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Evaluation of Hot Melt Extruded Caffeine Pellets Containing POLYOX™ Water Soluble Resins

Nasrin Mahmoudi, Kevin O'Donnell, Brandon Rowe, Harold Bernthal, Amina Faham

Pharma Solutions, DuPont Nutrition & Biosciences

CONTACT INFORMATION: Nasrin.mahmoudi@dupont.com

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PURPOSE

Hot Melt Extrusion (HME) is a continuous manufacturing method for controlled and fast preparation of many solid dosage forms including pellets, tablets and films. It requires minimum processing steps which makes it highly efficient. POLYOX™ (polyethylene oxide) resins are thermoplastic water-soluble polymers with a low melting point of 65 °C. These polymers are excellent choices for HME among other applications and used in many pharmaceutical dosage forms. The purpose of this study was to understand the impact of vitamin E succinate (VES) on the HME process[1] of high molecular weight POLYOX™ as well as the performance of the resulting extrudates using caffeine as model drug.

MATERIALS

Caffeine was purchased from J.T. Baker (NJ, USA). Vitamin E Succinate (VES) and hydroxypropyl cellulose (150 – 400 cP) were purchased from spectrum chemicals (NJ, USA). Magnesium stearate was purchased from Fisher Scientific (NJ, USA) and POLYOX™ WSR 301, POLYOX™ WSR 303, AFFINISOL™ HPMC HME 4M, Avicel® PH-102, METHOCEL™ K100M DC2 were obtained from DuPont (USA). All solvents utilized in the study were of analytical grade and obtained from Fisher Scientific (NJ, USA).

METHODS

Hot Melt Extrusion and Preparation of Caffeine Pellets

Two grades of high molecular weight polyethylene oxide, POLYOX™ WSR 301 NF and WSR 303 NF were selected for evaluation with vitamin E succinate as a processing aid/ antioxidant at 5-10% concentration as shown in Table 1.

Table 1. Placebo Compositions

Materials	% (w/w) PEO 1	PEO 2	PEO 3	PEO 4	PEO 5	PEO 6
POLYOX™, WSR 301 NF	100	95	90	0	0	0
POLYOX™, WSR 303 NF	0	0	0	100	95	90
Vitamin E Succinate	0	5	10	0	5	10
Total	100	100	100	100	100	100

Table 2. Caffeine Blends Compositions

Materials	% (w/w) HME – 1	HME – 2	HME – 3	HME – 4
Caffeine	20	20	20	20
Polyethylene Oxide (POLYOX™, WSR 301 NF)	50	50	50	50
HPMC (AFFINISOL™ HPMC HME 4M)	0	0	20	10
Vitamin E Succinate (VES)	0	10	10	10
Hydroxypropyl cellulose (HPC)	30	20	0	10
Total	100	100	100	100

Table 3. Hot Melt Extrusion Process Conditions

Set Up Parameters	Value
Feed Rate	8 g/min
Extrusion Temperature at Zone 1-2-3-4	115-140-155-150 °C
Screw Speed	150 rpm

Caffeine was selected as a crystalline water-soluble model drug (sparingly soluble at ambient temperature and highly soluble in water at 100 ºC) with a melting point of 235 ºC. Material was de-lumped by passing through a 30-mesh screen, weighed out (batch size 700 g, Table 2) and mixed in a twin-shell V- blender at 25 rpm for 10 minutes. Hot melt extrusion of the batches was conducted on a Leistritz Nano16 (16 mm) 25:1 L/D co-rotating extruder equipped with a 2 mm strand die. Powders were fed into the extruder by a KTron T20 feeder operating in gravimetric mode (Table 3). Die pressure and motor amperage (torque) were recorded. The resultant extrudates were pelletized using a pelletizer (Conair Model 304, USA) to approximately 2 mm x 2 mm particle size followed by assay testing and dissolution studies. To study the caffeine extrudates in a tablet formulation, a portion of the pellets were milled to an average particle size of 584 µm on a Retsch Rotor Mill using 500 µm screen at 12K rpm. POLYOX™ strands are very ductile and tough which might become tacky during milling due to heat generation in the process. This could cause the milling and grinding a challenge. The milling conditions were optimized as shown in Table 4.

Table 4. Milling Optimizations

Screen Size (um)	RPM (x1000)	d10 (um)	d50 (um)	d90 (um)	notes
200	12	217	359.6	823.1	Low recovery < 15% and melting
500	6	464.8	755.9	1036	Particles are still large.
500	12	310.6	583.7	860.9	significant agglomeration due to
500	18	392.8	714.5	1923	heat generation

Table 5. Caffeine Tablets Composition

Ingredients	% w/w
Caffeine extrudate, HME-1 or HME-2	25
HPMC (METHOCEL™ K100M DC2)	30
Microcrystalline cellulose (Avicel PH-102)	44.5
Magnesium Stearate	0.5
Total (g)	100

Preparation and Physical Testing of Caffeine Tablets

To evaluate the performance of the caffeine pellets in controlled release tablets, two formulations, HME-1 and HME-2 with and without vitamin E succinate were selected. A DC grade of Hydroxypropyl methylcellulose (HPMC), METHOCEL™ K100M Premium DC2 was used as an additional rate controlling polymer in the tablets. Microcrystalline cellulose, Avicel® PH-102, was used as filler and magnesium stearate as lubricant. All ingredients according to Table 5, excluding the magnesium stearate, were accurately weighed to make a 500 g batch and blended in a 4-quart V-blender for 10 minutes. Magnesium stearate was passed through a 60-mesh screen prior adding to the blended powder mixture and blended for an additional 2 minutes. The formulation blends were compressed into 400 mg tablets using a Korsch XL 100 tablet press equipped with four sets of 13/32" SRC tooling at 20 rpm press speed.

