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

$$\mathrm{RHA_{solid}} \overset{K_{sp}}{\rightleftharpoons} \mathrm{R_{aq} + HA_{aq}} \tag{1}$$

$$\mathrm{HA_{aq}} \overset{K_a^{HA}}{\rightleftharpoons} \mathrm{A^-{}_{aq} + H^+{}_{aq}} \tag{2}$$

$$\mathrm{R_{aq} + M} \overset{K_s^{R}}{\rightleftharpoons} \mathrm{R_m} \tag{3}$$

$$\mathrm{HA_{aq} + M} \overset{K_s^{HA}}{\rightleftharpoons} \mathrm{HA_m} \tag{4}$$

$$\mathrm{A^-{}_{aq} + M} \overset{K_s^{A^-}}{\rightleftharpoons} \mathrm{A^-{}_m} \tag{5}$$

Associated equilibrium constants are given by

$$K_{sp} = [\mathrm{R}]_{aq}[\mathrm{HA}]_{aq} \tag{6}$$

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

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

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

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

Solubility of cocrystal RHA

Mass balance on R is given by

$$[\mathrm{R}]_T = [\mathrm{R}]_{aq} + [\mathrm{R}]_m \tag{11}$$

Substituting (6) and (8) into (11) gives

$$[\mathrm{R}]_\mathrm{T} = \frac{\mathrm{K}_\mathrm{sp}}{[\mathrm{HA}]_\mathrm{aq}}\left(1+\mathrm{K}_\mathrm{s}^\mathrm{R}[\mathrm{M}]\right) \tag{12}$$

Mass balance on A is given by

$$[\mathrm{A}]_\mathrm{T} = [\mathrm{HA}]_\mathrm{aq} + [\mathrm{A}^-]_\mathrm{aq} + [\mathrm{HA}]_\mathrm{m} + [\mathrm{A}^-]_\mathrm{m} \tag{13}$$

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

$$[\mathrm{A}]_\mathrm{T} = [\mathrm{HA}]_\mathrm{aq}\left(1+\frac{\mathrm{K}_\mathrm{a}^\mathrm{HA}}{[\mathrm{H}^+]}+\mathrm{K}_\mathrm{s}^\mathrm{HA}[\mathrm{M}]+\frac{\mathrm{K}_\mathrm{a}}{[\mathrm{H}^+]}\mathrm{K}_\mathrm{s}^{\mathrm{A}^-}[\mathrm{M}]\right) \tag{14}$$

Combining (12) and (14) gives the

$$[\mathrm{R}]_\mathrm{T} = \frac{\mathrm{K}_\mathrm{sp}}{[\mathrm{A}]_\mathrm{T}}\left(1+\mathrm{K}_\mathrm{s}^\mathrm{R}[\mathrm{M}]\right)\left(1+\frac{\mathrm{K}_\mathrm{a}^\mathrm{HA}}{[\mathrm{H}^+]}+\mathrm{K}_\mathrm{s}^\mathrm{HA}[\mathrm{M}]+\frac{\mathrm{K}_\mathrm{a}}{[\mathrm{H}^+]}\mathrm{K}_\mathrm{s}^{\mathrm{A}^-}[\mathrm{M}]\right) \tag{15}$$

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

$$[\mathrm{R}]_\mathrm{T} = \frac{\mathrm{K}_\mathrm{sp}}{[\mathrm{A}]_\mathrm{T}}\left(1+\mathrm{K}_\mathrm{s}^\mathrm{R}[\mathrm{M}]\right)\left(1+\frac{\mathrm{K}_\mathrm{a}^\mathrm{HA}}{[\mathrm{H}^+]}+\mathrm{K}_\mathrm{s}^\mathrm{HA}[\mathrm{M}]\right) \tag{16}$$

Eutectic solution concentrations of drug and coformer of cocrystal RHA

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

$$\mathrm{RHA}_\mathrm{solid} + \mathrm{R}_\mathrm{solid} \rightleftharpoons \mathrm{R}_\mathrm{aq} + \mathrm{HA}_\mathrm{aq} \tag{17}$$

