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)

H₂A – 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

\[ \text{RHA}_{\text{solid}} \xrightleftharpoons{K_{sp}} \text{R}_{aq} + \text{HA}_{aq} \]  \hspace{1cm} (1)

\[ \text{HA}_{aq} \xrightleftharpoons{K_{a}^{HA}} \text{A}^{-}_{aq} + \text{H}^{+}_{aq} \]  \hspace{1cm} (2)

\[ \text{R}_{aq} + \text{M} \xrightleftharpoons{K_{s}^{R}} \text{R}_{m} \]  \hspace{1cm} (3)

\[ \text{HA}_{aq} + \text{M} \xrightleftharpoons{K_{s}^{HA}} \text{HA}_{m} \]  \hspace{1cm} (4)

\[ \text{A}^{-}_{aq} + \text{M} \xrightleftharpoons{K_{s}^{A^{-}}} \text{A}^{-}_{m} \]  \hspace{1cm} (5)

Associated equilibrium constants are given by

\[ K_{sp} = [\text{R}]_{aq}[\text{HA}]_{aq} \]  \hspace{1cm} (6)

\[ K_{a}^{HA} = \frac{[\text{A}^{-}]_{aq}[\text{H}^{+}]_{aq}}{[\text{HA}]_{aq}} \]  \hspace{1cm} (7)

\[ K_{s}^{R} = \frac{[\text{R}]_{m}}{[\text{R}]_{aq}[\text{M}]} \]  \hspace{1cm} (8)

\[ K_{s}^{HA} = \frac{[\text{HA}]_{m}}{[\text{HA}]_{aq}[\text{M}]} \]  \hspace{1cm} (9)

\[ K_{s}^{A^{-}} = \frac{[\text{A}^{-}]_{m}}{[\text{A}^{-}]_{aq}[\text{M}]} \]  \hspace{1cm} (10)

**Solubility of cocrystal RHA**

Mass balance on R is given by

\[ [\text{R}]_{T} = [\text{R}]_{aq} + [\text{R}]_{m} \]  \hspace{1cm} (11)

Substituting (6) and (8) into (11) gives
\[ [R]_T = \frac{K_{sp}^{R}}{[HA]_{aq}} \left( 1 + K_{s}^{R} [M] \right) \]  

(12)

Mass balance on A is given by

\[ [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_{m} + [A^-]_{m} \]  

(13)

Substituting (7), (9), and (10) into (13) gives

\[ [A]_T = [HA]_{aq} \left( 1 + \frac{K_{s}^{HA}}{[H^+]} + K_{s}^{HA} [M] + \frac{K_{a}^{HA}}{[H^+] K_{s}^{A^-}} [M] \right) \]  

(14)

Combining (12) and (14) gives the

\[ [R]_T = \frac{K_{sp}^{R}}{[A]_T} \left( 1 + K_{s}^{R} [M] \right) \left( 1 + \frac{K_{s}^{HA}}{[H^+]} + K_{s}^{HA} [M] + \frac{K_{a}^{HA}}{[H^+] K_{s}^{A^-}} [M] \right) \]  

(15)

Where \([R]_T\) and \([A]_T\) are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When \(K_{s}^{HA} >> K_{s}^{A^-}\), (15) can be simplified to

\[ [R]_T = \frac{K_{sp}^{R}}{[A]_T} \left( 1 + K_{s}^{R} [M] \right) \left( 1 + \frac{K_{s}^{HA}}{[H^+]} + K_{s}^{HA} [M] \right) \]  

(16)

**Eutectic solution concentrations of drug and coformer of cocrystal RHA**

At eutectic point \(E_1\), solid drug, cocrystal, and solution coexist in equilibrium.

\[ \text{RHA}_{\text{solid}} + \text{R}_{\text{solid}} \rightarrow \text{R}_{\text{aq}} + \text{HA}_{\text{aq}} \]  

(17)

\([R]_{\text{eu,T}}\) and \([A]_{\text{eu,T}}\), the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (16) when the following condition is satisfied

\[ [R]_T = S_{R,T} \]  

(18)

where \(S_{R,T}\) is the solubility of R in the eutectic solution. When drug and solubilization are 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

\[ S_{R,T} = [R]_T = [R]_{aq} + [R]_{m} \]  

(19)
where $S_{R,aq}$ is the drug aqueous solubility. Thus,

$$[R]_{eu,T} = S_{R,aq} \left( 1 + K^R_s[M] \right)$$

(21)

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

(22)

The eutectic concentrations in water (no micellar solubilization) are found when $[M] = 0$,

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

(23)

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

(24)

Combining Equations (21) to (24), $[R]_{eu,T}$ and $[A]_{eu,T}$ at $[H^+] = [H^+]_T$ can be expressed in terms of $[R]_{eu,aq}$ and $[A]_{eu,aq}$ at $[H^+] = [H^+]_{aq}$.

$$[R]_{eu,T} = [R]_{eu,aq} \left( 1 + K^R_s[M] \right)$$

(25)

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

(26)

$E_2$, the eutectic between solid coformer, cocrytall, and solution, is described by

$$R_{\text{solid}} + HA_{\text{solid}} \rightleftharpoons R_{aq} + HA_{aq}$$

(27)

At $E_2$, $[R]_{eu,T}$ and $[A]_{eu,T}$ are special solutions to Equation (16) when the following condition is satisfied

$$[A]_T = S_{A,T}$$

(28)

When drug and solubilization are 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.
\[ S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_{m} \]  

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

where \( S_{HA,aq} \) is the coformer intrinsic solubility. Solving for \([R]_{eu,T}\) and \([A]_{eu,T}\) according to Equation (16) for \( E_2 \) yields the same expressions as (25) and (26).

