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PAPER

Engineering cocrystal thermodynamic stability and eutectic points by micellar solubilization and ionization†

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Pharmaceutical cocrystals are of great interest because of their potential to enhance solubility and bioavailability of poorly water-soluble drugs. Cocrystal development is however limited by their poor thermodynamic stability in aqueous environments. The work presented here describes the mechanisms by which cocrystal stability can be fine-tuned *via* micellar solubilization and ionization of cocrystal components. An important feature of cocrystal solution equilibria is the existence of eutectic points involving coexistence of three phases, a liquid and two solids. The solution composition at the eutectic points is a critical parameter that defines the conditions of thermodynamic stability. Equations that describe the sensitivity of eutectic points and phase diagrams to micellar surfactants and pH are presented. Predictions are in excellent agreement with the behavior of several carbamazepine cocrystals in aqueous solutions of sodium lauryl sulfate. Increasing the magnitude of micellar solubilization for one of the cocrystal components is found to confer greater thermodynamic stability to the cocrystal and expand its stability region. These findings provide an unprecedented level of control over cocrystal-solution phase behavior, and are applicable to multiple additives and solubilization mechanisms that may be required for the stabilization of highly soluble cocrystals.

Introduction

The ability to engineer the thermodynamic stability of cocrystals has important implications for the control and use of cocrystals in various industries and for the development of drug delivery systems in the pharmaceutical industry. Though surfactants have been widely investigated as a means to increase the solubility of hydrophobic drugs,[1–4] we recently demonstrated that surfactants can impart thermodynamic stability to cocrystals relative to drug crystal, and this behavior is dependent on surfactant concentration and pH.[5–7] Surfactants that have differential affinities for cocrystal components have the potential to reverse the thermodynamic stabilities of cocrystal and its components at a surfactant concentration called the *critical stabilization concentration* (CSC). The underlying mechanism for the CSC is the enrichment of the aqueous phase with the most soluble component (*i.e.* coformer) as the least soluble cocrystal component (*i.e.* drug) is preferentially solubilized by the micelles. A model was developed that explained cocrystal solubility, CSC, and pH_{max} based on cocrystal dissociation, component ionization, and micellar solubilization equilibria.[7]

The purpose of this work is to understand the role of micellar solubilization and ionization in altering cocrystal stability regions and to develop mathematical equations that predict cocrystal eutectic point behavior from experimentally accessible thermodynamic parameters; this enables fine-tuning cocrystal phase behavior based on a mechanistic understanding of cocrystal solution chemistry.

Eutectic points, also referred to as transition concentrations, offer an experimentally accessible method to assess cocrystal solubility and stability regardless of the solubility relationship between cocrystal and drug.[5,8,9] A cocrystal eutectic point is a point where two solids (one of which is cocrystal) and a solution coexist in equilibrium.

The solution conditions that favor transformation from cocrystal to drug (and *vice versa*) can be quantified by examining the solution concentrations of drug and coformer at the eutectic point as a function of micellar surfactant at a given temperature and pH. Equations are developed that describe the eutectic concentrations of drug and coformer in micellar solutions by considering the equilibria of the partitioning of drug and coformer between aqueous and micellar pseudophases. The eutectic concentrations of drug and coformer in micellar solutions are a function of their respective eutectic concentrations in pure water (or submicellar surfactant concentrations), component pK_a(s), solution pH, and K_s for the individual cocrystal components.

A eutectic constant K_{eu} (ratio of coformer to drug concentration at the eutectic) can be calculated that describes cocrystal thermodynamic stability relative to drug.[10] Eutectic constants are commonly applied to mixtures of racemic compounds with

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enantiomer and were recently adapted to other cocrystal systems.[11,12] This work extends the theoretical framework for eutectic points and K_{eu} to micellar systems and demonstrates for the first time their ability to tailor regions of stability according to ionization and micellar solubilization equilibria.

Model equations are derived for cocrystals of CBZ (non-ionizable, hydrophobic drug) with several ionization properties and stoichiometries. These cocrystals include 1 : 1 carbamazepine-salicylic acid (CBZ-SLC), 1 : 1 carbamazepine-saccharin (CBZ-SAC), 2 : 1 carbamazepine-succinic acid (CBZ-SUC), and 2 : 1 carbamazepine-4-aminobenzoic acid monohydrate (CBZ-4ABA-HYD). Salicylic acid and saccharin are monoprotic weak acids; salicylic acid has a reported pK_a of 3.0, saccharin has a range of reported pK_a values between 1.8 and 2.2.[13–15] Succinic acid is a diprotic weak acid with pK_a values of of 4.1 and 5.6.[16] 4-aminobenzoic acid is amphoteric with pK_a values of 2.6 and 4.8.[17]

Theoretical

The work presented here develops a mathematical model to predict the dependence of cocrystal eutectic points on ionization and micellar solubilization. This identifies the solution conditions where cocrystal is thermodynamically stable by considering the partitioning of drug and coformer into micelles. It is based on relatively simple solution phase equilibria and equilibrium constants for the cocrystal components that are experimentally accessible or available in the literature. A quantitative model for cocrystal solubility was presented previously and demonstrated that cocrystal solubility relative to drug crystal varies as a function of surfactant concentration.[7] Knowledge of cocrystal eutectic points is of critical importance during cocrystal synthesis, processing, and performance.

Cocrystal eutectic point dependence on micellar solubilization

Eutectic points as critical indicators of cocrystal solubility have been discussed thoroughly elsewhere.[5,8] The solution composition at the eutectic is independent of the mass of each phase at equilibrium, which has several important features: (1) indicates the thermodynamic stability of cocrystal relative to drug crystal, (2) enables estimation of cocrystal solubility in solution compositions where cocrystal is unstable, and (3) provides insight into solute-solute or solute–solvent interactions between drug, coformer, and solvent.

At least two eutectic points exist for a cocrystal, which are differentiated by the phases at equilibrium. E_1 refers to the eutectic between solid drug, cocrystal, and solution, and E_2 refers to the eutectic between solid coformer, cocrystal, and solution. Other eutectic points have been reported in the literature, such as between cocrystals of different stoichiometry.[9] The focus of this work is on E_1, which is of particular importance to cocrystals of poorly soluble drugs in aqueous solutions because it describes the conditions under which a cocrystal can transform to a less soluble crystalline drug form. The analyses presented here can be generalized to other solubilization mechanisms such as mixed micelles or complexation, though the equations may be of a different nature.

For a 1 : 1 cocrystal RHA whose components are R (non-ionizable drug) and HA (monoprotic, weakly acidic coformer), E_1 is described by

$$RHA_{solid} + R_{solid} \rightleftharpoons R_{aq} + HA_{aq} \quad (1)$$

and E_2 by

$$RHA_{solid} + HA_{solid} \rightleftharpoons R_{aq} + HA_{aq} \quad (2)$$

The solution phase equilibria that govern cocrystal solubility are given by

$$RHA_{solid} \overset{K_{sp}}{\rightleftharpoons} R_{aq} + HA_{aq} \quad (3)$$

$$HA_{aq} \overset{K_a^{HA}}{\rightleftharpoons} A^-_{aq} + H^+_{aq} \quad (4)$$

$$R_{aq} + M \overset{K_s^{R}}{\rightleftharpoons} R_m \quad (5)$$

$$HA_{aq} + M \overset{K_s^{HA}}{\rightleftharpoons} HA_m \quad (6)$$

$$A^-_{aq} + M \overset{K_s^{A^-}}{\rightleftharpoons} A^-_m \quad (7)$$

where aq refers to aqueous and m refers to micellar. K_{sp} is the cocrystal solubility product. K_a is the acid dissociation constant. M is micellar surfactant. K_s^R, K_s^{HA}, and K_s^{A-} are the micellar solubilization constants for R, HA, and A^- respectively. For the sake of simplicity this model assumes no solution complexation between drug and coformer, though theoretical treatments of such equilibria have been addressed elsewhere.[10,18,19]

The equilibrium constants that describe eqn (3)–(7) are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \quad (8)$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \quad (9)$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \quad (10)$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \quad (11)$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \quad (12)$$

where brackets refer to concentrations with recognition that under dilute solution conditions they approximate activities. K_s and K_a values are assumed to be independent of solution composition.

