

Determination of Processing Window for Hot Melt Extrusion and Milling of Hypromellose Acetate Succinate by Assessing Thermal Degradation

Lawrence Martin, Raxit Mehta, Manish Rane, Charles Cunningham and Ali Rajabi-Siahboomi

AAPS

Colorcon Inc., Harleysville, PA 19438, USA

Poster Reprint 2017

Purpose

Hypromellose acetate succinate (HPMCAS) is a versatile polymer used in various solid dosage pharmaceutical applications ranging from enteric film coatings to amorphous solid dispersions (ASDs) for improving the solubility of poorly soluble drugs. HPMCAS is frequently used for producing ASDs via spray drying, and interest is increasing in its potential applications in hot melt extrusion (HME) processes. HPMCAS may undergo hydrolysis resulting in increased levels of free acetic and succinic acids due to exposure to a combination of heat, humidity or shear stress imparted by the extruder. Post-extrusion operations, such as particle size reduction for incorporation into finished dosage forms like tablets or capsules, may also impact polymer stability due to heat generation during the high-energy multi-pass milling. The purpose of this study was to evaluate the effect of hot melt extrusion process conditions and post-extrusion milling on the thermal stability of HPMCAS and to provide guidance on suitable processing windows for the grades studied.

Methods

Hypromellose acetate succinate (AFFINISOL™ solubility enhancing polymers / HPMCAS 716G and 912G, DuPont, USA) were processed in a lab scale hot melt twin screw extruder (Pharma 11, Thermo Scientific, USA) at 2 g/min using a screw speed of 50 rpm, at temperatures ranging from 165°C to 195°C, with a 2.0 mm strand die. According to manufacturer recommendations for general HME applications, screw elements were configured with two kneading sections and three conveying sections. Process outputs of screw torque, die pressure and melt temperature were recorded for each set of process conditions. Extruded strands were air-cooled and pelletized to approximate lengths of 2 mm. Pelletized extrudates were reduced in size using a centrifugal mill (ZM200, Retsch, Germany) using 750 µm (first pass) and 500 µm (second pass) sieves with a 12-tooth rotor at 18,000 rpm. Particle size distributions of the milled extrudates were determined using laser diffraction (Mastersizer 2000, Malvern Instruments Ltd, UK). Loss on drying (LOD) was measured by infrared moisture analyzer (MA37-1, Sartorius, Germany) at 105°C and drying to a constant weight. Milled extrudates were subjected to accelerated stability conditions for two weeks at 40°C/75% RH (open dish) and 40°C (induction sealed HDPE bottle), with initial control samples stored at 5°C (sealed HDPE bottles in a polyethylene outer bag with desiccant). Free acetic and succinic acid content of the extrudates, before and after milling, were determined on a dry basis using high performance liquid chromatography according to the USP40-NF35 monograph for HPMCAS. Glass transition and thermal decomposition temperatures of the unprocessed polymers were determined using differential scanning calorimetry (DSC; Q200, TA Instruments, USA) and thermogravimetric analysis (TGA; Q500, TA Instruments, USA), respectively.

Results

Hot Melt Extrusion Process

An initial evaluation found that HPMCAS 912G could be extruded at 155°C while HPMCAS 716G could not, despite being well above the glass transition temperature (T_g) of both grades (Figure 1). Both were extrudable at 165°C, which was then selected as the common starting temperature for both grades. Onset of thermal decomposition of the polymers began around 200°C (Figure 2), which was selected as the upper limit for the processing temperatures in this study.