Pellets and Tablet Characterization

The caffeine pellets and tablets were evaluated for drug content, drug physical state, drug release and stability. Tablet properties including weight and dimensions (n=5) were measured manually. Crushing strength was measured using a Key International HT-300 tablet hardness tester. Friability of tablets (n=20) was performed at 100 & 400 drops using a Key International FT-400 friability tester. Tensile strength (TS) of tablets were calculated and tablets with TS of 1.0 ± 0.2 MPa were tested for dissolution. Drug release was measured using USP apparatus II (708-DS, Agilent Technologies, USA) at 100 rpm and 900 mL of deionized water (DIW) at 37±0.5 ºC. Additionally, the pellets were tested in 0.1 N HCl and 6.8 phosphate buffer.

RESULT(S)

All six drug-free polymeric powders were extruded into white slightly opaque strands under the processing conditions. As the level of VES increased, the melt pressure decreased. The influence of VES on melt pressure was similar for both POLYOX™ grades. The melt pressure significantly dropped from approximately 1200 psi to 800 psi during extrusion of neat polymer vs polymer with 10% VES, respectively (Figure 1). Melt pressure for caffeine blends with either hydroxypropyl cellulose (HPC) or VES were the lowest among the tested formulations. As the level of HPC increased the melt pressure decreased (Figure 2). Extruder torque was 12.7-13% vs 22% for the formulation without HPC. Average amount of caffeine was 18.6, 19.8, 20.0 and 20.2% in each of four extruded formulation. SEM and IR analysis (not shown here) confirmed the crystalline state of caffeine in the pellets. Table 6 compares properties of Caffeine 20 mg dose tablets tested for dissolution. Tablets containing HME-2 formulation showed lower TS as compared to that of tablets containing HME-1. Both tablets had low friability of less than 0.5%. There was no significant difference in drug release of the tested formulations in three dissolution media as expected considering the nonionic nature of the POLYOX™. Accelerated stability studies for 12 weeks indicated no significant changes in the drug release of either pellets or tablets (Figure 5-7). However, pellet formulation without VES showed faster release and higher variability (F2=55) compared to formulation with VES demonstrating the benefit of VES in making a more homogenous extrudate.

Figure 1. Melt viscosity of POLYOX™ extrudates in the presence of various levels of vitamin E succinate at constant extrusion process conditions.

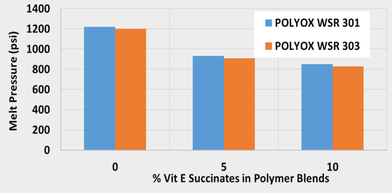

Figure 2. Melt viscosity of Caffeine/POLYOX™ formulations in the presence of various levels of HPC at constant extrusion process conditions.

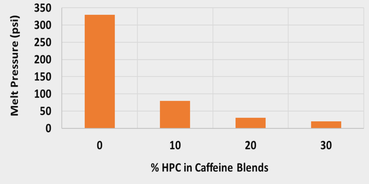

Figure 3. SEM of caffeine pellets, HME-1 formulation

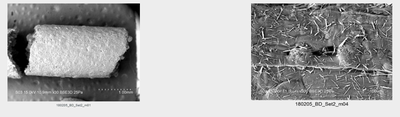

Figure 4. Effect of Media pH on drug release of caffeine pellets, HME-4 formulation

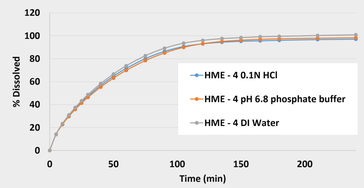

Figure 5. Drug release of caffeine pellets in DIW: HME-1 formulation without VES

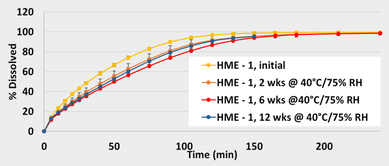

Figure 6. Drug release of caffeine pellets in DIW: HME-2 formulation with VES

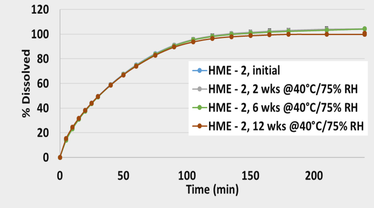

Figure 7. Drug release of caffeine tablets in DIW

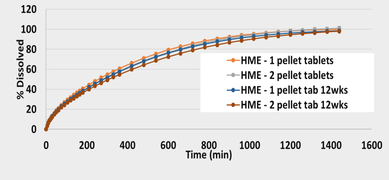

Table 6. Caffeine Tablets Physical Properties

Tablets	Compression Force (kN)	Average Weight (mg), RSD	Tensile Strength (MPa)	Friability (100)	Friability (400)
HME -1 milled pellets	10	400.2 ± 0.7	1.22	0.12%	0.37%
HME -2 milled pellets	15	403.5 ± 0.5	1.13	0.13%	0.45%

CONCLUSION(S)

The study showed that vitamin E succinate may be used as processing aid in hot melt extrusion of high molecular weight grades of POLYOX™ which is a common polymer for use in controlled release dosage forms particularly in abuse deterrent formulations. It is shown that the melt pressure significantly reduced from 1200 psi to 800 psi during extrusion of neat polymer vs polymer with 10% VES. Stability studies indicated there were no significant changes in drug release of HME pellets following extrusion. The stabilized HME pellets of POLYOX™ as multiparticulates or in tablet formulations provided flexibility of tailoring drug release profile.

References: Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Crowley MM., Zhang F, Keleng JJ, McGinity JW, Biomaterials. 2002 Nov;23(21):4241-8.

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