**Eutectic constant \( K_{eu} \) of cocrystal RHA**

The eutectic constant \( K_{eu} \) is given by

\[ K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \]  

Assuming dilute conditions where concentrations replace activities,

\[ K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \]  

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (25) and (26) can be substituted into (32), which yields

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

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 (33) when \( K_{eu,T} = 1 \) and solving for \([M]\),

\[ \text{CSC of cocrystal RHA} \]

The CSC at \([H^+]_T\) can be expressed as a function of \( K_{eu,aq} \) at \([H^+]_{aq}\). The CSC is determined by Equation (33) when \( K_{eu,T} = 1 \) and solving for \([M]\),
\[
[M]_{\text{CSC}} = \frac{K_{\text{eu,aq}} \left( 1 + \frac{K_{a}^{HA}}{[H^+]_{\text{T}}} \right)}{1 + \frac{K_{a}^{HA}}{[H^+]_{\text{aq}}}} - 1
\]

(34)

\[
K_{s}^{R} = \frac{K_{\text{eu,aq}} K_{s}^{HA}}{1 + \frac{K_{a}^{HA}}{[H^+]_{\text{aq}}}}
\]

\[
[M]_{\text{CSC}} \text{ is the micellar surfactant concentration associated with CSC. The CSC is}
\]

\[
\text{CSC} = \frac{K_{\text{eu,aq}} \left( 1 + \frac{K_{a}^{HA}}{[H^+]_{\text{T}}} \right)}{1 + \frac{K_{a}^{HA}}{[H^+]_{\text{aq}}}} - 1 + \text{CMC}
\]

(35)
HXHA (1:1 monoprotic weakly acidic drug HX, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by

$$
\text{HXHA}_{\text{solid}} \overset{K_{sp}}{\rightleftharpoons} \text{HX}_{\text{aq}} + \text{HA}_{\text{aq}}
$$

(36)

$$
\text{HX}_{\text{aq}} \overset{K_{a}^{\text{HX}}}{\rightleftharpoons} \text{X}^{-}_{\text{aq}} + \text{H}^{+}_{\text{aq}}
$$

(37)

$$
\text{HA}_{\text{aq}} \overset{K_{a}^{\text{HA}}}{\rightleftharpoons} \text{A}^{-}_{\text{aq}} + \text{H}^{+}_{\text{aq}}
$$

(38)

$$
\text{HX}_{\text{aq}} + \text{M} \overset{K_{s}^{\text{HX}}}{\rightleftharpoons} \text{HX}_{\text{m}}
$$

(39)

$$
\text{HA}_{\text{aq}} + \text{M} \overset{K_{s}^{\text{HA}}}{\rightleftharpoons} \text{HA}_{\text{m}}
$$

(40)

$$
\text{X}^{-}_{\text{aq}} + \text{M} \overset{K_{s}^{\text{X}^{-}}}{\rightleftharpoons} \text{X}^{-}_{\text{m}}
$$

(41)

$$
\text{A}^{-}_{\text{aq}} + \text{M} \overset{K_{s}^{\text{A}^{-}}}{\rightleftharpoons} \text{A}^{-}_{\text{m}}
$$

(42)

Associated equilibrium constants are given by

$$
K_{sp} = [\text{HX}]_{aq}[\text{HA}]_{aq}
$$

(43)

$$
K_{a}^{\text{HX}} = \frac{[\text{X}^{-}]_{aq}[\text{H}^{+}]_{aq}}{[\text{HX}]_{aq}}
$$

(44)

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

(45)

$$
K_{s}^{\text{HX}} = \frac{[\text{HX}]_{m}}{[\text{HX}]_{aq}[\text{M}]}
$$

(46)

$$
K_{s}^{\text{HA}} = \frac{[\text{HA}]_{m}}{[\text{HA}]_{aq}[\text{M}]}
$$

(47)
\[
K_s^{X^-} = \frac{[X^-]_m}{[X^-]_{aq}[M]} \quad (48)
\]

\[
K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \quad (49)
\]

**Solubility of cocrystal HXHA**

Mass balance on X is given by

\[
[X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m + [X^-]_m \quad (50)
\]

Substituting (43), (44), (46), and (48) into (50) gives

\[
[X]_T = \frac{K_{sp}^{HA}}{[HA]_{aq}} \left( 1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]} K_s^{X^-}[M] \right) \quad (51)
\]

Mass balance on A is given by

\[
[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \quad (52)
\]

Substituting (45), (47), and (49) into (52) gives

\[
[A]_T = [HA]_{aq} \left( 1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right) \quad (53)
\]

Combining (51) and (53) gives

\[
[X]_T = \frac{K_{sp}^{HA}}{[A]_T} \left( 1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] + \frac{K_a^{HX}}{[H^+]} K_s^{X^-}[M] \right) \left( 1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_a^{HA}}{[H^+]} K_s^{A^-}[M] \right) \quad (54)
\]

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 (54) can be simplified to

\[
[X]_T = \frac{K_{sp}^{HA}}{[A]_T} \left( 1 + \frac{K_a^{HX}}{[H^+]} + K_s^{HX}[M] \right) \left( 1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M] \right) \quad (55)
\]

**Eutectic solution concentrations of drug and coformer of cocrystal HXHA**
At eutectic point $E_1$, solid drug, cocystal, and solution coexist in equilibrium.

\[
\text{HXHA}_\text{solid} + \text{HX}_\text{solid} \rightleftharpoons \text{HX}_\text{aq} + \text{HA}_\text{aq}
\]  

(56)

[$X]_{\text{eu,T}}$ and [$A]_{\text{eu,T}}$, the total concentrations of drug and coformer at the eutectic, are special solutions of Equation (55) when the following condition is satisfied

\[
[X]_T = S_{X,T}
\]

