Hot Melt Extrusion Process Optimization and Formulation Development of Amorphous Solid Dispersions for a Poorly Soluble Calcium Channel Blocker

Hong-Guann Lee, Jonathan Yasosky, Pranjal Taskar, Brian Greco, Justin Hughey, Jamie James, Sanjay Konagurthu

hongguann.lee@thermofisher.com | sanjay.konagurthu@thermofisher.com

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PURPOSE

1. **Hot melt extrusion (HME)** process technology provides the pharmaceutical industry with a means to manufacture amorphous solid dispersions (ASDs) with advantages, such as solvent-free processing, reduced cost of goods (COGs) and continuous manufacturing, making it an attractive option for thermally stable active pharmaceutical ingredients (APIs).
2. A 25:75 Z-160:HPMCAS-MMP ASD formulation was successfully processed using a bench-scale mini conical twin-screw (HAAKE Mini-CTW) extruder (Lee et. al., Poster M1430-04-24, AAPS 2019). This goal of the current study was to **scale-up the HME process for the lead ASD** using a Pharma 11 twin-screw extruder.

OBJECTIVE

1. To perform initial process range finding studies on a Pharma 11 hot melt extruder followed by a **design of experiment (DOE) approach,** using a series of HME processing parameters for process optimization.

METHODS

1. A design of experiment (DOE) approach using a series of HME processing parameters (**high/low energy mixing input, temperature of heating zones, and screw rate**) was applied for the lead ASD process optimization with minimal chemical degradation.
2. All of the ASD extrudates were milled and passed through No. 60 sieve to control the ASD particle size range. ASD was characterized by using X-ray powder diffraction, modulated differential scanning calorimetry, and particle size distribution measurement.
3. ***In vitro* dissolution performance** of Z-160 ASD was evaluated by a two stage non-sink dissolution test in biorelevant dissolution media (0.1 N HCl and fasted-state simulated intestinal fluid), simulating pH and bile salt concentrations for both gastric and intestinal exposure.

RESULTS

Table 1. HME process summary of 25:75 Z-160:HPMCAS-MMP ASD.

Formulation	25:75 Z-160:HPMCAS-MMP ASD							
Batch Size (g)	~25-30g							
Lot Number	22-1	22-2	23-2	23-1	24-1	24-2	24-3	24-4
Screw Configuration	1 (30°, 60°, and 90° kneading element)				2 (30° kneading element only)			
Barrel Temperature (ºC)								
Zone 2	50		50		50		50	
Zone 3	125		125		125		125	
Zone 4	160		170		150		140	
Zone 5	160		170		150		140	
Zone 6	160		160		150		140	
Zone 7	160		160		150		140	
Zone 8	160		160		150		140	
Die	160		160		150		140	
Feed Rate (Kg/hr)	0.25							
Screw speed (rpm)	250	100	250	100	250	100	250	100
Torque (Nm)	~4.0	~4.8	~3.5	~7.0	~5.0	~5.6	~6.2	~7.2
Extrudate Appearance	Transparent yellowish							

1. Table 1 depicts the HME process summary for 25:75 Z-160:HPMCAS-MMP ASDs, showing the HME processing parameters with different energy mixing inputs, temperature of heating zones, and screw speeds.
2. Figure 1 shows two different screw configurations on a Pharma 11 scale-up twin-screw extruder with high energy mixing input (configuration 1) and low energy mixing input (configuration 2), demonstrating that mixing zones with different kneading elements would affect physical characteristics of the scale-up Z-160 ASD.
3. Figure 2 shows overlays of XRPD diffractograms for the 25:75 Z-160:HPMCAS-MMP ASDs, manufactured by Pharma 11 (Table 1). All lead ASDs are amorphous, showing a typical amorphous halo compared to crystalline Z-160.
4. All scale-up ASDs of 25:75 Z-160:HPMCAS-MMP HME had a single glass transition temperature (T_g) in Table 2, indicating good homogeneity without phase separation. The single T_g of each scale-up ASD is similar to the T_g (79°C) of feasibility ASD manufactured from Mini-CTW.

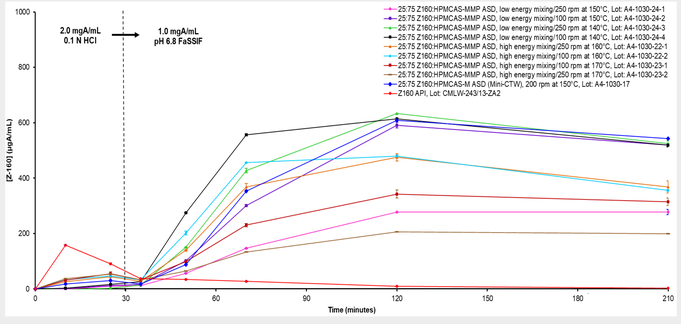

Figure 3. Non-sink dissolution profiles of 25:75 Z-160:HPMCAS-MMP scale-up ASDs.

