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On the thermodynamics of cocrystal formation

Richard R. Schartman*

Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492, United States

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ABSTRACT

The thermodynamics underpinning cocrystal formation are derived. The results provide the pharmaceutical scientist with the foundation to experimentally assess the thermodynamic stability of a cocrystal with respect to its component forms. Data for the carbamazepine–nicotinamide system are discussed as an example.

1. Introduction

A solid oral drug product requires an active pharmaceutical ingredient (API) that is chemically stable, that is physically stable, and that is sufficiently soluble in the GI tract to enable absorption. For APIs with ionizable groups, salt formation provides a means of endowing a biologically active molecule with an optimal mix of these properties. Cocrystal formation could potentially enable the solid state chemist to engineer such desirable characteristics into compounds that do not have ionizable groups (Remenar et al., 2003; Childs et al., 2004; Trask et al., 2005; McNamara et al., 2006).

In spite of the successful application of cocrystallization to manipulate the physical properties of a drug, no marketed drug products utilize cocrystals. One reason for this may be related to concern about the thermodynamic stability of cocrystals. Pharmaceutical companies are loath to develop metastable crystal forms because of the risk of a form change during the shelf life of the product. If such a change were to occur, the product would have to be recalled. Thus, an understanding of the thermodynamics underpinning cocrystal formation would be useful.

To date, the bulk of the thermodynamic measurements on cocrystals have been limited to identifying the phase behavior in the presence of solvent (Higuchi and Connors, 1965; Nehm et al., 2006; Chiarella et al., 2007; Jayasankar et al., 2007). The cocrystal phase boundary behaves in a fashion not unlike the solubility product (K_{sp}) for a salt in that the thermodynamic activities of the components in solution may be combined to yield a constant (Nehm et al., 2006). Because the compounds making up the cocrystal also have their own solubility limits, the solid phase in equilibrium with solution may be the cocrystal or one of the cocrystal components depending on the concentration of the components in solution. This leads to situations where dissolution of a cocrystal may or may not result in the cocrystal as the equilibrium solid phase. Complicating matters, this situation is solvent dependent (Chiarella et al., 2007); phase diagram work on the trans cinnamic acid/nicotinamide system showed that dissolution of the cocrystal in methanol gave cocrystal as the equilibrium phase, while dissolution in water did not.

These results do not speak to whether or not a cocrystal will be thermodynamically stable with respect to solid–solid transformations under normal atmospheric conditions of temperature and humidity. In this paper a relationship that provides such an understanding is developed and then applied to the carbamazepine–nicotinamide system. One implication of the relationship is that the observation of cocrystal reversion to its component parts in a solvent system (Childs et al., 2004; Trask et al., 2005; McNamara et al., 2006) does not prove that the cocrystal is thermodynamically unstable under normal atmospheric conditions. Thus slurry experiments, which have been used to determine hydrate–anhydrate phase boundaries (Zhu et al., 1996; Zhu and Grant, 1996) and the relative stability of polymorphs (Giordano et al., 2001; Gu et al., 2001; Getsoian et al., 2008), must be modified in order to have relevance to the assessment of a cocrystal's thermodynamic stability.

* Tel.: +1 203 677 6769; fax: +1 203 677 7072.
E-mail address: richard.schartman@bms.com.

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2. Theory

The terminology associated with cocrystal formation is unsettled. For a discussion of the perspectives on this issue see the paper by Stahly (2007) and the references therein. For this paper, the active pharmaceutical ingredient or the host molecule will be denoted by the letter A. The countermolecule or guest molecule will be called B. The symbols were selected to match those used by Nehm et al. (2006) whose data will be utilized later.