Total cocrystal solubility $S_{RHA,T}$, in terms of the total drug concentration at equilibrium $[R]_T$, is given by the sum of aqueous and micellar drug in solution,

$$S_{RHA,T} = [R]_T = [R]_{aq} + [R]_m \quad (13)$$

By considering the equilibrium constants in eqn (8) and (10), eqn (13) becomes

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$$[R]_T = \frac{K_{sp}}{[HA]_{aq}}(1 + K_s^R[M]) \quad (14)$$

The mass balance on coformer is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \quad (15)$$

Substituting eqn (9), (11) and (12) into (15),

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right) \quad (16)$$

Combining eqn (14) and (16),

$$S_{RHA,T} = [R]_T = \frac{K_{sp}}{[A]_T}(1 + K_s^R[M])\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right) \quad (17)$$

If the ionized species interacts more favorably with the aqueous environment than the micellar environment such that $K_s^{HA} \gg K_s^{A-}$, eqn (17) can be simplified to

$$S_{RHA,T} = [R]_T = \frac{K_{sp}}{[A]_T}(1 + K_s^R[M])\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \quad (18)$$

unless the ionized species is present at very high concentrations.[20,21]

The total cocrystal solubility in a solution of stoichiometric concentrations of drug and coformer ($S_{RHA,T}$*), is a special case of eqn (18) when $[R]_T = [A]_T$,

$$S_{RHA,T}* = \sqrt{K_{sp}(1 + K_s^R[M])\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right)} \quad (19)$$

A detailed discussion of micellar solubilization and ionization effects on cocrystal stoichiometric solubilities was presented previously.[5,7]

At eutectic point E_1 the solution is saturated with drug and cocrystal. E_1 is characterized by the solution concentrations of drug and coformer and is another special case of eqn (18) when $[R]_T = S_{R,T}$. The concentration of drug at the eutectic point, $[R]_{eu,T}$, is given by

$$[R]_{eu,T} = S_{R,T} \quad (20)$$

where $S_{R,T}$ is the solubility of drug R in the eutectic micellar solution. Assuming that the coformer does not affect the solubilization mechanisms of drug (and *vice versa*), then $S_{R,T}$ is simply the solubility of the drug R in a micellar solution.

The influence of micellar surfactant concentration on solubilization of hydrophobic drugs is well documented in the literature and is given by

$$S_{R,T} = S_{R,aq}(1 + K_s^R[M]) \quad (21)$$

where $S_{R,aq}$ is the aqueous solubility of drug R.[1–4,22,23] Therefore, by combining eqn (20) and (21),

$$[R]_{eu,T} = S_{R,aq}(1 + K_s^R[M]) \quad (22)$$

The total concentration of coformer at the eutectic point, $[A]_{eu,T}$, is obtained by combining eqn (18) and (22).

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \quad (23)$$

Cocrystal stoichiometric solubility can be related to the eutectic solution concentrations of drug and coformer by combining eqn (19), (22), and (23) to give

$$S_{RHA,T}* = \sqrt{[R]_{eu,T}[A]_{eu,T}} \quad (24)$$

Eqn (24) is specific to cocrystal stoichiometry (1 : 1) but general for ionization and micellar solubilization properties. For a 2 : 1 cocrystal (*e.g.* R_2H_2A with drug R and diprotic acid H_2A),

$$S_{R_2H_2A,T}* = \sqrt{\frac{[R]_{eu,T}[A]_{eu,T}}{4}} \quad (25)$$

$[R]_{eu,T}$ and $[A]_{eu,T}$ at a chosen $[H^+]$ (denoted by $[H^+]_T$) can be rewritten in terms of the drug and coformer concentrations and $[H^+]$ at the eutectic in water (denoted by $[R]_{eu,aq}$, $[A]_{eu,aq}$, and $[H^+]_{aq}$). Thus

$$[R]_{eu,T} = [R]_{eu,aq}(1 + K_s^R[M]) \quad (26)$$

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \frac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a^{HA}}{[H^+]_{aq}}}\right) \quad (27)$$

Eqn (26) and (27) show that the full dependence of the cocrystal eutectic point on pH and surfactant concentration can be calculated from a eutectic point measurement in water at a single pH, provided K_s and K_a for the cocrystal components are known. Eutectic concentrations of drug and coformer for cocrystals of different stoichiometries and ionization properties are shown in Table 1.

Fig. 1 shows the predicted dependence of drug and coformer eutectic concentrations on surfactant concentration for a cocrystal RHA according to eqn (26) and (27). Different dependencies of $[R]_{eu,T}$ and $[A]_{eu,T}$ on surfactant concentration are a consequence of differential solubilization of the cocrystal components ($K_s^R \gg K_s^{HA}$). The surfactant concentration where $[R]_{eu,T} = [A]_{eu,T}$ indicates the critical stabilization concentration (CSC) for cocrystal RHA. At the CSC, a liquid phase of equal molar ratio as the cocrystal is necessary for cocrystal to be thermodynamically stable. At the CSC for a 2 : 1 cocrystal, $0.5[R]_{eu,T} = [A]_{eu,T}$. Drug-rich stoichiometries require more drug to be solubilized by the micelles to achieve the coformer enrichment in the aqueous phase that is responsible for the CSC.

Though E_2 is less discussed in the pharmaceutical cocrystal literature than other eutectic points, similar methods can be used to calculate its dependence on surfactant concentration from eqn (18). At E_2, eqn (20) no longer applies because drug crystal is not one of the solid phases at equilibrium. Instead, the relevant solution condition at E_2 is that the total coformer concentration at the eutectic $[A]_{eu,T}$ is equal to the total solubility of the coformer in the eutectic micellar solution $S_{A,T}$,

$$[A]_{eu,T} = S_{A,T} \quad (28)$$

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Table 1 Equations that describe drug and coformer eutectic concentrations in micellar solutions at $[H^+]_T$, in terms of drug and coformer eutectic concentrations in pure water at $[H^+]_{aq}$, K_a and K_s of the cocrystal components, and micellar surfactant concentration [M][a]

Cocrystal	Drug eutectic concentration	Eqn	Coformer eutectic concentration	Eqn
RHA 1 : 1 nonionizable : monoprotic acidic	$[R]_{eu,T} = [R]_{eu,aq}(1 + K_s^R[M])$	(26)	$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \frac{K_a}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a}{[H^+]_{aq}}}\right)$	(27)
HXHA 1 : 1 monoprotic acidic : monoprotic acidic	$[X]_{eu,T} = [X]_{eu,aq}\left(\frac{1 + \frac{K_a^{HX}}{[H^+]_T} + K_s^{HX}[M]}{1 + \frac{K_a^{HX}}{[H^+]_{aq}}}\right)$	(32)	$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \frac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(33)
BHA 1 : 1 monoprotic basic : monoprotic acidic	$[B]_{eu,T} = [B]_{eu,aq}\left(\frac{1 + \frac{[H^+]_T}{K_a^B} + K_s^B[M]}{1 + \frac{[H^+]_{aq}}{K_a^B}}\right)$	(34)	$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \frac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(35)
R_2H_2A 2 : 1 nonionizable : diprotic acidic	$[R]_{eu,T} = [R]_{eu,aq}(1 + K_s^R[M])$	(36)	$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \frac{K_a^{H_2A}}{[H^+]_T} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2} K_s^{H_2A}[M]}{1 + \frac{K_a^{H_2A}}{[H^+]_{aq}} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right)$	(37)
R_2HAB 2 : 1 nonionizable : amphoteric	$[R]_{eu,T} = [R]_{eu,aq}(1 + K_s^R[M])$	(38)	$[AB]_{eu,T} = [AB]_{eu,aq}\left(\frac{1 + \frac{[H^+]_T}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]_T} K_s^{HAB}[M]}{1 + \frac{[H^+]_{aq}}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]_{aq}}}\right)$	(39)

[a] Subscript aq refers to values measured in submicellar concentrations of surfactant.

Assuming the solubilization mechanisms of drug and coformer are mutually independent, then $S_{A,T}$ is equal to the total solubility of the coformer in micellar solution.

$$S_{A,T} = S_{HA,aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \quad (29)$$

where $S_{HA,aq}$ is the intrinsic solubility of the weakly acidic coformer. Eqn (28) and (29) combine to give

$$[A]_{eu,T} = S_{HA,aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \quad (30)$$

Substituting (30) into (18) gives $[R]_{eu,T}$ at E_2.

$$[R]_{eu,T} = \frac{K_{sp}}{S_{HA,aq}}(1 + K_s^R[M]) \quad (31)$$

If eqn (30) and (31) are rewritten in terms of $[R]_{eu,aq}$ and $[A]_{eu,aq}$ at E_2, then the same equations as (26) and (27) are obtained. Thus, eqn (26) and (27) apply to both E_1 and E_2.

