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Stability assessment of hypromellose acetate succinate (HPMCAS) NF for application in hot melt extrusion (HME)

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ABSTRACT

HPMCAS is a widely used polymer in the pharmaceutical industry as an excipient. In this work, the physicochemical stability of HPMCAS was investigated for hot melt extrusion (HME) application. The reduction in zero rate viscosity (η_0) of the polymer with the increase in temperature was determined using rheological evaluation prior to HME processing. The energy of activation for AS-MF determined by fitting Arrhenius model to the temperature dependent reduction in η_0 was found to be slightly lower than that for the other grades of HPMCAS. Glassy yellowish HMEs were obtained using Haake Mini-Lab MicroCompounder operated at 160, 180, and 200 °C and 100, 200, and 300 rpm for all the grades at each temperature. Various physicochemical properties of HPMCAS such as glass transition temperature, semi-crystalline nature, solid state functional group properties, moisture content, and solution viscosity were not significantly affected by the HME processing. The most significant change was the release of acetic and succinic acid with the increase in HME temperature and speed. The free acid content release due to HME was directly proportional to the speed at lower operating temperatures. AS-LF was found to be the most stable with the lowest increase in total free acid content even at higher HME temperature and speed. Although the dissolution time was not affected due to HME for AS-LF and AS-MF grades, it was notably increased for AS-HF, perhaps due to significant reduction of succinoyl content. In conclusion, the HME processing conditions for solid dispersions of HPMCAS should be based on the acceptance levels of free acid for the drug and the drug product.

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1. Introduction

Hypromellose acetate succinate (HPMCAS) was originally developed and marketed in 1986 by Shin-Etsu Chemical Co., Ltd. (Japan) as an enteric polymer for aqueous dispersion coating (McGinity, 1997). The enteric coating prevents dissolution of certain drugs in the acidic pH in order to prevent degradation of the drug or irritation of the stomach by the drug. HPMCAS has a cellulose backbone with a substitution of hydroxypropoxy, methoxy, acetyl, and succinoyl groups (Fig. 1). The number and weight average molecular weights of the polymer are approximately 13,000 and 18,000, respectively (Fukasawa & Obara, 2004). There are 6 grades available based on the physicochemical properties of the polymer. The F (fine) and G (granular) grades differ only in their particle size, whereas L, M, and H grades are chemically different and vary in their pH solubility. The L, M, and H grades dissolve at pH ≥ 5.5, 6.0, and 6.8, respectively. This variable pH solubility is controlled by changing the acetyl and succinoyl content of the polymer (Tanno, Nishiyama, Kokubo & Obara, 2004). Thus, the release of a pharmaceutical drug in the gastrointestinal tract can be controlled as required by using a suitable grade of the polymer (Yamakita, Matsukawa, Maejima & Osawa, 1996). HPMCAS is majorly an amorphous polymer and has a glass transition temperature (Tg) of 120 °C.

Currently, the pharmaceutical industry is facing a challenge of developing feasible, effective, stable, ecological, and economical formulations for poorly water soluble drugs. More than 50% of the drug candidates that are being discovered by high throughput screening and combinatorial chemistry are crystalline hydrophobic compounds (Timpe & Forschung, 2007; Vasconcelos, Sarmento & Costa, 2007). These drugs exhibit low solubility in the aqueous environment of the gastrointestinal tract and subsequent low bioavailability after oral administration. In order to improve the water solubility of these drugs, solid dispersion technology is

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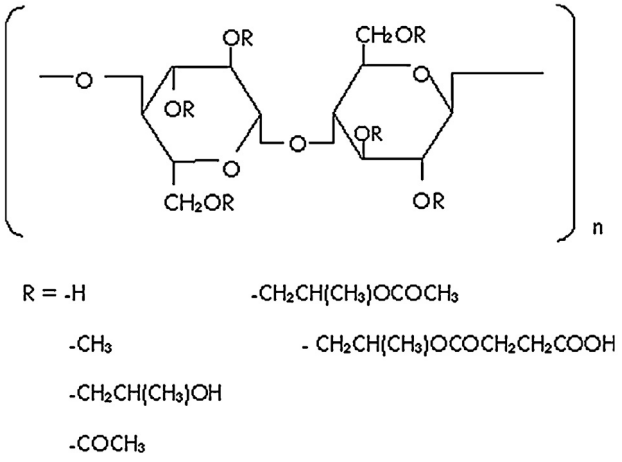

Fig. 1. Chemical structure of HPMCAS showing the cellulosic backbone with various functional groups. The pH solubility of different grades is controlled by changing the acetyl and succinoyl group content.

frequently used by dispersing the drug into the polymer matrix, preferably at molecular level (Alam, Ali, Al-Jenoobi & Al-Mohizea, 2012). Such amorphous solid dispersions (ASDs) can be manufactured by either solvent or hot melt methods. Solvent methods utilize a common organic solvent in order to dissolve the drug and the polymer, which is then removed rapidly by spray drying or the ASDs can be coprecipitated using an anti-solvent such as an aqueous buffer (Hu, Choi, Chokshi, Shah & Sandhu, 2013; Paudel, Worku, Meeus, Guns & Van den Mooter, 2012; Shah et al., 2013). In the case of hot melt extrusion (HME) method, the drug-polymer blend is mixed together at higher temperature and shear and the molten mass is extruded through a die into various shapes in order to manufacture solid dispersions (Wilson, Williams, Jones & Andrews, 2012). Thus, HME could be a better option due to its continuous processing and ecological and economical advantages over the solvent methods (Leuner & Dressman, 2000).

