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Comparison of HPMCAS Chemical Grades (L, M, and H) for Amorphous Solid Dispersion by Hot-Melt Extrusion. I: Rheology and Extrudability with Itraconazole as a Model Drug

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ABSTRACT

Original Article

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is widely used as a polymeric carrier for preparing amorphous solid dispersions (ASDs) of poorly water-soluble drugs due to its ability to maintain drug supersaturation in aqueous media. However, most marketed ASDs with HPMCAS are prepared by spray drying. Hot melt extrusion (HME), an environmentally friendly, solvent-free, and continuous process for preparing ASDs, is rarely used for HPMCAS because it requires processing temperatures of at least 170°C, which can degrade the polymer, the drug, or both. HPMCAS is available in three chemical grades (L, M, and H), but there is no comparative evaluation of their suitability for HME. We compared the three grades of HPMCAS for the development of ASDs by HME using itraconazole (ITZ) as the model drug, and the results are presented in a two-part series of papers. In the present Part I, the results of rheological analysis and extrudability testing of the three HPMCAS grades and their binary mixtures with ITZ (HPMCAS:ITZ, 80:20 w/w) and ternary mixtures with ITZ and surfactant (HPMCAS:ITZ:surfactant, 65:20:15 w/w) are described. Poloxamer 407 or TPGS was used as a surfactant. The complex viscosities of the materials as functions of temperature and angular frequencies at different temperatures were determined to select optimal melt extrusion temperatures for the mixtures. Then, the extrudability of the materials was assessed by torque analysis during extrusion through a hot-melt extruder. The addition of ITZ and surfactants reduced the complex viscosity and, thereby, the processing temperatures of all three HPMCAS grades; their ternary mixtures with drug and surfactant could be extruded at as low as 130°C. Despite chemical differences among the three HPMCAS grades, no significant differences were observed in their complex viscosities and extrudability as determined by torque analysis, indicating that all three grades can be processed by HME similarly.

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KEY WORDS: Hydroxypropyl methylcellulose acetate succinate; HPMCAS grades; itraconazole; amorphous solid dispersion; ASD; hot-melt extrusion; HME; complex viscosity; torque analysis

INTRODUCTION

Oral is the most common route of drug administration due to factors such as ease of administration, patient compliance, cost-effectiveness, and relative safety. However, in the pharmaceutical industry, nearly 90% of newly synthesized compounds and about two-thirds of the new chemical entities in development are poorly soluble in aqueous media and, thereby, have dissolution rate-limited oral absorption (1,2). Depending on the physicochemical properties of drug candidates, different solubility enhancement techniques like salt formation, co-crystallization, particle size reduction, lipid-based drug delivery systems, cyclodextrin complexation, and amorphous solid dispersions can be used to address the issue of poor aqueous solubility (3,4).

Among various techniques used to increase the dissolution rate and bioavailability of poorly water-soluble drugs, amorphous solid dispersion (ASD), where the drug is dispersed in water-soluble polymeric carriers either molecularly or in the amorphous state, is a useful technique to enhance drug solubility (5–8). During the past two decades, hydroxypropyl methylcellulose acetate succinate (HPMCAS) has become a popular polymeric carrier for preparing ASDs since it can provide drug supersaturation while preventing phase separation and drug recrystallization after dissolution in aqueous media (9–11). Importantly, ASDs can also maintain certain drugs in the amorphous state for extended periods, which is critical to producing final dosage forms with sufficient commercial shelf life (9).

Chemically, HPMCAS is a cellulose derivative. As shown in Figure 1, it is prepared by first converting cellulose to hydroxypropyl methylcellulose (HPMC) by conjugating with methyl (Me), hydroxypropyl (HP), and hydroxypropyl methyl (HPMe) groups. Then, HPMC is further modified by incorporating acetyl (Ac), succinoyl (Su), hydroxypropyl acetyl (HPAc), and hydroxypropyl succinoyl (HPSu) groups in the structure to prepare HPMCAS (12).

HPMCAS is available in three chemical grades: HPMCAS-L, HPMCAS-M, and HPMCAS-H. As shown in Table 1, the primary differences among these grades are in the percentages of succinoyl (Su + HPSu) and acetyl (Ac + HPAc) groups in the structure, which influences the pH of their solubility, dissolution rate, and aggregation in aqueous media (13–15). HPMCAS-L has the highest succinoyl content relative to acetyl content, with more -COOH groups to ionize, and, therefore, this grade starts dissolving to a larger extent at the lower pH of 5.5. In comparison, HPMCAS-M has medium succinoyl content and dissolves at a pH of 6 and higher, and HPMCAS-H has the least succinoyl content and the highest

Figure 1. Structural representation of the conversion of cellulose to hydroxypropyl methylcellulose (HPMC) and then to hydroxypropyl methylcellulose acetate succinate (HPMCAS) by adding different substituents or R groups to the structures. The R groups added to the HPMC structure to convert it to HPMCAS are denoted by an asterisk. Structures are adapted from Obara et al. (12).

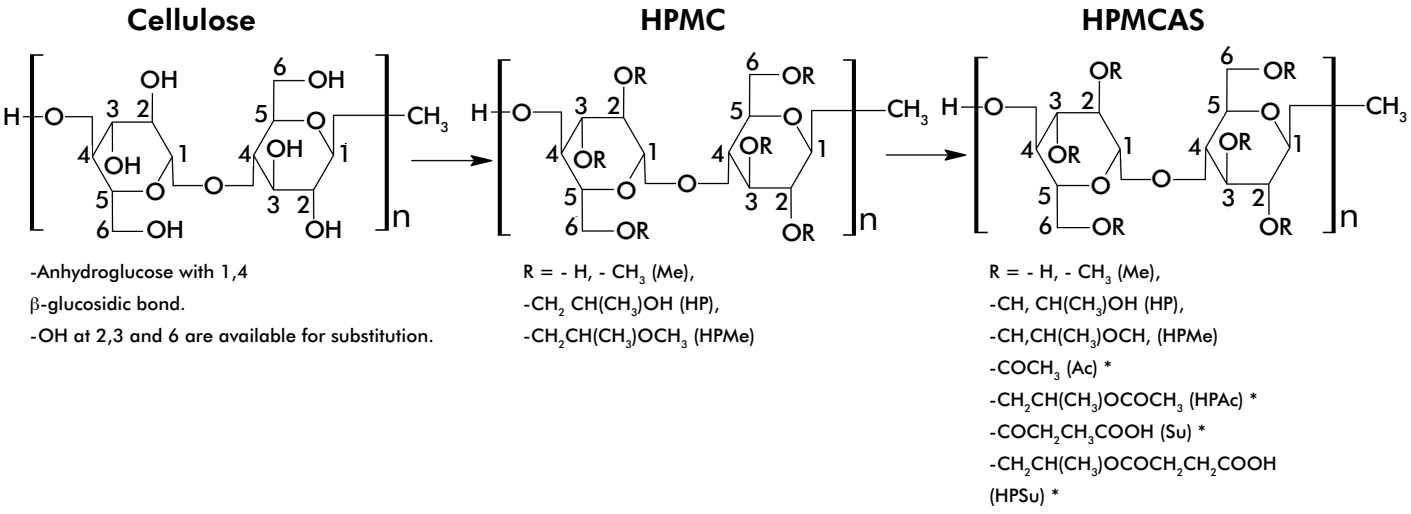


Table 1. Differences and similarities among different grades of hydroxypropyl methylcellulose acetate succinate (HPMCAS)[a].

HPMCAS Grade	Substituents (range)				Succinoyl/ acetyl ratio	Soluble at pH
	Succinoyl (%)	Acetyl (%)	Methoxy (%)	Hydroxypropyl (%)		
HPMCAS-L	15 (14-18)	8 (5-9)	23 (20-24)	7 (5-9)	High	≥ 5.5
HPMCAS-M	11 (10-14)	9 (7-11)	23 (21-25)	7 (5-9)	Medium	≥ 6.0
HPMCAS-H	7 (4-8)	12 (10-14)	23 (22-24)	7 (6-10)	Low	≥ 6.8

[a] Adapted from Obara et al. (12)

acetyl content, due to which it dissolves at pH ≥ 6.8. There are no other major chemical differences among the three grades of HPMCAS, as the percentages of other groups, such as methyl (Me + HPME) and hydroxypropyl (HP), are similar across the three grades (Table 1). The molecular weights of the three grades of HPMCAS are also similar; the weight-average molecular weights (Mw) of the three grades of HPMCAS range from 17,000 to 20,000, and the number-average molecular weight (Mn) is about 13,000 (16).

