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Predicting solubility/miscibility in amorphous dispersions: It's time to move beyond regular solution theories

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ABSTRACT

The evolving challenges associated with the development of poorly soluble drug molecules have been met with major advances in drug solubilization. In particular, amorphous solid dispersion technology is becoming an increasingly important option to enhance oral bioavailability by creating prolonged drug supersaturation to maximize the driving force for intestinal absorption. A primary concern in the development of amorphous solid dispersions is their physical stability, leading to increasing interest in predictive methodologies to assess the propensity for drug crystallization under various storage conditions. For most drug-excipient combinations of pharmaceutical interest, hydrogen-bonding is an important factor in determining miscibility, supersaturation potential, and the influence of water uptake during storage and after administration. The vast majority of publications to date have utilized mathematical models based on regular solution theory such as Flory-Huggins (F-H) theory to predict drug-polymer miscibility, despite the fact that they were never intended to be applied to hydrogen-bonded systems. In this commentary, regular solution theory is applied to simple hydrogen bonded alcohol-alkane solutions to explore trends in the F-H χ interaction parameter and possible pitfalls in its interpretation. More recent models that explicitly allow for specific interactions merit greater attention.