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Thermodynamic approach to improving solubility prediction of co-crystals in comparison with individual poorly soluble components

German L. Perlovich *

Krestov's Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Russia

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Dedicated to the memory of the late Professor Manuel Ribeira da Silva

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ABSTRACT

A novel thermodynamic approach to compare poorly soluble components (active pharmaceutical ingredient (API)) both in co-crystals and individual compounds was developed. An algorithm of choosing potential co-crystals with improved solubility characteristics on the basis of the known solvation/hydration API and co-former enthalpies is described. The applicability and operability of the algorithm were tested exemplified by some drugs and amino acids.

1. Introduction

The problem of poor API (active pharmaceutical ingredient) solubility in aqueous mediums is one of the key points in the design of effective drugs [1]. Approximately 40% of drugs on the markets of European countries, US and Japan are practically insoluble [2]. Therefore, a lot of research efforts are aimed at solving the problem. The last decade saw the development of an approach of producing soluble pharmaceutical systems based on co-crystal design [3–6]. One of the advantages of co-crystals is their high thermodynamic stability and essential improvement of solubility in comparison with individual API. Additional valuable advantages of co-crystal formation for the pharmaceutical industry include the possibility of extending the life cycles of old APIs and the opportunity of intellectual property protection. The considerable deficiency of co-crystal employment can be attributed to low predictability of co-crystal formation, therefore, this fact demands applying various screening methods and algorithms [7]. Various experimental methodologies are currently employed for co-crystallization including grinding [8,9], crystallization from the melt [10], traditional solution crystallization, such as solvent evaporation [11] cooling, or anti-solvent addition, and slurry crystallization [12]. These experimental techniques are usually time-consuming and expensive. Therefore, it is important to be able to predict the propensity of different co-formers to form a co-crystal with the given API. One of the approaches is based on the comparative analysis of co-crystal thermodynamic/energetic stability while creating different heterosynthons [13–16]. There are many *in silico* (or virtual) screening approaches in the literature. These approaches usually apply analysis of the relative stability (energy or Gibbs free energy) of crystals including individual components of the co-crystal studied in comparison with co-crystal crystal lattice energy. Several methods have been suggested in the literature, *viz.* an approach based on crystal structure prediction (CSP) with anisotropic potential [17,18] and quick methods of energy estimation based on molecular electrostatic potential surfaces [19]. COSMO-RS fluid-phase thermodynamics computations describing miscibility of co-crystal formers in a super-cooled liquid (melt) phase have been applied to virtual co-former screening by Abramov *et al.* [20]. In addition, Hansen solubility parameters were recently applied to describe miscibility of API and co-former to predict co-crystal formation to guide co-crystal screening [21].

All the above-mentioned approaches have substantial disadvantages as there is absolutely no information about the improvement or impairment of API solubility properties in co-crystals in comparison with individual compounds. In other words, obtaining a co-crystal from a chosen API and co-former does not guarantee API solubility improvement. It can be exemplified by solubility improvement of carbamazepine co-crystals in various buffers [22], where one out of eight co-crystals becomes less soluble. In their turn,

* Tel.: +7 4932 533784; fax: +7 4932 336237.
E-mail address: glp@isc-ras.ru

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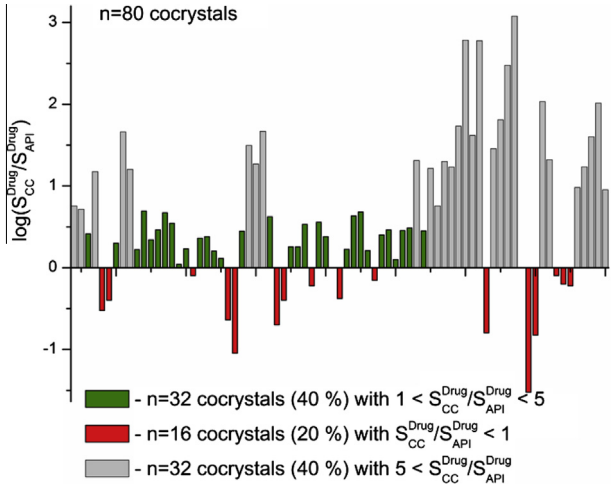

FIGURE 1. Solubility ratio of API in co-crystal (S_{CC}^{Drug}) to the individual compound (S_{API}^{Drug}) on the logarithmic scale for 80 co-crystals.

out of the two co-crystals-theophylline (THP) with nicotinamide (1:1) and THP with salicylic acid (1:1) – the solubility of the latter is 2.5 times lower. Similarly, the caffeine solubility for the caffeine with salicylic acid (1:1) co-crystal was also almost 3 times lower.

The analysis of literature data on improving co-crystal solubility in aqueous media has shown that the solubility of 20% of the co-crystals under study (a set of 80 co-crystals) worsened (figure 1).

It is this fact that accounts for the conditional division of pharmaceutical co-crystal searching algorithm into two parts. The first one includes the screening stage (*i.e.* proper obtainment of the co-crystal), whereas the second one is connected with studying the product solubility characteristics (*i.e.* verification if the co-crystal has better solubility characteristics in comparison with individual API). As is known, there is only one work concerning the evaluation of this parameter by *in silico* screening [23]. The present study is an attempt to describe the thermodynamic approach to prediction of co-crystals with better solubility characteristics in comparison with individual poorly soluble API components. Such predictions could considerably bridge the screening procedures as the systems with unfavorable thermodynamic characteristics could be excluded at the beginning.

