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Cocrystal transition points: Role of cocrystal solubility, drug solubility, and solubilizing agents

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Abstract

In this manuscript we bring together concepts that are relevant to the solubilization and thermodynamic stability of cocrystals in the presence of drug solubilizing agents. Simple equations are derived that allow calculation of cocrystal solubilization and transition point solubility. Analysis of 10 cocrystals in 6 different solubilizing agents shows that cocrystal solubilization is quantitatively predicted from drug solubilization. Drug solubilizing agents such as surfactants and lipid-based media are also shown to induce cocrystal transition points, where drug and cocrystal solubilities are equal, and above which the cocrystal solubility advantage over drug is eliminated. We have discovered that cocrystal solubility at the transition point (S^*) is independent of solubilizing agent, and can be predicted from knowledge of only the *aqueous solubilities* of drug and cocrystal. For 1:1 cocrystals, $S^* = (S_{\text{cocrystal, aq}})^2 / S_{\text{drug, aq}}$. S^* is a key indicator of cocrystal thermodynamic stability, and establishes the upper solubility limit below which cocrystal is more soluble than the constituent drug. These findings have important implications to tailor cocrystal solubility and stability in pharmaceutical formulations from commonly available drug solubility descriptors.

Graphical Abstract

Keywords

cocrystal; co-crystal; enhancing solubility; solubilizing agent; surfactant; micelles; lipids; formulation; biorelevant media; solubilization; transition point; stability

Introduction

Cocrystals are playing an important role in solving many of the challenges related to the bioavailability of poorly-water soluble drugs^{1–8}. One of the vital properties of cocrystals is their tunable solubility,^{2, 4, 9–17} offering dramatic benefits to drug absorption and bioavailability. Chemical interactions between cocrystal constituents and dissolution media

additives are critically important for cocrystals to achieve a wide range of solubility and thermodynamic stability behaviors.

We recently discovered that the same cocrystal can display higher, equal, or lower solubility than the constituent drug, depending on the concentration of drug solubilizing agents^{10–12}. As a result of this phenomenon, cocrystals can exhibit transition points at which the cocrystal solubility advantage over the parent drug is switched by the presence of drug solubilizing agents. The indomethacin-saccharin cocrystal, for example, has a solubility 26 times higher than indomethacin in pH 2 buffer¹⁶. This solubility advantage is however eliminated in the presence of drug solubilizing agents and the cocrystal becomes less soluble than indomethacin in solutions with sodium lauryl sulfate (SLS), Brij 99, or Tween 80 among others^{18, 19}. The underlying mechanism for this behavior was determined to be the solubilizing agent's preferential solubilization for the drug, and its indifference for coformer solubilization. Coformers are much more hydrophilic than the constituent drugs and therefore such selective drug solubilization is generally observed with solubilizing agents in aqueous media.

The solubilizing agent concentration at the transition point is referred to as the CSC or critical stabilization concentration^{10–12}. Studies on carbamazepine and indomethacin cocrystals led to the recognition of the transition point and established the factors that determine the value of the CSC^{10–12, 18, 19}. CSC was found to decrease with increasing drug solubilization and drug selectivity by the additive, and with decreasing cocrystal aqueous solubility (in the absence of solubilizing agents). CSC values for carbamazepine cocrystals in solutions of SLS were in the range of 23 to 187 mM^{10–12}, which can be encountered in formulation, processing, and dissolution media.

Cocrystal transition points are not only dependent on the effectiveness of the drug solubilizing agent but also on the extent of ionization and solubilization of cocrystal components, i.e., drug and coformer^{10–12, 18, 19}. These findings have challenged the traditional notion of cocrystal solubility and thermodynamic stability, since not only do cocrystals exhibit transition points, but the CSC shifts with the nature and concentration of solubilizing agents.

The aim of the work presented here is to develop simplified equations that establish the influence of drug solubilizing agents on cocrystal solubilization and transition points. While our previous work^{10–12} showed more rigorous mathematical models by considering the equilibrium constants of the processes that govern solubilization, we wished to develop a simplified version of the more rigorous theoretical models and evaluate their predictive power for a broad range of cocrystals and drug solubilizing agents. The selection criterion for cocrystals and solubilizing agents studied was that cocrystal and drug solubilities be measured under equilibrium conditions. We included cocrystals studied in our laboratory and in other laboratories that were reported in the literature. Solubilities and transition points of cocrystals of carbamazepine (CBZ), indomethacin (IND), danazol (DNZ), piroxicam (PXC), and pterostilbene (PTB) in the presence of drug solubilizing agents comprising surfactants and lipid-based systems were analyzed in light of the concepts presented here.

Theoretical

This section describes the theoretical basis of the simple relationships that allow for the quantitative prediction of cocrystal solubilization and transition points. We first show how cocrystal solubilization can be obtained from knowledge of only drug solubilization. We then demonstrate the parameters that determine cocrystal transition points.

The underlying assumption in deriving the simple models is that drug constituents, and not coformers are solubilized by solubilizing agents. While this assumption is justified for most cocrystals of hydrophobic drugs and hydrophilic coformers, there may be some level of coformer solubilization in some cases. We therefore examine in the last section, how coformer solubilization influences the cocrystal solubilization and transition points predicted by the simplified equations.

The goal is to understand the factors that determine cocrystal solubility relative to their constituent drugs in media with additives that solubilize poorly water-soluble drugs. This is of practical importance since drug solubilizing agents such as surfactants, lipids, and complexing agents among others, are often encountered in cocrystal formulations as well as in dissolution media (in vitro and in vivo). Here we consider solubilization by micellar surfactants but the treatment applies equally well to other solubilization processes where there is preferential affinity for the drug constituent of the cocrystal and not the coformer.

Relationship between cocrystal solubilization and drug solubilization

The relationship between cocrystal and drug solubilization ratios can be obtained by combining the equations that describe cocrystal and drug solubilities in the presence of solubilizing agents^{10–12}. We first consider a 1:1 cocrystal under nonionizing conditions where the solubility is

$$S_{\text{cocrystal},T} = \sqrt{K_{\text{sp}} (1 + K_s^{\text{drug}}[M]) (1 + K_s^{\text{coformer}}[M])} \quad (1)$$

$S_{\text{cocrystal},T}$ represents the sum of cocrystal solubilities in aqueous and micellar environments, $S_{\text{cocrystal},T} = S_{\text{cocrystal},\text{aq}} + S_{\text{cocrystal},\text{mic}}$. K_{sp} is the cocrystal solubility product, $K_{\text{sp}} = (S_{\text{cocrystal},\text{aq}})^2$. K_s stands for solubilization constants of cocrystal constituents, and the term in brackets is the concentration of solubilizing agent, which for a micellar surfactant is $[M]$. The concentration of micelles can be calculated from $[M] = [\text{surfactant}] - \text{CMC}$, where CMC is the critical micellar concentration.