Cocrystal formation between an API and a second compound may be described as

$$aA_{solid} + bB_{solid} \rightarrow A_aB_{b\ solid} \quad (1)$$

Our task is to determine whether the standard free energy change, ΔG°, for the above reaction is positive or negative. This is readily done through consideration of the solubility behavior of each of the materials. Consider a solution of the API in equilibrium with the solid phase of the API:

$$A_{solid} \leftrightarrow A_{solution} \quad (2)$$

If the thermodynamic activity of the solid is set to 1, the standard free energy change for the reaction is

$$\Delta G^\circ_A = -RT \ln a'_A \quad (3)$$

where a'_A is the activity of A in solution. Similar relationships can be written for compound B:

$$B_{solid} \leftrightarrow B_{solution} \quad (4)$$

$$\Delta G^\circ_B = -RT \ln a'_B \quad (5)$$

For the cocrystal, the following relations can be written:

$$A_aB_{b\ solid} \leftrightarrow aA_{solution} + bB_{solution} \quad (6)$$

$$\Delta G^\circ_{AB} = -RT \ln a_A^a a_B^b \equiv -RT \ln K_{sp} \quad (7)$$

The equilibria listed in (2), (4), and (6) may be algebraically combined to produce reaction (1). Eqs. (3), (5) and (7) may be combined in a like fashion to produce an equation for the standard free energy change for reaction (1):

$$\Delta G^\circ = -RT \ln \frac{(a'_A)^a (a'_B)^b}{K_{sp}} \quad (8)$$

In many cases of interest to the pharmaceutical scientist, Eq. (8) is well approximated by

$$\Delta G^\circ = -RT \ln \frac{S_A^a S_B^b}{K_{sp}} \quad (9)$$

where S_A and S_B represent the solubility of pure A and B, respectively.

3. Discussion

The preceding result will be discussed in terms of the carbamazepine–nicotinamide system which forms a 1:1 cocrystal ($a = b = 1$). Nehm et al. (2006) determined the phase diagram for solutions of carbamazepine (form III) and nicotinamide (form I) in three solvents. As part of this effort, the solubility of carbamazepine (A), the solubility of nicotinamide (B), and the K_{sp} of the one to one cocrystal (AB) were determined in each solvent. The results are listed in Table 1. Each set of results was entered into Eq. (9) to generate the free energy change associated with formation of the cocrystal (reaction (1)). Because reaction (1) does not involve solvent, the free energy change calculated using data from each of the solvents should give a similar result. This was seen to be the case (Table 1).

Table 1
Free energy of cocrystal formation for the carbamazepine/nicotinamide system

	S_A (M)	S_B (M)	K_{sp}	ΔG° (kJ/mol)
Ethanol	0.108	0.841	0.0129	−4.8
2-Propanol	0.039	0.496	0.0016	−6.1
Ethyl acetate	0.044	0.098	0.00045	−5.6

Interestingly, Nehm et al. demonstrated that solubilized carbamazepine and nicotinamide form a one to one complex in solution when the solvent utilized is propanol or ethyl acetate:

$$A_{solution} + B_{solution} \leftrightarrow AB_{solution} \quad (10)$$

However, solution complexation was not observed when the solvent was ethanol. None of this affects the validity of the derivation of Eq. (8), but care must be taken to measure the K_{sp} correctly. Nehm et al. (2006) demonstrated how to do so in their paper. Briefly, this consisted of measuring the concentration of carbamazepine in equilibrium with cocrystal as a function of the nicotinamide concentration. A plot of carbamazepine concentration vs. the reciprocal of the nicotinamide concentration yielded a line with the slope K_{sp}.

Cocrystals of drugs that have higher aqueous solubility than native forms of the drug are of particular interest to the pharmaceutical scientist, because such cocrystals have the potential to improve bioavailability. In the absence of complexation, the situation in vitro is described by the following reaction:

$$A_aB_{b\ solid} \overset{water}{\longleftrightarrow} aA_{solid} \downarrow + bB_{solution} \quad (11)$$

In vivo the precipitation described by (11) may not occur in the intestinal milieu for a variety of reasons producing enhanced bioavailability. However, any form change observed when the cocrystal is slurried in vitro naturally leads one to question whether the cocrystal is stable in air and has the shelf life required for development. After all, the routine procedure for determining the relative stability of two polymorphs is to slurry them together and monitor the transformation of the less stable form into the more stable form (Giordano et al., 2001; Gu et al., 2001; Getsoian et al., 2008).

