The Application of Temperature-Composition Phase Diagrams for Hot Melt Extrusion Processing of Amorphous Solid Dispersions to Prevent Residual Crystallinity

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Introduction

In hot melt extrusion (HME) processing of amorphous solid dispersions (ASD), a homogenous molecular dispersion must be generated, avoiding both thermal degradation of drug and polymer and residual crystalline content. Applying temperature-composition phase diagrams, based on melting point depression of a miscible-drug polymer system, and taking into account kinetic criteria, rationally selected process conditions can be identified to prepare ASDs free of residual crystalline content.

Theoretical Temperature-Composition Phase Diagram

Process Operating Design Space

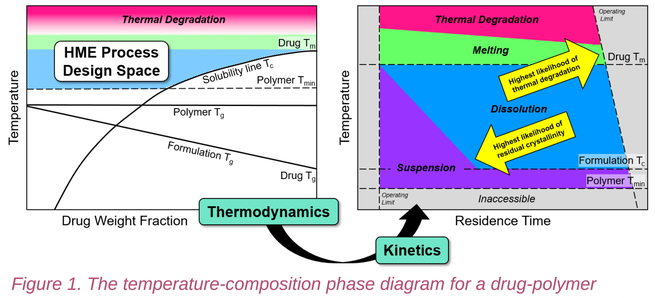
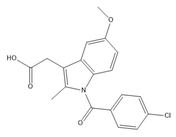


Figure 1. The temperature-composition phase diagram for a drug-polymer system can be used to guide processing temperature selection. By incorporating kinetic criteria, a process operating design space diagram can be constructed.

Materials

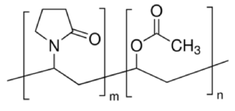


Indomethacin (BCS Class 2)

Crystalline solubility ~5 ug/mL (in pH 4.5 acetate buffer), melting point T_m 161°C, glass transition T_g 44°C

Polyvinylpyrrolidone/vinyl acetate copolymer (PVPVA)

Glass transition T_g 104°C



Extrusion & Characterization Methods

Formulation

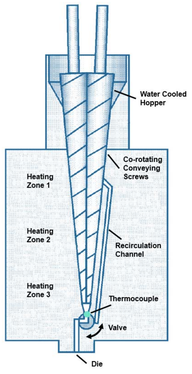
50% Indomethacin, 50% PVPVA

Extrusion

Xplore PME, 5 mL corotating conveying screw at 20 rpm, 10 g batch size, independently controlled operating melt temperature and residence time

Characterization

X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), polarized light microscopy (PLM)



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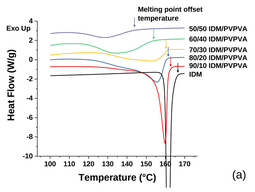
Melting Point Depression

$$\frac{1}{T_c}-\frac{1}{T_m}=-\frac{R}{\Delta H}\left[\ln\phi+\left(1-\frac{1}{m}\right)(1-\phi)+\chi(1-\phi)^2\right]$$

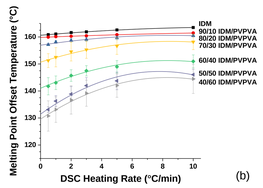
Melting point depression

Negative Flory-Huggins interaction parameter χ indicates favorable enthalpy of mixing & results in melting point depression



The indomethacin/PVPVA system is highly miscible, as indicated by the negative interaction parameter χ=-1.97.

Approximately 30°C of melting point depression is observed at the 50% drug loading composition.



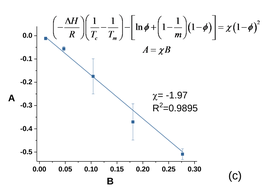
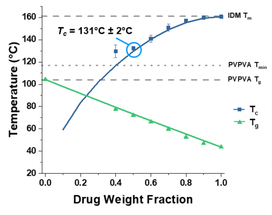


Figure 2. (a) Melting point depression is illustrated through DSC heat flow traces of various drug-polymer mixtures. (b) Melting point offset temperature is non-linear with respect to heating rate. (c) The interaction parameter χ can be extracted by linear regression analysis.