Although it is well known that different grades of HPMCAS dissolve at different pH values, providing modified drug release from coated tablets under varying intestinal pH conditions, no comprehensive study in the literature describes the implications of selecting one grade over others for the development of ASDs for poorly water-soluble drugs.

According to Moseson et al. (17), 39 ASDs were approved by the FDA from 2012 to 2023, of which 7 used HPMCAS as the principal polymeric carrier. Although HPMCAS possesses the exceptional capability to maintain drug supersaturation in aqueous media (9), it still faces many product development challenges that limit its wider application, including the need for more complex manufacturing processes, such as spray drying. In fact, most marketed products developed using HPMCAS are manufactured by spray drying (18), despite this being an expensive and relatively inefficient process that requires very large volumes of organic solvent to dissolve both the drug and the polymer (19). Moreover, the solvents must be recovered after spray drying, and any residual solvents must be removed from the products. In comparison, hot melt extrusion (HME) is a more straightforward solvent-free process that offers the potential for continuous manufacturing (20). However, its application in the development of drug products has been limited (21,22) because it requires high processing temperatures, which can degrade the drug, the polymer, or both (23,24). Indeed, only one of the seven HPMCAS-based ASDs (Noxafil® delayed-release tablet, Merck) listed by Moseson et al. (17) was produced by hot-melt extrusion (HME), but even that product was discontinued by its manufacturer in 2024 due to business reasons, unrelated to safety or efficacy.

The issue of HME processing temperature with HPMCAS was addressed previously by Solanki et al. (18,25,26), where the extrusion temperature of itraconazole (ITZ) solid dispersions could be lowered from 170ºC to 130ºC by incorporating 10 or 15% w/w surfactants like poloxamer 407, poloxamer 188, or tocopheryl polyethylene glycol succinate (TPGS). Clear homogeneous extrudates that dissolved or dispersed rapidly at an intestinal pH of 6.8 were obtained. However, only the M grade of HPMCAS was used in these studies, and whether other chemical grades of HPMCAS could exhibit similar behavior was not investigated.

The present investigation was undertaken to comprehensively compare the effects and performance of the three HPMCAS chemical grades (L, M, and H) on the development of ASD for a model drug, itraconazole, via hot-melt extrusion. In the present Part I of the study, we first investigated the comparative rheological properties of the three grades of HPMCAS, with and without the added model drug, itraconazole (ITZ), and surfactants, as a function of temperature and angular frequency. Such an investigation of rheology is essential because the rheological properties of formulations can influence their processability via HME, as well as product physical stability and drug release (27). Rheological analysis also guides the selection of optimal melt extrusion temperatures for ASDs (28).

Based on the rheological analysis, the extrudability of the three HPMCAS chemical grades and their polymer-drug and polymer-drug-surfactant mixtures was determined by

measuring the torque generated by the Thermo Scientific Process 11 melt extruder during melt extrusion. Later, in Part II of the study, the effect of HPMCAS grades on polymer-drug-surfactant miscibility and the drug release from formulations in aqueous media will be compared.

MATERIAL

Itraconazole (ITZ) was purchased from Attix Pharmaceuticals (Toronto, Canada). Hydroxypropyl methylcellulose acetate succinate (HPMCAS; AquaSolve®) of L, M, and H grades was donated by Ashland Inc. (Wilmington, DE, USA). It should be noted here that each chemical grade of HPMCAS exists in two physical forms: fine (F) and granular (G). Only granular materials from the three chemical grades were used in the present investigation. Poloxamer 407 (Kolliphor® P407) and tocopheryl polyethylene glycol succinate (Kolliphor® TPGS), which are also referred to as P407 and TPGS in the present investigation, were donated by BASF Corporation (Tarrytown, NY, USA).

METHODOLOGY

Thermogravimetry analysis (TGA)

TGA of neat ITZ, P407, TPGS, and the different grades of HPMCAS were conducted using a thermogravimetric analyzer (model TGA Q50) from TA Instruments (Wilmington, DE, USA) to determine any possible weight loss due to evaporation or degradation of materials. To perform TGA analysis, 5 to 8 mg of samples were heated from 30°C to 400°C at a heating rate of 10°C/min. The materials were pre-dried by flowing dry nitrogen over the sample for 1 hour before heating.

Rheological analysis

Oscillatory rheological analyses of neat HPMCAS-L, M, or H, their binary mixtures with ITZ (80:20 w/w), and their ternary mixtures with ITZ and each of the two surfactants (P407 or TPGS) at the ratio of 65:20:15 w/w were performed to determine their complex viscosity at high temperatures to identify appropriate processing conditions for HME. Complex viscosity (η) is a frequency-dependent rheological function, which is also referred to as dynamic viscosity (29), that is typically exhibited by most non-ideal polymer systems, including most viscoelastic pharmaceutical polymers (30). Generally, the complex viscosity of a polymer decreases with an increase in temperature due to the conversion from a stiff mass to a flowing material. Additionally, the complex viscosity and steady flow viscosity are nearly identical at low angular frequencies, and a distinct decrease in complex viscosity is observed at higher angular frequencies. In all studies, complex viscosity is denoted in Pascal-seconds (Pa.s), which is equivalent to Newton-seconds per meter squared ($N.s/m^2$).

A Discovery Hybrid Rheometer-2 (DHR-2; TA Instruments, Wilmington, DE, USA), which had an oven heating assembly and a 25-mm parallel plate geometry, was used according to the procedure developed by Gupta et al. (30). Firstly, a 500-mg slug of each sample was prepared using a Carver press at a compression pressure of 5000 lb. and a dwell time of 5s. Before analyzing the sample, the rheometer was calibrated to a zero-gap setting. Since complex viscosity is influenced by both temperature and angular frequency, it was determined in the present investigation in two different ways:

- ***Complex viscosity as a function of temperature***: This was performed for HPMCAS grades by gradually decreasing

Table 2: Compositions of different binary and ternary mixtures (%w/w) used for the purpose of HME.

Formulation Number	ITZ % w/w	HPMCAS-L	HPMCAS-M	HPMCAS-H	P407	TPGS
1	20%	80%				
2	20%		80%			
3	20%			80%		
4	20%	65%			15%	
5	20%		65%		15%	
6	20%			65%	15%	
7	20%	65%				15%
8	20%		65%			15%
9	20%			65%		15%

the temperature from 180°C to 130°C at a rate of 5°C/min and applying a strain of 0.5% at a constant angular frequency of 0.1 rad/s. For HPMCAS mixtures with ITZ, as well as for HPMCAS mixtures with ITZ plus surfactants, viscosity was studied from 170°C down to 130°C.

■ ***Complex viscosity as a function of angular frequency***: In this study, complex viscosity was measured by varying the angular frequency at constant temperatures. The test was performed at two different temperatures, 130°C and 150°C, by gradually increasing the angular frequency from 0.1 to 100 rad/s, with a constant strain of 0.5%.

