

Evaluation of Formulations Produced via Hot Melt Extrusion That Contain High API Loading and Exhibit Controlled Release

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Poster presented at the 2007 Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists
San Diego, California
November 11–15, 2007

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Introduction

Preparing formulations that contain high API (active pharmaceutical ingredient) loading and exhibit controlled API release via conventional pharmaceutical processing technology has proven to be difficult. As the amount of API increases, the quantity of dissolution rate controlling additives and other excipients must be reduced. This often has a negative impact on dosage form preparation processes and/or results in dosage forms with poor mechanical properties. The conventional solution is to increase the dosage size, but there is a practical limit to this approach.

The authors evaluated hot melt extrusion (HME) as a process for preparing these types of dosage forms. Formulations containing 50 wt % acetaminophen and ketoprofen were produced that exhibited the desired controlled release behavior. Hypromellose (HPMC), ethylcellulose (EC), and polyethylene oxide (PEO) are polymeric excipients that can be used in HME.¹ These polymers, in addition to a proprietary development product, were used in the acetaminophen and ketoprofen formulations. Tablet physical properties (hardness and friability) of the extruded formulations were measured.

There are other benefits to using HME over traditional processing techniques. These include fewer unit operations, better content uniformity, an anhydrous process, a dispersion mechanism for poorly soluble drugs, a low energy alternative to high shear granulation, and less processing time compared to conventional wet granulation.²

Materials and Methods

Materials

Acetaminophen (APAP) and ketoprofen were selected as model drugs for this study. Polymeric excipients and combinations of excipients based on ethylcellulose (ETHOCEL™ STD 10 Premium), hypromellose (METHOCEL™ E4M Premium), and polyethylene oxide (POLYOX™ WSR 1105 NF, N-10 NF, and 301 NF) were included. Material A is a proprietary developmental product.

Extrusion Trials

The materials to be extruded were preblended in 1500-g batches (10 min in a laboratory-scale V-blender). Extrusion trials were performed using a single screw extruder (SSE) (0.75 inch diameter, 28:1 length/diameter) equipped with a 0.325-inch-diameter rod die and a conical twin screw extruder (TSE) (42.5 mm to 28.6 mm diameter, 352 mm long) equipped with a 5-mm-diameter rod die. For the single screw extruder evaluations, the preblended formulations were flood-fed into the extruder hopper. A K-tron model K2MVT20 volumetric feeder was used to control feed of the preblended formulations into the conical twin screw extruder. The extruded rod was immediately cut into tablets (300 mg to 500 mg) using a utility knife. Processing conditions for the formulations discussed in this publication are shown in Table 1.

Table 1. Extrusion processing conditions.

Composition	Equip.	Temp. (°C)	Screw Speed (rpm)
50/50 APAP/Material A	SSE	170	100
50/50 APAP/HPMC E4M	SSE	180	100
50/50 APAP/HPMC E4M	TSE	190	60
50/50 APAP/PEO 1105	SSE	170	100
50/30/20 APAP/HPMC E4M/PEO N-10	SSE	170	100
50/37.5/12.5 APAP/EC STD 10/PEO 301	SSE	150	100

Direct Compression Tablet Preparation

For comparative purposes, direct compression tablets were produced from the identical formulation as the HME-prepared samples. A Carver laboratory press was used to produce the tablets. The tooling was 13/32, the tablet weight was 350 mg, the force used was 3000 lb, and the dwell time was 3 s.

Tablet Dissolution and Physical Properties

Dissolution studies were initiated within days of extrusion. Six replicate samples were run for each dissolution test. Dissolution testing was performed with a Distek TCS0200B dissolution system with a Hewlett-Packard 8452A diode array spectrophotometer. The media temperature was $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

USP Apparatus II was used (paddles) with a rotation speed of 50 rpm. Acetaminophen dissolution was performed in 900 mL deaerated (Distek MD-1 De-Gasser) phosphate buffer (pH 5.8) at a wavelength of 242 to 244 nm. Ketoprofen dissolution was performed in 900 mL deaerated (Distek MD-1 De-Gasser) phosphate buffer (pH 7.4) at a wavelength of 258 to 262 nm.