The physicochemical properties of HPMCAS make it suitable for manufacturing ASDs of active pharmaceutical ingredients (APIs) not only by solvent methods but also by HME (Friesen et al., 2008; Ghosh et al., 2011; Li, Harich, Wegiel, Taylor & Edgar, 2013; Li, Konecke, Harich, Wegiel, Taylor & Edgar, 2013). HPMCAS based commercial ASDs manufactured using coprecipitation by Roche and using spray drying by Vertex Pharmaceuticals were approved in 2011 by the FDA in the United States. Several researchers from the industry and academia are working on developing ASDs of HPMCAS using HME method, yet no commercial formulation is available. Not only the T_g and the melt viscosity of the polymer are suitable, but also this anionic polymer may interact with poorly water soluble drugs during HME processing in order to enhance their supersaturation in gastrointestinal fluid (Sarode, Sandhu, Shah, Malick & Zia, 2012). Furthermore, HPMCAS also restricts nucleation and crystal growth of the APIs during storage of their HME ASDs as well as after achieving the supersaturation levels in the gastrointestinal fluid (Murdande, Pikal, Shanker & Bogner, 2011; Rumondor, Stanford & Taylor, 2009). However, one of the concerns of using HME for manufacturing HPMCAS based ASDs is the stability of the polymer at higher temperature and shear. Although it has been identified that the polymer may release free acetic and succinic acids at higher temperature (Dong & Choi, 2008), no systematic work has been performed in order to determine the effect of temperature and shear during HME on the degradation and stability of the polymer. In this investigation, we have systematically evaluated the effects of HME processing conditions at three different temperatures and speeds on the physicochemical properties of LF, MF, and HF grades of HPMCAS. The objective of this work was to identify the changes in specific physicochemical properties of the polymer due to HME processing, which may affect the final drug product.

2. Experimental

2.1. Chemicals

Three grades of HPMCAS polymer (Shin-Etsu AQOAT®) – AS-LF (lot# 8103193), AS-MF (lot# 8053095), and AS-HF (lot# 8083178) manufactured by Shin-Etsu Chemical Co., Ltd., Japan were obtained from Biddle Sawyer Corp., USA. All other chemicals and reagents used for evaluation were of analytical grade.

2.2. Rheological evaluation

Advanced Rheometer AR 2000 (Thermo Instruments) was used for rheological evaluation of the polymer. The analysis was performed at three different temperatures – 160, 180, and 200 °C, as these temperatures were also used for HME. The instrument was calibrated for 20 mm steel plate geometry and the gap between the parallel plates was zeroed at the softening temperatures. The geometry was pulled up to back off distance of 4.5 cm and each polymer sample was mounted on the hot plate at the preset temperatures and allowed to equilibrate for 2 min. The geometry was then pushed down and the samples were compressed to 1 mm thickness between the two parallel plates. The shear rate was increased gradually in flow mode by rotating the geometry and the zero rate viscosity (η_0) was determined by Cross Model using a logarithmic plot of viscosity versus shear rate.

2.3. Hot melt extrusion

HME was performed using Haake MiniLab MicroCompounder (Thermo Electron). The polymer samples were fed manually using a funnel into the inlet of the extruder. Three different temperatures – 160, 180, and 200 °C were used at three different speeds of 100, 200, and 300 rpm and the temperature and speed were kept constant throughout the HME process. The hot melt extrudates (HMEs) were collected, allowed to cool, milled using a twin-blade rotary mill, and screened through US mesh # 50. The milled HMEs were stored in 60 cc amber colored glass bottles in a desiccator at room temperature for further analysis.

2.4. Analysis of yellowness index(YI)

The samples of polymers or their corresponding milled HMEs (480 mg each) were compressed into 13 mm flat faced compacts at 80 MPa using a single punch Tableting Tester (Sankyo Piotech). The yellowness index of the compact surface was then measured using an S&M SM-T Color Meter (Suga Test Instruments Co., Ltd.).

2.5. Thermal analysis

Thermal analysis was performed by using an SII 5200 Differential Scanning Calorimeter (DSC) (Perkin–Elmer) equipped with a liquid nitrogen cooling accessory. About 6–8 mg of the samples of the polymers or milled HMEs of the polymers were sealed in aluminum pans and subjected to heat–cool–heat cycle. The heating rate was 10 °C per minute and the cooling rate was 50 °C per minute. The glass transition temperature (T_g) was determined by Pyris Software.

