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Fall 2019 Travel Award Winner

Ashwini Gumireddy

Molecular Structure Predicts the Tendency of 6 API to Form Amorphous Solid Dispersions Using Melt-Quenching, Rotary-Evaporation, and Spray-Drying

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Purpose:

Successful formation of amorphous solid dispersions (ASD) depends on a complex combination of materials properties that facilitate prolonged interactions between API molecules and the carrier polymer matrix. It is hypothesized that the atomic mass weighted 3rd-order autocorrelation index (R3m molecular descriptor) is highly correlated with the combined structural attributes of the API molecule that facilitate dispersion in polyvinyl pyrrolidone-vinyl acetate co-polymer (PVPva). R3m has previously been used to predict ASD formation in PVPva for a library of 15 API at two compositions (15% and 75% w/w), resulting in an overall accuracy of 100% for predictions of dispersability when prepared by melt-quenching. Although successful by this preparation method, it remains uncertain whether R3m predictions of dispersability can be more broadly applied for the same API for different manufacturing routes. To examine this question, ASD attempts were prepared at 75% w/w loading using rotary-evaporation and spray-drying and subsequent characterization used to confirm dispersion formation predictions for 6 API from the original library.

Methods:

Molecular structures were used to calculate R3m for each API using E-Dragon (vcclab.org). Six API were selected: propranolol·HCl, nifedipine, sulfanilamide, ketoconazole, indomethacin, and felodipine, 3 with R3m<0.65 and 3 with R3m>0.65, where R3m>0.65 corresponds to the predictive boundary for dispersability in PVPva. Dry mixtures of 75% w/w API and PVPva were prepared in a fixed ratio for all dispersion attempts, which were then dissolved in methanol. The solvent was removed from the solutions using either rotary-evaporation (MeOH removal over several minutes) or spray-drying (MeOH removal in seconds). All co-solidified mixtures were characterized 24 hr after preparation. Dispersibility of each API in PVPva was inferred using a suite of analytical techniques, which included differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), polarized light microscopy (PLM), and hot stage microscopy (HSM) to determine if a single homogeneous phase had been produced.

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Results:

Complete dispersability was inferred when samples had a single glass transition temperature (T_g) by DSC, absence of birefringence under PLM at ambient temperature, and absence of Bragg diffraction peaks attributable to the API via PXRD. Preparations of propranolol·HCl, nifedipine, and sulfanilamide with PVPva showed Bragg diffraction peaks after melt-quenching and rotary-evaporation, although the same peaks were not detectable in PXRD patterns for the spray-dried particles of these drugs. PLM studies showed birefringence, suggesting that the crystallinity in spray-dried particles was below the detection limit of the PXRD instrument. DSC studies indicated immiscibility of propranolol·HCl, nifedipine, and sulfanilamide with PVPva by the presence of melting endotherms and/or multiple T_g events in the co-solidified mixtures regardless of preparation method. In contrast, characterization of the ketoconazole, indomethacin, and felodipine preparations showed no indications of phase separation from PVPva in co-solidified mixtures prepared by any method. **Table 1** summarizes all characterization data, indicating that propranolol·HCl, nifedipine, and sulfanilamide are not dispersable in PVPva at 75% w/w composition using any of the preparation methods, while ketoconazole, indomethacin, and felodipine are. These data are also consistent with the previously established R3m model, in which API having R3m>0.65 are dispersable in PVPva, while those with R3m<0.65 are not (**Figure 1**). Furthermore, observations of dispersability were consistent regardless of the rate of solvent evaporation.

Conclusion:

Molecular structure determines the subtle aspects of API chemistry that lead to successful dispersion formation in PVPva. Although the R3m model was originally developed for use with specific preparation conditions, this work demonstrates that the predictive power of this molecular descriptor remains applicable for the 6 API studied, when the production method changes significantly. These data indicate the utility of the R3m model for dispersability prediction as a formulation and process development tool for ASDs prepared using PVPva as a carrier polymer.

