ENGINEERING COCRYSTAL SOLUBILITY AND STABILITY VIA IONIZATION AND MICELLAR SOLUBILIZATION

by

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To my family and friends, who supported me in innumerable ways

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Table of Contents

List of Figures

List of Tables

Abstract

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Pharmaceutical cocrystals have generated enormous interest due to their potential for improving the physicochemical shortcomings of a drug, such as poor aqueous solubility. Poor aqueous solubility can compromise drug performance and cocrystallization is an emerging strategy to design materials with desirable properties. This approach is currently limited because cocrystal solution chemistry remains largely unexplored. This dissertation explores the influence of two critically important solution phase interactions, ionization and micellar solubilization, on cocrystal solubility and stability.

The objectives of this work are to (1) understand the effect of ionization on cocrystal solubility, (2) investigate the role of micellar solubilization on cocrystal solubility and stability, (3) develop mathematical models to describe cocrystal solubility and stability via ionization and micellar solubilization equilibria, and (4) understand how

ionization and micellar solubilization affect cocrystal eutectic points and regions of thermodynamic stability.

Cocrystal solubility, stability, and eutectic points were investigated as a function of pH and sodium lauryl sulfate concentration for a series of carbamazepine cocrystals in water. The cocrystals represented two stoichiometries (1:1 and 2:1) and four coformers (salicylic acid, saccharin, 4-aminobenzoic acid, and succinic acid) with various ionization properties. Mathematical models for cocrystal solubility were developed in terms of experimentally accessible thermodynamic parameters based on cocrystal dissociation, component ionization, and micellar solubilization. These models demonstrated that cocrystal solubility relative to drug could be strongly dependent on surfactant concentration and pH, and that the thermodynamic stability of cocrystals could be controlled via predictable parameters called the critical stabilization concentration (CSC) and pH_{max}. This enabled for the first time the thermodynamic stabilization of cocrystals that would otherwise be unstable in water under stoichiometric solution conditions. Several methods were developed to evaluate CSC and were challenged by the carbamazepine cocrystals. The important factors that affect CSC and pH_{max} were identified as (1) cocrystal aqueous solubility relative to drug, (2) micellar solubilization constants and acid dissociation constants for the cocrystal components, (3) cocrystal stoichiometry, and (4) surfactant CMC. The mathematical models demonstrated excellent predictive capacity in describing the influence of pH and surfactant concentration on cocrystal solubility, CSC, and eutectic points for the carbamazepine cocrystals.

CHAPTER 1

Introduction

Cocrystals have generated tremendous interest in pharmaceutical research and development because of the potentital to customize physicochemical properties of the solid while maintaining the chemical integrity of the drug. Cocrystals are part of a broader class of multicomponent crystals, where two or more molecules (commonly referred to as drug and coformer) populate a homogeneous crystalline lattice in a well-defined stoichiometry. What distinguishes cocrystals from other types of multicomponent crystals such as salts and solvates is that drug and coformer are solids at ambient temperature and that the intermolecular interactions are nonionic in nature. The diversity of solid forms that can be generated from a drug greatly increases through cocrystallization; the physicochemical properties of the cocrystals can vary depending on the characteristics of its constituent molecules.

Pharmaceutically relevant properties that can change via cocrystallization include but are not limited to solubility, dissolution, moisture uptake, chemical stability, mechanical properties, and bioavailability.[1-6] Of these properties, solubility is the most widely appreciated in the literature. Cocrystals have the potential to address the solubility limitations of poorly soluble pharmaceutical compounds, a problem which can pose a serious challenge to successful formulation. Lipinski reported that between 1987

and 1994, nearly one-third of newly synthesized compounds in academic laboratories had solubilities less than 20 μg/mL.[7, 8] Serajuddin estimates that one-third of newly synthesized compounds have aqueous solubilities less than 10 μg/mL, and another one-third have aqueous solubilities between 10 and 100 μg/mL.[9] Poor aqueous solubility can result in poor dissolution, which can then affect bioavailability and pharmacokinetics.

Other solid forms that have been investigated for solubility enhancement include salts, polymorphs, solvates, and amorphous, among others. High energy polymorphs and amorphous formulations can achieve improved solubilities but the system is at serious risk of crystallizing the thermodynamically stable form, even in the solid state.[10-15] Such transformations can compromise the performance of the formulation. Salt formation is a common approach to address poor aqueous solubility, but is limited to ionizable compounds. Adding ionizable moieties to a nonionizable drug can improve solubility but may affect the desired pharmacological effect of the molecule. Cocrystals offer the solid state stability of a crystalline compound and the solubility enhancement of a high-energy solid.

This chapter introduces cocrystals in the context of design, synthesis, physicochemical properties, the current understanding of cocrystal solution chemistry, and what role additives currently play in cocrystal research. This chapter will conclude with a statement of research objectives.

Cocrystal design

Cocrystals are designed based on the principles of crystal engineering and supramolecular chemistry, where cocrystal components are selected based on favorable

molecular recognition interactions. Table 1.1 gives several examples of reported

cocrystals of pharmaceutically active compounds. Typically, though not exclusively, the

drug component is hydrophobic and poorly soluble in water. In general the coformers are

small organic acids, though coformers with other ionization properties have been

successfully cocrystallized.[16-19]

Table 1.1. Examples of pharmaceutical cocrystals.

Drug	Coformers	References
Carbamazepine	succinic, benzoic, ketoglutaric, maleic, glutaric, malonic, oxalic, adipic, (+)-camphoric, 4-hydroxybenzoic, salicylic, 1-hydroxy-2-naphthoic, DL-tartaric, L-tartaric, glycolic, fumaric, DL-malic, L-malic, acetic, butyric, 5-nitroisophthalic, formic, 4-aminobenzoic, trifluoroacetic, 2,6-pyridinedicarboxylic, trimesic, adamantane-1,3,5,7-tetracarboxylic	17, 18
Piroxicam	L-tartaric, citric, fumaric, adipic acid succinic, L-malic, glutaric, DL-malic, oxalic, (+)-camphoric, ketoglutaric, benzoic, 4-hydroxybenzoic, malonic, salicylic, glycolic, 1-hydroxy-2-naphthoic, gentisic, DL-tartaric, maleic, caprylic, hippuric, L-pyroglutamic acid	16
Itraconazole	succinic, fumaric, L-malic, L-tartaric, D-tartaric, DL-tartaric	20

Cocrystals depend on noncovalent, nonionic interactions, which include hydrogen

bonding, π-π, and van der Waals interactions. Analysis of cocrystal structures in the

Cambridge Structural Database (CSD) indicates that hydrogen bonding is the most

prevalent mode of interaction among cocrystals.[21-24] These studies show that there exist

certain hydrogen bond motifs called synthons that occur frequently among reported

cocrystals. Examples of such synthons are shown in Figure 1.1. Synthons are generally

3

classified into two categories, homosynthons and heterosynthons. Homosynthons are interactions between two of the same functional group (I-II), and heterosynthons are interactions between two different functional groups (III-X).[24-28]
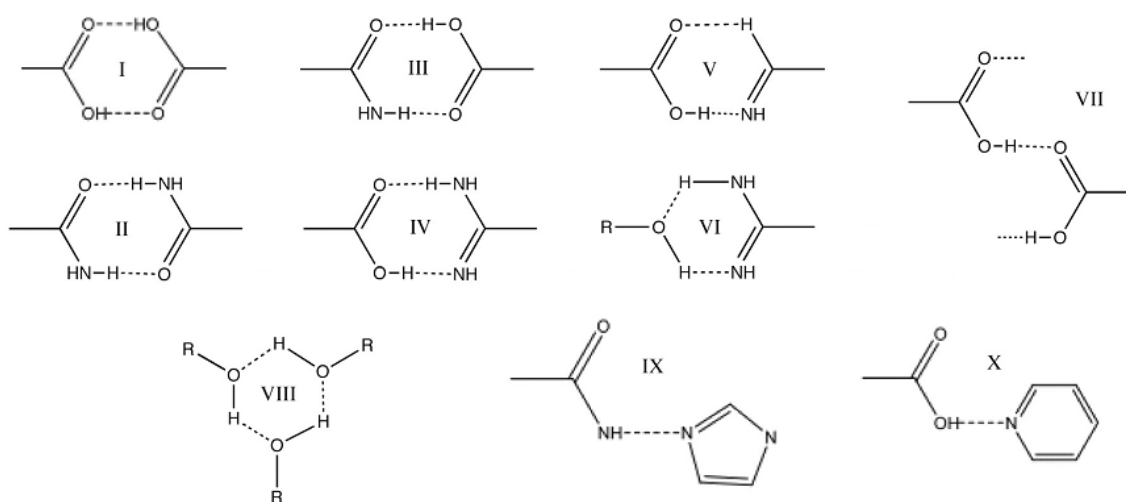
Figure 1.1. Hydrogen bond synthons common in cocrystal structures.[29]

Based on these principles and a statistical analysis of the CSD, a set of guidelines were developed for selecting favorable hydrogen bonding assemblies in the crystal structure. (1) all acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound (2) all good acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors, and (3) the best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another.[23, 30] These rules do have several notable limitations, *e.g.* steric hindrance, competing dipole/hydrogen bonding/ionic interactions, and conformational freedom.

The hydrogen bonding rules offer a good starting point for cocrystal synthesis and coformer selection, but are not able to *ab initio* determine crystal structure or the

4

existence of cocrystal. Crystal structure prediction is a complex discipline that requires consideration of a number of factors in addition to synthon formation, including van der Waals interactions, crystal packing, symmetry elements, and electrostatic interactions between within molecules.[31]

Cocrystal synthesis

Currently the most established methods for cocrystal formation are solvothermal and mechanical techniques. In solvothermal cocrystal synthesis, stoichiometric ratios of reactants are dissolved in a solvent of choice and supersaturation is achieved either through a temperature difference or through evaporation of the solvent. In mechanical cocrystal synthesis, stoichiometric ratios of reactants are mechanically agitated (*e.g.* by grinding in a mill) to induce phase transformations from a physical mixture into cocrystal.[32-35] Drops of solvent, which are considered plasticizers, have been shown to impact the crystallization outcome.[36-39] Mechanical methods are often favored due to their speed, procedural simplicity, and potential for green chemistry.

While these two methods have been largely successful in the discovery of cocrystals, they have some particular limitations. Solvothermal techniques often rely on empirical choices of solvent, temperature conditions, and molar ratio of reactants. There is a risk of crystallizing one or more undesirable phases if conditions are chosen such that cocrystal is not the thermodynamically stable phase. Mechanical techniques are also subject to empirically selected conditions (such as selection of solvent drop and grinding time), but the main challenges include process scalability, reactant stability during mechanically/thermally energetic processes, and extent of transformation.

Reaction crystallization is an emerging solution-mediated cocrystal synthesis method that complements the other more established methods.[40] The reaction crystallization method (RCM) relies on creating supersaturation through cocrystal solution phase chemistry. Cocrystal solubility is described by solubility product behavior, which indicates that cocrystal solubility decreases as coformer concentration increases.[1, 41] Cocrystal solubility is decreased below that of the drug by adding coformer at or near the coformer solubility. Therefore, conditions are chosen to maximize the likelihood of obtaining cocrystal by operating in a region of the phase diagram where cocrystal is least soluble. The theoretical framework developed for cocrystal solubility allows for rational selection of the solvent and solute concentrations to control and optimize cocrystallization processes. RCM is a scalable technique, amenable to both large and small scales. RCM has been successfully used in addition to other methods to screen for carbamazepine and piroxicam cocrystals,[16, 18] and can be applied with equal success in green solvents such as water.

Cocrystal properties

The main advantage of cocrystals is the ability to generate a variety of solid forms of a drug that have physicochemical properties distinct from the solid cocrystal components. Such properties include but are not limited to solubility, dissolution, bioavailability, hygroscopicity, hydrate/solvate formation, crystal morphology, fusion properties, chemical and thermal stability, and mechanical properties. These properties can directly or indirectly affect the suitability of a particular API as a pharmaceutical

product. Consideration of how these physicochemical properties change as a result of cocrystallization is an ongoing area of cocrystal research.

Bioavailability and dissolution

Several studies have demonstrated improved bioavailability with a cocrystal than with the crystalline API. McNamara *et al*. showed that a 1:1 cocrystal of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide, a poorly soluble developmental drug, with glutaric acid achieved 3-fold higher C_{max} and plasma AUC for two different doses (5 and 50 mg/kg) in dogs.[42] An investigation of the dissolution rate of cocrystal by rotating disk showed that dissolution rate was 18-fold higher for cocrystal than crystalline drug. Bak *et al.* showed similar results for a 1:1 cocrystal of an Amgen compound AMG517 with sorbic acid, where cocrystal demonstrated an 8 to 10-fold increase in C_{max} and plasma AUC relative to an equivalent dose (500 mg/kg) of the crystalline drug in rats.[43] The AMG517-sorbic acid cocrystal was shown to achieve 10-fold higher drug concentrations after 1 hour of powder dissolution in fasted-state simulated intestinal fluid (FaSSIF) relative to the crystalline drug, despite the crystalline drug having a smaller average particle size. Additional cocrystals that have demonstrated higher C_{max} and plasma AUC relative to pure drug include a 1:2 cocrystal of Merck L-883555 and L-tartaric acid in monkeys, and a 1:1 cocrystal of indomethacin and saccharin in dogs.[44, 45]

However, not all attempts have been successful in selecting a cocrystal with improved pharmacokinetics relative to drug based on a favorable dissolution rate. A 1:1 cocrystal of carbamazepine and saccharin did not exhibit statistically significant differences in C_{max} and plasma AUC when compared to the marketed form of

carbamazepine (Form III) in dogs.[46] A pharmacokinetic study of two 1:1 cocrystals of lamotrigine with nicotinamide (anhydrous and monohydrate) showed lower C_{max} and plasma AUC for cocrystal relative to drug, despite having comparable powder dissolution rates in water and acidic media.[47]

Other studies have shown that cocrystal can achieve a range of dissolution rates, depending on coformer selection. Remenar *et al.* showed that cocrystals of itraconazole (a poorly soluble antifungal agent) with four dicarboxylic acids (L-tartaric, maleic, succinic, and fumaric) achieved powder dissolution rates 4 to 20-fold that of the crystalline drug in 0.1 N HCl.[48] The highest dissolution rates achieved were comparable to the amorphous form of itraconazole.

Fusion properties

Melting point can be important for identification, processing in thermally sensitive environments, and is typically used as a gauge for solubility. In general, cocrystals have melting points distinct from the solid cocrystal components. Analysis of the melting temperatures of twenty-seven carbamazepine cocrystals indicates that cocrystal melting points can be either be between, less than, or greater than the melting points of the pure components.[18, 49, 50] The differences in melting points between pure drug and cocrystal can be attributed to changes in intermolecular interactions, composition, and crystal structure. Correlations between a cocrystal's melting point and its aqueous solubility were attempted on a limited set of carbamazepine cocrystals in various organic solvents and water.[49] The cocrystal melting point was shown to be a poor

indicator of cocrystal aqueous solubility, where solute-solvent interactions dominate over crystal lattice energies.

Hygroscopicity

Sensitivity to water is an important consideration for any drug candidate. For example, compounds that interact strongly with water are at risk of phase transformation from anhydrous solid into a hydrate.[51-55] Cocrystals have been shown to prevent hydrate formation in cocrystals of the drug carbamazepine with coformers saccharin and nicotinamide.[56, 57] Carbamazepine-saccharin and carbamazepine-nicotinamide showed no hydrate formation after 10 weeks at 98% RH and 3 weeks at 100% RH, whereas solid carbamazepine readily converted to the dihydrate form. Similar results have been reported for caffeine and theophylline cocrystals with dicarboxylic acids.[57]

Deliquescent additives have been shown to induce solution-mediated transformations from solid reactants to cocrystal.[53] Carbamazepine-saccharin cocrystals were formed in the presence of deliquescent additives sucrose, fructose, and citric acid at high relative humidities. The formation of cocrystal relied on differential dissolution rates of solid coformer and drug in the sorbed moisture, which led to the solution becoming supersaturated with respect to cocrystal.

Chemical stability

Cocrystallization can affect chemical stability through rearrangement of the molecules in the crystalline lattice. Carbamazepine undergoes photodegradation and its mechanism is dependent on distances between azepine rings in the crystal lattice

(requires <4.1 Å).[57, 58] Carbamazepine-saccharin and carbamazepine-nicotinamide cocrystals contain azepine ring distances long enough to disrupt the photodegradation mechanism. Thus, cocrystals can protect against unwanted degradation processes in the solid state.

Mechanical properties

The response of pharmaceutical solids to mechanical stresses can impact formulation and processing strategies. A series of paracetamol cocrystals were investigated for their tabletability and other mechanical properties.[59] The coformers were selected based on crystal engineering principles that promote intended crystallographic features. Two polymorphs of paracetamol were unable to be tabletted in their pure forms, while four cocrystals of paracetamol readily formed tablets.

The four cocrystals' mechanical properties were characterized in terms of tensile strength, breaking force, and other elastic properties. Each of the four cocrystals outperformed both paracetamol polymorphs in the mechanical properties tests. The authors' reasoning behind the improved tabletability is the successful formation of layers in the crystal structure that are critical for elasticity and strength. These studies demonstrate the utility of cocrystallization in the design of pharmaceutical solids.

Cocrystal solution chemistry

Cocrystal solubility

Cocrystal solution phase behavior was first investigated by Higuchi, Connors, and coworkers, though their focus was on solution complexation between cocrystal

components.[60-62] Their experiments showed that cocrystals adhered to solubility product behavior, where increasing coformer concentration led to decreasing drug concentration at equilibrium. The mathematical models to explicitly describe cocrystal solubility in terms of cocrystal solubility product (K_{sp}) and solution complexation constant (K_{11}) were introduced by Nehm *et al.*[41]

The chemical equilibria that describe cocrystal AB solubility, where A is drug and B is coformer, are

$$AB_{solid} \xrightleftharpoons{K_{sp}} A_{soln} + B_{soln} \tag{1.1}$$

$$A_{soln} + B_{soln} \xrightleftharpoons{K_{11}} AB_{soln} \tag{1.2}$$

where K_{sp} and K_{11} are the cocrystal solubility product and the complexation constant for a 1:1 solution complex between A and B. K_{sp} and K_{11} are given by

$$K_{sp} = [A][B] \tag{1.3}$$

$$K_{11} = \frac{[AB]}{[A][B]} \tag{1.4}$$

under the assumption of dilute conditions where activities are approximated by concentrations. By mass balance, where $[A]_T$ and $[B]_T$ are the total analytical concentrations of A and B,

$$[A]_T = [A] + [AB] \tag{1.5}$$

$$[A]_T = \frac{K_{sp}}{[B]_T} + K_{11}K_{sp} \tag{1.6}$$

Equation (1.6) is an expression of the cocrystal solubility (in terms of drug concentration) as a function of the coformer concentration at equilibrium. Figure 1.2 shows the solubility of a 1:1 cocrystal of carbamazepine and nicotinamide (CBZ-NCT) in three

organic solvents. Figure 1.2 shows that cocrystal solubility decreases as a function of

coformer concentration.
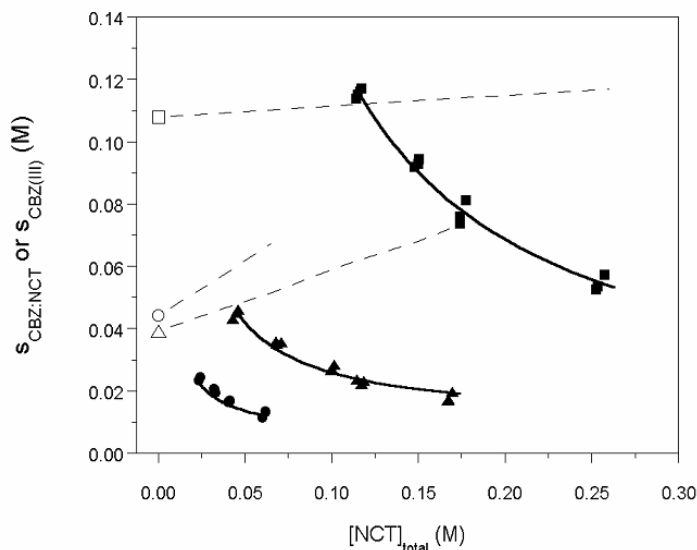
Figure 1.2. Solubility of 1:1 CBZ-NCT cocrystal at 25 °C as a function of total NCT concentration in ethanol, 2-propanol, and ethyl acetate.[41] The solid lines represent the predicted solubility according to Equation (1.6). Filled symbols are experimental cocrystal solubility values in ($\blacksquare$) ethanol, ($\blacktriangle$) 2-propanol, and ($\bullet$) ethyl acetate.

For a 1:1 cocrystal, the cocrystal solubility in solutions containing stoichiometric solution

concentrations of A and B, S_{AB}, is given by

$$S_{AB} = [A]_T = [B]_T \tag{1.7}$$

$$S_{AB} = \sqrt{K_{sp}} \tag{1.8}$$

if we assume $K_{11}K_{sp} \ll S_{AB}$.

Measuring solubility of metastable cocrystal phases

Cocrystals are often selected for their high solubilities relative to the drug.

Cocrystals that are highly soluble relative to drug can transform, sometimes very rapidly,

to the less soluble crystalline drug. Equilibrium solubilities that use drug concentration as a measure of cocrystal solubility are confounded by such conversions, which can lead to underestimation of true cocrystal solubilities. Kinetic solubility measurements are limited by the kinetics of transformation and depend highly on experimental conditions, which are often empirically selected.

A method was developed by Good et $al.$ to measure cocrystal solubility under equilibrium conditions and use mathematical models to extrapolate the solubility under stoichiometric conditions.[49] This method measured the solution composition where two solids (cocrystal and one of the cocrystal components) and a solution coexist at equilibrium. According to Gibbs' phase rule, at constant temperature (and pH) the solution concentrations of drug and coformer are independent of the ratios of solid components. This point is known as a eutectic point or transition concentration. Multiple eutectic points can exist depending on what solid phases coexist at equilibrium. In the case of a cocrystal AB with no other stoichiometries or polymorphs, two eutectics exist; the first is between solid drug, cocrystal, and solution, and the second is between solid coformer, cocrystal, and solution.

Figure 1.3 shows the schematic pathway to determine the solubility of cocrystal via the eutectic point. The intersection of cocrystal and drug solubilities is the eutectic between solid drug, cocrystal, and solution. From the concentrations of drug and coformer at the eutectic, the cocrystal solubility product K_{sp} can be calculated.
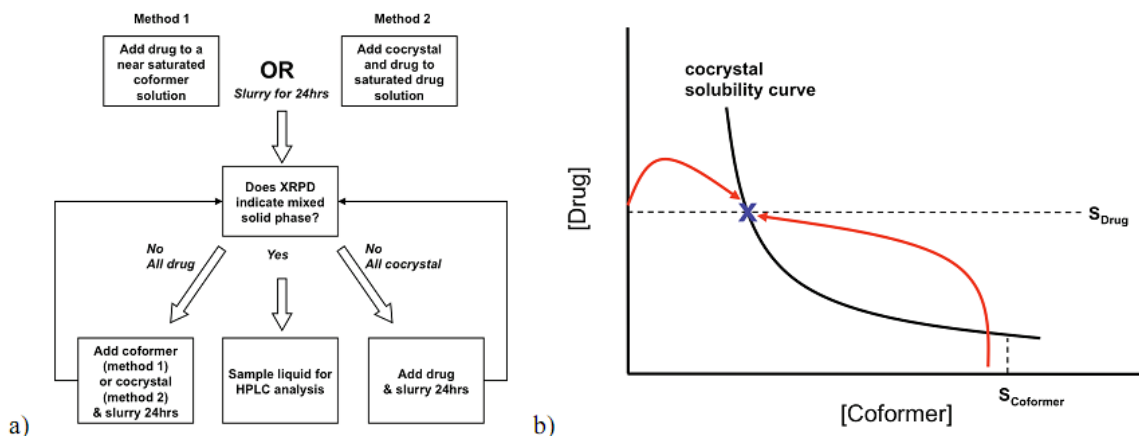
Figure 1.3. (a) Flowchart of method used to establish the invariant point and determine equilibrium drug and coformer eutectic concentrations. (b) Schematic phase solubility diagram that illustrates two pathways to the eutectic point (marked X).[49]

Cocrystal solubility dependence on coformer solubility

The solubilities of twenty-five cocrystals were studied and ranked according to their solubility advantage over drug.[49] The cocrystals were various combinations of three drugs (carbamazepine, theophylline, and caffeine) and seven coformers (malonic acid, nicotinamide, salicylic acid, saccharin, succinic acid, glutaric acid, and oxalic acid) in four solvents (water, isopropyl alcohol, methanol, and ethyl acetate). The measured cocrystal solubilities ranged from 0.1 to over 100-fold their respective drug solubilities and the coformer solubilities spanned several orders of magnitude, from 10^{-2} m to 10^{1} m.

Figure 1.4 shows the cocrystal to drug solubility ratio for against the coformer to drug solubility ratio for each respective cocrystal. The dependence was demonstrated to be linear, where larger coformer to drug solubility ratios resulted in cocrystals that were more soluble relative to the drug. The work demonstrated that cocrystal solubility enhancement could be rationally selected based on knowledge of the coformer solubility, and that measuring the drug and coformer eutectic concentrations was a rapid and reliable

14

method of assessing cocrystal solubility, especially with cocrystals that were highly

soluble relative to drug.
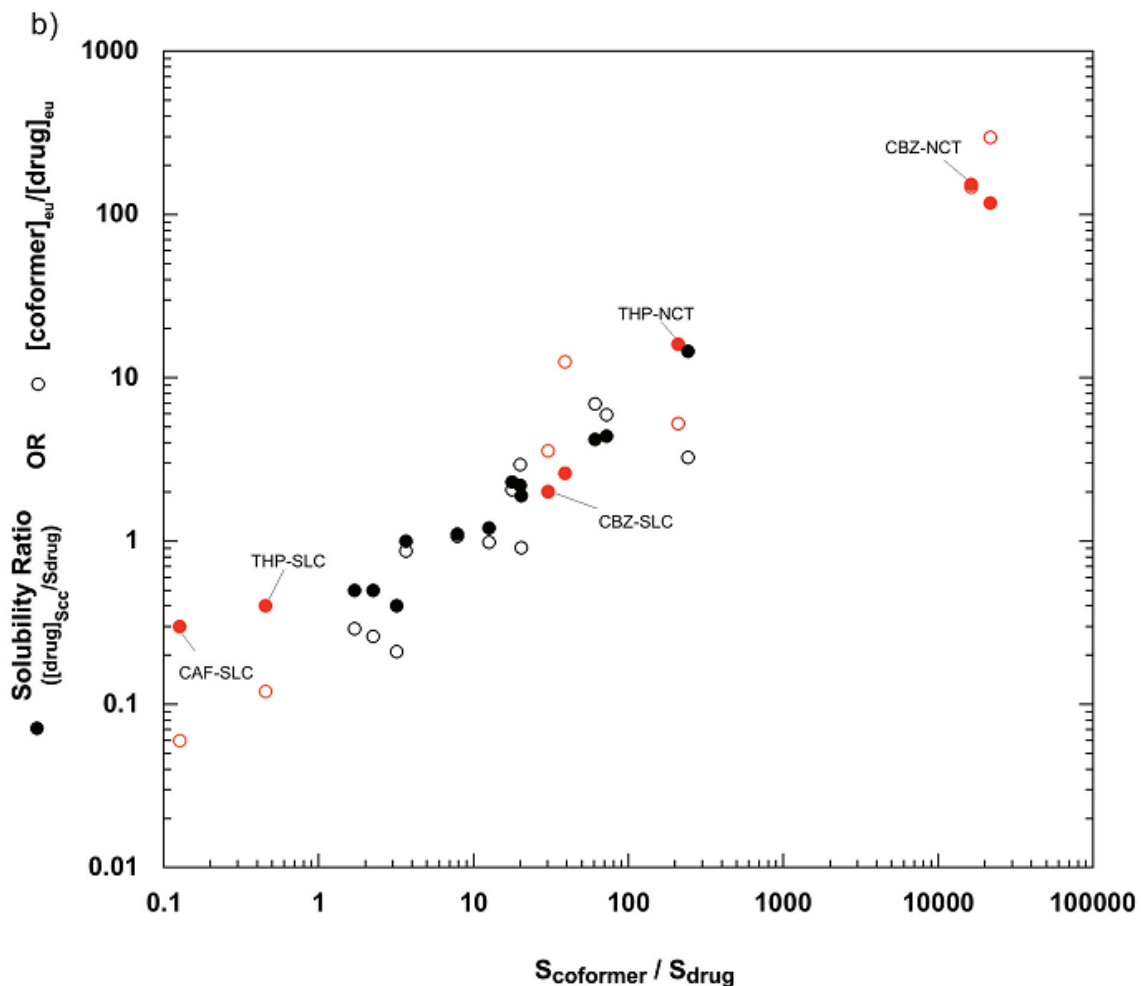
Figure 1.4. The ratio of coformer to drug solubility plotted against the cocrystal solubility ratio (filled circles) and the ratio of coformer to drug eutectic concentrations (open circles).[49] All aqueous samples are shown in red. Several cocrystals with the same coformers are labeled.

Cocrystal systems with multiple stoichiometries

A study of carbamazepine-4-aminobenzoic acid (CBZ-4ABA) cocrystal in

ethanol revealed that different cocrystal stoichiometries could be stable in the same

solvent depending on the solution concentration of coformer.[63] Solid phase analysis

showed that in pure solvent, 2:1 cocrystal transformed to the crystalline drug CBZ

(marketed form III). At low 4ABA concentrations, the 2:1 form was the most favorable

while at high 4ABA concentrations the 1:1 form was most favorable.

These findings were explained by investigation of the solubilities of CBZ-4ABA

cocrystal (2:1 and 1:1 forms) and CBZ measured as a function of 4ABA concentration,

shown in Figure 1.5. Mathematical models were developed based on cocrystal solution

phase chemistry that identified the solution concentrations of coformer where crystalline

CBZ, 2:1 cocrystal, and 1:1 cocrystal were thermodynamically stable. The work

demonstrated that (1) the thermodynamically favorable cocrystal stoichiometry depended

on solution concentrations of reactants, (2) a eutectic point existed where the solid phases

at equilibrium were 2:1 and 1:1 forms of CBZ-4ABA, (3) eutectic points were essential

in identifying the regions of stability for each cocrystal stoichiometry, and (4)

transformation pathways of cocrystal could be predicted from mathematical models

describing cocrystal solubility.
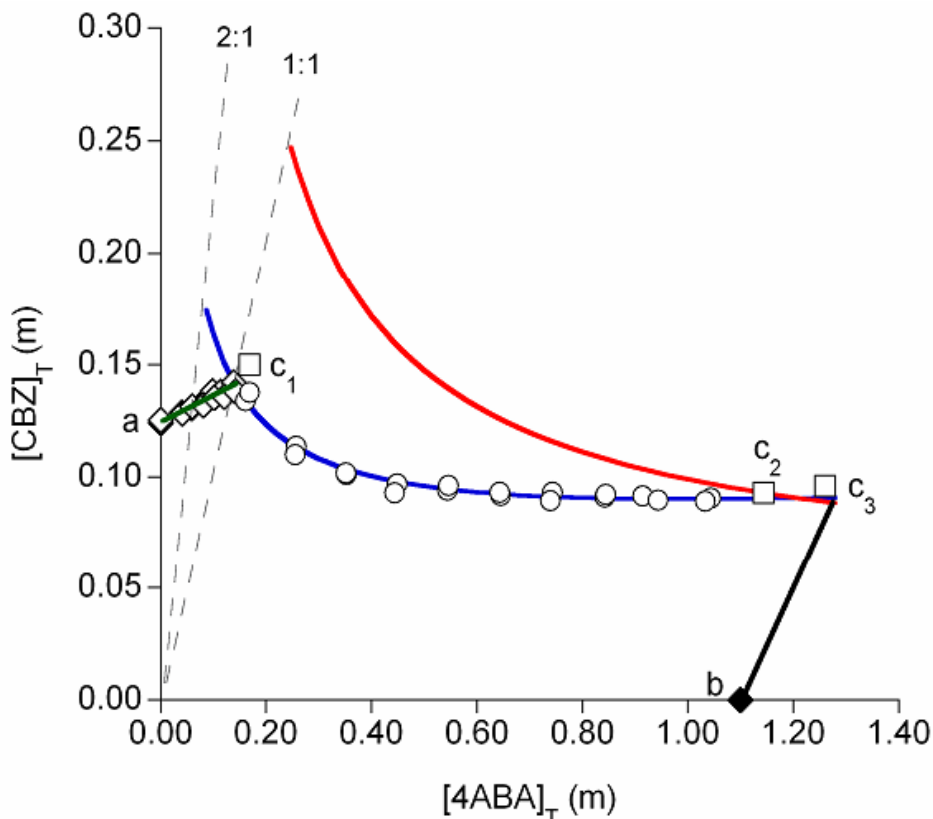
Figure 1.5. Phase solubility diagram for CBZ−4ABA in ethanol at 25˚C showing reactant solution concentrations ($[CBZ]_T$ and $[4ABA]_T$) at equilibrium with CBZ (◊), 2:1 cocrystal (○), or 4ABA (♦).[63] Measured solubility of CBZ(III) and 4ABA in neat ethanol are indicated by the points 'a' and 'b', respectively. Eutectic points c_1, c_2, and c_3 are represented by (□). Dashed lines correspond to solution reactant stoichiometries equal to that of cocrystals. Blue line refers to the 2:1 cocrystal, red line refers to 1:1 cocrystal, and green refers to CBZ.

Role of additives in cocrystal research

Additives and excipients are commonplace in pharmaceutical research, testing, and processing. Surfactants are particularly important additives that have multitudinous pharmaceutical applications as solubilizers, emulsifiers, detergents, foaming agents, lubricants, etc.[64-66] Currently there exist several instances of excipient use in cocrystal research.

In particular, Remenar *et al.* investigated the influence of surfactant (sodium lauryl sulfate, SLS) and polymer (polyvinylpyrollidone, PVP) mixtures on dissolution and phase stability of a 1:1 cocrystal of celecoxib and nicotinamide.[20] Celecoxib-nicotinamide cocrystal was suspended in aqueous media with varying pH, ionic strength, and SLS concentration for 5 minutes. Cocrystal was found to transform to drug in all cases, but the presence of SLS resulted in transformation to different polymorphs of celecoxib under certain conditions. This implies that excipients such as SLS can affect which solid forms are favorable in solution and the kinetics of transformation to those solid forms. Similarly, dissolution of celecoxib-nicotinamide cocrystal into aqueous media (pH 6.5) containing 1% SLS demonstrated that a 5-minute "presuspension" process could lead to variable dissolution rates based on extent of transformation from cocrystal to drug, which could compromise a potential dosage form. Thus, mixtures of cocrystal, PVP K-30, and SLS were formulated to inhibit the transformation to less soluble drug. Dissolution of cocrystal, PVP, and SLS mixtures into aqueous media (pH 6.5) containing 1% SLS exhibited dissolution rates comparable to amorphous form/PVP mixtures in the same media. The authors attributed this behavior to transformation from cocrystal to amorphous mediated by PVP. This investigation, while preliminary, clearly demonstrated that solution conditions (such as pH) and excipients (PVP, SLS) affected cocrystal solution phase behavior. The major limitation of this work is the lack of quantitative theoretical treatments and mechanistic understanding of excipient effects on cocrystal solution chemistry that can be applied across different cocrystal systems and solution conditions.

Bak *et al.* reported the serendipitous discovery of a 1:1 cocrystal of Amgen compound AMG517 with sorbic acid which precipitated in a suspending vehicle Oraplus®.[43, 50] The suspending vehicle had a number of components, which included 10% (w/v) Pluronic F108®, part of a class of block copolymer surfactants known to strongly solubilize hydrophobic drugs.[67-70] The authors maintained the use of Pluronic F108® in cocrystal synthesis and administration to rats for pharmacokinetic study. C_{max} and plasma AUC were greatly increased for equivalent doses of cocrystal relative to crystalline drug, and showed that AMG517-sorbic acid cocrystal had higher solubility and dissolution than drug in fasted state simulated intestinal fluid (FaSSIF, which contains the biorelevant surfactant sodium taurocholate). The authors noted the apparent contradictory nature of forming the cocrystal in certain surfactant solutions (Oraplus®) and obtaining improved solubility and dissolution characteristics over drug in other surfactant-containing solutions (FaSSIF). As with Remenar and coworkers, the major challenge is constructing a theoretical framework that explains excipient effects on cocrystal solution chemistry, which can then be applied to other cocrystal systems.

Others have investigated cocrystal dissolution in media that contains surfactants, without quantifying the contribution of the surfactant on cocrystal solution chemistry.[44, 71]

Statement of dissertation research

The purpose of this dissertation is to investigate the influence of pH and micellar solubilization on cocrystal solubility, stability, and eutectic points. The number of discovered cocrystals is increasing rapidly, and there is an emerging need for rational methods of selecting cocrystals and evaluating their physicochemical properties. Studies on cocrystal dissolution and bioavailability often use empirically selected pH conditions and additive concentrations without considering the impact of ionization and micellar solubilization. This creates a substantial risk of producing experimental results that are not generalizable to other solution conditions or cocrystal systems. The objective of this work is to develop a theoretical framework that explains cocrystal solution chemistry in terms of experimentally accessible thermodynamic parameters. The following chapters model and explain cocrystal solubility and stability by considering various solution phase equilibria.

Chapter 2 considers the contribution of ionization to cocrystal solubility. Most cocrystals contain at least one ionizable component; this chapter demonstrates that an ionizable coformer imparts pH-dependent solubility to a cocrystal of a nonionizable drug. Mathematical equations are developed that describe cocrystal solubility in terms of thermodynamic parameters (solubility product K_{sp} and acid dissociation constant K_a) and solution $[H^+]$. Cocrystal solubility is shown to increase as ionization increases, and can change by orders of magnitude when $pH > pK_a$. This can have important implications when selecting conditions to evaluate cocrystal solubility and dissolution.

Chapter 3 investigates the role of micellar solubilization on cocrystal solubility and stability. The objective of this chapter is to study the role of micellar surfactants in

changing cocrystal solubility and stability relative to drug. Mathematical equations are developed based on cocrystal dissociation, component ionization, and micellar solubilization equilibria that describe cocrystal solubility as a function of thermodynamic parameters (K_{sp}, K_a, and micellar solubilization constant K_s) and solution [H^+]. This chapter demonstrates for the first time that cocrystal phase stability depends on micellar surfactant concentration, whose mechanism is identified as a differential solubilization between drug and coformer by the micelles. Based on these equations, a novel concept called the critical stabilization concentration (CSC) is introduced that describes the surfactant concentration at which an otherwise unstable cocrystal (under stoichiometric conditions) achieves thermodynamic stability in micellar solutions.

Chapter 4 investigates methods to engineer cocrystal solubility, stability, and pH_{max} by micellar solubilization. This expands the theoretical framework introduced in the previous chapter to describe solubility and stability of cocrystals of different stoichiometry and ionization properties. Additional mathematical equations are developed that predict CSC from experimentally accessible thermodynamic parameters. Several methods are developed to measure and/or estimate CSC for a cocrystal, based on cocrystal solubilities measured in pure water and thermodynamic constants describing ionization and micellar solubilization (K_a, K_s). This chapter discusses and challenges the implications of the model's predictions of cocrystal solubility and CSC with a series of cocrystals of the poorly soluble drug carbamazepine (CBZ).

Chapter 5 considers the influence of micellar surfactants on cocrystal eutectic points. Cocrystal eutectic points are points that describe where two solid phases and solution coexist at equilibrium; eutectic points demarcate regions of thermodynamic

stability for the cocrystal and its components in the phase diagram. Mathematical equations based on cocrystal solution phase equilibria are developed that describe how the regions of cocrystal stability shift due to micellar solubilization of the cocrystal components. This chapter investigates the contribution of micellar solubilization and ionization on the solution concentrations of cocrystal components at the eutectic point for a series of CBZ cocrystals. The objective of this study is to identify and explain how micellar solubilization alters regions of cocrystal stability.

The conclusions of this dissertation and future directions of this research are discussed in Chapter 6. Several of the chapters in this dissertation are published. The work in Chapter 2 is presented in *Crystal Growth & Design* 2009, 9(9), 3976-3988. Chapter 3 is the topic of a publication in *Crystal Growth & Design* 2010, 10(5), 2050-2053. Chapter 4 is a manuscript currently under review in *Journal of Pharmaceutical Sciences* 2011. Chapter 5 is a manuscript currently under review in *Crystal Engineering Communications* 2011.

