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Screening Solubility-Enhancing Coformers in Amorphous Solid Dispersions: a Group Contribution based Miscibility Method

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Abstract

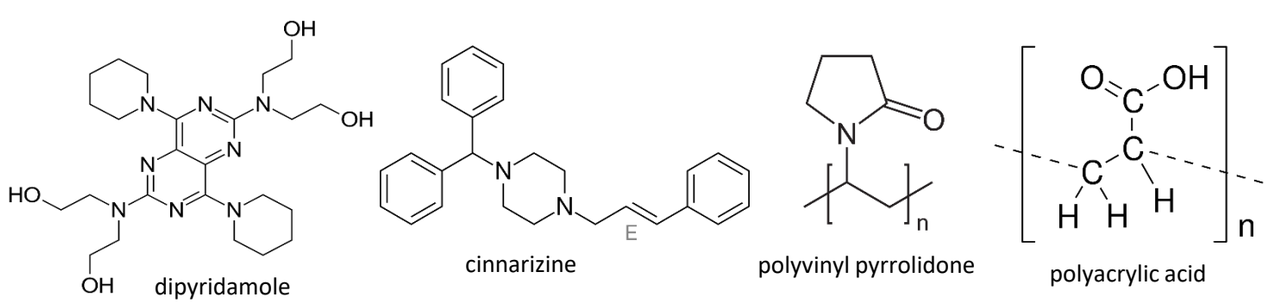
The thermodynamic behaviour of binary mixtures such as polymer blends, amorphous solid dispersions, cocrystal and salts, and etc. are of great interest in many active pharmaceutical ingredient applications where low solubility/bioavailability of drugs is an issue the pharma industry faced. Screening solubility-enhancing coformers and/or excipients for drug(s) of interest is therefore remained major challenge. A high throughput method for (1) screening of available materials and/or (2) design of possible candidates to be synthesized for each drug is of crucial importance. To address this challenge, here, a systematically improvable method is examined against its performance for different drug-polymer pairs commonly used in amorphous solid dispersion technology including dipyridamole, cinnarizine, itraconazole as drugs and polystyrene, polyvinyl pyrrolidone, polyacrylic acid as polymers. The other applications of reported code may include organic solvent selection, cocrystal and salt screening, and etc.

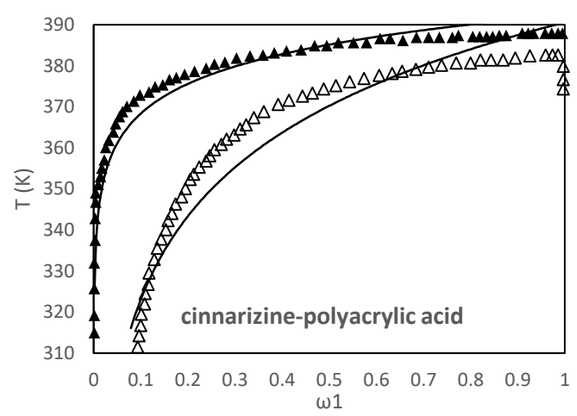
Code availability: https://sites.google.com/site/miladasgarpour/Posts/Completed/ASDx

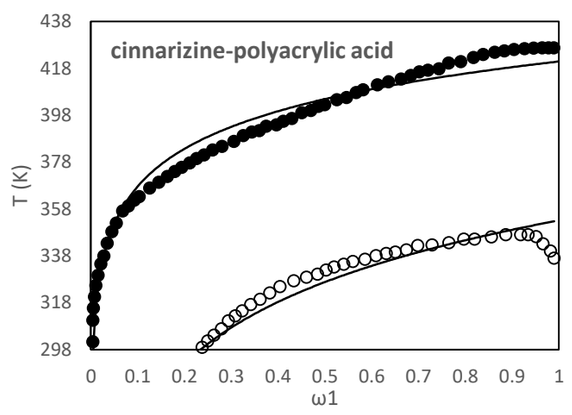
Introduction

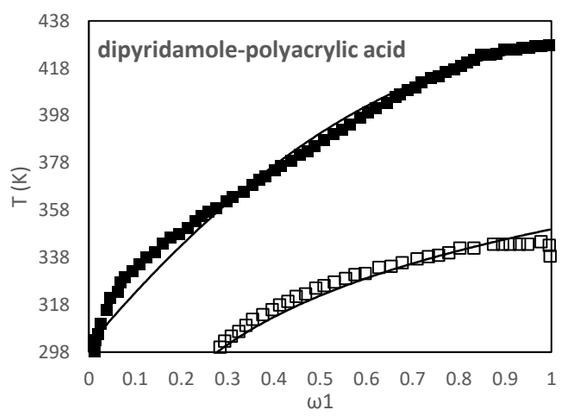
Low in-body solubility (bioavailability) of most produced drugs caused a big challenge facing pharma industry . These drugs belong to BCS Class II and BCS Class IV according to Biopharmaceutics Classification System (BCS). To enhance the solubility of these drugs, a number of technologies have been introduced such as salt formation, formation of nanocrystal active pharmaceutical ingredients, and amorphous solid dispersions using various pharmaceutically acceptable excipients (polymers) . These solid dispersions are practically a binary mixture of a drug and an amorphous polymer where they act as solute and solvent, respectively. Such dispersions are metastable, and therefore may undergo instabilities through phase separation paths like separation into two in-contact-in-equilibrium drug-rich and polymer-rich phases or crystallization of drug may proceed. This in turn lowers the bioavailability and increases the product risk and unreliability. Then, in design and performance analysis of amorphous solid dispersions, the drug–polymer interaction and miscibility are of greatest concern.