Eutectic constant K_{eu}

For a cocrystal RHA, at constant temperature and pH, K_{eu} is defined as

$$K_{eu} \equiv \frac{a_{A,eu}}{a_{R,eu}} \quad (40)$$

where $a_{A,eu}$ and $a_{R,eu}$ are the activities of coformer and drug in solution at the eutectic point. Eutectic constants have been discussed in the literature concerning enantiomeric purification and stability of racemic compounds but were recently applied to cocrystal systems.[10–12]

K_{eu} in the context of cocrystals has been shown to describe cocrystal thermodynamic stability relative to drug.[10] K_{eu} is determined under equilibrium conditions, though it is not a true equilibrium constant (such as eqn (3)–(7)). Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \quad (41)$$

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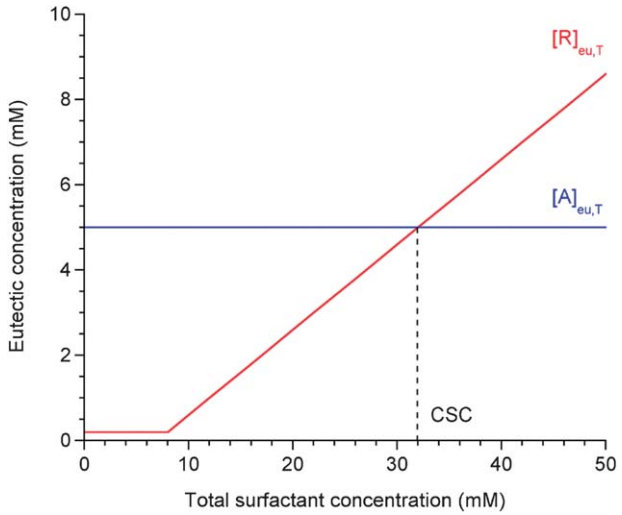

Fig. 1 Eutectic concentrations of drug ($[R]_{eu,T}$) and coformer ($[A]_{eu,T}$) as a function of surfactant concentration under nonionizing conditions. Predicted according to eqn (26) and (27) for cocrystal RHA at eutectic point E_1. The CSC for a 1 : 1 cocrystal is given by the surfactant concentration where $[R]_{eu,T} = [A]_{eu,T}$. $K_{sp} = 1\ mM^2$ ($S_{RHA,aq}/S_{R,aq} = 5$), $[R]_{eu,aq} = 0.2$ mM, $[A]_{eu,aq} = 5$ mM, $K_s^R = 1\ mM^{-1}$, $K_s^{HA} = 0$, CMC = 8 mM.

K_{eu} can be related to the ratio of cocrystal stoichiometric solubility to drug solubility. This can be accomplished when $[R]_{eu,T} = S_{R,T} = [R]_{aq} + [R]_m$ and $[A]_{eu,T} = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m$, indicating that ionization and micellar solubilization are the only mechanisms of solubilization. For a 1 : 1 cocrystal (*e.g.* RHA) eqn (22) and (23) can be substituted into (41) to yield

$$K_{eu} = \frac{K_{sp}}{S_{R,aq}{}^2}\left(\frac{1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]}{1 + K_s^R[M]}\right) \quad (42)$$

Eqn (42) can be combined with (19)–(21),

$$K_{eu} = \left(\frac{S_{RHA,T}*}{S_{R,T}}\right)^2 \quad (43)$$

which relates K_{eu} to the cocrystal to drug solubility ratio. For a 2 : 1 cocrystal (*e.g.* R_2H_2A),

$$K_{eu} = \frac{1}{2}\left(\frac{S_{R_2H_2A,T}*}{S_{R,T}}\right)^3 \quad (44)$$

where $S_{R_2H_2A,T}*$ is cocrystal R_2H_2A solubility under stoichiometric conditions in terms of drug concentration.

$K_{eu} \leq 1$ indicates that cocrystal is thermodynamically stable in stoichiometric solutions of drug and coformer. Likewise, 2 : 1 cocrystals achieve thermodynamic stability at $K_{eu} \leq 0.5$. The surfactant concentration and pH that achieve $K_{eu} = 1$ for a 1 : 1 cocrystal ($K_{eu} = 0.5$ for a 2 : 1 cocrystal) are the CSC and pH_{max} respectively.

K_{eu} in micellar solutions ($K_{eu,T}$) at $[H^+]_T$ can be expressed in terms of K_{eu} measured in pure water ($K_{eu,aq}$) at $[H^+]_{aq}$. Combining eqn (26), (27) and (41),

$$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1 + K_s^R[M]}\right)\left(\frac{1 + \frac{K_a}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a}{[H^+]_{aq}}}\right) \quad (45)$$

where $K_{eu,aq} = [R]_{eu,aq}/[A]_{eu,aq}$, or the K_{eu} of the cocrystal in water at $[H^+]_{aq}$. Eqn (45) predicts that $K_{eu,T}$ can either increase or decrease (as does the cocrystal to drug solubility ratio) as a function of surfactant concentration, depending on K_s^R and K_s^{HA}.

Fig. 2 shows the dependence of the cocrystal to drug solubility ratio and $K_{eu,T}$ on surfactant concentration in the absence of ionization effects. The parameter values used in this simulation are typical of cocrystals of hydrophobic drugs such as CBZ.

Fig. 2 shows that if the reduction in $K_{eu,T}$ is sufficient, a CSC exists where $K_{eu,T} = 1$. Equations that describe CSC as a function of K_{eu} are discussed in a subsequent section. It is notable that micellar solubilization is most effective in reducing the cocrystal to drug solubility ratio at surfactant concentrations very close to the CMC. Therefore, consideration of $K_{eu,T}$ plays an important role in micellar solutions even at surfactant concentrations far below the CSC.

$K_{eu,T}$ depends on two main factors: cocrystal solubility relative to drug in water (calculated from $K_{eu,aq}$) and micellar solubilization of cocrystal components (K_s^R and K_s^{HA}). Fig. 3 shows the predicted influence of cocrystal aqueous solubility and K_s^R on $K_{eu,T}$ and the cocrystal to drug solubility ratio according to eqn (43) and (45). Fig. 3 shows that (1) cocrystals with higher aqueous solubilities relative to drug, or larger $K_{eu,aq}$, require higher surfactant concentrations to achieve the CSC, (2) cocrystals with high K_s^R require lower surfactant concentrations to achieve the CSC, and (3) cocrystals highly soluble relative to drug and/or have high K_s^R values are the most susceptible to

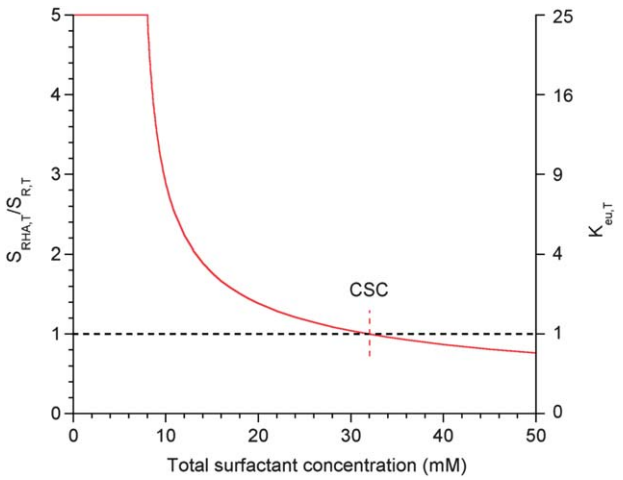

Fig. 2 Dependence of cocrystal to drug solubility ratio and K_{eu} on surfactant concentration according to eqn (43) and (45) for a 1 : 1 cocrystal RHA. $K_{eu,T}$ decreases as surfactant concentration increases, indicating that the cocrystal to drug solubility ratio is decreasing. CSC can be estimated from $K_{eu,aq}$ and K_s for the cocrystal components. Simulated under nonionizing conditions, with no interactions beyond micellar solubilization. $K_{sp} = 1\ mM^2$, $K_{eu,aq} = 25$ ($S_{RHA,aq}/S_{R,aq} = 5$), $S_{R,aq} = 0.2$ mM, $K_s^R = 1\ mM^{-1}$, $K_s^{HA} = 0$, and CMC = 8 mM.