(57)

where $S_{X,T}$ is the solubility of X at the eutectic. When drug and solubilization are 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

\[
S_{X,T} = [X]_T = [\text{HX}]_\text{aq} + [\text{X}^-]_\text{aq} + [\text{HX}]_\text{m}
\]

(58)

\[
S_{X,T} = S_{\text{HX},aq} \left( 1 + \frac{K_a^{\text{HX}}}{[\text{H}^+]_\text{aq}} + K_s^{\text{HX}}[\text{M}] \right)
\]

(59)

where $S_{\text{HX},aq}$ is the drug intrinsic solubility. Thus,

\[
[X]_{\text{eu},T} = S_{\text{HX},aq} \left( 1 + \frac{K_a^{\text{HX}}}{[\text{H}^+]_\text{aq}} + K_s^{\text{HX}}[\text{M}] \right)
\]

(60)

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

(61)

The eutectic concentrations in the absence of micellar solubilization are found when $[\text{M}] = 0$,

\[
[X]_{\text{eu},aq} = S_{\text{HX},aq} \left( 1 + \frac{K_a^{\text{HX}}}{[\text{H}^+]_\text{aq}} \right)
\]

(62)

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

(63)

Combining Equations (60) to (63), $[X]_{\text{eu,T}}$ and $[A]_{\text{eu,T}}$ at $[\text{H}^+] = [\text{H}^+]_T$ can be expressed in terms of $[X]_{\text{eu,aq}}$ and $[A]_{\text{eu,aq}}$ at $[\text{H}^+] = [\text{H}^+]_\text{aq}$.
E2, the eutectic between solid coformer, cocrystal, and solution, is described by

\[
[X]_{e_u,T} = [X]_{e_u,aq} \left( 1 + \frac{K_{s}^{HX}}{[H^+]_T} + \frac{K_{a}^{HX} [M]}{1 + \frac{K_{a}^{HX}}{[H^+]_{aq}}} \right) \tag{64}
\]

\[
[A]_{e_u,T} = [A]_{e_u,aq} \left( 1 + \frac{K_{s}^{HA}}{[H^+]_T} + \frac{K_{a}^{HA} [M]}{1 + \frac{K_{a}^{HA}}{[H^+]_{aq}}} \right) \tag{65}
\]

\[
\text{Eutectic constant } K_{e_u} \text{ of cocrystal } HXHA
\]

The eutectic constant \(K_{e_u}\) is given by
\[ K_{eu} = \frac{a_{A,eu}}{a_{X,eu}} \]  

(70)

Assuming dilute conditions where concentrations replace activities,

\[ K_{eu} = \frac{[A]_{eu,T}}{[X]_{eu,T}} \]  

(71)

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (64) and (65) can be substituted into (71), which yields

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

(72)

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 (72) when \( K_{eu,T} = 1 \) and solving for \([M]\),

\[
[M]_{CSC} = \frac{K_{eu,aq} K_s^{HA}}{\left( \frac{K_s^{HX}}{1 + \frac{K_s^{HX}}{[H^+]_T}} \right) - \left( \frac{K_s^{HX}}{1 + \frac{K_s^{HX}}{[H^+]_{aq}}} \right)}
\]  

(73)

\([M]_{CSC}\) is the micellar surfactant concentration associated with CSC. The CSC is
BHA (1:1 monoprotic weakly basic drug B, monoprotic weakly acidic coformer HA)

Relevant equilibria are given by:

\[
\text{BHA}_{\text{solid}} \xrightleftharpoons{K_{sp}} \text{B}_{\text{aq}}^+ + \text{HA}_{\text{aq}}
\]  

(75)

\[
\text{BH}^+_{\text{aq}} \xrightleftharpoons{K^B} \text{B}_{\text{aq}}^+ + \text{H}^+_{\text{aq}}
\]  

(76)

\[
\text{HA}_{\text{aq}} \xrightleftharpoons{K_a^{HA}} \text{A}^-_{\text{aq}} + \text{H}^+_{\text{aq}}
\]  

(77)

\[
\text{B}_{\text{aq}} + \text{M} \xrightleftharpoons{K_B^m} \text{B}_{\text{aq}}^m
\]  

(78)

\[
\text{HA}_{\text{aq}} + \text{M} \xrightleftharpoons{K_{s}^{HA}} \text{HA}_{\text{aq}}^m
\]  

(79)

\[
\text{BH}^+_{\text{aq}} + \text{M} \xrightleftharpoons{K_{s}^{BH^+}} \text{BH}^+_{\text{aq}}^m
\]  

(80)

\[
\text{A}^-_{\text{aq}} + \text{M} \xrightleftharpoons{K_{s}^{A^-}} \text{A}^-_{\text{aq}}^m
\]  

(81)

Associated equilibrium constants are given by:

\[K_{sp} = [B]_{aq}[HA]_{aq}\]  

(82)

\[K_B^m = \frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}}\]  

(83)
\[
K_a^\text{HA} = \frac{[A^-]_{aq}[H^+]_{aq}}{[HA]_{aq}} \quad (84)
\]

\[
K_a^B = \frac{[B]_m}{[B]_{aq}[M]} \quad (85)
\]

\[
K_a^{HA} = \frac{[HA]_m}{[HA]_{aq}[M]} \quad (86)
\]

\[
K_s^{BH^+} = \frac{[BH^+]_m}{[B]_{aq}[M]} \quad (87)
\]

\[
K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \quad (88)
\]

**Solubility of cocrystal BHA**

Mass balance on B is given by

\[
[B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m + [BH^+]_m \quad (89)
\]

Substituting (82), (83), (85), and (87) into (89) gives

\[
[B]_T = \frac{K_{sp}}{[HA]_{aq}} \left( 1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B} K_s^B[M] \right) \quad (90)
\]

Mass balance on A is given by

\[
[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \quad (91)
\]

