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

**Abstract**

The thermodynamic behavior 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.

**Keywords**: pharmaceutical industry; amorphous structure; miscibility;

# Backgrounds

Low in-body solubility (bioavailability) of most produced drugs caused a big challenge facing pharma industry [[1](#_ENREF_1)]. 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 nano crystal active pharmaceutical ingredients, and amorphous solid dispersions using various pharmaceutically acceptable excipients (polymers) [[2](#_ENREF_2), [3](#_ENREF_3)]. These solid dispersions are practically a binary mixture of a drug and an amorphous polymer [[4](#_ENREF_4)] 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 [[5](#_ENREF_5)].

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 [[6](#_ENREF_6)]. 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.

# Methods

The most used approach employed by researchers for interaction and miscibility analysis of binary mixtures is the concept of regular solution theory [[7](#_ENREF_7)]. The miscibility of drug and polymer can be predicted based on the phase diagram and the Flory-Huggins theory’s interaction parameter. However, most used methods failed to predict the composition effects on the miscibility behavior [[8](#_ENREF_8)], which should be noted. We recently introduced an improved modification for composition-dependent Flory–Huggins interaction parameter as given in Eq. 1 where is the volume fraction,  the reduced density of componentin Sanchez and Lacombe’s lattice-fluid theory,  the number of segments in the hard-core volume () of component, the hard-core solubility parameter at 298 K and is the hard-core solubility parameter at temperature of concern (for model details refer to Ref. [[9](#_ENREF_9)]). Subscript 1 refers to drug.

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The importance of this interaction parameter is due to the possibility of getting some insight regarding miscibility based on its value. In practice, this interaction parameter is directly related to the enthalpy of mixing, and thus considering favorable 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*.

In addition, the free energy of mixing per unit volume, Δ*gm* (as given in Eq. 2) vs. composition curves, themselves, can be used to identify regions of stability, metastability, and instability for a particular system [[10](#_ENREF_10)]. Generally, negative Δ*gm* indicates spontaneous mixing, which however won’t essentially result in a single-phase system. In fact, even in such a case (negative Δ*gm*), 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 favorable. Binodal boundary resembles compositions that the first derivative of, with respect to the composition (in terms of volume fraction) at constant temperature and pressure is zero (). Alternatively, for determination of binodal curve, the local thermodynamic equilibrium criteria i.e. equality of chemical potentials at the interface of two coexisting phases (, for phase *I* and *II* representing drug-rich and polymer-rich respectively). We introduced an improved consecutive substitution relationship based on a previous work [[11](#_ENREF_11)] as given in Eq. 3, where is partitioning coefficient of compound 1 between phases *I* and *II*.  and denote the molecular weight and density of drug, respectively. An initial guess of *K*=0.5 is suggested for improved performance. The boundary between metastable and unstable regions is known as the spinodal boundary which requires that the second derivative of, with respect to the composition at constant temperature and pressure to be positive . We introduced an improved consecutive substitution relationship based on a previous work [[10](#_ENREF_10)] as given in Eq. 4.

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Prior to application of these relationships for getting insight on phase behavior of drug-polymer pairs, an initial screening of compatibility of pairs can be performed to reduce design space and consequently lower computational costs and higher efficiencies. This can be done using the criteria for initial compatibility of two compounds as summarized in Table 1 where is non-polar (dispersion) forces,  polar forces and  hydrogen-bonding contributions in cohesive energy [[12](#_ENREF_12)].

Table . Criteria for initial compatibility of two compounds [[13](#_ENREF_13)]

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| **Criteria** |  |  |  |
| **Compatibility** | High | Poor | None |
| and | | | |

For cohesive energy contributions and lattice fluid theory, the group contribution methods of the Hoftyzer and van Krevelen [[14](#_ENREF_14)] and Boudouris et al. [[15](#_ENREF_15)] have been implemented. The performance of method is dictated by the groups introduced in these group contribution methods, and therefore by modification like addiction of new sub groups or definition of new classes of groups combining a number of other group contribution methods, the performance can be simply improved.

# Dataset and discussion

A number of model systems were collected from literature including (1) dipyridamole-polyvinyl pyrrolidone, (2) dipyridamole-polyacrylic acid, (3) cinnarizine-polyvinyl pyrrolidone, (4) cinnarizine-polyacrylic acid [[16](#_ENREF_16)]. Cinnarizine is used to treat cerebral apoplexy, post-trauma cerebral symptoms, and cerebral arteriosclerosis. Dipyridamole is a medication to inhibit blood clot formation or blood vessel dilation. For data extraction, *PlotDigitizer* was used. The volume fraction of drug () and mass fraction of drug () were converted by using equality where needed.

Presenting phase diagram in terms of temperature-composition is of great interest of formulation scientists as it may provide estimation of stability. It can be easily understood from such phase diagrams if the mixture is stable or may experience phase separation due to composition or temperature variations. From temperature-composition phase diagrams, the mixtures could be expected to be thermodynamically stable above the binodal curve where mixtures form one phase. In region surrounded by binodal and spinodal boundaries, the compounds are partially miscible and mixtures are metastable and two phases of polymer-rich and drug-rich coexist.

# Concluding remarks

A systematically improvable method is given for prediction of miscibility of binary mixtures and examined for application in amorphous solid dispersion analysis. The other applications of reported code may include organic solvent selection, cocrystal and salt screening, and etc. The performance of method in terms of computational and costs and accuracy is acceptable.

# Conflict of interest

There is no conflict of interest to declare.

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