T1330-10-077

Investigating the Impact of Extruder Process Parameters and Rotation Mode on HPMCAS Degradation

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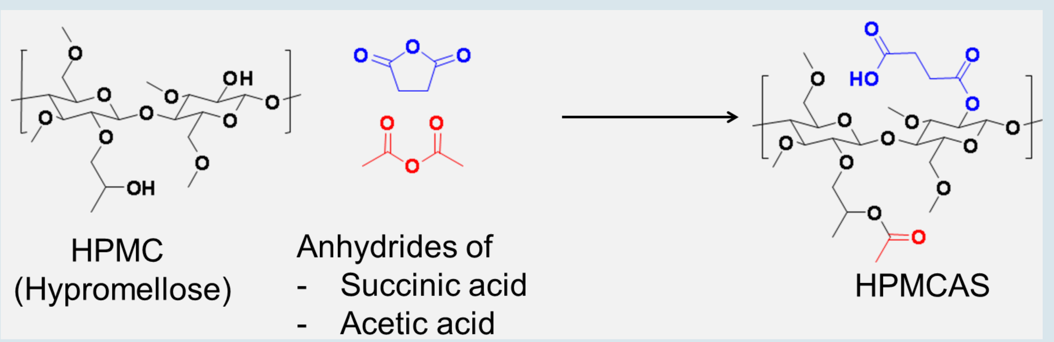
PURPOSE

Hot melt extrusion (HME) is a leading manufacturing technology for amorphous solid dispersion, taking advantage of the thermal and mechanical energy inputs to render a drug amorphous and disperse it homogeneously within the matrix. A key polymer in this application space is hydroxypropylmethylcellulose acetate succinate (HPMCAS). Its physical/chemical properties promote good stability of the resulting dispersion, and enable significant solubility enhancement without sacrificing permeability. However, HPMCAS can be challenging to process by HME due to processing difficulties, free acid liberation, and polymer degradation.

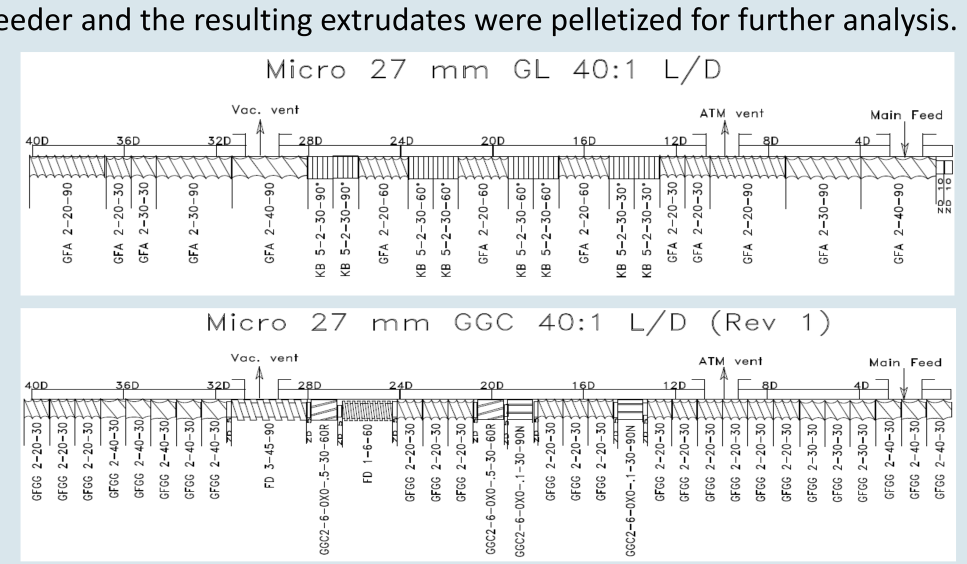


The purpose of this study was to first understand the impact of hot melt extrusion process parameters including screw speed, feed rate, and barrel temperatures, on AFFINISOL™ HPMCAS 912G (9 wt.% acetate, 12 wt.% succinate) as well as a developmental grade of chemical equivalency that has a reduced melt viscosity (HP HPMCAS) to determine differences in polymer processability. Furthermore, this study was performed to determine how extruder rotation direction, namely Corotating (screws rotating in the same direction) vs. Counter rotating (screws rotating in opposing directions) impacts polymer integrity to determine whether counter rotating systems may be suitable for processing HPMCAS.

