eye on excipients

Quyen Schwing, Marvin Davis, Divya Tewari, and Thomas Dürig
Ashland Specialty Ingredients

This edition of the column assesses the functionality and stability of HPMCAS when used in hot-melt extrusion.

The majority of today's new chemical entities are poorly water-soluble. One widely used means of overcoming that problem is to develop solid dispersions by mixing—at the molecular level—the drug candidate into a polymer matrix [1]. Spray drying and hot-melt extrusion (HME) are the most common technologies used to manufacture these amorphous solid dispersions. With spray drying, an organic solvent dissolves the API and polymer, followed by rapid removal of the solvent. With HME, an API-polymer blend is extruded at high temperature and high shear to create a solid dispersion. HME is preferred because it can operate continuously and offers economic advantages.

Hypromellose acetate succinate (HPMCAS)—a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose (HPMC)—has demonstrated the ability to improve solubility. The physicochemical properties and functions of HPMCAS, such as amphiphilicity, solubility in various organic solvents, and suitable melt viscosity, make it an ideal polymer for manufacturing amorphous solid dispersions either by spray drying or HME.

AquaSolve HPMCAS (Ashland Specialty Ingredients, Wilmington, DE) is available in several grades that vary in the extent of substitutions of acetyl and succinoyl groups and particle size [1]. Acetyl and succinoyl substitutions on the HPMC backbone dictate the pH-solubility behavior of the polymer (Figure 1). The L grade dissolves at pH 5.5, the M grade at pH 6.0, and the H grade at pH 6.8. Particle size is denoted F for fine and G for granular.

Although the use of HME is increasing, there are few commercially available products that entail extruded HPMCAS solid dispersions. Researchers are thus seeking to better understand the utility of existing HPMCAS grades [2] and to develop grades of HPMCAS that are especially suited for HME applications [3].

The goal of the study described here was to gain a fundamental understanding of the functional performance and physicochemical stability of HPMCAS used in HME to help researchers select the optimal processing temperature for various formulations.

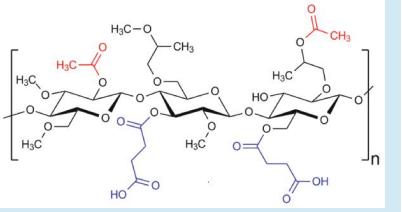
Methods

The study investigated the functionality and stability of three grades of HPMCAS: L (acetyl content 5.0 to 9.0 percent (%), succinoyl content 14.0% to 18.0%) M (acetyl content 7.0% to 11.0%, succinoyl content 10% to 14%), and H (acetyl content 10.0% to 14.0%, succinoyl content 4.0% to 8.0%). How temperature and HME processing conditions affected the physicochemical properties of the three grades and the API-polymer extrudates was also assessed.

Determining melt rheology. The rheological properties of the HPMCAS polymers before and after extrusion were studied using an AR-G2 controlled-stress rotational rheometer (TA Instruments, New Castle, DE) equipped with a 25-millimeter (mm) parallel-plate geometry. Dynamic frequency sweep experiments were conducted at 170°C and at a frequency range of 0.1 to 600 radians per second (rad/s). Dynamic temperature sweep was determined using a temperature range of 150° to 200°C, a ramp rate of 2°C per minute, and a fixed frequency of 6.28 rad/s (1 Hertz).