Substituting (84), (86), and (88) into (91) gives

\[
[A]_T = [HA]_{aq} \left( 1 + \frac{K_r^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_r^{HA}}{[H^+]} K_s^{A^-}[M] \right) \quad (92)
\]

Combining (90) and (92) gives

\[
[B]_T = \frac{K_{sp}}{[A]_T} \left( 1 + \frac{[H^+]}{K_a^B} + K_s^B[M] + \frac{[H^+]}{K_a^B} K_s^{BH^+}[M] \right) \left( 1 + \frac{K_r^{HA}}{[H^+]} + K_s^{HA}[M] + \frac{K_r^{HA}}{[H^+]} K_s^{A^-}[M] \right) \quad (93)
\]
Where $[B]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_{sB}^+ >> K_{sBH^+}$ and $K_{sHA} >> K_{sA^-}$, then Equation (54) can be simplified to

$$[B]_T = \frac{K_{sp}}{[A]_T} \left( 1 + \frac{[H^+]}{K_a^B} + K_s^B [M] \right) \left( 1 + \frac{K_{HA}^B}{[H^+]} + K_s^HA [M] \right)$$  \hspace{1cm} (94)

Eutectic solution concentrations of drug and coformer of cocrystal BHA

At eutectic point $E_1$, solid drug, cocrystal, and solution coexist in equilibrium.

$$BHA_{solid} + B_{solid} \xrightarrow{E_1} B_{aq} + HA_{aq}$$  \hspace{1cm} (95)

$[B]_{eu,T}$ and $[A]_{eu,T}$, the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (94) when the following condition is satisfied

$$[B]_T = S_{B,T}$$  \hspace{1cm} (96)

where $S_{B,T}$ is the solubility of B in the eutectic solution. When drug and solubilization are 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

$$S_{B,T} = [B]_T = [B]_{aq} + [BH^+]_{aq} + [B]_m$$  \hspace{1cm} (97)

$$S_{B,T} = S_{B,aq} \left( 1 + \frac{[H^+]}{K_a^B} + K_s^B [M] \right)$$  \hspace{1cm} (98)

where $S_{B,aq}$ is the drug intrinsic solubility. Thus,

$$[B]_{eu,T} = S_{B,aq} \left( 1 + \frac{[H^+]}{K_a^B} + K_s^B [M] \right)$$  \hspace{1cm} (99)

$$[A]_{eu,T} = \frac{K_{sp}}{S_{B,aq}} \left( 1 + \frac{K_{HA}^B}{[H^+]} + K_s^HA [M] \right)$$  \hspace{1cm} (100)

The eutectic concentrations in the absence of micellar solubilization are found when $[M] = 0$,

$$[B]_{eu,aq} = S_{B,aq} \left( 1 + \frac{[H^+]}{K_a^B} \right)$$  \hspace{1cm} (101)
\[ \left[ A \right]_{eu, aq} = \frac{K_{sp}}{S_{B, aq}} \left( 1 + \frac{K_{a}^{HA}}{[H^+]_{aq}} \right) \]  

(102)

Combining Equations (99) to (102), \([B]_{eu,T}\) and \([A]_{eu,T}\) at \([H^+] = [H^+]_{aq}\) can be expressed in terms of \([B]_{eu,aq}\) and \([A]_{eu,aq}\) at \([H^+] = [H^+]_{aq}\).

\[ \left[ B \right]_{eu,T} = \left[ B \right]_{eu,aq} \frac{1 + \frac{[H^+]_{aq}}{K_s^B} + K_s^B [M]}{1 + \frac{[H^+]_{aq}}{K_a^B}} \]  

(103)

\[ \left[ A \right]_{eu,T} = \left[ A \right]_{eu,aq} \frac{1 + \frac{K_a^{HA}}{[H^+]_{aq}} + K_s^{HA} [M]}{1 + \frac{K_a^{HA}}{[H^+]_{aq}}} \]  

(104)

E₂, the eutectic between solid coformer, cocrystal, and solution, is described by

\[ BHA_{solid} + HA_{solid} \rightleftharpoons B_{aq} + HA_{aq} \]  

(105)

\([B]_{eu,T}\) and \([A]_{eu,T}\) are special solutions to Equation (104) when the following condition is satisfied

\[ [A]_T = S_{A,T} \]  

(106)

When drug and solubilization are 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

\[ S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_{m} \]  

(107)

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

(108)

where \(S_{HA,aq}\) is the coformer intrinsic solubility. Solving for \([B]_{eu,T}\) and \([A]_{eu,T}\) according to Equation (55) for E₂ yields the same expressions as (103) and (104).
Eutectic constant $K_{eu}$ of cocrystal BHA

The eutectic constant $K_{eu}$ is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{B,eu}} \tag{109}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[B]_{eu,T}} \tag{110}$$

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (103) and (104) can be substituted into (110), which yields

$$K_{eu,T} = K_{eu,\text{aq}} \left( \frac{1 + \frac{[H^+]_{\text{aq}}}{K_a^B}}{1 + \frac{[H^+]_T}{K_a^B} + K_s^B[M]} \right) \left( \frac{1 + \frac{K_a^A}{[H^+]_T} + K_s^A[M]}{1 + \frac{K_a^A}{[H^+]_{\text{aq}}}} \right) \tag{111}$$

where $K_{eu,T}$ is the total $K_{eu}$ in micellar solution at $[H^+] = [H^+]_T$, and $K_{eu,\text{aq}}$ is the $K_{eu}$ in pure water at $[H^+] = [H^+]_{\text{aq}}$.