METHOD(S)

Extrusion

All extrusion trials were conducted on a Leistritz Micro 27 mm extruder. Variables of feed rate (1, 3, 5 kg/hr), screw speed (150, 300, 450 RPM) and temperature (150, 175, 200 °C) were controlled according to a Design of Experiments. The polymers were fed into the extruder via a loss in weight feeder and the resulting extrudates were pelletized for further analysis.



Free Acid Analysis

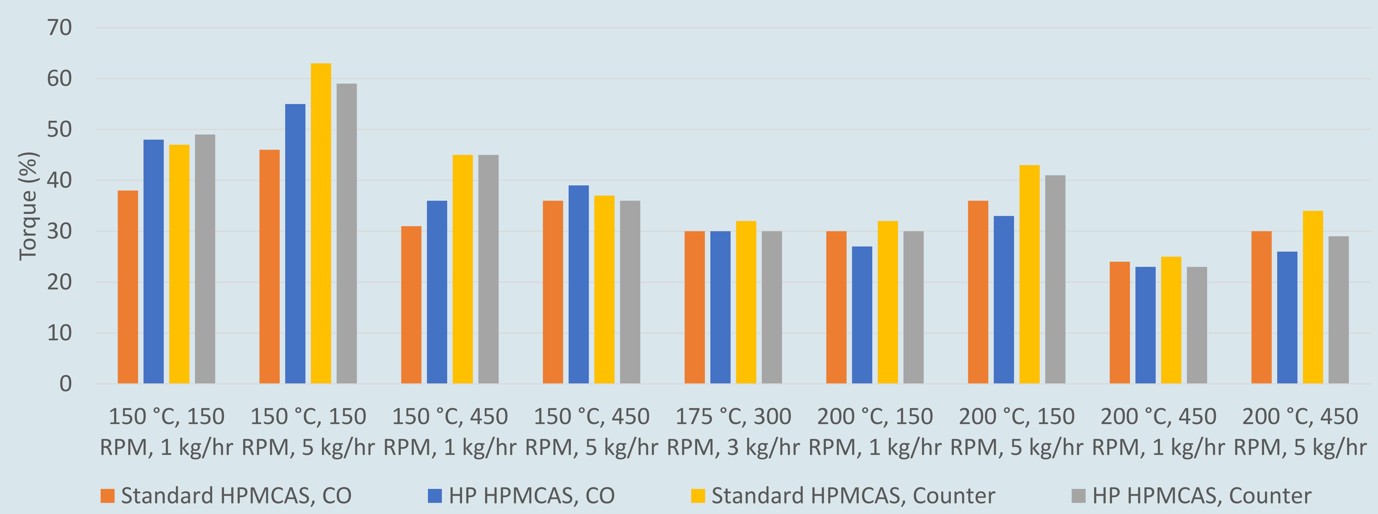
Free acid content of all HPMCAS samples was determined by HPLC as defined in the USPNF assay method.