FIGURE 1

Chemical structure of HPMCAS

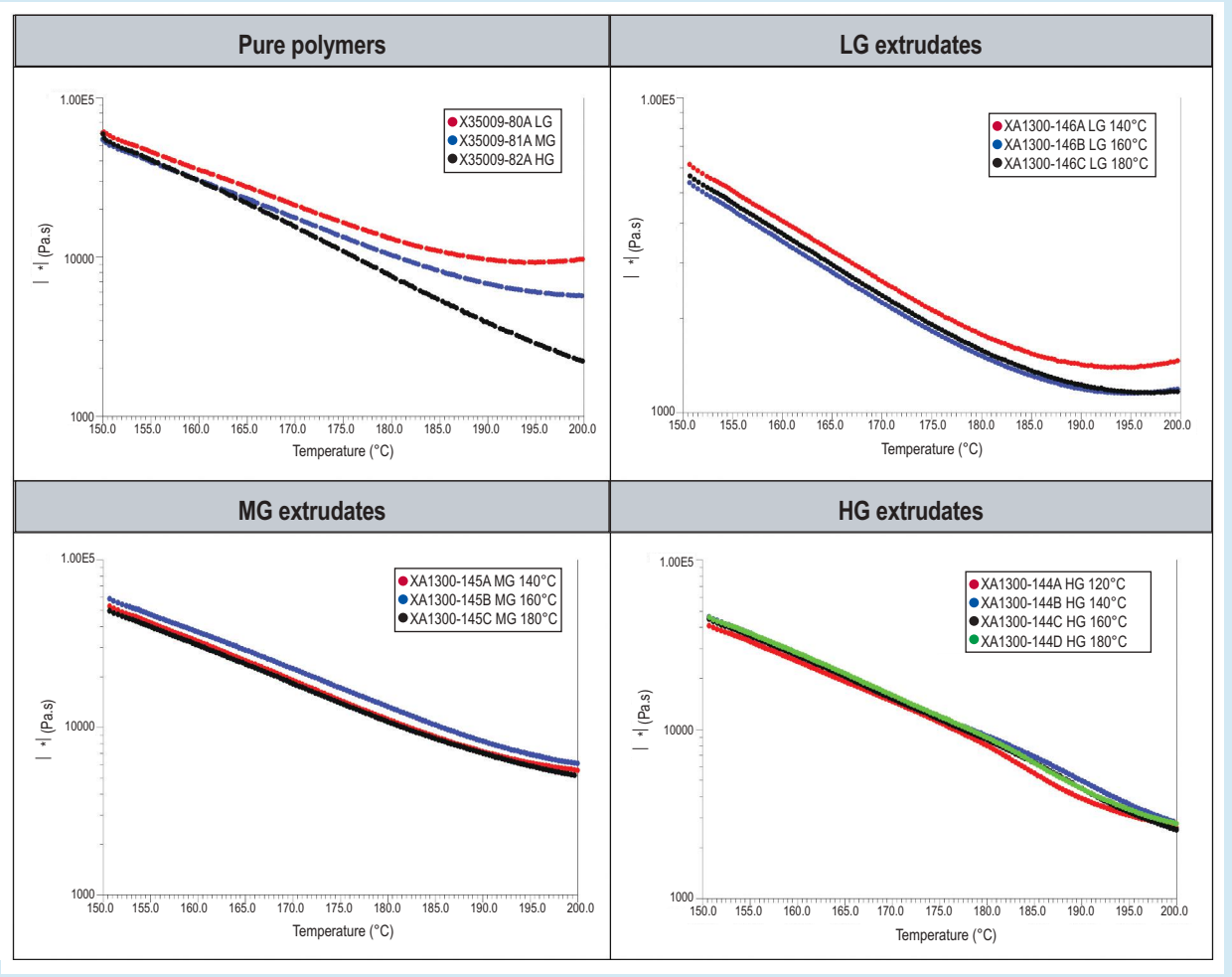


Profiling pH-solubility. A quartz crystal microbalance was used to measure the pH-solubility profiles of the HPMCAS polymers before and after extrusion. Two milliliters (ml) of 1% (by weight) HPMCAS solution was spin-coated at 3,000 rpm onto a gold-surfaced sensor for 60 seconds. Measurements were taken at 37°C. The coated sensor baseline was first established in a pH 4.5 buffer. A new buffer was introduced every 10 minutes until the film was mostly dissolved off the surface.

Determining substitution. To determine substitution of the HPMCAS, high-performance liquid chromatography (HPLC)—as described in the monograph for hypromellose acetate succinate in USP38/NF33—was used. HPLC of the polymer grades and their corresponding HME samples was performed using a 1200 Series Quaternary LC system (Agilent, Santa Clara, CA)

Figure 2

Melt rheology-temperature ramps of HPMCAS and HPMCAS extrudates produced at different temperatures



with an Ultra Aqueous C18 5-micron, 150-by-4.6-mm column (Restek, Bellefonte, PA). A phosphate buffer of 0.02 molarity (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 nanometers using a 1200 Series Infinity diode array detector (Agilent).

Determining molecular weight. Size exclusion chromatography was performed against polyethylene oxide standards with narrow molecular weight distribution using a solution of 55% of 0.1-M lithium acetate and 45% ethanol in mobile phase at a flow rate of 0.8 ml/min. Two linear TSKgel GMPWxl columns (Tosoh Bioscience, King of Prussia, PA) of 10 microns and measuring 300 by 8 mm were used. Both the column and the differential refractive index detector were maintained at 40°C. Samples at 2 mg/ml concentration were dissolved in mobile phase and filtered. The injection volume was 150 microliters.