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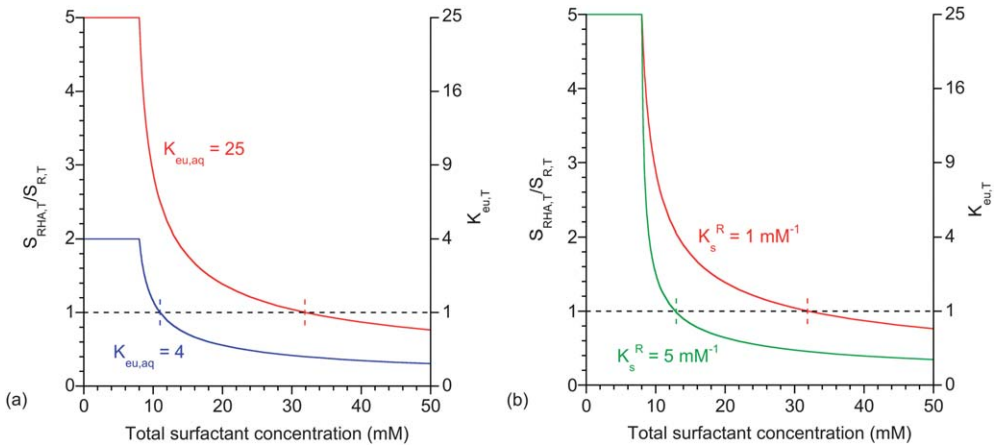

Fig. 3 Influence of cocrystal aqueous solubility and micellar solubilization on $K_{eu,T}$ and CSC. (a) impact of cocrystal aqueous solubility ($K_{eu,aq} = 4$ and 25) when drug solubilization is constant ($K_s^R = 1$ mM^{-1}), (b) impact of drug solubilization ($K_s^R = 1$ and 5 mM^{-1}) when cocrystal aqueous solubility is constant ($K_{eu,aq} = 25$). Curves generated according to eqn (43) and (45) for a 1 : 1 cocrystal RHA with $K_s^{HA} = 0$, CMC = 8 mM.

changes in $K_{eu,T}$ in small concentrations of micellar surfactant. Changes in $K_{eu,aq}$ (Fig. 3(a)) can be the result of pH or selection of a different coformer whose cocrystal is more soluble. Changes in K_s^R (Fig. 3(b)) can be achieved by surfactant selection.

Fig. 4 shows the predicted $K_{eu,T}$ dependence on total surfactant concentration and pH for cocrystal RHA according to eqn (45), where a cross-section at constant pH is represented by Fig. 2. $K_{eu,T}$ increases as a function of pH (which is a consequence of $K_{eu,aq}$ increasing) and decreases as a function of surfactant concentration. The intersection of surfaces indicates the CSC and pH_{max}, or the surfactant concentrations and pHs where the cocrystal stoichiometric solubility is equal to the drug solubility. Together, the CSC and pH_{max} values identify the solution conditions where cocrystal and drug are the thermodymically stable phases. Solving eqn (45) for [M] when $K_{eu,T} = 1$ gives the micellar surfactant concentration at the CSC. Thus, the CSC at $[H^+]_T$ (in this case, $[H^+]_T = [H^+]_{max}$) for a 1 : 1 cocrystal RHA can be written in terms of $K_{eu,aq}$ at $[H^+]_{aq}$, and is given by

$$CSC = \frac{K_{eu,aq}\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right) - 1}{K_s^R - \frac{K_{eu,aq}K_s^{HA}}{\left(1+\frac{K_a^{HA}}{[H^+]_{aq}}\right)}} + CMC \qquad (46)$$

When $K_s^R \gg K_s^{HA}$, which is typical for hydrophobic drugs and hydrophilic coformers, and the pH in micellar solution and water are equal ($[H^+]_T = [H^+]_{aq}$), eqn (46) simplifies to

$$CSC = \frac{K_{eu,aq} - 1}{K_s^R} + CMC \qquad (47)$$

$K_{eu,aq}$ and $[H^+]_{aq}$ also refer to values in solutions of submicellar surfactant concentrations. Equations that predict $K_{eu,T}$ and CSC at $[H^+]_T$ from measurement of $K_{eu,aq}$ at $[H^+]_{aq}$ for cocrystals of different stoichiometry and ionization properties are presented in Table 2.

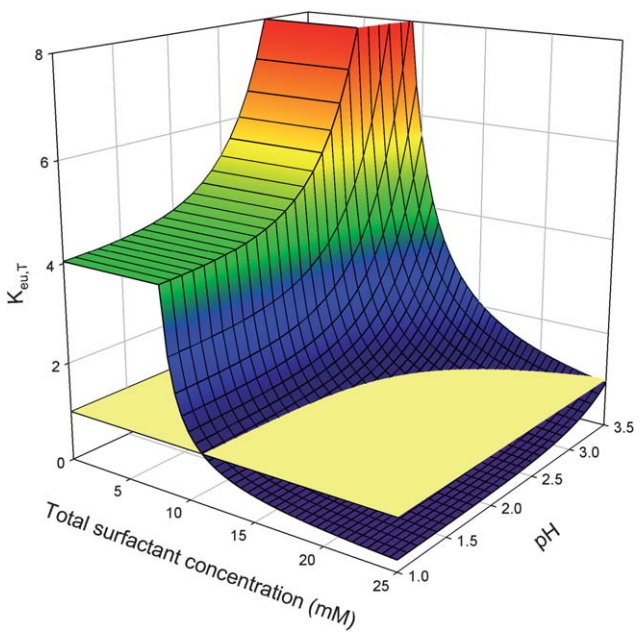

Fig. 4 Dependence of $K_{eu,T}$ on total surfactant concentration and pH. Multicolored surface represents $K_{eu,T}$ for a cocrystal RHA according to eqn (45). Yellow surface represents $K_{eu,T} = 1$, where cocrystal and drug are equally soluble. The intersection points indicate CSC and pH_{max}, values that describe the conditions where cocrystal and drug are thermodynamically stable without excess of either component in solution. $K_{eu,aq}$ (pH 1.0) = 4, $pK_a = 3.0$, $K_s^R = 1$ mM^{-1}, and CMC = 8 mM.

Effect of micellar solubilization on cocrystal phase stability regions

Micellar solubilization has the ability to shift the regions of cocrystal stability by differentially solubilizing drug relative to coformer. The presented model allows prediction of such changes in the phase diagram *via* the eutectic points. Fig. 5 illustrates how differential solubilization of cocrystal components results in a shift in the cocrystal stability region. The points designated by E_1 and E_2 are the cocrystal eutectic points that

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Table 2 Equations that allow for calculation of $K_{eu,T}$ and CSC at $[H^+]_T$ from $K_{eu,aq}$ at $[H^+]_{aq}$, and K_a and K_s values for cocrystal components[a]

Cocrystal	$K_{eu,T}$	Eqn	CSC	Eqn
RHA 1 : 1 nonionizable : monoprotic acidic	$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1+K_s^R[M]}\right)\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(45)	$CSC = \frac{K_{eu,aq}\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)-1}{K_s^R-\frac{K_{eu,aq}K_s^{HA}}{\left(1+\frac{K_a^{HA}}{[H^+]_{aq}}\right)}}+CMC$	(46)
HXHA 1 : 1 monoprotic acidic : monoprotic acidic	$K_{eu,T} = K_{eu,aq}\left(\frac{1+\frac{K_a^{HX}}{[H^+]_{aq}}}{1+\frac{K_a^{HX}}{[H^+]_T}+K_s^{HX}[M]}\right)\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(48)	$CSC = \frac{K_{eu,aq}\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\frac{1+\frac{K_a^{HX}}{[H^+]_T}}{1+\frac{K_a^{HX}}{[H^+]_{aq}}}\right)}{\frac{K_s^{HX}}{\left(1+\frac{K_a^{HX}}{[H^+]_{aq}}\right)}-\frac{K_{eu,aq}K_s^{HA}}{\left(1+\frac{K_a^{HA}}{[H^+]_{aq}}\right)}}+CMC$	(49)
BHA 1 : 1 monoprotic basic : monoprotic acidic	$K_{eu,T} = K_{eu,aq}\left(\frac{1+\frac{[H^+]_{aq}}{K_a^B}}{1+\frac{[H^+]_T}{K_a^B}+K_s^B[M]}\right)\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(50)	$CSC = \frac{K_{eu,aq}\left(\frac{1+\frac{K_a^{HA}}{[H^+]_T}}{1+\frac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\frac{1+\frac{[H^+]_T}{K_a^B}}{1+\frac{[H^+]_{aq}}{K_a^B}}\right)}{\frac{K_s^B}{\left(1+\frac{[H^+]_{aq}}{K_a^B}\right)}-\frac{K_{eu,aq}K_s^{HA}}{\left(1+\frac{K_a^{HA}}{[H^+]_{aq}}\right)}}+CMC$	(51)
R_2H_2A 2 : 1 nonionizable : diprotic acidic	$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1+K_s^R[M]}\right)\left(\frac{1+\frac{K_a^{H_2A}}{[H^+]_T}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2}+K_s^{H_2A}[M]}{1+\frac{K_a^{H_2A}}{[H^+]_{aq}}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right)$	(52)	$CSC = \frac{2K_{eu,aq}\left(\frac{1+\frac{K_a^{H_2A}}{[H^+]_T}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2}}{1+\frac{K_a^{H_2A}}{[H^+]_{aq}}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right)-1}{K_s^R-\frac{2K_{eu,aq}K_s^{H_2A}}{\left(1+\frac{K_a^{H_2A}}{[H^+]_{aq}}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}\right)}}+CMC$	(53)

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Table 2 (*Contd.*)