An example will demonstrate that it is possible for a cocrystal to have higher solubility than the API, and yet be the thermodynamically stable form under normal atmospheric conditions. Consider a case where a 1:1 cocrystal and its components have the following aqueous solubilities:

$$S_{AB} = 0.12\,M, \qquad S_A = 0.1\,M, \quad \text{and} \quad S_B = 0.8\,M$$

In the above, the solubility of the cocrystal is taken as $\sqrt{K_{sp}}$. Based on these relative solubilities, precipitation of API as described by (11) is to be expected, but the reader may verify that the cocrystal is the most stable solid form under normal atmospheric conditions by using Eq. (9).

Another subtle feature of cocrystals is that the three solid phases described by reaction (1) are generally not in equilibrium with each other. This is because at a fixed temperature, the phase rule informs us that there exists only one pressure at which the three phases can be in equilibrium. At other pressures, the reaction will either thermodynamically lie completely to the left or completely to the right. This fact has been used to great effect by Zhang et al. (2007) who developed an efficient cocrystal screening technique based on this result.

The result may be turned around and used to judge the relative stability of a cocrystal and its components. If the cocrystal and its components are slurried together in a solvent, reaction (1) will tend in the direction of the more stable crystal form(s). Note that any decomposition seen by slurrying the cocrystal alone does *not* prove that the cocrystal is unstable with respect to its component

parts. All three phases must be present for the experiment to have meaning.

The situation is somewhat more complex when the system under study exhibits hydrate formation. Such is the case with carbamazepine, which at 25 °C has been reported to exhibit a dihydrate–anhydrate phase boundary at a water activity of ~0.64 (Qu et al., 2006). Thus at relative humidities above ~64%, reaction (1) would not correctly describe cocrystal formation. The situation is instead described by the following reaction:

$$A \cdot (H_2O)_{2\,solid} + B_{solid} \rightarrow AB_{solid} + 2H_2O \quad (12)$$

The standard free energy change for (12) is

$$\Delta G^{\circ}_{hyd-AB} = -RT \ln a^2_{H_2O} \quad (13)$$

Reaction (12) is the result of subtracting the hydrate formation reaction:

$$A_{solid} + 2H_2O \rightarrow A \cdot (H_2O)_{2\ solid} \quad (14)$$

from reaction (1). The free energy for the hydrate formation reaction:

$$\Delta G^{\circ}_{hyd} = -RT \ln \frac{1}{a'^2_{H_2O}} \approx -RT \ln \frac{1}{(0.64)^2} \quad (15)$$

may be combined with the free energy for reaction (1) in a similar fashion to give a result for the left hand side of Eq. (13). Taking the free energy for reaction (1) as the average of the results in Table 1, this gives $\Delta G^{\circ}_{hyd-AB} = -3.3$ kJ/mol. The reader may verify by using Eq. (13) that a water activity greater than that of pure water (>1) is required to push reaction (12) to the left and destabilize the cocrystal. Thus the cocrystal is not unstable with respect to the solid hydrate (and solid B) under normal conditions of humidity at 25 °C.

This is not to say that the cocrystal will be impervious toward high humidity or liquid water. There exists a humidity beyond which one of the species in reaction (1) will deliquesce. The situation may be described by simple dissolution of the cocrystal as in reaction (6), or alternatively one of the components may precipitate as depicted in reaction (11). Parenthetically, the carbamazepine system apparently precipitates as the hydrate (Rodriguez-Hornedo et al., 2005). The task of the solid state scientist is to determine the humidity at which such thermodynamic instabilities could arise.

Barring a kinetic limitation, the solid state scientist may be able to infer from moisture sorption data the humidity at which phase conversion of the solid cocrystal becomes thermodynamically favored. However, this humidity may also be found using the sort of solution-based phase diagram work described by Nehm et al. (2006). To see this it must be remembered that as a solute is dissolved, the vapor pressure of the solvent is lowered. The problem of finding the humidity at which a cocrystal is thermodynamically unstable toward humidity then reduces to measuring the humidity over a particular aqueous solution of the cocrystal components. The particular solution to use for such a measurement can be inferred from the phase diagram as follows.

Consider the hypothetical case depicted in Fig. 1, which is meant to describe reaction (6) with $a = b = 1$. The solid curve depicts the phase boundary for the cocrystal, while the horizontal crosshatched line depicts the solubility limit for component A. Dissolution of the cocrystal in water is depicted by a line drawn from the origin with a slope equal to the ratio of the components in the cocrystal. In this hypothetical case, the cocrystal is a 1:1 cocrystal, so the slope of the line is 1. The solubility of the cocrystal is less than that of either of its components in the region of interest, so the intersection of the dissolution line with the cocrystal phase boundary gives the solution whose humidity is to be measured (indicated by an arrow).