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

$$[\mathrm{R}]_\mathrm{T} = \mathrm{S}_\mathrm{R,T} \tag{18}$$

where $\mathrm{S}_\mathrm{R,T}$ is the solubility of R in the eutectic solution. When drug and solubilization are mutually unaffected by coformer (and vice versa), then $\mathrm{S}_\mathrm{R,T}$ is equivalent to the drug solubility in micellar solution (no coformer), which is given by

$$\mathrm{S}_\mathrm{R,T} = [\mathrm{R}]_\mathrm{T} = [\mathrm{R}]_\mathrm{aq} + [\mathrm{R}]_\mathrm{m} \tag{19}$$

$$S_{R,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{20}$$

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

$$[R]_{eu,T} = S_{R,aq}\left(1 + K_s^R[M]\right) \tag{21}$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]} + K_s^{HA}[M]\right) \tag{22}$$

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

$$[R]_{eu,aq} = S_{R,aq} \tag{23}$$

$$[A]_{eu,aq} = \frac{K_{sp}}{S_{R,aq}}\left(1 + \frac{K_a^{HA}}{[H^+]_{aq}}\right) \tag{24}$$

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 $[H^+] = [H^+]_{aq}$.

$$[R]_{eu,T} = [R]_{eu,aq}\left(1 + K_s^R[M]\right) \tag{25}$$

$$[A]_{eu,T} = [A]_{eu,aq}\left(\frac{1 + \dfrac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) \tag{26}$$

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

$$RHA_{solid} + HA_{solid} \rightleftharpoons R_{aq} + HA_{aq} \tag{27}$$

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

$$[A]_T = S_{A,T} \tag{28}$$

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

$$S_{A,T} = [A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m \tag{29}$$

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

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

$$K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \tag{31}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \tag{32}$$

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

$$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1 + K_s^R[M]}\right)\left(\frac{1 + \frac{K_a^{HA}}{[H^+]_T} + K_s^{HA}[M]}{1 + \frac{K_a^{HA}}{[H^+]_{aq}}}\right) \tag{33}$$

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],

$$[\mathrm{M}]_{\mathrm{CSC}} = \frac{\mathrm{K}_{\mathrm{eu,aq}}\left(\dfrac{1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{T}}}}{1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{aq}}}}\right)-1}{\mathrm{K}_{\mathrm{s}}^{\mathrm{R}} - \dfrac{\mathrm{K}_{\mathrm{eu,aq}}\mathrm{K}_{\mathrm{s}}^{\mathrm{HA}}}{\left(1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{aq}}}\right)}} \qquad (34)$$

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

$$\mathrm{CSC} = \frac{\mathrm{K}_{\mathrm{eu,aq}}\left(\dfrac{1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{T}}}}{1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{aq}}}}\right)-1}{\mathrm{K}_{\mathrm{s}}^{\mathrm{R}} - \dfrac{\mathrm{K}_{\mathrm{eu,aq}}\mathrm{K}_{\mathrm{s}}^{\mathrm{HA}}}{\left(1+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]_{\mathrm{aq}}}\right)}} + \mathrm{CMC} \qquad (35)$$

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

Relevant equilibria are given by

$$\mathrm{HXHA_{solid}} \xrightleftharpoons{K_{sp}} \mathrm{HX_{aq}} + \mathrm{HA_{aq}} \tag{36}$$

$$\mathrm{HX_{aq}} \xrightleftharpoons{K_a^{HX}} \mathrm{X^-{}_{aq}} + \mathrm{H^+{}_{aq}} \tag{37}$$

$$\mathrm{HA_{aq}} \xrightleftharpoons{K_a^{HA}} \mathrm{A^-{}_{aq}} + \mathrm{H^+{}_{aq}} \tag{38}$$

$$\mathrm{HX_{aq}} + \mathrm{M} \xrightleftharpoons{K_s^{HX}} \mathrm{HX_m} \tag{39}$$

$$\mathrm{HA_{aq}} + \mathrm{M} \xrightleftharpoons{K_s^{HA}} \mathrm{HA_m} \tag{40}$$

$$\mathrm{X^-{}_{aq}} + \mathrm{M} \xrightleftharpoons{K_s^{X^-}} \mathrm{X^-{}_m} \tag{41}$$

$$\mathrm{A^-{}_{aq}} + \mathrm{M} \xrightleftharpoons{K_s^{A^-}} \mathrm{A^-{}_m} \tag{42}$$