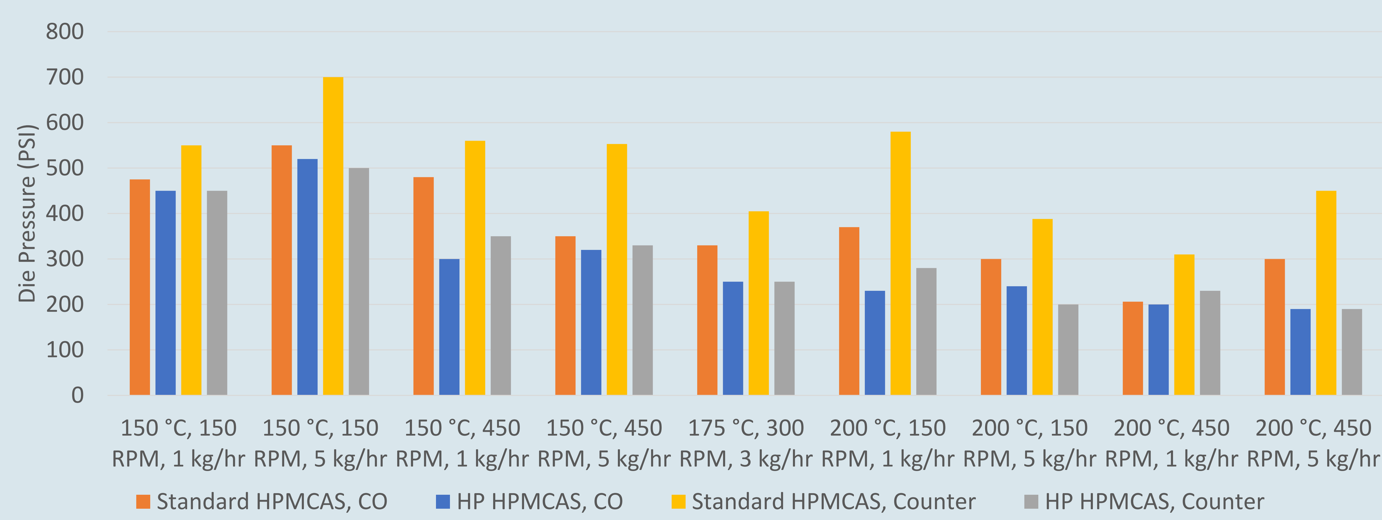
Color Assessment

Strands were assessed visually for changes in color and analyzed by a proprietary method for quantitative determination of color levels.

RESULT(S)

Extrusion

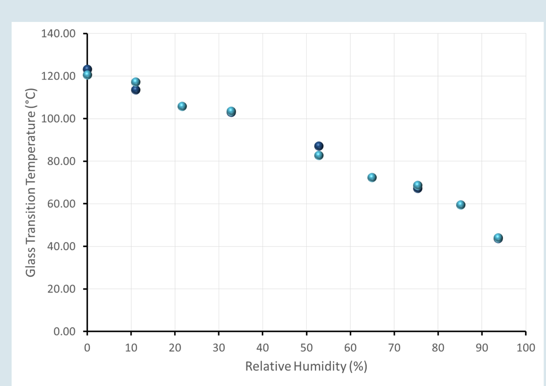


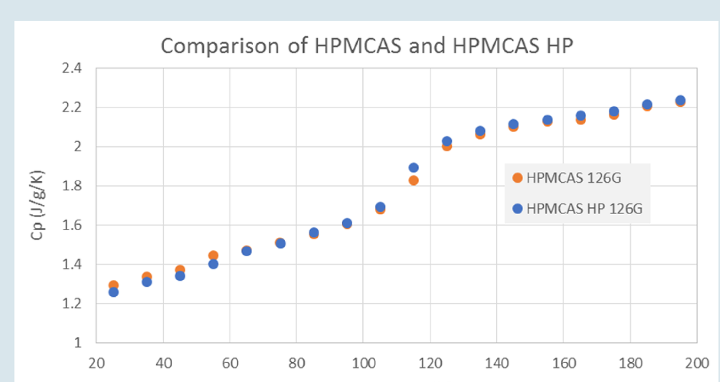


Residence time as determined via tracer die addition: Times denote first observed tracer exit