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CHAPTER 2

Customizing cocrystal solubility-pH dependence

Introduction

Cocrystals have the potential to increase the solubility of a poorly soluble drug, which can then enhance delivery of solubility-limited pharmaceutical compounds.[1-4] Selecting coformers of different physicochemical nature than the drug can generate a wide variety of solid forms that have physicochemical properties distinct from the solid drug. Though a preponderance of cocrystals reported in the literature includes ionizable components,[5-7] the dependence of cocrystal solubility on ionization is rarely addressed. Literature on other multicomponent systems such as salts recognize the importance of pH in determining solubility and phase stability.[8, 9]

Current mathematical models that describe cocrystal solubility consider the contributions of cocrystal dissociation and solution complexation.[10] The solution chemistry of cocrystals has been shown to be critical in determining the solubility advantage of cocrystals and the solution conditions where cocrystal is the thermodynamically stable phase.[7, 10, 11] This chapter provides a theoretical framework for considering the effect of ionization on cocrystal solubility. Mathematical models are developed based on cocrystal solution phase chemistry that predict cocrystal solubility,

eutectic point, and the eutectic constant K_{eu} as a function of pH based on experimentally accessible thermodynamic parameters (cocrystal K_{sp} and component pK_a).

The model is evaluated by a series of cocrystals of a poorly soluble nonionizable drug carbamazepine (CBZ). The selected cocrystals include 1:1 carbamazepine-salicylic acid (CBZ-SLC), 1:1 carbamazepine-saccharin (CBZ-SAC), and 2:1 carbamazepine-4-aminobenzoic acid monohydrate (CBZ-4ABA-HYD). The cocrystals include the two most abundant stoichiometries and the coformers have ionization properties common among reported cocrystals. Salicylic acid and saccharin are monoprotic weak acids; salicylic acid has a reported pK_a of 3.0,[12] and saccharin has a range of reported pK_a values between 1.8 and 2.2.[13, 14] 4-aminobenzoic acid is amphoteric with pK_a values of 2.6 and 4.8.[15]

Theoretical

Cocrystal solubility-pH dependence

Cocrystal solubility was previously shown to be governed by solubility product behavior and solution complexation constants (if applicable).[10] The solubility of a 1:1 cocrystal RHA, where R is a nonionizable hydrophobic drug and HA is a weakly acidic coformer, can be determined by considering the solution equilibria that affect R and HA. The derivations for all equations presented here can be found in the Appendix. The relevant equilibria that describe cocrystal dissociation and component ionization are

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{2.1}$$

$$HA_{aq} \xrightleftharpoons{K_a} A^-_{aq} + H^+_{aq} \tag{2.2}$$

where K_{sp} is the cocrystal solubility product and K_a is the acid dissociation constant. Subscript aq indicates aqueous phase. In this analysis, solution complexation is negligible. Assuming dilute conditions where concentrations replace activities, the equilibrium constants are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \tag{2.3}$$

$$K_a = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{2.4}$$

The cocrystal solubility in solutions containing the stoichiometric solution concentrations of cocrystal components (referred to as the cocrystal stoichiometric solubility), S_{RHA}, is given by

$$S_{RHA,aq} = [R]_T = [A]_T \tag{2.5}$$

where subscript T indicates total (unionized + ionized). Therefore,

$$S_{RHA} = [R]_{aq} = [HA]_{aq} + [A^-]_{aq} \tag{2.6}$$

Substituting (2.3) and (2.4) into (2.6),

$$S_{RHA} = \sqrt{K_{sp}\left(1 + \frac{K_a}{[H^+]}\right)} \tag{2.7}$$

Equation (2.7) indicates that cocrystal RHA solubility is dependent on the cocrystal solubility product K_{sp}, the K_a of the ionizable coformer, and solution $[H^+]$. The dependence of stoichiometric solubility on pH for cocrystal RHA is shown in Figure 2.1.
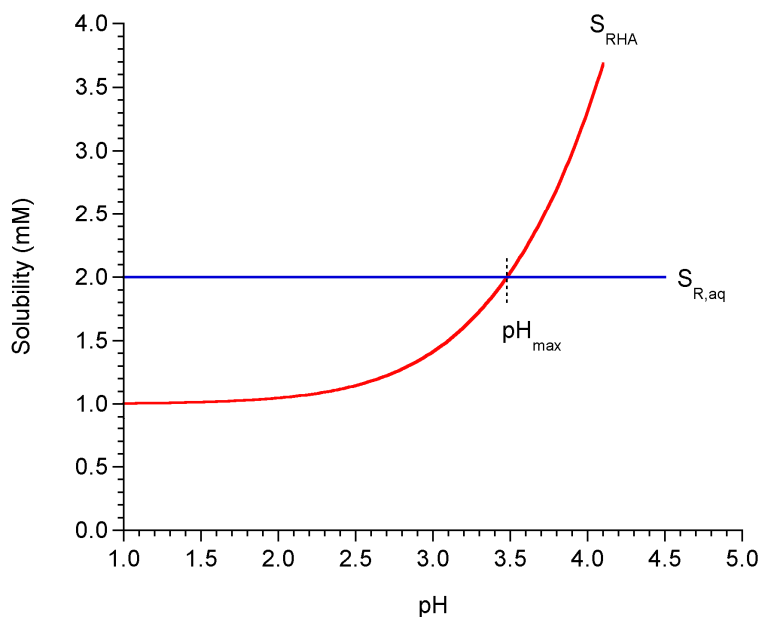
Figure 2.1. Dependence of cocrystal stoichiometric solubility and drug solubility on pH according to Equation (2.7) for a hypothetical cocrystal RHA. There exists a pH_{max} at the pH where cocrystal stoichiometric solubility equals drug solubility. $K_{sp} = 1$ mM^2, $pK_a = 3$, $S_{R,aq} = 2$ mM.

Cocrystal solubility increases with increasing pH when the coformer is a weak acid. Cocrystal RHA achieves pH-dependent solubility while crystal R solubility remains unaffected by pH. This analysis shows that an ionizable coformer imparts pH-dependent solubility to a cocrystal, even when the drug is nonionizable. When $pH = pK_a$, cocrystal solubility is $\sqrt{2}$-fold higher than under unionized conditions, whereas a weak acid's solubility under the same conditions is 2-fold greater than the intrinsic solubility of the acid.

Figure 2.1 predicts the existence of a pH_{max}, a pH where cocrystal stoichiometric solubility and drug solubility are equal. A cocrystal with a pH_{max} is thermodynamically stable in nonionizing conditions and unstable in ionizing conditions.

Cocrystal solubility as a function of coformer concentration (which includes nonstoichiometric solution concentrations of drug and coformer) is determined from the mass balance on each of the cocrystal components,

$$[R]_T = [R]_{aq} \tag{2.8}$$

$$[A]_T = [HA]_{aq} + [A^-]_{aq} \tag{2.9}$$

By combining Equations (2.3), (2.4), (2.8), and (2.9)

$$[R]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a}{[H^+]}\right) \tag{2.10}$$

The total drug concentration at equilibrium, $[R]_T$, is inversely proportional to the total coformer concentration at equilibrium $[A]_T$. Thus, $[R]_T$ decreases with increasing $[A]_T$, which is a consequence of cocrystal solubility product behavior.

Figure 2.2 shows the dependence of cocrystal solubility (given by $[R]_T$) on coformer concentration and pH according to Equation (2.10). Figure 2.2 shows that cocrystal solubility is predicted to increase with increasing ionization (pH > pK$_a$) and decrease with increasing coformer concentration. According to this analysis, drug and cocrystal can be equally soluble under certain solution conditions, which are denoted by the intersection between drug and cocrystal solubilities.

Cocrystal eutectic point-pH dependence

These intersection points, referred to as the eutectic points (and also known as transition concentrations) have several main features. At the eutectic point, two solid phases (*i.e.* cocrystal and one of the cocrystal components) and one liquid phase (solution) coexist in equilibrium. At constant temperature and pH, the solution

composition is independent of the relative ratios of solid components, which makes eutectic point measurements an experimentally accessible method of evaluating cocrystal solubility regardless of the solubility relationship between cocrystal and its components. The eutectic point is characterized by the solution concentrations of drug and coformer and the solution pH at equilibrium. In Figure 2.2 the intersections between the cocrystal and drug solubilities indicate the eutectic concentrations of drug and coformer of the cocrystal RHA, which demarcate the regions of thermodynamic stability and instability for the cocrystal. A thorough discussion of cocrystal eutectic points is presented elsewhere.[7, 16]

At least two eutectic points exist for any given cocrystal. For a cocrystal RHA, there exists a eutectic between solid drug, cocrystal, and solution (E_1), and another between solid coformer, cocrystal, and solution (E_2). Other eutectic points exist depending on which solid phases coexist at equilibrium, such as cocrystals of two different stoichiometries.[17] E_1 is the focus for the work described here; E_1 is relevant for cocrystals of poorly soluble drugs because it describes the minimum coformer concentration required for the cocrystal to be thermodynamically stable. The maximum coformer concentration where the cocrystal is thermodynamically stable is given by E_2, and is generally limited by the solubility of the coformer.
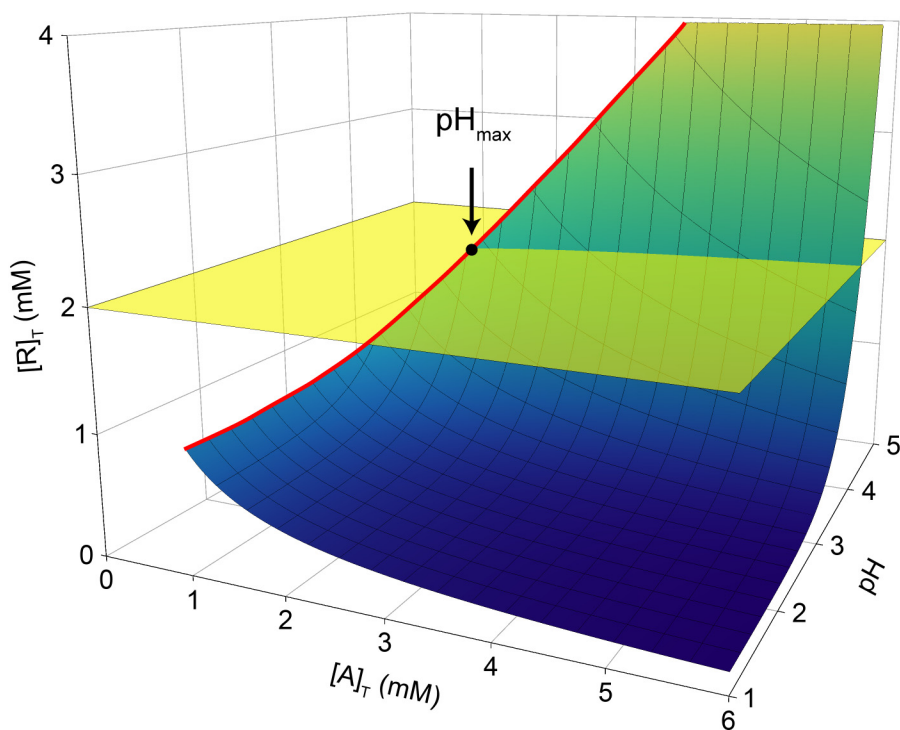
Figure 2.2. Dependence of drug concentration ($[R]_T$) on coformer concentration ($[A]_T$) and pH for a hypothetical cocrystal RHA and solution at equilibrium according to Equation (2.10). Blue/green surface indicates cocrystal solubility, red line indicates cocrystal stoichiometric solubility. Yellow plane indicates drug solubility. Eutectic points are given by the intersection of cocrystal and drug solubilities. The intersection of the cocrystal stoichiometric solubility and drug solubility is the pH$_{max}$. $K_{sp} = 1$ mM^2, pK$_a$ = 3, $S_{R,aq} = 2$ mM.

At the eutectic between solid drug, cocrystal, and solution (E_1), the total concentration of drug at the eutectic point, $[R]_{eu}$, is given by the solubility of R in the eutectic solution. In the absence of solution complexation between drug and coformer, this is equivalent to the aqueous solubility of the drug crystal,

$$[R]_{eu} = S_{R,aq} \tag{2.11}$$

and the total concentration of coformer at the eutectic point, $[A]_{eu}$, is given by Equation (2.10).

$$[A]_{eu} = \frac{K_{sp}}{[R]_{eu}} \left(1 + \frac{K_a}{[H^+]} \right)$$

(2.12)

Equations (2.11) and (2.12) predict that eutectic coformer concentrations increase with pH according to the pK_a of the coformer, and that eutectic drug concentrations remain constant with respect to pH. For cocrystal RHA, the predicted drug and coformer concentrations at the eutectic are shown in Figure 2.3.
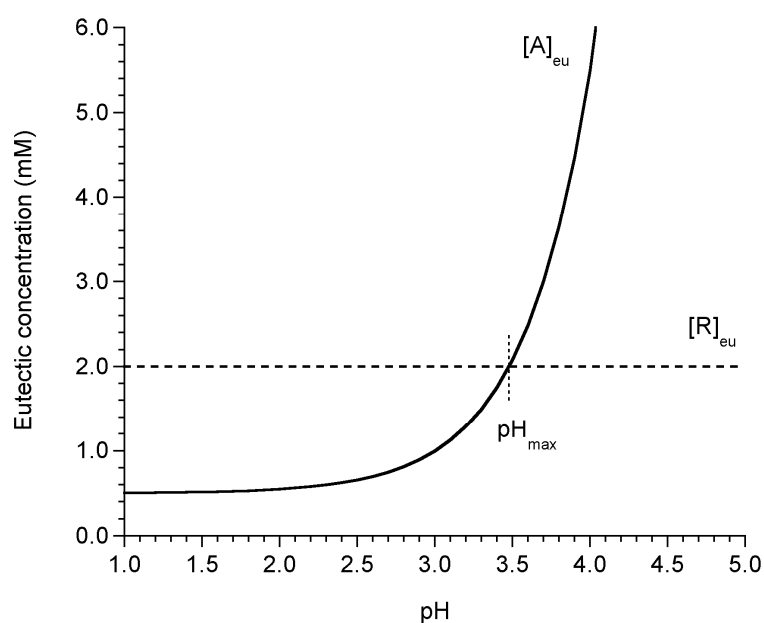
Figure 2.3. Predicted dependence of drug and coformer eutectic concentrations ([R]$_{eu}$ and [A]$_{eu}$) on pH according to Equations (2.11) and (2.12) for a hypothetical cocrystal RHA. Intersection of [R]$_{eu}$ and [A]$_{eu}$ indicates pH$_{max}$, where cocrystal stoichiometric solubility is equal to the drug solubility. $K_{sp} = 1$ mM^2, $pK_a = 3$ $S_{R,aq} = 2$ mM.

Cocrystal solubilities for cocrystals of different stoichiometry and ionization properties are listed in Table 2.1. The cocrystal and drug solubility-pH profiles for these cocrystals are shown in Figure 2.4. These cocrystals represent the two most abundant cocrystal stoichiometries and the coformers have ionization properties common among reported cocrystals. Figure 2.4 shows that a variety of cocrystal solubility-pH profiles

39

can be generated from combinations of drug/coformer ionization properties. This allows cocrystals to have customizable solubility-pH dependencies that are distinct from the drug crystal.
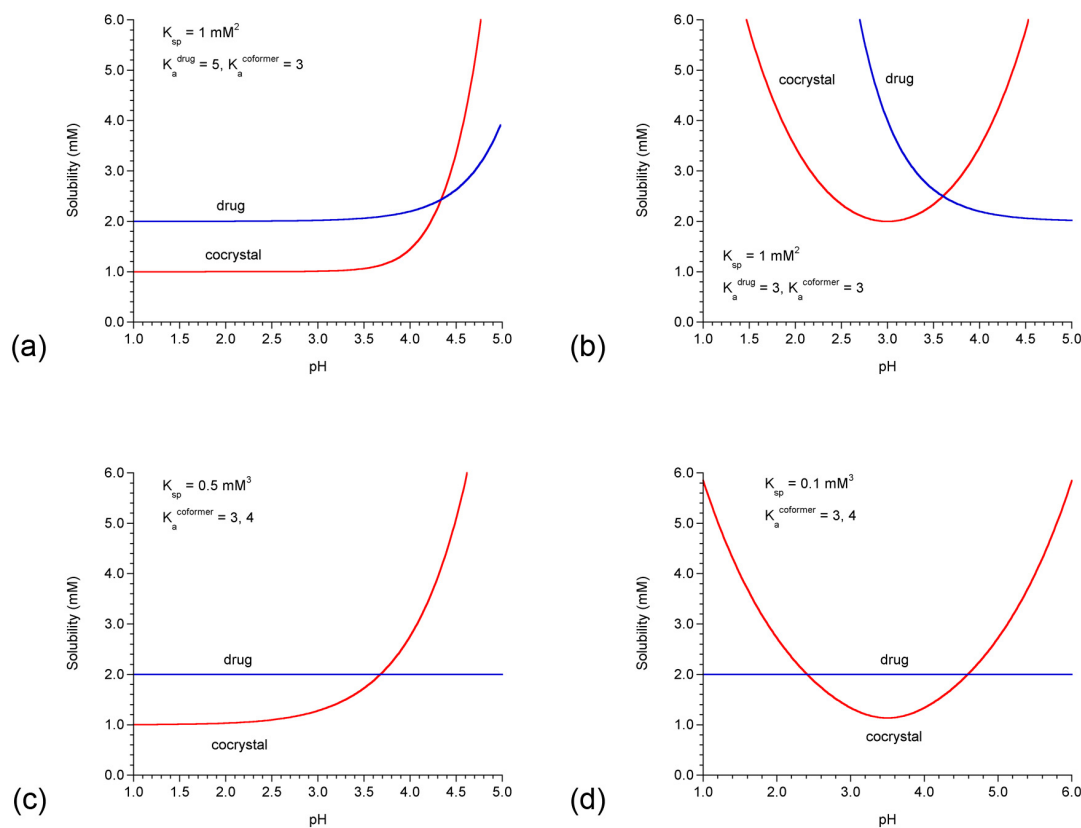
Figure 2.4. Cocrystal stoichiometric solubility-pH dependence for hypothetical cocrystals of different stoichiometry and ionization properties according to equations in Table 2.1. Cocrystals represented are (a) HXHA (b) BHA (c) R_2H_2A (d) R_2HAB.

Eutectic constant K_{eu}

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

$$K_{eu} = \frac{a_{A,eu}}{a_{R,eu}}$$
(2.13)

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.[16, 18, 19]

K_{eu} in the context of cocrystals has been shown to describe cocrystal thermodynamic stability relative to drug.[16] K_{eu} is measured under equilibrium conditions, though it is not a true equilibrium constant. Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}}$$ (2.14)

Under certain conditions, K_{eu} can be related to the ratio of cocrystal to drug solubility. This can be accomplished when $[R]_{eu,T} = S_{R,T} = [R]_{aq}$ and $[A]_{eu,T} = [HA]_{aq} + [A^-]_{aq}$. If the preceding assumptions are justified, then for a 1:1 cocrystal (*i.e.* RHA)

$$K_{eu} = \left(\frac{S_{RHA}}{S_{R,aq}}\right)^2$$ (2.15)

For a 2:1 cocrystal (*i.e.* R_2H_2A),

$$K_{eu} = \frac{1}{2}\left(\frac{S_{R_2H_2A}}{S_{R,aq}}\right)^3$$ (2.16)

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

Table 2.1. Equations that describe cocrystal solubility as a function of cocrystal K_{sp}, component $K_a(s)$, and solution $[H^+]$.

Cocrystal	Solubility	Equation
RHA 1:1 nonionizable : monoprotic acidic	$S_{RHA} = \sqrt{K_{sp}\left(1 + \dfrac{K_a}{[H^+]}\right)}$	(2.12)
HXHA 1:1 monoprotic acidic : monoprotic acidic	$S_{HXHA} = \sqrt{K_{sp}\left(1 + \dfrac{K_a^{HX}}{[H^+]}\right)\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right)}$	(2.17)
BHA 1:1 monoprotic basic : monoprotic acidic	$S_{BHA} = \sqrt{K_{sp}\left(1 + \dfrac{[H^+]}{K_a^B}\right)\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right)}$	(2.18)
R$_2$H$_2$A 2:1 nonionizable : diprotic acidic	$S_{R_2H_2A} = \sqrt[3]{\dfrac{K_{sp}}{4}\left(1 + \dfrac{K_a^{H_2A}}{[H^+]} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}\right)}$	(2.19)
R$_2$HAB 2:1 nonionizable : amphoteric	$S_{R_2HAB} = \sqrt[3]{\dfrac{K_{sp}}{4}\left(1 + \dfrac{[H^+]}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]}\right)}$	(2.20)

Table 2.2. Equations that describe the dependence of drug and coformer eutectic concentrations on cocrystal K_{sp}, component $K_a(s)$, drug aqueous solubility, and solution $[H^+]$.

Cocrystal	Drug eutectic concentration	Equation	Coformer eutectic concentration	Equation
RHA 1:1 nonionizable : monoprotic acidic	$[R]_{eu} = S_{R,aq}$	(2.11)	$[A]_{eu} = \dfrac{K_{sp}}{[R]_{eu}}\left(1 + \dfrac{K_a}{[H^+]}\right)$	(2.12)
HXHA 1:1 monoprotic acidic : monoprotic acidic	$[X]_{eu} = S_{HX,aq}\left(1 + \dfrac{K_a^{HX}}{[H^+]}\right)$	(2.21)	$[A]_{eu} = \dfrac{K_{sp}}{[X]_{eu}}\left(1 + \dfrac{K_a^{HX}}{[H^+]}\right)\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right)$	(2.22)
BHA 1:1 monoprotic basic : monoprotic acidic	$[B]_{eu} = S_{B,aq}\left(1 + \dfrac{[H^+]}{K_a^{B}}\right)$	(2.23)	$[A]_{eu} = \dfrac{K_{sp}}{[B]_{eu}}\left(1 + \dfrac{[H^+]}{K_a^{B}}\right)\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right)$	(2.24)
R$_2$H$_2$A 2:1 nonionizable : diprotic acidic	$[R]_{eu} = S_{R,aq}$	(2.25)	$[A]_{eu} = \dfrac{K_{sp}}{[R]_{eu}^2}\left(1 + \dfrac{K_a^{H_2A}}{[H^+]} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}\right)$	(2.26)
R$_2$HAB 2:1 nonionizable : amphoteric	$[R]_{eu} = S_{R,aq}$	(2.27)	$[AB]_{eu} = \dfrac{K_{sp}}{[R]_{eu}^2}\left(1 + \dfrac{[H^+]}{K_a^{HABH^+}} + \dfrac{K_a^{HAB}}{[H^+]}\right)$	(2.28)

Materials and Methods

Materials

Anhydrous monoclinic carbamazepine (CBZ(III); lot #013K1381 USP grade) was purchased from Sigma Chemical Company (St. Louis, MO), stored at 5 °C over anhydrous calcium sulfate and used as received. Saccharin (SAC; lot # 03111DD) (pK_a = 1.8), salicylic acid (SLC; lot #11111KC) (pKa = 3.0), and 4-aminobenzoic acid (4ABA; lot #05102HD) (pKa = 2.6, 4.8) 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 carbamazepine to nearly saturated solutions of coformer.[11] CBZ-SLC and CBZ-SAC were prepared in ethanol while CBZ-4ABA-HYD was prepared in water. Solid phases were isolated and characterized by XRPD.

Measurement of cocrystal eutectic points

The eutectic concentrations of drug and coformer were measured by HPLC after equilibrating carbamazepine dihydrate and cocrystal in solution at various pH values and at ambient temperature 24±1°C). Solid phases at equilibrium were CBZD and cocrystal. The pH of the solution was adjusted by the addition of small volumes of concentrated HCl or NaOH and the pH at equilibrium was measured. The solid phases at equilibrium

were characterized by XRPD. The system was determined to have reached equilibrium

when two solid phases, drug and cocrystal, were confirmed by XRPD and the solution

concentration remained constant over consecutive days.

Cocrystal solubilities were determined from eutectic concentrations of drug and

coformer from the relations

$$S_{RHA} = \sqrt{[R]_{eu}[A]_{eu}} \tag{2.29}$$

$$S_{R_2HAB} = \sqrt[3]{\frac{[R]_{eu}[A]_{eu}}{4}} \tag{2.30}$$

Equation (2.29) applies to 1:1 cocrystals and (2.30) to 2:1 cocrystals, and both consider

ionization of the coformer.

High performance liquid chromatography (HPLC)

The solution concentration of CBZ and coformer was analyzed by Waters HPLC

(Milford, MA) equipped with a UV/Vis spectrometer detector. Waters' operation

software, Empower, was used to collect and process the data. A C18 Atlantis column

(5μm, 4.6 x 250mm; Waters, Milford, MA) at ambient temperature was used to separate

the drug and the coformer. The mobile phase was composed of 55% methanol and 45%

water with 0.1% trifluoroacetic acid and the flow rate was 1mL/min using an isocratic

method. Injection sample volume was 20μL or 50μL. Absorbance of CBZ, SAC,

4ABA, and SLC was monitored at 284, 260, 284, and 303nm, respectively.

X-ray powder diffraction (XRPD)

XRPD patterns of solid phases were collected with a bench top Rigaku Miniflex X-ray Diffractometer (Danvers, MA) using Cu-Kα radiation ($\lambda = 1.54\text{Å}$), a tube voltage of 30 kV, and a tube current of 15 mA. Data were collected from 2 to 40° at a continuous scan rate of $2.5°$ min^{-1}.

Results

The theoretical framework presented earlier explains the contributions of drug and coformer ionization to cocrystal solubility. A cocrystal of a nonionizable drug can achieve pH-dependent solubility if the coformer is ionizable. This is demonstrated for a series of cocrystals of carbamazepine (CBZ, a nonionizable drug with low aqueous solubility), which include 1:1 cocrystals with monoprotic weakly acidic coformers salicylic acid and saccharin (CBZ-SLC and CBZ-SAC) and a 2:1 cocrystal monohydrate with an amphoteric coformer 4-aminobenzoic acid (CBZ-4ABA-HYD).

Because these cocrystals are reported to transform to CBZD in water, cocrystal stoichiometric solubility is determined from the solution concentrations of drug and coformer at the eutectic point (where CBZD, CBZ cocrystal, and solution coexist in equilibrium at constant temperature and pH) according to equations in Table 2.1. Table 2.3 summarizes the eutectic points measured for CBZ-SLC, CBZ-SAC, and CBZ-4ABA-HYD measured in water as a function of pH, and their estimated cocrystal solubilities under stoichiometric solution conditions according to Equations (2.29) and (2.30). The pH-dependent solubilities of the CBZ cocrystals are shown in Table 2.3.

According to Equations (2.7) and (2.20), cocrystal solubility increases as ionization increases; cocrystal RHA (CBZ-SLC and CBZ-SAC) solubility increases with

46

increasing pH and cocrystal R_2HAB (CBZ-4ABA-HYD) solubility forms a U-shape

solubility-pH profile where solubility reaches a minimum at a certain pH and cocrystal

solubility increases away from that pH.

Figure 2.3 shows the predicted and experimental cocrystal stoichiometric

solubility-pH dependence for CBZ cocrystals according to Equations (2.7) and (2.20).

K_{sp} and K_a values used in predictions are found in

Table 2.4, which are either reported in literature or determined from linear regression of

the coformer eutectic concentrations as a function of pH (Figure 2.7). Figure 2.3 shows

that experiments are in excellent agreement with predicted behavior. CBZ-SLC and

CBZ-SAC have dramatically increased solubilities at pH > pK_a (3.0 and 1.8,

respectively). CBZ-4ABA-HYD solubility, due to the coformer's acidic and basic

properties, achieves a minimum between pH 3 and 4 and increases as pH > 4.8 (pK_a^{HAB})

and pH < 2.6 (pK_a^{HABH+}).

CBZ cocrystal stoichiometric solubilities were higher than the aqueous solubility

of CBZD (0.53 mM REF) at all pH values, thus no pH_{max} exists for the cocrystals

investigated. CBZ-SLC solubility ranged from 1.3 to 6.3-fold that of CBZD between pH

1.0 and 3.9, while CBZ-SAC solubility ranged from 2.3 to 14.4-fold that of CBZD

between pH 1.1 and 3.0. CBZ-4ABA-HYD solubility ranged from 2.5 to 9.3-fold that of

CBZD between pH 4.0 and 1.1. This shows that a cocrystal's solubility advantage over

drug crystal is highly dependent on pH, where high cocrystal solubilities can be achieved

in environments that favor high levels of coformer ionization.

CBZ eutectic concentrations are expected to remain constant because CBZ is

nonionizable while SLC, SAC, and 4ABA eutectic concentrations are expected to

47

increase with increasing ionization according to their respective pK_a values. $[CBZ]_{eu}$ measured in this study varies between 0.59±0.04 mM for CBZ-4ABA-HYD to 0.69±0.03 mM for CBZ-SAC. This value is slightly higher than the reported aqueous solubility of CBZD (0.53 mM[20]). By contrast, Figure 2.6 shows the experimental coformer eutectic concentrations and their predicted dependences according equations in Table 2.2. The experiments confirm the expected behavior that coformer eutectic concentrations increase at pHs where ionization is favorable. Thermodynamic values used in predictions of drug and coformer eutectic concentration pH-dependence are listed in Table 2.4.

The eutectic constant K_{eu} (the ratio of coformer to drug concentrations at the eutectic) increases as the eutectic solution composition becomes more enriched with coformer. K_{eu} is a critical parameter that is proportional to the cocrystal to drug solubility ratio in a manner dependent on cocrystal stoichiometry.[16] The pH-dependence of K_{eu} (Figure 2.6) is evidence that the cocrystal to drug solubility ratio increases as ionization increases, thereby increasing the cocrystal solubility advantage but also making the cocrystal more thermodynamically unstable in solution.

The model equations that predict cocrystal solubility and eutectic concentrations of drug and coformer in Figure 2.5 and Figure 2.6 assume that the thermodynamic parameters (K_{sp}, K_a) are independent of solute concentration. The excellent agreement between experimental and predicted cocrystal solubilities and eutectic concentrations indicates that this assumption is reasonable for the cocrystals studied. Improving the prediction power of the model can be achieved by introducing corrections for activity

when ionic strength is significant or when deviations from Henderson-Hasselbalch behavior is observed for the ionizable compound(s).[21-23]

If the stated assumptions are justified, cocrystal solubility-pH dependence can be estimated for a wide range of pH conditions based on a single eutectic point measurement at a single pH. This can provide a good first approximation for cocrystal solubility and K_{sp} while minimizing the number of necessary experiments.

Table 2.3. Eutectic concentrations of drug and coformer and K_{eu} for CBZ-SLC, CBZ-SAC, and CBZ-4ABA-HYD in water at various pH values. Values in bold measured without adjusting pH.

Cocrystal	pH	[CBZ]$_{eu}$ (mM)	[Coformer]$_{eu}$ (mM)	K_{eu}	Stoichiometric solubility[b] (mM CBZ)
CBZ-SLC	1.04[a]	0.40	1.10	2.75	0.66
	1.05	0.53	1.19	2.24	0.80
	1.07	0.58	1.22	2.12	0.84
	1.94[a]	0.63	1.10	1.75	0.83
	1.98	0.58	1.40	2.40	0.90
	2.16	0.54	1.47	2.73	0.89
	2.87	**0.58**	**2.62**	**4.53**	**1.23**
	2.90	**0.60**	**2.30**	**3.83**	**1.17**
	2.96	**0.59**	**2.79**	**4.75**	**1.28**
	3.76	0.57	12.25	21.49	2.64
	3.78	0.59	12.40	20.91	2.71
	3.87[a]	0.78	14.10	18.08	3.32
CBZ-SAC	1.07	0.61	2.43	3.99	1.21
	1.10[a]	0.70	2.10	3.00	1.21
	1.17	0.57	2.45	4.28	1.19
	1.98	**0.65**	**9.17**	**14.09**	**2.44**
	2.08	**0.57**	**8.88**	**15.45**	**2.26**
	2.12[a]	**0.69**	**8.60**	**12.46**	**2.44**
	2.54	0.68	27.52	40.53	4.32
	2.58	0.62	24.85	39.89	3.93
	2.77	0.74	46.63	63.19	5.87
	2.80[a]	0.83	30.30	36.51	5.01
	2.84	0.69	46.52	67.60	5.66
	2.95[a]	0.90	65.10	72.33	7.65
CBZ-4ABA-HYD	1.08	0.93	138.15	148.55	4.93
	1.52	0.67	55.75	83.21	2.93
	3.93	**0.59**	**6.70**	**11.36**	1.33
	4.75	0.46	10.20	22.17	1.63
	5.28	0.57	29.05	50.96	2.11
	5.33	0.54	22.22	41.48	1.89
	5.34	0.54	22.29	41.58	1.86
	5.36	0.55	24.40	44.60	1.85
	5.36	0.53	24.08	45.22	1.94
	5.37	0.54	24.24	44.93	1.92
	5.39	0.55	22.11	39.89	1.90

[a] Courtesy of Sarah Bethune, University of Michigan[24]
[b] Stoichiometric solubilities calculated according to Equations (2.29) for 1:1 cocrystals and (2.30) for 2:1 cocrystals.
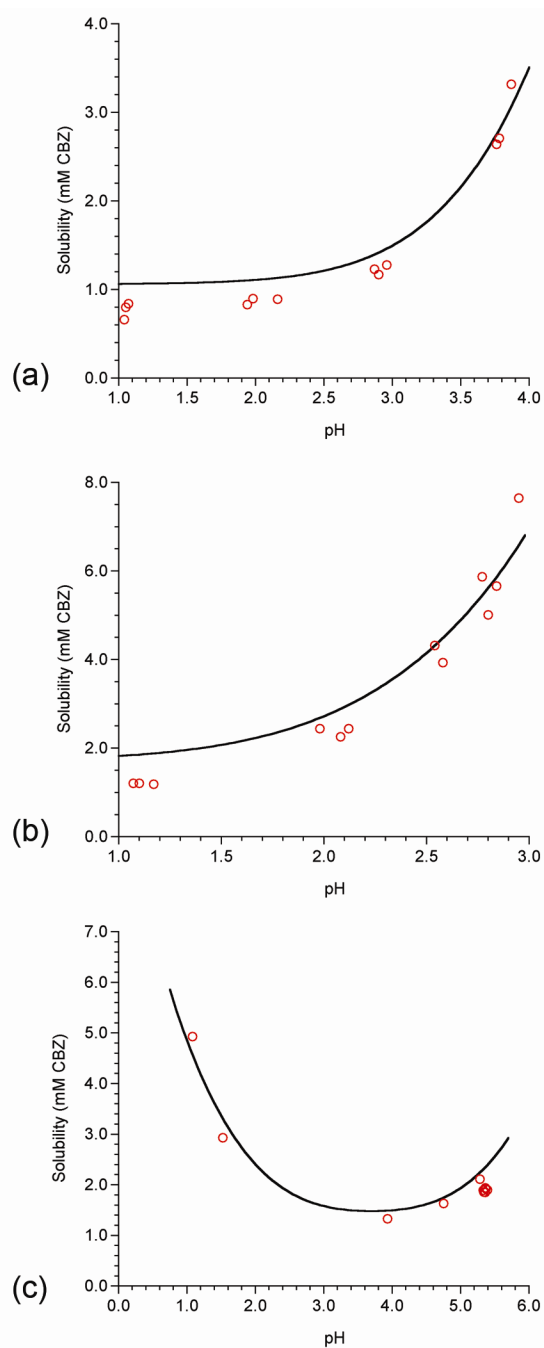
Figure 2.5. Experimental and predicted cocrystal stoichiometric solubilities for (a) CBZ-SLC, (b) CBZ-SAC, and (c) CBZ-4ABA-HYD. Predictions according to Equations (2.7) and (2.20), using K_{sp} and K_a values listed in Table **2.4**.
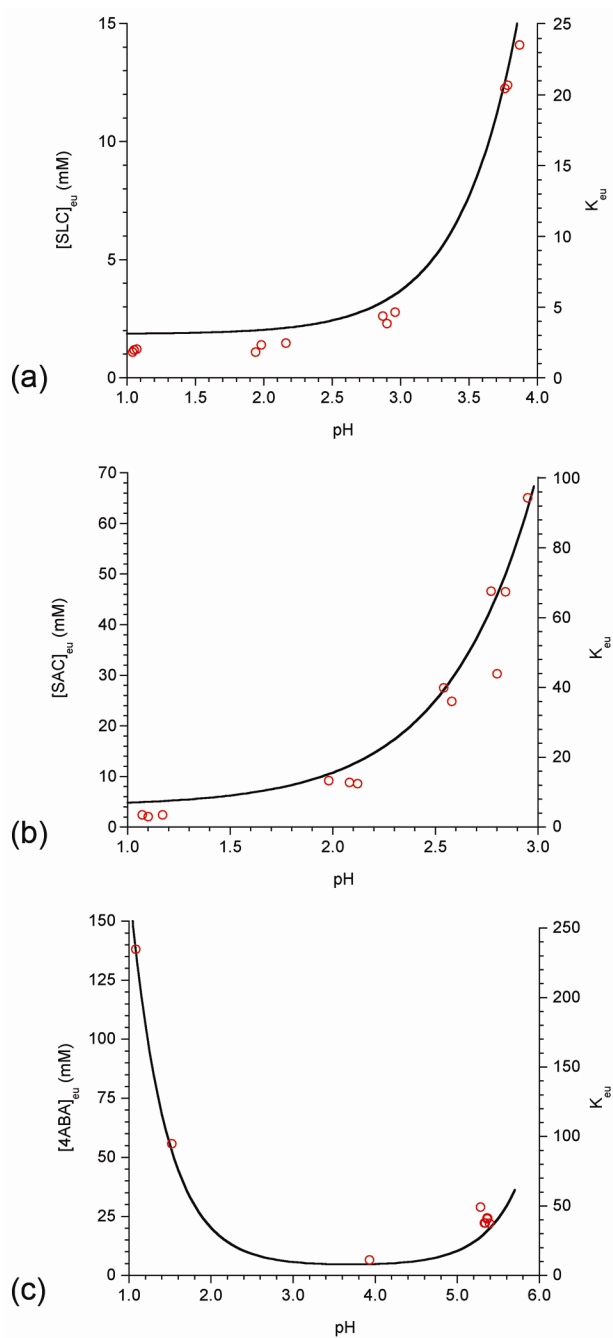
Figure 2.6. Experimental and predicted eutectic concentrations of drug and coformer and K_{eu} for (a) CBZ-SLC, (b) CBZ-SAC, and (c) CBZ-4ABA-HYD. Predictions according to Equations (2.12) and (2.28), using K_{sp} and K_a values listed in Table **2.4**. Solid phases at equilibrium are CBZD and cocrystal.

Table 2.4. Thermodynamic parameters used in predictions of cocrystal solubility and eutectic points. K_a values were obtained from literature. K_{sp} values were calculated from linear regression of eutectic coformer concentrations (Figure 2.7).

Cocrystal	Coformer pK$_a$(s)	Slope[d]	[CBZ]$_{eu}$ (mM)	K_{sp} (mM^2 or mM^3)
CBZ-SLC	3.0[a]	1.87±0.04	0.60±0.03	1.13±0.06
CBZ-SAC	1.8[b]	4.18±0.03	0.68±0.03	2.84±0.13
CBZ-4ABA-HYD	2.6, 4.8[c]	3.87±0.01	0.58±0.04	2.24±0.15

[a] from reference 12
[b] from references 13, 14
[c] from reference 15
[d] from Figure 2.7.
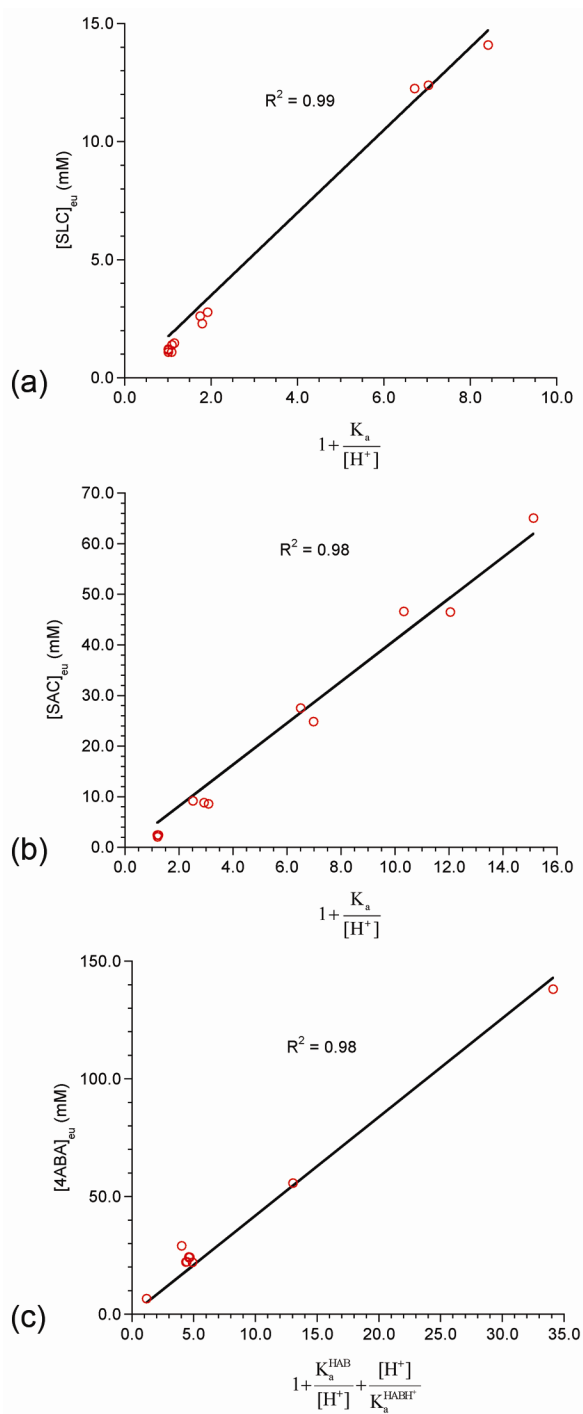
Figure 2.7. Linear regression of CBZ cocrystal eutectic concentrations to determine K_{sp} for (a) CBZ-SLC, (b) CBZ-SAC, and (c) CBZ-4ABA-HYD. Slope = $K_{sp}/[R]_{eu}$ for 1:1 cocrystals and slope = $K_{sp}/([R]_{eu}^2)$ for 2:1 cocrystals.