Associated equilibrium constants are given by

$$K_{sp} = [\mathrm{HX}]_{aq}[\mathrm{HA}]_{aq} \tag{43}$$

$$K_a^{HX} = \frac{[\mathrm{X^-}]_{aq}[\mathrm{H^+}]_{aq}}{[\mathrm{HX}]_{aq}} \tag{44}$$

$$K_a^{HA} = \frac{[\mathrm{A^-}]_{aq}[\mathrm{H^+}]_{aq}}{[\mathrm{HA}]_{aq}} \tag{45}$$

$$K_s^{HX} = \frac{[\mathrm{HX}]_m}{[\mathrm{HX}]_{aq}[\mathrm{M}]} \tag{46}$$

$$K_s^{HA} = \frac{[\mathrm{HA}]_m}{[\mathrm{HA}]_{aq}[\mathrm{M}]} \tag{47}$$

$$K_s^{X^-} = \frac{[X^-]_m}{[X^-]_{aq}[M]} \tag{48}$$

$$K_s^{A^-} = \frac{[A^-]_m}{[A^-]_{aq}[M]} \tag{49}$$

Solubility of cocrystal HXHA

Mass balance on X is given by

$$[X]_T = [HX]_{aq} + [X^-]_{aq} + [HX]_m + [X^-]_m \tag{50}$$

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

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

Mass balance on A is given by

$$[A]_T = [HA]_{aq} + [A^-]_{aq} + [HA]_m + [A^-]_m \tag{52}$$

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

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

Combining (51) and (53) gives

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

where $[X]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^{HX} >> K_s^{X-}$ and $K_s^{HA} >> K_s^{A-}$, then Equation (54) can be simplified to

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

Eutectic solution concentrations of drug and coformer of cocrystal HXHA

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

$$\mathrm{HXHA}_{\mathrm{solid}} + \mathrm{HX}_{\mathrm{solid}} \rightleftharpoons \mathrm{HX}_{\mathrm{aq}} + \mathrm{HA}_{\mathrm{aq}} \qquad (56)$$

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

$$[\mathrm{X}]_{\mathrm{T}} = \mathrm{S}_{\mathrm{X,T}} \qquad (57)$$

where $\mathrm{S}_{\mathrm{X,T}}$ is the solubility of X at the eutectic. When drug and solubilization are mutually unaffected by coformer (and vice versa), then $\mathrm{S}_{\mathrm{X,T}}$ 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

$$\mathrm{S}_{\mathrm{X,T}} = [\mathrm{X}]_{\mathrm{T}} = [\mathrm{HX}]_{\mathrm{aq}} + [\mathrm{X}^-]_{\mathrm{aq}} + [\mathrm{HX}]_{\mathrm{m}} \qquad (58)$$

$$\mathrm{S}_{\mathrm{X,T}} = \mathrm{S}_{\mathrm{HX,aq}}\left(1 + \frac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HX}}}{[\mathrm{H}^+]} + \mathrm{K}_{\mathrm{s}}^{\mathrm{HX}}[\mathrm{M}]\right) \qquad (59)$$

where $\mathrm{S}_{\mathrm{HX,aq}}$ is the drug instrinsic solubility. Thus,

$$[\mathrm{X}]_{\mathrm{eu,T}} = \mathrm{S}_{\mathrm{HX,aq}}\left(1 + \frac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HX}}}{[\mathrm{H}^+]} + \mathrm{K}_{\mathrm{s}}^{\mathrm{HX}}[\mathrm{M}]\right) \qquad (60)$$

$$[\mathrm{A}]_{\mathrm{eu,T}} = \frac{\mathrm{K}_{\mathrm{sp}}}{\mathrm{S}_{\mathrm{HX,aq}}}\left(1 + \frac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]} + \mathrm{K}_{\mathrm{s}}^{\mathrm{HA}}[\mathrm{M}]\right) \qquad (61)$$