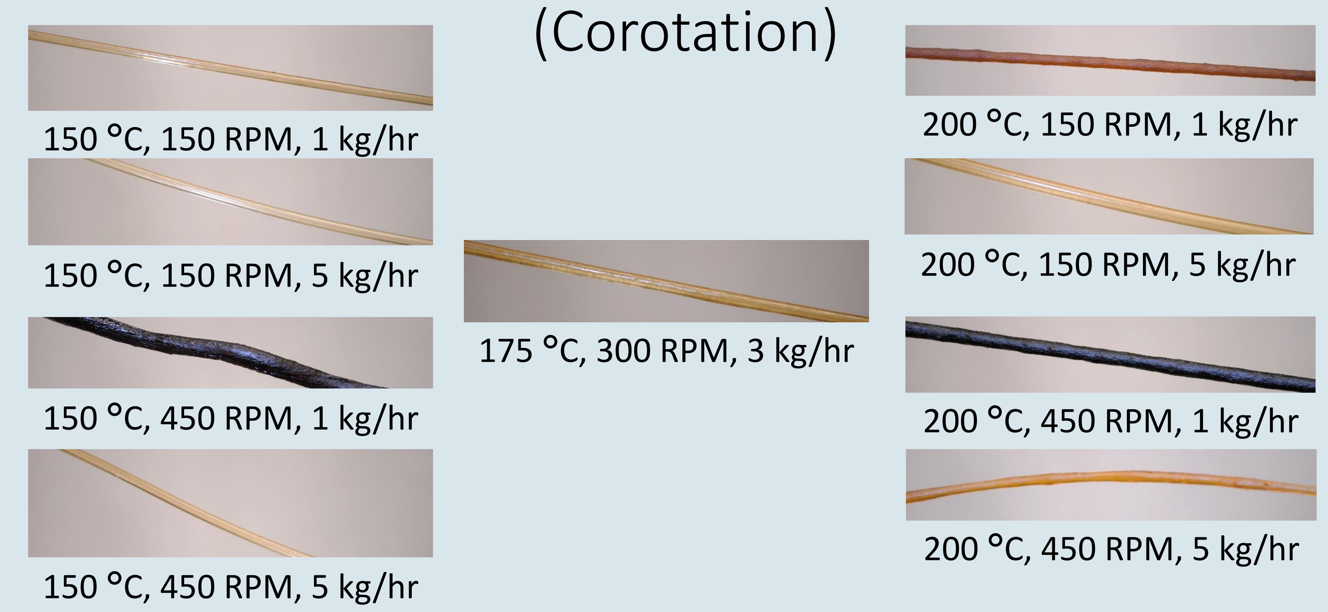
Conditions (175 °C)	Corotation (Time to Exit)	Counter Rotation (Time to Exit
1 kg/hr, 150 RPM	2:55	7:10
3 kg/hr, 150 RPM	1:40	3:15
5 kg/hr, 150 RPM	1:15	2:20
3 kg/hr, 300 RPM	1:17	2:05
1 kg/hr, 450 RPM	2:25	5:45
5 kg/hr, 450 RPM	40	1:35

- Residence time for counter rotation system significantly longer than co-rotation system
- Screw design selected for approximate functional equivalence. Could be modified to reduce residence time for counter rotation system