Tablet hardness was measured with a Key International Model HT-300. For the hardness test, three hot melt extrudate tablets were used and 10 direct compression tablets were used.

Tablet friability was measured with a Vanderkamp Model #10801. Twenty tablets were used in the friability test at a speed of 28 rotations/min.

NIR Imaging

Near infrared (NIR) data were generated using a Sapphire NIR chemical imaging system (Spectral Dimensions/Malvern Instruments, Olney, MD). The tablets were prepared for evaluation by carefully cutting a relatively flat surface onto the tablet. The NIR data were collected in the diffuse reflectance mode. The data collection parameters used are tabulated below.

Table 2. Typical NIR data collection parameters for imaging tablets.

Spectral Range	1500 – 2400 nm, 10 nm increments
Resolution	38.8 $\mu\text{m}/\text{pixel}$
Background Reference	White ceramic
Dark Reference	Stainless steel mirror
Data Collection Time	~ 4.0 min/image

Results and Discussion

Extended release of formulations with high API loading was demonstrated for compositions produced using both the single screw extruder and conical twin screw extruder. In general, similar dissolution performance was observed for formulations produced by either extrusion technology. Figure 1 contains representative data for a formulation comprising 50/50 APAP/HPMC E4M. Figure 2 shows dissolution results for various formulations incorporating 50% APAP.

Figure 1. Dissolution data for a 50/50 APAP/HPMC E4M formulation produced by single screw extrusion and conical twin screw extrusion.

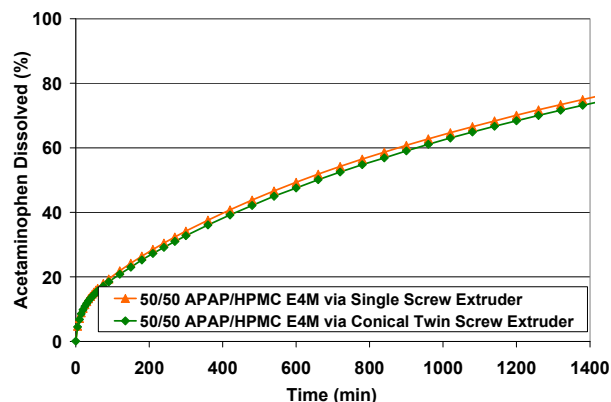
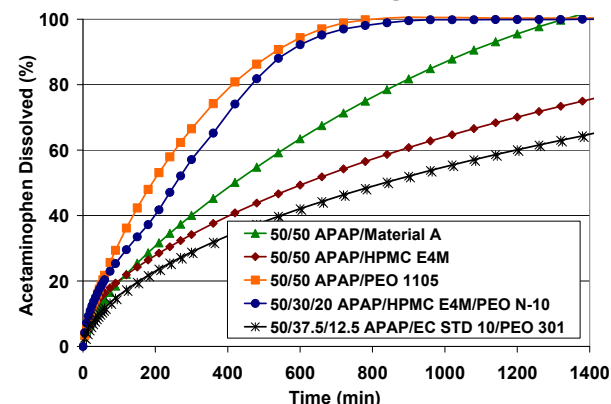


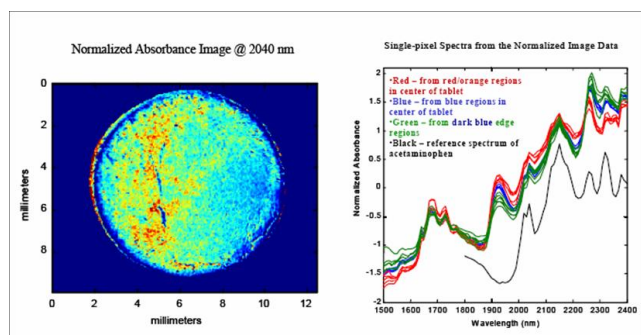
Figure 2. Dissolution results for various formulations containing 50% APAP.



Fifty percent APAP release ranged from 210 and 840 min, depending upon the excipients included in the formulation. Further, at 1000 min, two of the formulations exhibited 100% APAP dissolution, but the remaining three formulations studied exhibited APAP dissolution of 85 to 55%. As shown in Figure 2, blends of excipients were used to alter release rates from those obtained with a single excipient. This is consistent with previously published data.³ Similar results were observed for ketoprofen-based formulations (data not shown).