2. Results and discussions

2.1. Background

In order to estimate the solubility differences between co-crystal **AB** (in our case we selected stoichiometry 1:1 as an example) and individual component **A**, the Gibbs free energy analysis of the solubility processes of the considered substances in the solvent studied was applied. The solvent can be selected arbitrarily, but in our case we would like to focus on water, as it is in aqueous solutions that drugs reveal their poor solubility best of all.

$$\Delta_{sol}G_m^{0,298}(AB) = \Delta_{sol}H_m^{0,298}(AB) - T\Delta_{sol}S_m^{0,298}(AB), \quad (1)$$

$$\Delta_{sol}G_m^{0,298}(A) = \Delta_{sol}H_m^{0,298}(A) - T\Delta_{sol}S_m^{0,298}(A), \quad (2)$$

where $\Delta_{sol}G_m^{0,298}(X)$, $\Delta_{sol}H_m^{0,298}(X)$ and $\Delta_{sol}S_m^{0,298}(X)$ are, respectively, Gibbs free energy, enthalpy and entropy of solubility (in standard conditions) for co-crystal (X = **AB**) or individual API (X = **A**).

$$\begin{aligned}\Delta\Delta_{sol}G_m^{0,298} &= \Delta_{sol}G_m^{0,298}(AB) - \Delta_{sol}G_m^{0,298}(A)\\ &= \left[\Delta_{sol}H_m^{0,298}(AB) - \Delta_{sol}H_m^{0,298}(A)\right]\\ &\quad - T\left[\Delta_{sol}S_m^{0,298}(AB) - \Delta_{sol}S_m^{0,298}(A)\right]. \quad (3)\end{aligned}$$

Due to the thermodynamic cycle the first term of equation (3) can be presented as:

$$\begin{aligned}\Delta_{sol}H_m^{0,298}(AB) - \Delta_{sol}H_m^{0,298}(A) &= \left[\Delta_{sub}H_m^{0,298}(AB) + \Delta_{solv}H_m^{0,298}(AB)\right]\\ &\quad - \left[\Delta_{sub}H_m^{0,298}(A) + \Delta_{solv}H_m^{0,298}(A)\right] = \left[\Delta_{sub}H_m^{0,298}(AB) - \Delta_{sub}H_m^{0,298}(A)\right]\\ &\quad + \left[\Delta_{solv}H_m^{0,298}(AB) - \Delta_{solv}H_m^{0,298}(A)\right], \quad (4)\end{aligned}$$

where $\Delta_{sub}H_m^{0,298}(X)$ and $\Delta_{solv}H_m^{0,298}(X)$ are sublimation and solvation/hydration enthalpies of co-crystal (X = **AB**) or individual API (X = **A**).

2.1.1. $\Delta\Delta_{sub}H_m^{0,298}$-value estimation

Let us consider the sublimation terms of equation (4):

$$\Delta\Delta_{sub}H_m^{0,298} = \Delta_{sub}H_m^{0,298}(AB) - \Delta_{sub}H_m^{0,298}(A). \quad (5)$$

It is not difficult to carry out the sublimation experiments with co-crystals, but it is rather difficult to interpret the thermodynamic characteristics of the process correctly due to the complexity of understanding both the mechanism and the limiting stages of multicomponent system sublimation. As it is shown below, parameter $\Delta\Delta_{sub}H_m^{0,298}$ is among the key ones for selecting co-crystals with improved solubility. Therefore, we tried to summarize the available X-ray data for selected individual compounds and their co-crystals/crystallo-solvates and evaluate the differences between the energies (table 1). The crystal structures were analyzed using the classical atom–atom potential (Coulomb–London–Pauli) model [24]. The energies of crystals in table 1 have just illustrative character (in order to demonstrate our approach). The mentioned energies can be estimated by alternative calculation procedure (for example [23]), but we believe that the result will not change. As follows from table 1, each group of compounds can be described by their own $\Delta\Delta_{sub}H_m^{0,298}$-values and this fact should improve predictive power of the model. It should be mentioned that for the each individual compound there are a different number of co-crystals/crystallo-solvates with solved crystal structures and this instance impacts on the effectiveness of the model as well. In the ideal case, the predictive power of the model will increase with increasing a number of solved co-crystal structures for the selected individual drug.

2.1.2. $\Delta\Delta_{solv}H_m^{0,298}$-value estimation

The next step consisted in evaluating the solvation terms of equation (4):

$$\Delta\Delta_{solv}H_m^{0,298} = \Delta_{solv}H_m^{0,298}(AB) - \Delta_{solv}H_m^{0,298}(A). \quad (6)$$

Co-crystal solvation can be represented as solvating 1 mol of mixture (**A** + **B**), *i.e.* transferring a mole from the gaseous phase into the solvent. One mole of the mixture (**A** + **B**) forms ½ mole of the co-crystal (**AB**) with (1:1) stoichiometry. So, equation (6) can be solved:

$$\begin{aligned}\Delta\Delta_{solv}H_m^{0,298} &= 1/2[\Delta_{solv}H_m^{0,298}(A) + \Delta_{solv}H_m^{0,298}(B)]\\ &\quad - \Delta_{solv}H_m^{0,298}(A) = 1/2[\Delta_{solv}H_m^{0,298}(B) - \Delta_{solv}H_m^{0,298}(A)]. \quad (7)\end{aligned}$$

2.1.3. Estimation of the entropic term

The changes of entropy terms during the dissolution of the co-crystal and the individual component can be roughly evaluated as:

$$\begin{aligned}T\Delta\Delta_{sol}S_m^{0,298} &= T\Delta_{sol}S_m^{0,298}(AB) - T\Delta_{sol}S_m^{0,298}(A) = RT\ln 2\\ &= 1.7/(\text{kJ}\cdot\text{mol}^{-1}). \quad (8)\end{aligned}$$