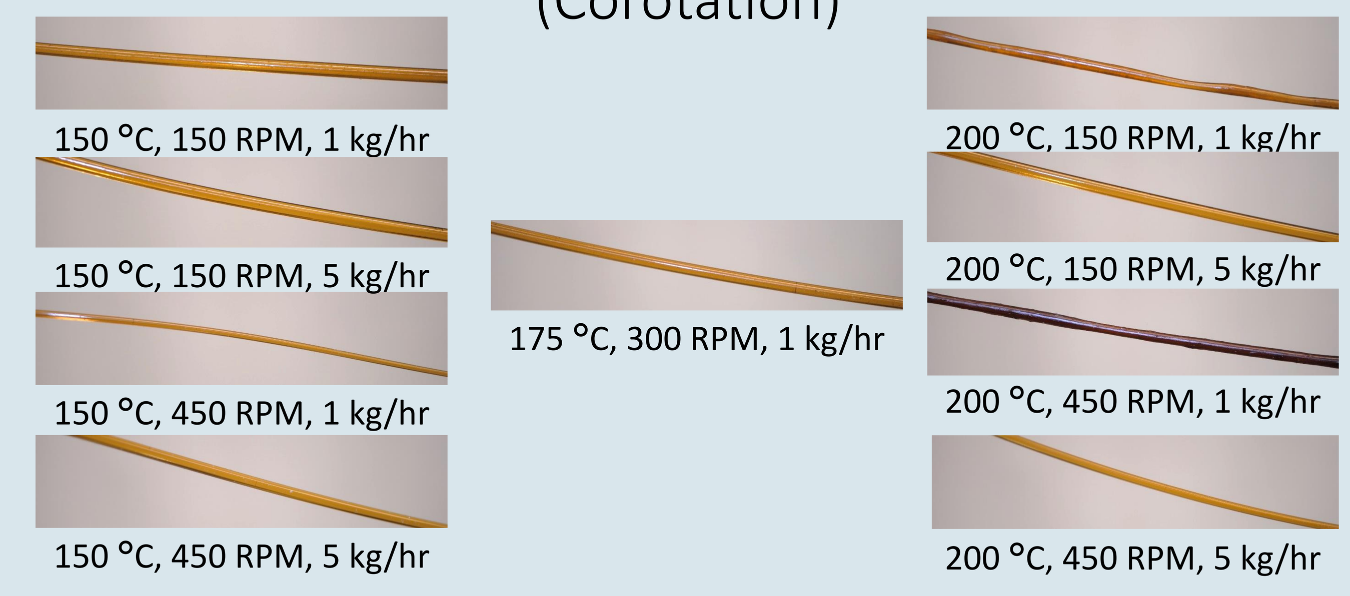




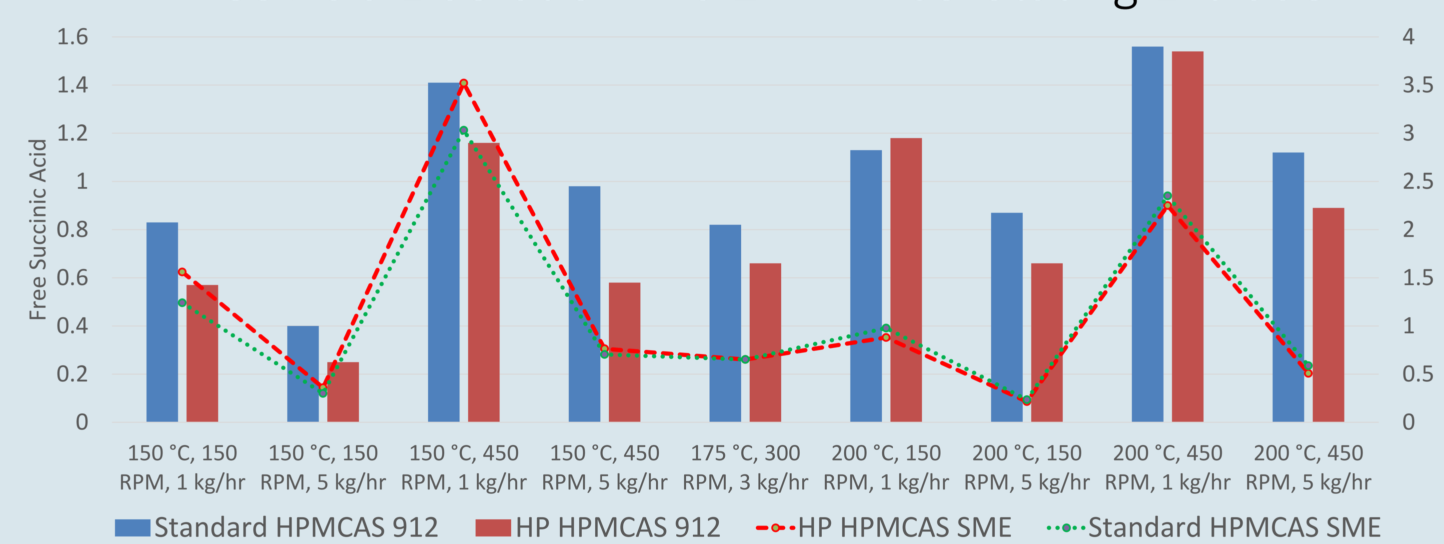
Images of Standard HPMCAS Extrudates (Corotation)