CSC of cocrystal BHA

The CSC at $[H^+]_T$ can be expressed as a function of $K_{eu,\text{aq}}$ at $[H^+]_{\text{aq}}$. The CSC at a given pH is determined by Equation (111) when $K_{eu,T} = 1$ and solving for $[M]$,

$$[M]_{\text{CSC}} = \frac{K_{eu,\text{aq}} \frac{K_s^B}{1 + \frac{[H^+]_{\text{aq}}}{K_a^B}} - K_{eu,\text{aq}} \frac{K_s^A}{1 + \frac{[H^+]_T}{K_a^A}}}{K_{eu,\text{aq}} \frac{K_s^B}{1 + \frac{[H^+]_{\text{aq}}}{K_a^B}} - K_{eu,\text{aq}} \frac{K_s^A}{1 + \frac{[H^+]_T}{K_a^A}}} \tag{112}$$

$[M]_{\text{CSC}}$ is the micellar surfactant concentration associated with CSC. The CSC is
\[ K_{\text{eq,q}} = \frac{1 + \frac{K_a^{HA}}{[H^+]}_T}{1 + \frac{K_a^{HA}}{[H^+]}_aq} \]  
\[ \frac{1 + \frac{[H^+]_aq}{K_a^{HA}}}{1 + \frac{[H^+]_aq}{K_a^{HA}}} \]  

CSC = \left( \frac{K_s^B}{1 + [H^+]_aq} \right) - \left( \frac{K_s^A}{1 + [H^+]_aq} \right) + CMC \tag{113}

\[ R_2H_2A \text{ (2:1 monoprotic weakly basic drug } R, \text{ diprotic weakly acidic coformer } H_2A) \]

Relevant equilibria are given by

\[ R_2H_2A \text{ solid} \xrightleftharpoons{K_{sp}} 2R_{aq} + H_2A_{aq} \tag{114} \]

\[ H_2A_{aq} \xrightarrow{K_{HA}} HA_{aq} + H^+_{aq} \tag{115} \]

\[ HA_{aq} \xrightarrow{K_{HA^-}} A^{2-}_{aq} + H^+_{aq} \tag{116} \]

\[ R_{aq} + M \xrightarrow{K^R_s} R_m \tag{117} \]

\[ H_2A_{aq} + M \xrightarrow{K_{H_2A}} H_2A_m \tag{118} \]

\[ HA_{aq} + M \xrightarrow{K_{HA^-}} HA_m \tag{119} \]

\[ A^{2-}_{aq} + M \xrightarrow{K_{A^{2-}}^s} A^{2-}_m \tag{120} \]

Associated equilibrium constants are given by

\[ K_{sp} = [R]_{aq}^2[H_2A]_{aq} \tag{121} \]

\[ K_a^{HA} = \frac{[HA^-]_{aq}[H^+]_{aq}}{[H_2A]_{aq}} \tag{122} \]
\( K_{a}^{HA^{-}} = \frac{[A^{2-}]_{aq}[H^{+}]_{aq}}{[HA^{-}]_{aq}} \)  
(123)

\( K_{s}^{R} = \frac{[R]_{m}}{[R]_{aq}[M]} \)  
(124)

\( K_{s}^{H_{2}A} = \frac{[H_{2}A]_{aq}}{[H_{2}A]_{aq}[M]} \)  
(125)

\( K_{s}^{HA^{-}} = \frac{[HA^{-}]_{aq}}{[HA^{-}]_{aq}[M]} \)  
(126)

\( K_{s}^{A^{2-}} = \frac{[A^{2-}]_{aq}}{[A^{2-}]_{aq}[M]} \)  
(127)

**Solubility of cocrystal \( R_{2}H_{2}A \)**

Mass balance on \( R \) is given by

\([R]_{T} = [R]_{aq} + [R]_{m} \)  
(128)

Substituting (121) and (124) into (128) gives

\([R]_{T}^{2} = \frac{K_{sp}}{[H_{2}A]_{aq}} \left( 1 + K_{s}^{R}[M] \right)^{2} \)  
(129)

Mass balance on \( A \) is given by

\([A]_{T} = [H_{2}A]_{aq} + [HA^{-}]_{aq} + [A^{2-}]_{aq} + [H_{2}A]_{m} + [HA^{-}]_{m} + [A^{2-}]_{m} \)  
(130)

Substituting (122), (123), and (125)-(127) into (130) gives

\([A]_{T} = [H_{2}A]_{aq} \left( 1 + \frac{K_{s}^{H_{2}A}}{[H^{+}]_{aq}} + \frac{K_{s}^{H_{2}A}K_{s}^{HA^{-}}}{[H^{+}]^{2}_{aq}} + K_{s}^{H_{2}A}K_{s}^{HA^{-}}[M] + \frac{K_{s}^{H_{2}A}K_{s}^{HA^{-}}}{[H^{+}]^{2}_{aq}} + K_{s}^{H_{2}A}K_{s}^{HA^{-}}[M] \right) \)  
(131)

Combining (129) and (131) gives

\([R]_{T}^{2} = \frac{K_{sp}}{[A]_{T}} \left( 1 + K_{s}^{R}[M] \right)^{2} \left( 1 + \frac{K_{s}^{H_{2}A}}{[H^{+}]_{aq}} + \frac{K_{s}^{H_{2}A}K_{s}^{HA^{-}}}{[H^{+}]^{2}_{aq}} + K_{s}^{H_{2}A}K_{s}^{H_{2}A}K_{s}^{HA^{-}}[M] + \frac{K_{s}^{H_{2}A}K_{s}^{HA^{-}}}{[H^{+}]^{2}_{aq}} + K_{s}^{H_{2}A}K_{s}^{HA^{-}}[M] \right) \)  
(132)
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 \(K_{s}^{H_2A} \gg K_{s}^{A^2-}\), (132) can be simplified to

\[
[R]_T^2 = \frac{K_{sp}}{[A]_T} \left(1 + K_{s}^R[M]\right)^2 \left(1 + \frac{K_{a}^{H_2A}}{[H^+]} + \frac{K_{a}^{H_2A}K_{a}^{HA^-}}{[H^+]^2} + K_{s}^{H_2A}[M]\right)
\]  