Figure 1: DSC Thermograms Indicating T_g of HPMCAS Grades

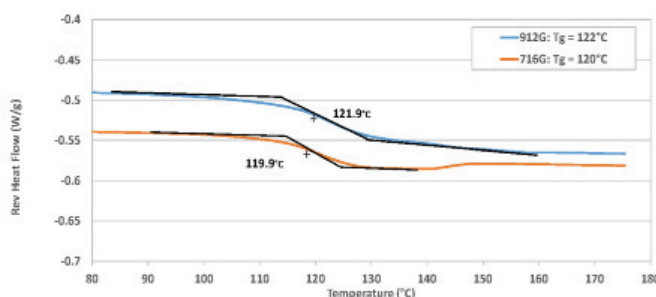
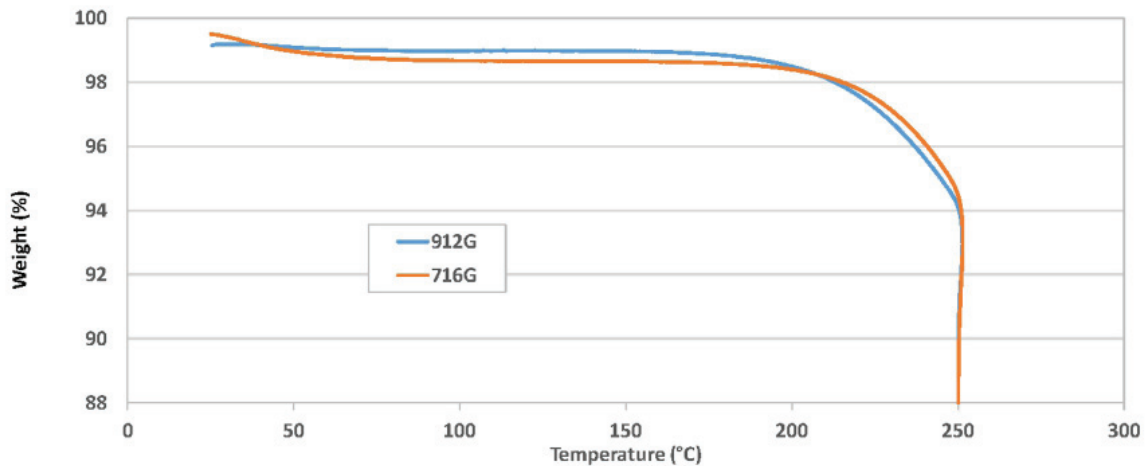


Figure 2: TGA Thermograms Indicating Thermal Decomposition Temperature of HPMCAS Grades



The machine parameters of measured screw torque and pressure at the die were different for each grade. HPMCAS 912G generally experienced greater torque than HPMCAS 716G at comparable temperatures, but the die pressures of 912G at higher temperatures were lower than those of 716G (Table 1). At 165°C, measured torque for both grades was near the machine maximum limit of 12 N-m, requiring the use of higher temperatures to reduce melt viscosity and lower torque values. Die pressure values were reasonable for both grades at all temperatures, well below the machine maximum limit of 100 bar. Temperatures of the melt at the die were generally several degrees higher than the target temperature due to frictional heating by the mechanical energy imparted by the screws.

Table 1: Hot Melt Extrusion Process Conditions and Outputs

HPMCAS Grade	Target Temp. (°C)	Torque (N-m)	Die Pressure (bar)	Melt Temp (°C)
912G	165	10.8 - 11.5	40	169
	175	9.3 - 9.6	28	181
	185	7.3 - 8.0	16	191
	195	6.4 - 7.0	10	200
716G	165	11.3 - 12.0	35	168
	175	8.2 - 8.6	26	180
	185	6.8 - 7.3	19	189
	195	5.6 - 6.0	16	198

Physical Characterization of Milled Extrudates

Pelletized HPMCAS extrudates showed high mechanical strength and toughness, so study samples were subjected to high energy milling using up to two passes to simulate a procedure for producing suitable granules in solid dosage formulations. During milling, pelletized extrudates experienced two physical impacts: first by a high-speed rotor blade, then by collision with a perforated sieve of defined hole size. Pellets were fed into the mill at a low rate of 5 g/min to minimize heat generation. Different product temperatures were measured depending on grade (912G, 53-63°C; 716G, 60-70°C), likely indicating that 716G pellets had greater strength and required more mechanical energy to mill. Particle size distributions for the first and second pass milling of each batch are shown in Table 2. No trends were observed in particle size as a function of extrusion process temperature. After the first milling pass, the particle size of 716G granules were notably larger than those of 912G, further indicating greater strength of 716G extrudates. This particle size disparity between the two grades was reduced by the second pass milling step. The size distributions could be further optimized for solid dosage formulations (approx. 100 µm) by using a finer screen in the second milling step.

Table 2: Particle Size Distribution of Milled HPMCAS Extrudates

HPMCAS Grade	Target Temp (°C)	Particle Size (µm) after 1 st Pass Milling			Particle Size (µm) after 2 nd Pass Milling		
		d ₁₀	d ₅₀	d ₉₀	d ₁₀	d ₅₀	d ₉₀
912G	165	189	351	599	126	243	425
	175	261	450	735	105	228	409
	185	204	381	654	129	254	441
	195	192	357	614	128	254	439
716G	165	285	486	795	185	317	517
	175	321	518	817	135	263	460
	185	338	544	863	111	221	392
	195	290	501	839	137	263	456

No trends were observed in moisture content of milled extrudates with respect to process temperature or polymer grade, with initial control samples having LOD values ranging from 2.7% to 4.2%. Open dish samples stored at 40°C/75% RH had LOD values ranging from 6.4% to 9.0%, while samples stored in sealed bottles ranged from 3.3% to 4.9%. LOD values for each sample were used in subsequent weight correction calculations for HPLC analysis to calculate free acid content of the HPMCAS granules on a dry basis.