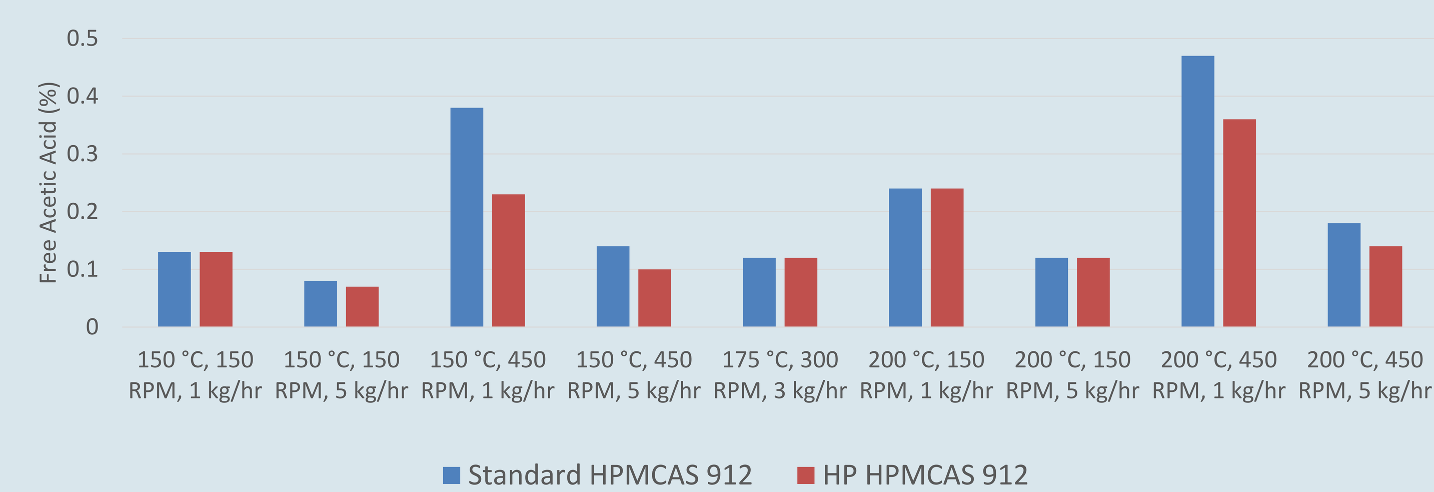


Images of HP HPMCAS Extrudates (Corotation)



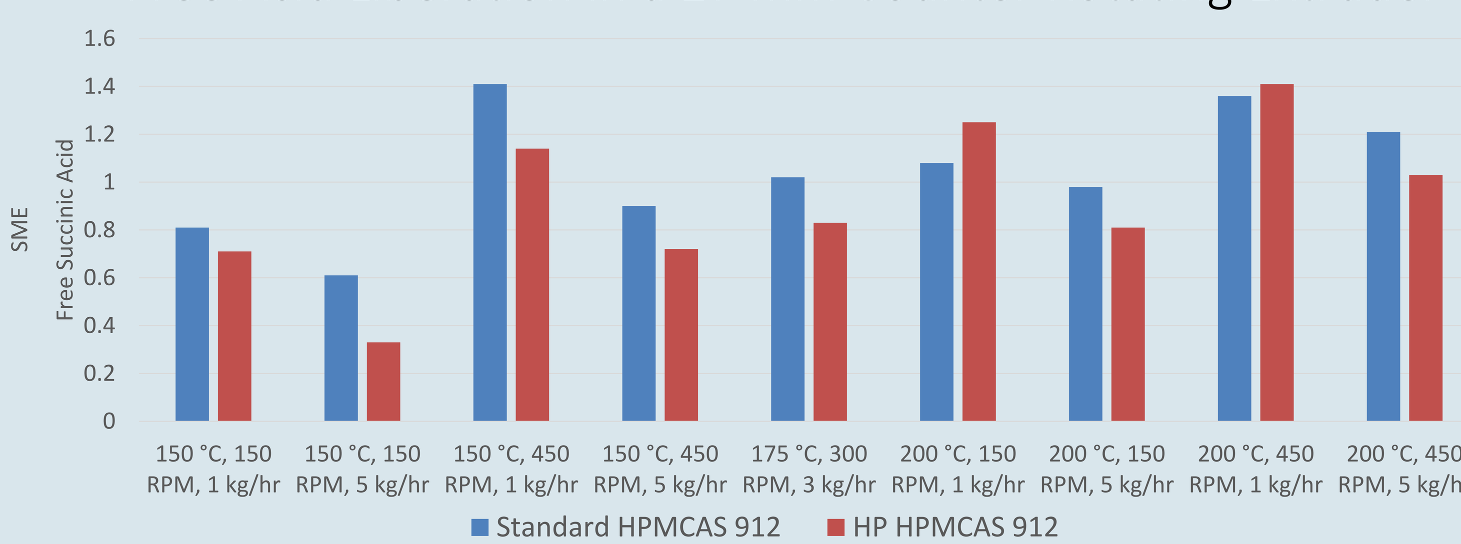
Free Acid Liberation in a 27 mm Corotating Extruder