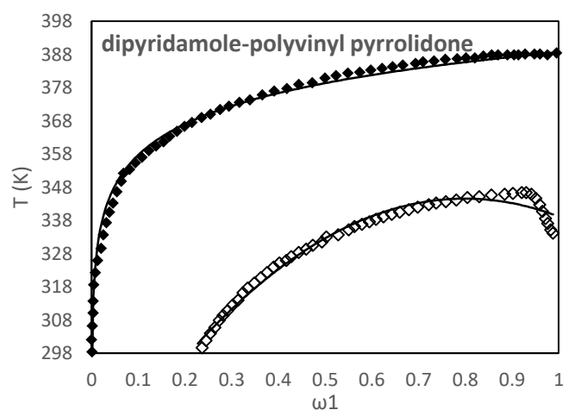
A variety of experimental methods such as differential scanning calorimetry, Fourier-transform infrared spectroscopy, and powder X-ray diffraction has been used to investigate miscibility. However, when determined by experiments, usually, measurements suffer from the uncertainty and experimental disturbance or misconduct. Indeed, it's impossible to examine all possible drug-polymer pairs due to wide range of polymers available, and therefore nomination of candidate polymers is a knowledge-based task needing previous experiences of miscibility by researcher. On the other hand, it is not applicable to seek alternative formulations and excipients. These motivated researchers to find and develop theoretical methods for prediction of miscibility of drug-polymer pairs as followed in this work.











Basic phase calculations

1. Initial compatibility check

An initial screening of compatibility of drug-polymer can be performed using Hansen solubility rule to reduce design space and consequently lower computational costs and higher efficiencies.

Criteria	Compatibility
$\lvert\delta_{p,2}-\delta_{p,1}\rvert \le R_0$ $\lvert\delta_{h,2}-\delta_{h,1}\rvert \le R_0$	High
$R_0 \le \lvert\delta_{p,2}-\delta_{p,1}\rvert \le R_1$ $R_0 \le \lvert\delta_{h,2}-\delta_{h,1}\rvert \le R_1$	Poor
$\lvert\delta_{p,2}-\delta_{p,1}\rvert > R_1$ $\lvert\delta_{h,2}-\delta_{h,1}\rvert > R_1$	None

$R_0 = \sqrt{\delta_{d,1}^2+\delta_{p,1}^2}-\delta_{h,1}$ and $R_1 = \sqrt{\delta_{d,1}^2+\delta_{p,1}^2}-\delta_{d,1}$ where δ_d is non-polar (dispersion) forces, δ_p polar forces and δ_h hydrogen-bonding contributions in cohesive energy.

2. Phase diagram

The miscibility of drug and polymer can be predicted based on the phase diagram and the Flory-Huggins theory (Eq. 1) with interaction parameter corrected (Eq. 2) to account for composition effects on the miscibility behaviour (binodal boundary as in Eq. 3 and spinodal boundary as in Eq. 4). Subscript 1 refers to drug.

1: $\frac{\Delta g_m}{kT} = \frac{\phi_1}{N_1\nu_1}\ln\phi_1 + \frac{1-\phi_1}{N_2\nu_2}\ln[1-\phi_1] + \frac{\phi_1[1-\phi_1]}{\sqrt{\nu_1\nu_2}}\chi_{12}$

2: $\chi_{12} = (\tilde{\rho}_1-1)\frac{\sqrt{\nu_1\nu_2}}{N_1\nu_1}\frac{\phi_1}{1-\phi_1}\ln\phi_1 + (\tilde{\rho}_2-1)\frac{\sqrt{\nu_1\nu_2}}{N_2\nu_2}\frac{1-\phi_1}{\phi_1}\ln[1-\phi_1] + \tilde{\rho}_1\tilde{\rho}_2\sqrt{\nu_1\nu_2}\left(\delta_{1,0}-\delta_{2,0}\right)^2 + (\tilde{\rho}_1-\tilde{\rho}_2)(\delta_1^2-\delta_2^2)\sqrt{\nu_1\nu_2}$

3: $\frac{K-1}{K} = \frac{\rho_1}{Mw_1}\left[[\chi_{12}{}^I - \chi_{12}{}^{II}K^2](\varphi_1{}^I)^3 - 2[\chi_{12}{}^I - \chi_{12}{}^{II}K](\varphi_1{}^I)^2 + \left[\chi_{12}{}^I - \chi_{12}{}^{II} + \ln\frac{1}{K}\right](\varphi_1{}^I)\right]$

4: $\phi_1 = \left[1 - \frac{1}{2\chi_{12}}\left[\frac{1-\phi_1}{\phi_1} + \frac{N_1\nu_1}{N_2\nu_2}\right]\right]$

Methods reliability

- The FH interaction parameter is directly related to the enthalpy of mixing, and thus considering favourable entropy of mixing, its non-positive (negative or nearly zero) values would indicate complete miscibility and one phase formation. It shows adhesive interaction between drug and polymer molecules which would facilitate mixing. On the other hand, positive values show the aggregation of similar particles by themselves which may end up to emerge of two separate phases at enough high value of χ.
- A negative free energy of mixing per unit volume indicates spontaneous mixing, which however won't essentially result in a single-phase system. In fact, even in such a case, phase separation still may occur if there's room for system to lower its free energy by dividing into two phases. The boundary between stable and metastable regions is known as binodal curve, which represents the local thermodynamic equilibrium. Below the equilibrium composition of the two components i.e. within binodal boundary, the free energy of mixing is less than zero and phase separation is thermodynamically not favourable.

Notes

European Journal of Pharmaceutics and Biopharmaceutics 107 (2016) 16–31.

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Environmental Science and Pollution Research 24(2017):2627-2631

Funding

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No. 801165 with co-funding through Confirm smart manufacturing centre by its funding body, Science Foundation Ireland (SFI), grant no. 16/rc/3918.

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