 407 ot TPGS. All cast films and melt extrudates were confirmed to be amorphous by DSC and PXRD analyses.

During the two-step dissolution testing of ASDs at pH 1, followed by the change in pH to 6.8, the dissolution of ITZ from ASDs at pH 1 was low and less than 10% from all three HPMCAS grades, since the polymers were enteric in nature and did not dissolve at low pH. Thus, all three grades exerted similar protective effects on drug dissolution at low pH. The effects of polymer grades on drug dissolution, however, differed after a pH change from 1 to 6.8. The drug release rates from L and M grades at pH 6.8 were high (94% and 73%, respectively), and there was close to 100% drug release from these polymer grades in the presence of surfactants. In contrast, the drug release from the H grade at pH 6.8 was much lower; the total ITZ released from an ASD without surfactant was <10%, and from those with surfactants was <40%. In addition, colloidal dispersions that passed through 0.45 μm pore-size filters (i.e., <0.45 μm particles) were formed during the dissolution testing of HPMCAS-ITZ-surfactant ASDs containing L and M grades at pH 6.8, but not with the H grade, where the ASD did not disperse completely. Together, parts I and II of the study demonstrate that all three chemical grades of HPMCAS have similar physicochemical, formulation, and processing attributes for the development of ASDs by melt extrusion, but the drug release from the H grade was compromised and much lower because of its chemical nature. It should, however, be noted that only one poorly water-soluble drug, itraconazole, was used in the present investigation, and whether HPMCAS-H would also provide similarly low dissolution of other drugs from ASDs must be investigated on a case-by-case basis.

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CONFLICT OF INTEREST

There is no conflict of interest, and no financial support was received from any external sources for this study.

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