54

Conclusions

Investigation of several CBZ cocrystals of various stoichiometries and ionization properties demonstrates that cocrystals of nonionizable drugs can achieve pH-dependent solubilities when the coformer is ionizable. A mathematical model based on a mechanistic understanding of cocrystal dissociation and ionization is developed that predicts cocrystal solubility, eutectic points, and K_{eu} from cocrystal K_{sp}, component $K_a(s)$, and solution $[H^+]$. pH is shown to be a powerful variable in determining cocrystal solubility and the solution compositions where cocrystal is thermodynamically stable.

The findings presented here are valuable to (1) estimate cocrystal solubility-pH dependence with a minimum number of critical experiments, (2) guide selection of coformers to achieve pH-dependent cocrystal solubilities, and (3) determine the pH conditions that favor precipitation or thermodynamic stabilization of cocrystal.

Appendix

Explanation of terms

Subscript aq – aqueous

Subscript T – total

Subscript eu – eutectic

R – nonionizable drug

HA – monoprotic weakly acidic coformer (nonionized)

HAB – amphoteric coformer (nonionized)

K_{sp} – cocrystal solubility product

K_a – acid dissociation constant

K_{eu} – eutectic constant

S – solubility

RHA (1:1 nonionizable drug R, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{2A.1}$$

$$HA_{aq} \xrightleftharpoons{K_a} A^-_{aq} + H^+_{aq} \tag{2A.2}$$

and the associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \tag{2A.3}$$

56

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \qquad (2A.4)$$

Solubility-pH dependence of cocrystal RHA

Mass balance on R is given by

$$[R]_T = [R]_{aq} \qquad (2A.5)$$

Mass balance on A is given by the sum of unionized and ionized A.

$$[A]_T = [HA]_{aq} + [A^-]_{aq} \qquad (2A.6)$$

Substituting (2A.3) into (2A.5),

$$[R]_T = \frac{K_{sp}}{[HA]_{aq}} \qquad (2A.7)$$

and (2A.4) into (2A.6),

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \qquad (2A.8)$$

Combining Equations (2A.7) and (2A.8),

$$[R]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \qquad (2A.9)$$

Stoichiometric solubility for cocrystal RHA, S_{RHA}, is given by $S_{RHA} = [R]_T = [A]_T$, so

Equation (2A.9) becomes

$$S_{RHA} = \sqrt{K_{sp}\left(1 + \frac{K_a^{HA}}{[H^+]}\right)} \qquad (2A.10)$$

Eutectic drug and coformer concentration pH-dependence of cocrystal RHA

The eutectic point, where solid drug, cocrystal, and solution coexist in equilibrium, is described by

$$\text{RHA}_{\text{solid}} + \text{R}_{\text{solid}} \rightleftharpoons \text{R}_{\text{aq}} + \text{HA}_{\text{aq}} \tag{2A.11}$$

The concentrations of R and A at the eutectic point, $[\text{R}]_{\text{eu}}$ and $[\text{A}]_{\text{eu}}$, are special solutions to Equation (2A.9), where $[\text{R}]_{\text{eu}} = [\text{R}]_{\text{T}}$ and $[\text{A}]_{\text{eu}} = [\text{A}]_{\text{T}}$,

$$[\text{R}]_{\text{eu}} = \frac{K_{\text{sp}}}{[\text{A}]_{\text{eu}}}\left(1 + \frac{K_a^{\text{HA}}}{[\text{H}^+]}\right) \tag{2A.12}$$

At the eutectic point, $[\text{R}]_{\text{eu}}$ is equal to the solubility of R in the eutectic solution. A simplifying assumption is that the solubility of R is unaffected by the presence of coformer, thus $[\text{R}]_{\text{eu}}$ is given by the aqueous solubility of R.

$$[\text{R}]_{\text{eu}} = S_{\text{R,aq}} \tag{2A.13}$$

According to Equation (2A.12) $[\text{A}]_{\text{eu}}$ is given by

$$[\text{A}]_{\text{eu}} = \frac{K_{\text{sp}}}{S_{\text{R,aq}}}\left(1 + \frac{K_a^{\text{HA}}}{[\text{H}^+]}\right) \tag{2A.14}$$

HXHA (1:1 monoprotic weakly acidic drug HX, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$\text{HXHA}_{\text{solid}} \xrightleftharpoons{K_{\text{sp}}} \text{HX}_{\text{aq}} + \text{HA}_{\text{aq}} \tag{2A.15}$$

$$\text{HX}_{\text{aq}} \xrightleftharpoons{K_a^{\text{HX}}} \text{X}^-_{\text{aq}} + \text{H}^+_{\text{aq}} \tag{2A.16}$$

$$\text{HA}_{\text{aq}} \xrightleftharpoons{K_a^{\text{HA}}} \text{A}^-_{\text{aq}} + \text{H}^+_{\text{aq}} \tag{2A.17}$$

Associated equilibrium constants are given by

$$K_{sp} = [HX]_{aq}[HA]_{aq} \tag{2A.18}$$

$$K_a^{HX} = \frac{[X^-]_{aq}[H^+]_{aq}}{[HX]_{aq}} \tag{2A.19}$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{2A.20}$$

Solubility-pH dependence of cocrystal RHA

Mass balance on X is given by the sum of unionized and ionized X.

$$[X]_T = [HX]_{aq} + [X^-]_{aq} \tag{2A.21}$$

Mass balance on A is given by the sum of unionized and ionized A.

$$[A]_T = [HA]_{aq} + [A^-]_{aq} \tag{2A.22}$$

Substituting (2A.18) and (2A.19) into (2A.21),

$$[X]_T = \frac{K_{sp}}{[HA]_{aq}}\left(1 + \frac{K_a^{HX}}{[H^+]}\right) \tag{2A.23}$$

and (2A.20) into (2A.22),

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \tag{2A.24}$$

Combining Equations (2A.23) and (2A.24) ,

$$[X]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a^{HX}}{[H^+]}\right)\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \tag{2A.25}$$

Stoichiometric solubility for cocrystal HXHA, S_{HXHA}, is given by $S_{HXHA} = [X]_T = [A]_T$,

so Equation (2A.25) becomes

$$S_{HXHA} = \sqrt{K_{sp}\left(1+\frac{K_a^{HX}}{[H^+]}\right)\left(1+\frac{K_a^{HA}}{[H^+]}\right)} \tag{2A.26}$$

Eutectic drug and coformer concentration pH-dependence of cocrystal HXHA

The eutectic point, where solid drug, cocrystal, and solution coexist in equilibrium, is

described by

$$HXHA_{solid} + HX_{solid} \rightleftharpoons HX_{aq} + HA_{aq} \tag{2A.27}$$

The concentrations of X and A at the eutectic point, $[X]_{eu}$ and $[A]_{eu}$, are special solutions

to Equation (2A.27), where $[X]_{eu} = [X]_T$ and $[A]_{eu} = [A]_T$,

$$[X]_{eu} = \frac{K_{sp}}{[A]_{eu}}\left(1+\frac{K_a^{HX}}{[H^+]}\right)\left(1+\frac{K_a^{HA}}{[H^+]}\right) \tag{2A.28}$$

At the eutectic point, $[X]_{eu}$ is equal to the solubility of X in the eutectic solution. A

simplifying assumption is that the solubility of X is unaffected by the presence of

coformer, thus $[X]_{eu}$ is given by the aqueous solubility of X.

$$[X]_{eu} = S_{HX,aq}\left(1+\frac{K_a^{HX}}{[H^+]}\right) \tag{2A.29}$$

where $S_{HX,aq}$ is the intrinsic solubility of X. According to Equation (2A.28) $[A]_{eu}$ is given

by

$$[A]_{eu} = \frac{K_{sp}}{S_{HX,aq}}\left(1+\frac{K_a^{HA}}{[H^+]}\right) \tag{2A.30}$$

BHA (1:1 monoprotic weakly basic drug B, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

60

$$BHA_{solid} \xrightleftharpoons{K_{sp}} B_{aq} + HA_{aq} \qquad (2A.31)$$

$$BH^+_{aq} \xrightleftharpoons{K_a^B} B_{aq} + H^+_{aq} \qquad (2A.32)$$

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq} + H^+_{aq} \qquad (2A.33)$$

Associated equilibrium constants are given by

$$K_{sp} = [B]_{aq}[HA]_{aq} \qquad (2A.34)$$

$$K_a^B = \frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}} \qquad (2A.35)$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \qquad (2A.36)$$

Solubility-pH dependence of cocrystal BHA

Mass balance on B is given by the sum of unionized and ionized B.

$$[B]_T = [B]_{aq} + [BH^+]_{aq} \qquad (2A.37)$$

Mass balance on A is given by the sum of unionized and ionized A.

$$[A]_T = [HA]_{aq} + [A^-]_{aq} \qquad (2A.38)$$

Substituting (2A.34) and (2A.35) into (2A.37),

$$[B]_T = \frac{K_{sp}}{[HA]_{aq}}\left(1 + \frac{K_a^B}{[H^+]}\right) \qquad (2A.39)$$

and (2A.36) into (2A.38),

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \qquad (2A.40)$$

Combining Equations (2A.23) and (2A.24) ,

$$[B]_T = \frac{K_{sp}}{[A]_T}\left(1+\frac{[H^+]}{K_a^B}\right)\left(1+\frac{K_a^{HA}}{[H^+]}\right) \tag{2A.41}$$

Stoichiometric solubility for cocrystal BHA, S_{BHA}, is given by $S_{BHA} = [B]_T = [A]_T$, so Equation (2A.41) becomes

$$S_{BHA} = \sqrt{K_{sp}\left(1+\frac{[H^+]}{K_a^B}\right)\left(1+\frac{K_a^{HA}}{[H^+]}\right)} \tag{2A.42}$$

Eutectic drug and coformer concentration pH-dependence of cocrystal BHA

The eutectic point, where solid drug, cocrystal, and solution coexist in equilibrium, is described by

$$BHA_{solid} + B_{solid} \rightleftharpoons B_{aq} + HA_{aq} \tag{2A.43}$$

The concentrations of B and A at the eutectic point, $[B]_{eu}$ and $[A]_{eu}$, are special solutions to Equation (2A.42), where $[B]_{eu} = [B]_T$ and $[A]_{eu} = [A]_T$,

$$[B]_{eu} = \frac{K_{sp}}{[A]_{eu}}\left(1+\frac{[H^+]}{K_a^B}\right)\left(1+\frac{K_a^{HA}}{[H^+]}\right) \tag{2A.44}$$

At the eutectic point, $[B]_{eu}$ is equal to the solubility of B in the eutectic solution. A simplifying assumption is that the solubility of B is unaffected by the presence of coformer, thus $[B]_{eu}$ is given by the aqueous solubility of B.

$$[B]_{eu} = S_{B,aq}\left(1+\frac{[H^+]}{K_a^B}\right) \tag{2A.45}$$

where $S_{B,aq}$ is the intrinsic solubility of B. According to Equation (2A.44) $[A]_{eu}$ is given by

$$[A]_{eu} = \frac{K_{sp}}{S_{B,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \tag{2A.46}$$

R₂H₂A (2:1 monoprotic weakly basic drug R, diprotic weakly acidic coformer H₂A)

Relevant equilibria are given by

$$R_2H_2A_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq} + H_2A_{aq} \tag{2A.47}$$

$$H_2A_{aq} \xrightleftharpoons{K_a^{H_2A}} HA^-_{aq} + H^+_{aq} \tag{2A.48}$$

$$HA^-_{aq} \xrightleftharpoons{K_a^{HA^-}} A^{2-}_{aq} + H^+_{aq} \tag{2A.49}$$

Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}^2 [H_2A]_{aq} \tag{2A.50}$$

$$K_a^{H_2A} = \frac{[HA^-]_{aq}[H^+]_{aq}}{[H_2A]_{aq}} \tag{2A.51}$$

$$K_a^{HA^-} = \frac{[A^{2-}]_{aq}[H^+]_{aq}}{[HA^-]_{aq}} \tag{2A.52}$$

Solubility-pH dependence of cocrystal R₂H₂A

Mass balance on R is given by

$$[R]_T = [R]_{aq} \tag{2A.53}$$

Mass balance on A is given by the sum of unionized and ionized A.

$$[A]_T = [H_2A]_{aq} + [HA^-]_{aq} + [A^{2-}]_{aq} \tag{2A.54}$$

Substituting (2A.50) into (2A.53),

$$[R]_T^{\;2} = \frac{K_{sp}}{[HA]_{aq}} \tag{2A.55}$$

and (2A.51) and (2A.52) into (2A.55),

$$[A]_T = [H_2A]_{aq} \left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} \right) \tag{2A.56}$$

Combining Equations (2A.55) and (2A.56),

$$[R]_T^{\;2} = \frac{K_{sp}}{[A]_T} \left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} \right) \tag{2A.57}$$

Stoichiometric solubility for cocrystal R_2H_2A, $S_{R_2H_2A}$, is given by

$S_{R_2H_2A} = 0.5[R]_T = [A]_T$ (because cocrystal contains 2 moles of drug per mole of

cocrystal), so Equation (2A.57) becomes

$$S_{RHA} = \sqrt[3]{\frac{K_{sp}}{4} \left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} \right)} \tag{2A.58}$$

Eutectic drug and coformer concentration pH-dependence of cocrystal R₂H₂A

The eutectic point, where solid drug, cocrystal, and solution coexist in equilibrium, is

described by

$$R_2H_2A_{solid} + R_{solid} \rightleftharpoons R_{aq} + H_2A_{aq} \tag{2A.59}$$

The concentrations of R and A at the eutectic point, $[R]_{eu}$ and $[A]_{eu}$, are special solutions

to Equation (2A.57), where $[R]_{eu} = [R]_T$ and $[A]_{eu} = [A]_T$,

$$[R]_{eu}^{\;2} = \frac{K_{sp}}{[A]_{eu}} \left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} \right) \tag{2A.60}$$

At the eutectic point, $[R]_{eu}$ is equal to the solubility of R in the eutectic solution. A

simplifying assumption is that the solubility of R is unaffected by the presence of

coformer, thus $[R]_{eu}$ is given by the aqueous solubility of R.

$$[R]_{eu} = S_{R,aq} \tag{2A.61}$$

According to Equation (2A.60) $[A]_{eu}$ is given by

$$[A]_{eu} = \frac{K_{sp}}{S_{R,aq}^2}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}\right) \tag{2A.62}$$

R₂HAB (2:1 monoprotic weakly basic drug R, amphoteric coformer HAB)

Relevant equilibria are given by

$$R_2HAB_{solid} \xmapsto{K_{sp}} 2R_{aq} + HAB_{aq} \tag{2A.63}$$

$$H_2AB^+{}_{aq} \xmapsto{K_a^{H_2AB^+}} HAB_{aq} + H^+{}_{aq} \tag{2A.64}$$

$$HAB_{aq} \xmapsto{K_a^{HAB}} AB^-{}_{aq} + H^+{}_{aq} \tag{2A.65}$$
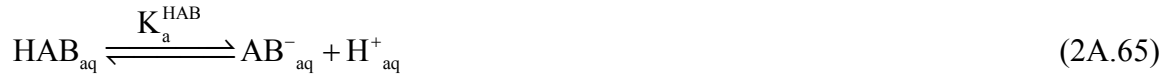
Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}^2[HAB]_{aq} \tag{2A.66}$$

$$K_a^{H_2AB^+} = \frac{[HAB]_{aq}[H^+]_{aq}}{[H_2AB^+]_{aq}} \tag{2A.67}$$

$$K_a^{HAB} = \frac{[AB^-]_{aq}[H^+]_{aq}}{[HAB]_{aq}} \tag{2A.68}$$

Solubility-pH dependence of cocrystal R₂HAB

Mass balance on R is given by

$$[R]_T = [R]_{aq} \tag{2A.69}$$

Mass balance on AB is given by the sum of unionized and ionized A.

$$[AB]_T = [HAB]_{aq} + [H_2AB^+]_{aq} + [AB^-]_{aq} \tag{2A.70}$$

Substituting (2A.66) into (2A.69),

$$[R]_T^2 = \frac{K_{sp}}{[HAB]_{aq}} \tag{2A.71}$$

and (2A.67) and (2A.68) into (2A.70),

$$[AB]_T = [HAB]_{aq} \left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} \right) \tag{2A.72}$$

Combining Equations (2A.71) and (2A.72),

$$[R]_T^2 = \frac{K_{sp}}{[AB]_T} \left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} \right) \tag{2A.73}$$

Stoichiometric solubility for cocrystal R_2HAB, S_{R_2HAB}, is given by

$S_{R_2HAB} = 0.5[R]_T = [AB]_T$ (because cocrystal contains 2 moles of drug per mole of

cocrystal), so Equation (2A.73) becomes

$$S_{RHA} = \sqrt[3]{\frac{K_{sp}}{4} \left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} \right)} \tag{2A.74}$$

Eutectic drug and coformer concentration pH-dependence of cocrystal R₂HAB

The eutectic point, where solid drug, cocrystal, and solution coexist in equilibrium, is

described by

$$R_2HAB_{solid} + R_{solid} \rightleftharpoons R_{aq} + HAB_{aq} \tag{2A.75}$$

The concentrations of R and A at the eutectic point, $[R]_{eu}$ and $[AB]_{eu}$, are special

solutions to Equation (2A.73), where $[R]_{eu} = [R]_T$ and $[AB]_{eu} = [AB]_T$,

$$[R]_{eu}{}^2 = \frac{K_{sp}}{[AB]_{eu}} \left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} \right) \tag{2A.76}$$

At the eutectic point, $[R]_{eu}$ is equal to the solubility of R in the eutectic solution. A

simplifying assumption is that the solubility of R is unaffected by the presence of

coformer, thus $[R]_{eu}$ is given by the aqueous solubility of R.

$$[R]_{eu} = S_{R,aq} \tag{2A.77}$$

According to Equation (2A.76) $[AB]_{eu}$ is given by

$$[AB]_{eu} = \frac{K_{sp}}{S_{R,aq}{}^2} \left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} \right) \tag{2A.78}$$

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CHAPTER 3

Effect of micellar solubilization on cocrystal solubility and stability

Introduction

Cocrystals are part of the broader class of multicomponent solids that offer the ability to generate materials that exhibit different physicochemical properties than their constituents.[1-6] There are several advantages for developing cocrystal forms of a drug. Among the most important is aqueous solubility higher than the parent drug, which can translate to higher bioavailability for BCS Class II drugs (low aqueous solubility and high permeability).[7, 8] Cocrystal forms with higher solubilities are however characterized by conversion to a less soluble form of the drug when exposed to solvent or solution, and deliberate efforts are required to prevent such transformations. This represents a challenge for dosage form development and drug delivery. Current approaches aim at delaying the conversion to drug but may require high additive levels to achieve transient stability. We have discovered that micellar additives with different solubilization capacity for cocrystal components, such as surfactants, impart thermodynamic stability to otherwise unstable cocrystal phases. This chapter presents the mechanism for cocrystal stabilization and a rational basis for surfactant or stabilizer selection.

Cocrystal eutectic points, where two solid phases are in equilibrium with solution, are key indicators of cocrystal solubility.[9] Recently the effect of ionization on cocrystal solubility was demonstrated through the measurement and prediction of eutectic points.[10] The effect of micellar solubilization and pH on cocrystal solubility and eutectic points is modeled based on solution phase chemistry. A preliminary analysis based on a pseudophase model of micellar solubilization is proposed that predicts cocrystal solubility and eutectic points in surfactant solutions. Solubilization is considered as the equilibrium of solute or solutes between the aqueous and micellar pseudophases. The concept of *differential solubilization*, where micelles interact preferentially with one of the components in solution, is applied for the first time to cocrystal solubility and stability relative to its constituents. Pharmaceutical cocrystals generally comprise a hydrophobic drug and a relatively hydrophilic coformer, and different affinities/solubilities in micellar nanophases with hydrophobic cores are to be expected in aqueous solutions. Differential solubilization has been previously discussed by others in the context of binary oil mixtures and extraction of oil components from membranes.[11]

Theoretical

Cocrystal stabilization is related to several equilibria between the cocrystal solid phase and its components in the aqueous and micellar psueodophases as illustrated in Figure 3.1. The effect of differential solubilization on cocrystal solubility is modeled by examining the homogeneous and heterogeneous reaction equilibria that have previously described cocrystal solubility product behavior and ionization of cocrystal components.[10,]
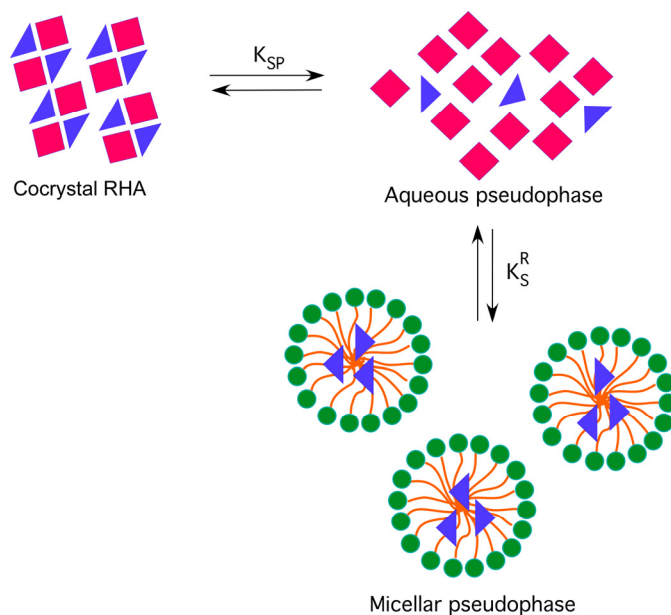
Figure 3.1. Schematic illustration of the equilibria between cocrystal phase and its components in the aqueous and micellar subphases. This scheme represents micellar solubilization of one cocrystal component (for instance drug) leading to excess coformer in the aqueous pseudophase and in this way stabilizing the cocrystal phase.

The relevant equilibria for a 1:1 cocrystal RHA, where R represents a nonionizable drug, HA represents a weakly acidic coformer, and M represents micellar surfactant, are

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{3.1}$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \tag{3.2}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{3.3}$$

$$HA_{aq} \xrightleftharpoons{K_a} A^-_{aq} + H^+_{aq} \tag{3.4}$$

and their associated equilibrium constants are

$$K_{sp} = [R][HA]$$

(3.5)

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]}$$

(3.6)

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]}$$

(3.7)

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

(3.8)

Subscript aq denotes species in the aqueous phase. Subscript m refers to species in the micellar phase. K_{sp} is the cocrystal solubility product. K_s^R and K_s^{HA} are the equilibrium constants for the solubilization of R and HA, respectively. This way of defining the solubilization constants is in agreement with the mass action model where solubilization is treated as a stepwise addition of solute molecules to the micelles. K_a is the ionization constant for the coformer HA. Activities are replaced by concentrations as a first approximation applicable to dilute solutions.

The total solubility of cocrystal RHA, $S_{RHA,T} = S_{aq} + S_m$, is derived by considering the above equilibria and mass balances on R and HA,

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

(3.9)

where the micellar surfactant concentration [M] is the total surfactant concentration minus the critical micellar concentration (CMC). The CMC is assumed to be constant in the range of concentrations and solubilizations reported here. Large extent of micellar solubilization and higher solute concentrations will not justify this assumption. Equation (3.9) applies to cocrystal solubility in solutions of stoichiometric concentrations

(equimolar concentration of cocrystal components in this case), and assumes that partitioning of ionized coformer is negligible compared to unionized species. This relationship may serve as a guide for surfactant selection and concentration to meet a target cocrystal solubility. K_s and K_a values are often available from the literature and it will only require a single measurement of cocrystal K_{sp} and solution pH.

The concept of micellar solubilization has been known for over a century and is generally applied to solubilize hydrophobic drugs over the surrounding aqueous media.[11, 13-18] Figure 2 compares the solubility of a hydrophobic drug and a more water soluble cocrystal of that drug, whose solubility is calculated from Equation (3.9). The total solubility of the crystalline drug, $S_{R,T}$, increases linearly in surfactant solutions above the CMC according to

$$S_{R,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{3.10}$$

where $S_{R,aq}$ is the aqueous solubility of R in the absence of surfactant. The cocrystal solubility $S_{RHA,T}$, by contrast, is nonlinear with respect to micellar surfactant concentration, when the components are differentially solubilized by the surfactant. This nonlinear behavior is dependent on the relative magnitude of K_s^R and K_s^{HA}. Consequently, the thermodynamic stability of cocrystal relative to drug is dependent on micellar concentration.

Figure 3.2 shows that there is a concentration of surfactant at which the solubility curves of cocrystal and pure drug intersect. At this surfactant concentration, crystalline drug and cocrystal are thermodynamically stable. We are calling this the critical stabilization concentration (CSC). At surfactant concentrations above the CSC, cocrystal is thermodynamically stable with respect to the drug, and cocrystal persists in aqueous

suspensions. The CSC exists due to the differential solubilization of R compared to HA; if R and HA have equal K_s, Equation (3.9) predicts that no CSC exists. It can be seen that the CSC, like the cocrystal solubility, depends on the relative magnitude of K_s^R and K_s^{HA}. The effectiveness of a surfactant in stabilizing cocrystals is based on lowering the CSC, and is related to higher K_s^R and lower K_s^{HA} values.
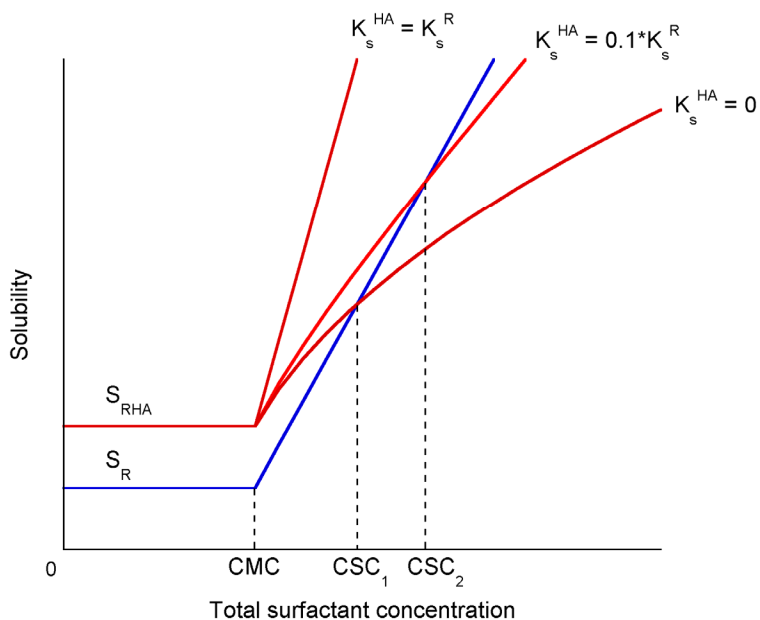
Figure 3.2. Schematic representation of the cocrystal (RHA) and drug (R) solubility with respect to the total surfactant concentration according to Equations (3.9) and (3.10). Differential solubilization of cocrystal components represented by the relative values of K_s^{HA} and K_s^R leads to nonlinear cocrystal solubility dependence and to intersection of the cocrystal and drug solubility curves. CSC refers to the critical stabilization concentration at which both cocrystal and drug are thermodynamically stable.

The phase stability of cocrystal, drug, and coformer can be described by its eutectic points E_1 and E_2, as shown in Figure 3. The eutectic points are isothermal invariant points where two solid phases are in equilibrium with the solution. E_1, the eutectic between cocrystal, solid drug, and solution, is the more relevant eutectic for

77

incongruently saturating cocrystals of drugs with low aqueous solubility. Micellar

solubilization shifts these eutectics in a predictable manner based on Equations (3.9) and

(3.10), which can result in cocrystal becoming the thermodynamically stable phase at the

stoichiometric ratio of components.
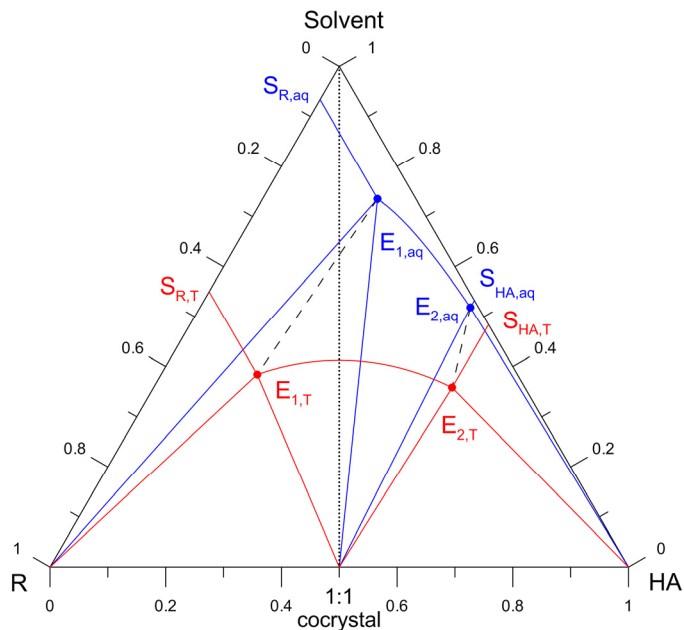
Figure 3.3.   Hypothetical triangular phase diagram showing how differential solubilization of cocrystal components changes the eutectic points and cocrystal stability regions. E_1 and E_2 are the cocrystal eutectic points. Subscript aq refers to aqueous and subscript T refers to total (aqueous + micellar). Differential solubilization of the drug compared to the coformer shifts the cocrystal stability region to cross the 1:1 stoichiometric composition line (dotted), which results in a congruently saturating cocrystal.

In the interest of forming cocrystals from solutions of stoichiometric composition,

it is common to select a solvent in which the solubilities of the components are similar.[19,]

[20] This condition can be achieved by the addition of surfactants with very different K_s

values for cocrystal components or differential solubilization such that the cocrystal

becomes congruently saturating.

Although the focus of this work is on E_1, the concept of differential solubilization is equally applicable to E_2. E_2 describes the equilibrium between solid coformer, cocrystal, and solution, whereas E_1 describes the equilibrium between solid drug, cocrystal, and solution. The composition at E_2 depends on the solubilization of the cocrystal relative to the solubilization of the coformer. A CSC can theoretically exist for E_2. However, due to the generally low magnitudes of K_s^{HA} and the high aqueous solubility of coformers for most cocrystals, the calculated CSCs may not be experimentally accessible.

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) 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

Carbamazepine-salicylic acid cocrystal (CBZ-SLC) was prepared by reaction crystallization at 24±1 °C.[21] Carbamazepine and salicylic acid were added in stoichiometric amounts to near saturated solutions of salicylic acid in acetonitrile.

Carbamazepine dihydrate (CBZD) was prepared in water from anhydrous carbamazepine (CBZ). Solid phases were analyzed by X-ray powder diffraction (XRPD).

Cocrystal stability in aqueous SLS solutions

Excess CBZ-SLC was suspended in pure water or in a 1% w/w (35 mM) aqueous SLS solution for 24 hours at room temperature (24±1 °C). Solid phases were analyzed by XRPD.

Measurement of cocrystal eutectic points

The eutectic point between cocrystal and solid drug was measured using methods described previously.[9] Two solids, cocrystal and drug, were equilibrated in either pure water or in 1% w/w aqueous SLS solution. Samples were maintained at 25±0.1 °C for up to 3 days. Solid phases were analyzed by XRPD and the solution concentrations were analyzed by high performance liquid chromatography (HPLC).

Measurement of K_s

Excess solid was equilibrated in varying concentrations of aqueous SLS solution. Samples were maintained at 25±0.1 °C for the duration of 24 hours. Solid phases were analyzed by XRPD and the solution concentrations by HPLC.

K_s^R was calculated from Equation (3.10). K_s^{HA} was calculated from the equation

$$S_{A,aq} = S_{HA,aq}\left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M]\right),$$ where $S_{A,aq}$ is the total solubility of acid, $S_{HA,aq}$ is the intrinsic solubility of the acid, and [M] is micellar surfactant. K_s^{CBZ} was calculated from reported values.[22] CMC of SLS is reported to be 8 mM in water.[23]

High performance liquid chromatography (HPLC)

Solution concentrations were analyzed using a Waters Alliance 2695 autosampler equipped with a Waters 2996 photodiode array UV/vis detector. A C18 Thermo Electron Corp. column (5 μm, 4.6 x 250 mm) at room temperature was used for separation. Mobile phase consisted of 55% methanol, 45% water and 0.1% trifluoroacetic acid in an isocratic method. Flow rate was 1 mL/min. CBZ and SLC were analyzed at 284 nm and 304 nm respectively.

X-ray powder diffraction (XRPD)

XRPD patterns were collected with a benchtop Rigaku Miniflex X-ray Diffractometer (Danvers, MA) with Cu Kα ($\lambda = 1.54$ Å) radiation, 30 kV tube voltage, and 15 mA tube current. Data were collected from 2-theta of 5 to 40° at a scan rate of 2.5°/min.

Results

Predictions based on the micellar solubilization models presented were tested for the carbamazepine-salicylic acid (CBZ-SLC) cocrystal in aqueous solutions of sodium lauryl sulfate (SLS). SLS is a commonly used anionic surfactant with a CMC reported at 8 mM (0.24%).[23] Carbamazepine (CBZ) is a nonionizable, low aqueous solubility drug and its anhydrous crystal quickly transforms to carbamazepine dihydrate (CBZD) in water. Salicylic acid (SLC) is weakly acidic with a reported pK_a of 3.0 and a reported

aqueous solubility of 14 mM at pH 3, approximately 26 times more soluble than

CBZD.[22, 24, 25]

Table 3.1. Eutectic point and eutectic constant (±SE) for the equilibrium of CBZ-SLC and CBZD at 25 °C in water with and without SLS.

[SLS] (mM)	pH	[CBZ]$_{eu}$ (mM)	[SLC]$_{eu}$ (mM)	K_{eu} (exp.)	K_{eu} (pred.)*
0	3.0 ± 0.1	0.61 ± 0.03	2.88 ± 0.04	4.75 ± 0.17	-
35	3.2 ± 0.1	9.38 ± 0.07	5.25 ± 0.03	0.56 ± 0.01	0.59

* Calculated from theoretical solubility dependence of cocrystal and drug on surfactant concentration. $K_s^{CBZ} = 0.6$ mM^{-1} calculated from literature values between 0 and 17 mM SLS.[22] $K_s^{SLC} = 0.06$ mM^{-1} (measured from solubility between 0 and 69 mM SLS).

Table 3.1 shows the eutectic concentrations at E_1 for CBZ-SLC in pure water and

in aqueous solutions of SLS. CBZ-SLC cocrystal has been shown to be more soluble

than CBZD in water and at pH values between 1 and 7.[10] It can be seen that addition of

surfactant reverses this solubility relationship. [CBZ]$_{eu}$ and [SLC]$_{eu}$ denote the total

analytical concentrations of drug and coformer at the eutectic point. In the absence of

surfactant, [SLC]$_{eu}$ is higher than [CBZ]$_{eu}$, indicating that the cocrystal requires excess

coformer to be at equilibrium with pure drug. This situation is reversed in the 35 mM

(1%) SLS solution, where [CBZ]$_{eu}$ is higher than [SLC]$_{eu}$.

The utility of the eutectic constant K_{eu} has been described recently for

cocrystals.[26] The eutectic constant was introduced in the context of chiral mixtures

containing racemic compounds.[27] For cocrystals, K_{eu} is defined as the ratio of activities

of coformer to drug at the eutectic point ($K_{eu} = a_{coformer,eu}/a_{drug,eu} \approx$ [coformer]$_{eu}$/[drug]$_{eu}$).

K_{eu} values are important indicators of cocrystal stability.[26] $K_{eu} > 1$ for a 1:1

cocrystal indicates that cocrystal is thermodynamically unstable with respect to drug

under stoichiometric solution conditions.   Observed K_{eu} values for CBZ-SLC cocrystal

decrease from 4.75 in water to 0.56 in 35 mM SLS, evidence of an unstable cocrystal in

water becoming stable by addition of SLS. A decrease to K_{eu} below the cocrystal

stoichiometric ratio, *e.g.*, < 0.5 for a 2:1 cocrystal or < 1 for a 1:1 cocrystal (from K_{eu} >

cocrystal stoichiometric ratio) indicates a reversal in the thermodynamic stability, where

cocrystal is more stable than drug. In instances where activities are not well

approximated by concentrations, the K_{eu} where the activities of drug and coformer at the

eutectic are equal may deviate from the stoichiometric ratio. Therefore, the K_{eu} at which

the thermodynamic stability of drug and cocrystal reverse may shift depending on

solution nonidealities.

Predicted K_{eu} values, based on Equations (3.9) and (3.10) using experimental K_s

values for the solubilization of pure drug and coformer in aqueous SLS solutions, are in

excellent agreement with observed K_{eu} values. Results in Table 1 also imply that there is

a CSC between 0 and 35 mM SLS, which is calculated to be 15 mM (0.43%) SLS.
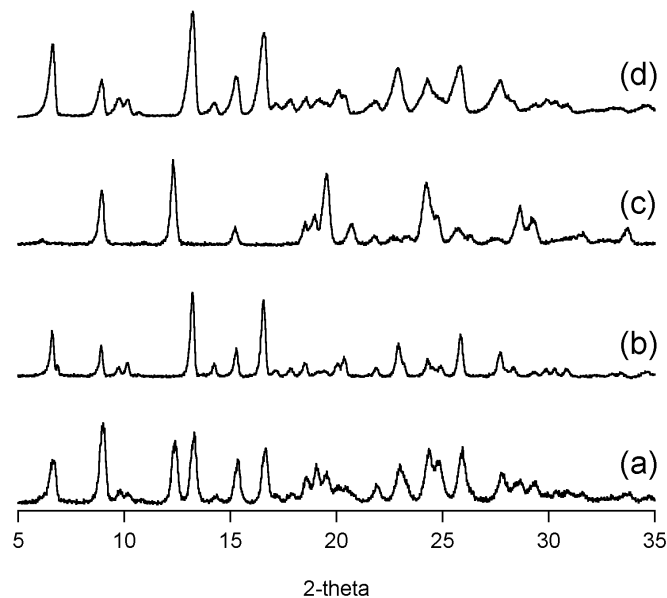
Figure 3.4. X-ray powder diffraction patterns of solid phases after suspending CBZ-SLC cocrystal in aqueous solutions with and without surfactant for 24 h at pH 3 and 24 °C. (a) 0 mM SLS, (b) 35 mM SLS, (c) CBZD reference, (d) CBZ-SLC reference.

XRPD patterns in Figure 3.4 show that CBZ-SLC cocrystal converts to CBZD in water, whereas in 35 mM SLS solution, cocrystal is the only solid phase detected after 24 hours. These results are in agreement with the cocrystal phase stability dependence on surfactant concentration observed and predicted by K_{eu} values. Without knowledge of eutectic points, solid phase analysis alone is not sufficient to determine whether stabilization is of a kinetic or a thermodynamic nature.

Conclusions

The findings presented here have broad implications for cocrystals in general and for pharmaceutical cocrystals in particular. The selection of additives that prevent cocrystal conversions has been mostly an empirical exercise, requiring extensive experimentation and resources. A mechanism for cocrystal stabilization is presented

whereby additives with different solubilization capacities for cocrystal components impart thermodynamic stability to cocrystal phases exposed to solvent. A mathematical model that describes the dependence of cocrystal solubility on micellar solubilization of cocrystal components explains the stabilization of CBZ-SLC cocrystal in aqueous SLS solutions. Extension of this model to other cocrystal/surfactant systems is the subject of the next chapter.