2.6. Powder X-ray diffraction (PXRD)

PXRD was performed using a powder X-ray diffractometer (Thermo Electron, NH). The polymers and the milled HMEs of the polymers were analyzed using Cu Kα radiation in order to determine the morphological changes due to HME. The X-ray pattern was collected in the angular range of $1 < 2\theta < 40^\circ$ in the step scan mode with step width of 0.02° and scan rate of 1° per minute.

2.7. Polarized light microscopy (PLM)

Optical image analysis system (Leitz Wetzlar, Germany) was used to perform the PLM experiments. Samples of the polymers and their corresponding milled HMEs were mounted on the slides, spread with mineral oil, covered with cover slips and observed under a microscope. The magnification was 10× and the light intensity was 5.0 for all the samples.

2.8. Fourier transform infrared (FTIR) spectroscopy

The pellets of the polymer samples and their corresponding milled HMEs were prepared using Smart Orbit Accessory. These pellets were analyzed by FTIR analyzer and the IR plots were obtained using Omnic Software.

2.9. Moisture analysis

Moisture analysis was performed using loss on drying (LOD) instrument by keeping the pre-weighed polymer samples and their corresponding milled HMEs on the aluminum pans and the drying was performed at 105 °C. The percent weight loss of the samples was recorded as the percent moisture content. The moisture analysis was also performed using Karl Fischer (KF) volumetric titrator (Aquacounter AQV-2100, Hiranuma Sangyo Co., Ltd.).

2.10. Evaluation of viscosity

Sodium hydroxide solution was prepared by dissolving 4.3 g of sodium hydroxide in carbon dioxide free water to make 1000 ml. HPMCAS solution was prepared by dissolving 2 g of the polymer or its corresponding milled HME in sodium hydroxide solution to make 100 g by constant shaking for 30 min. The viscosity of this aqueous solution was then measured using Ubbelohde viscometer (Cannon, ASTM-D445) at 20 ± 0.1 °C.

2.11. Quantitative analysis of the substituents

The quantitative estimation of substituent moieties (acetyl and succinoyl group, and free acetic and succinic acid) was carried out in accordance with NF monograph for hypromellose acetate succinate. HPLC analysis of the polymer grades and their corresponding HME samples was performed using a Shimadzu Prominence 20A system with a Phenomenex Aqua (5 μm C18 125A 150 × 4.6 mm) column. Phosphate buffer (0.02 M) adjusted to pH 7.5 was used as the mobile phase. The flow rate was 1 ml/min at 25 °C and UV detection was employed at 215 nm using Shimadzu SPD-20AV UV detector.

2.12. Solubility evaluation at various pH conditions

The film specimens were cast from an organic solvent solution of 20% polymer or its corresponding milled HMEs in 1:1 chloroform:ethanol w/w solvent mixture. The films were cut into 1 cm × 1 cm pieces of 100 μm thickness and put into the USP phosphate buffer of various pH, according to USP disintegration test and the dissolution time of the film specimens was then recorded.

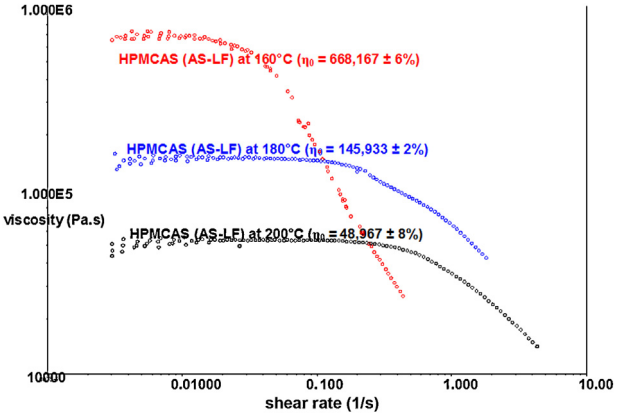

Fig. 2. Rheological cross model plots of reduction in viscosity as a function of shear rate for HPMCAS (AS-LF grade), where the zero rate viscosity (η_0) was reduced with the increase in temperature.

3. Results and discussion

3.1. Rheological evaluation

The cross model plots of AS-LF grade are shown in Fig. 2, where the η_0 values determined at the beginning of first Newtonian plateau can be considered as the initial viscosity of the polymer in a hot melt extruder at a particular temperature. Like AS-LF, the η_0 was significantly reduced when the rheological evaluation was performed at higher temperatures for AS-MF and AS-HF grades. These results suggest that HME processing of drugs with HPMCAS would be easier at higher temperatures due to low η_0 that might help in producing one phase systems. Although several other models are recommended in order to interpret reduction in melt viscosity of the polymers with respect to temperature (Avramov, 2007; Khandare, Zondlo, Stansberry & Stiller, 1999), the Arrhenius plot was well fitted to all the grades of HPMCAS with an excellent coefficient of regression (Fig. 3). The energy of activation values determined from the slope of linear regression for AS-LF, AS-MF, and AS-HF were found to be 139, 126, and 137 kJ/mol respectively, suggesting slightly better flow properties of AS-MF during HME compared to other grades.

