# Hot Melt Extrusion Processing Regimes Based on Temperature-Composition Phase Diagrams

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## Introduction

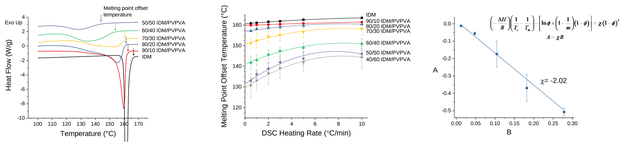
In hot melt extrusion processing of amorphous solid dispersions, a homogenous molecular dispersion must be generated, avoiding both thermal degradation of drug and polymer and residual crystalline content. The melting point depression method provides insight to rationally select process conditions, and correlate with product characteristics.

## Thermodynamic Phase Diagram

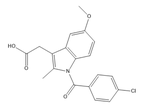
$$\frac{1}{T_c}-\frac{1}{T_m}=-\frac{R}{\Delta H}\left[\ln\phi+\left(1-\frac{1}{m}\right)(1-\phi)+\chi(1-\phi)^2\right]$$

Melting point depression

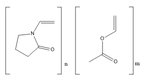
Negative Flory-Huggins interaction parameter $\chi$ indicates favorable enthalpy of mixing & results in melting point depression



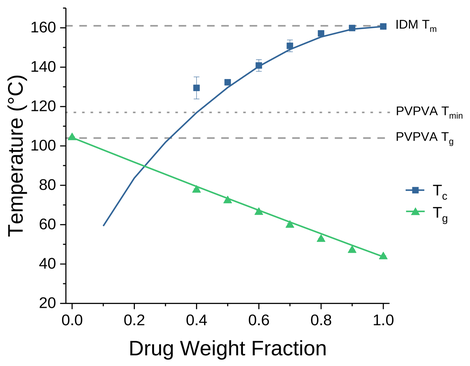

## Indomethacin:PVPVA



Indomethacin
(BCS Class 2)



Polyvinylpyrrolidone/ vinyl acetate copolymer (PVPVA)
(n ≈ 1.2 m)




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.

## Methods

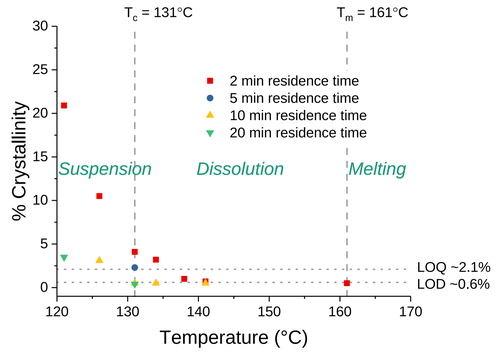
Formulation: 50% Indomethacin, 50% PVPVA

HME: Xplore PME, 5 mL corotating conveying screw, 10 g batch size, controlled operating melt temperature and residence time

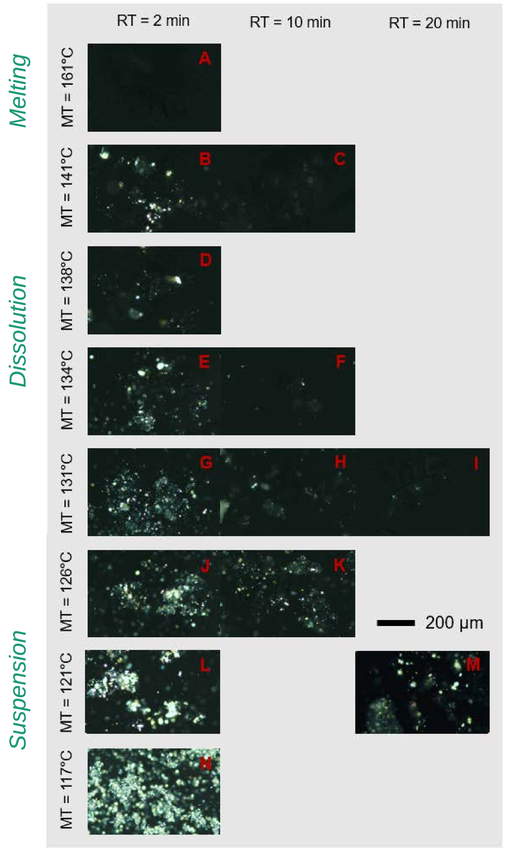
Characterization: X-ray powder diffraction (XRPD), polarized light microscopy (PLM), micro computed tomography (Micro-CT)