Results show that cocrystal solubility and K_{eu} are controlled by micellar solubilization of cocrystal components. The effectiveness of the surfactant to stabilize cocrystals is associated with different micellar solubilization of cocrystal components. This stabilization mechanism is not limited to micellar solubilization, but is applicable to other processes involving differential affinities of components such as complexation, adsorption, etc. These findings serve as a guide for surfactant selection to control cocrystal solubility and conversion during pharmaceutical processes, storage, and dissolution.

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CHAPTER 4

Engineering cocrystal solubility, stability, and pH$_{max}$ by micellar solubilization

Introduction

The ability to engineer the aqueous solubility of inherently insoluble pharmaceutical compounds by cocrystal formation has important implications for the development of drug delivery systems. Cocrystals owe their large solubility range to the numerous structures, diverse molecular characteristics of cocrystal components and solution phase behavior.[1, 2] One of the fundamental consequences related to the nature of cocrystal components and their solution phase behavior is the ability to tailor the solubility-pH dependence of cocrystals of nonionizable or ionizable drugs by the careful selection of coformers and control of solution conditions. The contributions of ionization and complexation of cocrystal components to cocrystal solubility have been reported and quantitative models have been developed that allow for tailoring cocrystal solubility behavior.[3-5] While surfactants are commonly used in cocrystal dissolution studies and formulations,[6-9] and the role of micelles on drug solubilization is widely appreciated in the literature,[10-15] their role on cocrystal solubility has been virtually unexplored.

Cocrystals that are more soluble than the parent drug can transform, sometimes very rapidly, to the less soluble drug upon contact with solution.[16-19] Thus, understanding

and controlling cocrystal thermodynamic stability is essential if they are to become pharmaceutical products.

We recently showed that surfactants can impart thermodynamic stability to cocrystals that are otherwise unstable in solution.[20] A surfactant *critical stabilization concentration* (CSC) was discovered where cocrystal and drug phases become thermodynamically stable in micellar solutions. Below CSC, cocrystal is thermodynamically unstable whereas at the CSC and above, cocrystal is thermodynamically stable. A theoretical treatment predicted that the stabilizing effect of micellar surfactants is related to their *differential solubilization of cocrystal components.* In other words, when a surfactant system has superior solubilization power for the least soluble cocrystal component, its effectiveness as a cocrystal stabilizer increases.

The work presented here establishes the contributions of micellar solubilization and ionization of cocrystal components on cocrystal solubility, develops mathematical models that predict cocrystal solubility behavior in terms of thermodynamic parameters that are readily available in the literature or experimentally accessible, and provides a mechanistic basis for tailoring cocrystal CSC and pH_{max} to meet solubility and stability requirements.

This work shows for the first time that *micellar solubilization can induce a pH_{max}* for cocrystals that do not have one otherwise. Mathematical models are derived that describe the dependence of cocrystal solubility, CSC, and pH_{max} on cocrystal K_{sp}, component $K_s(s)$ and $K_a(s)$, and micellar surfactant concentration.

The predictive power of the models is evaluated from studies that examine the influence of a surfactant (sodium lauryl sulfate, SLS) and coformer ionization on

91

cocrystal solubility, stability, and CSC for a range of cocrystals of a hydrophobic,

nonionizable drug (carbamazepine, CBZ) and hydrophilic coformers with several

ionization properties and stoichiometries. The cocrystals studied include the following:

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). The selected cocrystals cover the two most

abundant stoichiometries and the coformers have ionization properties common among

reported cocrystals. Salicylic acid and saccharin are monoprotic weak acids; salicylic

acid has a reported pK_a of 3.0,[21] saccharin has a range of reported pK_a values between 1.8

and 2.2.[22, 23] Succinic acid is a diprotic weak acid with pK_a values of of 4.1 and 5.6.[24] 4-

aminobenzoic acid is amphoteric with pK_a values of 2.6 and 4.8.[25]

Theoretical

This section describes the theoretical basis of our quantitative approach to predict

cocrystal solubilization and thermodynamic stability from solution phase properties of

cocrystal components and micellar surfactants. We first present the solution phase

equilibria that govern the solubilization properties of cocrystals in micellar solutions.

Relatively simple equations to calculate cocrystal solubility are derived by considering

the contributions of ionization and micellar solubilization of cocrystal components.

Several important physicochemical factors are identified that can be used to make

cocrystal solubility and stability predictions.

The interested reader is directed to the appendix for derivations of the equations presented in this section. The analysis can be generalized to mixed micelles and other solubilization mechanisms, although they may be of a different nature.

Cocrystal solubilization and thermodynamic stabilization in micellar solutions

A micellar solution phase in equilibrium with a solid cocrystal phase consists of molecules of cocrystal components and surfactant in several states of self-association, complexation, and ionization. Surfactants self-assemble in solution at a critical micellar concentration (CMC) and provide a means to solubilize cocrystal components. The solubility of a cocrystal (RHA) composed of the nonionized forms of its components, a nonionizable drug (R) and an ionizable coformer, in this case a monoprotic weak acid (HA), is described by the equilibria for cocrystal dissociation, ionization, complexation and micellar solubilization. For the sake of simplicity solution complexation of cocrystal components is assumed to be negligible and the expressions for the other equilibria are:

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{4.1}$$

$$HA_{aq} \xrightleftharpoons{K_a} A^-_{aq} + H^+_{aq} \tag{4.2}$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \tag{4.3}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{4.4}$$

$$A^-_{aq} + M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{4.5}$$
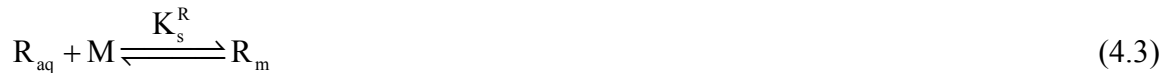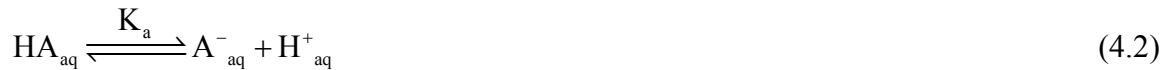
where subscripts m and aq refer to micellar and to aqueous pseudophases, respectively. K_{sp} is the cocrystal solubility product and K_a is the dissociation constant for the acidic

coformer. M is the micellar surfactant. K_s^R, K_s^{HA}, and K_s^{A-} are the micellar solubilization constants for cocrystal components and their ionized forms.

The cocrystal solubility, $S_{RHA,T}$, under stoichiometric conditions, is equal to the total concentration of each cocrystal component in equilibrium with solution, $S_{RHA,T} = [R]_T = [A]_T$. The contributions of ionization and micellar solubilization of each cocrystal component to the solubility of a cocrystal RHA, is given by

$$S_{RHA,T} = [R]_{aq} + [R]_m = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \qquad (4.6)$$

An expression for cocrystal solubility in terms of experimentally accessible solution properties is obtained

$$S_{RHA,T} = \sqrt{K_{sp}\left(1 + K_s^R[M]\right)\left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]}K_s^{A^-}[M]\right)} \qquad (4.7)$$

by combining Equation (4.6) with the equilibrium constant equations below

$$K_{sp} = [R]_{aq}[HA]_{aq} \qquad (4.8)$$

$$K_a = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \qquad (4.9)$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \qquad (4.10)$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \qquad (4.11)$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \qquad (4.12)$$

where the terms in brackets refer to concentrations with the recognition that under dilute solution conditions they approximate activities.

Equation (4.7) can be further simplified to

94

$$S_{RHA,T} = \sqrt{K_{sp}\left(1+K_s^R[M]\right)\left(1+\frac{K_a}{[H^+]}+K_s^{HA}[M]\right)} \tag{4.13}$$

when $K_s^{HA} \gg K_s^{A-}$, and the micellar solubilization of ionized species negligibly affects total solubility unless present at very high concentrations.[26-28] Equation (4.13) predicts that cocrystal solubility increases with increasing cocrystal K_{sp}, component K_s^R and K_s^{HA}, coformer ionization $K_a/[H^+]$, and surfactant micellar concentration, [M].

It is evident from Equations (4.7) and (4.13) that cocrystal solubility is not linearly dependent on micellar concentration. This is in contrast to the well-known linear dependence of the micellar solubilization of a single-component solid phase of a nonionzable drug R

$$S_{R,T} = S_{R,aq}\left(1+K_s^R[M]\right) \tag{4.14}$$

where $S_{R,aq}$ is the solubility of crystal R in the aqueous pseudophase. In this analysis, K_s values are assumed to be independent of solute and surfactant concentrations.

Equations (4.13) and (4.14) are shown graphically in Figure 1 for the case of a nonionizable, hydrophobic drug and its cocrystal with an ionizable, hydrophilic, coformer where $K_s^{HA} = 0$. This plot reveals that cocrystal and drug solubility surfaces intersect along a curve of given surfactant concentration and pH values and identifies stability regions for cocrystal or drug by two critical parameters. The first is the CSC, or the surfactant concentration where cocrystal and drug solid phases are in equilibrium with solution. The second is the pH_{max}, or the pH value at the CSC. Above the CSC or below pH_{max} the cocrystal becomes the stable phase relative to the drug phase. When one or more cocrystal components ionize, both CSC and pH_{max} are necessary to describe the

solution conditions under which cocrystal and/or drug solid phase are thermodynamically stable.
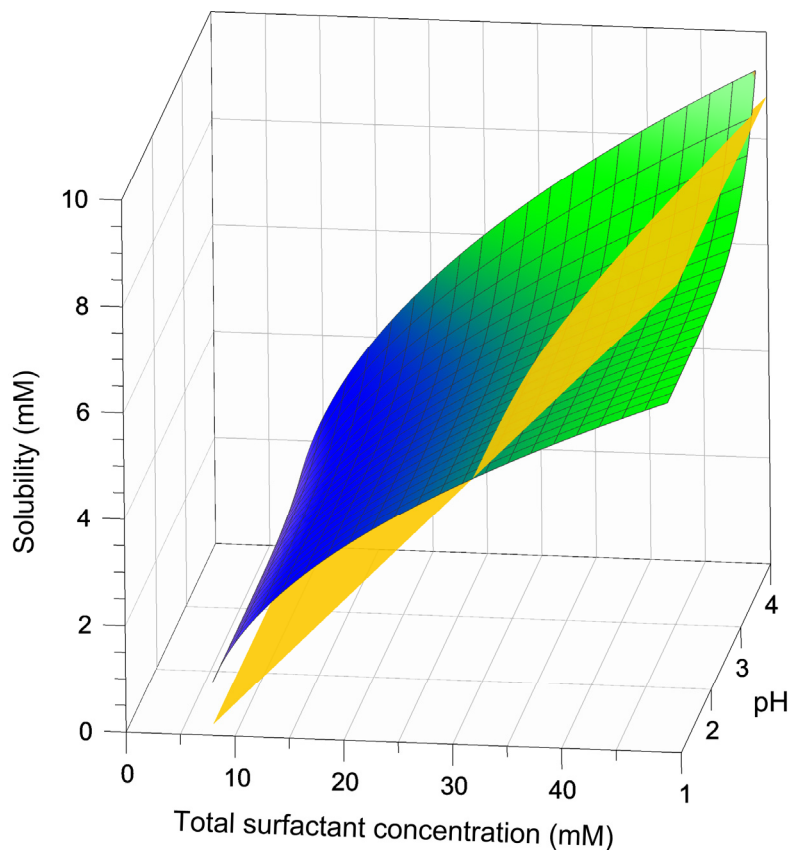
Figure 4.1. Cocrystal RHA (blue/green surface) and drug R (yellow surface) solubility dependence on surfactant concentration and pH. The intersection of the cocrystal and drug solubility surfaces represents the surfactant concentrations (CSC) and pH values (pH$_{max}$), where cocrystal and drug are in thermodynamic equilibrium with solution. Solubilities were calculated from Equations (4.13) and (4.14) with $K_{sp} = 1$ mM^2 ($S_{RHA,aq}/S_{R,aq} = 5$), $S_{R,aq} = 0.2$ mM, $pK_a = 4$, $K_s^R = 1$ mM^{-1}, $K_s^{HA} = 0$, and CMC = 8 mM.

The existence of a CSC and a pH$_{max}$ (in the case of ionizable cocrystal component) is a consequence of the slower rate of increase of cocrystal solubility with surfactant concentration compared to that of drug solubility. It is evident from Equations (4.13) and (4.14) that cocrystal solubility depends on $\sqrt{[M]}$ (when $K_s^{HA} = 0$) whereas drug solubility depends on [M].

96

Estimation of cocrystal solubilization from drug solubilization

A useful estimate of the surfactant influence on cocrystal solubilization can be calculated from knowledge of the drug solubilization according to

$$\frac{S_{RHA,T}}{S_{RHA,aq}} = \sqrt{\frac{S_{R,T}}{S_{R,aq}}} \qquad (4.15)$$

This expression is obtained by combining Equations (4.13) and (4.14) for a nonionizable drug R when K_s^R is unaffected by the coformer and $K_s^{HA} = 0$. A surfactant concentration that increases drug solubility by 100-fold is predicted to increase cocrystal solubility by 10-fold. Equation (4.15) implies that a surfactant will increase the solubility of all 1:1 cocrystals of a drug by the same ratio as long as the stated assumptions are justified.

Equation (4.15) can be rewritten for a general cocrystal stoichiometry, R_nX_m, as

$$\frac{S_{R_nX_m,T}}{S_{R_nX_m,aq}} = \left(\frac{S_{R,T}}{S_{R,aq}}\right)^{\frac{n}{n+m}} \qquad (4.16)$$

for a nonionizable drug R and coformer X. The solubility increase for a 2:1 cocrystal is predicted to be $100^{2/3}$ or 21.5-fold its aqueous solubility, when the drug solubility is increased by 100-fold. Thus cocrystal stoichiometries richer in hydrophobic drug will exhibit a weaker dependence of total cocrystal solubility on micellar solubilization, leading to higher CSC or pH_{max} values.

Mechanism by which micelles stabilize cocrystals

The influence of micellar solubilization on cocrystal thermodynamic stability and CSC can be explained by considering the species distribution in micellar solutions at

equilibrium with cocrystal and/or drug solid phases. Figure 4.2 shows the distribution of

the drug in micellar and aqueous environments for a crystal of a hydrophobic drug R and

its cocrystal with a hydrophilic coformer HA, under nonionizing conditions where $K_s^{HA} =$

0.
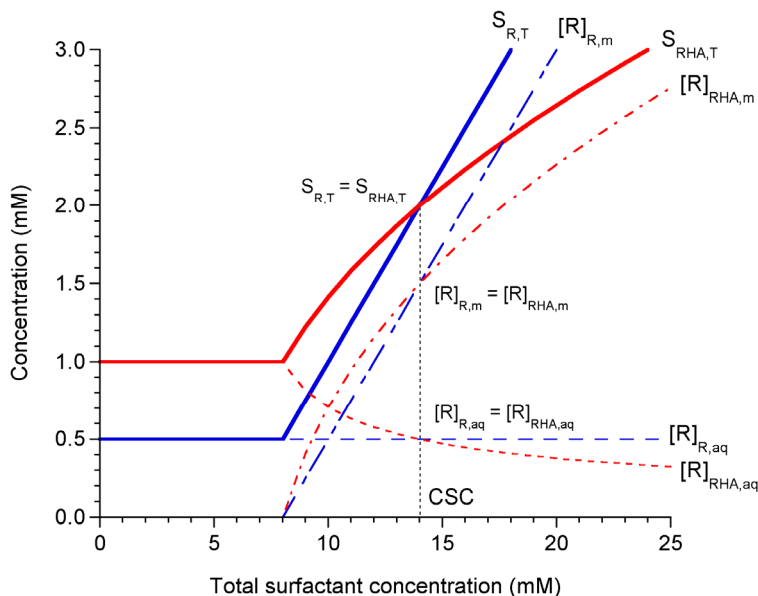
Figure 4.2. Distribution of drug (R) between the aqueous and micellar environments in surfactant solutions at equilibrium with cocrystal (RHA) and crystal (R). The cocrystal thermodynamic stability relative to the drug decreases with surfactant concentration. A thermodynamically unstable cocrystal in pure solvent becomes stable at the CSC where all curves intersect. Cocrystal is more soluble than drug below the CSC, cocrystal is equally soluble to drug at the CSC, and cocrystal is less soluble than drug above the CSC. Subscripts aq, m, and t, refer to aqueous, micellar and total. Solubilities and drug distributions were calculated from Equations (4.13) and (4.14) with $K_{sp} = 1$ mM^{-1}, $K_s^R = 0.5$ mM^{-1}, $K_s^{HA} = 0$ mM^{-1}, $S_{R,aq} = 0.5$ mM, and CMC = 8 mM.

When drug crystal phase (R) is in equilibrium with micellar solution, the drug

concentration in the aqueous environment, $[R]_{R,aq}$, remains constant with increasing

surfactant concentration. At surfactant concentrations above the CMC, the drug

concentration in the micellar environment, $[R]_{R,m}$, increases linearly. For cocrystal

(RHA) in equilibrium with micellar solution (where drug is solubilized by the micelle and the coformer is not) the drug concentration in the aqueous environment, $[R]_{RHA,aq}$, is not constant but decreases with increasing surfactant concentration above the CMC. Because the coformer is not solubilized by the micelle, the aqueous phase becomes enriched with coformer and $[R]_{RHA,aq}$ decreases to maintain a constant solubility product as described by the cocrystal dissociation equilibrium. This imbalance of cocrystal components in the aqueous environment leads to a decrease in the rate of cocrystal solubilization as drug solubilized by the micelle increases with surfactant concentration. A CSC where cocrystal is in equilibrium with drug is reached as indicated by the intersection of the total drug concentration curves, $[R]_{RHA,T} = [R]_{R,T}$, as well as the speciation in the aqueous and micellar environments $[R]_{RHA,m} = [R]_{R,m}$ and $[R]_{RHA,aq} = [R]_{R,aq}$.

CSC and pH$_{max}$ dependence on cocrystal and surfactant properties

Cocrystals of higher solubilities in water are predicted to exhibit higher CSC values as illustrated in Figure 4.3. For cocrystals of the same drug, aqueous solubilities can be altered by different coformers or by coformer ionization behavior in solution (by adjusting solution pH).
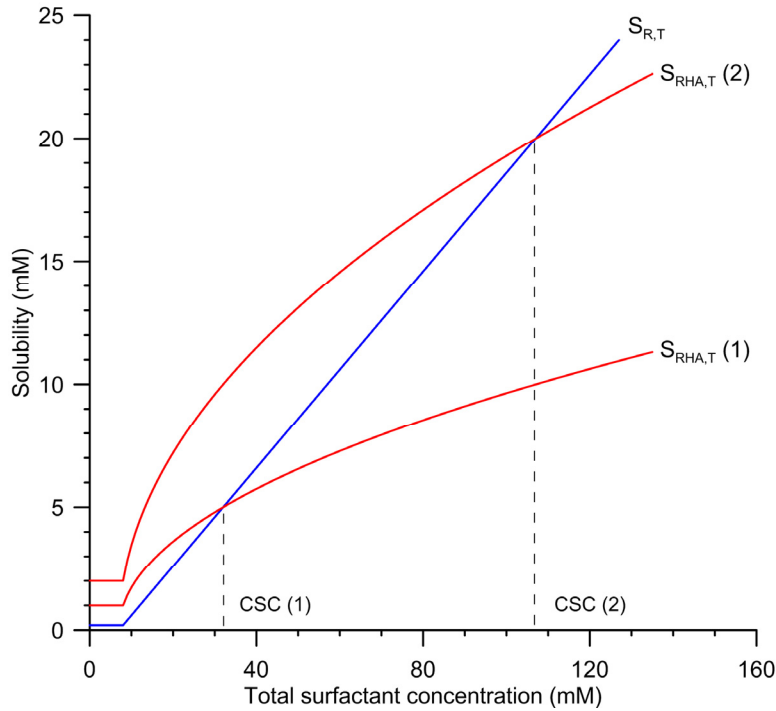
Figure 4.3. Influence of surfactant solubilization on cocrystal solubility and CSC for cocrystals of the same drug with different aqueous solubilities. More soluble cocrystals relative to drug require higher surfactant concentration to achieve the CSC. Total solubilities of cocrystal RHA ($S_{RHA,T}$) and drug ($S_{R,T}$) were calculated from Equations (4.13) and (4.14) with cocrystal $K_{sp} = 1$ and 4 mM^2 ($S_{RHA,aq}/S_{R,aq} = 5$ and 10), $S_{R,aq} = 0.2$ mM, $K_s^R = 1$ mM^{-1}, $K_s^{HA} = 0$, and CMC $= 8$ mM.

The influence of cocrystal aqueous solubility on CSC may be calculated from

$$CSC = \frac{\left(\dfrac{S_{RHA,aq}}{S_{R,aq}}\right)^2 - 1}{K_s^R} + CMC \qquad (4.17)$$

by solving for the surfactant concentration at which $S_{RHA,T} = S_{R,T}$ from Equations (4.13) and (4.14). This expression applies to a 1:1 cocrystal with no micellar solubilization of coformer and negligible solution complexation of cocrystal components.

The influence of drug and coformer micellar solubilization on the CSC has been recently presented.[20] The basis for the existence of the CSC for cocrystal and drug was described from the differential micellar solubilization of drug and coformer. The greater the drug micellar solubilization, K_s^R, relative to that of the coformer, K_s^{HA}, the lower is the CSC value. In the case of pharmaceutical cocrystals drugs are generally much more hydrophobic than coformers and $K_s^R \gg K_s^{HA}$.

Figure 4.4 shows the dependence of CSC on drug micellar solubilization (K_s^R) and cocrystal aqueous solubility, as predicted by Equation (4.17). CSC is inversely proportional to drug micellar solubilization and directly proportional to cocrystal aqueous solubility. This equation allows for estimation of the required K_s^R to achieve the CSC for cocrystal and its drug component, and in this way provide guidance for the rational selection of surfactant and concentration.
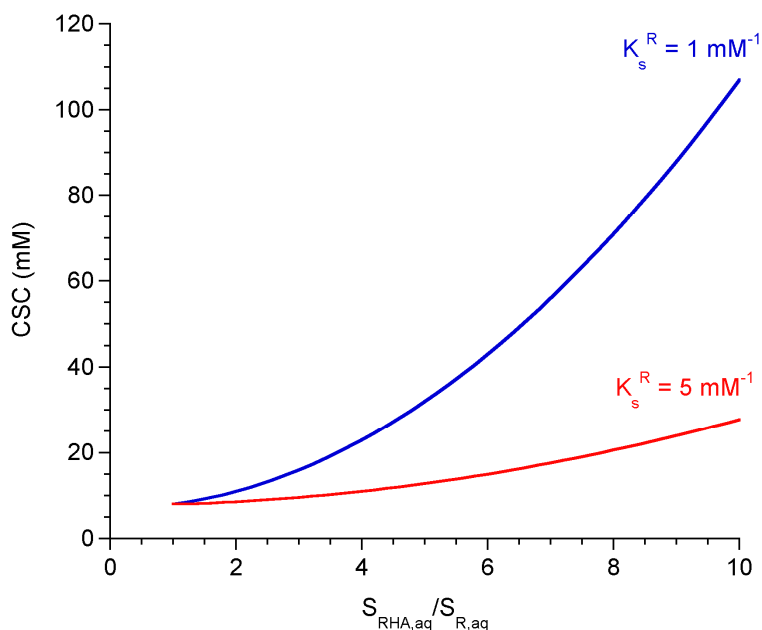
Figure 4.4. The CSC increases with increasing cocrystal to drug solubility ratio in pure water (or below CMC) and with decreasing drug micellar solubilization K_s^R. CSC calculated from Equation (4.17) with $K_s^{HA} = 0$ and CMC = 8 mM.

Micellar solubilization of cocrystal components can also impart a pH_{max} to a cocrystal that otherwise does not have one as shown in Figure 4.5. The solubility-pH dependence for a cocrystal RHA of a nonionizable drug and a weakly acidic coformer, where the cocrystal is more soluble than drug R at all pH values, is presented in Figure 4.5(a). Many CBZ cocrystals, including CBZ-SAC, CBZ-SLC and CBZ-4ABA-HYD, have been shown to exhibit this behavior and consequently have no pH_{max} in aqueous solutions.[4, 29, 30] This behavior, however, is changed by micellar solubilization and ionization of cocrystal components (Figure 4.5(b)) where the cocrystal and drug solubility curves intersect at a given pH, or pH_{max}. The surfactant concentration at this intersection is the CSC. The drug micellar solubilization leading to coformer enrichment in the aqueous environment is responsible for the CSC and pH_{max}.

(a)　　　　　　　　　　　　　　　　　　(b)
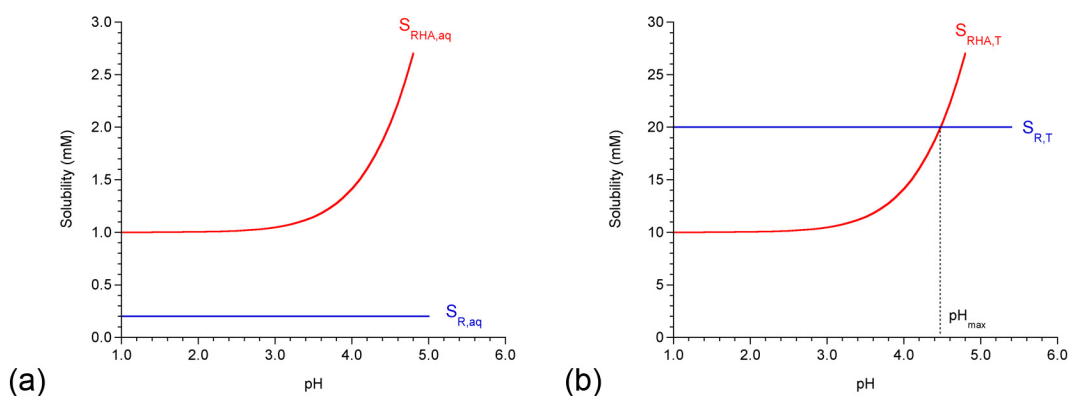
Figure 4.5. pH_{max} of a cocrystal can be tailored by micellar solubilization of cocrystal components. Solubility-pH dependence for a cocrystal RHA and drug R (a) in water and (b) in a micellar solution. Calculations are based on Equation (4.18) with $K_{sp} = 1$ mM^2 ($S_{RHA,aq}/S_{R,aq} = 5$), $S_{R,aq} = 0.2$ mM, $[M] = 99$ mM ($S_{R,T}/S_{R,aq} = 100$ and $S_{RHA,T}/S_{RHA,aq} = 10$), $pK_a = 4$, and $K_s^R = 1$ mM^{-1}.

Considering the contributions of coformer solubilization and ionization in addition to drug solubilization, leads to a more general form of Equation (4.17) expressed by

$$CSC = \frac{\dfrac{K_{sp}}{S_{R,aq}^2}\left(1 + \dfrac{K_a}{[H^+]}\right) - 1}{K_s^R - \dfrac{K_{sp}}{S_{R,aq}^2}K_s^{HA}} + CMC \qquad (4.18)$$

where $[H^+]$ represents $[H^+]_{max}$. According to Equation (4.18), the CSC for a 1:1 cocrystal RHA is dependent on several critical parameters: $K_{sp}/S_{R,aq}^2$, K_a, $[H^+]$, K_s^R, and K_s^{HA}. This equation can also be solved for $[H^+]$ to predict the pH_{max} dependence on micellar surfactant concentration and other cocrystal and surfactant properties. Equation (4.18) and Figure 4.6 show that if a CSC exists, there also is a pH_{max} value associated with that CSC and vice versa. CSC is predicted to increase as ionization increases. Higher levels of ionization increase cocrystal solubility, and thus more surfactant is required to achieve the CSC. Equation (4.18) can also be used to engineer a cocrystal's pH_{max} based on selection of an appropriate surfactant and concentration.

103
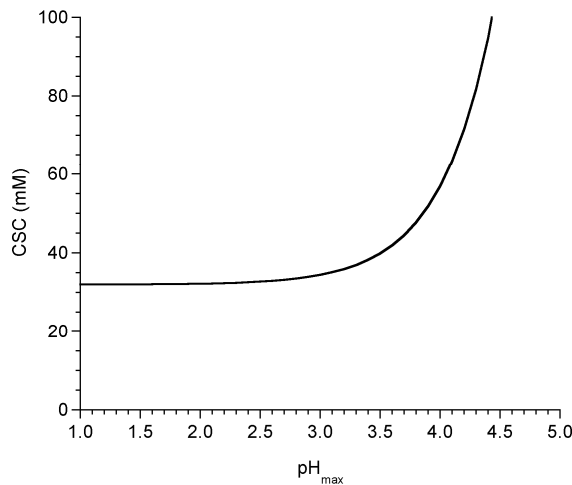
Figure 4.6. CSC dependence on pH_{max} according to Equation (4.18) for a cocrystal RHA. CSC increases greatly at pH above the coformer pK_a (*i.e.* increased ionization). Calculations are based on Equation (4.18) with $K_{sp} = 1$ mM^2, $S_{R,aq} = 0.2$ mM, $K_s^R = 1$ mM^{-1}, $K_s^{HA} = 0$, $pK_a = 4$, and CMC = 8 mM.

Table 4.1 summarizes the equations that describe cocrystal solubility and CSC for several common classes of cocrystals, with varying stoichiometries and component ionization properties.

The theoretical treatment of cocrystal micellar solubilization suggests that the CSC, where cocrystal and drug phases are in thermodynamic equilibrium, is most readily achieved by (1) preferential drug solubilization ($K_s^R \gg K_s^{HA}$), (2) cocrystals of lower aqueous solubility relative to drug, and (3) cocrystal stoichiometries that are higher in coformer.

Surfactant selection to achieve CSC

The CSC is a consequence of differential solubilization where drug is more highly solubilized than coformer. From Equation (4.18) a criterion can be obtained that determines if a particular surfactant, which has a given K_s^R and K_s^{HA} for the cocrystal components, can achieve the CSC. A CSC for cocrystal RHA can be achieved if

$$\frac{K_{sp}}{S_{R,aq}^2} < \frac{K_s^R}{K_s^{HA}} \tag{4.19}$$

This expression is obtained by examining Equation (4.18) for which positive values can be obtained (denominator > 0). Equation (4.19) relates the dimensionless parameter $K_{sp}/S_{R,aq}^2$ to the ratio of drug to coformer K_s, thus providing simple guidelines to select surfactants that are able to achieve CSC.

$K_{sp}/S_{R,aq}^2$ for a 1:1 cocrystal RHA in the absence of ionization and micellar solubilization, is related to the cocrystal to drug solubility ratio in water,

$$\frac{K_{sp}}{S_{R,aq}^2} = \left(\frac{S_{RHA,aq}}{S_{R,aq}}\right)^2 \tag{4.20}$$

If a surfactant is chosen such that Equation (4.19) is satisfied, there exists a CSC and pH$_{max}$ for that cocrystal and surfactant combination. Cocrystals that are more soluble relative to drug (higher $K_{sp}/S_{R,aq}^2$) require surfactants with more highly differential solubilization (higher K_s^R/K_s^{HA}) to achieve CSC. Equation (4.19) is not indicative of the magnitude of CSC and does not guarantee that the CSC and pH$_{max}$ are within reasonably achievable conditions.

Table 4.1. Equations that describe cocrystal solubility and CSC as a function of cocrystal K_{sp}, component K_a and K_s, solution $[H^+]$, micellar surfactant concentration $[M]$ and CMC.

Cocrystal	Solubility	Equation	CSC	Equation
RHA 1:1 nonionizable : monoprotic acidic	$S_{RHA,T} = \sqrt{K_{sp}\left(1+K_s^R[M]\right)\left(1+\dfrac{K_a}{[H^+]}+K_s^{HA}[M]\right)}$	(4.13)	$CSC = \dfrac{\dfrac{K_{sp}}{S_{R,aq}^2}\left(1+\dfrac{K_a}{[H^+]}\right)-1}{K_s^R-\dfrac{K_{sp}}{S_{R,aq}^2}K_s^{HA}}+CMC$	(4.18)
HXHA 1:1 monoprotic acidic : monoprotic acidic	$S_{HXHA,T} = \sqrt{K_{sp}\left(1+\dfrac{K_a^{HX}}{[H^+]}+K_s^{HX}[M]\right)\left(1+\dfrac{K_a^{HA}}{[H^+]}+K_s^{HA}[M]\right)}$	(4.21)	$CSC = \dfrac{\dfrac{K_{sp}}{S_{HX,aq}^2}\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)-\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)}{K_s^{HX}-\dfrac{K_{sp}}{S_{HX,aq}^2}K_s^{HA}}+CMC$	(4.22)
BHA 1:1 monoprotic basic : monoprotic acidic	$S_{BHA,T} = \sqrt{K_{sp}\left(1+\dfrac{[H^+]}{K_a^B}+K_s^B[M]\right)\left(1+\dfrac{K_a^{HA}}{[H^+]}+K_s^{HA}[M]\right)}$	(4.23)	$CSC = \dfrac{\dfrac{K_{sp}}{S_{B,aq}^2}\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)-\left(1+\dfrac{[H^+]}{K_a^B}\right)}{K_s^B-\dfrac{K_{sp}}{S_{B,aq}^2}K_s^{HA}}+CMC$	(4.24)
R₂H₂A 2:1 nonionizable : diprotic acidic	$S_{R_2H_2A,T} = \sqrt[3]{\dfrac{K_{sp}}{4}\left(1+K_s^R[M]\right)^2\left(1+\dfrac{K_a^{H_2A}}{[H^+]}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]\right)}$	(4.25)	$CSC = \dfrac{\dfrac{2K_{sp}}{S_{R,aq}^3}\left(1+\dfrac{K_a^{H_2A}}{[H^+]}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}\right)-1}{K_s^R-\dfrac{2K_{sp}}{S_{R,aq}^3}K_s^{H_2A}}+CMC$	(4.26)
R₂HAB 2:1 nonionizable : amphoteric	$S_{R_2HAB,T} = \sqrt[3]{\dfrac{K_{sp}}{4}\left(1+K_s^R[M]\right)^2\left(1+\dfrac{[H^+]}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]}+K_s^{HAB}[M]\right)}$	(4.27)	$CSC = \dfrac{\dfrac{2K_{sp}}{S_{R,aq}^3}\left(1+\dfrac{[H^+]}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]}\right)-1}{K_s^R-\dfrac{2K_{sp}}{S_{R,aq}^3}K_s^{HAB}}+CMC$	(4.28)

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.[17] 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) was prepared in water. Solid phases were characterized by XRPD.

CSC measurement from solid phase stability (Method 1)

Cocrystal was suspended in aqueous solutions of different SLS concentrations. Suspensions were seeded with ~5% w/w of CBZD after several hours. 30-40 mg of CBZ-SLC or CBZ-SAC were added to 3 mL of aqueous SLS solution. 70-80 mg of CBZ-SUC or CBZ-4ABA-HYD were added to 3 mL of aqueous SLS solution. Samples

were maintained at 25 ± 0.1 °C for the duration of 3 days, when the solids were recovered and analyzed by XRPD. Examination of the XRPD patterns revealed that 24 hours was sufficient for samples to reach equilibrium. The CSC was determined to be above the highest SLS concentration where CBZD is detected and below the lowest concentration where CBZD is no longer detected in the solid phase.

CSC predicted from cocrystal aqueous solubility and micellar solubilization of cocrystal components (Method 2)

CSC was predicted from model equations in Table 4.1 (Equations (4.18), (4.26), (4.28)), with thermodynamic parameters measured in pure water or obtained from literature. K_{sp} was calculated from cocrystal aqueous solubilities according to the model equations in Table 4.1 (Equations (4.13), (4.25) and (4.27) when [M]=0); cocrystal aqueous solubilities were determined by measuring eutectic concentrations of drug and coformer in pure water at 25 ± 0.1°C. 50-100 mg of cocrystal and 25-50 mg of CBZD were suspended in 3 mL of pure water up to 3 days. pH at equilibrium was measured but not independently modified. The equations to determine cocrystal aqueous solubility from eutectic concentrations are $S_{RHA,aq} = \sqrt{[R]_{eu,aq}[A]_{eu,aq}}$ and

$$S_{R_2H_2A,aq} = \sqrt[3]{\frac{[R]_{eu,aq}[A]_{eu,aq}}{4}}$$ for 1:1 and 2:1 cocrystals, respectively. Equations are

specific to cocrystal stoichiometry but general to cocrystal ionization properties. The evaluation of cocrystal solubilities and stabilities via eutectic points has been discussed thoroughly elsewhere.[4, 29, 31] At the eutectic or transition point the solution is saturated with respect to two solid phases, in this case cocrystal and CBZD. This method allows

for cocrystal solubility measurement under thermodynamic equilibrium that may not otherwise be accessible due to transformation to less soluble forms.

Micellar solubilization constants (K_s) for cocrystal components were determined by linear regression of the measured solubilities of the individual components as a function of micellar SLS concentration at $25 \pm 0.1°C$. K_a values were obtained from literature. Drug and coformer concentrations were analyzed by HPLC. Solid phases at equilibrium were confirmed by XRPD.

CSC measurement of cocrystal solubility in SLS solutions (Method 3)

The CSC was evaluated by measuring cocrystal and drug solubilities as a function of SLS concentration in water at $25 \pm 0.1°C$. Cocrystal solubilities were obtained from measuring eutectic concentrations of drug and coformer in aqueous SLS solutions at $25 \pm 0.1°C$. 50-100 mg of cocrystal and 25-50 mg of CBZD were suspended in 3 mL of pure water up to 3 days. pH at equilibrium was measured but not independently modified. Cocrystal solubilities were determined from the equations $S_{RHA,T} = \sqrt{[R]_{eu,T}[A]_{eu,T}}$ and

$$S_{R_2H_2A,T} = \sqrt[3]{\frac{[R]_{eu,T}[A]_{eu,T}}{4}}$$ for 1:1 and 2:1 cocrystals, respectively. Equations are specific

to cocrystal stoichiometry but general to cocrystal ionization properties. CBZD solubilities were measured as a function of SLS concentration in water at $25 \pm 0.1°C$ and are consistent with reported values.[32] 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 x 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 using an isocratic method. Injection

sample volume was 20 or 40 μL. Absorbance of CBZ, SLC, SUC, and 4ABA was

monitored at 284, 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 CuKα 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.

Results

The equations presented above for cocrystal solubility in terms of micellar

solubilization and ionization of cocrystal components, suggest that cocrystal CSC and

pH_{max} in micellar solutions can be *a priori* calculated from knowledge of cocrystal and

drug solubilities in water, pK_a and K_s values of cocrystal components, and surfactant

CMC. At the CSC, cocrystals otherwise unstable in aqueous media will become

thermodynamically stable.   To evaluate the predictive power of the model, the solubility

and stability of cocrystals of a nonionizable drug (carbamazepine) with coformers of

different ionization properties and stoichiometries were investigated as a function of SLS solution concentration. These included 1:1 cocrystals where coformers are monoprotic weak acids (CBZ-SLC and CBZ-SAC), and 2:1 cocrystals with a diprotic weak acid (CBZ-SUC) or with an amphoteric coformer (CBZ-4ABA-HYD). The cocrystal aqueous solubilities range from 1.32 mM for CBZ-SLC to 2.38 mM for CBZ-SUC (expressed in terms of drug concentration) at 25 °C, or 2.5 to 4.5 times the solubility of CBZD (0.53 mM).[32] Cocrystal solubilities in pure water are in agreement with those reported in previous studies.[29]

For cocrystals with ionizable components, the CSC is dependent on pH and while the pH was not independently adjusted in these studies, the pH of surfactant solutions at equilibrium with solid phases was measured. The pH at the CSC corresponds to the pH_{max}, where two solid phases (cocrystal and drug in this case) are in equilibrium with solution.

The cocrystal CSCs were evaluated by three methods: (1) measurement of solid phase stability and pH as a function of SLS solution concentration, (2) calculation from cocrystal and drug solubility measurement in pure water, in conjunction with values of cocrystal component ionization (K_a), micellar solubilization (K_s), surfactant CMC, and solution pH, and (3) measurement of cocrystal solubility, drug solubility and pH as a function of SLS solution concentration. Further, the dependence of CSC on pH_{max} was estimated from the evaluation of CSC at a single pH.