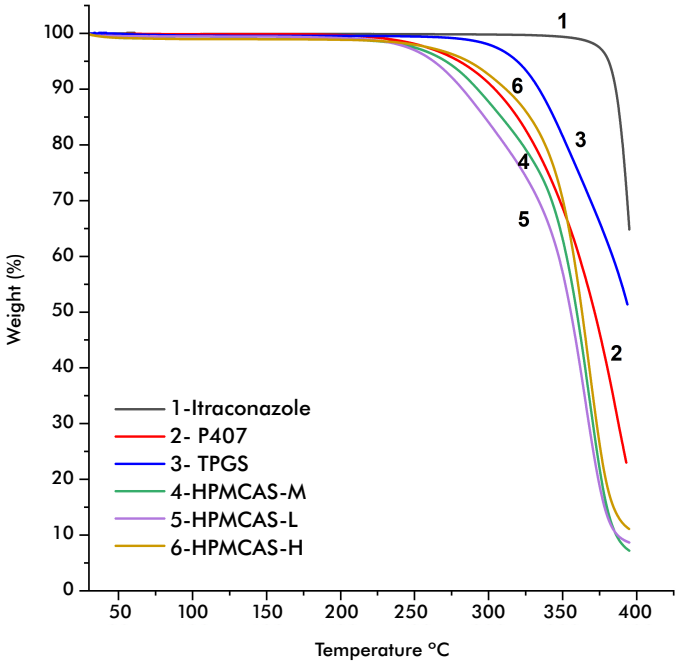
Determination of Extrudability by Torque Analysis

A co-rotating twin screw extruder (Process 11, Thermo Scientific, Waltham, MA, USA) was used to conduct the extrusion of the physical mixtures as listed in Table 2. The hot-melt extrusion of all three neat polymers was conducted at 170ºC, the extrusion of binary mixtures was conducted at 160ºC and 150ºC, and the extrusion of all the ternary mixtures was conducted at temperatures of 160ºC and 130ºC. The screw speed and feed rate were set to 200 RPM and 1.8 g/min, respectively. The die diameter used was 1.5 mm. The screw configuration used in the present investigation was previously described (31). Briefly, along with conveying elements, the screw configuration included 3 kneading zones. The first kneading zone, located near the feeder, consisted of 7 kneading elements with an offset angle of 30°, followed by 7 kneading elements with an offset angle of 60°. The intermediate kneading zone consisted of 6 kneading elements with an offset angle of 60°, while the third kneading zone consisted of 4 kneading elements with an offset angle of 60°, followed by 7 kneading elements with an offset angle of 90°. During HME processing, the torque exerted on the screw shafts is indicative of the relative extrudability of the materials. In this study, torque measurements were used to compare the processability of various blends.

RESULTS

Thermal degradation, complex viscosity, and torque analysis are essential considerations when developing a suitable processing method for HME. In the present investigation, we first performed a thermogravimetric analysis (TGA) on the HPMCAS polymers, ITZ, and the surfactants to confirm whether any weight loss occurred in the materials when exposed to elevated temperatures. Then, rheological testing and torque analysis of all three grades of HPMCAS were conducted, with and without added drug and surfactants, to compare their performance. The results of these studies are provided below:

Figure 2. Thermogravimetry analysis of itraconazole, different HPMCAS grades, and surfactants used: 1, itraconazole; 2, poloxamer (P407); 3, tocopheryl polyethylene glycol succinate (TPGS); 4, HPMCAS-M; 5, HPMCAS-L; and 6, HPMCAS-H.



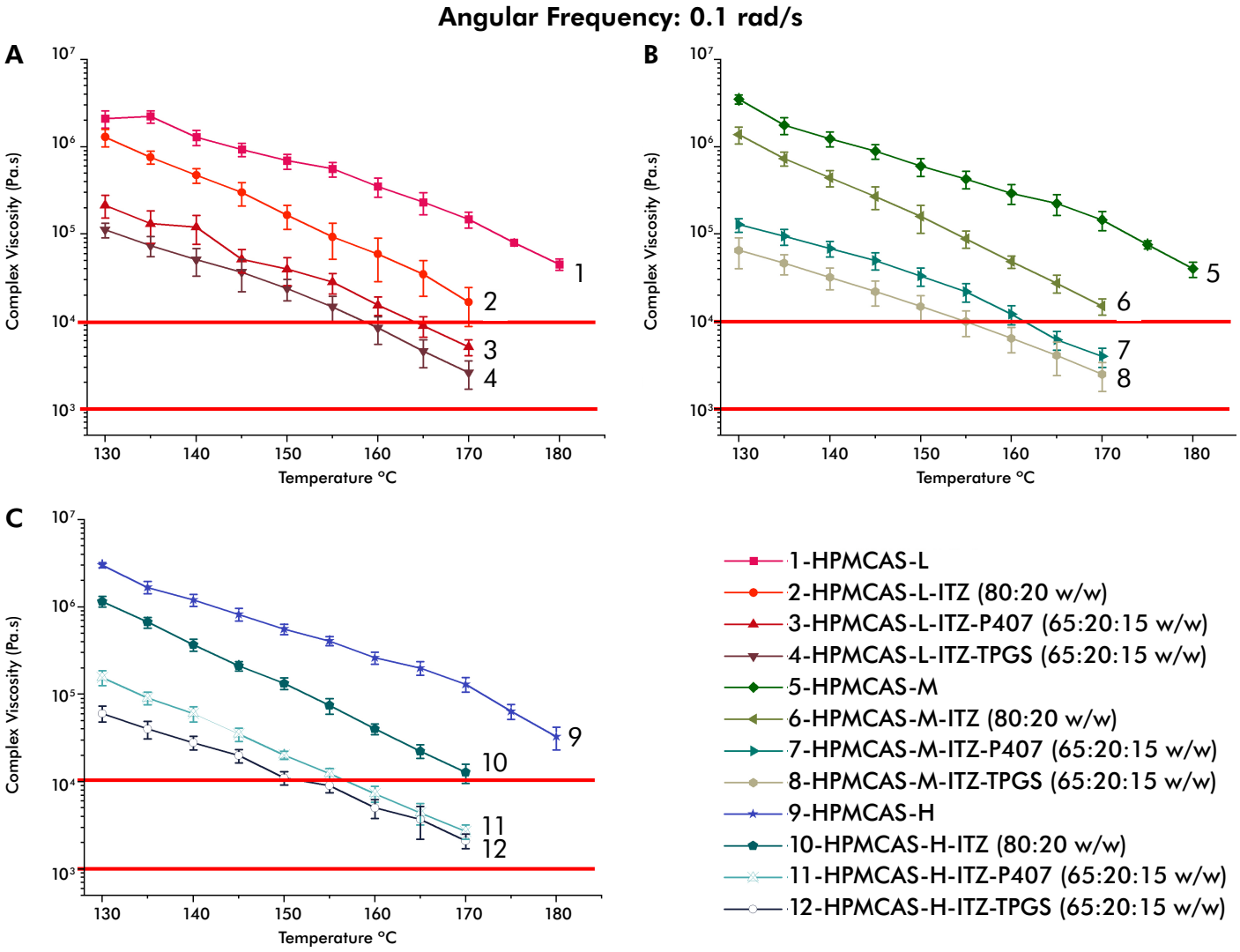
Thermogravimetric analysis (TGA)

Due to exposure to elevated temperatures during the process of HME, there could be weight loss from materials due to dehydration or chemical degradation. Figure 2 provides the results for TGA analysis when ITZ, P407, TPGS, and HPMCAS-L, M, and H were individually exposed to elevated temperatures. As shown in Figure 2, ITZ did not exhibit any weight loss up to 360ºC, suggesting that it should remain physically stable at elevated temperatures. Similarly, Figure 2 also shows that there was practically no weight loss by any of the three grades of HPMCAS as well as by P407 and TPGS up to 200ºC, and the weight loss at 250ºC was <3%, which indicated that the excipients could be physically stable (no weight loss) up to at least 200ºC.

Although HPMCAS L, M, and H could be considered physically stable up to 200°C based on TGA, as there was no weight loss, there are, however, certain limitations of TGA in delineating chemical stability during hot-melt extrusion (32). For instance, the TGA may not always indicate chemical

degradation unless it is accompanied by substantial weight loss. In the case of HPMCAS, various literature reports suggest the potential for its chemical degradation, with the liberation of acetic acid and succinic acid, when the polymer is melt-extruded at high temperatures (12,21,24). Obara et al. (12) observed that, as compared to the presence of 0.03-0.04% w/w acetic acid in neat HPMCAS L, M, and H, the concentrations of acetic acid increased to 0.08-0.17% w/w at 160°C and then to 0.14-0.23% w/w at 200°C. Similarly, from the baseline level of 0.02-0.03% w/w, the succinic acid content increased to 0.24-0.77% w/w at 160°C and 0.62-1.19% w/w at 200°C. Since the liberation of the two acids was relatively small, their possible evaporation was not reflected in the TGA scans as weight loss. Yet, such a degradation of the polymers could significantly affect the stability of drug products. Based on these considerations, the highest melt extrusion temperature used in the present investigation was 170°C, and, as discussed in the next section, the rheological testing of the neat polymers commenced at 180°C, at which the weight loss was still relatively low.