## Hot Melt Extrusion Results

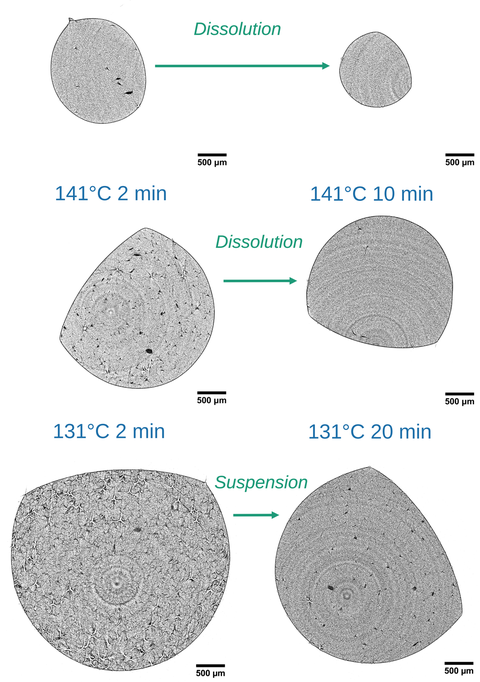
### X-ray Powder Diffraction




### Polarized Light Microscopy




### Micro Computed Tomography




2D cross-section
Dark spots represent higher density crystals

## Discussion

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

Dissolution regime: 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: Below the $T_c$, a fully amorphous sample could not be prepared.

Detection methods: Although non-quantitative, PLM was more sensitive to detect residual crystallinity than PXRD. Micro-CT was effectively used to qualitatively image the intact extrudate for residual crystalline content and microstructure.

## Acknowledgements

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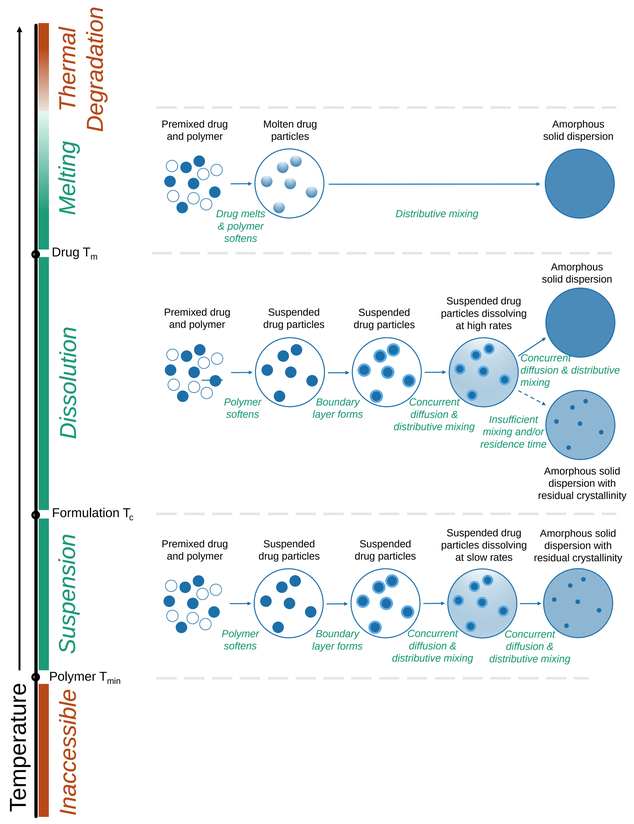
## HME Processing Regimes




## Conclusion

The temperature-composition phase diagram provides an effective pre-formulation tool to understand the complex interplay between formulation, process, and product characteristics.

The outcome of an HME process used to prepare an amorphous solid dispersion can be understood through categorization of temperature into three processing regimes: (a) melting, (b) dissolution, and (c) suspension.

## References

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