CSC from measurement of solid phase stability (Method 1)

Evaluation of the CSC from cocrystal phase stability measurements was done by XRPD analysis of solid phases after suspension in aqueous solutions of varying SLS concentration for 72 hours, though 24 hours was sufficient for equilibration to occur. Figure 4.7 shows that cocrystal conversion to drug (CBZD) decreases and becomes undetectable as surfactant concentration increases. The incremental variation of SLS concentrations for each cocrystal studied led to the following range of CSC values: CBZ-SLC 15 mM < CSC ≤ 20 mM, CBZ-SAC 50 mM < CSC ≤ 55 mM, CBZ-4ABA-HYD 69 mM < CSC ≤ 104 mM, and CBZ-SUC 120 mM < CSC ≤ 140 mM. The solution pH value associated with each CSC measurement is reported in the legend of Figure 4.7. The CSC range for CBZ-SLC is in agreement with previous results where cocrystal was found to be stable in 35 mM (1% w/v) SLS.[20]

While the solid phase analysis approach is convenient for a quick assessment of the CSC range, it must be recognized that its accuracy is limited by the changes of solution composition from initial to equilibrium states as solid phase(s) dissolve and crystallize. It is also not sufficient to establish whether the stabilization achieved is of a thermodynamic or kinetic nature. These issues may be resolved by measuring the changes in solution composition that result from equilibration of cocrystal and solid drug with the solution phase, and/or calculating the CSC according to the equations presented as shown below.
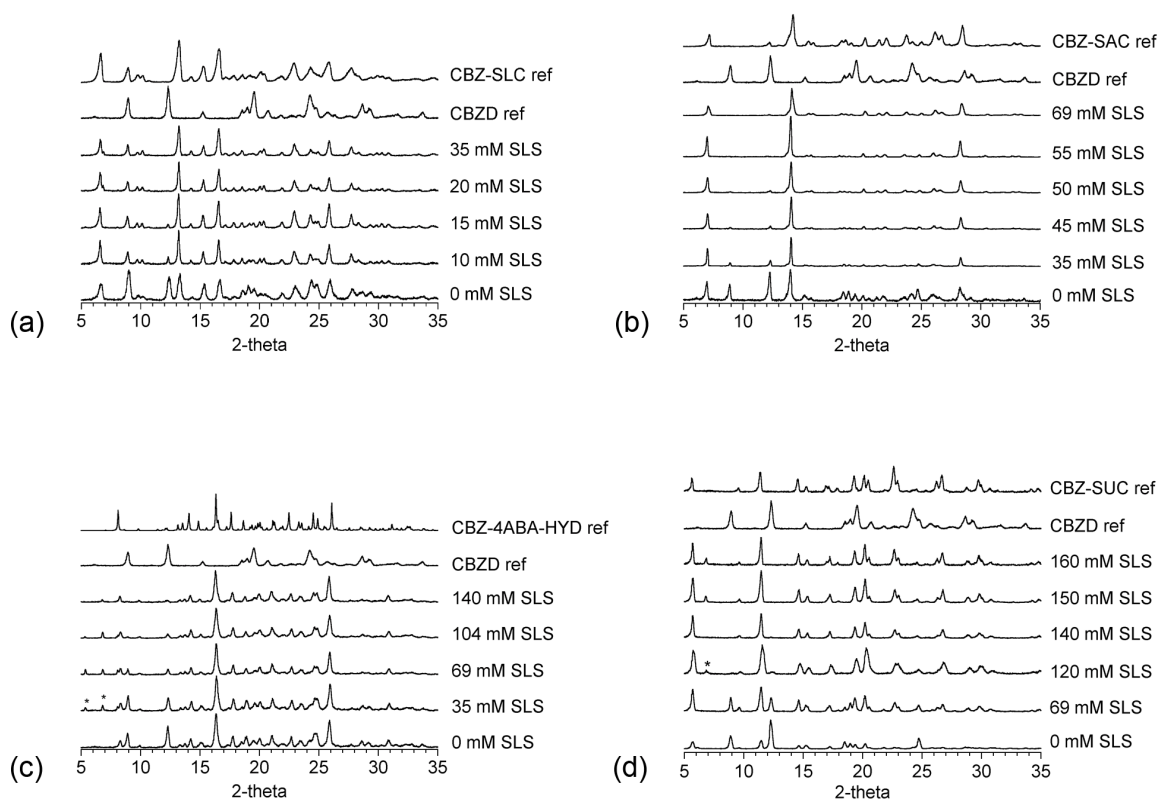
Figure 4.7. XRPD patterns showing the influence of SLS concentration on the cocrystal to drug conversion at 25 °C for (a) CBZ-SLC at pH 3.0 (b) CBZ-SAC at pH 2.2 (c) CBZ-4ABA-HYD at pH 4.0, and (d) CBZ-SUC at pH 3.1. pH was not independently adjusted and represents the values measured at 24 h before solid phase recovery for XRPD analysis. Initial solid phase consisted of cocrystal and a small fraction of CBZD. Peaks associated with SLS are indicated by *.

CSC from measured cocrystal solubility in pure water (Method 2)

Figure 4.8 shows the calculated cocrystal and drug solubilities in micellar SLS solutions according to Equations (4.13), (4.25) and (4.27) for cocrystal and Equation (4.14) for drug, from thermodynamic parameter values presented in Table 4.2. The CSC where cocrystal and CBZD are in equilibrium with solution is given by the SLS concentration and pH at the intersection of the solubility curves. CSC is strongly influenced by pH and the calculations were done for pH values measured at saturation.

113

This pH value changed by 0.2 units or less at the concentrations of SLS studied. The pH at the CSC is the pH_{max}, where two solid phases (cocrystal and drug in this case) are in equilibrium with solution.

Predicted CSC values for these cocrystals range from 20 to 187 mM which are in reasonably good agreement with the experimentally measured values listed in Table 4.3. Results of CSC measurement according to method 3, from solubility measurement in surfactant solutions are described in the next section.

The range of measured CSCs for each cocrystal by direct experimental measurement (methods 1 and 3) can be narrowed by examining smaller increments of SLS concentrations, and by approaching equilibrium from above and below saturation with respect to cocrystal and drug phases. Estimation of the CSC from thermodynamic properties of cocrystal and surfactant solutions (such as solubility in water, K_s, K_a and CMC) provides useful guidance for the selection of surfactant, its concentration and solution pH, and decreases the number of experiments required by other methods.
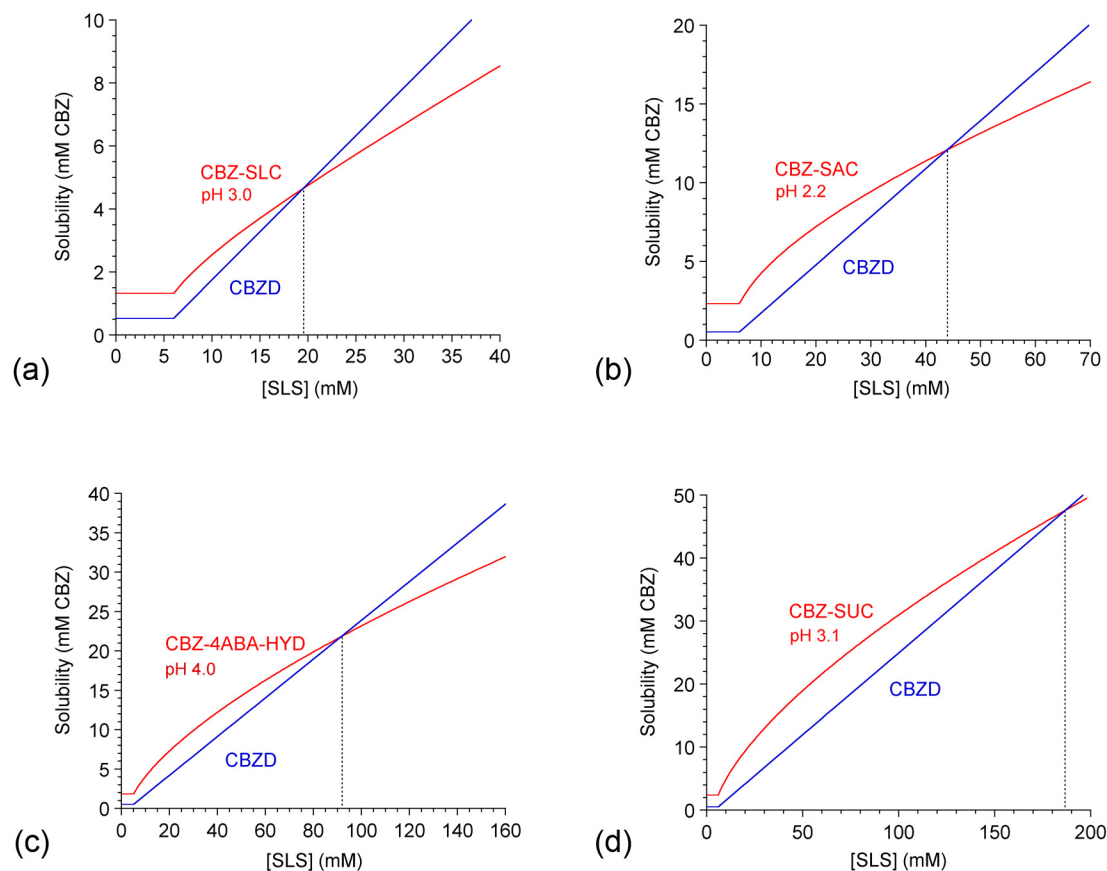
Figure 4.8. Calculated solubility and CSC of CBZ cocrystals in SLS aqueous solutions from measured solubility in water and values of K_s, K_a and pH listed in Table 4.2. Values of solution pH measured at equilibrium with solid phases are indicated. Dashed line shows the SLS concentration at the CSC, where cocrystal and drug are thermodynamically stable. The solid lines represent solubility predictions for cocrystal and drug, according to Equations (4.13), (4.14), (4.25) and (4.27). The CMC value of 6 mM for SLS measured at saturation with CBZD was used in these calculations.

Table 4.2 presents the thermodynamic parameter values for the CBZ cocrystals studied. Cocrystal K_{sp} in water and the corresponding solubility and pH are within 30% of those reported in previous studies.[20, 29] Coformer K_a values were obtained from the literature. Surfactant CMC and K_s values for drug and coformer were determined from solubility measurements of individual components (drug or coformer) in SLS solutions. The CMC of SLS was experimentally measured to be 6 mM in solutions saturated with

CBZ and is used in these calculations unless otherwise specified. The reported CMC value for SLS in water (8.3 mM[33]) is higher than the value measured in this study and those reported for carbamazepine solutions without coformer (5.3 mM[32]). The purity, ionic strength, and interactions with solutes are well documented to induce changes in the CMC of ionic surfactants.[10, 34-36] K_s values for hydrophobic compounds have been reported to be influenced by solute and surfactant concentration[10, 37-41] K_s values as well as the concentration ranges in which they were measured are shown in Table 4.2. An expression that describes the K_s dependence on surfactant concentration could also be used for more accurate predictions.

Table 4.2. Cocrystal K_{sp} and drug solubilities in water, pK_a and K_s values for cocrystal components in SLS solutions used in calculation of CSC and pH_{max}.

Solid phase	K_{sp} mM^2 or mM^3	pK_a	K_s^{CBZ} mM^{-1}	$K_s^{coformer}$ mM^{-1}	Aqueous solubility mM CBZ
CBZ-SLC (1:1)	0.88	3.0[a]	0.58[e]	0.060	1.32±0.06 pH 3.0
CBZ-SAC (1:1)	2.08	2.0[b]	0.58[e]	0.013	2.36±0.05 pH 2.2
CBZ-4ABA-HYD (2:1)	2.56	2.6, 4.8[c]	0.49[f]	0[g]	1.83±0.02 pH 4.0
CBZ-SUC (2:1)	6.15	4.1, 5.6[d]	0.49[f]	0[g]	2.38±0.02 pH 3.1
CBZD	n/a	n/a	0.49 (0 to 140 mM) 0.58 (0 to 50 mM)	n/a	0.53±0.01[h]

[a] from reference 21
[b] from reference 22
[c] from reference 25
[d] from reference 24
[e] average K_s in lower concentrations of SLS (0 to 50 mM)
[f] average K_s in higher concentrations of SLS (0 to 140 mM)
[g] K_s values <0.010 mM^{-1} are considered to = 0.
[h] from reference 32

Table 4.3. CSCs and solubilities of CBZ cocrystals in SLS aqueous solutions.

Cocrystal	pH	$S_{cocrystal}/S_{drug}$ in terms of CBZ mM	CSC measured from solid phase stability in SLS solutions (1) SLS mM	CSC calculated from measured cocrystal solubility in water (2) SLS mM	CSC measured from cocrystal solubility in SLS solutions (3) SLS mM
CBZ-SLC (1:1)	3.0	2.5	$15 < CSC \leq 20$	23 (CMC = 9 mM) 20 (CMC = 6 mM)	$18 < CSC < 27$
CBZ-SAC (1:1)	2.2	4.5	$50 < CSC \leq 55$	44	$35 < CSC < 50$
CBZ-4ABA-HYD (2:1)	4.0	3.5	$69 < CSC \leq 104$	92	$70 < CSC < 140$
CBZ-SUC (2:1)	3.1	4.5	$120 < CSC \leq 140$	187	$140 < CSC$

· (Method 1) CSCs determined from XRPD analysis of the solid phase in Figure 4.7. The lower boundary is the highest concentration of SLS where CBZD is detected in the solid phase, and the upper boundary is the lowest concentration of SLS where no CBZD is detected in the solid phase.

· (Method 2) CSCs calculated according to Equations (4.18), (4.26), (4.28) from K_{sp}, pK_a, and K_s values in Table 4.2.

· (Method 3) CSCs determined from measurement of cocrystal and drug solubilities in SLS solutions (Figures 4.9-4.11).

CSC from measured cocrystal solubility in SLS solutions (Method 3)

Figure 4.9 shows the experimental and predicted cocrystal solubility dependence on surfactant concentration and pH. The pH was not independently adjusted and experimental measurements represent the narrow pH range of micellar solutions saturated with cocrystal. Changes in pH, however, can profoundly affect cocrystal solubility as indicated by the surfaces predicted from Equations (4.13), (4.14), (4.25) and (4.27) using parameter values in Table 4.2. Coformer ionization, in this case determines the shape of the curves, since the drug is not ionizable and coformer is not solubilized by micelles. The solubility of cocrystals with acidic coformers increases with pH, whereas solubility decreases and increases with an amphoteric coformer. The contribution of coformer ionization to cocrystal solubility is consistent with the behavior in water that we previously reported .[4]
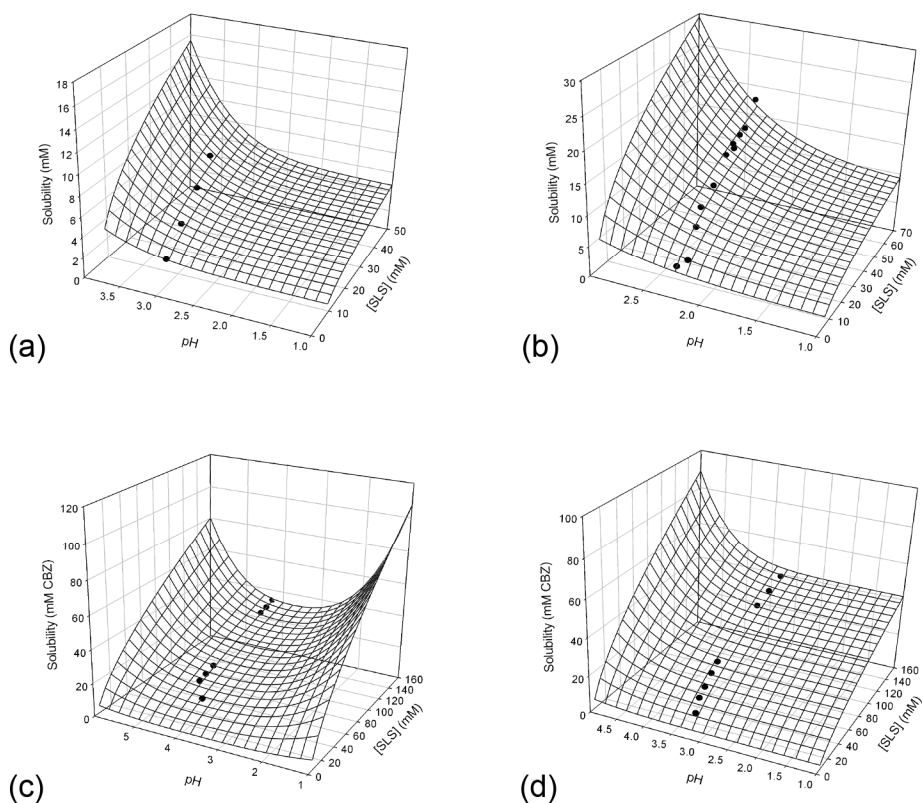
Figure 4.9. Influence of pH and surfactant concentration on cocrystal solubility for (a) CBZ-SLC (b) CBZ-SAC (c) CBZ-4ABA-HYD (d) CBZ-SUC. Points refer to cocrystal solubilities measured in surfactant solutions, while surfaces represent cocrystal solubilities calculated from Equations (4.13), (4.25) and (4.27) using measured cocrystal solubility in water at a given pH and thermodynamic values listed in Table 4.2.

Figures 4.10 and 4.11 show the predicted and measured cocrystal and drug solubilities as a function of surfactant concentration. The CMC for SLS was constant at 6 mM for cocrystals in Figure 4.9, whereas a CMC of 9 mM was estimated from solubility of CBZ-SLC cocrystal (Figure 4.10). Results show very good agreement between predicted and experimental cocrystal solubility and CSC behavior. The largest deviations were observed with the CBZ-SUC cocrystal at high SLS concentration and may be a result of changes in K_s with SLS and coformer concentration. CSC values obtained by the three methods are listed in Table 4.3 and show very good agreement

between the predicted (method 2) and experimentally measured CSC values (methods 1 and 3). A small variation in the CMC of SLS, such as from 6 mM to 9 mM for CBZ-SLC, has a relatively minor impact on the CSC (20 mM to 23 mM).

Improving the predictive power of the model requires more rigorous consideration of various solution interactions on equilibrium constants (such as K_a and K_s) and on surfactant properties (such as CMC). The model equations assume that solubilization of one cocrystal component is unaffected by the presence of the other; that is, K_s for a component under pure conditions is a good approximation for the K_s in the presence of cocrystal. Factors that cause K_s, K_a, and CMC to change (such as ionic strength) influence the predictions and these differences may be considered by measuring the parameters as a function of solution composition. A 0.2 unit pH or pK_a change when pH $\approx pK_a$ (*e.g.* CBZ-SAC) can lead to errors in the CSC on the order of 15-30%, and even greater errors when pH > pK_a. A 10% error in K_s^{CBZ} (*e.g.* CBZ-SUC) leads to an error in the CSC of 10%.

An alternative approach would have been to fit the models to the experimental data and evaluate the corresponding parameters. Given that this is the first manuscript on this topic, we chose to use thermodynamic parameter values reported in the literature or measured for single components of cocrystals, to evaluate the predicted cocrystal solubilities and CSC values with all the established assumptions.
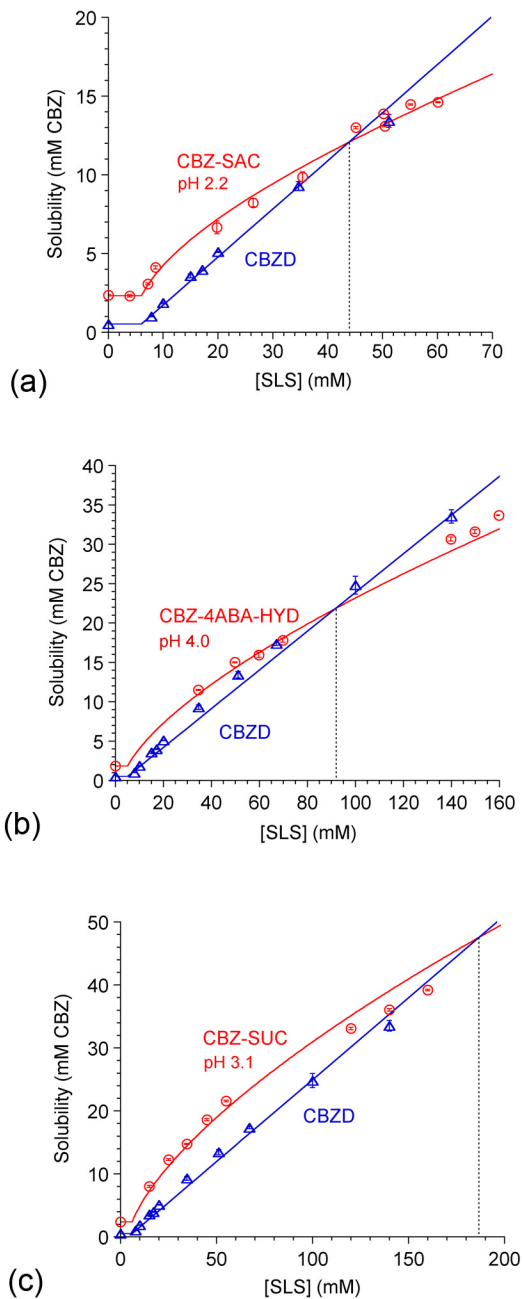
Figure 4.10. Experimental and predicted influence of SLS on drug (CBZD) solubility and CBZ cocrystal solubilities for (a) CBZ-SAC, (b) CBZ-4ABA-HYD, and (c) CBZ-SUC. The experimental solubilities were measured in unbuffered surfactant aqueous solutions. The pH measured at equilibrium is indicated. Predicted drug and cocrystal solubilities were calculated according to Equations (4.13), (4.14), (4.25) and (4.27) with thermodynamic values in Table 2. The CSC is indicated by the SLS concentration (dashed line) at the intersection of the predicted cocrystal and drug solubility curves.
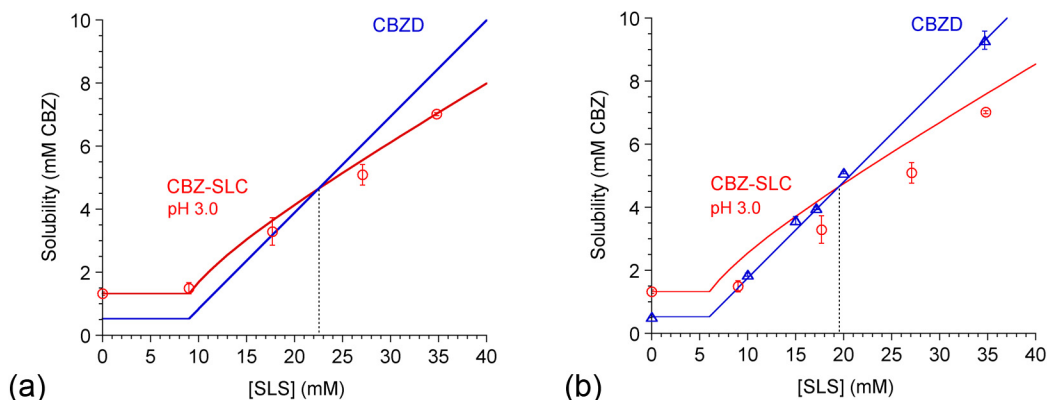
Figure 4.11. Influence of SLS on the solubility of CBZ-SLC and CBZD. The lines represent predictions according to Equations (4.13) and (4.14) from two different CMC values (a) 9 mM and (b) 6 mM. The points are experimental values.

CSC and pH_{max} dependence on cocrystal and surfactant properties

The treatment developed in the theoretical section is based on cocrystal component ionization and micellar solubilization. This treatment identified the existence of a CSC and the factors that determine its value: (1) cocrystal K_{sp} and solubility relative to drug, (2) ionization of cocrystal components, (3) micellar solubilization of cocrystal components, (4) cocrystal stoichiometry, and (5) surfactant CMC. CSC is predicted to increase with increasing cocrystal solubility, ionization, coformer K_s, and surfactant CMC and with decreasing drug K_s.

For this series of CBZ cocrystals, the magnitude of the CSC is mostly influenced by the cocrystal K_{sp}, stoichiometry, and coformer ionization. Between cocrystals of the same stoichiometry such as CBZ-SLC and CBZ-SAC, the experiments confirm the prediction that higher solubility relative to drug results in a higher CSC (Table 4.3).

123

These have similar % ionized (since pH ≈ pK_a of the coformer), and $K_s^{HA} \ll K_s^R$. The

CSC is mainly determined by cocrystal solubility relative to drug. Similar behavior is

observed for the 2:1 cocrystals CBZ-4ABA-HYD and CBZ-SUC. These cocrystals have

low levels of ionization under the pH conditions studied (10-20% of the coformer

ionized), and negligible coformer solubilization. The experiments also show that the 2:1

cocrystal CBZ-SUC has a higher CSC than the 1:1 cocrystal CBZ-SAC of equal

solubility (in terms of CBZ moles). The higher CSC of drug rich stoichiometries is a

consequence of the higher surfactant concentrations required to solubilize more drug to

achieve the same level of coformer enrichment in the aqueous pseudo phase as a 1:1

cocrystal.

The pH value at the CSC is the pH_{max}, where cocrystal and drug (in this case) are

in equilibrium with solution. The predicted CSC and pH_{max} values for the CBZ

cocrystals studied are plotted in Figure 12. These were calculated from Equations (4.18),

(4.26), and (4.28) using values presented in Table 4.2. CSC is shown to be strongly

dependent on pH and follows the coformer ionization behavior. It is recognized that

these calculations assume that ionized components do not interact with the micelles and

that K_a, K_s, and CMC are independent of solution composition.
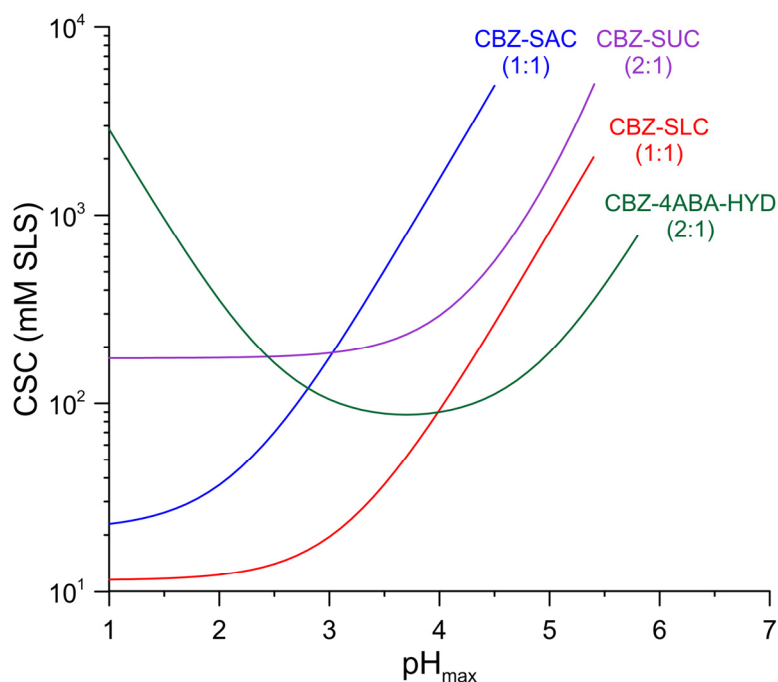
Figure 4.12. Calculated CSC (mM SLS) and pH_{max} for CBZ cocrystals according to Equations (4.18), (4.26), and (4.28) using measured values presented in Table 4.2. CSC dependence on pH may be tailored based on the ionization properties of the coformer.

Conclusions

A theoretical treatment that considers the contributions of cocrystal dissociation, component ionization, and micellar solubilization, demonstrates that surfactants can impart thermodynamic stability to cocrystals that otherwise convert to parent drug solid in aqueous solutions. The CSC and pH_{max} represent the surfactant concentration and solution pH, where cocrystal is in thermodynamic equilibrium with solid drug and solution phases. Therefore, both CSC and pH_{max} (in the case of ionizable cocrystal components) are key indicators of cocrystal stability. This behavior is confirmed by the stabilization of several CBZ cocrystals in SLS micellar solutions.

How effective a surfactant is in changing the thermodynamic stability of a cocrystal, CSC and pH_{max}, is determined mostly by the differential solubilization of cocrystal components by micelles. Such differential solubilization of cocrystal components leads to a slower rate of solubility increase with surfactant micellar concentration for the cocrystal, compared to that of the drug solubility increase (when the drug has the superior micellar solubilization of coocrystal components).

For cocrystals of nonionzable, hydrophobic drugs with ionizable, hydrophilic coformers, the theoretical treatment predicts that surfactant CSC is decreased by: (1) preferential drug solubilization ($K_s^R \gg K_s^{HA}$), (2) low ionization of coformer, (3) low cocrystal aqueous solubility relative to drug, and (4) cocrystal stoichiometries that are lower in drug than coformer. This generalization assumes that there is no additional solution complexation, and that ionized coformer is not solubilized by the micelles. The relationship between CSC and pH_{max} is determined by the ionization behavior of the coformer, with CSC changing orders of magnitude at pH values where coformer ionizes. Acidic coformers exhibit an increase in pH_{max} with increasing surfactant concentration, whereas amphoteric coformers exhibit pH_{max} decrease and increase.

CSC and pH_{max} for cocrystals in micellar solutions are quantitatively predicted by mathematical models from solution phase properties of cocrystal (K_{sp}), cocrystal components (K_s and K_a) and surfactant (CMC). CSC, pH_{max}, and cocrystal solubility predicted by the models are in very good agreement with experimental measurements. The proposed models provide a rational basis for selecting additives and solution conditions to achieve desired cocrystal solubility/stability from parameter values that are generally available in the literature or experimentally accessible. Since cocrystals owe

their solubility to the ionization and association of their components in solution, it is essential to consider the influence of solution conditions such as pH, presence of surfactants and other additives, for meaningful cocrystal assessment and selection.

Appendix

Derivation of equations

Explanation of terms:

Subscript aq – aqueous

Subscript m – micellar

Subscript T – total (aqueous + micellar)

R – nonionizable drug

HA – monoprotic weakly acidic coformer (nonionized)

H_2A – diprotic weakly acidic coformer (nonionized)

HAB – amphoteric coformer (nonionized)

M – micellar surfactant

K_{sp} – cocrystal solubility product

K_a – acid dissociation constant

K_s – micellar solubilization constant

K_{eu} – eutectic constant

S – solubility

CMC – critical micellar concentration

CSC – critical stabilization concentration

RHA (1:1 nonionizable drug R, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{4A.1}$$

$$HA_{aq} \xrightleftharpoons{K_a} A^-_{aq} + H^+_{aq} \tag{4A.2}$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \tag{4A.3}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{4A.4}$$

$$A^-_{aq} + M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{4A.5}$$

Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \tag{4A.6}$$

$$K_a = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{4A.7}$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{4A.8}$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \tag{4A.9}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{4A.10}$$

Cocrystal RHA total solubility in micellar solutions

Mass balance on R is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{4A.11}$$

Substituting (4.8) and (4.10) into (4A.11) gives

$$[R]_T = \frac{K_{sp}}{[HA]_{aq}}\left(1 + K_s^R[M]\right) \tag{4A.12}$$

129

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{4A.13}$$

Substituting (4.9), (4.11), and (4.12) into (4A.13) gives

$$[A]_T = [HA]_{aq} \left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]} K_s^{A^-}[M] \right) \tag{4A.14}$$

Combining (4A.12) and (4A.14) gives

$$[R]_T = \frac{K_{sp}}{[A]_T} \left(1 + K_s^R[M] \right) \left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]} K_s^{A^-}[M] \right) \tag{4A.15}$$

Cocrystal solubility in micellar solutions containing stoichiometric solution concentrations of cocrystal components, in the absence of solution complexation, is given by

$$S_{RHA,T} = [R]_T = [A]_T \tag{4A.16}$$

Substituting (4A.16) into (4A.15),

$$S_{RHA,T} = \sqrt{K_{sp} \left(1 + K_s^R[M] \right) \left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]} K_s^{A^-}[M] \right)} \tag{4A.17}$$

When $K_s^{HA} \gg K_s^{A^-}$, then (4A.17) can be simplified to

$$S_{RHA,T} = \sqrt{K_{sp} \left(1 + K_s^R[M] \right) \left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] \right)} \tag{4A.18}$$

Solubility of drug R in micellar solutions

Relevant equilibria are given by

$$R_{solid} \rightleftharpoons R_{aq} \tag{4A.19}$$

$$R_{aq} + M \xrightarrow{\quad K_s^R \quad} R_m \tag{4A.20}$$

with the associated equilibrium constant

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{4A.21}$$

According to mass balance on R,

$$[R]_T = [R]_{aq} + [R]_m \tag{4A.22}$$

$$[R]_T = [R]_{aq}\left(1 + K_s^R[M]\right) \tag{4A.23}$$

In this case, $S_{R,T} = [R]_T$ and $[R]_{aq} = S_{R,aq}$ so

$$S_{R,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{4A.24}$$

Solubility enhancement of cocrystal is related to solubility enhancement of drug

From (4A.18), the ratio of cocrystal solubility in micellar solutions to pure water is given by

$$\frac{S_{RHA,T}}{S_{RHA,aq}} = \frac{\sqrt{\left(1 + K_s^R[M]\right)\left(1 + \dfrac{K_a}{[H^+]} + K_s^{HA}[M]\right)}}{\sqrt{\left(1 + \dfrac{K_a}{[H^+]}\right)}} \tag{4A.25}$$

Assuming $K_s^{HA} = 0$, this simplifies to

$$\frac{S_{RHA,T}}{S_{RHA,aq}} = \sqrt{\left(1 + K_s^R[M]\right)} \tag{4A.26}$$

Substituting (4A.24) into (4A.26) gives

$$\frac{S_{RHA,T}}{S_{RHA,aq}} = \sqrt{\frac{S_{R,T}}{S_{R,aq}}} \tag{4A.27}$$

Critical stabilization concentration (CSC) of cocrystal RHA

At the CSC,

$$S_{RHA,T} = S_{R,T} \tag{4A.28}$$

Substituting (4A.18) and (4A.24) into (4A.28) and solving for [M],

$$[M]_{CSC} = \frac{\dfrac{K_{sp}}{S_{R,aq}^2}\left(1+\dfrac{K_a}{[H^+]}\right)-1}{K_s^R - \dfrac{K_{sp}}{S_{R,aq}^2}K_s^{HA}} \tag{4A.29}$$

CSC is given by

$$CSC = [M]_{CSC} + CMC \tag{4A.30}$$

Therefore

$$CSC = \frac{\dfrac{K_{sp}}{S_{R,aq}^2}\left(1+\dfrac{K_a}{[H^+]}\right)-1}{K_s^R - \dfrac{K_{sp}}{S_{R,aq}^2}K_s^{HA}} + CMC \tag{4A.31}$$

In the absence of micellar solubilization, cocrystal RHA aqueous solubility, according to (4A.18) is given by

$$S_{RHA,aq} = \sqrt{K_{sp}\left(1+\frac{K_a}{[H^+]}\right)} \tag{4A.32}$$

Combining (4A.31) and (4A.32), with the assumption that $K_s^{HA} = 0$, gives

$$CSC = \frac{\left(\dfrac{S_{RHA,T}}{S_{R,aq}}\right)^2 - 1}{K_s^R} + CMC \tag{4A.33}$$

HXHA (1:1 monoprotic weakly acidic drug HX, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$\text{HXHA}_{\text{solid}} \xrightleftharpoons{K_{sp}} \text{HX}_{aq} + \text{HA}_{aq} \tag{4A.34}$$

$$\text{HX}_{aq} \xrightleftharpoons{K_a^{HX}} \text{X}^-_{aq} + \text{H}^+_{aq} \tag{4A.35}$$

$$\text{HA}_{aq} \xrightleftharpoons{K_a^{HA}} \text{A}^-_{aq} + \text{H}^+_{aq} \tag{4A.36}$$

$$\text{HX}_{aq} + \text{M} \xrightleftharpoons{K_s^{HX}} \text{HX}_m \tag{4A.37}$$

$$\text{HA}_{aq} + \text{M} \xrightleftharpoons{K_s^{HA}} \text{HA}_m \tag{4A.38}$$

$$\text{X}^-_{aq} + \text{M} \xrightleftharpoons{K_s^{X^-}} \text{X}^-_m \tag{4A.39}$$

$$\text{A}^-_{aq} + \text{M} \xrightleftharpoons{K_s^{A^-}} \text{A}^-_m \tag{4A.40}$$
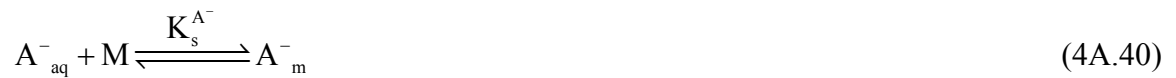
Associated equilibrium constants are given by

$$K_{sp} = [\text{HX}]_{aq}[\text{HA}]_{aq} \tag{4A.41}$$

$$K_a^{HX} = \frac{[\text{X}^-]_{aq}[\text{H}^+]_{aq}}{[\text{HX}]_{aq}} \tag{4A.42}$$

$$K_a^{HA} = \frac{[\text{A}^-]_{aq}[\text{H}^+]_{aq}}{[\text{HA}]_{aq}} \tag{4A.43}$$

$$K_s^{HX} = \frac{[\text{HX}]_m}{[\text{HX}]_{aq}[\text{M}]} \tag{4A.44}$$

$$K_s^{HA} = \frac{[\text{HA}]_m}{[\text{HA}]_{aq}[\text{M}]} \tag{4A.45}$$

$$K_s^{X^-} = \frac{[X^-]_m}{[X^-]_{aq}[M]} \tag{4A.46}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{4A.47}$$

Cocrystal HXHA total solubility in micellar solutions

Mass balance on X is given by

$$[X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m + [X^-]_m \tag{4A.48}$$

Substituting (4A.41), (4A.42), (4A.44), and (4A.46) into (4A.48) gives

$$[X]_T = \frac{K_{sp}}{[HA]_{aq}}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right) \tag{4A.49}$$

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{4A.50}$$

Substituting (4A.43), (4A.45), and (4A.47) into (4A.50) gives

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]}K_s^{A^-}[M]\right) \tag{4A.51}$$

Combining (4A.49) and (4A.51) gives

$$[X]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right) \tag{4A.52}$$

Cocrystal solubility in micellar solutions containing stoichiometric solution concentrations of cocrystal components, in the absence of solution complexation, is given by

$$S_{HXHA,T} = [X]_T = [A]_T \tag{4A.53}$$

Substituting (4A.52) into (4A.53),

$$S_{HXHA,T} = \sqrt{K_{sp}\left(1+\frac{K_a^{HX}}{[H^+]}+K_s^{HX}[M]+\frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right)\left(1+\frac{K_a^{HA}}{[H^+]}+K_s^{HA}[M]+\frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right)} \quad (4A.54)$$

When $K_s^{HX} \gg K_s^{X^-}$ and $K_s^{HA} \gg K_s^{A^-}$ then (4A.54) can be simplified to

$$S_{HXHA,T} = \sqrt{K_{sp}\left(1+\frac{K_a^{HX}}{[H^+]}+K_s^{HX}[M]\right)\left(1+\frac{K_a^{HA}}{[H^+]}+K_s^{HA}[M]\right)} \quad (4A.55)$$

Solubility of drug HX in micellar solutions

Relevant equilibria are given by

$$HX_{solid} \rightleftharpoons HX_{aq} \quad (4A.56)$$

$$HX_{aq} \xrightleftharpoons{K_a^{HX}} X^-_{aq} + H^+_{aq} \quad (4A.57)$$

$$HX_{aq} + M \xrightleftharpoons{K_s^{HX}} HX_m \quad (4A.58)$$

$$X^-_{aq} + M \xrightleftharpoons{K_s^{X^-}} X^-_m \quad (4A.59)$$
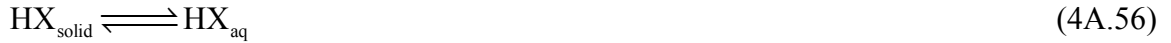
with the associated equilibrium constants

$$K_a^{HX} = \frac{[X^-]_{aq}[H^+]_{aq}}{[HX]_{aq}} \quad (4A.60)$$

$$K_s^{HX} = \frac{[HX]_m}{[HX]_{aq}[M]} \quad (4A.61)$$

$$K_s^{X^-} = \frac{[X^-]_m}{[X^-]_{aq}[M]} \quad (4A.62)$$

According to the mass balance on X,

$$[X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m + [X^-]_m \qquad (4A.63)$$

Substituting (4A.60)-(4A.62) into (4A.63) gives

$$[X]_T = [HX]_{aq}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right) \qquad (4A.64)$$

When $K_s^{HX} \gg K_x^{X-}$, (4A.64) can be simplified to

$$[X]_T = [HX]_{aq}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M]\right) \qquad (4A.65)$$

In this case, $S_{X,T} = [X]_T$ and $S_{HX,aq} = [HX]_{aq}$ (the intrinsic solubility of X), so

$$S_{X,T} = S_{HX,aq}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M]\right) \qquad (4A.66)$$

CSC of cocrystal HXHA

At the CSC,

$$S_{HXHA,T} = S_{X,T} \qquad (4A.67)$$

Substituting (4A.55) and (4A.66) into (4A.67) and solving for [M] gives

$$[M]_{CSC} = \frac{\dfrac{K_{sp}}{S_{HX,aq}^2}\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right) - \left(1 + \dfrac{K_a^{HX}}{[H^+]}\right)}{K_s^{HX} - \dfrac{K_{sp}}{S_{HX,aq}^2}K_s^{HA}} \qquad (4A.68)$$