When solubilizing agents enhance drug solubility and not coformer solubility ($K_s^{\text{coformer}} = 0$), the cocrystal solubility equation (equation 1) becomes

$$S_{\text{cocrystal},T} = \sqrt{K_{\text{sp}} (1 + K_s^{\text{drug}}[M])} \quad (2)$$

The above equation can be written in terms of $S_{\text{cocrystal},\text{aq}}$ as

$$S_{\text{cocystal,T}} = S_{\text{cocystal,aq}} \sqrt{(1 + K_s^{\text{drug}} [M])} \quad (3)$$

The solubility of a single component, nonionizable drug in micellar solutions is

$$S_{\text{drug,T}} = S_{\text{drug,aq}} (1 + K_s^{\text{drug}} [M]) \quad (4)$$

where $S_{\text{drug,T}}$ represents the sum of the drug solubilities in the aqueous and micellar environments, $S_{\text{drug,T}} = S_{\text{drug,aq}} + S_{\text{drug,mic}}$. The relationship between cocystal and drug solubilization ratios can be easily found by combining equations 3 and 4 to give

$$\left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{cocystal}} = \sqrt{\left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}} \quad (5)$$

This form of the equation also applies to ionizable drugs and coformers at a particular pH, under the assumption that coformer solubility is not enhanced by solubilizing agents. Solubilizing agents in aqueous media may favor interactions with drugs over coformers, since the drug constituents of cocrystals generally are quite hydrophobic whereas coformers are hydrophilic. We have confirmed such behavior for cocrystals of hydrophobic drugs such as CBZ, IND, and DNZ with hydrophilic coformers in solutions of synthetic and biorelevant solubilizing agents^{10–12, 18–23}.

For the case of a 2:1 cocrystal (drug:coformer), the relationship between cocystal and drug solubilization ratios becomes

$$\left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{cocystal}} = \left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}^{\frac{2}{3}} \quad (6)$$

A general form of this equation for cocrystals A_xB_y , can be written as

$$\left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{cocystal}} = \left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}^{\frac{x}{x+y}} \quad (7)$$

where A and B are the cocrystal constituents, drug and coformer, and x and y are the stoichiometric coefficients or molar ratios. This relationship provides useful primary information for cocrystal formulation as it allows for calculation of cocrystal solubilization ratio (SR_{cocystal}) from knowledge of a common descriptor of drug solubilization, the drug solubilization ratio (SR_{drug}). SR is defined as

$$SR \equiv \left(\frac{S_T}{S_{aq}} \right)$$

The dependence of SR_{cocystal} on SR_{drug} is shown in Figure 1 for cocrystals of different stoichiometries. The curvature of the plots is due to preferential solubilization of drug over coformer. SR_{cocystal} is expected to be much lower than SR_{drug} , with SR for 1:1 cocrystals being lower than for 2:1. For example, drug solubilizing agents where SR_{drug} values are 100 and 1000 will result in SR_{cocystal} values of 10 and 32 for 1:1 cocrystals (equation 5), and SR_{cocystal} values of 22 and 102 for 2:1 cocrystals (equation 6). SR_{drug} can reach values in the order of 10^6 with some solubilizing agents, and therefore one would expect cocrystals of these drugs to have solubilization ratios that are orders of magnitude lower than the drug. These predictions will be compared with experimental observations for several cocrystals and solubilizing agents in the results section.

Cocystal transition points

Drug solubilizing agents have been shown to switch the cocrystal solubility advantage^{10–12, 18, 19}. That is, a cocrystal that is more soluble than the drug in aqueous solution can become less soluble than the drug depending on the nature and concentration of the solubilizing agent.

Cocrystals were shown to possess transition points in the presence of solubilizing agents that have selective affinity for the drug. This behavior was mathematically explained by a drug solubility that is *linearly* dependent on solubilizing agent concentration (equation 4) and a cocrystal solubility that exhibits *nonlinear* dependence (equation 1). Cocrystal solubility exhibits a *square root* dependence on solubilizing agent concentration (equation 2) for 1:1 cocrystals when coformer solubilization is negligible. For the case of 2:1 cocrystals, the solubility exhibits a *2/3 power* dependence. Predictions according to these equations were recently reported to be in excellent agreement with experimental observations for the solubility of CBZ and IND cocrystals in the presence of several solubilizing agents^{10–12, 18, 19, 21, 23}.

Figure 2 illustrates the concept of cocrystal transition points, indicated by the intersection of the cocrystal and drug solubility curves. The position of the transition point is defined by the solubility (S^*) and a solubilizing agent concentration (CSC or critical stabilization concentration). Since the transition point that we are referring to is that between cocrystal and drug crystalline phases, the solubilities of the drug and the cocrystal are equal at this point.

The transition point for a given cocrystal and its drug, (depicted in Figure 2) varies with solubilizing agent or with the degree to which the drug is solubilized (K_s^{drug}). For a given cocrystal and drug, the transition points exhibit a constant S^* but a variable CSC. A lower CSC is obtained with a stronger drug solubilizing agent ($K_s = 1.5 \text{ mM}^{-1}$) than with a weaker one ($K_s = 0.5 \text{ mM}^{-1}$). In other words, a lower concentration of solubilizing agent is required to reach the transition point with a stronger solubilizing agent.

In contrast to the CSC, whose values differ for both solubilizing agents, the value of S^* is constant. This property of S^* is found by examining the mathematical models that describe cocrystal and drug solubilization as follows.

At the transition point, the solubilities of cocrystal and drug are equal

$$S_{\text{cocrystal},T} = S_{\text{drug},T} = S^* \quad (8)$$

The solubilization ratio equations of cocrystal and drug at the transition point can be rewritten in terms of S^* , which for a 1:1 cocrystal (from equation 5) is

$$\left(\frac{S^*}{S_{\text{aq}}}\right)_{\text{cocrystal}} = \sqrt{\left(\frac{S^*}{S_{\text{aq}}}\right)_{\text{drug}}} \quad (9)$$

and solving for S^* gives

$$S^* = \frac{(S_{\text{cocrystal},\text{aq}})^2}{S_{\text{drug},\text{aq}}} \quad (10)$$

This equation shows that the solubility value at the transition point is governed by two fundamental parameters, the *aqueous solubilities of cocrystal and of drug*. S_{aq} refers to the (unionized + ionized) aqueous solubilities of cocrystal and of drug and therefore equation 10 applies to a range of ionizing conditions (pH and appropriate solubility values).