Experimental Phase Diagram



The formulation critical temperature (T_c) represents the minimum processing temperature for a given composition, where drug crystals can dissolve/melt and mix with the molten polymer.

For some compositions, the polymer minimum temperature (T_{min}) represents a lower bound of processing temperature, due to high viscosity.

Figure 3. Indomethacin-PVPVA temperature-composition phase diagram, identifying the solubility line and glass transition temperature across the composition range.

Acknowledgements

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Hot Melt Extrusion Results

Melting Regime (>T_m)

Even at short residence times, a fully amorphous sample is generated.

Dissolution Regime (T_m>T_c)

At short residence times (2 minutes), a processing temperature of 10°C above the T_c was required to generate a fully amorphous sample. At the T_c, residence time exceeding 20 minutes was required to generate a fully amorphous sample.

Suspension Regime (<T_c)

Below the T_c, a fully amorphous sample could not be prepared.

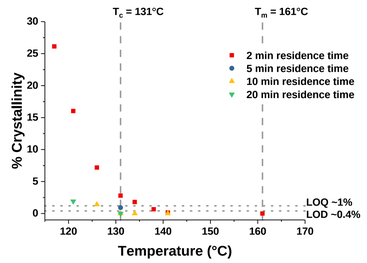
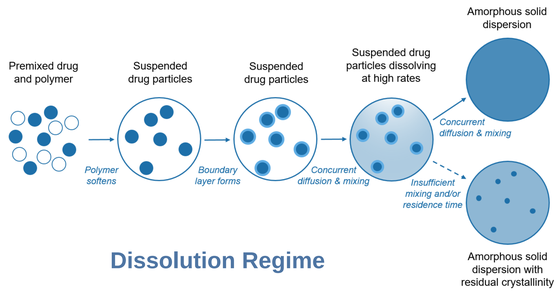


Figure 4. Quantification of crystalline content of 1:1 indomethacin:PVPVA ASDs by XRPD as a function of product melt temperature.

HME Processing Regimes



Dissolution Regime

A homogenous molecular dispersion forms if the system achieves thermodynamic solubility equilibrium, given appropriate kinetic conditions.

The risk for residual crystallinity is controlled by selection of key process variables (e.g. temperature, residence time, equipment configuration, drug particle size distribution).

Figure 6. Formation mechanism of ASDs by HME processed at temperatures between T_m and T_c. Residual crystallinity may result if insufficient mixing and/or residence time is provided.

Experimental Process Operating Design Space

The expected trends between temperature and residence time are observed, with longer residence times being required to produce amorphous samples at lower temperatures.

The crystalline-to amorphous zone transition boundary depends significantly on the measurement technique employed.

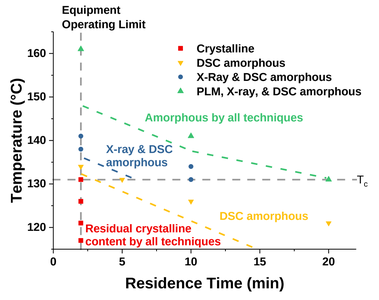


Figure 6. HME process operating design space of 1:1 indomethacin:PVPVA . Based on the sensitivity of the characterization technique, the sample can be classified as amorphous or crystalline. These classifications create zones where samples can be considered amorphous.

Conclusion

The temperature-composition phase diagram provides an rational framework for designing HME processes to manufacture ASD to prevent residual crystalline content, delineating the minimum processing temperature based on thermodynamic considerations.

This approach can be further refined by developing a process operating design space diagram which incorporates both thermodynamic and kinetic considerations, wherein processes using lower temperatures and shorter residence times are more susceptible to residual crystallinity. Accurate determination of the processing regime zone boundaries lessens the risk of residual crystallinity, and depends on the analytical approach employed.

For More Information

Moseson, DE, and LS Taylor. “The application of temperature-composition phase diagrams for hot melt extrusion processing of amorphous solid dispersions to prevent residual crystallinity.” Int J Pharm 553, p. 454-466 (2018).