CSC is given by

$$CSC = [M]_{CSC} + CMC \qquad (4A.69)$$

Therefore

$$CSC = \frac{\dfrac{K_{sp}}{S_{HX,aq}^2}\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)-\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)}{K_s^{HX}-\dfrac{K_{sp}}{S_{HX,aq}^2}K_s^{HA}}+CMC \tag{4A.70}$$

BHA (1:1 monoprotic weakly basic drug B, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$BHA_{solid} \xrightleftharpoons{K_{sp}} B_{aq}+HA_{aq} \tag{4A.71}$$

$$BH^+_{aq} \xrightleftharpoons{K_a^B} B_{aq}+H^+_{aq} \tag{4A.72}$$

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq}+H^+_{aq} \tag{4A.73}$$

$$B_{aq}+M \xrightleftharpoons{K_s^B} B_m \tag{4A.74}$$

$$HA_{aq}+M \xrightleftharpoons{K_s^{HA}} HA_m \tag{4A.75}$$

$$BH^+_{aq}+M \xrightleftharpoons{K_s^{BH^+}} BH^+_m \tag{4A.76}$$

$$A^-_{aq}+M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{4A.77}$$

Associated equilibrium constants are given by

$$K_{sp}=[B]_{aq}[HA]_{aq} \tag{4A.78}$$

$$K_a^B=\frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}} \tag{4A.79}$$

$$K_a^{HA}=\frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{4A.80}$$

$$K_s^B = \frac{[B]_m}{[B]_{aq}[M]}$$ (4A.81)

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]}$$ (4A.82)

$$K_s^{BH^+} = \frac{[BH^+]_m}{[B]_{aq}[M]}$$ (4A.83)

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]}$$ (4A.84)

Cocrystal BHA total solubility in micellar solutions

Mass balance on B is given by

$$[B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m + [BH^+]_m$$ (4A.85)

Substituting (4A.78), (4A.79), (4A.81), and (4A.83) into (4A.85) gives

$$[B]_T = \frac{K_{sp}}{[B]_{aq}}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B}K_s^{BH^+}[M]\right)$$ (4A.86)

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m$$ (4A.87)

Substituting (4A.80), (4A.82), and (4A.84) into (4A.87) gives

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]}K_s^{A^-}[M]\right)$$ (4A.88)

Combining (4A.86) and (4A.88) gives

$$[B]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B}K_s^{BH^+}[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right)$$ (4A.89)

Cocrystal solubility in micellar solutions containing stoichiometric solution concentrations of cocrystal components, in the absence of solution complexation, is given by

$$S_{BHA,T} = [B]_T = [A]_T \tag{4A.90}$$

Substituting (4A.89) into (4A.90),

$$S_{BHA,T} = \sqrt{K_{sp}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B}K_s^{BH^+}[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right)} \tag{4A.91}$$

When $K_s^B \gg K_s^{BH^+}$ and $K_s^{HA} \gg K_s^{A^-}$ then (4A.91) can be simplified to

$$S_{BHA,T} = \sqrt{K_{sp}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right)} \tag{4A.92}$$

Solubility of drug B in micellar solutions

$$B_{solid} \rightleftharpoons B_{aq} \tag{4A.93}$$

$$BH^+_{aq} \overset{K_a^B}{\rightleftharpoons} B_{aq} + H^+_{aq} \tag{4A.94}$$

$$B_{aq} + M \overset{K_s^B}{\rightleftharpoons} B_m \tag{4A.95}$$
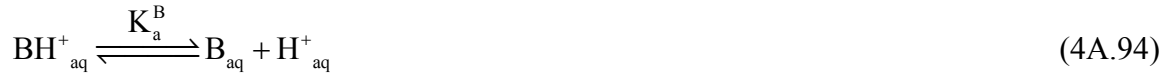
$$BH^+_{aq} + M \overset{K_s^{BH^+}}{\rightleftharpoons} BH^+_m \tag{4A.96}$$

with associated equilibrium constants

$$K_a^B = \frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}} \tag{4A.97}$$

$$K_s^B = \frac{[B]_m}{[B]_{aq}[M]} \tag{4A.98}$$

$$K_s^{BH^+} = \frac{[BH^+]_m}{[B]_{aq}[M]} \tag{4A.99}$$

According to the mass balance on B,

$$[B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m + [BH^+]_m \tag{4A.100}$$

Substituting (4A.97)-(4A.99) into (4A.100) gives

$$[B]_T = [B]_{aq}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B}K_s^{BH^+}[M]\right) \tag{4A.101}$$

When $K_s^B \gg K_s^{BH+}$, (4A.101) can be simplified to

$$[B]_T = [B]_{aq}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M]\right) \tag{4A.102}$$

In this case, $S_{B,T} = [B]_T$ and $S_{B,aq} = [B]_{aq}$ (the intrinsic solubility of B), so

$$S_{B,T} = S_{B,aq}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M]\right) \tag{4A.103}$$

CSC of cocrystal BHA

At the CSC,

$$S_{BHA,T} = S_{B,T} \tag{4A.104}$$

Substituting (4A.92) and (4A.103) into (4A.104) and solving for [M] gives

$$[M]_{CSC} = \frac{\dfrac{K_{sp}}{S_{B,aq}^2}\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right) - \left(1 + \dfrac{[H^+]}{K_a^B}\right)}{K_s^B - \dfrac{K_{sp}}{S_{B,aq}^2}K_s^{HA}} \tag{4A.105}$$

CSC is given by

140

$$CSC = [M]_{CSC} + CMC \tag{4A.106}$$

Therefore

$$CSC = \frac{\dfrac{K_{sp}}{S_{B,aq}^{2}}\left(1 + \dfrac{K_a^{HA}}{[H^+]}\right) - \left(1 + \dfrac{[H^+]}{K_a^{B}}\right)}{K_s^{B} - \dfrac{K_{sp}}{S_{B,aq}^{2}}K_s^{HA}} + CMC \tag{4A.107}$$

R₂H₂A (2:1 monoprotic weakly basic drug R, diprotic weakly acidic coformer H₂A)

Relevant equilibria are given by

$$R_2H_2A_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq} + H_2A_{aq} \tag{4A.108}$$

$$H_2A_{aq} \xrightleftharpoons{K_a^{H_2A}} HA^-_{aq} + H^+_{aq} \tag{4A.109}$$

$$HA^-_{aq} \xrightleftharpoons{K_a^{HA^-}} A^{2-}_{aq} + H^+_{aq} \tag{4A.110}$$

$$R_{aq} + M \xrightleftharpoons{K_s^{R}} R_m \tag{4A.111}$$

$$H_2A_{aq} + M \xrightleftharpoons{K_s^{H_2A}} H_2A_m \tag{4A.112}$$

$$HA^-_{aq} + M \xrightleftharpoons{K_s^{HA^-}} HA^-_m \tag{4A.113}$$

$$A^{2-}_{aq} + M \xrightleftharpoons{K_s^{A^{2-}}} A^{2-}_m \tag{4A.114}$$
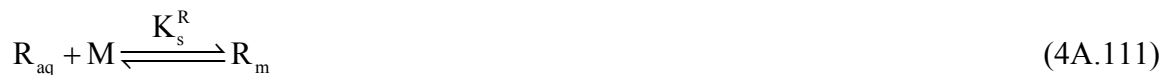
Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}^{2}[H_2A]_{aq} \tag{4A.115}$$

$$K_a^{H_2A} = \frac{[HA^-]_{aq}[H^+]_{aq}}{[H_2A]_{aq}} \tag{4A.116}$$

$$K_a^{HA^-} = \frac{[A^{2-}]_{aq}[H^+]_{aq}}{[HA^-]_{aq}} \tag{4A.117}$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{4A.118}$$

$$K_s^{H_2A} = \frac{[H_2A]_m}{[H_2A]_{aq}[M]} \tag{4A.119}$$

$$K_s^{HA^-} = \frac{[HA^-]_m}{[HA^-]_{aq}[M]} \tag{4A.120}$$

$$K_s^{A^{2-}} = \frac{[A^{2-}]_m}{[A^{2-}]_{aq}[M]} \tag{4A.121}$$

Cocrystal R$_2$H$_2$A total solubility in micellar solutions

Mass balance on B is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{4A.122}$$

Substituting (4A.115) and (4A.118) into (4A.122) gives

$$[R]_T^2 = \frac{K_{sp}}{[H_2A]_{aq}}\left(1 + K_s^R[M]\right)^2 \tag{4A.123}$$

Mass balance on A is given by

$$[A]_T = [H_2A]_{aq} + [HA^-]_{aq} + [A^{2-}]_{aq} + [H_2A]_m + [HA^-]_m + [A^{2-}]_m \tag{4A.124}$$

Substituting (4A.116), (4A.117), and (4A.119)-(4A.121) into (4A.124) gives

$$[A]_T = [H_2A]_{aq}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M] + \frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M] + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \tag{4A.125}$$

Combining (4A.123) and (4A.125) gives

$$[R]_T^2 = \frac{K_{sp}}{[A]_T}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]+\frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M]+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \quad (4A.126)$$

Cocrystal solubility in micellar solutions containing stoichiometric solution concentrations of cocrystal components, in the absence of solution complexation, is given by

$$S_{R_2H_2A,T} = \frac{1}{2}[R]_T = [A]_T \quad (4A.127)$$

Substituting (4A.126) into (4A.127),

$$S_{R_2H_2A,T} = \sqrt[3]{\frac{K_{sp}}{4}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]+\frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M]+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right)} \quad (4A.128)$$

When $K_s^{H_2A} \gg K_s^{HA^-}$ and $K_s^{H_2A} \gg K_s^{A^{2-}}$ then (4A.128) can be simplified to

$$S_{R_2H_2A,T} = \sqrt[3]{\frac{K_{sp}}{4}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]\right)} \quad (4A.129)$$

Solubility of drug R in micellar solutions

Relevant equilibria are given by

$$R_{solid} \rightleftharpoons R_{aq} \quad (4A.130)$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \quad (4A.131)$$

with the associated equilibrium constant

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \quad (4A.132)$$

According to mass balance on R,

$$[R]_T = [R]_{aq} + [R]_m \quad (4A.133)$$

143

$$[R]_T = [R]_{aq} \left(1 + K_s^R [M] \right) \tag{4A.134}$$

In this case, $S_{R,T} = [R]_T$ and $[R]_{aq} = S_{R,aq}$ so

$$S_{R,T} = S_{R,aq} \left(1 + K_s^R [M] \right) \tag{4A.135}$$

CSC of cocrystal R_2H_2A

At the CSC,

$$2S_{R_2H_2A,T} = S_{R,T} \tag{4A.136}$$

Substituting (4A.129) and (4A.135) into (4A.136) and solving for [M] gives

$$[M]_{CSC} = \frac{\dfrac{2K_{sp}}{S_{R,aq}^{3}} \left(1 + \dfrac{K_a^{H_2A}}{[H^+]} + \dfrac{K_a^{H_2A} K_a^{HA^-}}{[H^+]^2} \right) - 1}{K_s^R - \dfrac{2K_{sp}}{S_{R,aq}^{3}} K_s^{H_2A}} \tag{4A.137}$$

CSC is given by

$$CSC = [M]_{CSC} + CMC \tag{4A.138}$$

Therefore

$$CSC = \frac{\dfrac{2K_{sp}}{S_{R,aq}^{3}} \left(1 + \dfrac{K_a^{H_2A}}{[H^+]} + \dfrac{K_a^{H_2A} K_a^{HA^-}}{[H^+]^2} \right) - 1}{K_s^R - \dfrac{2K_{sp}}{S_{R,aq}^{3}} K_s^{H_2A}} + CMC \tag{4A.139}$$

R_2HAB (2:1 monoprotic weakly basic drug R, amphoteric coformer HAB)

Relevant equilibria are given by

$$R_2HAB_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq} + HAB_{aq} \tag{4A.140}$$

$$H_2AB^+{}_{aq} \xrightleftharpoons{K_a^{H_2AB^+}} HAB_{aq} + H^+{}_{aq} \tag{4A.141}$$

$$HAB_{aq} \xrightleftharpoons{K_a^{HAB}} AB^-{}_{aq} + H^+{}_{aq} \tag{4A.142}$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \tag{4A.143}$$

$$H_2AB^+{}_{aq} + M \xrightleftharpoons{K_s^{H_2AB^+}} H_2AB^+{}_m \tag{4A.144}$$

$$HAB_{aq} + M \xrightleftharpoons{K_s^{HAB}} HAB_m \tag{4A.145}$$

$$AB^-{}_{aq} + M \xrightleftharpoons{K_s^{AB^-}} AB^-{}_m \tag{4A.146}$$
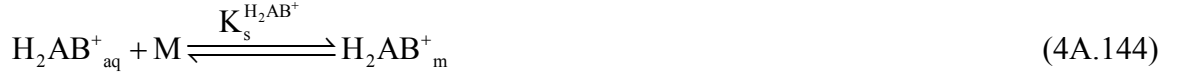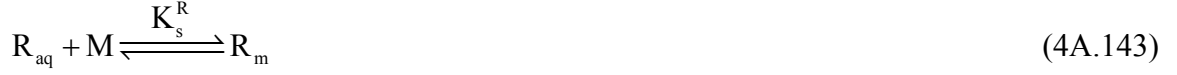
Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}^2 [HAB]_{aq} \tag{4A.147}$$

$$K_a^{H_2AB^+} = \frac{[HAB]_{aq}[H^+]_{aq}}{[H_2AB^+]_{aq}} \tag{4A.148}$$

$$K_a^{HAB} = \frac{[AB^-]_{aq}[H^+]_{aq}}{[HAB]_{aq}} \tag{4A.149}$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{4A.150}$$

$$K_s^{H_2AB^+} = \frac{[H_2AB^+]_m}{[H_2AB^+]_{aq}[M]} \tag{4A.151}$$

$$K_s^{HAB} = \frac{[HAB]_m}{[HAB]_{aq}[M]} \tag{4A.152}$$

$$K_s^{AB^-} = \frac{[AB^-]_m}{[AB^-]_{aq}[M]} \tag{4A.153}$$

Cocrystal R₂HAB total solubility in micellar solutions

Mass balance on B is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{4A.154}$$

Substituting (4A.147) and (4A.150) into (4A.154) gives

$$[R]_T^2 = \frac{K_{sp}}{[HAB]_{aq}}\left(1 + K_s^R[M]\right)^2 \tag{4A.155}$$

Mass balance on AB is given by

$$[AB]_T = [HAB]_{aq} + [H_2AB^+]_{aq} + [AB^-]_{aq} + [HAB]_m + [H_2AB^+]_m + [AB^-]_m \tag{4A.156}$$

Substituting (4A.148), (4A.149), and (4A.151)-(4A.153) into (4A.156) gives

$$[AB]_T = [HAB]_{aq}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{4A.157}$$

Combining (4A.155) and (4A.157) gives

$$[R]_T^2 = \frac{K_{sp}}{[AB]_T}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{4A.158}$$

Cocrystal solubility in micellar solutions containing stoichiometric solution concentrations of cocrystal components, in the absence of solution complexation, is given by

$$S_{R_2HAB,T} = \frac{1}{2}[R]_T = [A]_T \tag{4A.159}$$

Substituting (4A.126) into (4A.127),

$$S_{R_2HAB,T} = \sqrt[3]{\frac{K_{sp}}{4}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right)} \tag{4A.160}$$

When $K_s^{HAB} \gg K_s^{H_2AB^+}$ and $K_s^{HAB} \gg K_s^{AB^-}$ then (4A.160) can be simplified to

$$S_{R_2HAB,T} = \sqrt[3]{\frac{K_{sp}}{4}\left(1+K_s^R[M]\right)^2\left(1+\frac{[H^+]}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]}+K_s^{HAB}[M]\right)}$$ (4A.161)

Solubility of drug R in micellar solutions

Relevant equilibria are given by

$$R_{solid} \rightleftharpoons R_{aq}$$ (4A.162)

$$R_{aq} + M \xrightarrow{K_s^R} R_m$$ (4A.163)

with the associated equilibrium constant

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]}$$ (4A.164)

According to mass balance on R,

$$[R]_T = [R]_{aq} + [R]_m$$ (4A.165)

$$[R]_T = [R]_{aq}\left(1+K_s^R[M]\right)$$ (4A.166)

In this case, $S_{R,T} = [R]_T$ and $[R]_{aq} = S_{R,aq}$ so

$$S_{R,T} = S_{R,aq}\left(1+K_s^R[M]\right)$$ (4A.167)

CSC of cocrystal R₂HAB

At the CSC,

$$2S_{R_2H_2A,T} = S_{R,T}$$ (4A.168)

Substituting (4A.161) and (4A.167) into (4A.168) and solving for [M] gives

$$[M]_{CSC} = \frac{\dfrac{2K_{sp}}{S_{R,aq}{}^3}\left(1 + \dfrac{[H^+]}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]}\right) - 1}{K_s^R - \dfrac{2K_{sp}}{S_{R,aq}{}^3}K_s^{HAB}} \tag{4A.169}$$

CSC is given by

$$CSC = [M]_{CSC} + CMC \tag{4A.170}$$

Therefore

$$CSC = \frac{\dfrac{2K_{sp}}{S_{R,aq}{}^3}\left(1 + \dfrac{[H^+]}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]}\right) - 1}{K_s^R - \dfrac{2K_{sp}}{S_{R,aq}{}^3}K_s^{HAB}} + CMC \tag{4S.171}$$

Coformer solubilities as a function of SLS concentration

Table 4A.1. CBZD and coformer solubilities (±SE) measured as a function of SLS concentration, from which K_s values were calculated.

Cocrystal component	[SLS] (mM)	Concentration (mM)
CBZ	8	1.00±0.01
	10	1.86±0.05
	15	3.58±0.12
	17	3.97±0.05
	20	5.10±0.03
	35	9.30±0.29
	51	13.43±0.41
	67	17.35±0.19
	100	24.81±1.13
	140	33.53±0.85
SLC, pH 3.0	35	34.01±0.46
	52	43.44±0.97
	69	50.32±0.63
SAC, pH 2.2	35	26.15±0.10
	52	28.89±0.07
	69	30.46±0.46

* 4ABA and SUC did not exhibit significant solubilization by SLS ($K_s < 0.010$).

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CHAPTER 5

Engineering cocrystal eutectic points and stability regions by micellar solubilization and ionization

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 the cocrystal components have the potential to reverse the thermodynamic stabilities of cocrystal and drug 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, 9, 10] A cocrystal eutectic point is a point where two solids (one of which is cocrystal) and 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. 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 in 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.[11] Eutectic constants are commonly applied to mixtures of racemic compounds with enantiomer but were recently adapted to cocrystal systems.[12, 13] This work extends the theoretical framework for eutectic points and K_{eu} to micellar systems and demonstrates their ability to tailor regions of stability according to ionization and micellar solubilization equilibria.

Model equations are derived for cocrystals of CBZ (nonionizable, 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.[14-16] Succinic acid is a diprotic weak acid with pK_a values of of 4.1 and 5.6.[17] 4-aminobenzoic acid is amphoteric with pK_a values of 2.6 and 4.8.[18]

Theoretical

The work presented here develops a 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 is 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. 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.[10] 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 (nonionizable drug) and HA (monoprotic, weakly acidic coformer), E_1 is described by

$$RHA_{solid} + R_{solid} \rightleftharpoons R_{aq} + HA_{aq} \tag{5.1}$$

and E_2 by

$$RHA_{solid} + HA_{solid} \rightleftharpoons R_{aq} + HA_{aq} \tag{5.2}$$

The solution phase equilibria that govern cocrystal solubility are given by

$$RHA_{solid} \overset{K_{sp}}{\rightleftharpoons} R_{aq} + HA_{aq} \tag{5.3}$$

159

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq} + H^+_{aq} \tag{5.4}$$

$$R_{aq} + M \xrightleftharpoons{K_s^{R}} R_m \tag{5.5}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{5.6}$$

$$A^-_{aq} + M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{5.7}$$

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.[11, 19, 20]

The equilibrium constants that describe Equations (5.3)-(5.7) are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \tag{5.8}$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{5.9}$$

$$K_s^{R} = \frac{[R]_m}{[R]_{aq}[M]} \tag{5.10}$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \tag{5.11}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{5.12}$$

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,

$$S_{RHA,T} = [R]_T = [R]_{aq} + [R]_m \tag{5.13}$$

By considering the equilibrium constants in Equations (5.8) and (5.10), Equation (5.13) becomes

$$[R]_T = \frac{K_{sp}}{[HA]_{aq}} \left(1 + K_s^R [M] \right) \tag{5.14}$$

The mass balance on coformer is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{5.15}$$

Substituting Equations (5.9), (5.11) and (5.12) into (5.15),

$$[A]_T = [HA]_{aq} \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right) \tag{5.16}$$

Combining Equations (5.14) and (5.16),

$$S_{RHA,T} = [R]_T = \frac{K_{sp}}{[A]_T} \left(1 + K_s^R[M] \right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right) \tag{5.17}$$

If the ionized species interacts more favorably with the aqueous environment than the micellar environment such that $K_s^{HA} \gg K_s^{A^-}$, Equation (5.17) can be simplified to

$$S_{RHA,T} = [R]_T = \frac{K_{sp}}{[A]_T} \left(1 + K_s^R[M] \right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] \right) \tag{5.18}$$

unless the ionized species is present at very high concentrations.[21, 22]

The total cocrystal solubility in a solution of stoichiometric concentrations of drug and coformer ($S_{RHA,T}$*), is a special case of Equation (5.18) when $[R]_T = [A]_T$,

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

(5.19)

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 Equation (5.18) when $[R]_T = S_{R,T}$. The concentration of drug at the eutectic point, $[R]_{eu,T}$, is given by

$$[R]_{eu,T} = S_{R,T}$$

(5.20)

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

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

(5.21)

where $S_{R,aq}$ is the aqueous solubility of drug R.[1-4, 23, 24] Therefore, by combining Equations (5.20) and (5.21),

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

(5.22)

The total concentration of coformer at the eutectic point, $[A]_{eu,T}$, is obtained by combining Equations (5.18) and (5.22).

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right)$$ (5.23)

Cocrystal stoichiometric solubility can be related to the eutectic solution concentrations of drug and coformer by combining Equations (5.19), (5.22), and (5.23) to give

$$S_{RHA,T}{}^* = \sqrt{[R]_{eu,T}[A]_{eu,T}}$$ (5.24)

Equation (5.24) 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),

$$S_{R_2H_2A,T}{}^* = \sqrt{\frac{[R]_{eu,T}[A]_{eu,T}}{4}}$$ (5.25)

$[R]_{eu,T}$ 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

$$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right)$$ (5.26)

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)$$ (5.27)

Equations (5.26) and (5.27) show that the full dependence of the cocrystal eutectic point on pH and surfactant concentration can be calculated from a eutectic point measurement in pure 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 5.1.
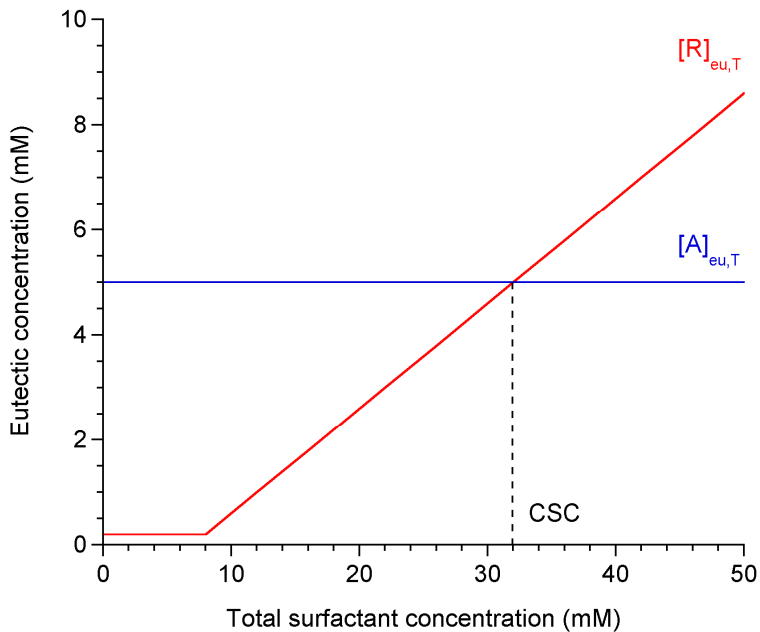
Figure 5.1. Eutectic concentrations of drug ($[R]_{eu,T}$) and coformer ($[A]_{eu,T}$) as a function of surfactant concentration under nonionizing conditions. Predicted according to Equations (5.26) and (5.27) for cocrystal RHA at eutectic point E_1. The CSC for a 1:1 cocrystal is given by the surfactant 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.

Figure 5.1 shows the predicted dependence of drug and coformer eutectic concentrations on surfactant concentration for a cocrystal RHA according to Equations (5.26) and (5.27). 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.

164

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 Equation (5.18). At E_2, Equation (5.20) 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 $S_{A,T}$

$$[A]_{eu,T} = S_{A,T} \tag{5.28}$$

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.

$$S_{A,T} = S_{HA,aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5.29}$$

where $S_{HA,aq}$ is the intrinsic solubility of the weakly acidic coformer. Equations (5.28) and (5.29) combine to give

$$[A]_{eu,T} = S_{HA,aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5.30}$$

Substituting (5.30) into (5.18) gives $[R]_{eu,T}$ at E_2.

$$[R]_{eu,T} = \frac{K_{sp}}{S_{HA,aq}}\left(1 + K_s^R[M]\right) \tag{5.31}$$

If Equations (5.30) and (5.31) are rewritten in terms of $[R]_{eu,aq}$ and $[A]_{eu,aq}$ at E_2, then the same equations as (5.26) and (5.27) are obtained. Thus, equations (5.26) and (5.27) apply to both E_1 and E_2.

Table 5.1. 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 $[M]$.

Cocrystal	Drug eutectic concentration	Eqn	Coformer eutectic concentration	Eqn
RHA 1:1 nonionizable : monoprotic acidic	$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right)$	(5.26)	$[A]_{eu,T} = [A]_{eu,aq}\left(\dfrac{1 + \dfrac{K_a}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a}{[H^+]_{aq}}}\right)$	(5.27)
HXHA 1:1 monoprotic acidic : monoprotic acidic	$[X]_{eu,T} = [X]_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{HX}}{[H^+]_T} + K_s^{HX}[M]}{1 + \dfrac{K_a^{HX}}{[H^+]_{aq}}}\right)$	(5.32)	$[A]_{eu,T} = [A]_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(5.33)
BHA 1:1 monoprotic basic : monoprotic acidic	$[B]_{eu,T} = [B]_{eu,aq}\left(\dfrac{1 + \dfrac{[H^+]_T}{K_a^B} + K_s^B[M]}{1 + \dfrac{[H^+]_{aq}}{K_a^B}}\right)$	(5.34)	$[A]_{eu,T} = [A]_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)$	(5.35)
R$_2$H$_2$A 2:1 nonionizable : diprotic acidic	$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right)$	(5.36)	$[A]_{eu,T} = [A]_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{H_2A}}{[H^+]_T} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2} K_s^{H_2A}[M]}{1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right)$	(5.37)
R$_2$HAB 2:1 nonionizable : amphoteric	$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right)$	(5.38)	$[AB]_{eu,T} = [AB]_{eu,aq}\left(\dfrac{1 + \dfrac{[H^+]_T}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]_T} K_s^{HAB}[M]}{1 + \dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]_{aq}}}\right)$	(5.39)

* Subscript aq represents values measured in submicellar concentrations of surfactant.

Eutectic constant K_{eu}

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

$$K_{eu} \equiv \frac{a_{A,eu}}{a_{R,eu}} \tag{5.40}$$

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 other cocrystal systems.[11-13]

K_{eu} in the context of cocrystals has been shown to describe cocrystal thermodynamic stability relative to drug.[11] K_{eu} is determined under equilibrium conditions, though it is not a true equilibrium constant (such as Equations (5.3)-(5.7)). Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \tag{5.41}$$

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) Equations (5.22) and (5.23) can be substituted into (5.41) to yield

$$K_{eu} = \frac{K_{sp}}{S_{R,aq}^{2}} \left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]}{1 + K_s^{R}[M]} \right) \tag{5.42}$$

Equation (5.42) can be combined with (5.19)-(5.21),

$$K_{eu} = \left(\frac{S_{RHA,T}*}{S_{R,T}} \right)^2 \qquad (5.43)$$

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

$$K_{eu} = \frac{1}{2} \left(\frac{S_{R_2H_2A,T}*}{S_{R,T}} \right)^3 \qquad (5.44)$$

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 Equations (5.26), (5.27) and (5.41),

$$K_{eu,T} = K_{eu,aq} \left(\frac{1}{1 + K_s^R[M]} \right) \left(\frac{1 + \dfrac{K_a}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a}{[H^+]_{aq}}} \right) \qquad (5.45)$$

where $K_{eu,aq} = [R]_{eu,aq}/[A]_{eu,aq}$, or the K_{eu} of the cocrystal in water at $[H^+]_{aq}$. Equation (5.45) 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}.

Figure 5.2 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.

Figure 5.2 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} is 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.
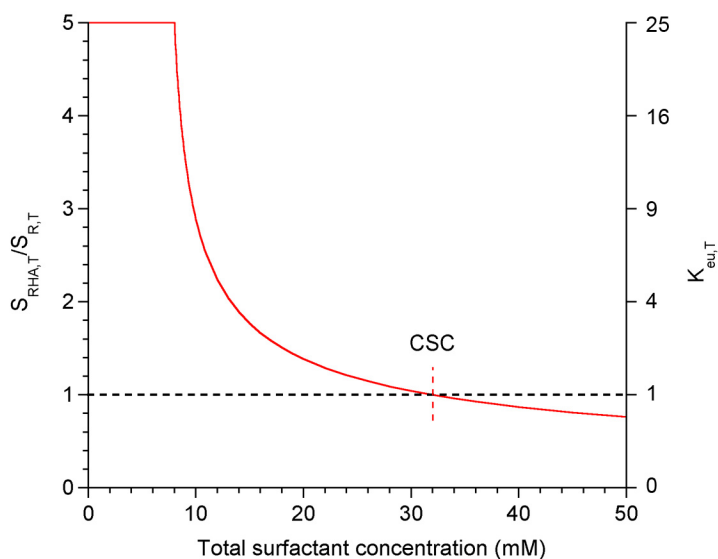
Figure 5.2. Dependence of cocrystal to drug solubility ratio and K_{eu} on surfactant concentration according to Equations (5.43) and (5.45) for a 1:1 cocrystal RHA. $K_{eu,T}$ decreases as surfactant concentration increases, indicating that the cocrystal to drug solubility ratio is decreasing. CSC can 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.

$K_{eu,T}$ 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}). Figure 5.3 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 Equations (5.43) and (5.45)

. Figure 5.3 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 changes in $K_{eu,T}$ in small concentrations of micellar surfactant. Changes in $K_{eu,aq}$ (Figure 5.3(a)) can be the result of pH or selection of a different coformer whose cocrystal is more soluble. Changes in K_s^R (Figure 5.3(b)) can be achieved by surfactant selection.
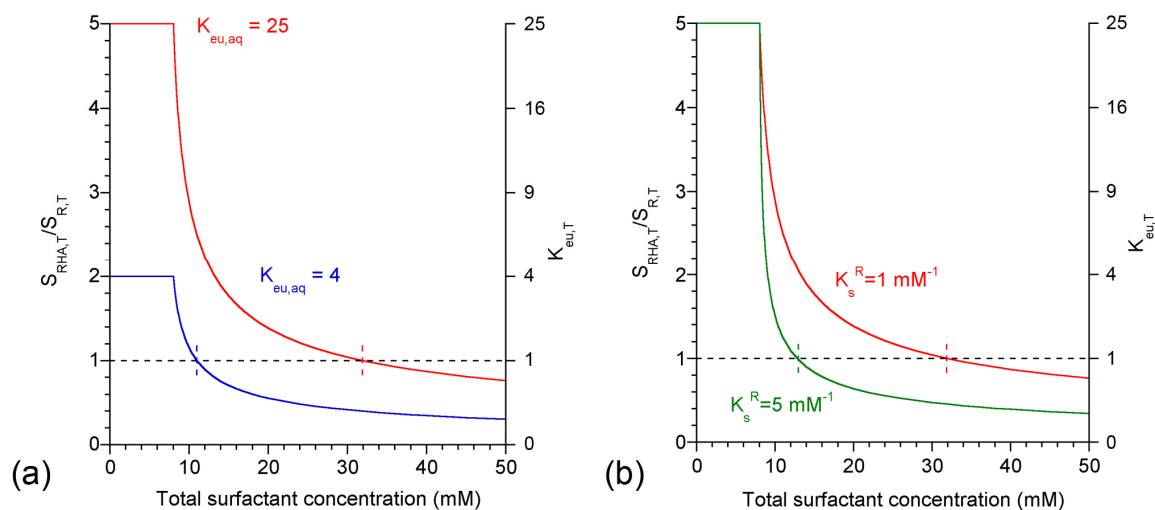
Figure 5.3. Influence of cocrystal aqueous solubility and micellar solubilization on $K_{eu,T}$ and CSC. (a) impact of cocrystal aqueous solubility ($K_{eu,aq}$ = 4 and 25) when drug solubilization is constant (K_s^R = 1 mM^{-1}), (b) impact of drug solubilization (K_s^R = 1 and 5 mM^{-1}) when cocrystal aqueous solubility is constant ($K_{eu,aq}$ = 25). Curves generated according to Equations (5.43) and (5.45) for a 1:1 cocrystal RHA with K_s^{HA} = 0, CMC = 8 mM.
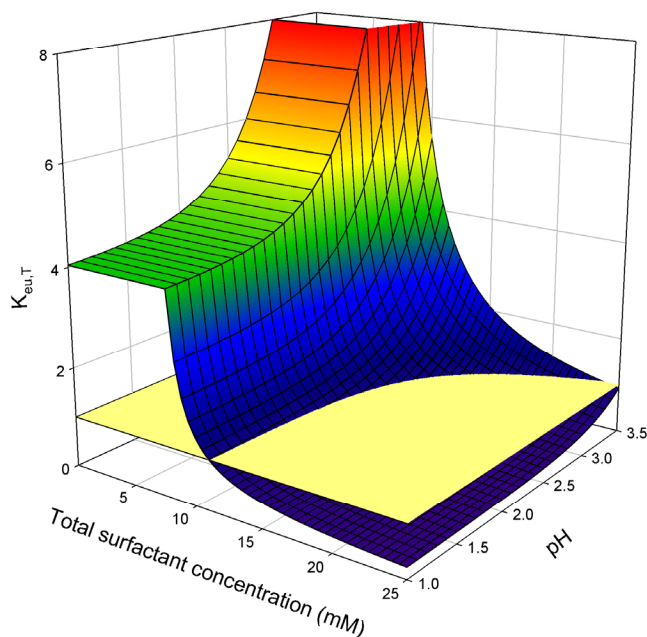
Figure 5.4. Dependence of $K_{eu,T}$ on total surfactant concentration and pH. Multicolored surface represents $K_{eu,T}$ for a cocrystal RHA according to Equation (5.45). Yellow surface represents $K_{eu,T} = 1$, where cocrystal and drug are equally soluble. The intersection points indicate CSC and 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.

Figure 5.4 shows the predicted $K_{eu,T}$ dependence on total surfactant concentration and pH for cocrystal RHA according to Equation (5.45), where a cross-section at constant pH is represented by Figure 5.2. $K_{eu,T}$ 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 Equation (5.45) 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

$$CSC = \frac{K_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T}}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) - 1}{K_s^R - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} + CMC \tag{5.46}$$

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 ($[H^+]_T = [H^+]_{aq}$), Equation (5.46) simplifies to

$$CSC = \frac{K_{eu,aq} - 1}{K_s^R} + CMC \tag{5.47}$$

$K_{eu,aq}$ and $[H^+]_{aq}$ also refers 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 5.2

Table 5.2. 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.

Cocrystal	$K_{eu,T}$	Eqn	CSC	Eqn
RHA 1:1 nonionizable : monoprotic acidic	$K_{eu,T} = K_{eu,aq} \left(\dfrac{1}{1+K_s^R[M]} \right) \left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)$	(5.45)	$CSC = \dfrac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)-1}{K_s^R - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} + CMC$	(5.46)
HXHA 1:1 monoprotic acidic : monoprotic acidic	$K_{eu,T} = K_{eu,aq} \left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}{1+\dfrac{K_a^{HX}}{[H^+]_T}+K_s^{HX}[M]} \right) \left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)$	(5.48)	$CSC = \dfrac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)-\left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_T}}{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}} \right)}{\dfrac{K_s^{HX}}{\left(1+\dfrac{K_a^{HX}}{[H^+]_{aq}}\right)} - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} + CMC$	(5.49)
BHA 1:1 monoprotic basic : monoprotic acidic	$K_{eu,T} = K_{eu,aq} \left(\dfrac{1+\dfrac{[H^+]_{aq}}{K_a^B}}{1+\dfrac{[H^+]_T}{K_a^B}+K_s^B[M]} \right) \left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)$	(5.50)	$CSC = \dfrac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}} \right)-\left(\dfrac{1+\dfrac{[H^+]_T}{K_a^B}}{1+\dfrac{[H^+]_{aq}}{K_a^B}} \right)}{\dfrac{K_s^B}{\left(1+\dfrac{[H^+]_{aq}}{K_a^B}\right)} - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} + CMC$	(5.51)

* Subscript aq represents values measured in submicellar concentrations of surfactant.

173

Table 5.2 (cont'd). 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.

Cocrystal	$K_{eu,T}$	Eqn	CSC	Eqn
R₂H₂A 2:1 nonionizable : diprotic acidic	$K_{eu,T} = K_{eu,aq} \left(\dfrac{1}{1+K_s^R[M]} \right) \left(\dfrac{1 + \dfrac{K_a^{H_2A}}{[H^+]_T} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2} + K_s^{H_2A}[M]}{1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}} \right)$	(5.52)	$\text{CSC} = \dfrac{2K_{eu,aq}\left(\dfrac{1 + \dfrac{K_a^{H_2A}}{[H^+]_T} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2}}{1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}} \right) - 1}{K_s^R - \dfrac{2K_{eu,aq}K_s^{H_2A}}{\left(1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2} \right)}} + \text{CMC}$	(5.53)
R₂HAB 2:1 nonionizable : amphoteric	$K_{eu,T} = K_{eu,aq} \left(\dfrac{1}{1+K_s^R[M]} \right) \left(\dfrac{1 + \dfrac{[H^+]_T}{K_a^{HAB}} + \dfrac{K_a^{H_2AB^+}}{[H^+]_T} + K_s^{HAB}[M]}{1 + \dfrac{[H^+]_{aq}}{K_a^{HAB}} + \dfrac{K_a^{H_2AB^+}}{[H^+]_{aq}}} \right)$	(5.54)	$\text{CSC} = \dfrac{2K_{eu,aq}\left(\dfrac{1 + \dfrac{[H^+]_T}{K_a^{HAB}} + \dfrac{K_a^{H_2AB^+}}{[H^+]_T}}{1 + \dfrac{[H^+]_{aq}}{K_a^{HAB}} + \dfrac{K_a^{H_2AB^+}}{[H^+]_{aq}}} \right) - 1}{K_s^R - \dfrac{2K_{eu,aq}K_s^{HAB}}{\left(1 + \dfrac{[H^+]_{aq}}{K_a^{HAB}} + \dfrac{K_a^{H_2AB^+}}{[H^+]_{aq}} \right)}} + \text{CMC}$	(5.55)

* Subscript aq represents values measured in submicellar concentrations of surfactant.

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. Figure 5.5 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 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 Equations (5.26) and (5.27), 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. Figure 5.5 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. Equations (5.26) and (5.27) are applicable to both E_1 and E_2. E_1 is governed by the drug solubility (Equation (5.21)) and E_2 by the coformer solubility (Equation (5.29)). 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.

Figure 5.5 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 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.