S^* for a 2:1 cocrystal is found by a similar approach and is

$$S^* = \frac{(S_{\text{cocrystal},\text{aq}})^3}{(S_{\text{drug},\text{aq}})^2} \quad (11)$$

The impact of changing aqueous solubilities of drug and cocrystal on S^* (using equation 10 for a 1:1 cocrystal) is shown in Figure 3. $S_{\text{cocrystal},\text{aq}} \gg S_{\text{drug},\text{aq}}$ yields larger S^* values. For poorly water-soluble drugs, cocrystals of much higher solubilities will provide greater solubility range over which the cocrystal is solubilized while still maintaining its solubility advantage.

For the case of a drug with $S_{\text{drug},\text{aq}} = 0.3$ mM and its (1:1) cocrystal with $S_{\text{cocrystal},\text{aq}} = 3.0$ mM, the transition solubility for this system is $S^* = 30$ mM. This means that a cocrystal will not maintain its solubility advantage over the drug above 30 mM (under the conditions of this example) since cocrystal is less soluble than drug at S values above S^* . Another factor that influences the value of S^* is the solution pH. For the case of cocrystals with ionizable components, pH will determine the drug and coformer ionization and change the aqueous

solubilities of drug and cocrystal, thereby altering the value of S^* . It is therefore possible to calculate the influence of pH on cocrystal transition points.

S^* can also be expressed in terms of the cocrystal solubility enhancement or advantage over drug (SA), which is defined as

$$SA \equiv \left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)$$

S^* in terms of the cocrystal solubility advantage can be re-written as

$$S^* = S_{\text{cocrystal, aq}} (SA_{\text{aq}}) \quad (12)$$

for a 1:1 cocrystal, and

$$S^* = S_{\text{cocrystal, aq}} (SA_{\text{aq}})^2 \quad (13)$$

for a 2:1 cocrystal.

This analysis shows that cocrystals with low SA_{aq} will have low S^* values, which means that lower concentrations of drug solubilizing agents are required to eliminate cocrystal to drug solubility advantage.

Implications of coformer solubilization on $SR_{\text{cocrystal}}$ and S^*

The equations presented above assume that cocrystal solubilization by solubilizing agents is governed by the constituent drug solubilization and that coformer solubilization is negligible ($K_s^{\text{coformer}} = 0$). Under some conditions this assumption is not justified ($K_s^{\text{coformer}} > 0$) and relevant terms need to be included in the $SR_{\text{cocrystal}}$ and S^* equations to account for the deviations due to coformer solubilization.

The contribution of coformer solubilization is included in the following equations as a factor by which the simpler equations are multiplied. Cocrystals (1:1) of nonionizable drugs and monoprotic acidic coformers are considered in this analysis as they represent most of the cocrystals studied in this work. Cocrystal solubility can be expressed in terms of both solubilization and ionization through the relationship

$$S_{\text{cocrystal, T}} = \sqrt{K_{\text{sp}} \left(1 + K_s^{\text{drug}} [M] \right) \left(1 + 10^{\text{pH} - \text{pK}_a, \text{coformer}} + K_s^{\text{coformer}} [M] \right)} \quad (14)$$

where K_a represents the dissociation constant of a monoprotic acidic coformer. The interested reader is referred to the original literature describing the conceptual framework of cocrystal solubilization in the presence of solubilizing agents^{10–12}

The influence of coformer solubilization and ionization is taken into account by substituting equation 14 into equation 5, similar to the $SR_{\text{cocrystal}}$ and S^* analysis presented in the previous sections. Cocrystal solubilization ratio can be expressed as

$$\left(\frac{S_T}{S_{\text{aq}}}\right)_{\text{cocrystal}} = \sqrt{\epsilon \left(\frac{S_T}{S_{\text{aq}}}\right)_{\text{drug}}} \quad (15)$$

and the solubility at the transition point as

$$S^* = \epsilon \frac{(S_{\text{cocrystal, aq}})^2}{S_{\text{drug, aq}}} \quad (16)$$

where

$$\epsilon = \frac{(1 + 10^{\text{pH} - \text{pK}_{\text{a, coformer}}} + K_{\text{s}}^{\text{cof}}[M])}{(1 + 10^{\text{pH} - \text{pK}_{\text{a, coformer}}})} \quad (17)$$

Equation 17 shows that $\epsilon = 1$ when $K_{\text{s}}^{\text{coformer}} = 0$, and as expected SR and S^* (equations 15 and 16) revert to the simpler relationships (equations 5 and 10). As coformer solubilization becomes appreciable, $K_{\text{s}}^{\text{coformer}} > 0$ and $\epsilon > 1$. In this case, the product of $K_{\text{s}}^{\text{coformer}}$ and solubilizing agent concentration determines ϵ . For cocrystals of ionizable coformers, the ionization constants and pH must also be considered. The above analysis shows that coformer solubilization by solubilizing agents will increase ϵ and result in higher SR and S^* values.

Materials and Methods

Materials

Cocrystal components—Anhydrous carbamazepine form III (CBZ), anhydrous indomethacin form γ (IND) were purchased from Sigma Chemical Company (St. Louis, MO) and used as received. Anhydrous piroxicam form I (PXC) was received as a gift from Pfizer (Groton, CT) and used as received. Anhydrous danazol was received as a gift from Renovo Research (Atlanta, GA) and used as received.

Anhydrous saccharin (SAC), 4-aminobenzoic acid (4ABA), succinic acid (SUC), and salicylic acid (SLC), were purchased from Sigma Chemical Company (St. Louis, MO) and used as received. Anhydrous hydroxybenzoic acid was purchased from Acros Organics (Pittsburgh, PA) and used as received. Anhydrous vanillin was purchased from Fisher Scientific (Fair Lawn, NJ) and used as received. Carbamazepine dihydrate (CBZD) and piroxicam monohydrate (PXCH) were prepared by slurring in deionized water for at least 24 hours. All crystalline drugs and coformers were characterized by X-ray power diffraction (XRPD) and differential scanning calorimetry (DSC) before carrying out experiments.

Solvents and buffer components—Ethyl acetate and ethanol were purchased from Acros Organics (Pittsburgh, PA) and used as received, and HPLC grade methanol and acetonitrile were purchased from Fisher Scientific (Pittsburgh, PA). Trifluoroacetic acid spectrophotometric grade 99% was purchased from Aldrich Company (Milwaukee, WI) and phosphoric acid ACS reagent 85% was purchased from Sigma Chemical Company (St. Louis, MO). Water used in this study was filtered through a double deionized purification system (Milli Q Plus Water System) from Millipore Co. (Bedford, MA).

Tween 80 solutions, FeSSIF, and acetate buffer were prepared using Tween 80 purchased from Sigma Chemical Company (St. Louis, MO), sodium taurocholate (NaTC) purchased from Sigma Chemical Company (St. Louis, MO), lecithin purchased from Fisher Scientific (Pittsburgh, PA), sodium hydroxide pellets (NaOH) purchased from J.T. Baker (Philipsburg, NJ), and acetic acid and potassium chloride (KCl) purchased from Acros Organics (Pittsburgh, PA).