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Table 1: Final characterization inferences based on interpretations of data from the suite of analytical techniques

API	R3m	Melt-Quenching			Rotary-Evaporation			Spray-Drying			Dispersable?
		PXRD Diffraction peaks	DSC	PLM (Birefringence)	PXRD Diffraction peaks	DSC	PLM (Birefringence)	PXRD Diffraction peaks	DSC	PLM (Birefringence)	
Propranolol HCl	0.342	Yes	Immiscible	-	Yes	Immiscible	Yes	No	Immiscible	Yes	No
Nifedipine	0.568	Yes	Immiscible	-	Yes	Immiscible	Yes	No	Immiscible	Yes	No
Sulfanilamide	0.595	Yes	Immiscible	-	Yes	Immiscible	Yes	-	Immiscible	Yes	No
Indomethacin	0.737	No	Miscible	-	No	Miscible	No	No	Miscible	No	Yes
Ketoconazole	0.814	No	Miscible	-	No	Miscible	No	No	Miscible	No	Yes
Felodipine	0.964	No	Miscible	-	No	Miscible	No	No	Miscible	No	Yes

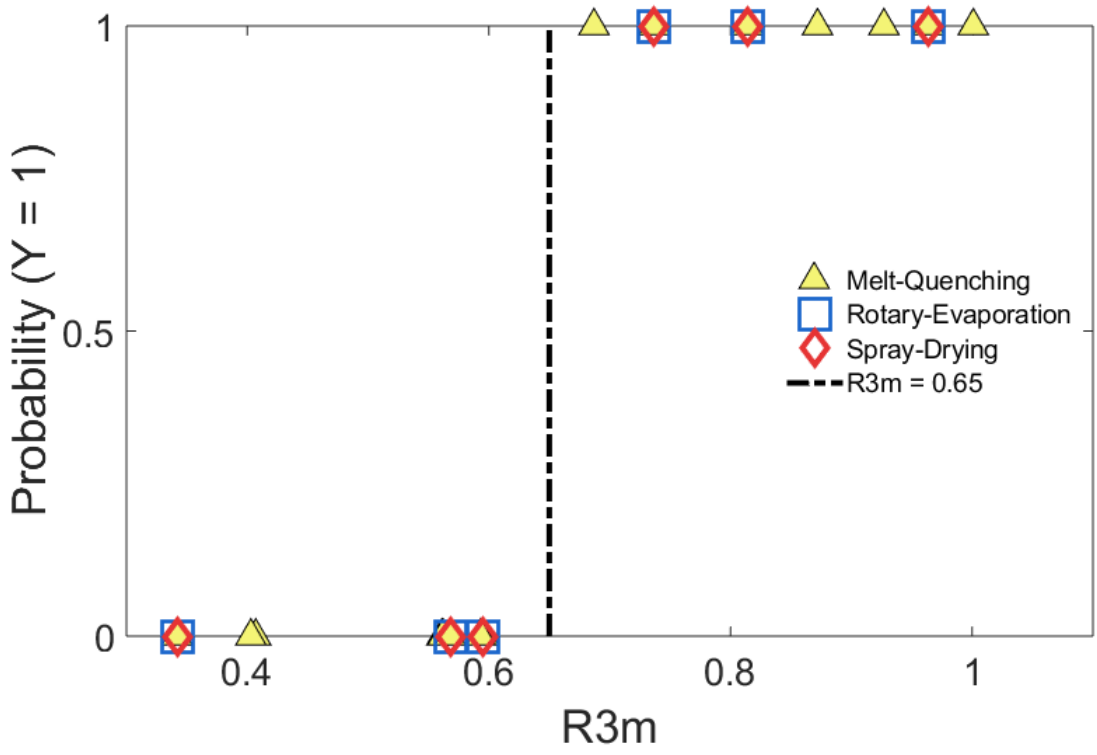

Figure 1: Modeling of dichotomous classifications of API dispersability in PVPva for co-solidified mixtures prepared by (a) Melt-quenching (yellow triangles), (b) Rotary-evaporation (blue squares), and (c) Spray-Drying (red diamonds) against the molecular descriptor R3m. All API having R3m >0.65 were dispersible in PVPva by all three different manufacturing methods

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