Figure 3. Complex viscosities of three grades of HPMCAS as a function of temperature at an angular frequency of 0.1 rad/s, shear strain of 0.5%, and the temperature range from 180°C to 130°C for neat polymers and 170°C to 130°C for polymer-ITZ and polymer-ITZ-surfactant mixtures. Sub-figures A, B, and C present results for HPMCAS-L, M, and H, respectively. Samples used were HPMCAS alone, an 80:20 w/w mixture of HPMCAS and ITZ, and a 65:20:15 w/w mixture of HPMCAS, ITZ, and P407/TPGS. The two parallel horizontal red lines in the subfigures indicate the ideal range of complex viscosity, 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graph represents the mean value of three determinations.



Rheological analysis

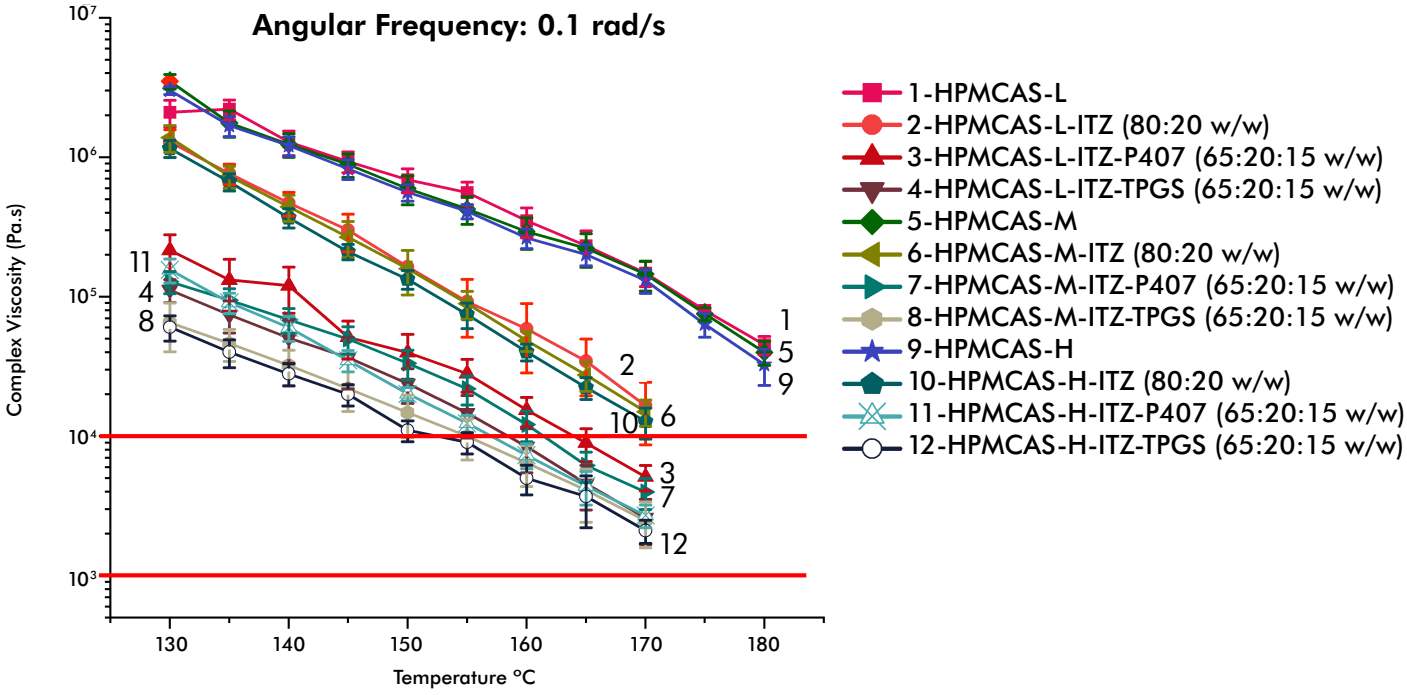
Pharmaceutical polymers are viscoelastic in nature, and they can exhibit both solid-like and liquid-like properties (27,30). During HME, these polymers are exposed to varied temperatures, shear rates, and stresses, which considerably influence the viscoelastic properties that, in turn, significantly impact the polymer's deformation, flow, complex viscosity, and the drug's dissolution in the polymer. Therefore, understanding various viscoelastic properties, such as complex viscosity, which is essentially the material's resistance to flow as a function of angular frequency, plays a critical role in determining the optimal processing conditions required to prepare ASDs by HME.

It was previously reported that the complex viscosities of polymers decrease within the extruder barrel due to the increasing temperature and shear rate (18,30,33). Hence, understanding the effect of temperature and shear rate of different grades of HPMCAS can help optimize the HME conditions required for their processing (28). To conduct the rheological analysis, the complex viscosity of the HPMCAS grades was studied individually as a function of temperature and angular frequency (analogous to shear rate).

Effect of temperature on complex viscosity of HPMCAS L, M, and H

Figures 3A, 3B, and 3C provide complex viscosities of HPMCAS-L, HPMCAS-M, and HPMCAS-H, respectively, at an angular frequency of 0.1 rad/s. It should be noted that the rheology of polymers is typically tested from high to low temperatures to map their complete flow behavior, moving from a fluid-like molten state (low viscosity) at higher temperatures into the glassy, solid state (high viscosity) at lower temperatures. This is especially required for mixtures of polymers with additives, such as ASD formulations, where the components must first be miscibilized at high temperatures before complex viscosity can be determined. In the present investigation, a starting temperature of 180°C was used to determine the complex viscosity of neat polymers (L, M, and H grades) as a function of temperature, as the polymers were fluid enough at this temperature to initiate rheological testing. It was observed that the viscosity of the polymers decreased in the presence of ITZ, P407, and TPGS, and, therefore, the highest temperature used for determining complex viscosity of the HPMCAS mixtures with ITZ alone and with ITZ plus surfactants was reduced to 170°C.

Figure 4. A direct comparison of complex viscosities of three grades of HPMCAS as a function of temperature in the range of 180°C to 130°C and of mixtures of HPMCAS, ITZ, and surfactant (P407 or TPGS) in the range of 170°C to 130°C at a constant angular frequency of 0.1 rad/s and a shear strain of 0.5% by overlaying graphs previously presented in subfigures 3A, 3B, and 3C. The two parallel horizontal red lines in the figure indicate the ideal range of complex viscosity, from 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graph represents the mean value of three determinations.



The three sets of graphs in Figure 3 subfigures are overlaid in Figure 4 to determine whether there is a difference in viscosity among the three polymer grades. In the absence of any added drug or plasticizer, complex viscosities of all three grades of HPMCAS were essentially similar within a narrow range. At a temperature of 160ºC, for example, the complex viscosity of the three grades of HPMCAS was within the range of ~260,000 to 350,000 Pa·s. This decreased to ~130,000-150,000 Pa·s at 170ºC and further decreased at 180ºC. The almost identical plots obtained in Figure 4 indicate that there were no significant differences in complex viscosity of the three grades of HPMCAS.

ITZ was added to neat HPMCAS at 20% w/w to assess the drug's plasticizing effect on complex viscosity. The reported glass transition temperature (Tg) of ITZ is ~60ºC (34), and the different grades of HPMCAS have Tg values of 121-123ºC (35). Based on an earlier observation of the effect of another drug, carbamazepine, on the complex viscosity of the polymer Soluplus® (36), it was anticipated that ITZ would reduce the Tg and the complex viscosity of neat HPMCAS, making it processable at a lower temperature. As indicated in Figures 3 and 4, the complex viscosity of all three HPMCAS grades indeed decreased after the incorporation of 20% w/w ITZ, confirming ITZ's potential to plasticize all three grades of HPMCAS; however, the performance of the three grades of HPMCAS was essentially similar even in the presence of 20% ITZ, as the plots of their complex viscosities as a function of temperature overlapped on each other. As will be presented later, such a reduction in complex viscosity in the presence of 20% w/w ITZ lowers the HME processing temperature from ~170ºC to about 150ºC, which could still be relatively high for HME.