Stability of Functional Groups with Respect to Process Parameters

Although the onset of thermal degradation of the HPMCAS polymers occurred around 200°C, thermally induced loss of functional groups from HPMCAS in the form of free acetic and succinic acids can occur around 165°C and may be exacerbated by the shear conditions experienced by the molten polymer. Acetic and succinic acids are designated as GRAS materials; however, HPMCAS has a compendial limit of not more than 1% total free acid content (USP40-NF35). In this study, unprocessed AFFINISOL™ 716G had no detectable free acids, and unprocessed AFFINISOL™ 912G had an acetic acid concentration of 0.077% with no detectable succinic acid.

The two grades of HPMCAS demonstrated different degradation profiles in terms of the composition and concentration of free acids as a function of process temperature, and after first pass milling using a 750 µm sieve (Figures 3a and 3b). Although free acetic acid levels for both grades remained mostly stable over the range of process temperatures evaluated, free succinic acid concentrations increased with process temperatures for both grades. HPMCAS 912G experienced greater increases in free succinic acid concentration than 716G, and at the highest process temperature of 195°C had a total free acid content of 1.03%. After second pass milling of the granules using the 500 µm sieve, the free acid profiles of both grades were similar despite the additional mechanical and thermal stress imposed by the second milling process.

Figure 3a: Free Acid Content of HPMCAS 912G as a Function of Extrusion Temperature

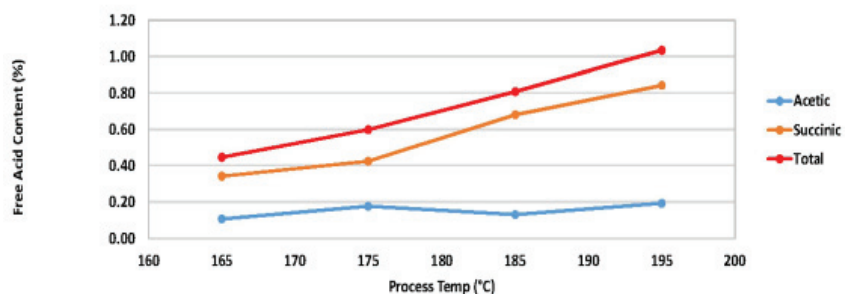
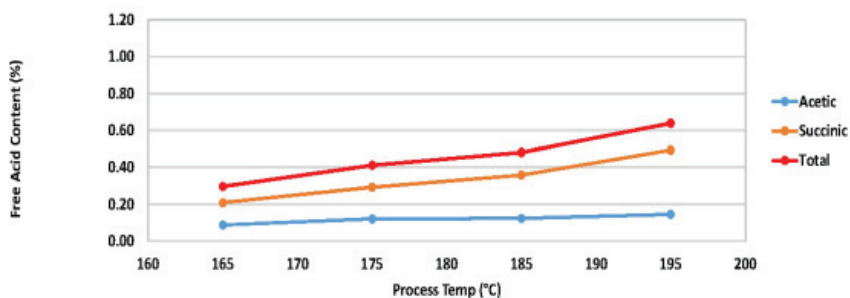


Figure 3b: Free Acid Content of HPMCAS 716G as a Function of Extrusion Temperature



Stability of Functional Groups with Respect to Storage Conditions

The concentrations of free acetic acid in open dish samples stored at 40°C/75% RH were found to be nearly zero (<0.02%) for all process temperatures and milling conditions, likely due to the vaporization of the low concentration of acetic acid (melting point 17°C) initially present. Therefore, the total free acid content of samples stored at 40°C/75% RH was almost entirely composed of succinic acid, which was a solid at this temperature (melting point 188°C). After two weeks storage at 40°C in sealed HDPE bottles, free acetic acid values for all samples were unchanged from the initial values, suggesting that acetic acid concentrations in HPMCAS were stable (unlikely to increase) even at high storage temperatures. Storage conditions did not have a significant impact on the total free acid content of milled extrudates under accelerated stability conditions regardless of the number of milling passes used (Figures 4a and 4b). Total free acid content of samples stored at 40°C were unchanged from initial values, while those at 40°C/75% RH decreased due to the vaporization of acetic acid over time.