Crystallinity determination of the solid dispersions. Absence of crystallinity was measured using differential scanning calorimetry (DSC) and powder x-ray diffraction (PXRD). DSC was performed using a Q2000 differential scanning calorimeter (TA Instruments) and PXRD was performed with a D8 Focus analyzer using a copper tube element and a PSD LynxEye detector (Bruker, Madison, WI).

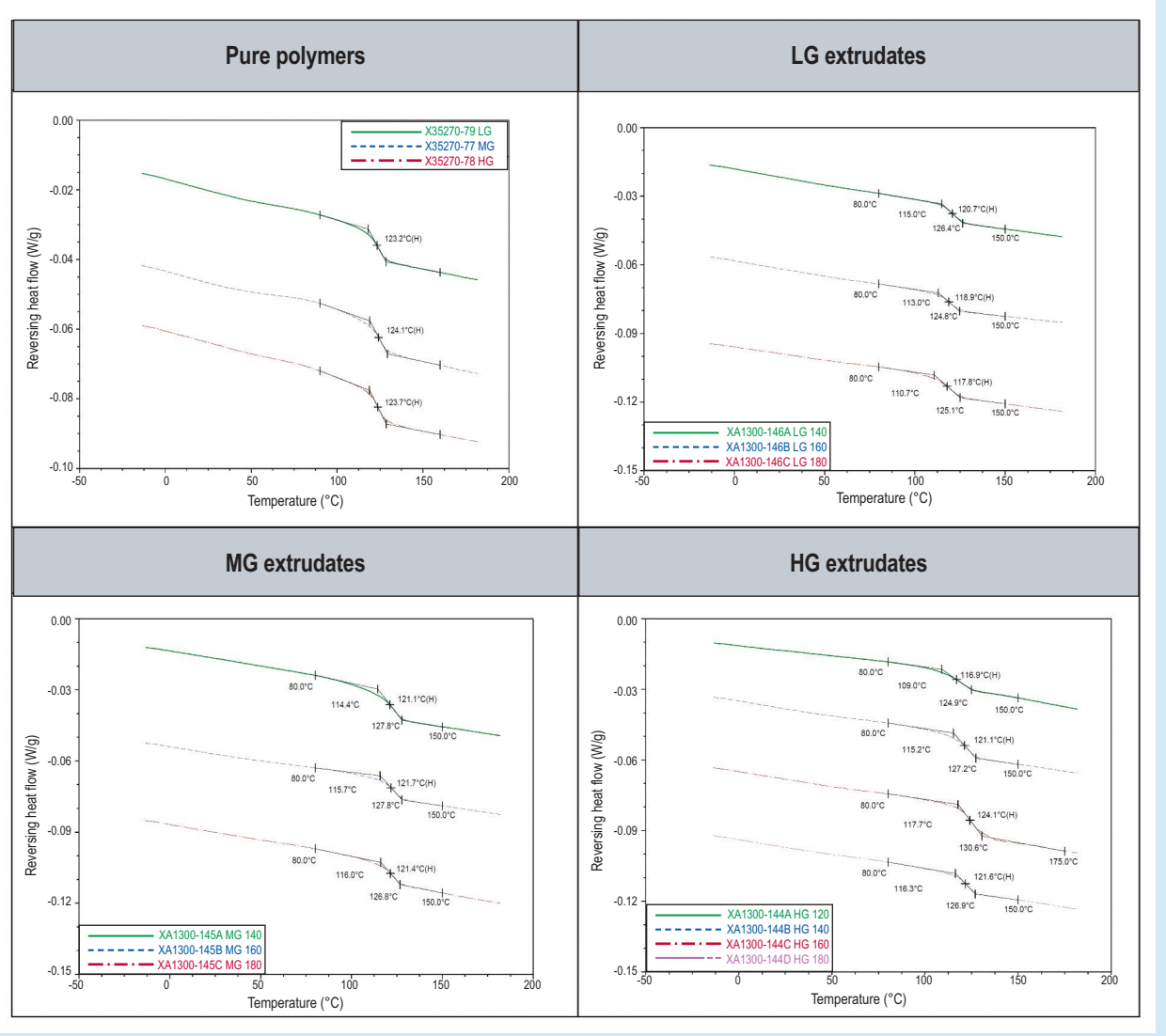
Dissolution testing. Dissolution testing of felodipine-HPMCAS (40:60) extrudate powder was carried out using USP Apparatus II in Fasted State Simulated Intestinal Fluid (FASSIF) at 6.5 pH, 37°C, and paddle speed of 200 rpm.