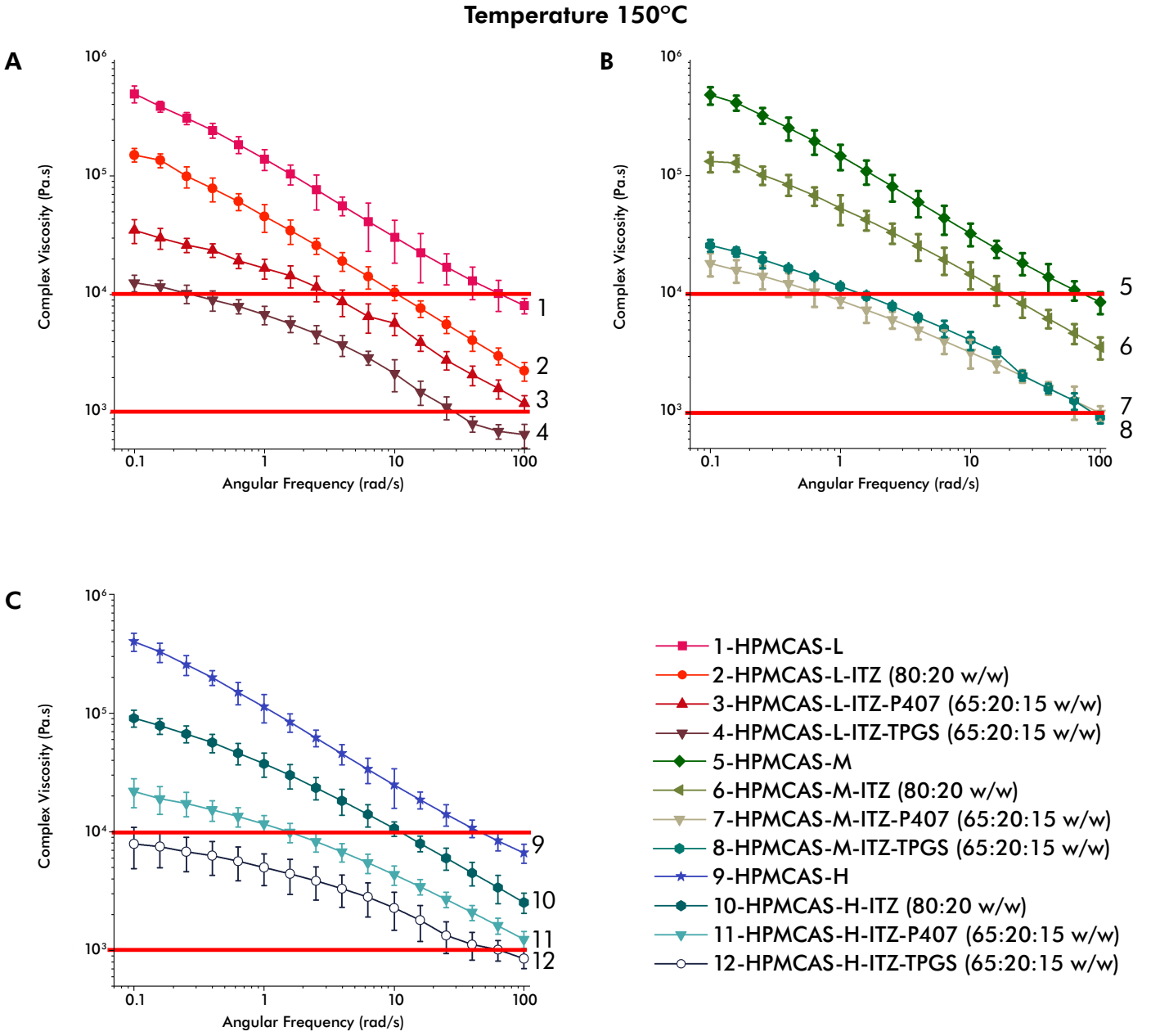
The incorporation of P407 and TPGS as surfactants further reduced the complex viscosity of HPMCAS, as they can also plasticize the polymers. As indicated in Figure 4, a larger drop in complex viscosity was observed when TPGS was used instead of P407. It was hypothesized that the higher solubility of ITZ in TPGS than in P407 could be responsible for greater miscibility between ITZ and TPGS and, therefore, the greater plasticization effect of TPGS (25). Previously, it was reported that the ideal range of complex viscosity for HME was 1000-10,000 Pa.s (30,37,38). As indicated in Figures 3 and 4, the complex viscosities of all three grades of HPMCAS at 160ºC in the presence of 15% w/w P407 and TPGS were, respectively, ~ 7000-15,000 Pa.s and ~ 5000-9000 Pa.s. These ranges of complex viscosity were considered favorable for hot melt extrusion because the polymer was fluid enough to dissolve the drug, and its plasticity was suitable for maintaining adequate flow during processing.

Effects of angular frequency on complex viscosity of all three grades of HPMCAS

It may be noted in Figures 3 and 4 that the complex viscosities of the different grades of HPMCAS at 170ºC (~ 130,000-150,000 Pa.s) and that of their binary mixtures with 20% w/w ITZ at 150ºC (~135,000-165,000 Pa.s) were much higher than the complex viscosity of 1000-10,000 Pa.s considered optimal for melt extrusion. But the viscosities as a function of temperature presented in Figures 3 and 4 were determined using a constant angular frequency of 0.1 rad/s only. During the process of hot melt extrusion, the shear rate within the extruder barrel would be much higher than what is reflected by the angular frequency of 0.1 rad/s because of the effects of co-rotating screws at high RPM. This would improve the processability of HPMCAS. However, since it is not possible to exactly simulate the effects of higher shear rates in the melt extrusion barrels by studying complex viscosity with a rotational rheometer, we instead used a change in angular frequency, ranging from 0.1 to 100 rad/s, to assess the effect of shear rate. This can be done based on the relation between angular frequency and shear rate through the Cox-Merz relationship (39). In a previous study (28), we confirmed the validity of this relationship using angular frequency sweep data to infer viscosity under high shear conditions for mixtures of itraconazole and Soluplus®. Thus, the angular frequency sweep can be used to assess the relative processability of various ITZ-HPMCAS blends in this present study.

