Melt Extrusion and Injection Molding for the Development of Pharmaceutical Mini-Tablets – Case Study Using Clotrimazole

Ethan McCarthy\textsuperscript{1}, Stephen Johnston\textsuperscript{1}, Maria Barsom\textsuperscript{2}, and James DiNunzio\textsuperscript{2}

\textsuperscript{1} University of Massachusetts Lowell, Lowell, MA
\textsuperscript{2} Merck & Co., Inc., Rahway, NJ

Abstract

Injection molding and hot melt extrusion are well developed plastic forming processes that have recently been garnering more attention in the pharmaceutical industry. The use of these thermal processing techniques reduces the need for hazardous solvents in order to create amorphous solid dispersions, which can improve the efficacy of poorly soluble drug compounds through increased solubility and bioavailability. This article describes the application of hot melt extrusion and injection molding to create pharmaceutical doses using clotrimazole in hydroxypropylcellulose.

Introduction

Around 40\% of active pharmaceutical ingredients have poor aqueous solubility so methods are required to increase solubility and oral bioavailability of these drugs.\[1\] Hot melt extrusion is one method used to create amorphous solid dispersions from a crystalline active pharmaceutical ingredient (API) and excipients. These amorphous solid dispersions can greatly increase the solubility and bioavailability of the drug.\[2\] The compounded solid dispersions can then be directly formed into dosage such as tablets through injection molding. Injection molding has been studied because it could rapidly produce multi-layered tablets for pulsatile release profiles, and tablets for immediate release.\[3\]

Injection molding and melt extrusion could be combined for a continuous automated process that scales easily from development to mass production. The FDA has suggested that continuous manufacturing has the potential to reduce manufacturing costs through: increased safety due to less material handling, increased efficiency, reduced inventory, lower capital costs, and consistent quality.\[4\]

Materials

Powdered hydroxypropylcellulose was chosen as the excipient for this study (Ashland: Klucel\textsuperscript{TM} EF Pharm, MS 3.3) since it is amenable to the injection molding process and rapidly soluble in aqueous solution.\[5\] Clotrimazole (Merck), an antifungal, was chosen as the model API because of its poor solubility and difficulty in thermal recrystallization. Figure 1 shows the chemical structures of the materials.

Extrusion

Formulations of unfilled Klucel (placebo) and 50wt\% clotrimazole filled Klucel were prepared using a twin screw extruder (Technovel, 15mm). The powder was dry blended and then fed into the extruder using a gravimetric feeder. Material was extruded through a 2.5mm strand die, onto a brass belt conveyer for air cooling.

The screw design was primarily forward conveying elements with a single mixing zone to avoid significant shear induced degradation (Figure 2). Initially, barrel temperatures were set to 160°C, which is 5°C above the melting point of the API. However, this resulted in significant discoloration indicating degradation. The temperature was lowered to 140°C to minimize thermal degradation. Process conditions are shown in Table 1. The API filled material ran with notably lower motor load and
die pressure than the unfilled material suggesting that the drug had a plasticizing effect on the polymer viscosity. The filled material displayed an amber hue, but this was attributed to the natural hue of the drug and not degradation, as the unfilled material was untinted and clotrimazole itself does not degrade below 200°C.

Table 1 – Process Conditions for Twin Screw Extrusion

<table>
<thead>
<tr>
<th></th>
<th>Unfilled Klucel</th>
<th>50% API Filled Klucel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>140°C</td>
<td>140°C</td>
</tr>
<tr>
<td>Screw Speed</td>
<td>120-130 RPM</td>
<td>140-150 RPM</td>
</tr>
<tr>
<td>Feed Rate</td>
<td>1.1 kg/hr</td>
<td>1.1 kg/hr</td>
</tr>
<tr>
<td>Motor Load</td>
<td>45-55 amps</td>
<td>27-30 amps</td>
</tr>
<tr>
<td>Head Pressure</td>
<td>2-2.3 MPa</td>
<td>0.8-1 MPa</td>
</tr>
</tbody>
</table>