Methods

FeSSIF, acetate buffer, and Tween 80 solution preparation—FeSSIF and acetate buffer were prepared according to the protocol of Galia and coworkers²⁴. Acetate buffer was prepared as a stock solution at room temperature by dissolving 8.08 g NaOH (pellets), 17.3 g glacial acetic acid and 23.748 g NaCl in 2 L of purified water. The pH was adjusted to 5.00 with 1 N NaOH and 1 N HCl. FeSSIF was prepared by dissolving 0.41 g sodium taurocholate in 12.5 mL of pH 5 acetate buffer. 0.148 g lecithin was added with magnetic stirring at 37 °C until dissolved. The volume was adjusted to exactly 50 mL with acetate buffer.

Tween 80 solutions were prepared by dissolving an appropriate amount (25 mM, 50 mM, and 150 mM) of Tween 80 in pH 5 acetate buffer.

Cocrystal synthesis—Cocrystals were prepared by the reaction crystallization method²⁵. The 1:1 indomethacin-saccharin cocrystal (IND-SAC) was synthesized by adding stoichiometric amounts of cocrystal components (IND and SAC) to nearly saturated SAC solution in ethyl acetate. The 1:1 carbamazepine saccharin cocrystal (CBZ-SAC) and 2:1 carbamazepine-succinic acid cocrystals (CBZ-SUC) were prepared by adding CBZ to nearly saturated solutions of coformers. The 1:1 carbamazepine-salicylic acid cocrystal (CBZ-SLC) was prepared by adding stoichiometric amounts of cocrystal components (CBZ and SLC) to nearly saturated SLC solution in acetonitrile. The 2:1 carbamazepine-4-aminobenzoic acid monohydrate cocrystal (CBZ-4ABA-HYD) was prepared by suspending stoichiometric amounts of cocrystal components (CBZ and 4ABA) in a 0.01 M 4ABA aqueous solution at pH 3.9. The 1:1 piroxicam-saccharin cocrystal (PXC-SAC) was prepared by adding stoichiometric amounts of cocrystal components (PXC and SAC) to nearly saturated solution of SAC in acetonitrile. The 1:1 danazol-hydroxybenzoic acid cocrystal (DNZ-HBA) was prepared by adding stoichiometric amounts of cocrystal components (DNZ and HBA) to nearly saturated HBA solution in ethyl acetate. The 1:1 danazol-vanillin cocrystal (DNZ-VAN) was prepared by adding stoichiometric amounts of cocrystal components (DNZ and VAN) to nearly saturated VAN solution in ethyl acetate. Prior to

carrying out any solubility experiments, solid phases were characterized by XRPD and DSC and stoichiometry verified by HPLC. Full conversion to cocrystal was observed in 24 hours.

Drug solubility measurements—Drug solubilities were either reported in the literature or experimentally determined in this work. When reported values at a specific surfactant concentration were not available, drug solubility values at the surfactant concentration of the cocrystal solubility measurements were interpolated from data at other surfactant concentrations. Drug solubility values in sodium lauryl sulfate (SLS), Myrj 52, Brij 99, Tween 80 (IND only), and a lipid formulation were obtained from the literature^{12, 19, 26–28}. Drug solubilities were measured in FeSSIF, Tween 80, and pH 5 acetate buffer (FeSSIF without NaTC and lecithin or Tween 80). The solubilities of the drugs were determined by adding excess solid to 3 mL of media (FeSSIF, Tween 80, or buffer). Suspensions were magnetically stirred and maintained at $25 \pm 0.1^\circ\text{C}$ using a water bath for up to 96 hours. In 24 hour intervals, 0.30 mL of samples were collected, pH of solutions measured, and filtered through a 0.45 μm pore membrane. After dilution with mobile phase, drug solution concentrations were analyzed by HPLC. The final solid phases were characterized by XRPD and DSC.

Cocrystal solubility measurements—Cocrystal equilibrium solubilities were measured in our laboratory with the exception of pterostilbene and its cocrystals which were obtained from the literature^{26–28}. Cocrystal equilibrium solubilities were measured in FeSSIF, Tween 80, and pH 5.0 acetate buffer (FeSSIF without NaTC and lecithin) at the eutectic point, where drug and cocrystal solid phases are in equilibrium with solution. The eutectic point between cocrystal and drug was approached by cocrystal dissolution (suspending solid cocrystal (~100 mg) and drug (~50 mg) in 3 mL of media (FeSSIF or buffer)) and by cocrystal precipitation (suspending solid cocrystal (~50 mg) and drug (~100 mg) in 3 mL of media (FeSSIF or buffer) nearly saturated with coformer). Solutions were magnetically stirred and maintained at $25 \pm 0.1^\circ\text{C}$ using a water bath for up to 96 hours. In 24 hour intervals, 0.30 mL of samples were collected, pH of solutions measured, and filtered through a 0.45 μm pore membrane. Solid phases were also collected in 24 hour intervals to ensure the sample was at the eutectic (confirmed by presence of both drug and cocrystal solid phases). After dilution with mobile phase, drug and coformer solution concentrations were analyzed by HPLC. The final solid phases were characterized by XRPD and DSC.

X-ray powder diffraction—X-ray powder diffraction diffractograms of solid phases were collected on a benchtop Rigaku Miniflex X-ray diffractometer (Rigaku, Wilmington, MA) using Cu K α radiation ($\lambda = 1.54\text{\AA}$), a tube voltage of 30 kV, and a tube current of 15 mA. Data were collected from 5 to 40° at a continuous scan rate of $2.5^\circ/\text{min}$.

Thermal analysis—Solid phases collected from the slurry studies were dried at room temperature and analyzed by differential scanning calorimetry (DSC) using a TA instrument (Newark, DE) 2910MDSC system equipped with a refrigerated cooling unit. DSC experiments were performed by heating the samples at a rate of $10^\circ\text{C}/\text{min}$ under a dry nitrogen atmosphere. A high purity indium standard was used for temperature and enthalpy calibration. Standard aluminum sample pans were used for all measurements.