Cocrystal	$K_{eu,T}$	Eqn	CSC	Eqn
R_2HAB 2 : 1 nonionizable : amphoteric	$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1+K_s^R[M]}\right)\left(\frac{1+\frac{[H^+]_T}{K_a^{HAB}}+\frac{K_a^{H_2AB^+}}{[H^+]_T}+\frac{K_s^{HAB}[M]}{[H^+]_T}}{1+\frac{[H^+]_{aq}}{K_a^{HAB}}+\frac{K_a^{H_2AB^+}}{[H^+]_{aq}}}\right)$	(54)	$\mathrm{CSC} = \frac{2K_{eu,aq}K_s^{HAB}}{K_s^R - \left(\frac{[H^+]_{aq}}{K_a^{HAB}}+\frac{K_a^{H_2AB^+}}{[H^+]_{aq}}\right)}\left(\frac{1+\frac{[H^+]_T}{K_a^{HAB}}+\frac{K_a^{H_2AB^+}}{[H^+]_T}}{1+\frac{[H^+]_{aq}}{K_a^{HAB}}+\frac{K_a^{H_2AB^+}}{[H^+]_{aq}}}-1\right)+\mathrm{CMC}$	(55)

[a] Subscript aq represents values measured in submicellar concentrations of surfactant.

identify the range of solution compositions where cocrystal is stable in water (subscript aq) and in a micellar solution (subscript T). Line $E_{1,aq}$-$E_{1,T}$, which is generated according to eqn (26) and (27), shows that increasing surfactant concentration leads to the eutectic point E_1 becoming more enriched with drug.

At the CSC, the eutectic point E_1 intersects the stoichiometric composition line, indicating that RHA becomes congruently saturating. This shows that a system that is incongruently saturating in pure water can achieve congruent saturation in micellar solutions. Fig. 5 shows that micellar solubilization can shift or even widen the range of solution compositions where cocrystal is the thermodynamically stable phase.

E_2, like E_1, becomes more enriched with drug at the eutectic as a function of surfactant concentration due to the differential solubilization of drug over coformer. Eqn (26) and (27) are applicable to both E_1 and E_2. E_1 is governed by the drug solubility (eqn (21)) and E_2 by the coformer solubility (eqn (29)). In principle micellar solubilization can cause E_2 to intersect the stoichiometric composition line at a certain concentration of surfactant, which causes an otherwise congruently saturating cocrystal to become incongruently saturating. In instances where micellar solubilization is highly differential in favor of drug, the concentrations of surfactant required to destabilize a congruently saturating cocrystal may not be experimentally achievable.

Fig. 5 illustrates a simple system where only one cocrystal stoichiometry exists. The solid phase(s) at equilibrium (cocrystal, drug, or coformer) is controlled by how E_1 and E_2 respond to micellar solubilization. Cocrystal systems that have more than one stoichiometry can have multiple CSCs, which describe the conditions where each cocrystal stoichiometry becomes

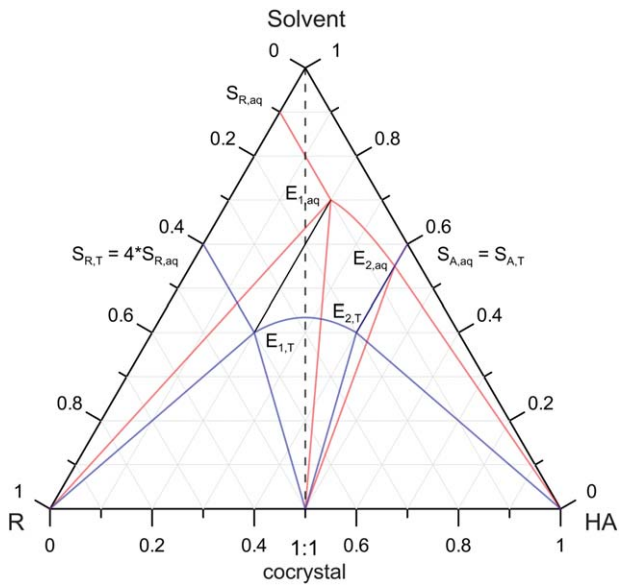

Fig. 5 Schematic triangular phase diagram of cocrystal RHA and its components illustrating the influence of micellar solubilization on eutectic points and phase stability regions. Differential solubilization of R results in the solution composition at the eutectic becoming enriched with drug as surfactant concentration increases. Cocrystals that are incongruently saturating in the absence of micelles can become congruently saturating in micellar solutions. Dotted line indicates stoichiometric ratio of cocrystal components.

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congruently saturating. Cocrystals of different stoichiometry are influenced differently by the micelles, such that more drug-rich stoichiometries are solubilized to a much greater extent than coformer-rich stoichiometries. As such, the eutectic point between cocrystals of different stoichiometries is expected to change as a result of micellar solubilization. Our mathematical models indicate that coformer-rich stoichiometries become more thermodynamically favorable than drug rich stoichiometries as surfactant concentration increases (provided drug is preferentially solubilized relative to coformer). Therefore, micellar solubilization can be a tool not only to thermodynamically stabilize cocrystals but also to select conditions where a particular stoichiometry is favorable.

Materials and methods

Materials

Anhydrous monoclinic carbamazepine (CBZ(III); lot no. 057K11612 USP grade) was purchased from Sigma Chemical Company (St. Louis, MO), stored at 5 °C over anhydrous calcium sulfate and used as received. Salicylic acid (SLC; lot no. 09004LH), saccharin (SAC; lot no. 03111DD), succinic acid (SUC; lot no. 037K0021), 4-aminobenzoic acid (4ABA; lot no. 068K0698), and sodium lauryl sulfate (SLS; lot no. 104H0667) were purchased from Sigma Chemical Company (St. Louis, MO) and used as received. Water used in this study was filtered through a double deionized purification system (Milli Q Plus Water System from Millipore Co., Bedford, MA).

Cocrystal synthesis

Cocrystals were prepared by the reaction crystallization method at room temperature by adding CBZ to nearly saturated solutions of coformer.[24] CBZ-SLC was prepared in acetonitrile, CBZ-SAC and CBZ-SUC were prepared in ethanol, and CBZ-4ABA-HYD was prepared in water. CBZ dihydrate (CBZD), the most stable form of CBZ in water, was prepared from anhydrous CBZ in water. Solid phases were characterized by XRPD.

Measurement of cocrystal eutectic points

Cocrystal eutectic points were measured as a function of SLS concentration in water at 25 ± 0.1 °C. A detailed discussion of eutectic point measurements has been discussed elsewhere.[8,10] 50–100 mg of cocrystal and 25–50 mg of CBZD were suspended in 3 mL of aqueous SLS solution up to 3 days. pH at equilibrium was measured but not independently modified. Cocrystal stoichiometric solubilities were determined from eqn (43) and (44). Drug and coformer concentrations were analyzed by HPLC. Solid phases at equilibrium were confirmed by XRPD.

High performance liquid chromatography (HPLC)

The solution concentrations of CBZ and coformer were analyzed by Waters HPLC (Milford, MA) equipped with a UV/vis spectrometer detector. Waters' operation software, Empower 2, was used to collect and process the data. A C18 Thermo Electron Corporation column (5 μm, 250 × 4.6 mm) at ambient temperature (24 °C) was used. The mobile phase was composed of 55% methanol and 45% water with 0.1% trifluoroacetic acid and the flow rate was 1 mL min^{-1} using an isocratic method. Injection sample volume was 20 or 40 μL. Absorbance of CBZ, SAC, SLC, SUC, and 4ABA was monitored at 284, 260, 303, 230, and 284 nm, respectively.

X-ray powder diffraction (XRPD)

XRPD diffractograms of solid phases were collected with a benchtop Rigaku Miniflex X-ray diffractometer (Danvers, MA) using Cu-Kα radiation ($\lambda = 1.54$ Å), 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° min^{-1}.

Results

The model equations presented above predict the dependence of cocrystal eutectic points on micellar solubilization, which identifies and enables engineering of the solution compositions where cocrystal is thermodynamically stable. Eutectic concentrations of drug and coformer at E_1 in micellar solutions are predicted from eutectic concentrations in water, K_a and K_s values for the cocrystal components, solution pH, and surfactant CMC. The work discussed here focuses on E_1 (solid phases at equilibrium are CBZ cocrystal, CBZD, and solution) because it is the relevant eutectic point in aqueous media, since it describes the cocrystal tendency to transform to the less soluble drug. The concepts discussed in the context of E_1 are relevant to other eutectic points, but E_1 better addresses the challenges of cocrystals whose purpose is to increase the solubility of a hydrophobic drug. However, consideration of all eutectic points in a cocrystal system is necessary for complete understanding of the phase diagram and control of crystallization outcomes.