Rheology

Rheological properties of the compounded materials were investigated through capillary rheometry (Dynisco LCR 7000). Shear rates ranged from 10⁵ to 10⁶ s⁻¹ using a 10:1 L:D die. Figure 3 shows the apparent viscosity as a function of shear rate and temperature. The materials do not display a Newtonian plateau, but rather exhibit power law behavior over the entire shear regime. The plasticising effect that the drug had on the polymer is clearly evident. Lower consistency indices and lower overall viscosities show this effect, with over 40% drop in consistency index in the filled material. The lower power law indices of the filled system indicate increased shear sensitivity with the addition of clotrimazole.

Injection Molding

Injection molding was performed using a Nissei AU3E screw-over-plunger micro-injection molding machine. Material was injected into a prototype mold (Figure 4) that made eight mini-tablets (2.5mm diameter by 2.5mm long cylinders). Parts of both formulations were molded successfully. Parts occasionally stuck onto the stationary side of the mold, but were easily removed with brass tools.

A conventional molding process with velocity controlled filling and pressure controlled packing was used for the trials. The chosen processing conditions are shown in Table 2. Similar set points were used for both the unfilled and filled systems, with the exception of a lowered pack pressure for the filled system. This was necessary to prevent flashing of the lower viscosity filled material. The plasticizing effect of the clotrimazole was evident when considering actual fill times and pressures recorded during molding, all of which were reduced with the lower viscosity filled system.

Table 2 – Process Conditions for Injection Molding and Machine Readouts Including Standard Deviations

<table>
<thead>
<tr>
<th></th>
<th>Unfilled Klucel</th>
<th>50% filled Klucel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Settings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrel Temp (°C)</td>
<td>137.8</td>
<td>132.2</td>
</tr>
<tr>
<td>Inj. Velocity (mm/s)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Total Shot Built (mm)</td>
<td>9.48</td>
<td>9.48</td>
</tr>
<tr>
<td>V-P Switchover (mm)</td>
<td>3.70</td>
<td>3.70</td>
</tr>
<tr>
<td>Hold Pressure (MPa)</td>
<td>50.0</td>
<td>35.0</td>
</tr>
<tr>
<td><strong>Average Readouts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fill Time (sec)</td>
<td>0.10 ± 0.00</td>
<td>0.08 ± 0.00</td>
</tr>
<tr>
<td>Peak Pressure (MPa)</td>
<td>136.4 ± 4.1</td>
<td>95.8 ± 8.7</td>
</tr>
<tr>
<td>V-P Position (mm)</td>
<td>3.43 ± 0.03</td>
<td>3.42 ± 0.03</td>
</tr>
<tr>
<td>V-P Pressure (MPa)</td>
<td>118.0 ± 3.1</td>
<td>32.3 ± 1.5</td>
</tr>
<tr>
<td>Cushion (mm)</td>
<td>0.66 ± 0.04</td>
<td>0.80 ± 0.05</td>
</tr>
<tr>
<td>Shot Weight (mg)</td>
<td>990.0 ± 2.1</td>
<td>1027.5 ± 4.4</td>
</tr>
</tbody>
</table>

Individual mini-tablets were de-gated from the runner system using a 2.5mm punch. These mini-tablets were then inspected with a polarized light microscope prior to running disintegration studies. Figure 5 shows the polarized light microscopy images of the active mini-tablets, which did not exhibit signs of residual crystallinity. This indicated that the material was well dispersed without observable crystal domains, potentially having formed an amorphous solid dispersion.
**Figure 5** – Polarized light microscopy of IM active tablets

**Thermal Characterization**

In order to verify that amorphous solid dispersions were created, Differential Scanning Calorimetry (DSC) was conducted on the raw materials, compounded extrudate, and injection molded mini-tablets. DSC samples were crimped in aluminum pans with pierced lids and dried for 24 hours at 50°C prior to testing. Pans were tared and then dried samples were weighed before starting the scan. DSC was performed over a range of -20°C to 210°C at 5°C/min.