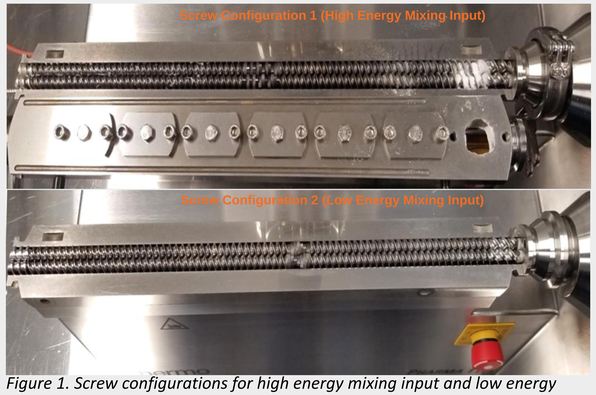

Figure 1. Screw configurations for high energy mixing input and low energy mixing input on a Pharma 11 twin-screw extruder.

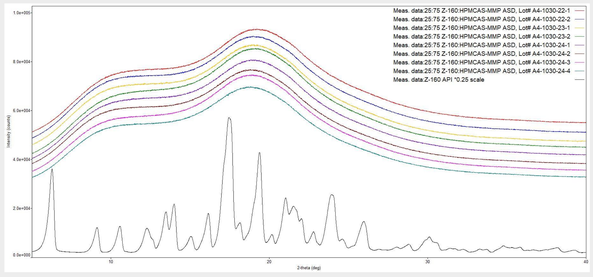

Figure 2. XRPD diffractograms of 25:75 Z-160:HPMCAS-MMP scale-up ASDs.

Table 2. MDSC results of 25:75 Z-160:HPMCAS-MMP scale-up ASDs.

Processing Condition	Glass Transition Temperature (°C)
Low energy mixing/250 rpm at 150°C	77.6
Low energy mixing/100 rpm at 150°C	79.2
Low energy mixing/250 rpm at 140°C	80.1
Low energy mixing/100 rpm at 140°C	80.0
High energy mixing/250 rpm at 160°C	80.0
High energy mixing/100 rpm at 160°C	80.5
High energy mixing/100 rpm at 170°C	80.6
High energy mixing/250 rpm at 170°C	76.6

5. Figure 3 shows non-sink dissolution profiles of Pharma 11 ASDs, HAAKE mini-CTW ASDs and crystalline Z-160. ASDs processed by high energy mixing input (screw configuration 1) exhibited lower Z-160 supersaturation and sustainment compared with the feasibility ASD processed from mini-CTW. Increasing processing temperature using screw configuration 1 showed low Z-160 dissolution performance, probably due to polymer degradation.

RESULTS

Table 3. Particle size distribution of 25:75 Z-160:HPMCAS-MMP Pharma 11 ASDs using screw configuration 2.

Processing Condition	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)
Low energy mixing/250 rpm at 150°C	158	250	389
Low energy mixing/100 rpm at 150°C	119	207	336
Low energy mixing/250 rpm at 140°C	125	215	364
Low energy mixing/100 rpm at 140°C	89	168	286

6. With the exception of ASD processed at 250 rpm/150°C, most ASDs processed by low energy mixing input (screw configuration 2) exhibited similar Z-160 supersaturation and sustainment compared with the feasibility ASD processed from HAAKE mini-CTW in Figure 3. Screw configuration 2/250 rpm/150°C ASD exhibited significantly lower dissolution performance compared to the HAAKE mini-CTW ASD, probably due to high screw shear stress at 250 rpm.
7. Decreasing the processing temperature using screw configuration 2, improved the scale-up ASD dissolution performance, which matches feasibility ASD dissolution performance, indicating that low energy mixing input at 140°C (Z-160 T_m ~ 127°C) is sufficient to manufacture the 25:75 Z-160:HPMCAS-MMP ASD.
8. As shown in Figure 3, three ASDs processed by screw configuration 2 exhibited faster dissolution rate than the ASD prepared on the HAAKE mini-CTW at 20 and 40 minutes after gastric transfer in FaSSIF medium. Table 3 shows the particle size distribution difference of the Pharma 11 milled HMEs, and demonstrates that particle size changed Z-160 initial dissolution rate but it did not have any impact on the Z-160 supersaturation and sustainment.

CONCLUSIONS

1. 25:75 Z-160:HPMCAS-MMP ASD was successfully scaled up to a Pharma 11 twin screw extruder with optimized processing parameters from a HAAKE mini-CTW.
2. Processing with low energy input and extrusion temperature facilitated the scale-up of 25:75 Z-160:HPMCAS-MMP ASD.
3. Particle size differences post milling had an impact on the initial dissolution rate of Z-160 ASD, indicating that ASD particle size may be critical to dissolution performance.

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