High performance liquid chromatography—Solution concentrations were analyzed by a Waters HPLC (Milford, MA) equipped with an ultraviolet-visible spectrometer detector. For the IND-SAC and CBZ cocrystals and their components, a C18 Thermo Electron Corporation (Quebec, Canada) column (5 μ m, 250 $\times$ 4.6 mm) at ambient temperature was used. For the IND-SAC cocrystal, the injection volume was 20 μ l and analysis conducted using an isocratic method with a mobile phase composed of 70% acetonitrile and 30% water with 0.1% trifluoroacetic acid and a flow rate of 1 ml/min. Absorbance of IND and SAC were monitored at 265 nm. For the CBZ cocrystals, the injection volume was 20 μ l and analysis conducted using an isocratic method with a mobile phase composed of 55% methanol and 45% water with 0.1% trifluoroacetic acid and a flow rate of 1 mL/min. Absorbance was monitored as follows: CBZ and 4ABA at 284 nm, SAC at 265 nm, SLC at 303 nm, SUC 230 nm. For the PXC-SAC, DNZ-HBA, and DNZ-VAN cocrystals and their components, a C18 Waters Atlantis (Milford, MA) column (5 μ M 250 $\times$ 6 mm) at ambient temperature was used. For PXC-SAC, the injection volume was 20 μ L and analysis was conducted using an isocratic method with a mobile phase composed of 70% methanol and 30% water with 0.3% phosphoric acid and a flow rate of 1 mL/min. Absorbance of PXC was monitored at 340 nm and SAC at 240 nm. For the DNZ cocrystals, the injection volume was 20 μ L in FeSSIF experiments, and 100 μ L in buffer experiments due to the extremely low solubility of DNZ in aqueous solutions. Analysis was conducted using an isocratic method composed of 80% methanol and 20% water with 0.1% trifluoroacetic acid and a flow rate of 1 mL/min. Absorbance of DNZ was monitored at 285 nm, HBA at 242 nm, and VAN at 300 nm. For all cocrystals, the Waters' operation software Empower 2 was used to collect and process data.

Results

Solubilization ratios of cocrystals and drugs

Figure 4 shows the observed and predicted dependence of cocrystal solubilization ratio ($SR_{\text{cocrystal}}$) on drug solubilization ratio (SR_{drug}) for (1:1) and (2:1) cocrystals in several solubilizing agents. The (1:1) cocrystals included: carbamazepine-saccharin (CBZ-SAC), carbamazepine-salicylic acid (CBZ-SLC), piroxicam-saccharin (PXC-SAC), indomethacin-saccharin (IND-SAC), danazol-hydroxybenzoic acid (DNZ-HBA), danazol-vanillin (DNZ-VAN) and pterostilbene-caffeine (PTB-CAF). The (2:1) cocrystals included: carbamazepine-4-aminobenzoic acid monohydrate (CBZ-4ABA-HYD), carbamazepine-succinic acid (CBZ-SUC), and pterostilbene-piperazine (PTB-PIP). Solubilizing agents included: anionic surfactants (SLS, FeSSIF), nonionic surfactants (Tween 80, Myrj 52, and Brij 99), and a lipid formulation (Captex 355/Capmul MCM (1/3): Cremophor EL (3/7).

Logarithmic plots are presented since values range across 6 orders of magnitude for SR_{drug} and 4 orders of magnitude for $SR_{\text{cocrystal}}$. The cocrystal solubilization ratio for a 1:1 cocrystal is equal to square root of the drug solubilization ratio (equation 5), which in logarithmic form becomes

$$\text{Log} \left(\frac{S_T}{S_{aq}} \right)_{\text{cocrystal}} = \frac{1}{2} \text{Log} \left(\frac{S_T}{S_{aq}} \right)_{\text{drug}}$$

The line in Figure 4a has a slope of 1/2.

The 2:1 cocrystal solubilization ratio is equal to the drug solubilization ratio to the 2/3 power (equation 6) and in logarithmic form is

$$\text{Log} \left(\frac{S_T}{S_{aq}} \right)_{\text{cocrystal}} = \frac{2}{3} \text{Log} \left(\frac{S_T}{S_{aq}} \right)_{\text{drug}}$$

The line in Figure 4b has a slope of 2/3.

These plots reveal that (1) $SR_{\text{cocrystal}}$ is well approximated by SR_{drug} over a wide range of values for different drugs, cocrystals, and drug solubilizing agents assuming coformer solubilization is negligible, and that (2) 1:1 cocrystals are solubilized to a lesser extent than the 2:1 cocrystals for the same value of SR_{drug} .

Drug solubilizing agents with SR_{drug} values as high as 12,200 (PTB) and 20,000 (DNZ) resulted in $SR_{\text{cocrystal}}$ of 100 (1:1 PTB-CAF in lipids), 300 (1:1 DNZ-HBA and DNZ-VAN in Tween 80), and 500 (2:1 cocrystal PTB-PIP). Solubilization ratios of 2:1 cocrystals are well predicted for the systems studied, CBZ-SUC and CBZ-4ABA-HYD in SLS, and PTB-PIP in lipid-based media (Fig. 4b). The positive deviations observed for several 1:1 cocrystals at high values of SR_{drug} appear to be a result of coformer solubilization under the conditions studied, which will be further examined in a later section.

These results indicate that if drug solubilization is known then cocrystal solubilization can be calculated (under the same experimental conditions). Although small changes in coformer solubilization by the additive can result in deviations from predictions, the simple relationships presented can guide additive selection for cocrystal formulation and dissolution.

Prediction of cocrystal solubility ($S_{\text{cocrystal},T}$) in the presence of drug solubilizing agents

From the results of cocrystal and drug SR relationships presented above one can anticipate the impact that formulating poorly soluble drugs with very effective solubilizing agents may have on cocrystal solubility. An example of this analysis is applied to understanding the solubilization of PTB cocrystals in lipid-based solubilizers^{26, 28} (Table 1).

PTB is poorly water-soluble. Two cocrystals with caffeine and piperazine were shown to enhance the aqueous solubility of PTB by orders of magnitude^{26, 27}. However, this cocrystal solubility advantage was eliminated when cocrystals were formulated in a lipid system²⁸. In fact, the cocrystals became less soluble than PTB in the presence of these lipids. A key question to ask is whether this observation could have been predicted from the simple relationships presented here.

Cocrystal solubility in media containing drug solubilizing agents such as lipid-based systems can be obtained by rearranging equations 5 and 6 as follows, for a 1:1 cocrystal

$$S_{\text{cocrystal,T}} = S_{\text{cocrystal,aq}} \sqrt{\left(\frac{S_{\text{T}}}{S_{\text{aq}}}\right)_{\text{drug}}}$$

and for a 2:1 cocrystal

$$S_{\text{cocrystal,T}} = S_{\text{cocrystal,aq}} \left(\frac{S_{\text{T}}}{S_{\text{aq}}}\right)_{\text{drug}}^{\frac{2}{3}}$$

Once the cocrystal aqueous solubility and drug solubilization ratio are known then the cocrystal solubility in the media containing the solubilizing agents can be readily calculated.