Formulation stability. Formulations were placed on stability at 25°C/60% relative humidity (RH) and 40°C/75% RH conditions. Felodipine-HPMCAS extrudate powders were removed after 1 month, 3 months, and 6 months and tested for API release rate and presence of crystallinity.

HME processing. HME was performed using an 18-mm twin-screw extruder (Leistritz, Sommerville, NJ). The collected extrudates were milled through a set of three screens, sizes 6350, 2007, and 1017, using a Comil mill (Quadro, Waterloo, ON Canada) at an impeller speed of 4,000 rpm. The milled extrudates were stored at room temperature for further analysis. The effect of extrusion temperature (between 140°C and 180°C) and shear during HME on the degradation and stability of the polymer and felodipine-polymer formulations was assessed. Physicochemical characterization of the polymer and felodipine-polymer extrudate was performed before and after extrusion.

Figure 3

DSC of HPMCAS and HPMCAS extrudates produced at different temperatures



Results and discussion: Evaluating the HPMCAS grades and their extrudates

Evaluating melt rheology. Melt rheology showed all three grades had complex viscosities *) of not more than 1,000 centipoise, which is desirable for HME (Figure 2). The H grade of the polymer exhibited the most desirable melt rheology behavior. The HPMCAS extrudates' melt rheology behavior was similar to that of the HPMCAS polymers before extrusion.

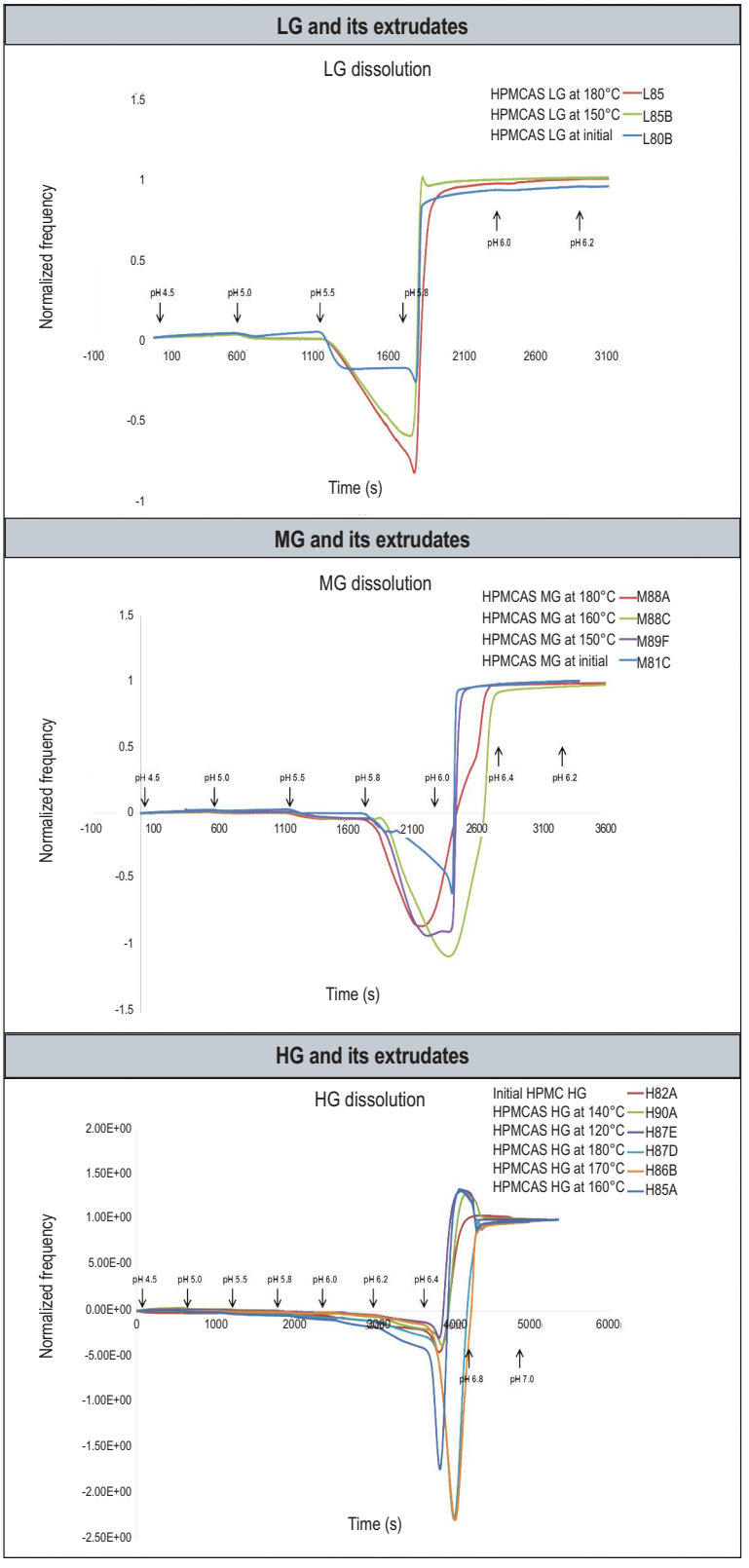
Determining glass transition temperature. DSC revealed that the HPMCAS grades and their corresponding extrudates have similar glass transition temperatures (Tg), indicating that process temperature does not impact Tg, and no thermal degradation of the polymers was observed (Figure 3).