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

$$[\mathrm{X}]_{\mathrm{eu,aq}} = \mathrm{S}_{\mathrm{HX,aq}}\left(1 + \frac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HX}}}{[\mathrm{H}^+]}\right) \qquad (62)$$

$$[\mathrm{A}]_{\mathrm{eu,aq}} = \frac{\mathrm{K}_{\mathrm{sp}}}{\mathrm{S}_{\mathrm{HX,aq}}}\left(1 + \frac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HA}}}{[\mathrm{H}^+]}\right) \qquad (63)$$

Combining Equations (60) to (63), $[\mathrm{X}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ at $[\mathrm{H}^+] = [\mathrm{H}^+]_{\mathrm{T}}$ can be expressed in terms of $[\mathrm{X}]_{\mathrm{eu,aq}}$ and $[\mathrm{A}]_{\mathrm{eu,aq}}$ at $[\mathrm{H}^+] = [\mathrm{H}^+]_{\mathrm{aq}}$.

$$[\mathrm{X}]_{\mathrm{eu,T}} = [\mathrm{X}]_{\mathrm{eu,aq}} \left(\frac{1 + \frac{K_a^{HX}}{[\mathrm{H}^+]_T} + K_s^{HX}[\mathrm{M}]}{1 + \frac{K_a^{HX}}{[\mathrm{H}^+]_{aq}}} \right) \tag{64}$$

$$[\mathrm{A}]_{\mathrm{eu,T}} = [\mathrm{A}]_{\mathrm{eu,aq}} \left(\frac{1 + \frac{K_a^{HA}}{[\mathrm{H}^+]_T} + K_s^{HA}[\mathrm{M}]}{1 + \frac{K_a^{HA}}{[\mathrm{H}^+]_{aq}}} \right) \tag{65}$$

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

$$\mathrm{HXHA}_{\mathrm{solid}} + \mathrm{HA}_{\mathrm{solid}} \rightleftharpoons \mathrm{HX}_{\mathrm{aq}} + \mathrm{HA}_{\mathrm{aq}} \tag{66}$$

At E_2, $[\mathrm{X}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ are special solutions to Equation (55) when the following condition is satisfied

$$[\mathrm{A}]_T = S_{A,T} \tag{67}$$

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

$$S_{A,T} = [\mathrm{A}]_T = [\mathrm{HA}]_{aq} + [\mathrm{A}^-]_{aq} + [\mathrm{HA}]_m \tag{68}$$

$$S_{A,T} = S_{HA,aq} \left(1 + \frac{K_a^{HA}}{[\mathrm{H}^+]} + K_s^{HA}[\mathrm{M}] \right) \tag{69}$$

where $S_{HA,aq}$ is the coformer intrinsic solubility. Solving for $[\mathrm{X}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ according to Equation (55) for E_2 yields the same expressions as (64) and (65).

Eutectic constant K_{eu} of cocrystal HXHA

The eutectic constant K_{eu} is given by

$$K_{eu} = \frac{a_{A,eu}}{a_{X,eu}} \tag{70}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[X]_{eu,T}} \tag{71}$$

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

$$K_{eu,T} = K_{eu,aq}\left(\frac{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}{1+\dfrac{K_a^{HX}}{[H^+]_T}+K_s^{HX}[M]}\right)\left(\frac{1+\dfrac{K_a^{HA}}{[H^+]_T}+K_s^{HA}[M]}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right) \tag{72}$$

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],

$$[M]_{CSC} = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_T}}{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}\right)}{\dfrac{K_s^{HX}}{\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)}-\dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)}} \tag{73}$$