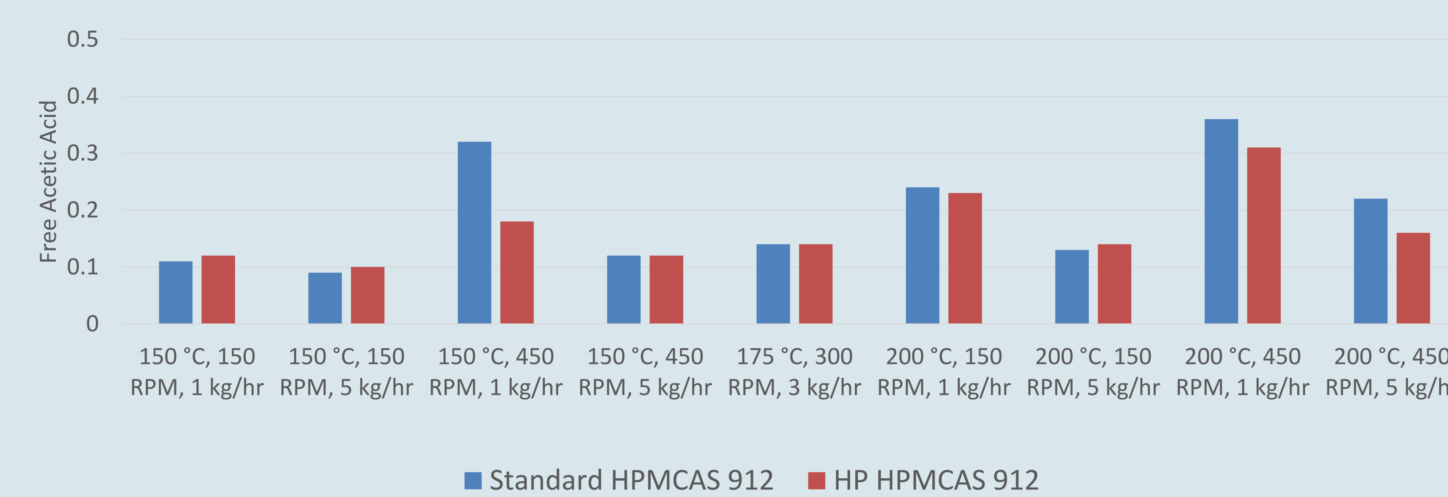




- Generally, HP HPMCAS displays lower free acid generation than standard HPMCAS due to reduction in viscous heating in restrictive zones
- At this scale, the impact of screw speed on polymer integrity is apparent both visually and by high free acid levels; this is a crucial process parameter to consider upon scaling
- The primary free acid contributor is succinic acid (boiling point of acetic acid is 118 °C)
- At high temperatures, proper control of feed rate and screw speed enables successful extrusion of both grades with acceptable acid levels (< 1% total free acids)

Free Acid Liberation in a 27 mm Counter Rotating Extruder





- As with corotation, HP HPMCAS displays lower free acid generation than standard HPMCS in counter rotation mode
- The residence time in counter rotation mode was significantly longer than in corotation yet similar levels of free acids were found
- Counter rotation may enable longer time within the extruder to facilitate drug dissolution into the polymer matrix without significantly increasing free acid content
- Modification of the screw design can shorten residence time and reduce free acids

CONCLUSION(S)

Proper control of process parameters enables successful extrusion of HPMCAS with free acids levels below the required limit of 1%, even at high temperatures. Due to the lower melt viscosity of HP HPMCAS, less viscous heating occurs in the restrictive elements reducing localized heating resulting in lower free acid generation. HP HPMCAS can be used successfully at more aggressive conditions than standard HPMCAS demonstrating a broader process window for this polymer. Counter rotating extruders can be used to successfully process HPMCAS. Using a screw design with functional equivalence to a co-rotating system, significantly longer process times resulted in similar free acid levels indicating this technology may be advantageous for formulations with slow dissolution of the drug into the polymer matrix. With proper screw design, counter rotation extruders can reduce free acid liberation substantially for HPMCAS.

DUPONT

Leistritz