For PTB-CAF (1:1 cocrystal) the solubility in the lipid formulation, $S_{\text{cocrystal,T}}$ is

$$S_{\text{cocrystal,T}} = S_{\text{cocrystal,aq}} \sqrt{\left(\frac{S_{\text{T}}}{S_{\text{aq}}}\right)_{\text{drug}}} = 2.19 \sqrt{1.22 \times 10^4} = 242 \text{ mM}$$

For PTB-PIP (2:1 cocrystal), $S_{\text{cocrystal,T}}$ is

$$S_{\text{cocrystal,T}} = S_{\text{cocrystal,aq}} \left(\frac{S_{\text{T}}}{S_{\text{aq}}}\right)_{\text{drug}}^{\frac{2}{3}} = 4.92 \times 10^{-1} (1.22 \times 10^4)^{\frac{2}{3}} = 261 \text{ mM}$$

The predicted cocrystal solubilities in the lipid formulation are in very good agreement with the measured values (222 and 246 mM) shown in Table 1. These simple relationships provide quantitative information about cocrystal solubility without the need of more rigorous equations (equations 1 or 14, for example) that require knowledge of equilibrium constants associated with the solution processes. The full equations are however valuable when the assumptions underlying the simple relationships are no longer warranted.

The PTB cocrystal formulation in lipid-based systems also teaches us about the ability of strong drug solubilizing agents to reverse the cocrystal solubility advantage over drug. The particular combination and concentration of lipids/surfactants in this formulation induced this reversal. Lower concentrations of these lipids/surfactants would have decreased the cocrystal solubility advantage without reversing it. This switch of cocrystal solubility over drug solubility has been shown for other cocrystals with solubilizing agents and indicates the existence of a cocrystal transition point.

Cocrystal transition points

Figures 5 and 6 show the transition points for several CBZ cocrystals in aqueous solutions of SLS. It is noted that two parameters characterize the transition point: (1) solubility at which

both drug and cocrystal exhibit the same solubility (S^*) and (2) solubilizing agent concentration (CSC). Our previous work focused on the CSC^{10–12, 18, 19}, here we will focus on S^* . One important observation that emerged from the present study is that aqueous solubility is a key indicator of the transition point. In fact, S^* as described in the theoretical section, is independent of the solubilizing agent, and is only determined by the drug and cocrystal aqueous solubilities.

S^* values in the following analysis were obtained by a graphical method from experimentally measured cocrystal and drug solubility dependence on solubilizing agent concentrations (Figures 5 and 6). These experimentally determined S^* values were then compared with those predicted by simple equations based on knowledge of drug and cocrystal aqueous solubilities.

S^* values, determined graphically from the intersection of solubility vs solubilizing agent curves for drug and cocrystal (Figures 5 and 6) are presented in Table 2. S^* is observed to increase with cocrystal aqueous solubility and with the molar content of drug in the cocrystal. For this small series of cocrystals the range of S^* is 4.6 to 47.6 mM. S^* can play an important role in cocrystal selection as it establishes the upper solubility limit at which a cocrystal has an advantage over drug in solutions with solubilizing agents.

S^* values were also predicted at a given solution pH from the simplified equations (equations 10 and 11 for 1:1 and 2:1 cocrystals, respectively) under the assumption that $K_{s, \text{coformer}} = 0$. As described in the methods section, $S_{\text{cocrystal, aq}}$ and $S_{\text{drug, aq}}$ were measured in aqueous solutions without solubilizing agents at a particular pH. $S_{\text{drug, aq}}$ is the CBZ dihydrate (CBZD) solubility since this is the thermodynamically stable form of CBZ under the experimental conditions studied.

Results in Table 2 indicate that there is excellent agreement between predicted and observed S^* values. The largest deviation was observed for the SLC cocrystal, where coformer solubilization leads to a positive deviation in predicted S^* . Deviations in S^* due to coformer solubilization are further examined in a subsequent section.

It is instructive to apply this analysis to estimate the S^* values of PTB cocrystals. S^* values of 59 mM (PTB-CAF) and 18 mM (PTB-PIP) were predicted, from equations 10 and 11, with values for the aqueous solubilities of drug and cocrystals presented in Table 1. Comparing the predicted S^* values with the PTB solubility in lipid-based media (1 M) reveals that the lipid mixture concentration used in the reported study was above the transition point for each cocrystal. This is also consistent with the observed cocrystal solubilities (222 mM and 246 mM) being lower than the PTB solubility (1 M) in the lipid formulation.

Comparing the S^* values for the CBZ and PTB cocrystals reveals that S^* increases with cocrystal solubility for the 1:1 and 2:1 cocrystals studied. S^* values are within the range of 4.6 to 59 mM for both CBZ and PTB cocrystals even though the aqueous solubility of CBZD is about 700 times higher than the solubility of PTB. S^* is inversely related to $S_{\text{drug, aq}}$ and proportional to $S_{\text{cocrystal, aq}}$ squared or cubed. PTB cocrystals have aqueous

solubilities higher than the CBZ cocrystals considered here, and compensate for the low aqueous solubility of PTB.

Solubilization ratio and cocrystal transition points

The relationships between cocrystal and drug solubilization ratios according to equations 5 and 6 and plotted in Figure 4 are useful to predict the $SR_{\text{cocrystal}}$ from knowledge of SR_{drug} but do not provide information about the cocrystal transition point and particularly S^* . The question is how to establish where a cocrystal stands with respect to its transition point in a given formulation or in the presence of solubilizing agents from knowledge of SR_{drug} and without having to measure $SR_{\text{cocrystal}}$.

The relationship between solubilization ratio (SR), cocrystal solubility advantage (SA) and transition point can be obtained by rewriting equation 5 for 1: 1 cocrystals as

$$\left(\frac{S_T}{S_{\text{aq}}}\right)_{\text{cocrystal}}^2 = \left(\frac{S_T}{S_{\text{aq}}}\right)_{\text{drug}}$$

and solving for $(SA)_{\text{aq}}$ to yield

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}}\right)_{\text{aq}} = \left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}}\right)_T \sqrt{\left(\frac{S_T}{S_{\text{aq}}}\right)_{\text{drug}}} \quad (18)$$

The criterion for the cocrystal transition point is that $S_{\text{cocrystal},T} = S_{\text{drug},T}$, therefore

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}}\right)_T = 1$$

and equation 18 becomes

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}}\right)_{\text{aq}} = \sqrt{\left(\frac{S_T^*}{S_{\text{aq}}}\right)_{\text{drug}}} \quad (19)$$

In other words, *at the transition point*

$$SA_{\text{aq}} = \sqrt{SR_{\text{drug}}^*} = SR_{\text{cocrystal}}^* \quad (20)$$

and the cocrystal solubility advantage over drug in aqueous media $(SA)_{\text{aq}}$ is equal to the square root of the drug solubilization ratio, $(SR_{\text{drug}})^{1/2}$, and to the cocrystal solubilization ratio ($SR_{\text{cocrystal}}$).