(133)

**Eutectic solution concentrations of drug and coformer of cocrystal \(R_2H_2A\)**

At eutectic point \(E_1\), solid drug, cocrystal, and solution coexist in equilibrium.

\[
R_2H_2A_{\text{solid}} + R_{\text{solid}} \rightleftharpoons R_{\text{aq}} + HA_{\text{aq}}
\]

(134)

\([R]_{eu,T}\) and \([A]_{eu,T}\), the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (133) when the following condition is satisfied

\[
[R]_T = S_{R,T}
\]

(135)

where \(S_{R,T}\) is the solubility of \(R\) in the eutectic solution. When drug and solubilization are 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

\[
S_{R,T} = [R]_T = [R]_{aq} + [R]_{m}
\]

(136)

\[S_{R,T} = S_{R,aq} \left(1 + K_{s}^R[M]\right)
\]

(137)

where \(S_{R,aq}\) is the drug aqueous solubility. Thus,

\[
[R]_{eu,T} = S_{R,aq} \left(1 + K_{s}^R[M]\right)
\]

(138)

\[
[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^2} \left(1 + \frac{K_{a}^{H_2A}}{[H^+]} + \frac{K_{a}^{H_2A}K_{a}^{HA^-}}{[H^+]^2} + K_{s}^{H_2A}[M]\right)
\]

(139)

The eutectic concentrations in the absence of micellar solubilization are found when \([M] = 0\),

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

(140)
\[ [A]_{\text{eu,aq}} = \frac{K_{sp}}{S_{R,\text{aq}}} \left( 1 + \frac{K_{a}^{H_{2}A}}{[H^{+}]} + \frac{K_{a}^{H_{2}A} K_{a}^{HA^-}}{[H^{+}]^2} \right) \]  

(141)

Combining Equations (138) to (141), \([R]_{\text{eu,T}}\) and \([A]_{\text{eu,T}}\) at \([H^{+}] = [H^{+}]_{\text{aq}}\) can be expressed in terms of \([R]_{\text{eu,aq}}\) and \([A]_{\text{eu,aq}}\) at \([H^{+}] = [H^{+}]_{\text{aq}}\).

\[ [R]_{\text{eu,T}} = [R]_{\text{eu,aq}} \left( 1 + K_{R}^{M} \right) \]  

(142)

\[ [A]_{\text{eu,T}} = [A]_{\text{eu,aq}} \left( 1 + \frac{K_{a}^{H_{2}A}}{[H^{+}]_{\text{aq}}} + \frac{K_{a}^{H_{2}A} K_{a}^{HA^-}}{[H^{+}]_{\text{aq}}^2} + K_{s}^{H_{2}A}[M] \right) \]  

(143)

E2, the eutectic between solid coformer, cocrystal, and solution, is described by

\[ R_{2}H_{2}A_{\text{solid}} + HA_{\text{solid}} \rightleftharpoons R_{\text{aq}} + HA_{\text{aq}} \]  

(144)

At E2, \([R]_{\text{eu,T}}\) and \([A]_{\text{eu,T}}\) are special solutions to Equation (133) when the following condition is satisfied

\[ [A]_{\text{T}} = S_{A,T} \]  

(145)

When drug and solubilization are 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

\[ S_{A,T} = [A]_{\text{T}} = [H_{2}A]_{\text{aq}} + [HA^-]_{\text{aq}} + [A^{2-}]_{\text{aq}} + [H_{2}A]_{\text{m}} \]  

(146)

\[ S_{A,T} = S_{HA,\text{aq}} \left( 1 + \frac{K_{a}^{H_{2}A}}{[H^{+}]} + \frac{K_{a}^{H_{2}A} K_{a}^{HA^-}}{[H^{+}]^2} + K_{s}^{H_{2}A}[M] \right) \]  

(147)

where \(S_{HA,\text{aq}}\) is the coformer intrinsic solubility. Solving for \([R]_{\text{eu,T}}\) and \([A]_{\text{eu,T}}\) according to Equation (133) for E2 yields the same expressions as (142) and (143).

\[ Eutectic constant K_{eu} of cocrystal R_2H_2A \]

The eutectic constant \(K_{eu}\) is given by
\[ K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \]  

(148)

Assuming dilute conditions where concentrations replace activities,

\[ K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \]  

(149)

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (142) and (143) can be substituted into (149), which yields

\[ K_{eu,T} = K_{eu,aq} \left( \frac{1}{1 + K_s^R [M]} \right) \left( \frac{1 + \frac{K_a^{H_A}}{[H^+]_T} + \frac{K_a^{H_A} K_a^{HA^-}}{[H^+]_T^2} + K_s^{H_A}[M]}{1 + \frac{K_a^{H_A}}{[H^+]_{aq}} + \frac{K_a^{H_A} K_a^{HA^-}}{[H^+]_{aq}^2}} \right) \]  

(150)

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 \( R_2H_2A \)**

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 (33) when \( K_{eu,T} = 0.5 \) and solving for \([M]\),

\[ 2K_{eu,aq} \left( \frac{1 + \frac{K_a^{H_A}}{[H^+]_T} + \frac{K_a^{H_A} K_a^{HA^-}}{[H^+]_T^2} + K_s^{H_A}[M]}{1 + \frac{K_a^{H_A}}{[H^+]_{aq}} + \frac{K_a^{H_A} K_a^{HA^-}}{[H^+]_{aq}^2}} \right) - 1 \]

\[ [M]_{CSC} = \]  

\[ K_s^R = \frac{2K_{eu,aq} K_a^{H_A}}{1 + \frac{K_a^{H_A}}{[H^+]_{aq}} + \frac{K_a^{H_A} K_a^{HA^-}}{[H^+]_{aq}^2}} \]  