The DSC scans of the API (Figure 6A) showed a sharp melting transition at approximately 145°C that was not present on the second heating cycle. The API did show a primary transition on the second heat cycle corresponding to the amorphous form of the API.

Preliminary scans of the Klucel, which started at -50°C, did not reveal a primary glass transition in the testing range. However, the material did have a broad shallow melting point at 190°C (Figure 6B) resembling that of a semi-crystalline polymer with low crystallinity.

The 1st heat scans of the Klucel-clotrimazole compound (Figure 6D) showed a glass transition and melting point. The clotrimazole in the compounded material had amorphous and crystalline phases in the dispersion indicating it did not completely dissolve into the excipient at the temperatures used. The 2nd heat scans of the Klucel-clotrimazole compound showed a glass transition at the same temperature as the clotrimazole transition. It would be expected that if Klucel exhibited a T_g and the materials were miscible that the T_g would have shifted from the T_g of the pure clotrimazole.

Comparing the heat of fusion between the dry blended mixture (Figure 6C) and the molded active material (Figure 6E), there was approximately 16% residual crystallinity of the API in the excipient.

**Crystallography**

To verify the residual crystallinity found in the DSC thermograms, powder X-Ray Diffraction (XRD) was performed on the raw materials and formulations. Powder samples were placed in a SiO2 sample holder in the XRD (Scintag PADX). Scans were performed over a 2θ range of 5° to 40° at a speed of 2°/min. The XRD analysis

**Figure 6** – DSC thermograms showing 1st (solid) and 2nd (dashed) heating cycles for clotrimazole (A), Klucel (B), 1:1 physical mixture (C), compound extrudate (D), and injection molded sample (E)
(Figure 7) showed peaks in the Klucel-clotrimazole extrudate aligning to pure clotrimazole, which indicated some residual crystallinity in the compound.

![Figure 7 – XRD scans from clotrimazole (A), Klucel (B), 1:1 physical mixture (C), compound extrudate (D), and injection molded sample (E)]](image)

**Disintegration Trials**

Active (filled) and placebo (unfilled) mini-tablets were placed in a disintegration apparatus and the time to disintegration was recorded (Figure 8). Injection molded placebo mini-tablets maintained their appearance during the testing and disintegrated in 17.7 minutes with a standard deviation 4.4 minutes. Active mini-tablets did not disintegrate within the 45 minutes over which the test was conducted, which indicated that the formulation did not increase the dissolution rate as expected. The slower disintegration of active pellets was attributed to clotrimazole precipitation in the hydrated gel layer.

![Figure 8 – Disintegration of placebo and active injection molded mini-tablets](image)

Mini-tablets were placed in purified water at 37°C for 5 minutes and imaged to show the difference in opacity between the systems. The placebo mini-tablets did not show a change in opacity while the active mini-tablets quickly became opaque. Cross-sectioned active mini-tablets (Figure 9) showed the development of a hydrated opaque layer indicative of clotrimazole precipitation in the hydrated dissolution front. A solid non-hydrated amorphous core was also observed.

![Figure 9 – Images of immersed placebo and active mini-tablets (left) and a cross sectioned active mini-tablet after 35 minutes immersion (right)](image)

**Conclusions**

Hot melt extrusion of the API and excipient was performed to create an amorphous solid dispersion while minimizing degradation. The materials were successfully injection molded into mini-tablets. The injection molded placebo mini-tablets disintegrated in less than 20 minutes, which make it very attractive in a potential immediate release platform. However, the solid dispersion with the poorly soluble API did not disintegrate in the target time. Most of the API was converted to the amorphous form during melt extrusion. However, approximately 16% residual crystallinity remained. Future investigations have commenced using excipients that can be processed further above the melting point of the API to ensure a fully amorphous solid dispersion.

**Acknowledgements**

The authors would like to thank Merck & Co. for providing the support that made this research possible.

**References**