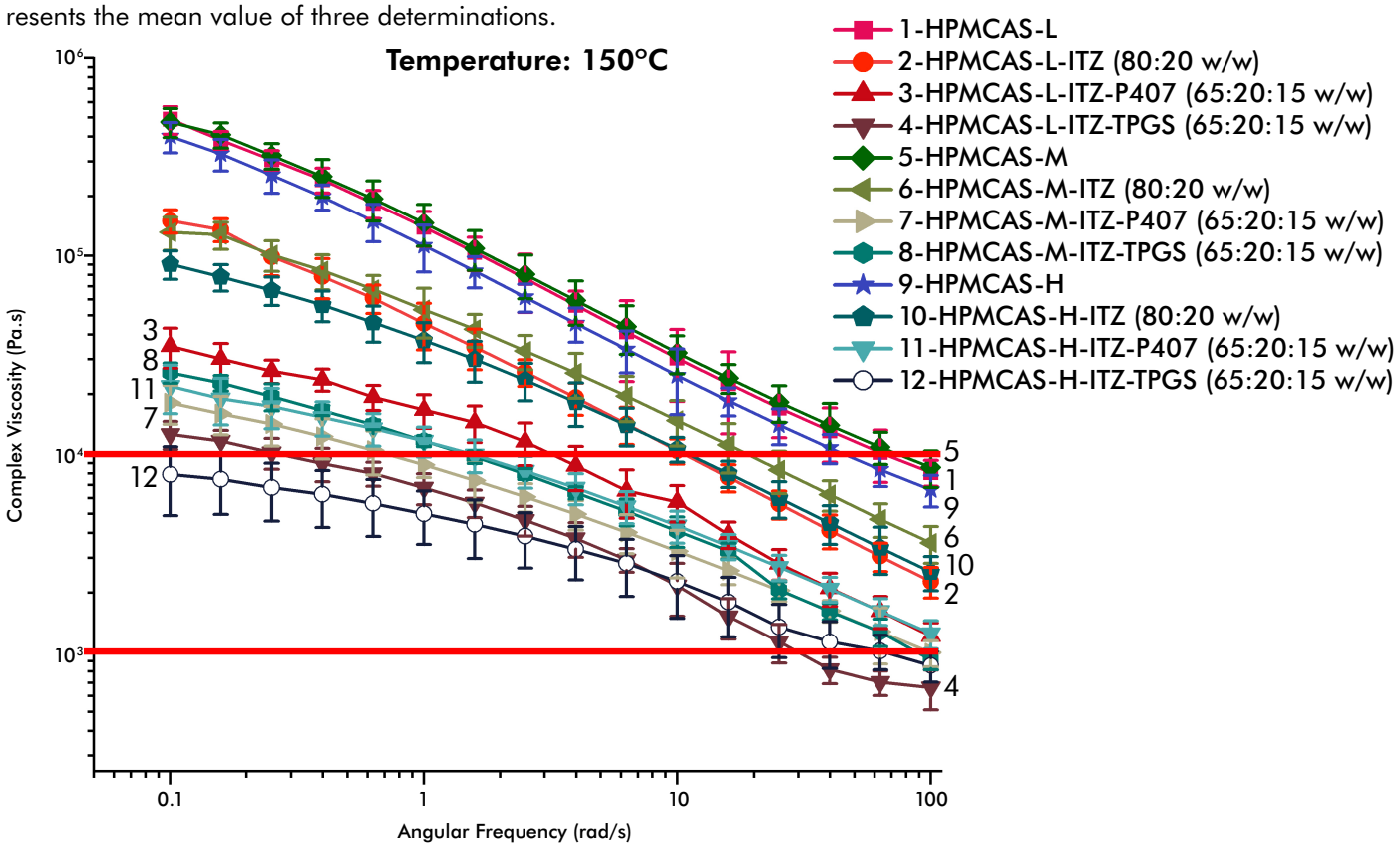
The effects of angular frequencies on complex viscosities of neat HPMCAS-L, HPMCAS-M, and HPMCAS-H, along with their binary mixtures with ITZ and ternary mixtures with ITZ and surfactants at a constant temperature of 150ºC, are shown in Figures 5A, 5B, and 5C, respectively. The complex viscosity data for all three grades of HPMCAS, with and without drug and surfactants, are overlaid in Figure 6 for direct comparison. In this study, a constant strain of 0.5% and angular frequencies ranging from 0.1 to 100 rad/s were applied. A gradual drop in complex viscosity was observed when the angular frequency increased from 0.1 to 100 rad/s. However, all three grades of HPMCAS exhibited similar complex viscosity at varied angular frequencies. The incorporation of ITZ significantly reduced the complex viscosity of all three polymer grades, and this reduction was further pronounced when surfactants were added. However, the effects were similar across the various HPMCAS grades.

Figure 5. Complex viscosities of (A) HPMCAS-L, (B) HPMCAS-M, and (C) HPMCAS-H as a function of angular frequency in the range of 0.1 to 100 rad/s at a constant temperature of 150°C and shear strain of 0.5%. Samples used were HPMCAS alone (lines 1, 5, and 9), 80:20 w/w mixture of HPMCAS and ITZ (lines 2, 6, and 10), 65:20:15 w/w mixture of HPMCAS, ITZ, and P407 (lines 3, 7, and 11), and a 65:20:15 w/w mixture of HPMCAS, ITZ, and TPGS (lines 4, 8, and 12). The two parallel red lines in each subfigure indicate the ideal range of complex viscosity, from 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graphs represents the mean value of three determinations.



The effects of formulation composition on melt viscosity and, consequently, processing temperatures can be assessed from Figures 5 and 6. For example, as shown in Figure 6, the complex viscosity of HPMCAS-L at the temperature of 150°C and angular frequency of 10 rad/s was ~30,000 Pa.s, and HPMCAS-M and H also exhibited similar viscosities. Hence, in the absence of plasticizers, neat HPMCAS exhibited high complex viscosity, which would require elevated temperatures for HME. There was a drop in complex viscosity upon incorporation of 20% w/w ITZ. It could be interpreted from Figures 5 and 6 that, at 150°C, binary mixtures of all three HPMCAS grades with 20% w/w ITZ showed the

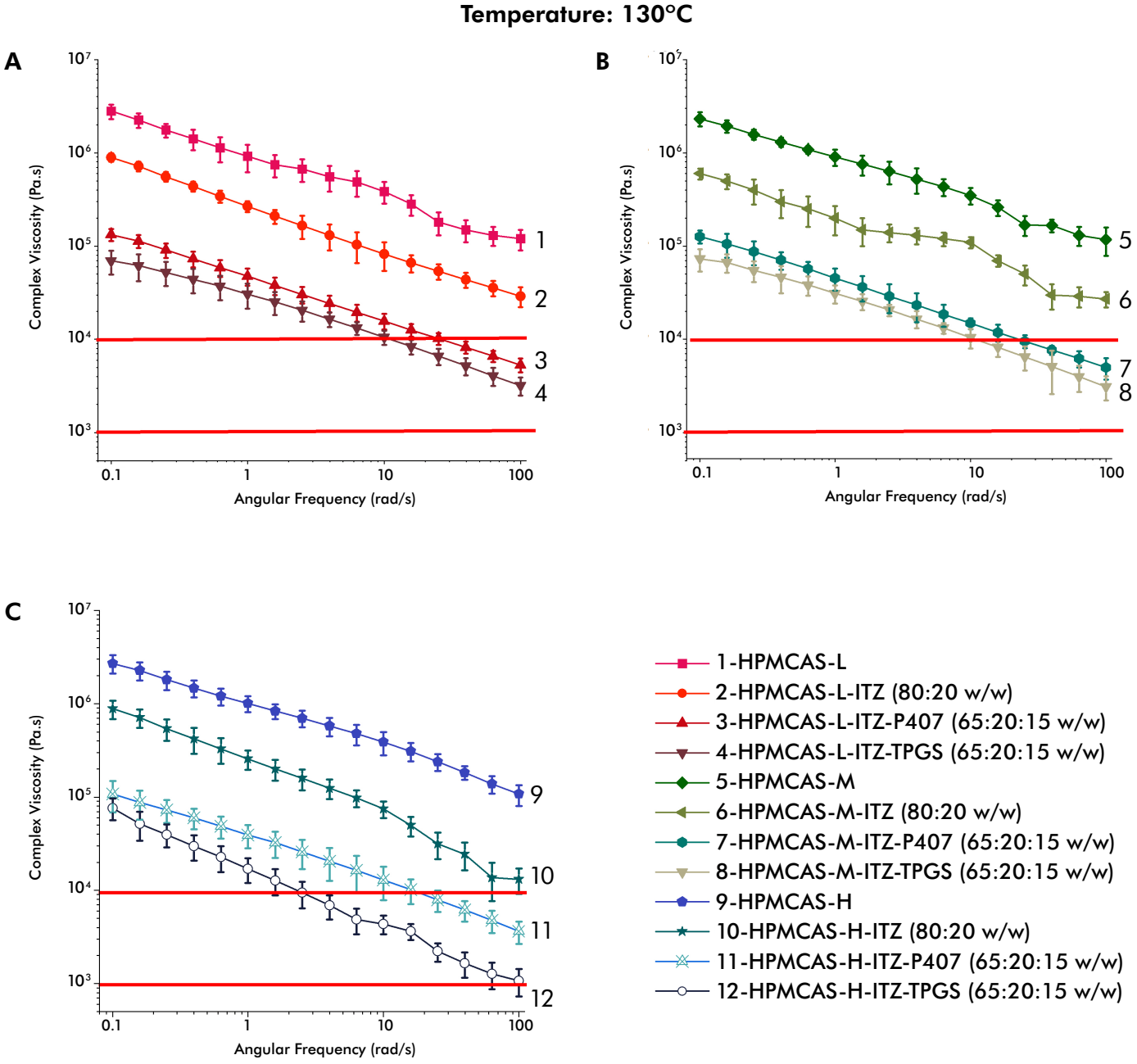
Figure 6. A direct comparison of complex viscosities of three grades of HPMCAS as a function of angular frequency in the range of 0.1 to 100 rad/s at a constant temperature of 150°C and shear strain of 0.5% by overlaying graphs previously presented in subfigures 5A, 5B, and 5C. Samples used were HPMCAS alone (lines 1, 5, and 9), 80:20 w/w mixture of HPMCAS and ITZ (lines 2, 6, and 10), 65:20:15 w/w mixture of HPMCAS, ITZ, and P407 (lines 3, 7, and 11), and 65:20:15 w/w mixture of HPMCAS, ITZ, and TPGS (lines 4, 8, and 12). The two parallel horizontal red lines highlight the ideal range of complex viscosity, from 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graphs represents the mean value of three determinations.



complex viscosity in the range of ~10,000 to 15,000 Pa.s at an angular frequency of 10 rad/s. Based on this additional rheological data, the extrusion of binary mixtures of all three grades of HPMCAS could be possible at 150°C.