Assessing pH-solubility behavior. Figure 4 shows the swelling curves of the initial HPMCAS polymer grades and their extrudate films in different pH solutions. It was seen that the swelling pH and the dissolution pH of the HPMCAS polymer grades before and after extrusion were unchanged. This indicates that the pH-solubility behavior of the LG, MG, and HG grades was unaffected by HME processing temperature.

Determining chemical composition and molecular weight. Quantitative analysis of molecular weight and substituent levels before and after extrusion at different HME process temperatures was performed. HPMCAS LG grade showed a slight increase in the level of free acid from 0.0% to 0.6% and a corresponding decrease in succinoyl content from 16.1% to 15.8% above the extrusion temperature of 160°C. This indicates that—due to the higher concentration of more labile succinoyl groups—the LG grade is most susceptible to changes at higher temperatures during extrusion. Nonetheless, the change was minimal and the molecular weight determination before and after extrusion showed no evidence of degradation. In short, the chemical composition and molecular weight of HPMCAS MG and HG appear to be unaffected by the HME processing temperatures and are stable.

FIGURE 4

Effect of extrusion temperature on pH-solubility behavior



HME of felodipine-HPMCAS and evaluation of solid dispersions. A 40:60 felodipine:HPMCAS grade was prepared and extruded under the processing conditions listed in Table 1.

The specific energy (SE) was calculated using two equations:

$$1.\ kW(applied) = \frac{kW(motor\ rating) \times \%\ torque\ rpm}{max.\ rpm \times 0.97\ (gearbox\ efficiency)}$$

$$2.\ SE = \frac{kW(applied)}{kg/hr}$$

where

kW = kilowatt rating of the motor (*kW* = horsepower × 0.746)

% *torque* = percentage of maximum allowable torque used

rpm = screw revolutions per minute

Melt pressures and specific energy inputs were used to indicate ease of extrusion. As Table 1 shows, the felodipine-HPMCAS H grade required much lower melt pressure and specific energy than the L and M grades, which indicates the superior extrudability of the H grade. This was confirmed by the lower melt viscosity observed during frequency-sweep experiments on the API-polymer extrudates that were collected after extrusion at 160ºC (data not shown).

The Tg of the felodipine-polymer extrudates were much lower than those of the HPMCAS polymer grades, which indicates that felodipine acts as a plasticizer for these polymers during extrusion (Figure 5).

Chemical composition and molecular weight determinations of the felodipine-HPMCAS extrudates were performed to assess the polymer's stability during extrusion. Because felodipine was able to plasticize the polymer, the API-polymer mixture extruded faster than all grades of the HPMCAS alone. It was seen that the substitution levels, free-acid levels, and the molecular weights of the API-