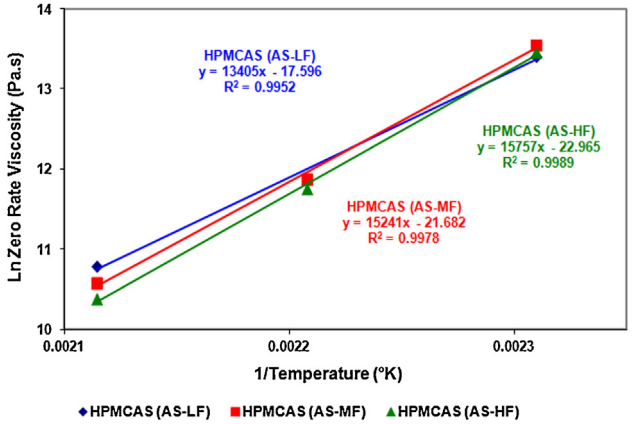

Fig. 3. Arrhenius plots of HPMCAS polymer grades where reduction in melt viscosity of the polymer as a function of temperature could be well fitted with an excellent coefficient of regression.

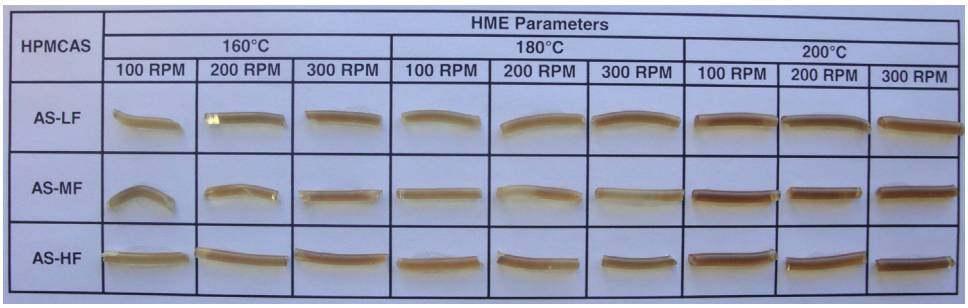

Fig. 4. Images of glassy yellowish HME product showing increase in yellowness with the increase in processing temperature and speed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.2. Hot melt extrusion (HME)

As shown in Fig. 4, glassy yellowish HMEs were obtained for all the grades of HPMCAS at various processing conditions. The increase in yellowness with processing temperature and speed of HME processing can be clearly observed visually, suggesting possible degradation of the functional groups of the polymer or release of free acid.

3.3. Analysis of yellowness index (YI)

The analysis of yellowness index correlated well with visual observations of HME product showing higher values at higher processing temperatures and speeds. As shown in Table 1, the yellowness index was increased with rpm at lower temperatures – 160 and 180 °C, whereas it was found to be independent of speed at higher temperature of 200 °C for all the grades of HPMCAS.

3.4. Thermal analysis

HPMCAS polymer exhibited glass transition endotherm at 120 °C as shown in Fig. 5. Similar endotherms were observed for HME products processed at various processing conditions and no change in T_g was detected. These results suggest that there may not be significant thermal degradation of the polymer due to various temperatures and speeds used during HME.

3.5. Morphological characteristics

As depicted in Fig. 6, no difference was observed in the X-Ray diffractograms of the polymer grades and their corresponding HME products. Due to semi-crystalline nature of the cellulosic backbone, HPMCAS depicted birefringence in PLM images. As shown in Fig. 7, the birefringence of AS-HF grade can be seen in polymer sample as well as in its HME product at various processing conditions, suggesting no change in semi-crystalline form of the polymer due to HME processing. Since the milled HMEs were screened through US mesh # 50, their particle size was greater than the polymer samples used for PLM analysis. Similar results were obtained for AS-LF and AS-MF grades. Since significant changes in morphological characteristics of the polymer were not detected, it can be estimated that there should be no changes in dissolution characteristics of the polymer unless there is degradation of functional groups or release of free acids.

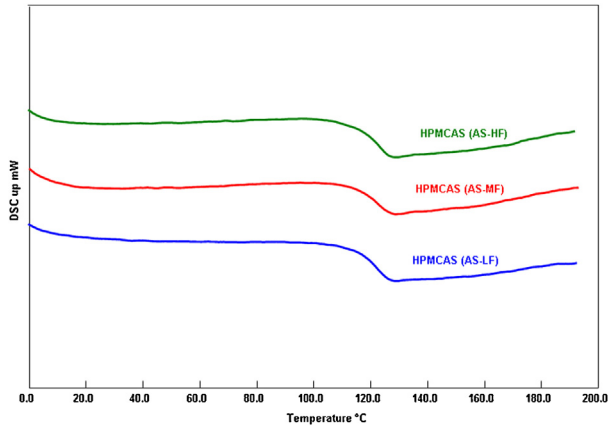

Fig. 5. DSC plots for HPMCAS polymer grades, where the glass transition endotherms were detected at 120 °C.