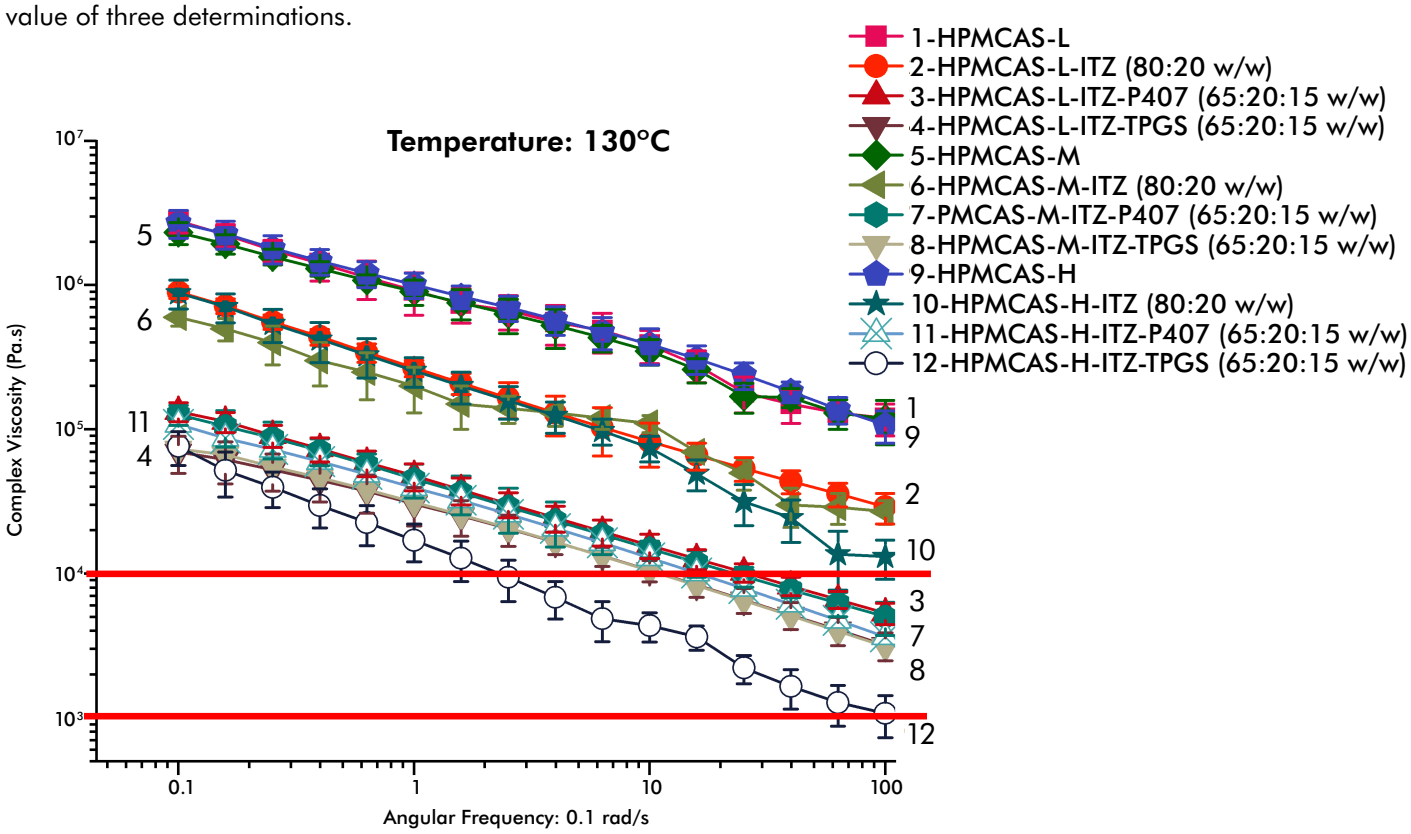
Finally, the impact of angular frequency on the complex viscosity of the different HPMCAS chemical grades and their mixtures with ITZ and surfactants was studied at a constant temperature of 130°C. The results are presented in Figures 7 and 8. After exposing neat HPMCAS to the highest angular frequency of 100 rad/s studied in the present investigation, the complex viscosity of all three grades of HPMCAS at 130°C by themselves was very high in the range of ~105,000 to 120,000 Pa.s., essentially confirming that the neat HPMCAS cannot be extruded at 130°C. However, as shown in Figures 7 and 8, the complex viscosity obtained as a function of angular frequency decreased when 20% w/w ITZ was added to HPMCAS, and it further decreased when both ITZ (20% w/w) and surfactant (15% w/w of either P407 or TPGS) were added to HPMCAS. Indeed, in ternary mixtures of different HPMCAS grades with 20% w/w ITZ and 15% w/w surfactant (P407 or TPGS), the complex viscosity at 130°C and 10 rad/s angular frequency was in the range of ~ 4,000 to 15,000 Pa.s, which further decreased to 1,000-5,000 Pa.s when the angular frequency at the same temperature increased to 100 rad/s. Between the two surfactants, P407 and TPGS, it appears that there is a greater reduction in the complex viscosity of the HPMCAS-ITZ-surfactant mixture with increasing angular frequency in the presence of TPGS than in the presence of P407 (Figures 7 and 8). However, no mechanistic study of the possible differences between the effects of TPGS and P407 was conducted in the present investigation. As mentioned earlier, this could be due to the greater miscibility between ITZ and TPGS.

Figure 7. Complex viscosities of (A) HPMCAS-L, (B) HPMCAS-M, and (C) HPMCAS-H as a function of angular frequency in the range of 0.1 to 100 rad/s at a constant temperature of 130°C and shear strain of 0.5%. Samples used were HPMCAS alone (lines 1, 5, and 9), 80:20 w/w mixture of HPMCAS and ITZ (lines 2, 6, and 10), 65:20:15 w/w mixture of HPMCAS, ITZ, and P407 (lines 3, 7, and 11), and 65:20:15 w/w mixture of HPMCAS, ITZ, and TPGS (lines 4, 8, and 12). The two parallel horizontal red lines in each subfigure indicate the ideal range of complex viscosity, from 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graphs represents the mean value of three determinations.



Considering that the optimal complex viscosity for the melt extrusion of ASDs is considered to be around 1,000 to 10,000 Pa.s (40), these results of the rheological analysis indicate that HPMCAS-based ASDs could be prepared by conducting HME at a temperature as low as 130°C because of the plasticizing effects of the drug and surfactants when both are present with HPMCAS. Moreover, all three HPMCAS grades exhibited similar behavior in lowering the processing temperature.

Figure 8. A direct comparison of the complex viscosity of three grades of HPMCAS as a function of angular frequency in the range of 0.1 to 100 rad/s at a constant temperature of 130°C and shear strain of 0.5% by overlaying graphs previously presented in subfigures 7A, 7B, and 7C. Samples used were HPMCAS alone (lines 1, 5, and 9), 80:20 w/w mixture of HPMCAS and ITZ (lines 2, 6, and 10), 65:20:15 w/w mixture of HPMCAS, ITZ, and P407 (lines 3, 7, and 11), and 65:20:15 w/w mixture of HPMCAS, ITZ, and TPGS (lines 4, 8, and 12). The two parallel red horizontal lines highlight the ideal range of complex viscosity, from 1000 to 10,000 Pa.s., to enable melt extrusion. Each data point in the graph represents the mean value of three determinations.