Liquid

0   1

$S_{R,aq}$

0.2   0.8

$E_{1,aq}$

0.4   0.6

$S_{R,T} = 4*S_{R,aq}$ $E_{2,aq}$ $S_{A,aq} = S_{A,T}$

0.6 $E_{2,T}$ 0.4

$E_{1,T}$

0.8   0.2

1   0

R   HA

0   0.2   0.4   1:1   0.6   0.8   1
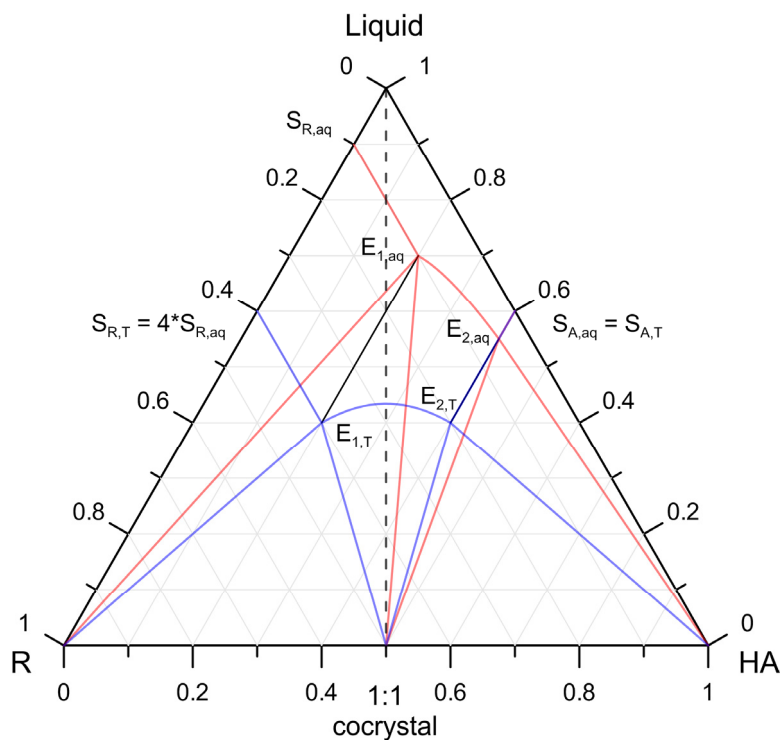
cocrystal

Figure 5.5. 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.

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.[25] 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 $25 \pm 0.1°C$. A detailed discussion of eutectic point measurements has been discussed elsewhere.[9, 11] 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 Equations (5.43) and (5.44). 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 x 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 using an isocratic method. Injection

sample volume was 20 or 40 μL. Absorbance of CBZ, SLC, SUC, and 4ABA was

monitored at 284, 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 CuKα 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.

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

179

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, 26]

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

Figure 5.6 shows the solution concentrations of drug and coformer at the eutectic point E_1 as a function of SLS concentration for the CBZ cocrystals. Figure 5.6 shows that drug and coformer concentrations increase at different rates with respect to SLS concentration. The CBZ eutectic concentration increases at a faster rate 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 predicted behavior according

to Equations (5.26) and (5.27), which predict that eutectic concentrations of drug and coformer increase according to their respective K_s values.
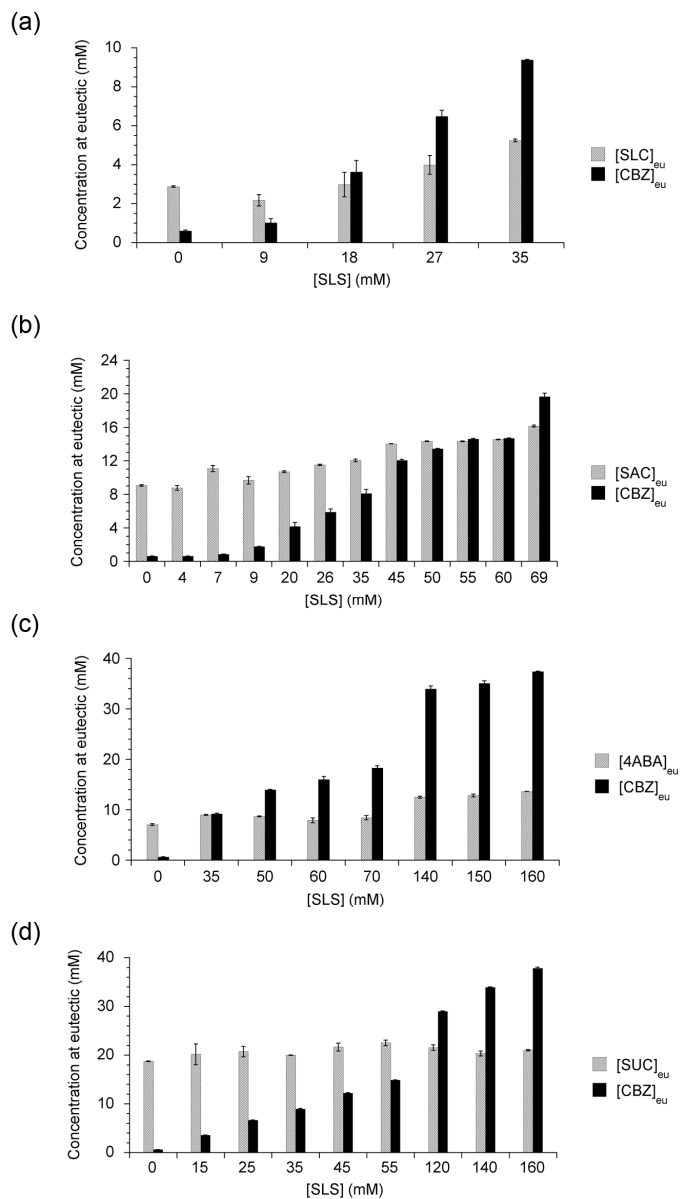
Figure 5.6. Dependence of eutectic concentrations of CBZ and coformer on SLS concentration in aqueous solutions. Solid phases at equilibrium are CBZ cocrystal and CBZD. (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1.

Figure 5.7 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 5.1 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. Figure 5.7 shows very good correlation between experimental and predicted behavior.

The K_s values generated by linear regression (Table 5.3), 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 Figure 5.8, 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 Figure 5.8 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[26]). CBZ-SLC has a fitted CMC value 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.
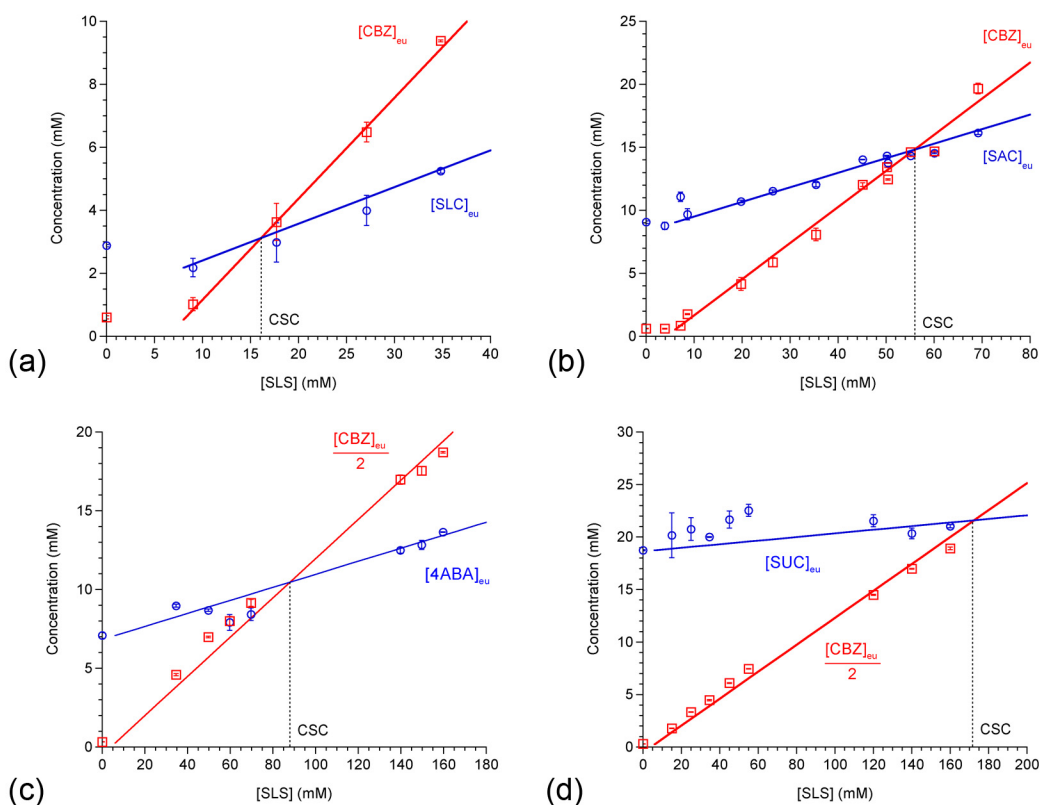
Figure 5.7. Eutectic concentrations of drug and coformer at E_1 in aqueous SLS solutions for (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1. Lines represent linear regression from equations in Table 5.1, where K_s and CMC values are allowed to vary (Table 5.3, K_s values denoted by "cocrystal+drug"), eutectic concentrations measured in aqueous solutions without SLS, and all other parameters were fixed.

Table 5.3. 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 (Figure 5.7) according to equations in Table 5.1, 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 Equations (5.21) and (5.29). 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 (Figure 5.7).
[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.
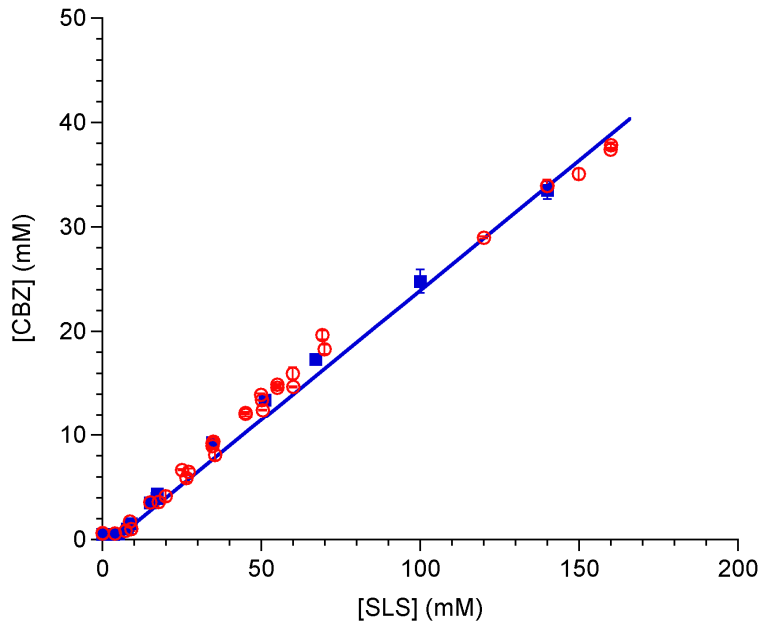
Figure 5.8. Comparison of CBZD solubility as a function of SLS concentration (■) in the absence of coformer and (○) at the eutectic for four CBZ cocrystals (CBZ-SLC, CBZ-SAC, CBZ-4ABA-HYD, CBZ-SUC). Eutectic concentrations show that CBZD solubility is unaffected by the presence of coformer. Predicted line is drawn according to Equation (5.21), $S_{R,aq} = 0.53$ mM, $K_s = 0.49$ mM^{-1}, CMC = 6 mM.

The CSC can be calculated from the eutectic concentrations of drug and coformer as a function of SLS concentration in Figure 5.7 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 (Figure 5.7). $K_{eu} > 1$ 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}.

Figure 5.9 shows the predicted and experimental K_{eu} dependence on SLS concentration according to the model equations (Table 5.2) using K_s and CMC values in Table 5.3 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 (Equations (5.43) and (5.44)). 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.
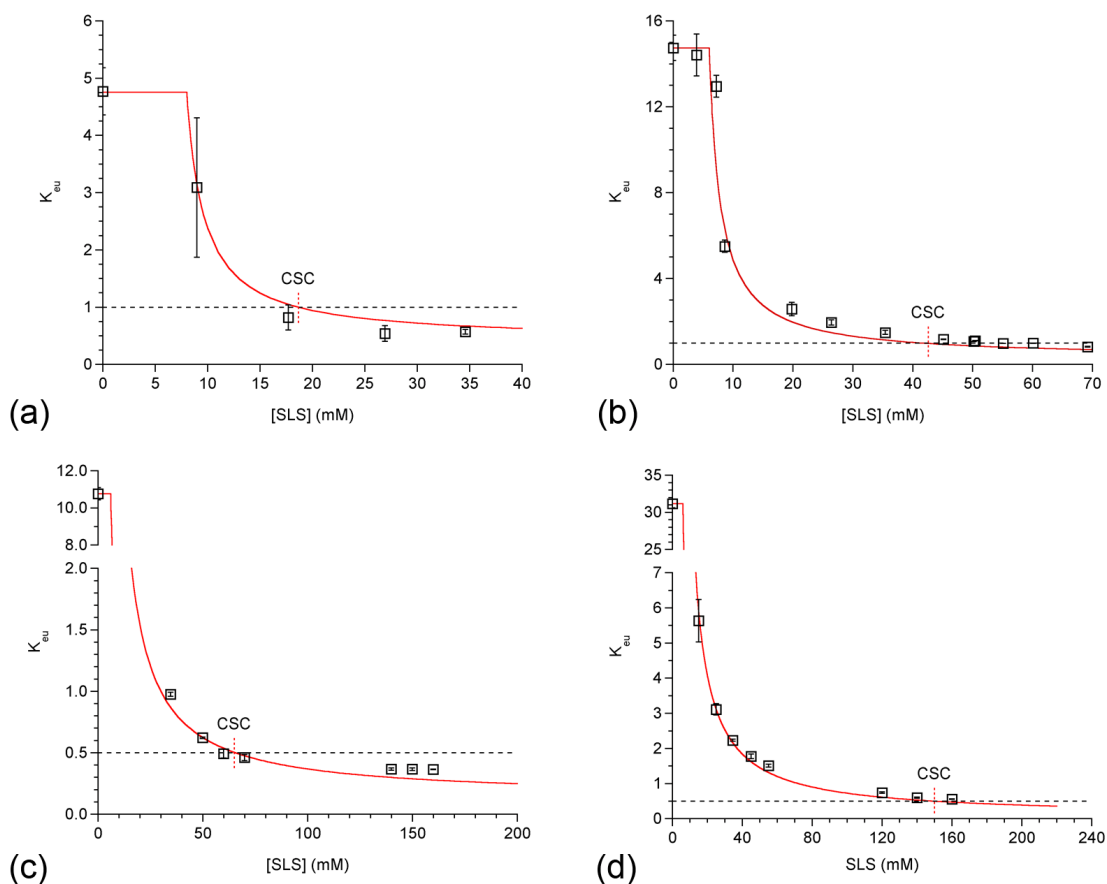
Figure 5.9. Dependence of K_{eu} on SLS concentration in water for (a) CBZ-SLC pH 3.0 (b) CBZ-SAC pH 2.2 (c) CBZ-4ABA-HYD pH 4.0 (d) CBZ-SUC pH 3.1. Predicted curves and CSCs are generated according to equations in Table 5.2 using the K_{eu} measured in pure water and the K_s values for drug and coformer 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.

In this work CSC is evaluated by three methods: (1) K_{eu} measured as a function of SLS concentration, (2) calculated from $K_{eu,aq}$, $[H^+]_{aq}$, K_s and K_a for the separate components, and surfactant CMC according to equations in Table 5.2, and (3) calculated according to the linear regressions of the eutectic drug and coformer concentrations in Figure 5.7. These three 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 Figure 5.9 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 with K_s values measured separately in surfactant solutions. Method (3) is a calculation similar to Method (2) but is more appropriate for K_s values that are dependent on solute-solute and solute-solvent interactions.

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 Figure 5.9(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.

The previous chapter evaluated three other methods of determining CSC based on solid phase analysis of cocrystal phase transformations, calculation from cocrystal stoichiometric solubilities in water, and measurement from cocrystal stoichiometric solubilities in SLS solutions.[7] The six methods presented are in good agreement with each other. Inconsistencies between individual methods may be due to the influence of solutes (surfactant, drug or coformer) on the K_s and K_a of the components, which the six methods consider in varying degrees.

Table 5.4. CSC values determined from (a) measured K_{eu} dependence on SLS, (b) calculated according to equations in Table 5.2 using measured $K_{eu,aq}$, and (c) calculated according to linear regression of eutectic drug and coformer concentrations.

Cocrystal	pH	CSC range measured from K_{eu} dependence on SLS[a] mM SLS	CSC calculated from $K_{eu,aq}$[b] mM SLS	CSC calculated from linear regression at eutectic[c] mM SLS
CBZ-SLC	3.0	$9 < CSC < 18$	19	16
CBZ-SAC	2.2	$50 < CSC < 55$	42	56
CBZ4-ABA-HYD	4.0	$50 < CSC < 60$	64	88
CBZ-SUC	3.1	$160 < CSC$	142	172

[a] Range of CSC determined by SLS concentrations where $K_{eu}>1$ to $K_{eu}\leq1$ for 1:1 cocrystals and where $K_{eu}>0.5$ to $K_{eu}\leq0.5$ for 2:1 cocrystals.
[b] Predictions according to equations in Table 5.2 using measured $K_{eu,aq}$ (Figure 5.9) and K_s values for the separate components in SLS solutions (Table 5.3).
[c] Predictions according to linear regressions in Figure 5.7, where $[R]_{eu,T} = [A]_{eu,T}$ for 1:1 cocrystals and $0.5*[R]_{eu,T} = [A]_{eu,T}$ for 2:1 cocrystals.

Engineering cocrystal stability regions

Micellar solubilization provides a mechanism to engineer the stability regions for cocrystal and drug. Figure 5.10 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 5.1 with K_s and CMC values in Table 5.3 and K_{eu} measured in pure water. The predicted E_1 lines shown are analogous to the $E_{1,aq}$-$E_{1,T}$ line in Figure 5.5.

In Figure 5.10, 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 5.1 and K_s values in Table 5.3. 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 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 Figure 5.10 have utility in designing solution conditions that either favor or disfavor cocrystal formation and stability in solution.
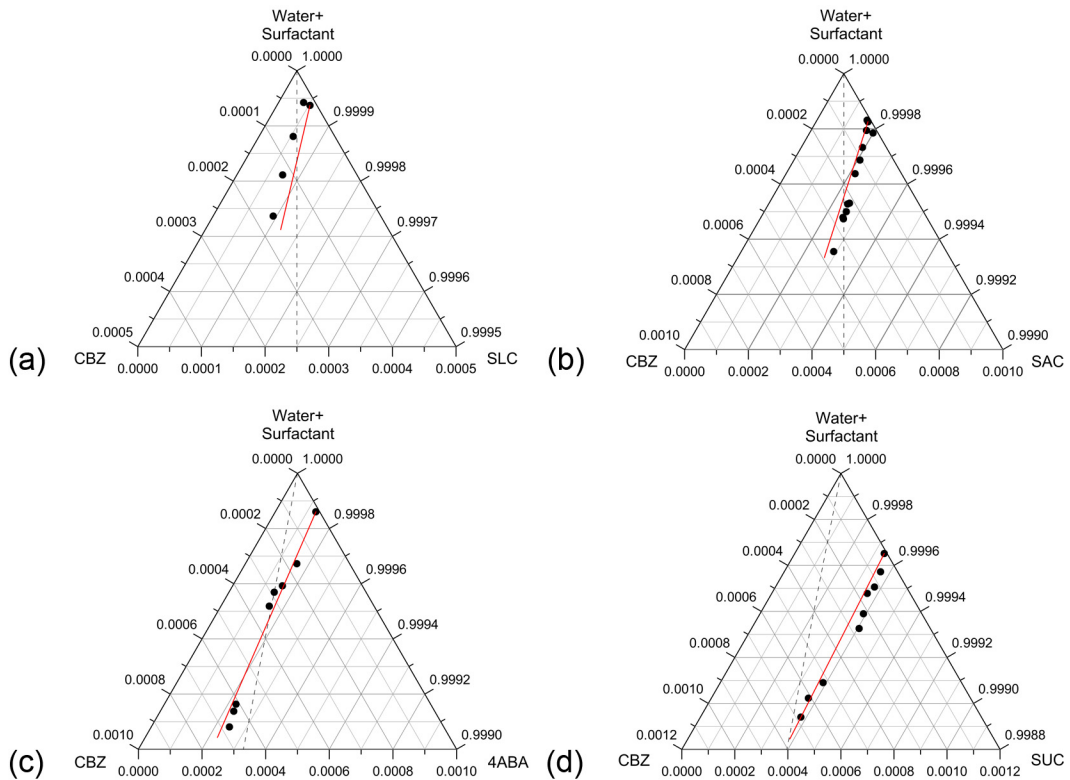
Figure 5.10. Triangular phase diagram showing predicted and experimental dependence of eutectic point E_1 on SLS concentration for (a) CBZ-SLC (b) CBZ-SAC (c) CBZ-4ABA-HYD (d) CBZ-SUC. Surfactant concentrations increase towards the base of the triangle. Predicted lines generated according to equations in Table 5.1, K_s values in Table 5.3, 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.

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 (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. Understanding the sensitivity of cocrystal thermodynamic stability to solution chemistry is critical for our ability to control, develop, and use cocrystals.

Appendix

Derivation of equations

Explanation of terms:

Subscript aq – aqueous

Subscript m – micellar

Subscript T – total (aqueous + micellar)

R – nonionizable drug

HA – monoprotic weakly acidic coformer (nonionized)

H_2A – diprotic weakly acidic coformer (nonionized)

HAB – amphoteric coformer (nonionized)

M – micellar surfactant

K_{sp} – cocrystal solubility product

K_a – acid dissociation constant

K_s – micellar solubilization constant

K_{eu} – eutectic constant

S – solubility

CMC – critical micellar concentration

CSC – critical stabilization concentration

RHA (1:1 nonionizable drug R, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$RHA_{solid} \xrightleftharpoons{K_{sp}} R_{aq} + HA_{aq} \tag{5A.56}$$

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq} + H^+_{aq} \tag{5A.57}$$

$$R_{aq} + M \xrightleftharpoons{K_s^R} R_m \tag{5A.58}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{5A.59}$$

$$A^-_{aq} + M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{5A.60}$$

Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}[HA]_{aq} \tag{5A.61}$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{5A.62}$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{5A.63}$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \tag{5A.64}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{5A.65}$$

Solubility of cocrystal RHA

Mass balance on R is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{5A.66}$$

Substituting (5A.61) and (5A.63) into (4A.11) gives

$$[R]_T = \frac{K_{sp}}{[HA]_{aq}} \left(1 + K_s^R[M]\right) \tag{5A.67}$$

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{5A.68}$$

Substituting (5A.62), (5A.64), and (5A.65) into (4A.13) gives

$$[A]_T = [HA]_{aq} \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]} K_s^{A^-}[M]\right) \tag{5A.69}$$

Combining (4A.12) and (4A.14) gives the

$$[R]_T = \frac{K_{sp}}{[A]_T} \left(1 + K_s^R[M]\right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a}{[H^+]} K_s^{A^-}[M]\right) \tag{5A.70}$$

Where $[R]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^{HA} \gg K_s^{A^-}$, (4A.15) can be simplified to

$$[R]_T = \frac{K_{sp}}{[A]_T} \left(1 + K_s^R[M]\right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5A.71}$$

Eutectic solution concentrations of drug and coformer of cocrystal RHA

At eutectic point E_1, solid drug, cocrystal, and solution coexist in equilibrium.

$$RHA_{solid} + R_{solid} \rightleftharpoons R_{aq} + HA_{aq} \tag{5A.72}$$

$[R]_{eu,T}$ and $[A]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (5A.71) when the following condition is satisfied:

$$[R]_T = S_{R,T} \tag{5A.73}$$

where $S_{R,T}$ is the solubility of R in the eutectic solution. When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{R,T}$ is equivalent to the drug solubility in micellar solution (no coformer), which is given by:

$$S_{R,T} = [R]_T = [R]_{aq} + [R]_m \qquad (5A.74)$$

$$S_{R,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \qquad (5A.75)$$

where $S_{R,aq}$ is the drug aqueous solubility. Thus,

$$[R]_{eu,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \qquad (5A.76)$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \qquad (5A.77)$$

The eutectic concentrations in water (no micellar solubilization) are found when $[M] = 0$,

$$[R]_{eu,aq} = S_{R,aq} \qquad (5A.78)$$

$$[A]_{eu,aq} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]_{aq}}\right) \qquad (5A.79)$$

Combining Equations (5A.76) to (5A.79), $[R]_{eu,T}$ and $[A]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[R]_{eu,aq}$ and $[A]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$.

$$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right) \qquad (5A.80)$$

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) \qquad (5A.81)$$

E_2, the eutectic between solid coformer, cocrystal, and solution, is described by

$$RHA_{solid} + HA_{solid} \rightleftharpoons R_{aq} + HA_{aq} \qquad (5A.82)$$

At E_2, $[R]_{eu,T}$ and $[A]_{eu,T}$ are special solutions to Equation (5A.71) when the following condition is satisfied:

$$[A]_T = S_{A,T} \tag{5A.83}$$

When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{A,T}$ is equivalent to the pure coformer solubility in micellar solution (no drug), which is given by the total coformer concentration in the aqueous and micellar environments:

$$S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m \tag{5A.84}$$

$$S_{A,T} = S_{HA,aq} \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] \right) \tag{5A.85}$$

where $S_{HA,aq}$ is the coformer intrinsic solubility. Solving for $[R]_{eu,T}$ and $[A]_{eu,T}$ according to Equation (5A.71) for E_2 yields the same expressions as (5A.80) and (5A.81).

Eutectic constant K_{eu} of cocrystal RHA

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \tag{5A.86}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \tag{5A.87}$$

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (5A.80) and (5A.81) can be substituted into (5A.87), which yields

$$K_{eu,T} = K_{eu,aq} \left(\frac{1}{1 + K_s^R[M]} \right) \left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) \tag{5A.88}$$

where $K_{eu,T}$ is the total K_{eu} in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,aq}$ is the K_{eu} in pure water at $[H^+] = [H^+]_{aq}$.

CSC of cocrystal RHA

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,aq}$ at $[H^+]_{aq}$. The CSC is determined by Equation (5A.88) when $K_{eu,T} = 1$ and solving for $[M]$,

$$[M]_{CSC} = \frac{K_{eu,aq} \left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T}}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) - 1}{K_s^R - \dfrac{K_{eu,aq} K_s^{HA}}{\left(1 + \dfrac{K_a^{HA}}{[H^+]_{aq}} \right)}} \tag{5A.89}$$

$[M]_{CSC}$ is the micellar surfactant concentration associated with CSC. The CSC is

$$CSC = \frac{K_{eu,aq} \left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T}}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) - 1}{K_s^R - \dfrac{K_{eu,aq} K_s^{HA}}{\left(1 + \dfrac{K_a^{HA}}{[H^+]_{aq}} \right)}} + CMC \tag{5A.90}$$

HXHA (1:1 monoprotic weakly acidic drug HX, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$\text{HXHA}_{\text{solid}} \xrightleftharpoons{K_{\text{sp}}} \text{HX}_{\text{aq}} + \text{HA}_{\text{aq}} \tag{5A.91}$$

$$\text{HX}_{\text{aq}} \xrightleftharpoons{K_a^{\text{HX}}} \text{X}^-_{\text{aq}} + \text{H}^+_{\text{aq}} \tag{5A.92}$$

$$\text{HA}_{\text{aq}} \xrightleftharpoons{K_a^{\text{HA}}} \text{A}^-_{\text{aq}} + \text{H}^+_{\text{aq}} \tag{5A.93}$$

$$\text{HX}_{\text{aq}} + \text{M} \xrightleftharpoons{K_s^{\text{HX}}} \text{HX}_{\text{m}} \tag{5A.94}$$

$$\text{HA}_{\text{aq}} + \text{M} \xrightleftharpoons{K_s^{\text{HA}}} \text{HA}_{\text{m}} \tag{5A.95}$$

$$\text{X}^-_{\text{aq}} + \text{M} \xrightleftharpoons{K_s^{\text{X}^-}} \text{X}^-_{\text{m}} \tag{5A.96}$$

$$\text{A}^-_{\text{aq}} + \text{M} \xrightleftharpoons{K_s^{\text{A}^-}} \text{A}^-_{\text{m}} \tag{5A.97}$$

Associated equilibrium constants are given by

$$K_{\text{sp}} = [\text{HX}]_{\text{aq}}[\text{HA}]_{\text{aq}} \tag{5A.98}$$

$$K_a^{\text{HX}} = \frac{[\text{X}^-]_{\text{aq}}[\text{H}^+]_{\text{aq}}}{[\text{HX}]_{\text{aq}}} \tag{5A.99}$$

$$K_a^{\text{HA}} = \frac{[\text{A}^-]_{\text{aq}}[\text{H}^+]_{\text{aq}}}{[\text{HA}]_{\text{aq}}} \tag{5A.100}$$

$$K_s^{\text{HX}} = \frac{[\text{HX}]_{\text{m}}}{[\text{HX}]_{\text{aq}}[\text{M}]} \tag{5A.101}$$

$$K_s^{\text{HA}} = \frac{[\text{HA}]_{\text{m}}}{[\text{HA}]_{\text{aq}}[\text{M}]} \tag{5A.102}$$

$$K_s^{X^-} = \frac{[X^-]_m}{[X^-]_{aq}[M]} \tag{5A.103}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{5A.104}$$

Solubility of cocrystal HXHA

Mass balance on X is given by

$$[X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m + [X^-]_m \tag{5A.105}$$

Substituting (2A.18), (2A.19), (4A.44), and (4A.46) into (4A.48) gives

$$[X]_T = \frac{K_{sp}}{[HA]_{aq}}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right) \tag{5A.106}$$

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{5A.107}$$

Substituting (2A.20), (4A.45), and (4A.47) into (4A.50) gives

$$[A]_T = [HA]_{aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right) \tag{5A.108}$$

Combining (4A.49) and (4A.51) gives

$$[X]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]}K_s^{X^-}[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]}K_s^{A^-}[M]\right) \tag{5A.109}$$

Where $[X]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^{HX} \gg K_s^{X^-}$ and $K_s^{HA} \gg K_s^{A^-}$, then Equation (4A.52) can be simplified to

$$[X]_T = \frac{K_{sp}}{[A]_T}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M]\right)\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5A.110}$$

Eutectic solution concentrations of drug and coformer of cocrystal HXHA

At eutectic point E_1, solid drug, cocrystal, and solution coexist in equilibrium.

$$HXHA_{solid} + HX_{solid} \rightleftharpoons HX_{aq} + HA_{aq} \tag{5A.111}$$

$[X]_{eu,T}$ and $[A]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are special solutions of Equation (5A.110) when the following condition is satisfied:

$$[X]_T = S_{X,T} \tag{5A.112}$$

where $S_{X,T}$ is the solubility of X in the eutectic solution. When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{X,T}$ is equivalent to the pure drug solubility in micellar solution (no coformer), which is given by the total drug concentration in the aqueous and micellar environments:

$$S_{X,T} = [X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m \tag{5A.113}$$

$$S_{X,T} = S_{HX,aq}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M]\right) \tag{5A.114}$$

where $S_{HX,aq}$ is the drug instrinsic solubility. Thus,

$$[X]_{eu,T} = S_{HX,aq}\left(1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M]\right) \tag{5A.115}$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{HX,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5A.116}$$

The eutectic concentrations in the absence of micellar solubilization are found when [M] = 0,

$$[X]_{eu,aq} = S_{HX,aq}\left(1 + \frac{K_a^{HX}}{[H^+]}\right) \tag{5A.117}$$

$$[A]_{eu,aq} = \frac{K_{sp}}{S_{HX,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \tag{5A.118}$$

Combining Equations (5A.115) to (5A.118), $[X]_{eu,T}$ and $[A]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[X]_{eu,aq}$ and $[A]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$.

$$[X]_{eu,T} = [X]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{HX}}{[H^+]_T} + K_s^{HX}[M]}{1 + \dfrac{K_a^{HX}}{[H^+]_{aq}}}\right) \tag{5A.119}$$

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) \tag{5A.120}$$

E_2, the eutectic between solid coformer, cocrystal, and solution, is described by

$$HXHA_{solid} + HA_{solid} \rightleftharpoons HX_{aq} + HA_{aq} \tag{5A.121}$$

At E_2, $[X]_{eu,T}$ and $[A]_{eu,T}$ are special solutions to Equation (5A.110) when the following condition is satisfied:

$$[A]_T = S_{A,T} \tag{5A.122}$$

When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{A,T}$ is equivalent to the pure coformer solubility in micellar solution (no drug), which is given by the total coformer concentration in the aqueous and micellar environments:

$$S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m \tag{5A.123}$$

$$S_{A,T} = S_{HA,aq}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5A.124}$$

where $S_{HA,aq}$ is the coformer intrinsic solubility. Solving for $[X]_{eu,T}$ and $[A]_{eu,T}$ according to Equation (5A.110) for E_2 yields the same expressions as (5A.119) and (5A.120).

Eutectic constant K_{eu} of cocrystal HXHA

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{X,eu}} \tag{5A.125}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[X]_{eu,T}} \tag{5A.126}$$

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (5A.119) and (5A.120) can be substituted into (5A.126), which yields

$$K_{eu,T} = K_{eu,aq} \left(\frac{1 + \dfrac{K_a^{HX}}{[H^+]_{aq}}}{1 + \dfrac{K_a^{HX}}{[H^+]_T} + K_s^{HX}[M]} \right) \left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) \tag{5A.127}$$

where $K_{eu,T}$ is the total K_{eu} in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,aq}$ is the K_{eu} in pure water at $[H^+] = [H^+]_{aq}$.

CSC of cocrystal HXHA

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,aq}$ at $[H]_{aq}$. The CSC is determined by Equation (5A.127) when $K_{eu,T} = 1$ and solving for $[M]$,

$$[M]_{CSC} = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) - \left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_T}}{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}\right)}{\dfrac{K_s^{HX}}{\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)} - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)}} \tag{5A.128}$$

[M]$_{CSC}$ is the micellar surfactant concentration associated with CSC. The CSC is

$$CSC = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) - \left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_T}}{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}\right)}{\dfrac{K_s^{HX}}{\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)} - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)}} + CMC \tag{5A.129}$$

BHA (1:1 monoprotic weakly basic drug B, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$BHA_{solid} \xrightleftharpoons{K_{sp}} B_{aq} + HA_{aq} \tag{5A.130}$$

$$BH^+_{aq} \xrightleftharpoons{K_a^B} B_{aq} + H^+_{aq} \tag{5A.131}$$

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq} + H^+_{aq} \tag{5A.132}$$

$$B_{aq} + M \xrightleftharpoons{K_s^B} B_m \tag{5A.133}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{5A.134}$$

$$BH^+{}_{aq} + M \xrightleftharpoons{\quad K_s^{BH^+} \quad} BH^+{}_m \tag{5A.135}$$

$$A^-{}_{aq} + M \xrightleftharpoons{\quad K_s^{A^-} \quad} A^-{}_m \tag{5A.136}$$

Associated equilibrium constants are given by

$$K_{sp} = [B]_{aq}[HA]_{aq} \tag{5A.137}$$

$$K_a^B = \frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}} \tag{5A.138}$$

$$K_a^{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \tag{5A.139}$$

$$K_s^B = \frac{[B]_m}{[B]_{aq}[M]} \tag{5A.140}$$

$$K_s^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \tag{5A.141}$$

$$K_s^{BH^+} = \frac{[BH^+]_m}{[B]_{aq}[M]} \tag{5A.142}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{5A.143}$$

Solubility of cocrystal BHA

Mass balance on B is given by

$$[B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m + [BH^+]_m \tag{5A.144}$$

Substituting (2A.34), (2A.35), (4A.81), and (4A.83) into (5A.144) gives

$$[B]_T = \frac{K_{sp}}{[HA]_{aq}} \left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B} K_s^B[M] \right)$$ (5A.145)

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m$$ (5A.146)

Substituting (2A.36), (4A.82), and (4A.84) into (5A.146) gives

$$[A]_T = [HA]_{aq} \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right)$$ (5A.147)

Combining (5A.145) and (5A.147) gives

$$[B]_T = \frac{K_{sp}}{[A]_T} \left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B} K_s^{BH^+}[M] \right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right)$$ (5A.148)

Where $[B]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^B \gg K_s^{BH+}$ and $K_s^{HA} \gg K_s^{A-}$, then Equation (4A.52) can be simplified to

$$[B]_T = \frac{K_{sp}}{[A]_T} \left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M] \right) \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] \right)$$ (5A.149)

Eutectic solution concentrations of drug and coformer of cocrystal BHA

At eutectic point E_1, solid drug, cocrystal, and solution coexist in equilibrium.

$$BHA_{solid} + B_{solid} \rightleftharpoons B_{aq} + HA_{aq}$$ (5A.150)

$[B]_{eu,T}$ and $[A]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (5A.149) when the following condition is satisfied:

$$[B]_T = S_{B,T}$$ (5A.151)

where $S_{B,T}$ is the solubility of B in the eutectic solution. When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{B,T}$ is equivalent to the pure drug solubility in micellar solution (no coformer), which is given by the total drug concentration in the aqueous and micellar environments:

$$S_{B,T} = [B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m \tag{5A.152}$$

$$S_{B,T} = S_{B,aq}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M]\right) \tag{5A.153}$$

where $S_{B,aq}$ is the drug instrinsic solubility. Thus,

$$[B]_{eu,T} = S_{B,aq}\left(1 + \frac{[H^+]}{K_a^B} + K_s^B[M]\right) \tag{5A.154}$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{B,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{5A.155}$$

The eutectic concentrations in the absence of micellar solubilization are found when [M] = 0,

$$[B]_{eu,aq} = S_{B,aq}\left(1 + \frac{[H^+]}{K_a^B}\right) \tag{5A.156}$$

$$[A]_{eu,aq} = \frac{K_{sp}}{S_{B,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]}\right) \tag{5A.157}$$

Combining Equations (5A.154) to (5A.157), $[B]_{eu,T}$ and $[A]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[B]_{eu,aq}$ and $[A]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$.

$$[B]_{eu,T} = [B]_{eu,aq}\left(\frac{1 + \dfrac{[H^+]_T}{K_a^B} + K_s^B[M]}{1 + \dfrac{[H^+]_{aq}}{K_a^B}}\right) \tag{5A.158}$$

$$[A]_{eu,T} = [A]_{eu,aq} \left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) \tag{5A.159}$$

E_2, the eutectic between solid coformer, cocrystal, and solution, is described by

$$BHA_{solid} + HA_{solid} \rightleftharpoons B_{aq} + HA_{aq} \tag{5A.160}$$
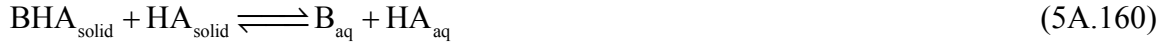
$[B]_{eu,T}$ and $[A]_{eu,T}$ are special solutions to Equation (5A.159) when the following

condition is satisfied:

$$[A]_T = S_{A,T} \tag{5A.161}$$

When drug and solubilization is mutually unaffected by coformer (and vice versa), then

$S_{A,T}$ is equivalent to the pure coformer solubility in micellar solution (no drug), which is

given by the total coformer concentration in the aqueous and micellar environments:

$$S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m \tag{5A.162}$$

$$S_{A,T} = S_{HA,aq} \left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] \right) \tag{5A.163}$$

where $S_{HA,aq}$ is the coformer intrinsic solubility. Solving for $[B]_{eu,T}$ and $[A]_{eu,T}$ according

to Equation (5A.110) for E_2 yields the same expressions as (5A.158) and (5A.159).

Eutectic constant K_{eu} of cocrystal BHA

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{B,eu}} \tag{5A.164}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[B]_{eu,T}} \tag{5A.165}$$

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (5A.158) and (5A.159) can be substituted into (5A.165), which yields

$$K_{eu,T} = K_{eu,aq} \left(\frac{1 + \dfrac{[H^+]_{aq}}{K_a^B}}{1 + \dfrac{[H^+]_T}{K_a^B} + K_s^B[M]} \right) \left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) \tag{5A.166}$$

where $K_{eu,T}$ is the total K_{eu} in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,aq}$ is the K_{eu} in pure water at $[H^+] = [H^+]_{aq}$.