3.6. Fourier transform infra-red (FTIR) spectroscopy

As shown in Fig. 8, significant changes were not detected in the IR plots of AS-MF HME products processed at various conditions as compared to the polymer sample. Similar results were obtained for AS-LF and AS-HF grades, suggesting that there may not be significant changes in the functional groups of the polymer in solid state followed by HME processing at different temperatures and speeds. Thus, non-covalent intermolecular interactions of HPMCAS with the drugs may not be adversely affected due to HME processing in solid state during storage as well as in the aqueous medium of gastro-intestinal tract.

3.7. Moisture analysis

No significant differences were detected between the moisture content values determined using LOD and KF titration for all the samples (Table 1). Also, the moisture content values of HPMCAS were not significantly different as compared to their HME products for all the grades processed at various conditions. This data indicates that HME process did not affect the moisture content of the polymer.

3.8. Evaluation of viscosity

The HME products of AS-LF and AS-MF grades exhibited slightly lower solution viscosity as compared to the polymer samples (Table 1). The reduction in viscosity of these grades was dependent on HME processing conditions and the viscosity was reduced with the increase in temperature and speed. On the other hand, no reduction in solution viscosity was detected for AS-HF grade due to HME processing. Since the reduction in solution viscosity of the polymer is negligible, it can be speculated that HME processing would not adversely affect the nucleation and crystal growth inhibiting nature of HPMCAS, which is dependent on its solution viscosity and other physicochemical properties.

Table 1
The effect of HME processing conditions on the physicochemical properties of HPMCAS grades (a) AS-LF, (b) AS-MF, and (c) AS-HF.

HME Conditions		Moisture (%)		Viscosity cP	YI	Substituent content (%)				Free acid content (%)			Film dissolution time (min)			
Temp (°C)	Speed (rpm)	LOD	KF			Methoxy	Hydroxy propoxy	Acetyl	Succinoyl	Succinic acid	Acetic acid	Total acid	pH 6.0	pH 6.2	pH 6.4	pH 6.8
(a)																
Before HME		1.4	1.7	2.79	6.0	22.6	7.2	7.9	14.7	0.02	0.03	0.05	27	16	11	7
160	100	1.4	1.4	2.67	21.9	22.6	7.2	7.9	14.6	0.24	0.10	0.34	24	16	12	7
	200	1.5	1.4	2.60	26.5	22.7	7.1	7.8	14.4	0.35	0.14	0.49	24	16	12	8
	300	1.6	1.5	2.56	28.6	22.4	7.1	7.7	14.3	0.51	0.17	0.68	26	17	11	7
180	100	1.6	1.6	2.70	25.7	22.5	7.1	7.7	14.3	0.38	0.13	0.51	24	17	12	8
	200	1.5	1.5	2.62	29.3	22.6	7.2	7.9	14.3	0.44	0.14	0.58	24	17	12	8
	300	1.6	1.6	2.56	31.5	22.5	7.1	7.7	14.2	0.50	0.17	0.67	26	17	12	7
200	100	1.7	1.7	2.53	40.1	22.6	7.1	7.7	14.1	0.62	0.14	0.76	28	18	13	8
	200	1.5	1.6	2.49	40.1	22.6	7.1	7.7	14.1	0.70	0.18	0.88	27	18	13	8
	300	1.4	1.5	2.50	38.5	22.6	7.0	8.1	14.1	0.70	0.23	0.93	27	17	12	8
HME Conditions		Moisture (%)		Viscosity cP	YI	Substituent content (%)				Free acid content (%)			Film dissolution time (min)			
Temp (°C)	Speed (rpm)	LOD	KF			Methoxy	Hydroxy propoxy	Acetyl	Succinoyl	Succinic acid	Acetic acid	Total acid	pH 6.0	pH 6.2	pH 6.4	pH 6.8
(b)																
Before HME		1.3	1.3	2.76	11.8	23.0	7.2	9.3	11.4	0.03	0.04	0.07	41	19	13	7
160	100	1.3	1.3	2.66	30.9	22.9	7.1	9.4	11.1	0.44	0.10	0.53	38	19	12	8
	200	1.1	1.1	2.60	38.3	23.1	7.2	9.3	10.8	0.68	0.12	0.80	37	19	13	8
	300	1.1	1.0	2.60	47.5	23.0	7.1	9.4	10.7	0.85	0.14	1.00	36	20	13	8
180	100	1.2	1.2	2.62	32.9	23.0	7.3	9.2	10.8	0.72	0.11	0.82	38	18	12	7
	200	1.1	1.1	2.59	35.6	23.0	7.2	9.3	10.8	0.77	0.12	0.89	42	20	13	7
	300	1.1	1.0	2.59	46.5	23.1	7.2	9.3	10.9	0.88	0.12	1.00	39	20	13	8
200	100	1.1	1.0	2.50	37.6	23.0	7.2	9.2	10.4	1.19	0.16	1.35	41	19	13	8
	200	1.0	0.9	2.46	35.5	23.0	7.2	9.3	10.5	1.09	0.15	1.23	41	21	13	8
	300	1.2	1.1	2.50	44.1	23.0	7.2	9.1	10.1	1.13	0.16	1.29	38	20	13	8
HME conditions		Moisture (%)		Viscosity cP	YI	Substituent content (%)				Free acid content (%)			Film dissolution time (min)			
Temp (°C)	Speed (rpm)	LOD	KF			Methoxy	Hydroxy propoxy	Acetyl	Succinoyl	Succinic acid	Acetic acid	Total acid	pH 6.4	pH 6.8	pH 7.0	pH 7.2
(c)																
Before HME		1.5	1.5	2.69	7.5	23.6	7.5	11.8	7.7	0.03	0.04	0.07	>120	27	15	13
160	100	1.4	1.4	2.76	28.6	23.4	7.4	11.8	7.3	0.47	0.08	0.55	>120	34	18	15
	200	1.3	1.3	2.65	32.5	23.6	7.5	11.7	7.1	0.63	0.10	0.73	>120	38	19	14
	300	1.4	1.3	2.62	36.8	23.6	7.5	11.7	7.1	0.71	0.11	0.82	>120	43	21	16
180	100	1.4	1.5	2.70	34.7	23.6	7.5	11.7	7.0	0.72	0.10	0.82	>120	45	23	17
	200	1.5	1.6	2.70	37.8	23.4	7.5	11.7	7.0	0.78	0.10	0.88	>120	49	22	18
	300	1.6	1.6	2.65	41.3	23.5	7.4	11.7	7.0	0.88	0.12	1.00	>120	47	24	18
200	100	1.4	1.5	2.65	41.3	23.4	7.4	11.6	6.8	1.03	0.12	1.15	>120	60	27	19
	200	1.6	1.7	2.65	40.6	23.3	7.4	11.7	6.8	0.94	0.11	1.05	>120	60	25	19
	300	2.0	2.0	2.64	41.9	23.4	7.4	11.7	6.8	0.97	0.13	1.10	>120	59	26	19