Below the cocrystal transition point $S^* > S_{\text{cocrystal},T} > S_{\text{drug},T}$ which means that

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_T > 1$$

Substituting the above equation into equation 18 leads to

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_{\text{aq}} > \sqrt{\left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}} \quad (21)$$

or

$$SA_{\text{aq}} > SR_{\text{cocrystal}} \quad (22)$$

which is indicative of a cocrystal that is below its transition point and thus will possess a higher solubility than the drug in the solubilizing media.

The expression for a 2:1 cocrystal is obtained by a similar analysis where equation 6 yields

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_{\text{aq}} = \left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_T \left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}^{\frac{1}{3}} \quad (23)$$

A 2:1 cocrystal is then at the transition point when

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_{\text{aq}} = \left(\frac{S_T^*}{S_{\text{aq}}} \right)_{\text{drug}}^{\frac{1}{3}} \quad (24)$$

or

$$SA_{\text{aq}} = SR_{\text{drug}}^{\frac{1}{3}} = \sqrt{SR_{\text{cocrystal}}^*} \quad (25)$$

Cocrystal is below the transition point when

$$\left(\frac{S_{\text{cocrystal}}}{S_{\text{drug}}} \right)_{\text{aq}} > \left(\frac{S_T}{S_{\text{aq}}} \right)_{\text{drug}}^{\frac{1}{3}} \quad (26)$$

or

$$SA_{aq} > \sqrt{SR_{cocrystal}} \quad (27)$$

Applying this analysis to DNZ cocrystals in Tween 80 and PTB cocrystals in lipid-based media (Figure 7) demonstrates the important role of cocrystal solubility advantage ($SA_{aq} = (S_{cocrystal}/S_{drug})_{aq}$) in determining the position of the cocrystal solubility with respect to the transition point and S^* . For instance, it can be seen that both DNZ cocrystals meet the criteria for being below the transition point in 150 mM Tween 80 since $SA_{aq} > \sqrt{SR_{cocrystal}}$. SA_{aq} values for the two DNZ cocrystals (770 and 370) are greater than their SR values (264 and 300), indicating that the DNZ cocrystals are below the transition point (at this concentration of Tween 80). PTB cocrystals are however above the transition point in the lipid mixture²⁸ since $SA_{aq} < \sqrt{SR_{cocrystal}}$ for the 1:1 cocrystal ($26 < 100$), and $SA_{aq} < \sqrt{SR_{cocrystal}^{1/2}}$ for the 2:1 cocrystal ($6 < 22$). These findings are in excellent agreement with the observed cocrystal and drug solubility behavior as explained by the transition points.

Whether a cocrystal is above or below the transition point in a given formulation, can be determined by comparing the S^* value with the cocrystal solubility in the formulation. S^* values for the cocrystals studied are between 16 and 94mM indicating the adjustments that could be made in drug solubilizing agent concentration to move closer to or further away from the transition point.

Influence of coformer solubilization

As shown in Figure 4a, some of the observed $SR_{cocrystal}$ values are higher than those predicted from SR_{drug} using equation 5 as for DNZ-HBA and DNZ-VAN in 150 mM Tween 80, and IND-SAC at increasing concentrations of Tween 80, Brij 99, Myrj 52. Under these conditions, $K_s^{coformer} > 0$ and $\epsilon > 1$, leading to an underprediction of $SR_{cocrystal}$ when coformer solubilization is ignored.

Deviations in $SR_{cocrystal}$ for a 1:1 cocrystal due to coformer solubilization can be accounted for by the factor ϵ . The value of ϵ can be calculated from equation 17 and by comparing the experimental and predicted $SR_{cocrystal}$ according to

$$\sqrt{\epsilon} = \frac{SR_{cocrystal,observed}}{SR_{cocrystal,predicted}} \quad (28)$$

where $SR_{cocrystal}$ is predicted from equation 5 and the observed $SR_{cocrystal}$ is obtained from experimental measurements of cocrystal solubility with and without solubilizing agents.

The ϵ values obtained from the two methods are shown in Table 3 and are in excellent agreement. Ignoring ϵ can lead to underpredicting $SR_{cocrystal}$ by as much as 2 fold for the solubilizing agents studied and for their high concentrations and/or high $K_s^{coformer}$ values.

The value of ϵ can also be obtained from deviations in S^* due to coformer solubilization according to

$$\varepsilon = \frac{S^*_{\text{observed}}}{S^*_{\text{predicted}}} \quad (29)$$

where S^* is predicted using equation 10 assuming $K_s^{\text{coformer}} = 0$. Table 4 shows the ε values obtained using equations 17 and 29. S^* is influenced by coformer solubilization to a greater extent than SR, since SR has a square root dependence on ε (equation 15) whereas S^* is linearly dependent on ε (equation 16).

Figure 8 demonstrates the sensitivity of S^* on coformer solubilization by solubilizing agent, represented by the parameter ε . The S^* values for CBZ cocrystals are well predicted when ε is taken into account for SAC and SLC solubilization (which have nonzero K_s^{coformer} values) in SLS as shown in Table 4. Thus, small solubilization of cofomers (compared to drug) can have a significant influence on S^* .

Conclusions

This manuscript presents key findings of cocrystal transition point properties, measurement, and prediction. We have discovered that cocrystal transition points are defined by two parameters: (1) a solubility value (S^*) and (2) a CSC. An important property of S^* is that it is determined by the cocrystal and drug aqueous solubilities (and does not involve any parameters associated with solubilizing agents as long as coformer solubilization by the agent is negligible). This means that once cocrystal and drug solubilities in aqueous media are known at a particular temperature and pH, then S^* can be estimated from the equations derived in this work. Knowledge of S^* for a given cocrystal will guide the selection and concentrations of solubilizing agents since S^* has associated CSCs. A key consequence of this work is that the influence of drug solubilizing agents on cocrystal solubility is greatly simplified.

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Figure 1. Dependence of $SR_{cocrystal}$ on SR_{drug} according to equations 5 and 6 for cocrystal stoichiometries 1:1 (—) and 2:1 (----), using typical range of SR_{drug} values.

Figure 2.

Transition points (S^* and CSC) for a cocrystal (—) and its constituent drug cocrystal (red line) and its constituent drug (blue line) in two different solubilizing agents, a and b . S^* is constant and CSC varies with the extent of drug solubilization by the solubilizing agent. Drug is solubilized to a greater extent by a than by b and thus $CSC_a < CSC_b$. The curves were generated from equations 3 and 4 with parameter values $S_{\text{drug,aq}} = 0.5 \text{ mM}$, $S_{\text{cocrystal,aq}} = 2.4 \text{ mM}$ ($K_{\text{sp}} = 5.76 \text{ mM}^2$), $K_s^{\text{drug}} = 1.5 \text{ mM}^{-1}$ and 0.5 mM^{-1} for solubilizing agents a and b , respectively.

Figure 3. Graphical representation of S^* as a function of cocrystal and drug aqueous solubilities (mM) for a 1:1 cocrystal, according to equation 10 using typical values for drug and cocrystal solubilities. S^* is reached at the transition point when cocrystal and drug solubilities become equal.