The predictions are evaluated for a series of CBZ cocrystals of different stoichiometries and ionization properties in aqueous solutions. The cocrystals include 1 : 1 cocrystals with monoprotic acids (CBZ-SLC and CBZ-SAC) and 2 : 1 cocrystals with a diprotic acid (CBZ-SUC) and an amphoteric coformer (CBZ-4ABA-HYD). The cocrystal stoichiometric solubilities in pure water were reported previously, and ranged from 1.32 mM for CBZ-SLC at pH 3.0 to 2.38 mM for CBZ-SUC at pH 3.1 (in terms of CBZ concentration), or 2.5 to 4.5-fold the aqueous solubility of CBZD (0.53 mM).[7,25]

pH was not independently adjusted for the studies presented here but the pH of the eutectic solutions at equilibrium were measured. pH varied by less than 0.2 units between eutectics measured in water and in SLS solutions.

Drug and coformer eutectic concentration dependence on SLS concentration

Fig. 6 shows the solution concentrations of drug and coformer at the eutectic point E_1 as a function of SLS concentration for the CBZ cocrystals. Fig. 6 shows that drug and coformer concentrations increase at different rates with respect to SLS concentration. The CBZ eutectic concentration has a faster rate of increase than the coformer with respect to SLS concentration, such that there is a reversal in the relative eutectic concentrations from coformer-rich in low surfactant concentrations to drug-rich in high surfactant concentrations. This is in agreement with

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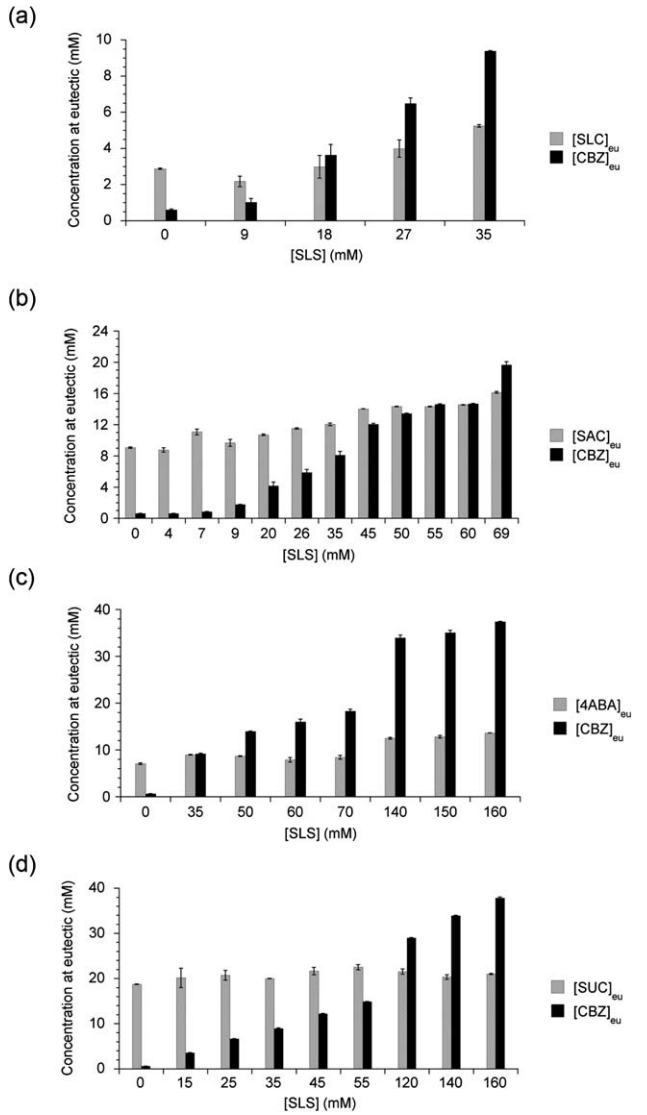

Fig. 6 Dependence of eutectic concentrations of CBZ and coformer on SLS concentration in aqueous solutions. Solid phases at equilibrium are CBZ cocrystal and CBZD. (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1.

predicted behavior according to eqn (26) and (27), which predict that eutectic concentrations of drug and coformer increase according to their respective K_s values.

Fig. 7 shows the predicted and experimental drug and coformer eutectic concentrations for each cocrystal as a function of SLS concentration. The predicted lines were generated by linear regression according to equations in Table 1 where K_s values and surfactant CMC were allowed to vary; drug and coformer eutectic concentrations in pure water, solution $[H^+]$, and K_a values remained fixed. Fig. 7 shows very good correlation between experimental and predicted behavior.

The K_s values generated by linear regression (Table 3), are a measure of the drug and coformer K_s values in the eutectic solution, and represent the influence of coformer on K_s. There is good agreement between these and the K_s values of the separate cocrystal components in aqueous SLS solutions, suggesting that the presence of coformer negligibly affected drug solubilization and *vice versa*. This finding is supported by Fig. 8, which compares the CBZD solubilities at the eutectic and in the absence of coformer as a function of SLS concentration. The excellent agreement between CBZ eutectic concentrations and CBZD solubilities in Fig. 8 shows that the coformers had minimal impact on the solubilization of CBZ.

The CMC value of 6 mM SLS for CBZ-SAC, CBZ-4ABA-HYD, and CBZ-SUC are in good agreement with reported CMC of SLS in saturated CBZ solutions (5.3 mM SLS[25]). CBZ-SLC has a CMC value of 8 mM. Our previous cocrystal solubility studies indicate that SLC exhibits a weak effect on the CMC of SLS in saturated CBZ solutions, which was reported as 9 mM SLS.[7] In these studies the magnitude of the changes in CMC as a result of solutes and solution conditions are generally small relative to the total surfactant concentrations.

When drug, coformer, and surfactant exhibit solution interactions that affect ionization or micellar solubilization, using parameters measured for the separate components (K_a, K_s, and CMC) in the model equations may not be justified. If necessary, more rigorous expressions that describe the thermodynamic parameters as a function of solute and surfactant concentration may be substituted in place of a constant value.

The CSC can be calculated from the eutectic concentrations of drug and coformer as a function of SLS concentration in Fig. 7 where the molar ratios of drug and coformer at E_1 are equal to the cocrystal stoichiometry. The CSC indicates the minimum surfactant concentration such that no excess coformer in solution is required for the cocrystal to be thermodynamically stable, thereby creating unfavorable conditions for cocrystal to transform to drug. The CSCs for the 1 : 1 cocrystals CBZ-SLC and CBZ-SAC are indicated by the surfactant concentration where $[drug]_{eu} = [coformer]_{eu}$, illustrated by the intersection of the drug and coformer eutectic concentration dependencies. For the 2 : 1 cocrystals CBZ-4ABA-HYD and CBZ-SUC, $0.5[drug]_{eu} = [coformer]_{eu}$ at the CSC.

K_{eu} dependence on SLS concentration

The ratio of coformer to drug activities at the eutectic, known as the eutectic constant K_{eu}, is an indicator of the thermodynamic stability of cocrystal and cocrystal component solid phases. Under dilute conditions where activities are replaced by concentrations, K_{eu} values can be calculated from drug and coformer eutectic concentrations in SLS solutions (Fig. 7). $K_{eu} > 1$ for 1 : 1 cocrystals (> 0.5 for 2 : 1 cocrystals) indicates that cocrystal is thermodynamically unstable and $K_{eu} \leq 1$ for 1 : 1 cocrystals (≤ 0.5 for 2 : 1 cocrystals) indicates cocrystal is thermodynamically stable. The surfactant concentration and pH where $K_{eu} = 1$ for 1 : 1 cocrystals ($= 0.5$ for 2 : 1 cocrystals) are the CSC and pH_{max}.