(151)

\([M]_{CSC}\) is the micellar surfactant concentration associated with CSC. The CSC is
\[ 2K_{eu,aq} \left( \frac{\left[ R \right]_{aq} + K_{a} H_{A} \left[ H^{+} \right]_{aq}^{2}}{\left[ H^{+} \right]_{aq}} \right) - 1 \]

\[ K_{s}^{R} = \frac{2K_{eu,aq} K_{s} H_{A}}{1 + \frac{K_{a} H_{A}}{\left[ H^{+} \right]_{aq}} + \frac{K_{a} H_{A} K_{H}^{A}}{\left[ H^{+} \right]_{aq}^{2}}} \] + CMC

\[(152)\]

\[ R_{2} HAB \ (2:1 \ monoprotic \ weakly \ basic \ drug \ R, \ amphoteric \ coformer \ HAB) \]

Relevant equilibria are given by

\[ R_{2} HAB \ \text{solid} \xrightarrow{K_{sp}} 2 R_{aq} + HAB_{aq} \] (153)

\[ H_{2} AB^{+} \ \text{aq} \xrightarrow{K_{s}^{HAB^{+}}} HAB_{aq} + H_{aq} \] (154)

\[ HAB_{aq} \xrightarrow{K_{s}^{HAB}} AB^{-}_{aq} + H_{aq} \] (155)

\[ R_{aq} + M \xrightarrow{K_{s}^{R}} R_{m} \] (156)

\[ H_{2} AB^{+} \ \text{aq} + M \xrightarrow{K_{s}^{H_{2}AB^{+}}} H_{2} AB_{m} \] (157)

\[ HAB_{aq} + M \xrightarrow{K_{s}^{HAB}} HAB_{m} \] (158)

\[ AB^{-} \ \text{aq} + M \xrightarrow{K_{s}^{AB^{-}}} AB^{-}_{m} \] (159)

Associated equilibrium constants are given by

\[ K_{sp} = \left[ R \right]_{aq}^{2} \left[ HAB \right]_{aq} \] (160)

\[ K_{a}^{H_{2}AB^{+}} = \frac{[HAB]_{aq} [H^{+}]_{aq}}{[H_{2}AB^{+}]_{aq}} \] (161)
\[ K_{a}^{HAB} = \frac{[AB^-]_{aq}[H^+]_{aq}}{[HAB]_{aq}} \]  \hfill (162)

\[ K_{s}^{R} = \frac{[R]_{m}}{[R]_{aq}[M]} \]  \hfill (163)

\[ K_{a}^{H_{2}AB^+} = \frac{[H_{2}AB^+]_{m}}{[H_{2}AB^+]_{aq}[M]} \]  \hfill (164)

\[ K_{s}^{HAB} = \frac{[HAB]_{m}}{[HAB]_{aq}[M]} \]  \hfill (165)

\[ K_{s}^{AB^-} = \frac{[AB^-]_{m}}{[AB^-]_{aq}[M]} \]  \hfill (166)

**Solubility of cocrystal R\_2HAB**

Mass balance on B is given by

\[ [R]_{T} = [R]_{aq} + [R]_{m} \]  \hfill (167)

Substituting (160) and (163) into (167) gives

\[ [R]_{T}^2 = \frac{K_{sp}}{[HAB]_{aq}} \left( 1 + K_{s}^{R}[M] \right)^2 \]  \hfill (168)

Mass balance on AB is given by

\[ [AB]_{T} = [HAB]_{aq} + [H_{2}AB^+]_{aq} + [AB^-]_{aq} + [HAB]_{m} + [H_{2}AB^+]_{m} + [AB^-]_{m} \]  \hfill (169)

Substituting (161), (162), and (164)-(166) into (169) gives

\[ [AB]_{T} = [HAB]_{aq} \left( 1 + \frac{[H^+]}{K_{a}^{H_{2}AB^+}} + \frac{K_{s}^{HAB}}{[H^+] + K_{s}^{HAB}[M]} + \frac{[H^+]}{K_{s}^{H_{2}AB^+}K_{s}^{AB^-} + K_{s}^{AB^-}K_{s}^{HAB} + K_{s}^{HAB}} \right) \]  \hfill (170)

Combining (168) and (170) gives

\[ [R]_{T}^2 = \frac{K_{sp}}{[AB]_{T}} \left( 1 + K_{s}^{R}[M] \right)^2 \left( 1 + \frac{[H^+]}{K_{a}^{H_{2}AB^+}} + \frac{K_{s}^{HAB}}{[H^+] + K_{s}^{HAB}[M]} + \frac{[H^+]}{K_{s}^{H_{2}AB^+}K_{s}^{AB^-} + K_{s}^{AB^-}K_{s}^{HAB} + K_{s}^{HAB}} \right) \]  \hfill (171)
where \([R]_T\) and \([AB]_T\) are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When \(K_s^{HAB} \gg K_s^{H,AB^+}\) and \(K_s^{HAB} \gg K_s^{AB^+}\), (171) can be simplified to

\[
[R]_T^2 = \frac{K_{sp}}{[AB]_T} \left(1 + K_s^R [M]\right)^2 \left(1 + \frac{[H^+]}{K_a^{H,AB^+}} + \frac{K_s^{HAB}}{[H^+] + K_s^{HAB}[M]}\right)
\]  

(172)

**Eutectic solution concentrations of drug and coformer of cocrystal \(R_2HAB\)**

At eutectic point \(E_1\), solid drug, cocrystal, and solution coexist in equilibrium.