FIGURE 5

Effect of felodipine on glass transition temperature of extrudates

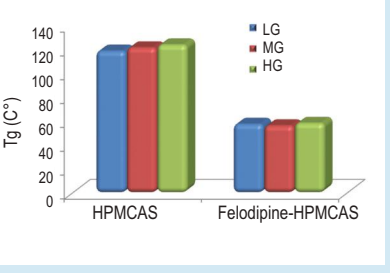


Table 1

Effect of extrusion temperature on pH-solubility behavior

HMPCAS type	Extruder target process temperature: Zones (C°) 1	2	3	4	5	6	7	8	Extruder process condition: Feeder speed	Extruder speed	Extruder load (%)	Melt pressure	Specific energy
Felodipine-HMPCAS LG	40	80	100	140	163	162	161	151	300	330	21	119	0.36
Felodipine-HMPCAS MG	40	80	110	140	165	160	162	150	300	330	25	30	0.23
Felodipine-HMPCAS HG	40	82	100	140	162	162	161	151	300	330	22	0	0.17

polymer extrudates remained unchanged under the processing temperatures studied.

It was also observed that API-polymer extrudates processed at or above 160°C released more API than API-polymer extrudates processed at 140°C. This could be attributed to the API's melting point, which plays a role in API-polymer miscibility: When processed at 140°C (below its 147°C melting point), the API stays in crystalline form, thereby limiting its release (Figure 6). Furthermore, it was observed that HPMCAS substitution level plays an important role in enhancing the solubility of felodipine, which released faster and more completely from the felodipine-HPMCAS L-grade extrudates (Figure 7). This result stems from felodipine's higher lipophilicity (logP of 3.9), which makes it dissolution-rate-limited, and from the higher succinoyl content of the L-grade polymer, which offers higher hydrophilicity and thereby improves the dissolution rate.

The PXRD of the felodipine-HPMCAS extrudates showed that the API is completely amorphous for 6 months under accelerated conditions. DSC of the stability samples at 25°C/60% RH and 40°C/75% RH for 6 months showed no exothermic peaks of recrystallization. These results indicate that the API in the felodipine-HPMCAS solid dispersion remains in the amorphous state (Figure 8). Also, the Tg of both formulations was lower at 40°C/75% RH than it was for formulations held at 25°C/60% RH, which indicates that moisture plays a critical role in the stability of the solid dispersions. Figure 9 shows that the dissolution profiles of the felodipine-HPMCAS extrudates (L and M grades)

Figure 6

Effect of extrusion temperature on felodipine-HPMCAS LG

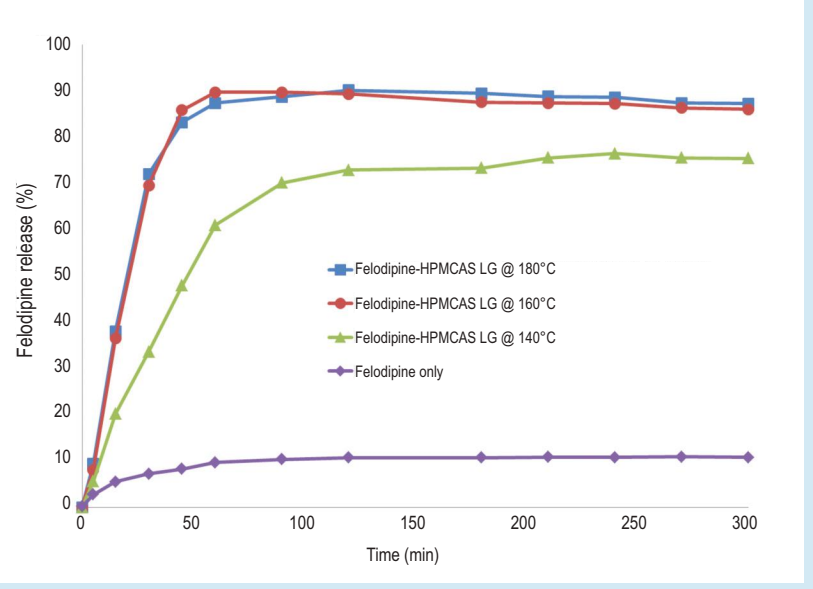
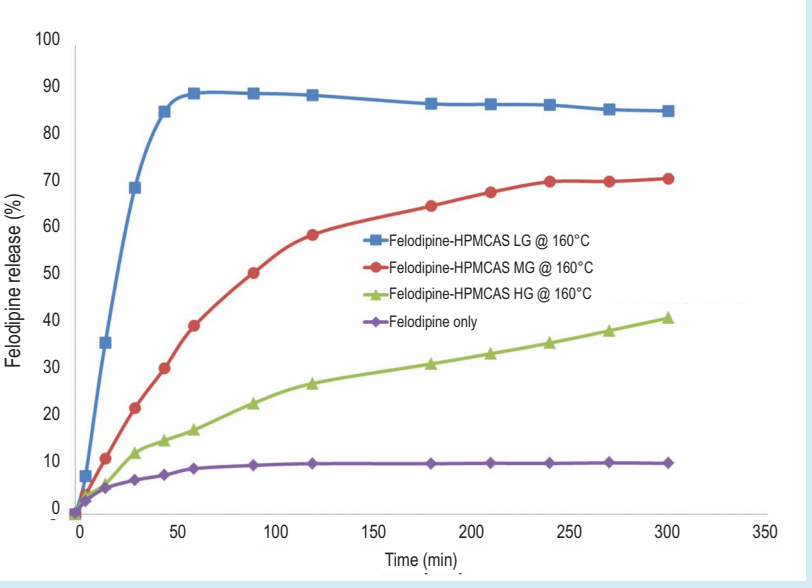