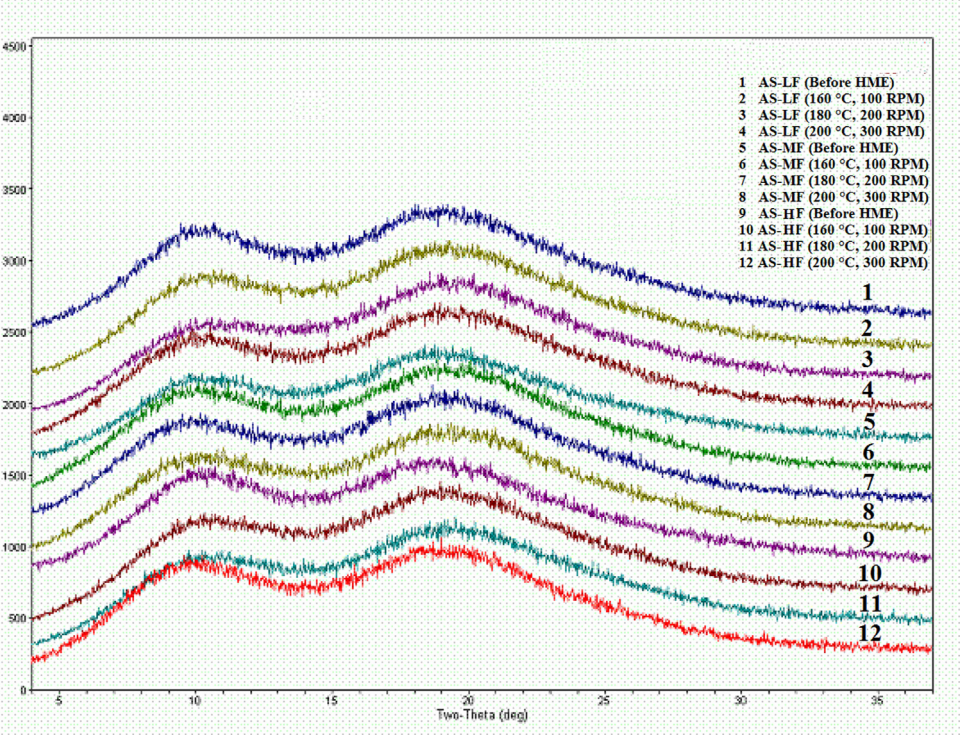

Fig. 6. PXRD graphs of HPMCAS and its HME products manufactured at various temperatures and speeds showing no change in the diffractogram pattern.