Figure 4a: Total Free Acid Content of HPMCAS 912G: Process Temperature and Storage Conditions

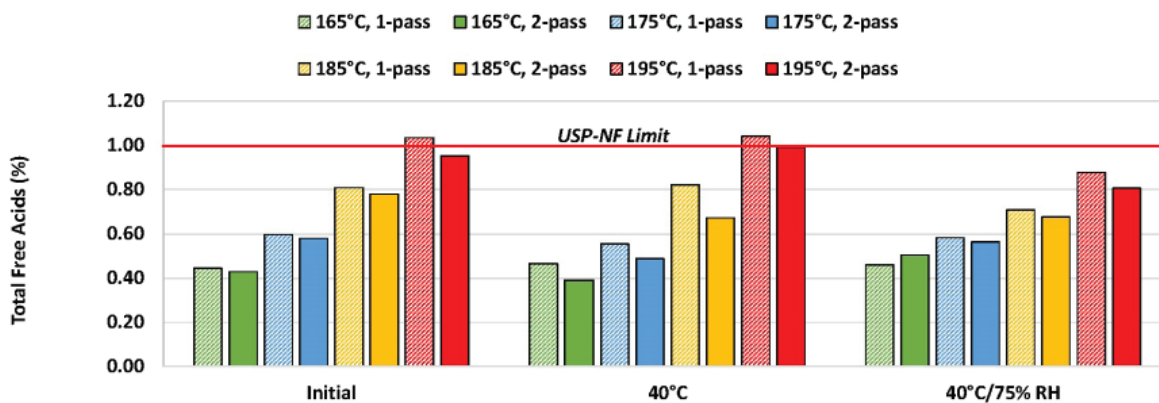
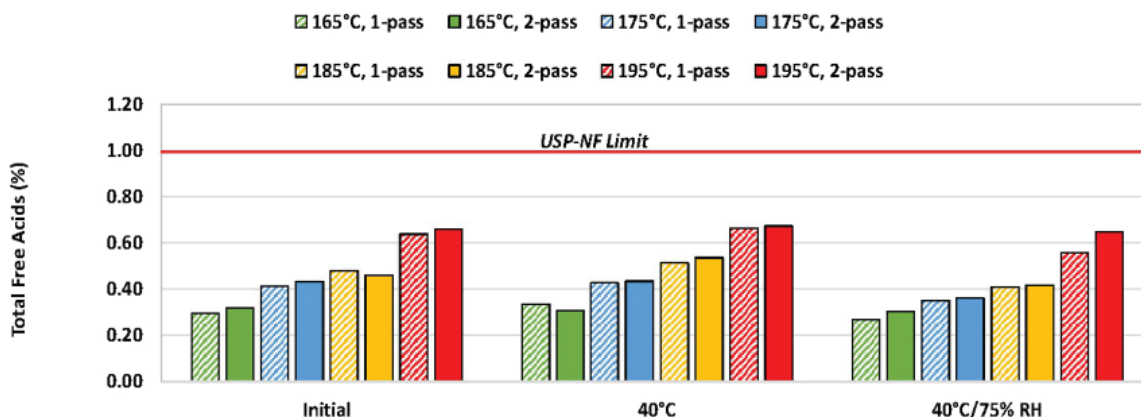


Figure 4b: Total Free Acid Content of HPMCAS 716G: Process Temperature and Storage Conditions



Conclusions

Two grades of AFFINISOL™ HPMCAS powders were successfully hot melt extruded, and the free acid content of their milled extrudates remained below the 1% USP-NF limit prior to stability storage. The two grades of hot melt extruded HPMCAS had different degradation profiles with respect to free acid generation and were impacted to different extents by processing temperatures. With respect to succinic acid generation, HPMCAS 912G was more sensitive to processing temperatures and resulted in total free acid content at the USP-NF compendial limit at the uppermost temperature. Post-extrusion milling operations and storage conditions had minimal effect on generation of free acetic or succinic acids above levels established during the earlier extrusion process.

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade name, copyright, patent or other rights held by any third person or entity when used in the customer's application.

For more information, contact your Colorcon representative or call:

North America
+1-215-699-7733

Europe/Middle East/Africa
+44-(0)-1322-293000

Latin America
+54-1-5556-7700

India
+91-832-672373

China
+86-21-61982300

AFFINISOL™

You can also visit our website at www.colorcon.com



Controlled Release Alliance

All trademarks, except where noted, are property of BPSI Holdings LLC. The information contained in this document is proprietary to Colorcon, Inc. and may not be used or disseminated inappropriately.

©BPSI Holdings LLC 2017

AFFINISOL™ is a registered trademark of DuPont or its affiliates.

pr_aaps_proc_hmelt_ext_shyp_ac_su_09_2019