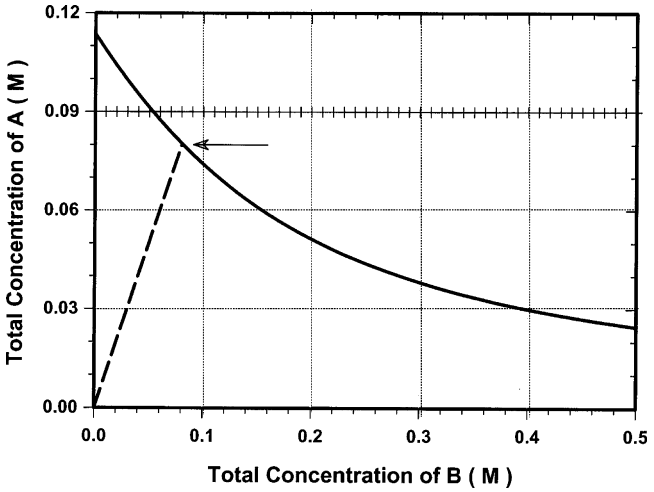

Fig. 1. Phase diagram for a cocrystal, AB, whose solubility is less than that of component A. Solid curve: the cocrystal phase boundary. Crosshatched line: solubility of component A. Dashed line: concentration of species produced as the cocrystal dissolves. The water vapor pressure over the solution indicated by the arrow corresponds to the humidity at which deliquescence becomes thermodynamically favored.

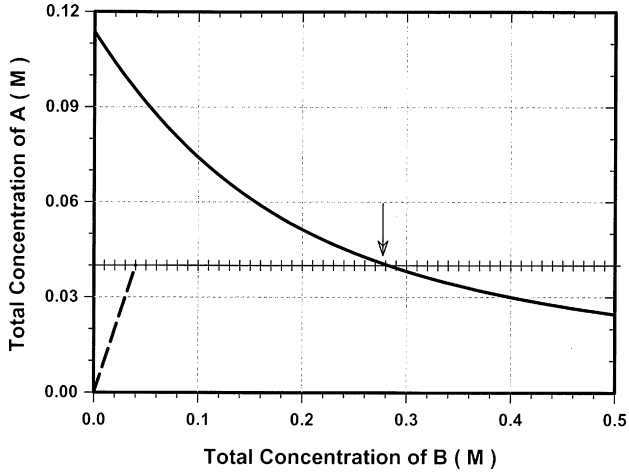

Fig. 2. Phase diagram for a cocrystal, AB, whose solubility is more than that of component A. Solid curve: the cocrystal phase boundary. Crosshatched line: solubility of component A. Dashed line: concentration of species produced as the cocrystal dissolves. The water vapor pressure over the solution indicated by the arrow corresponds to the humidity at which the cocrystal becomes thermodynamically unstable.

Fig. 2 depicts a similar case except that component A is less soluble than the cocrystal. In this case, the cocrystal dissolution line intersects the solubility limit of A before hitting the cocrystal phase boundary. Further dissolution is possible, but it is accompanied by decomposition and precipitation of component A. This is the situation described by reaction (11) with $a = b = 1$. Graphically, the horizontal solubility line for A is followed to its intersection with the cocrystal phase boundary. The humidity over this solution (indicated by an arrow) would represent the humidity at which the cocrystal becomes thermodynamically unstable.

4. Conclusions

A thermodynamic relationship was derived that enables the solid state scientist to assess cocrystal stability. The relationship demonstrates how to rationally design solubility measurements or slurry experiments that prove cocrystal stability with respect

to solid–solid conversions under normal atmospheric conditions of temperature and humidity. It is apparent however that the assessment of cocrystal stability is a complex affair. Polymorphs and hydrates must be elucidated not only for the cocrystal but for the cocrystal components as well. The failure to find a critical form may completely alter a conclusion concerning a particular cocrystal's stability.

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