Fig. 9 shows the predicted and experimental K_{eu} dependence on SLS concentration according to the model equations (Table 2) using K_s and CMC values in Table 3 and K_{eu} measured in pure water ($K_{eu,aq}$). Measured K_{eu} values decrease as a function of SLS concentration, indicating that the cocrystal becomes more stable relative to drug as SLS concentration increases. If we assume that solution interactions other than ionization and micellar solubilization are negligible, decreasing K_{eu} values can be related to decreasing cocrystal to drug solubility ratios (eqn

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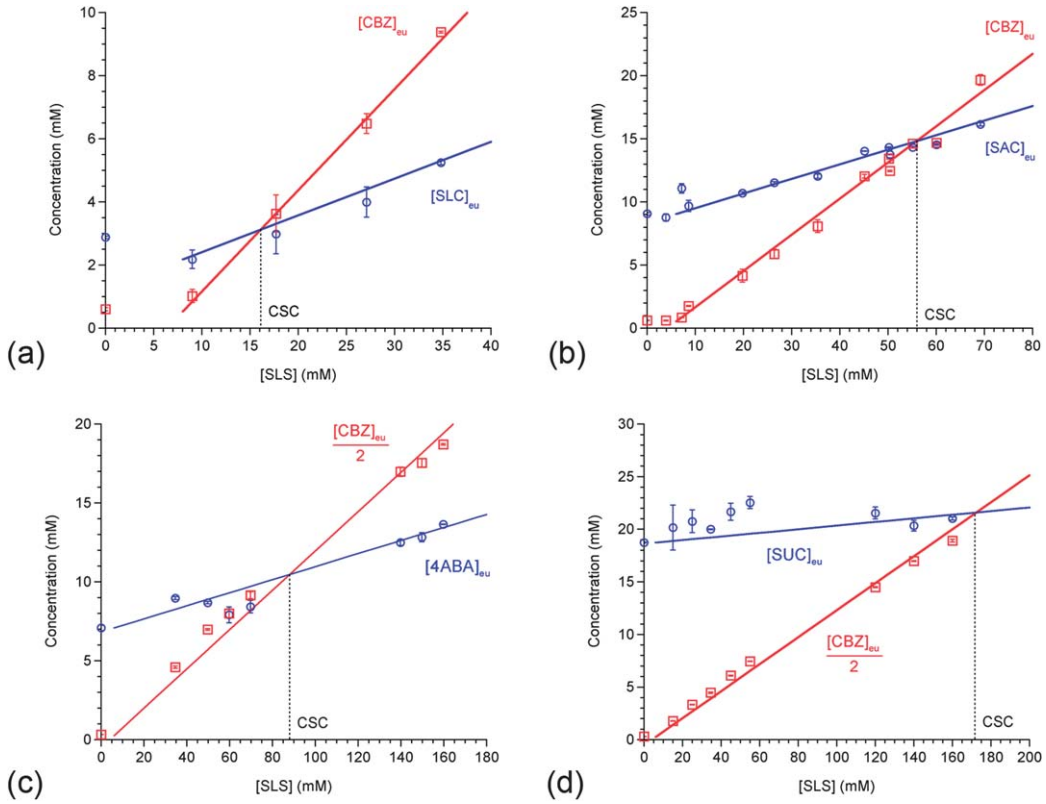

Fig. 7 Eutectic concentrations of drug and coformer at E_1 in aqueous SLS solutions for (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1. Lines represent linear regression from equations in Table 1, where K_s and CMC values are allowed to vary (Table 3). Eutectic concentrations measured in aqueous solutions without SLS, and all other parameters were fixed.

(43) and (44)). The experimental K_{eu} dependence on SLS concentration is in excellent agreement with the predicted behavior. This demonstrates that solution conditions where cocrystal is stable (pH and additive concentration) cannot be generalized to other solution conditions without considering ionization and micellar solubilization equilibria, even at low micellar surfactant concentrations where the CSC is not achieved.

In this work CSC is evaluated by two methods: (1) K_{eu} measured as a function of SLS concentration, and (2) K_{eu} calculated from $K_{eu,aq}$, $[H^+]$, K_s and K_a for the cocrystal components, and surfactant CMC according to equations in Table 2. These two methods are complementary to other methods of evaluating CSC which were studied previously.[7] Method (1) determines a CSC range between the highest concentration of surfactant where $K_{eu} > 1$ and the lowest concentration of surfactant where $K_{eu} \leq 1$ for a 1 : 1 cocrystal (from $K_{eu} > 0.5$ to $K_{eu} \leq 0.5$ for 2 : 1 cocrystals). The surfactant concentrations in Fig. 9 were not selected for the purpose of narrowing this range, as the kinetics of reaching equilibrium become slow at concentrations near the CSC. Method (2) is a calculation based on a eutectic point measured in water, which avoids the possible kinetic limitations at surfactant concentrations near the CSC.

Table 3 Comparison of K_s values for the drug and coformer measured at saturation when the solid phases at equilibrium are (a) cocrystal and drug at eutectic point E_1 (b) drug or coformer only

Cocrystal	K_s(drug)[a] cocrystal + drug mM^{-1}	K_s(drug)[b] drug only mM^{-1}	K_s(cof)[a] cocrystal + drug mM^{-1}	K_s(cof)[b] coformer only mM^{-1}	CMC[a] mM
CBZ-SLC	0.605 ± 0.023	0.576 ± 0.017[c]	0.107 ± 0.010	0.060 ± 0.005	8
CBZ-SAC	0.541 ± 0.020	0.576 ± 0.017[c]	0.027 ± 0.002	0.013 ± 0.002	6
CBZ4-ABA-HYD	0.470 ± 0.009	0.494 ± 0.012[d]	0.007 ± 0.001	<0.010	6
CBZ-SUC	0.484 ± 0.009	0.494 ± 0.012[d]	0.001 ± 0.020[e]	<0.010	6

[a] K_s and CMC determined by linear regression of eutectic concentrations as a function of SLS concentration (Fig. 7) according to equations in Table 1, where K_s and CMC were allowed to vary and all other parameters remained fixed. [b] K_s determined by linear regression of measured solubilities of pure drug or coformer at saturation as a function of SLS concentration according to eqn (21) and (29). CBZ K_s demonstrated a weak dependence on SLS concentration, so K_s values were determined in a range of SLS concentrations similar to those used in eutectic point experiments (Fig. 7). [c] K_s measured between 0 mM and 50 mM SLS. [d] K_s measured between 0 mM and 140 mM SLS. [e] Statistically insignificant from 0.

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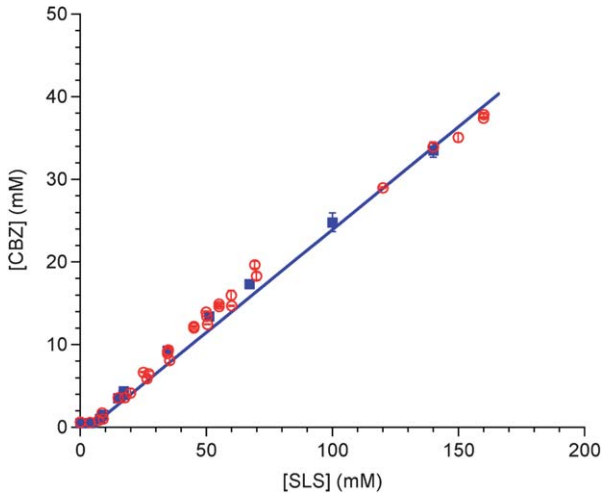

Fig. 8 Comparison of CBZD solubility as a function of SLS concentration (■) in the absence of coformer and (○) at the eutectic for four CBZ cocrystals (CBZ-SLC, CBZ-SAC, CBZ-4ABA-HYD, CBZ-SUC). Eutectic concentrations show that CBZD solubility is unaffected by the presence of coformer. Predicted line is drawn according to eqn (21), $S_{R,aq} = 0.53$ mM, $K_s = 0.49$ mM^{-1}, CMC = 6 mM.

CSC values predicted from $K_{eu,aq}$ measurements are in good agreement with CSC values measured in micellar solutions for three cocrystals (CBZ-SLC, CBZ-SAC, and CBZ-4ABA-HYD). CBZ-SUC shows deviation between the two methods which may be due to K_{eu} decreasing very slowly at surfactant concentrations near the CSC. In Fig. 9(d) the rate of change of K_{eu} with respect to SLS concentration is predicted to be very low near the CSC. This indicates that cocrystal and drug have very similar solubilities, which could limit the kinetics of transformation between phases. CSC values measured are consistent with previously reported methods of evaluating CSC.[7]

Engineering cocrystal stability regions

Micellar solubilization provides a mechanism to engineer the cocrystal stability regions. Fig. 10 shows phase diagrams with the predicted and experimental eutectic points of CBZ cocrystals as a function of SLS concentration in a triangular phase diagram. Predicted lines are generated according to equations in Table 1 with K_s and CMC values in Table 3 and $K_{eu,aq}$ measured in water. The predicted E_1 lines shown are analogous to the $E_{1,aq}$-$E_{1,T}$ line in Fig. 5.

