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Kevin Altman
kjaltman@purdue.edu

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The Effect of Drug Particle Size, Temperature, and Residence Time on Hot Melt Extrusion Processing of Amorphous Solid Dispersions

Kevin J. Altman1, Dana E. Moseson2, and Lynne S. Taylor2

1 Department of Chemistry, 2 Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN

Abstract

Introduction: The molecular dispersion of poorly soluble drug molecules into a polymer matrix is a popular oral drug delivery strategy known as amorphization. In this type of molecular dispersion, the amorphous form of the drug achieves a thermodynamic solubility advantage over the crystalline form, resulting in higher bioavailability. Hot melt extrusion (HME) is one of two major techniques used to manufacture these amorphous solid dispersions (ASDs). Material, equipment, and process design variables contribute to the product performance of the ASD, and the goal of this study is to evaluate the impact of drug particle size on ASD formation.

Methods: Physical mixtures of bicalutamide and PVPVA were prepared and analyzed using differential scanning calorimetry, and the calorimetric data was used to construct a temperature-composition phase diagram. The acceptable processing design space for extrusion was derived from this phase diagram and guided the preparation of bicalutamide-PVPVA ASDs at various temperatures and residence times.

Results and Discussion: The extent of residual crystallinity was determined by polarized light microscopy and powder X-ray diffraction. As expected, residual crystallinity decreases with increasing temperature and residence times across all particle sizes. ASDs prepared with larger starting particle sizes consistently possess more residual crystallinity than ASDs prepared with smaller starting particle sizes.

Conclusion: The extent of crystallinity in extruded ASDs reflect the kinetic nature of crystal dissolution in a polymer melt.

Materials & Powder Properties

<table>
<thead>
<tr>
<th>Bicalutamide</th>
<th>Polyvinylpyrrolidone/</th>
<th>Vinyl acetate copolymer (PVPVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(BCS Class 2)</td>
<td>Tm = 195°C</td>
<td>Tm = 104°C</td>
</tr>
</tbody>
</table>

Small particle size

Large particle size

25x increase in average particle size
20x decrease in surface area
Improvement in powder flow properties

Two particle sizes were used to investigate the impact of input material attributes on the kinetics of ASD formation in the HME process.

Phase Diagram Construction

(a) Melting point depression is illustrated through DSC heat flow traces of various drug-polymer mixtures. (b) Melting point offset temperature is non-linear with respect to heating rate. (c) The interaction parameter γ can be extracted by linear regression analysis. (d) Temperature-composition phase diagram of bicalutamide and PVPVA.

The bicalutamide/PVPVA system is highly miscible, as indicated by the negative interaction parameter γ = -1.53.

Approximately 5°C of melting point depression is observed at the 30% drug loading composition.

Phase Diagram

Residual crystallinity decreases with increasing temperature and residence times across all particle sizes. ASDs prepared with larger starting particle size material consistently possess more residual crystallinity than ASDs prepared with smaller starting particle sizes.

Hot Melt Extrusion Processing & Solid State Characterization

Equipment Setup:
- Xplore PME
- 5 mL co-rotating conveying screw at 50 rpm
- 8 g batch size

Processing Parameters:
- Independently controlled operating melt temperature and residence time
- Temperature range: >145°C

References


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Future Work

Additional work will include preparation of ASDs from an intermediate particle size, additional sample characterization, and comparison of results to existing dissolution models.


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