Determination of Extrudability by Torque Analysis

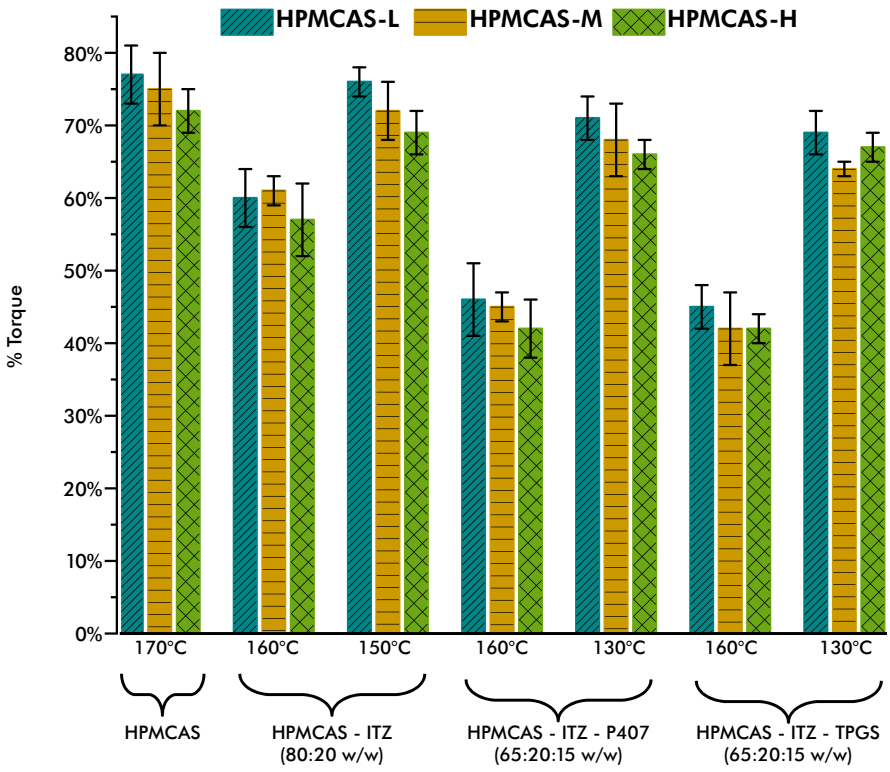
Extrudability refers to the ease with which a material flows through an extruder. In the present investigation, the comparative extrudability of different grades of HPMCAS and their mixtures with ITZ and surfactants was determined by measuring extrusion torque, which reflects the rotational force exerted by the twin screws of the extruder. Torque is essentially an indirect measurement of viscosity as it determines the energy required to rotate screws against the resistance exerted by the viscosity within the barrel (41,42). The maximum torque that can be applied depends on the extruder; the extruder will stop working once the torque reaches 100% of its capacity. The lower the torque, the better the flow, and thus, the extrudability of the material. However, the torque should not be so low that the material is too soft, flows as a liquid, and fails to form filaments. Figure 9 gives the results of the torque analysis of all three grades of HPMCAS and their mixtures with drug and surfactants, which are described in the next sections.

Torque Analysis for neat HPMCAS Grades (no Additives)

The torque analysis of the three HPMCAS grades without any additives was conducted by using the Thermo Scientific Process 11 twin screw extruder. As shown in Figure 9, the neat polymers exerted a torque of 72-77% at 170°C. It should be noted here that although a starting temperature as high as 180ºC was used to facilitate the determination of complex viscosity of the three neat polymers as a function of temperature, the highest temperature used during torque analysis of neat polymers was 170°C to avoid the possibility of any significant degradation. The polymers were not extrudable at 160ºC, as torque exceeded 80% (data not shown), making extrusion difficult. At 170ºC, there was no significant difference in torque among the three grades of HPMCAS, indicating that all had similar extrudability.

The high torque in Figure 9 is consistent with the polymers' high complex viscosity at elevated temperatures. As shown earlier in Figure 3, all three grades of HPMCAS possess

Figure 9. Torque analysis of all three grades of neat HPMCAS at 170°C, HPMCAS-ITZ binary mixtures at 160°C and 150°C, and HPMCAS-ITZ-P407 and HPMCAS-ITZ-TPGS ternary mixtures at 160°C and 130°C. Each bar graph represents the mean value of three determinations.



high complex viscosities, however the neat materials could ultimately be extruded at 170°C because, as shown in Figures 6 and 8, the increase in angular frequency decreases complex viscosity, which would be the case inside the extruder barrel during melt extrusion due to high rotational speed, high pressure, and increased shear rate.

Torque Analysis for HPMCAS-itraconazole Mixtures

Although the neat HPMCAS grades could be extruded only at 170°C and higher, Figure 9 shows that binary mixtures of all three grades of the polymer with 20% w/w ITZ could be successfully extruded at 160°C, generating a torque within the 57-61% range. This is due to the plasticizing effects of the ITZ, which reduced the complex viscosity of the binary mixtures, as observed in Figure 3, and to the effects of increased angular frequency observed in Figures 6 and 8.

To determine the lowest possible temperature at which HPMCAS-ITZ binary mixtures could be extruded, the torque analysis was also conducted at a lower temperature of 150°C, where all three binary mixtures generated torque within the range of 69 to 76%, which is considered barely acceptable for HME. Furthermore, when an attempt was made to extrude the binary samples HPMCAS-L, M, or H with ITZ (80:20% w/w), at a temperature below 150°C, the torque increased to 100% and the extruder stopped working. Hence, the binary mixtures could not be extruded below 150°C.

These results demonstrate that mixtures of HPMCAS with ITZ can be processed at 150°C rather than at 170°C, as required for neat HPMCAS. A similar lowering of the processing temperature may also be encountered when HPMCAS is mixed with other drugs. Importantly, the torque analysis at both 160°C and 150°C reveals no appreciable difference in the extrudability of the three HPMCAS grades, even when mixed with the drug ITZ.

Torque Analysis for HPMCAS-Itraconazole-Surfactant Mixtures

The torque of HPMCAS grades decreased further, and extrudability improved, when 15% w/w surfactant, either P407 or TPGS, was added to the HPMCAS-ITZ mixtures. Figure 9 shows that, at 160°C, the ternary HPMCAS-ITZ-surfactant (65:20:15 w/w) mixtures with both P407 and TPGS exhibited torque values in the range of 42 to 46%, demonstrating the effects of surfactants, along with the drug, on the extrudability of HPMCAS. In agreement with the decrease in complex viscosity in the presence of both P407 and TPGS, the HPMCAS-ITZ-surfactant mixtures (65:20:15 w/w) could also be extruded at 130°C, generating torque within the range of 67 to 71%. These torque values are somewhat high for optimal extrudability but demonstrate that the plasticizing effects of P407 and TPGS were equal across all three HPMCAS grades, with no significant differences in torque at either 160°C or 130°C, resulting in similar processability across all HPMCAS grades.

CONCLUSIONS

Three different chemical grades of HPMCAS, namely L, M, and H, were evaluated alone and in combination with itraconazole (ITZ) as the model drug and poloxamer 407 (P407) or tocopheryl polyethylene glycol succinate (TPGS) as surfactants and plasticizing agents, for their physicochemical properties relevant to the development of ASDs by hot-melt

extrusion (HME). Despite chemical differences among the three grades of HPMCAS, all exhibited similar thermal behavior, complex viscosity, and extrudability.

Results from thermogravimetric analysis (TGA) showed that there was practically no weight loss when the three polymer grades, as well as ITZ, P407, and TPGS, were heated up to 200ºC. The lowest temperature at which all three grades of HPMCAS could be extruded by themselves was 170ºC, where they exerted a relatively high but similar torque of 72-77% during HME. The drug had a plasticizing effect on all HPMCAS grades; at 20% w/w ITZ, all polymer grades were extrudable at 160ºC with 57-61% torque, or at 150ºC with a higher 69-76% torque. When 15% w/w poloxamer 407 or TPGS was added along with 20% ITZ, the processing temperature of all three polymer grades could be reduced to as low as 130ºC, with a torque of 65-70%. The results demonstrated that the three grades of HPMCAS performed similarly during processing by HME. The results of further studies on the miscibility of the three grades in polymer-drug-surfactant mixtures and the drug release from melt-extruded ASDs of such mixtures are presented in Part II of this two-part series of papers.

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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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