In Fig. 10, the eutectic solution composition at E_1 becomes more enriched in CBZ as micellar solubilization increases. The predicted lines are generated from equations in Table 1 and K_s values in Table 3. The experimental E_1 values are in excellent agreement with the predicted behavior. The intersection of the predicted E_1 dependence with the equimolar composition line of components (dotted line) is the CSC, which describes a solution composition where drug, cocrystal, and micellar solution are in

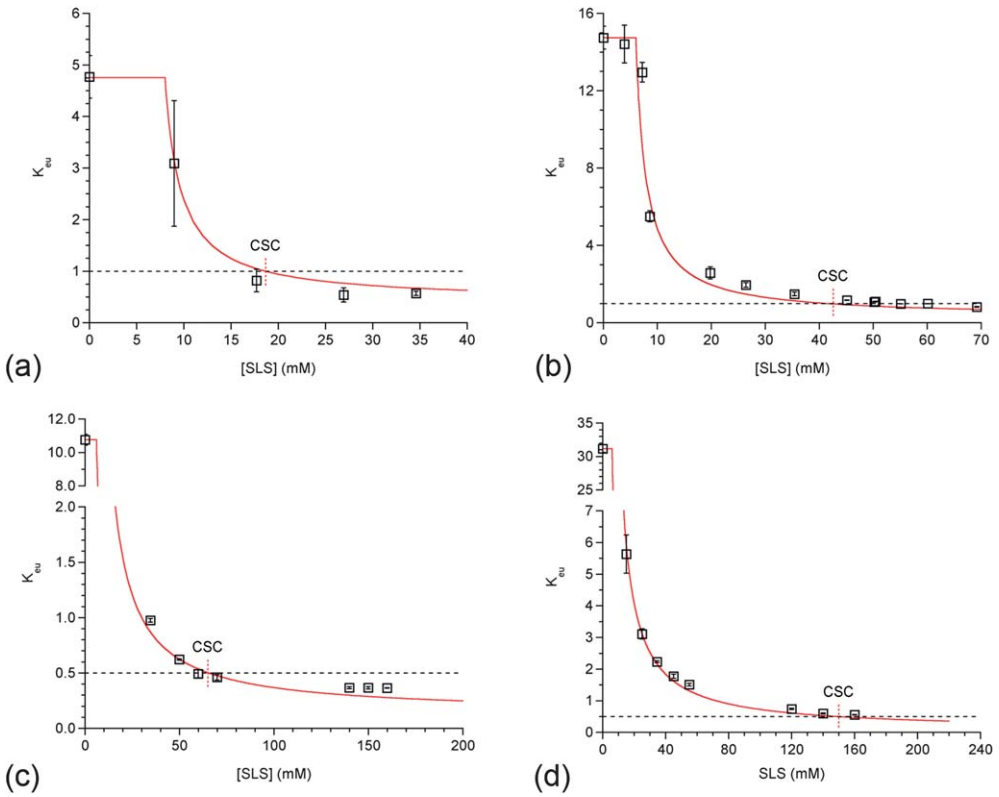

Fig. 9 Dependence of K_{eu} on SLS concentration in water for (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1. Predicted curves and CSCs are generated according to equations in Table 2 using the K_{eu} measured in pure water and the K_s values for drug and coformer found in Table 1. K_{eu} dependence shows that cocrystal to drug solubility ratios decrease with increasing surfactant concentration. K_{eu} values below the horizontal dotted line (≤ 1 for 1 : 1 cocrystals and ≤ 0.5 for 2 : 1 cocrystals) indicate the solution contains SLS concentration above the cocrystal's CSC.

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Table 4 CSC values determined from (a) measured K_{eu} dependence on SLS and (b) estimated according to equations in Table 2 using measured $K_{eu,aq}$

Cocrystal	pH	CSC range measured from K_{eu} dependence on SLS[a] mM SLS	CSC calculated from $K_{eu,aq}$[b] mM SLS
CBZ-SLC	3.0	9 < CSC < 18	19
CBZ-SAC	2.2	50 < CSC < 55	42
CBZ4-ABA-HYD	4.0	50 < CSC < 60	64
CBZ-SUC	3.1	160 < CSC	142

[a] Range of CSC determined by SLS concentrations where $K_{eu} > 1$ to $K_{eu} \leq 1$ for 1 : 1 cocrystals and where $K_{eu} > 0.5$ to $K_{eu} \leq 0.5$ for 2 : 1 cocrystals. [b] Predictions according to equations in Table 2 using measured $K_{eu,aq}$ (Fig. 9) and K_s values (Table 3).

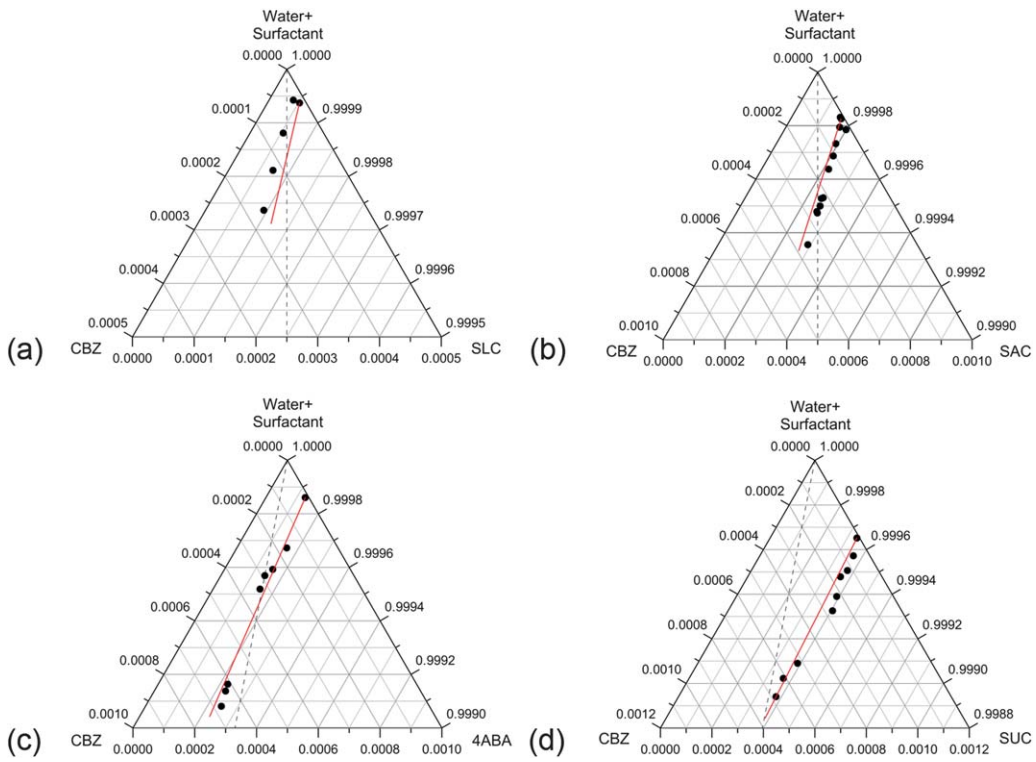

Fig. 10 Triangular phase diagrams showing predicted and experimental dependence of eutectic point E_1 on SLS concentration for (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1. Surfactant concentrations increase towards the base of the triangle. Predicted lines generated according to equations in Table 1, K_s values in Table 3, and eutectic concentrations of cocrystal components measured in pure water. Micellar solubilization alters the cocrystal regions of stability such that cocrystal is congruently saturating. Dotted lines indicate ratio of cocrystal components equivalent to cocrystal stoichiometry.

equilibrium with no excess of either cocrystal component in solution. An incongruently saturating cocrystal below CSC becomes congruently saturating above CSC.

Triangular phase diagrams such as Fig. 10 have utility in designing solution conditions that either favor or disfavor cocrystal formation and stability in solution.

Conclusions

The work presented here describes the mechanisms by which cocrystal eutectic points can be fine-tuned *via* micellar solubilization and ionization of cocrystal components. Quantitative models developed allow for *a priori* calculation of cocrystal eutectic points in micellar solutions from a single eutectic point in pure water, K_s and K_a values of cocrystal components, and solution pH. The sensitivity of eutectic points and phase diagrams to the choice of surfactant and pH is shown for several carbamazepine cocrystals in aqueous solutions of sodium lauryl sulfate.

Increasing the magnitude of micellar solubilization for one of the cocrystal components is found to confer greater thermodynamic stability to the cocrystal and expand its stability region. This brings a shift in eutectic points and phase stability regions to solutions of stoichiometry equal to the cocrystal (there is no excess concentration of either cocrystal component). Thus, cocrystals which are otherwise unstable can achieve thermodynamic stability at a given surfactant concentration and pH, regarded as CSC and pH_{max}.

The eutectic constant K_{eu} is an important parameter obtained from the solution composition at the eutectic and is an indicator of cocrystal solubility and thermodynamic stability relative to drug. The CSC can be determined from K_{eu} measured in micellar solutions or can be predicted from K_{eu} measured in pure water

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(and its associated solution pH) and K_s values for the cocrystal components.

The variation of K_{eu} with surfactant concentration shows that cocrystal to drug solubility ratio decreases fastest close to the CMC. Applications that rely on a large cocrystal solubility advantage over drug must be cognizant of reductions in the cocrystal to drug solubility ratio that can result from differential solubilization of cocrystal components.

The concepts developed are applicable to other solubilization mechanisms that exhibit differential affinities for cocrystal components. Cocrystals with a high solubility advantage over drug may require multiple additives and/or solubilization mechanisms to achive the CSC. Understanding the sensitivity of cocrystal thermodynamic stability to solution chemistry is critical for our ability to control, develop, and use cocrystals.

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