Figure 4.

$SR_{\text{cocrystal}}$ dependence on SR_{drug} for (a) 1:1 cocrystals and (b) 2:1 cocrystals. Lines represent theoretical relationships between $SR_{\text{cocrystal}}$ and SR_{drug} according to equations 5 and 6 in log form for 1:1 and 2:1 cocrystals, respectively. The slope of the line is predicted to be 1/2 for 1:1 cocrystals and 2/3 for 2:1 cocrystals. Symbols represent experimentally determined SR values from cocrystal and drug solubilities measured under equilibrium conditions in solubilizing agents as indicated in the legend.

Figure 5.

Solubilities and transition points of CBZ cocrystals and CBZ dihydrate induced by SLS preferential solubilization of CBZ for (a) CBZ-SAC, (b) CBZ-4ABA-HYD, and (c) (CBZ-SUC). Adapted from reference 12. Transition points are characterized by a solubility (S^*) and a solubilizing agent concentration (CSC). Both S^* and CSC vary with cocrystal aqueous solubility and stoichiometry. Symbols represent experimentally measured cocrystal (O) and drug (Δ) solubility values¹². Lines were generated from the more rigorous solubility equations presented in reference 12.

Figure 6.

Solubilities and transition points of CBZ-SLC cocrystal and CBZ dihydrate induced by SLS preferential solubilization of CBZ. Adapted from reference 12. SLC was found to influence the CMC of SLS, raising it from 6 mM to 9 mM. This had a minor impact on the CSC (20–23 mM) and no impact on S^* . Symbols represent experimentally measured cocrystal (○) and drug (△) solubility values¹². Lines were generated from the more rigorous solubility equations presented in reference 12.

Figure 7.

Measured solubilities for DNZ and PTB and their cocrystals in aqueous solutions with and without solubilizing agents: Tween 80 aqueous solution (150 mM, pH 5.0) for DNZ and lipid mixture for PTB. PTB solubility values were obtained from references 26–28. How to determine where a cocrystal stands with respect to its transition point in a given formulation or in the presence of solubilizing agents from knowledge of SR_{drug} and without having to measure $SR_{cocrystal}$ is described in the text. Numbers in parentheses represent SR values, and numbers within the lines represent SA_{aq} . Transition point solubilities, S^* , were calculated from equation 10 for 1:1 DNZ and PTB cocrystals, and equation 11 for the 2:1 PTB-PIP cocrystal with the measured values of $S_{drug,aq}$ and $S_{cocrystal,aq}$.

Figure 8.

Influence of coformer solubilization, represented by ϵ , on the S^* dependence on $S_{\text{cocrystal,aq}}$ for CBZ-SLC (Δ), CBZ-SAC ($\circ$), CBZ-4ABA-HYD ($\square$), CBZ-SUC ($\diamond$) in SLS. $\epsilon=1$ when coformer is not solubilized by solubilizing agents. $\epsilon>1$ as coformer is solubilized. S^* is simulated using equation 16 for 1:1 (—), and equation 11 for 2:1 (---) cocrystals, with drug and cocrystal solubility values reported in Table 2, and predicted ϵ values in Table 4. For 2:1 cocrystals, $\epsilon=1$ since neither SUC or 4ABA were solubilized by SLS¹².

Table 1

Comparison of experimental and predicted PTB cocrystal solubilities in lipid-based formulations.

Solid phase	Aqueous solubility ^a S_{aq} (mM)	Experimental Total solubility in lipid ^b S_T (mM)	Predicted Total cocrystal solubility in lipid ^c S_T (mM)
PTB	0.0819	1002	
PTB-CAF (1:1)	2.19	222	242
PTB-PIP (2:1)	0.492	246	261

^{a)} From references 24 and 25.

^{b)} From reference 26.

^{c)} Calculated from equations 5 and 6 for 1:1 and 2:1 cocrystals as described in the text.

Table 2

Predicted and observed S^* values for CBZ cocrystals in aqueous solutions of SLS.

Cocrystal	pH	$S_{\text{cocrystal, aq}}^a$ (mM)	$S^*_{\text{pred}}^b$ (mM)	$S^*_{\text{obs}}^c$ (mM)
CBZ-SLC (1:1)	3.0	1.32 ± 0.06	3.3	4.6
CBZ-SAC (1:1)	2.2	2.36 ± 0.05	10.5	12.0
CBZ-4ABA-HYD (2:1)	4.0	1.83 ± 0.02	21.8	22.0
CBZ-SUC (2:1)	3.1	2.38 ± 0.02	48.0	47.6

^{a)} Solubility values at 25°C from reference 13, in terms of CBZ mM.

^{b)} Predicted from equations 10 and 11 for 1:1 and 2:1 cocrystals with $S_{\text{CBZD, aq}} = 0.53$ mM.

^{c)} Determined from the intersection of $S_{\text{cocrystal, T}}$ and $S_{\text{drug, T}}$ curves in Figures 5 and 6.

Table 3

SR_{cocrystal} deviations due to coformer solubilization.

Cocrystal	pH	Solubilizing agent	(K _s ^{coformer}) ^a (mM ⁻¹)	Concentration of solubilizing agent ^b (mM)	e ^{1/2} pred ^c	e ^{1/2} exp ^d
DNZ-VAN	5.02	Tween 80	0.0283±0.0009	150	2.28	2.14
DNZ-HBA	4.42	Tween 80	0.031±0.001	150	1.87	1.88
IND-SAC	2.1	Myrj 52	0.083±0.007	100	1.73	1.72
IND-SAC	2.1	Tween 80	0.059±0.003	124	1.66	1.69
IND-SAC	2.1	Brij 99	0.058±0.004	121	1.64	1.70
IND-SAC	2.1	SLS	0.008±0.002	199	1.18	1.17

^a) K_s^{coformer} for HBA and VAN were experimentally measured in this work and K_s^{coformer} for SAC reported in reference 21.

^b) Solubilizing agent concentration is the highest concentration studied for each system.

^c) Predicted using equation 17 with pKa HBA = 4.48, pKa VAN = 7.4, and pKa SAC = 1.6.

^d) Calculated using equation 28.

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Table 4

S* deviations due to coformer solubilization.

Co-crystal	pH	(K _s ^{coformer}) ^a (mM ⁻¹)	[SL _S] at CSC ^a (mM)	e _{pred} ^b	e _{exp} ^c
CBZ-SLC (1:1)	3.0	0.06	23	1.44	1.40
CBZ-SAC (1:1)	2.2	0.013	44	1.10	1.14

^{a)}Values reported in reference 13.

^{b)}Predicted using equation 17 with pKa SLC = 3.0 and pKa SAC = 1.6.

^{c)}Calculated from equation 29.