Figure 3 shows NIR results for a tablet containing 50/50 APAP/HPMC E4M prepared via HME. Excellent content uniformity was observed. No large domains of either component were observed in the normalized absorbance image (left side). Further, the single pixel data indicates that APAP content was constant in all areas of the tablet analyzed (right side).

Figure 3. NIR imaging of a 50/50 APAP/HPMC E4M tablet prepared via HME.



HME-prepared tablets had greater hardness values and lower friability values than control samples. These data are shown in Table 3.

Table 3. Comparison of mechanical properties for tablets produced via HME and direct compression.

Formulation and Source	Hardness (SD) (scu)	Friability (% Weight Loss @ 168 rotations)
50/50 APAP/Material A HME	>30 (N/A) ^a	0.05
Direct Compression	11.3 (0.5)	0.49
50/50 APAP/HPMC E4M HME	>30 (N/A) ^a	0
Direct Compression	6.7 (1.1)	3.1
50/50 APAP/PEO 1105 HME	N/A (N/A) ^b	N/A ^b
Direct Compression	9.6 (0.3)	0.04
50/30/20 APAP/HPMC E4M/PEO N-10 HME	29.2 (3.9)	0.42
Direct Compression	6.7 (0.4)	0.93
50/37.5/12.5 APAP/EC STD 10/PEO 301 HME	>30 (N/A) ^a	N/A ^b
Direct Compression	11.3 (0.5)	0.49

^aTablet hardness exceeded test capabilities.

^bInsufficient number of tablets to obtain data.

For example, the HME-prepared 50/30/20 APAP/E4M/N10 tablets had a hardness value of 29.2 scu while the control samples had a value of 6.7 scu (Table 3 and Figure 4). After six minutes, the friability measurement for the same formulation was 0.42% weight loss for the HME tablets and 0.93% for the control tablets (Table 3 and Figure 5).

Figure 4. Comparison of hardness values for tablets produced via HME and direct compression.

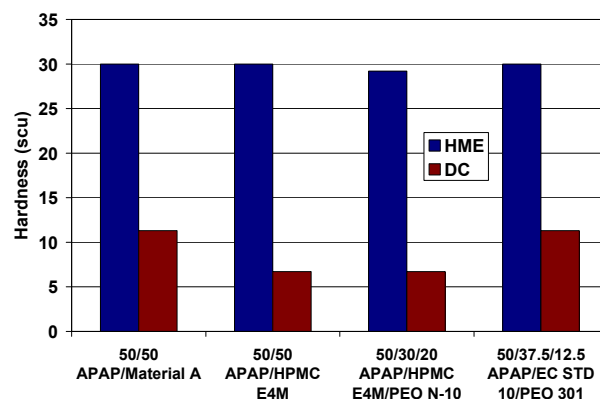
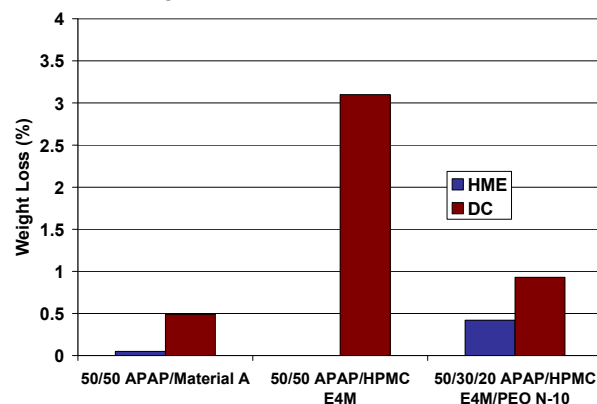


Figure 5. Comparison of friability values for tablets produced via HME and direct compression.



Conclusion

Formulations with high API loading, extended release properties, and excellent content uniformity were successfully produced via HME. HME-prepared tablets exhibited exceptional tablet hardness and friability results over control samples produced via direct compression. Hot melt extrusion appears to be a viable approach to produce dosage forms that contain high API loadings and exhibit controlled release behavior.

References

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