Figure 7

Effect of polymer grade on felodipine solubility enhancement



stored for 6 months at 25°C/60% RH and 40°C/75% RH were similar and stable under stressed conditions.

Conclusions

On the basis of the results provided above, extruding AquaSolve HMPCAS does not cause physicochemical degradation within the processing temperature ranges studied. However, the processing temperatures should be optimized based on the miscibility of the API with the polymer and should take into account the plasticizing effect (if any) of the API on the polymer.

T&C

References

1. Timpe, C. and Forschung, L. (2007). Strategies for formulation development of poorly water-soluble drug candidates—A recent perspective. American Pharmaceutical Review, 10(2), 104-109.

2. Sarode, A.L., Obara, S., Tanno, F.K., Sandhu, H., Iyer, R., and Shah, N. (2014). Stability assessment of hypromellose acetate succinate NF for application in hot melt extrusion (HME). Carbohydrate Polymers, 101, 146-153.

3. Scwhing, Q., Davis, M., Tewari, D., Dürig, T. (2015). Redesigning the hypromellose acetate succinate (HPMCAS) molecule for enhanced extrudability: Evaluation in solid dispersion formulations. Poster presentation at American Association of Pharmaceutical Scientists Annual Meeting in Orlando, FL, October 2015.

Quyen Schwing is a senior staff scientist, Marvin Davis is a scientist, Divya Tewari is the technical director of global pharmaceutical R&D, and Thomas Dürig is the senior technical director of pharmaceutical and nutrition specialties at Ashland Specialty Ingredients, 500 Hercules Road, Wilmington, DE 19808. Website: www.ashland.com.

FIGURE 8

DSC of felodipine-HPMCAS after 6 months at 40°C/75% RH

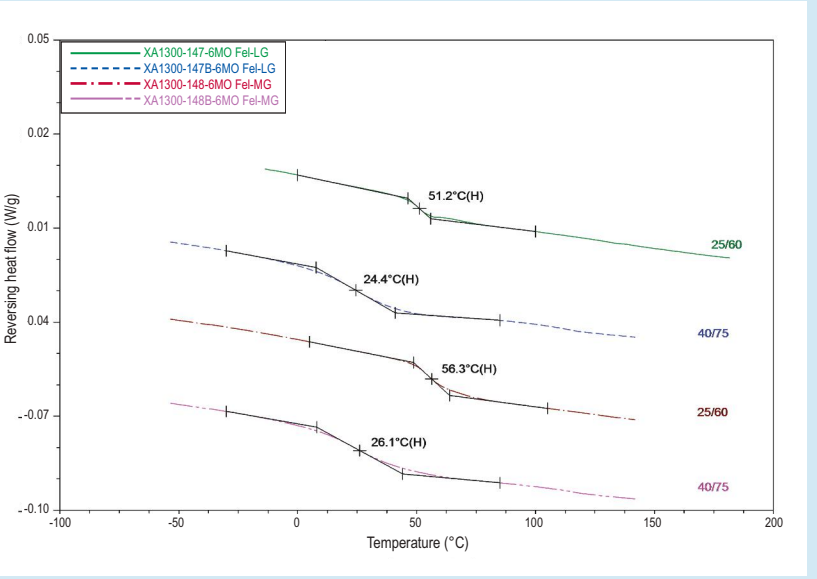


FIGURE 9

Dissolution (FASSIF pH 6.5) of felodipine-HPMCAS after 6 months at 25°C/60% RH and 40°C/75% RH