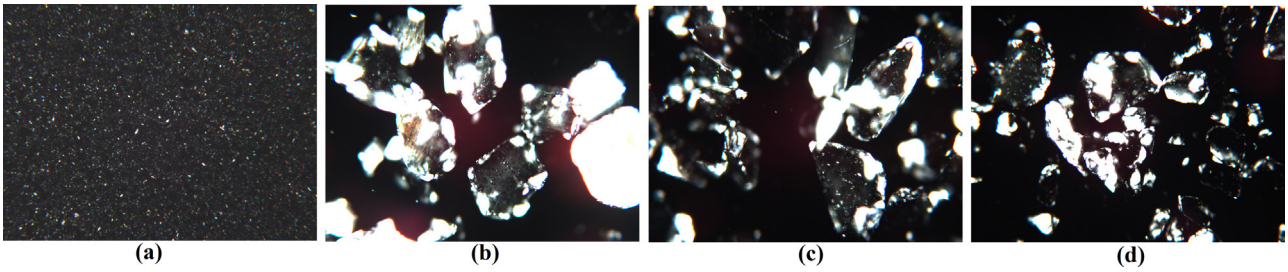

Fig. 7. PLM images of HPMCAS (AS-HF grade) showing birefringence for – (a) Polymer sample and its milled HMEs manufactured at (b) 160 °C, 100 rpm, (c) 180 °C, 200 rpm, and (d) 200 °C, 300 rpm.

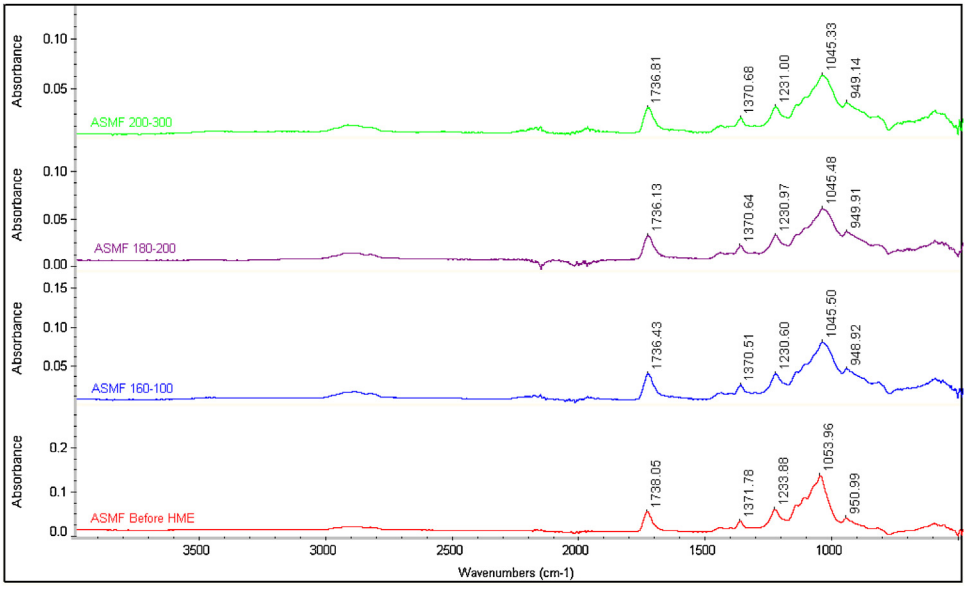

Fig. 8. FTIR plots for HPMCAS (AS-MF grade) polymer sample and its milled HMEs manufactured at various temperatures and speeds showing no significant shift or stretching in the peaks for functional groups of the polymer.

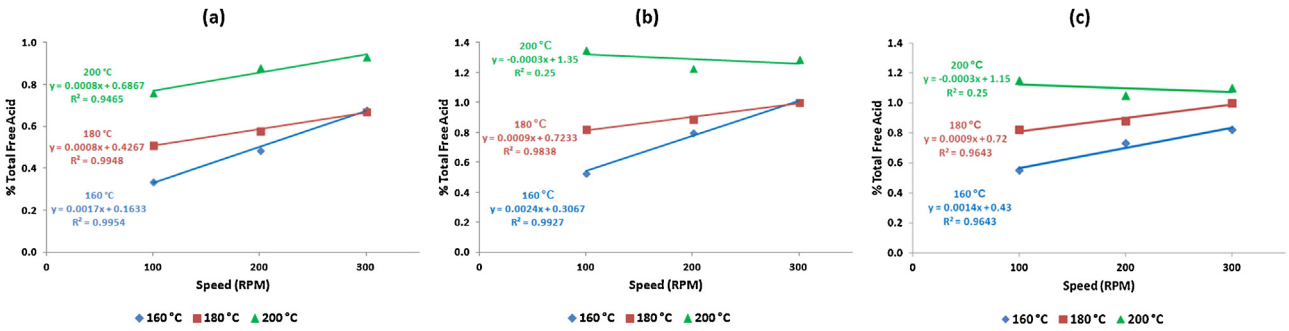

Fig. 9. Total free acid release from the polymer grades (a) AS-LF, (b) AS-MF, and (c) AS-HF followed by HME processing at various temperatures and speeds, which was found to be directly proportional to the speed at lower temperatures.