CSC of cocrystal BHA

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,aq}$ at $[H^+]_{aq}$. The CSC at a given pH is determined by Equation (5A.166) when $K_{eu,T} = 1$ and solving for [M],

$$[M]_{CSC} = \frac{K_{eu,aq} \left(\dfrac{1 + \dfrac{K_a^{HA}}{[H^+]_T}}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}} \right) - \left(\dfrac{1 + \dfrac{[H^+]_T}{K_a^B}}{1 + \dfrac{[H^+]_{aq}}{K_a^B}} \right)}{\dfrac{K_s^B}{\left(1 + \dfrac{[H^+]_{aq}}{K_a^B}\right)} - \dfrac{K_{eu,aq}K_s^{HA}}{\left(1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} \tag{5A.167}$$

$[M]_{CSC}$ is the micellar surfactant concentration associated with CSC. The CSC is

$$CSC = \cfrac{K_{eu,aq}\left(\cfrac{1+\cfrac{K_a^{HA}}{[H^+]_T}}{1+\cfrac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\cfrac{1+\cfrac{[H^+]_T}{K_a^B}}{1+\cfrac{[H^+]_{aq}}{K_a^B}}\right)}{\cfrac{K_s^B}{\left(1+\cfrac{[H^+]_{aq}}{K_a^B}\right)}-\cfrac{K_{eu,aq}K_s^{HA}}{\left(1+\cfrac{K_a^{HA}}{[H^+]_{aq}}\right)}}+CMC \tag{5A.168}$$

R₂H₂A (2:1 monoprotic weakly basic drug R, diprotic weakly acidic coformer H₂A)

Relevant equilibria are given by

$$R_2H_2A_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq}+H_2A_{aq} \tag{5A.169}$$

$$H_2A_{aq} \xrightleftharpoons{K_a^{H_2A}} HA^-_{aq}+H^+_{aq} \tag{5A.170}$$

$$HA^-_{aq} \xrightleftharpoons{K_a^{HA^-}} A^{2-}_{aq}+H^+_{aq} \tag{5A.171}$$

$$R_{aq}+M \xrightleftharpoons{K_s^R} R_m \tag{5A.172}$$

$$H_2A_{aq}+M \xrightleftharpoons{K_s^{H_2A}} H_2A_m \tag{5A.173}$$

$$HA^-_{aq}+M \xrightleftharpoons{K_s^{HA^-}} HA^-_m \tag{5A.174}$$

$$A^{2-}_{aq}+M \xrightleftharpoons{K_s^{A^{2-}}} A^{2-}_m \tag{5A.175}$$

Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}^2[H_2A]_{aq} \tag{5A.176}$$

$$K_a^{H_2A} = \frac{[HA^-]_{aq}[H^+]_{aq}}{[H_2A]_{aq}} \tag{5A.177}$$

$$K_a^{HA^-} = \frac{[A^{2-}]_{aq}[H^+]_{aq}}{[HA^-]_{aq}} \qquad (5A.178)$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \qquad (5A.179)$$

$$K_s^{H_2A} = \frac{[H_2A]_m}{[H_2A]_{aq}[M]} \qquad (5A.180)$$

$$K_s^{HA^-} = \frac{[HA^-]_m}{[HA^-]_{aq}[M]} \qquad (5A.181)$$

$$K_s^{A^{2-}} = \frac{[A^{2-}]_m}{[A^{2-}]_{aq}[M]} \qquad (5A.182)$$

Solubility of cocrystal R$_2$H$_2$A

Mass balance on R is given by

$$[R]_T = [R]_{aq} + [R]_m \qquad (5A.183)$$

Substituting (2A.50) and (4A.118) into (4A.122) gives

$$[R]_T^2 = \frac{K_{sp}}{[H_2A]_{aq}}\left(1 + K_s^R[M]\right)^2 \qquad (5A.184)$$

Mass balance on A is given by

$$[A]_T = [H_2A]_{aq} + [HA^-]_{aq} + [A^{2-}]_{aq} + [H_2A]_m + [HA^-]_m + [A^{2-}]_m \qquad (5A.185)$$

Substituting (2A.51), (2A.52), and (4A.119)-(4A.121) into (4A.124) gives

$$[A]_T = [H_2A]_{aq}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M] + \frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M] + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \quad (5A.186)$$

Combining (4A.123) and (4A.125) gives

$$[R]_T^2 = \frac{K_{sp}}{[A]_T}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]+\frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M]+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \quad (5A.187)$$

Where $[R]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal

and solution are in equilibrium. When $K_s^{H_2A} \gg K_s^{HA^-}$ and $K_s^{H_2A} \gg K_s^{A^{2-}}$, (4A.126) can

be simplified to

$$[R]_T^2 = \frac{K_{sp}}{[A]_T}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]\right) \quad (5A.188)$$

Eutectic solution concentrations of drug and coformer of cocrystal R₂H₂A

At eutectic point E_1, solid drug, cocrystal, and solution coexist in equilibrium.

$$R_2H_2A_{solid} + R_{solid} \rightleftharpoons R_{aq} + HA_{aq} \quad (5A.189)$$

$[R]_{eu,T}$ and $[A]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are

special solutions to Equation (4A.129) when the following condition is satisfied:

$$[R]_T = S_{R,T} \quad (5A.190)$$

where $S_{R,T}$ is the solubility of R in the eutectic solution. When drug and solubilization is

mutually unaffected by coformer (and vice versa), then $S_{R,T}$ is equivalent to the pure drug

solubility in micellar solution (no coformer), which is given by the total drug

concentration in the aqueous and micellar environments:

$$S_{R,T} = [R]_T = [R]_{aq} + [R]_m \quad (5A.191)$$

$$S_{R,T} = S_{R,aq}\left(1+K_s^R[M]\right) \quad (5A.192)$$

where $S_{R,aq}$ is the drug aqueous solubility. Thus,

$$[R]_{eu,T} = S_{R,aq}\left(1+K_s^R[M]\right) \quad (5A.193)$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^2}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M]\right) \tag{5A.194}$$

The eutectic concentrations in the absence of micellar solubilization are found when [M] = 0,

$$[R]_{eu,aq} = S_{R,aq} \tag{5A.195}$$

$$[A]_{eu,aq} = \frac{K_{sp}}{S_{R,aq}^2}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}\right) \tag{5A.196}$$

Combining Equations (5A.193) to (5A.196), $[R]_{eu,T}$ and $[A]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[R]_{eu,aq}$ and $[A]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$.

$$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right) \tag{5A.197}$$

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{H_2A}}{[H^+]_T} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2} + K_s^{H_2A}[M]}{1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right) \tag{5A.198}$$

E_2, the eutectic between solid coformer, cocrystal, and solution, is described by

$$R_2H_2A_{solid} + HA_{solid} \rightleftharpoons R_{aq} + HA_{aq} \tag{5A.199}$$

At E_2, $[R]_{eu,T}$ and $[A]_{eu,T}$ are special solutions to Equation (4A.129) when the following condition is satisfied:

$$[A]_T = S_{A,T} \tag{5A.200}$$

When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{A,T}$ is equivalent to the pure coformer solubility in micellar solution (no drug), which is given by the total coformer concentration in the aqueous and micellar environments:

$$S_{A,T} = [A]_T = [H_2A]_{aq} + [HA^-]_{aq} + [A^{2-}]_{aq} + [H_2A]_m \tag{5A.201}$$

$$S_{A,T} = S_{HA,aq}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M]\right) \tag{5A.202}$$

where $S_{H_2A,aq}$ is the coformer intrinsic solubility. Solving for $[R]_{eu,T}$ and $[A]_{eu,T}$

according to Equation (4A.129) for E_2 yields the same expressions as (5A.197) and

(5A.198).

Eutectic constant K_{eu} of cocrystal R_2H_2A

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \tag{5A.203}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \tag{5A.204}$$

Assuming there are no solution interactions aside from ionization and micellar

solubilization, Equations (5A.197) and (5A.198) can be substituted into (5A.204), which

yields

$$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1 + K_s^R[M]}\right)\left(\frac{1 + \dfrac{K_a^{H_2A}}{[H^+]_T} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^2} + K_s^{H_2A}[M]}{1 + \dfrac{K_a^{H_2A}}{[H^+]_{aq}} + \dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^2}}\right) \tag{5A.205}$$

where $K_{eu,T}$ is the total K_{eu} in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,aq}$ is the K_{eu} in

pure water at $[H^+] = [H^+]_{aq}$.

CSC of cocrystal R₂H₂A

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,aq}$ at $[H^+]_{aq}$. The CSC at a given pH is determined by Equation (5A.88) when $K_{eu,T} = 0.5$ and solving for [M],

$$[M]_{CSC} = \frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{H_2A}}{[H^+]_T}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^{\,2}}}{1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}}\right)-1}{K_s^R-\dfrac{2K_{eu,aq}K_s^{H_2A}}{\left(1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}\right)}} \tag{5A.206}$$

$[M]_{CSC}$ is the micellar surfactant concentration associated with CSC. The CSC is

$$CSC = \frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{H_2A}}{[H^+]_T}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^{\,2}}}{1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}}\right)-1}{K_s^R-\dfrac{2K_{eu,aq}K_s^{H_2A}}{\left(1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}\right)}}+CMC \tag{5A.207}$$

R₂HAB (2:1 monoprotic weakly basic drug R, amphoteric coformer HAB)

Relevant equilibria are given by

$$R_2HAB_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq}+HAB_{aq} \tag{5A.208}$$

$$H_2AB^+_{aq} \xrightleftharpoons{K_a^{H_2AB^+}} HAB_{aq}+H^+_{aq} \tag{5A.209}$$

$$HAB_{aq} \xrightleftharpoons{K_a^{HAB}} AB^-_{aq}+H^+_{aq} \tag{5A.210}$$

$$R_{aq}+M \xrightleftharpoons{K_s^R} R_m \tag{5A.211}$$

$$H_2AB^+{}_{aq} + M \xrightleftharpoons{K_s^{H_2AB^+}} H_2AB^+{}_m \tag{5A.212}$$

$$HAB_{aq} + M \xrightleftharpoons{K_s^{HAB}} HAB_m \tag{5A.213}$$

$$AB^-{}_{aq} + M \xrightleftharpoons{K_s^{AB^-}} AB^-{}_m \tag{5A.214}$$

Associated equilibrium constants are given by

$$K_{sp} = [R]_{aq}{}^2 [HAB]_{aq} \tag{5A.215}$$

$$K_a^{H_2AB^+} = \frac{[HAB]_{aq}[H^+]_{aq}}{[H_2AB^+]_{aq}} \tag{5A.216}$$

$$K_a^{HAB} = \frac{[AB^-]_{aq}[H^+]_{aq}}{[HAB]_{aq}} \tag{5A.217}$$

$$K_s^R = \frac{[R]_m}{[R]_{aq}[M]} \tag{5A.218}$$

$$K_s^{H_2AB^+} = \frac{[H_2AB^+]_m}{[H_2AB^+]_{aq}[M]} \tag{5A.219}$$

$$K_s^{HAB} = \frac{[HAB]_m}{[HAB]_{aq}[M]} \tag{5A.220}$$

$$K_s^{AB^-} = \frac{[AB^-]_m}{[AB^-]_{aq}[M]} \tag{5A.221}$$

Solubility of cocrystal R$_2$HAB

Mass balance on B is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{5A.222}$$

Substituting (2A.66) and (4A.150) into (4A.154) gives

$$[R]_T^2 = \frac{K_{sp}}{[HAB]_{aq}}\left(1 + K_s^R[M]\right)^2 \tag{5A.223}$$

Mass balance on AB is given by

$$[AB]_T = [HAB]_{aq} + [H_2AB^+]_{aq} + [AB^-]_{aq} + [HAB]_m + [H_2AB^+]_m + [AB^-]_m \tag{5A.224}$$

Substituting (2A.67), (2A.68), and (4A.151)-(4A.153) into (4A.156) gives

$$[AB]_T = [HAB]_{aq}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{5A.225}$$

Combining (4A.155) and (4A.157) gives

$$[R]_T^2 = \frac{K_{sp}}{[AB]_T}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{5A.226}$$

Where $[R]_T$ and $[AB]_T$ are the total concentrations of drug and coformer when cocrystal

and solution are in equilibrium. When $K_s^{HAB} \gg K_s^{H_2AB^+}$ and $K_s^{HAB} \gg K_s^{AB^-}$, (5A.226) can

be simplified to

$$[R]_T^2 = \frac{K_{sp}}{[AB]_T}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M]\right) \tag{5A.227}$$

Eutectic solution concentrations of drug and coformer of cocrystal R₂HAB

At eutectic point E_1, solid drug, cocrystal, and solution coexist in equilibrium.

$$R_2HAB_{solid} + R_{solid} \rightleftharpoons R_{aq} + HAB_{aq} \tag{5A.228}$$

$[R]_{eu,T}$ and $[AB]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are

special solutions to Equation (5A.227) when the following condition is satisfied:

$$[R]_T = S_{R,T} \tag{5A.229}$$

where $S_{R,T}$ is the solubility of R in the eutectic solution. When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{R,T}$ is equivalent to the pure drug solubility in micellar solution (no coformer), which is given by the total drug concentration in the aqueous and micellar environments:

$$S_{R,T} = [R]_T = [R]_{aq} + [R]_m \tag{5A.230}$$

$$S_{R,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{5A.231}$$

where $S_{R,aq}$ is the drug aqueous solubility. Thus,

$$[R]_{eu,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{5A.232}$$

$$[AB]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^2}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M]\right) \tag{5A.233}$$

The eutectic concentrations in the absence of micellar solubilization are found when [M] = 0,

$$[R]_{eu,aq} = S_{R,aq} \tag{5A.234}$$

$$[AB]_{eu,aq} = \frac{K_{sp}}{S_{R,aq}^2}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]}\right) \tag{5A.235}$$

Combining Equations (5A.232) to (5A.235), $[R]_{eu,T}$ and $[AB]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[R]_{eu,aq}$ and $[AB]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$

$$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right) \tag{5A.236}$$

$$[AB]_{eu,T} = [AB]_{eu,aq}\left(\frac{1 + \dfrac{[H^+]_T}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]_T} + K_s^{HAB}[M]}{1 + \dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}} + \dfrac{K_a^{HAB}}{[H^+]_{aq}}}\right) \tag{5A.237}$$

E_2, the eutectic between solid coformer, cocrystal, and solution, is described by

$$R_2HAB_{solid} + HAB_{solid} \rightleftharpoons R_{aq} + HAB_{aq} \tag{5A.238}$$

$[R]_{eu,T}$ and $[AB]_{eu,T}$ are special solutions to Equation (5A.227) when the following condition is satisfied:

$$[AB]_T = S_{AB,T} \tag{5A.239}$$

When drug and solubilization is mutually unaffected by coformer (and vice versa), then $S_{AB,T}$ is equivalent to the pure coformer solubility in micellar solution (no drug), which is given by the total coformer concentration in the aqueous and micellar environments:

$$S_{AB,T} = [AB]_T = [HAB]_{aq} + [H_2AB^+]_{aq} + [AB^-]_{aq} + [HAB]_m \tag{5A.240}$$

$$S_{AB,T} = S_{HAB,aq}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M]\right) \tag{5A.241}$$

where $S_{HAB,aq}$ is the coformer intrinsic solubility. Solving for $[R]_{eu,T}$ and $[AB]_{eu,T}$ according to Equation (5A.71) for E_2 yields the same expressions as (5A.80) and (5A.81).

Eutectic constant K_{eu} of cocrystal R_2HAB

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{AB,eu}}{a_{R,eu}} \tag{5A.242}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[AB]_{eu,T}}{[R]_{eu,T}} \tag{5A.243}$$

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (5A.236) and (5A.237) can be substituted into (5A.204), which yields

$$K_{eu,T} = K_{eu,aq} \left(\frac{1}{1+K_s^R[M]} \right) \left(\frac{1+\dfrac{[H^+]_T}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_T}+K_s^{HAB}[M]}{1+\dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_{aq}}} \right) \tag{5A.244}$$

where $K_{eu,T}$ is the total K_{eu} in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,aq}$ is the K_{eu} in pure water at $[H^+] = [H^+]_{aq}$.

CSC of cocrystal R₂HAB

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,aq}$ at $[H^+]_{aq}$. The CSC at a given pH is determined by Equation (5A.88) when $K_{eu,T} = 0.5$ and solving for $[M]$,

$$[M]_{CSC} = \frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{[H^+]_T}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_T}}{1+\dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_{aq}}} \right) - 1}{K_s^R - \dfrac{2K_{eu,aq}K_s^{HAB}}{\left(1+\dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_{aq}}\right)}} \tag{5A.245}$$

$[M]_{CSC}$ is the micellar surfactant concentration associated with CSC. The CSC is

$$CSC = \frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{[H^+]_T}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_T}}{1+\dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_{aq}}} \right) - 1}{K_s^R - \dfrac{2K_{eu,aq}K_s^{HAB}}{\left(1+\dfrac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\dfrac{K_a^{HAB}}{[H^+]_{aq}}\right)}} + CMC \tag{5A.246}$$

Table 5A.1. CBZD and coformer solubilities (±SE) measured as a function of SLS concentration, from which K_s values were calculated.

Cocrystal component	[SLS] (mM)	Concentration (mM)
CBZ	8	1.00±0.01
	10	1.86±0.05
	15	3.58±0.12
	17	3.97±0.05
	20	5.10±0.03
	35	9.30±0.29
	51	13.43±0.41
	67	17.35±0.19
	100	24.81±1.13
	140	33.53±0.85
SLC, pH 3.0	35	34.01±0.46
	52	43.44±0.97
	69	50.32±0.63
SAC, pH 2.2	35	26.15±0.10
	52	28.89±0.07
	69	30.46±0.46

* 4ABA and SUC did not exhibit significant solubilization by SLS ($K_s < 0.010$).

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CHAPTER 6

Conclusions and future work

This dissertation has investigated how cocrystal solubility and stability can be engineered via ionization and micellar solubilization. The objectives of this work were to (1) understand the effect of ionization on cocrystal solubility, (2) investigate the role of micellar solubilization on cocrystal solubility and stability, (3) develop mathematical models to describe cocrystal solubility and stability via ionization and micellar solubilization equilibria, and (4) understand how ionization and micellar solubilization affect cocrystal eutectic points and regions of thermodynamic stability. In summary, this work sought to more completely understand cocrystal solution phase chemistry in the presence of multiple equilibria that affect the cocrystal components in solution.

The pH-dependence of cocrystal solubility was elucidated by deriving mathematical equations that considered the solution equilibria governing cocrystal dissociation and ionization of cocrystal components. The model was validated for a series of cocrystals of the nonionizable, poorly water soluble drug carbamazepine (CBZ) with several coformers of different ionization properties (salicylic acid, saccharin, and 4-aminobenzoic acid).

Cocrystal solubilities were experimentally accessed via the cocrystal eutectic point where two solids (cocrystal and one of the cocrystal components) and a solution

coexist at equilibrium. Cocrystal solubility-pH dependencies of CBZ cocrystals revealed that experiments were in excellent agreement with those predicted by the model equations. Through cocrystallization, CBZ cocrystals achieved different pH-dependencies according to the ionization properties of the coformer. CBZ cocrystals with weakly acidic coformers had solubilities that increased exponentially when pH > pK_a, while cocrystals with amphoteric coformers had U-shaped solubility-pH profiles according to the coformer's two pK_as. The mathematical models provide a rational basis for selecting (1) coformers to customize cocrystal solubility-pH behavior, (2) solution conditions that promote (or avoid) cocrystal formation, and (3) experimental conditions that give meaningful assessments of cocrystal solubility.

Micellar solubilization was discovered to influence cocrystal solubility and stability in a profoundly different way than its parent drug. This study found that a cocrystal otherwise unstable in water can achieve stability in solutions containing a micellar surfactant. 1:1 CBZ-salicylic acid remained stable in a 1% w/w (35 mM) solution of sodium lauryl sulfate (SLS), despite having readily transformed to CBZ dihydrate in water. A mathematical model was developed based on cocrystal dissociation, component ionization, and micellar solubilization equilibria that explained cocrystal solubility as a function of micellar surfactant concentration. The model theorized a concentration of surfactant, called the critical stabilization concentration (CSC), where cocrystal solubility (under stoichiometric solution conditions) was equal to that of the drug. Preliminary experiments, which measured cocrystal eutectic points in pure water and in 1% w/w SLS solutions, demonstrated the existence of the CSC. The mechanism for the CSC is an enrichment of the aqueous phase in coformer and the

227

micellar phase in drug. This is due to the differential solubilization of the hydrophobic drug over relatively hydrophilic coformer. This study has important ramifications in the selection of additives to enhance cocrystal performance and to maintain cocrystal thermodynamic stability during pharmaceutical applications.

A series of CBZ cocrystals that would otherwise be unstable in water were thermodynamically stabilized via the CSC in aqueous SLS solutions. Mathematical models that described cocrystal solubility and CSC were derived in terms of experimentally accessible thermodynamic parameters for cocrystals of different stoichiometry and ionization properties. The models showed that CSC was dependent on cocrystal aqueous solubility relative to drug, micellar solubilization constants for the cocrystal components (K_s), acid dissociation constants (K_a), and surfactant CMC. The effectiveness of a surfactant in achieving CSC was shown to be the differential solubilization of the drug over coformer in the micellar solution. The existence of a CSC imparted a pH_{max} to cocrystals that otherwise did not have one. The CSC and pH_{max} described the solution conditions necessary for cocrystal to be thermodynamically stable. CSC was successfully evaluated by (1) monitoring conversion from cocrystal to drug as a function of surfactant concentration by solid phase analysis, (2) estimating from cocrystal and drug solubilities measured in pure water, combined with K_s and K_a for the cocrystal components, and (3) measuring cocrystal and drug solubilities in SLS solutions. The CSCs measured by the three methods were in agreement, which showed that CSC and pH_{max} could be quantitatively predicted with the assistance of the mathematical models. The models identify the critical parameters that influence CSC and pH_{max}, and provide

guidelines for the selection of additives suitable for modulating cocrystal solubility relative to drug.

It was demonstrated that the regions of cocrystal stability could be predictably altered by a surfactant. The dependencies of cocrystal eutectic points and the eutectic constant K_{eu} on ionization and micellar solubilization were derived according to mathematical models based on cocrystal solution phase equilibria. Investigation of a series of CBZ cocrystals in aqueous SLS solutions showed that the solution concentrations of cocrystal components at the eutectic point and K_{eu} were indeed influenced by micellar solubilization. At eutectic point E_1 (phases at equilibrium are cocrystal, drug, and solution), the solution compositions were initially coformer-rich due to the cocrystals having higher aqueous solubility than drug (CBZ dihydrate). As surfactant concentration increased, the solution compositions at the eutectic became drug-rich due to the differential solubilization of CBZ over the coformers. Experimental eutectic concentrations and K_{eu}s were in excellent agreement with the predictions by the model equations. Analysis of the cocrystal K_{eu} values indicated that cocrystal to drug solubility ratios were strongly dependent on SLS concentration. This dependence was predicted according to the mathematical models from K_{eu} measured in pure water, combined with K_s and K_a for the cocrystal components. The surfactant was most effective in decreasing the cocrystal to drug solubility ratio in concentrations far below the CSC. Therefore, a cocrystal's solubility advantage can be adjusted with judicious use of additives such as surfactants.

Future directions can focus on expanding the theoretical framework to consider additional solution phase equilibria not explicitly described in this dissertation. In

229

principle the concept of differential solubilization applies to other solubilization mechanisms such as complexation (*e.g.* cyclodextrins), mixed micelle formation, etc. Complexing agents have the potential to be highly effective in achieving differential solubilization of one cocrystal component over another. This creates the possibility of using a combination of solubilization strategies to adjust cocrystal solubilities relative to the drug.

The mathematical models developed here are preliminary in nature and do not consider the range of solution nonidealities that may result from an additive or from changing pH conditions. More rigorous considerations of the mathematical models can address the influence of ionic strength on cocrystal solubility and on additive properties such as the surfactant CMC. Though the models were highly successful in describing the behavior of CBZ cocrystals, there is a need for more comprehensive understanding of the extent to which solution nonidealities affect cocrystal solubility and stability.

There is increasing emphasis on measuring biorelevant solubilities, in media such as fasted state simulated intestinal fluid (FaSSIF), which contains biorelevant surfactants and other additives. However, there is insufficient understanding as to how cocrystal solubility and dissolution may be affected by the choice of media. This dissertation provides the theoretical foundation for describing the influence of FaSSIF on cocrystal solubility in terms of differential solubilization of cocrystal components. Applying the concepts developed here to biorelevant situations can assist efforts to rationally design cocrystals and select additives to achieve improved performance *in vivo*.

APPENDIX

This appendix addresses cocrystal dissolution in aqueous media containing surfactants and investigates the feasibility of coating cocrystal particles with surfactants to enhance their dissolution.

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 reaction crystallization. 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) was prepared in water. Solid phases were characterized by XRPD.

Rotating disk dissolution

Cocrystal was compressed in a USP standard Wood's die (8 mm diameter) using a Carver hydraulic press (Wabash, IN) by applying 1000-1500 psi for 15 minutes at ambient temperature. Solid phases were analyzed by FTIR. Rotation speed was set at 200 rpm in 150 mL aqueous media at ambient temperature (24±1 °C). Solution concentrations were measured by HPLC. Sink conditions were maintained throughout the experiment. Dissolution rates were determined from the initial linear portion of the concentration vs time profile. 35 mM SLS (1% w/w) was chosen due to its commonness as USP dissolution media.

Coating cocrystal particles with surfactant

Excess CBZ-SLC (500 mg) was suspended in a small volume (2 mL) of water containing 50 mM SLS. The concentration of SLS in solution was sufficiently high to achieve CSC for the cocrystal. Water was removed by evaporation at ambient temperature (24 ± 1 °C). The amount of SLS contained in the recovered solid was approximately 6-7 wt%.

Fourier-transformed infrared spectroscopy (FTIR)

IR absorbance spectra of CBZ-SAC and CBZ-4ABA-HYD after disk dissolution studies were collected on a Bruker Vertex 70 FT-IR (Billerica, MA) unit equipped with a

232

DTGS detector and compared with reference cocrystal and single component crystal spectra. Samples were placed on a ZnSe Attenuated Total Reflectance (ATR) crystal accessory and 64 scans were collected for each sample at a resolution of 4 cm^{-1} over a wavenumber region of 4000-600 cm^{-1}.

Results

Figures A.1 – A.3 show that CBZ dissolution rate is enhanced in 35 mM SLS relative to water. CBZ-SUC and CBZ-4ABA-HYD cocrystals transformed to CBZD, indicating that cocrystal was more soluble than CBZD in 35 mM SLS. No phase transformations were detected for CBZ-SLC in 0 mM or 35 mM SLS after 30 minutes. The lack of transformation of CBZ-SLC in 0 mM SLS may be due to the cocrystal and CBZD having very similar solubilities in water (Table A.2); kinetics of transformation may be limited by the low supersaturation. The lack of phase transformation of CBZ-SLC in 35 mM SLS was expected, because its critical stabilization concentration (CSC) is calculated to be 10 mM SLS at pH 1. The dissolution data alone are not able to discern if the stabilization is of a kinetic or thermodynamic nature.
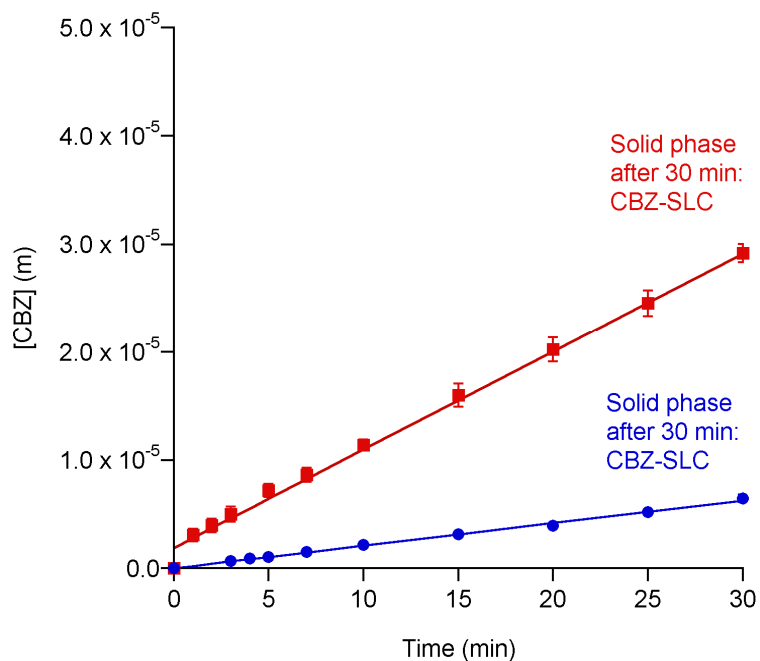
Figure A.1. [CBZ] vs time during rotating disk dissolution of CBZ-SLC cocrystal in water at pH 1 containing (■) 35 mM SLS and (●) 0 mM SLS.
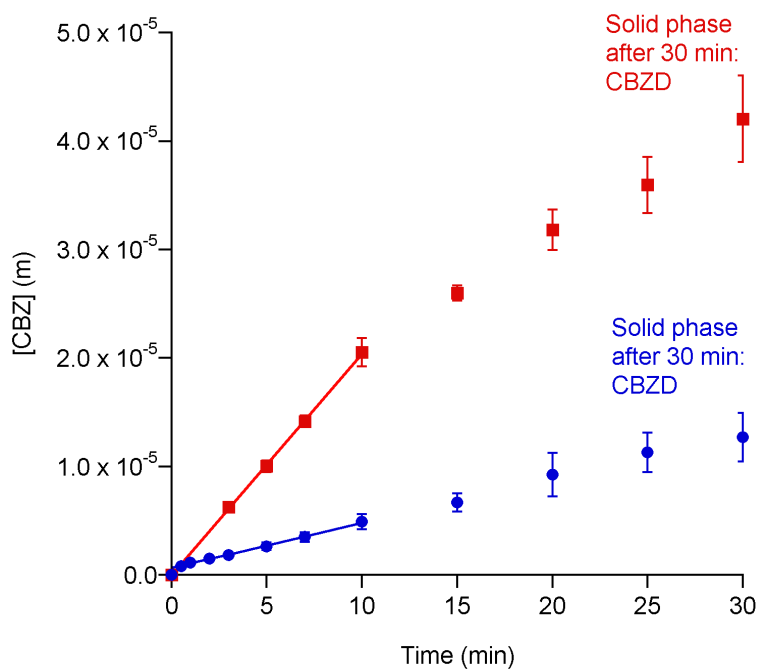
Figure A.2. [CBZ] vs time during rotating disk dissolution of CBZ-SUC cocrystal in water at pH 1 containing (■) 35 mM SLS and (●) 0 mM SLS.
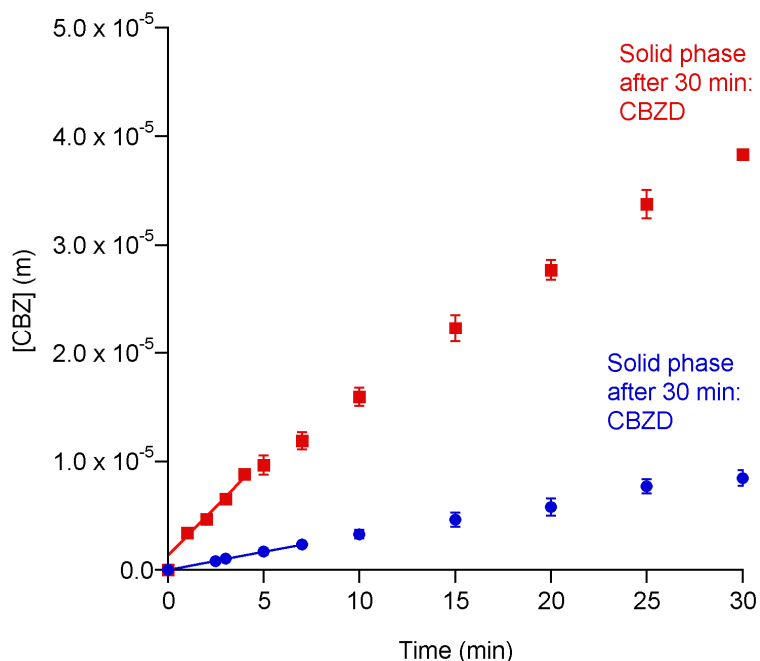
Figure A.3. [CBZ] vs time during rotating disk dissolution of CBZ-4ABA-HYD cocrystal in water at pH 4 containing (■) 35 mM SLS and (●) 0 mM SLS.

Table A.1 summarizes the dissolution rates in Figures A.1 – A.3, and calculates the enhancement ratio in 35 mM SLS relative to 0 mM SLS. These dissolution enhancement ratios were compared to the solubility enhancement ratios for the CBZ cocrystals in 35 mM SLS relative to 0 mM SLS, shown in Table A.2. According to Tables A.1 and A.2, there appears to be a reasonably good correlation between cocrystal solubility enhancement and dissolution rate enhancement. This finding suggests that the mathematical models developed in this dissertation can predict which cocrystals and what solution conditions yield improved dissolution characteristics. Future work could expand upon the limited series of cocrystals discussed here

Table A.1. Dissolution rates of CBZ cocrystal in water (±SE) containing 0 mM SLS or 35 mM SLS.

Cocrystal	(1) Dissolution rate 0 mM SLS mg(CBZ)/min/cm^2	(2) Dissolution rate 35 mM SLS mg(CBZ)/min/cm^2	Ratio of dissolution rates (2) / (1)
CBZ-SLC (1:1) pH 1	0.015 ± 0.001	0.063 ± 0.001	4.2
CBZ-SUC (2:1) pH 1	0.028 ± 0.001	0.14 ± 0.01	5.0
CBZ-4ABA-HYD (2:1) pH 4	0.027 ± 0.001	0.13 ± 0.01	4.8

Table A.2. Solubilities of CBZ cocrystals and CBZD in water (±SE) containing 0 mM SLS or 35 mM SLS.

| Cocrystal	(1) Solubility 0 mM SLS mm(CBZ)	(2) Solubility 35 mM SLS mm(CBZ)	Ratio of solubilities (2) / (1)
CBZ-SLC (1:1) pH 1	0.62 ± 0.03[a]	2.48 ± 0.02[a]	4.0
CBZ-SUC (2:1) pH 1	2.18 ± 0.02[a]	13.47 ± 0.04[a]	6.2
CBZ-4ABA-HYD (2:1) pH 4	1.83 ± 0.02	11.49 ± 0.08	6.3

[a] Solubility was measured at pH 3; solubility at pH 1 was calculated according to equations in Table 4.1.

**Table A.3**. Dissolution rates of CBZ-SAC and CBZD in water (±SE) containing 0 mM SLS or 22 mM SLS.

Solid phase	Dissolution rate 0 mM SLS mg(CBZ)/min/cm^2	Dissolution rate 22 mM SLS mg(CBZ)/min/cm^2
(1) CBZ-SAC (1:1) pH 1	0.021 ± 0.001	0.059± 0.001
(2) CBZD	0.012 ± 0.002	0.059 ± 0.001
Ratio of dissolution rates (1) / (2)	1.8	1.0

Surfactants have been shown to impact dissolution by reducing the drug's effective diffusivity when solubilized by a micelle. The distribution of drug in aqueous and micellar environments becomes an important factor in dissolution, especially for hydrophobic molecules. According to Chapter 4 (Figure 4.2), at the CSC the distribution of drug between aqueous and micellar environments are equal for cocrystal and solid drug in micellar solutions. Thus, the dissolution rates of drug and cocrystal should be equal at the CSC. Dissolution of CBZ-SAC corystal at its CSC (22 mM at pH 1) confirms this type of behavior (Figure A.4). Dissolution of CBZ-SAC cocrystal in 0 mM SLS (Figure A.5) reveals that cocrystal has a dissolution advantage over CBZD that was not apparent from the dissolution experiment at CSC. The dissolution rates of CBZ-SAC and CBZD in 0 mM and 22 mM SLS are shown in Table A.3. This experiment shows that cocrystal dissolution rates relative to drug can be strongly dependent on micellar solubilization.
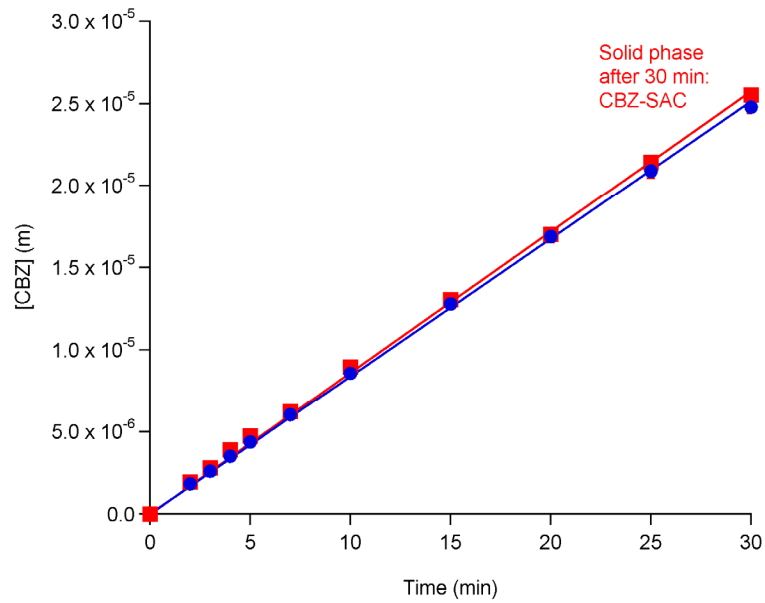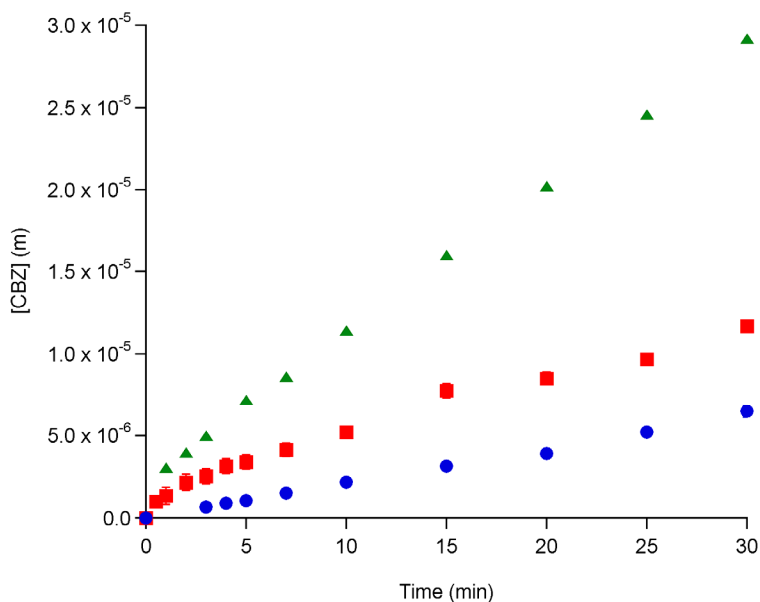
Figure A.4. [CBZ] vs time (±SE) during rotating disk dissolution of (■) CBZ-SAC cocrystal and (●) CBZ dihydrate. Media was 0.1 N HCl + 22 mM SLS (pH 1).
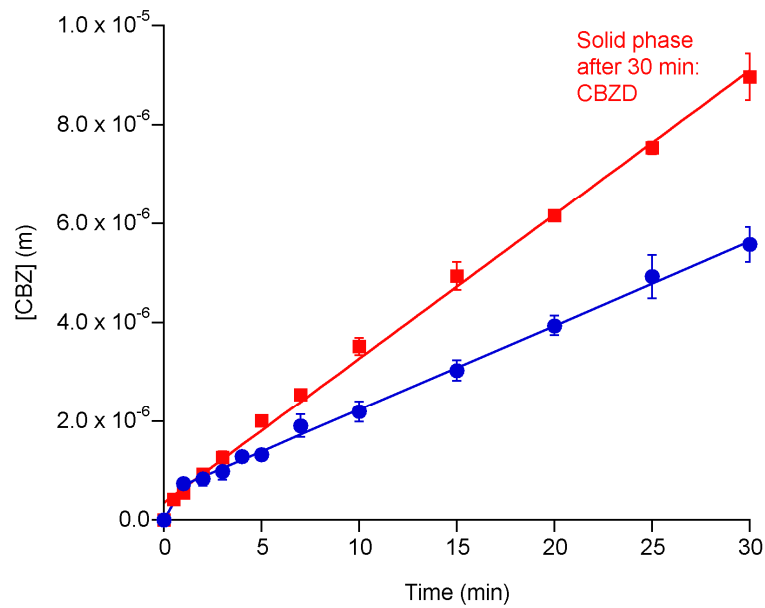
Figure A.5. [CBZ] vs time (±SE) during rotating disk dissolution of (■) CBZ-SAC cocrystal and (●) CBZ dihydrate. Media was 0.1 N HCl (pH 1).

Disk dissolution of coated and noncoated CBZ-SLC in water compared to noncoated CBZ-SLC in 35 mM SLS is shown in Figure A.6. The coated cocrystal achieves a 3-fold increased dissolution rate in water relative to the noncoated cocrystal (Table A.3). SLS dissolved into the media from the coated particles is vanishingly low, estimated at 0.03 mM (CMC of SLS is 8 mM). For comparison, the dissolution rate achieved by CBZ-SLC cocrystal in media containing 35 mM SLS (in the bulk) is 4-fold relative to water. This shows that the micelles are interacting with the cocrystal at the dissolving surface. However, it is yet unclear whether or not the cocrystalline nature of the solid contributes to the effectiveness of the surfactant coating in enhancing dissolution rates.

Figure A.6. [CBZ] vs time (±SE) during rotating disk dissolution of (▲) noncoated CBZ-SLC in 0.1 N HCl + 35 mM SLS, (■) coated CBZ-SLC in 0.1 N HCl, and (●) noncoated CBZ-SLC in 0.1 N HCl.

Table A.4. Dissolution rates (±SE) of coated CBZ-SLC cocrystal in 0.1 N HCl.

	(1) CBZ initial rate noncoated mg/min/cm^2	(2) CBZ initial rate coated mg/min/cm^2	Ratio of initial rates
CBZ-SLC (6 wt% SLS) pH 1	0.015 ± 0.001	0.045 ± 0.002	3.0