\[
R_2HAB_{\text{solid}} + R_{\text{solid}} \rightleftharpoons R_{\text{aq}} + HAB_{\text{aq}}
\]  

(173)

\([R]_{eu,T}\) and \([AB]_{eu,T}\), the total concentrations of drug and coformer at the eutectic, are special solutions to Equation (172) when the following condition is satisfied

\[
[R]_T = S_{R,T}
\]  

(174)

where \(S_{R,T}\) is the solubility of \(R\) in the eutectic solution. When drug and solubilization are 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

\[
S_{R,T} = [R]_T = [R]_{aq} + [R]_{sm}
\]  

(175)

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

(176)

where \(S_{R,aq}\) is the drug aqueous solubility. Thus,

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

(177)

\[
[AB]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^2} \left(1 + \frac{[H^+]}{K_a^{H,AB^+}} + \frac{K_s^{HAB}}{[H^+] + K_s^{HAB}[M]}\right)
\]  

(178)

The eutectic concentrations in the absence of micellar solubilization are found when \([M] = 0\),

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

(179)
Combining Equations (177) to (180), $[\text{R}]_{\text{eu},T}$ and $[\text{AB}]_{\text{eu},T}$ at $[\text{H}^+] = [\text{H}^+]_T$ can be expressed in terms of $[\text{R}]_{\text{eu},aq}$ and $[\text{AB}]_{\text{eu},aq}$ at $[\text{H}^+] = [\text{H}^+]_{aq}$

$$[\text{R}]_{\text{eu},T} = [\text{R}]_{\text{eu},aq} \left( 1 + K_s^R [M] \right)$$  \hspace{1cm} (181)

$$[\text{AB}]_{\text{eu},T} = [\text{AB}]_{\text{eu},aq} \left( 1 + \frac{[\text{H}^+]_T}{K_a^{\text{H}_2\text{AB}^+}} + \frac{K_a^{\text{HAB}}}{[\text{H}^+]_T} + K_s^{\text{HAB}} [M] \right)$$ \hspace{1cm} (182)

E₂, the eutectic between solid coformer, cocrystal, and solution, is described by

$$\text{R}_2\text{HAB}_{\text{solid}} + \text{HAB}_{\text{solid}} \xrightleftharpoons{\text{R}_{\text{aq}} + \text{HAB}_{\text{aq}}} \hspace{1cm} (183)$$

$[\text{R}]_{\text{eu},T}$ and $[\text{AB}]_{\text{eu},T}$ are special solutions to Equation (172) when the following condition is satisfied

$$[\text{AB}]_T = S_{\text{AB},T}$$  \hspace{1cm} (184)

When drug and solubilization are mutually unaffected by coformer (and vice versa), then $S_{\text{AB},T}$ 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

$$S_{\text{AB},T} = [\text{AB}]_T = [\text{HAB}]_{aq} + [\text{H}_2\text{AB}^+]_{aq} + [\text{AB}^-]_{aq} + [\text{HAB}]_{cm}$$  \hspace{1cm} (185)

$$S_{\text{AB},T} = S_{\text{HAB},aq} \left( 1 + \frac{[\text{H}^+]_{aq}}{K_a^{\text{H}_2\text{AB}^+}} + \frac{K_a^{\text{HAB}}}{[\text{H}^+]_{aq}} + K_s^{\text{HAB}} [M] \right)$$  \hspace{1cm} (186)

where $S_{\text{HAB},aq}$ is the coformer intrinsic solubility. Solving for $[\text{R}]_{\text{eu},T}$ and $[\text{AB}]_{\text{eu},T}$ according to Equation (16) for E₂ yields the same expressions as (25) and (26).

**Eutectic constant $K_{\text{eu}}$ of cocrystal R₂HAB**

The eutectic constant $K_{\text{eu}}$ is given by
\[ K_{eu} = \frac{a_{AB,eu}}{a_{R,eu}} \]  

(187)

Assuming dilute conditions where concentrations replace activities,

\[ K_{eu} = \frac{[AB]_{eu,T}}{[R]_{eu,T}} \]  

(188)

Assuming there are no solution interactions aside from ionization and micellar solubilization, Equations (181) and (182) can be substituted into (149), which yields

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

(189)

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 RJHAB**

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 (33) when \( K_{eu,T} = 0.5 \) and solving for \([M]\),

\[ 2K_{eu,aq} \left( 1 + \frac{[H^+]_T + K_a^{HAB} [H^+]_T}{K_s^{HAB} [H^+]_T} \right) - 1 \]

\[ [M]_{CSC} = \frac{2K_{eu,aq} K_a^{HAB}}{K_s^R - \left( 1 + \frac{[H^+]_{aq}}{K_a^{HAB}} \right)} \]  

(190)

\([M]_{CSC}\) is the micellar surfactant concentration associated with CSC. The CSC is
\[
\text{CSC} = \frac{2K_{eu,aq} \left( 1 + \frac{[H^+]_T + K_a^\text{HAB}}{K_s^\text{HAB} + [H^+]_T} \right) - 1}{K_s^R - \frac{2K_{eu,aq} K_a^\text{HAB}}{K_s^\text{HAB} + [H^+]_T}} + \text{CMC}
\]

(191)
Table 1. CBZD and coformer solubilities (±SE) measured as a function of SLS concentration, from which $K_s$ values were calculated.

<table>
<thead>
<tr>
<th>Cocrystal component</th>
<th>[SLS] (mM)</th>
<th>Concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>8</td>
<td>1.00±0.01</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.86±0.05</td>
</tr>
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<td></td>
<td>15</td>
<td>3.58±0.12</td>
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<td></td>
<td>17</td>
<td>3.97±0.05</td>
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<td></td>
<td>20</td>
<td>5.10±0.03</td>
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*4ABA and SUC did not exhibit significant solubilization by SLS ($K_s < 0.010$).