3.9. Quantitative analysis of the substituents

As shown in Table 1, free succinic acid and acetic acid values were increased and the succinoyl content was reduced accordingly with the increase in HME temperature and speed. The most significant change was the release of free succinic acid that raised the total free acid content of HPMCAS. As compared to other grades, AS-LF was found to be more stable with the lowest increase in total free acid content, which was below the specification limit of 1% even at higher HME temperature and speed. The release of acids was found to be directly proportional to the speed at lower temperatures of 160 and 180 °C with a better coefficient of regression, whereas it was independent of the speed at higher temperature of 200 °C (Fig. 9). Further, the slope of the line was lesser for 180 °C as compared to that for 160 °C. The coefficient of regression for dependence of acid release on the speed was better for AS-LF as compared to the other grades, suggesting better prediction of acid release with the processing speed for this grade. These results suggest that the processing conditions for HME should be carefully selected in order to prevent degradation of acid labile drugs while making solid dispersions using this technology. In general, it can be estimated that the acid release will increase with the HME speed at lower processing temperatures, whereas it will be independent of speed at higher processing temperatures. Furthermore, AS-LF grade would be safer as compared to other grades for HME technology due to its lower acid releasing nature even at higher processing temperatures. Nevertheless, presence of drugs may reduce or increase the actual acid release content during HME due to plasticization or anti-plasticization effects, respectively. In addition, use of plasticizers may reduce the release of acid during HME by facilitating flow properties.

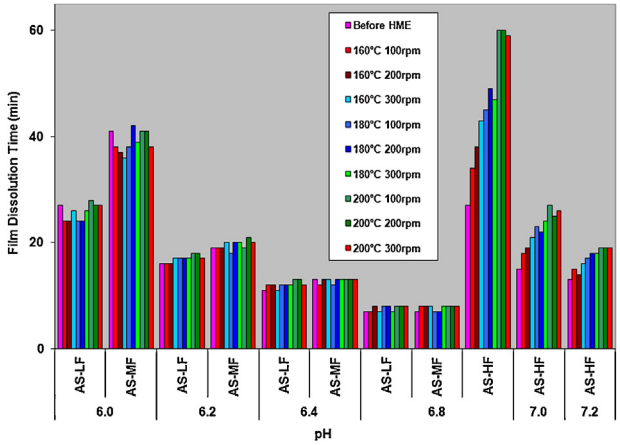

Fig. 10. Effect of HME processing conditions on the film dissolution time of HPMCAS, which was significantly increased for AS-HF grade, especially at lower pH of 6.8.

3.10. Solubility evaluation at various pH conditions

Although the film dissolution time was not affected by HME processing conditions for AS-LF and AS-MF grades, it was significantly increased for AS-HF grade, especially at lower pH of 6.8 (Fig. 10). This significant increase in dissolution time of AS-HF due to HME can be attributed to release of free succinic acid that might have reduced the ratio of succinoyl content over other substituents, which were relatively unaffected by HME processing. Therefore, it can be estimated that HME processing would not affect the dissolution characteristics of the polymer and consequently the solid dispersions formulated using AS-LF and AS-MF grades, whereas one may predict unusually prolonged dissolution periods for solid dispersions manufactured using AS-HF grade.

4. Conclusions

The η_0 of HPMCAS was significantly reduced with the increase in temperature and Arrhenius model could be well fitted to this temperature dependent reduction in η_0. The energy of activation determined by the slope of Arrhenius plot was slightly lower for AS-MF as compared to the other grades of HPMCAS, suggesting relatively better flow properties of the grade. Although various physicochemical properties of HPMCAS were not considerably affected, all the grades of the polymer released acetic and succinic acid as a result of HME processing. This release of free acid was found to be directly proportional to the speed at lower temperatures, whereas it was independent of speed at higher temperature. AS-LF seemed relatively more stable to HME processing as compared to other grades, since it released the lowest amount of acids even at higher processing temperature and speed. The dissolution time of AS-HF grade was significantly increased due to HME perhaps due to significant reduction in succinoyl content, whereas other grades didn't exhibit reduction in dissolution time. Based on these results, it can be concluded that HME processing doesn't result into significant physicochemical degradation of HPMCAS. However, the processing parameters should be optimized and grades should be selected by considering the acceptance levels of free acid for the drug and the drug product. Nonetheless, plasticizing or anti-plasticizing effects of the drugs as well as use of plasticizers for HME may change the actual acid content values, which requires further investigation.

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