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

$$\mathrm{CSC} = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\dfrac{1+\dfrac{K_a^{HX}}{[H^+]_T}}{1+\dfrac{K_a^{HX}}{[H^+]_{aq}}}\right)}{\dfrac{K_s^{HX}}{\left(1+\dfrac{K_a^{HX}}{[H^+]}\right)}-\dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]}\right)}}+\mathrm{CMC} \tag{74}$$

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

Relevant equilibria are given by

$$BHA_{solid} \xrightleftharpoons{K_{sp}} B_{aq} + HA_{aq} \tag{75}$$

$$BH^+_{aq} \xrightleftharpoons{K_a^B} B_{aq} + H^+_{aq} \tag{76}$$

$$HA_{aq} \xrightleftharpoons{K_a^{HA}} A^-_{aq} + H^+_{aq} \tag{77}$$

$$B_{aq} + M \xrightleftharpoons{K_s^B} B_m \tag{78}$$

$$HA_{aq} + M \xrightleftharpoons{K_s^{HA}} HA_m \tag{79}$$

$$BH^+_{aq} + M \xrightleftharpoons{K_s^{BH^+}} BH^+_m \tag{80}$$

$$A^-_{aq} + M \xrightleftharpoons{K_s^{A^-}} A^-_m \tag{81}$$

Associated equilibrium constants are given by

$$K_{sp} = [B]_{aq}[HA]_{aq} \tag{82}$$

$$K_a^B = \frac{[B]_{aq}[H^+]_{aq}}{[BH^+]_{aq}} \tag{83}$$

$$\mathrm{K_a^{HA}} = \frac{[\mathrm{A^-}]_{\mathrm{aq}}[\mathrm{H^+}]_{\mathrm{aq}}}{[\mathrm{HA}]_{\mathrm{aq}}} \tag{84}$$

$$\mathrm{K_s^{B}} = \frac{[\mathrm{B}]_{\mathrm{m}}}{[\mathrm{B}]_{\mathrm{aq}}[\mathrm{M}]} \tag{85}$$

$$\mathrm{K_s^{HA}} = \frac{[\mathrm{HA}]_{\mathrm{m}}}{[\mathrm{HA}]_{\mathrm{aq}}[\mathrm{M}]} \tag{86}$$

$$\mathrm{K_s^{BH^+}} = \frac{[\mathrm{BH^+}]_{\mathrm{m}}}{[\mathrm{B}]_{\mathrm{aq}}[\mathrm{M}]} \tag{87}$$

$$\mathrm{K_s^{A^-}} = \frac{[\mathrm{A^-}]_{\mathrm{m}}}{[\mathrm{A^-}]_{\mathrm{aq}}[\mathrm{M}]} \tag{88}$$

Solubility of cocrystal BHA

Mass balance on B is given by

$$[\mathrm{B}]_{\mathrm{T}} = [\mathrm{B}]_{\mathrm{aq}} + [\mathrm{BH^+}]_{\mathrm{aq}} + [\mathrm{B}]_{\mathrm{m}} + [\mathrm{BH^+}]_{\mathrm{m}} \tag{89}$$

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

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

Mass balance on A is given by

$$[\mathrm{A}]_{\mathrm{T}} = [\mathrm{HA}]_{\mathrm{aq}} + [\mathrm{A^-}]_{\mathrm{aq}} + [\mathrm{HA}]_{\mathrm{m}} + [\mathrm{A^-}]_{\mathrm{m}} \tag{91}$$

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

$$[\mathrm{A}]_{\mathrm{T}} = [\mathrm{HA}]_{\mathrm{aq}}\left(1 + \frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]} + \mathrm{K_s^{HA}}[\mathrm{M}] + \frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]}\mathrm{K_s^{A^-}}[\mathrm{M}]\right) \tag{92}$$

Combining (90) and (92) gives

$$[\mathrm{B}]_{\mathrm{T}} = \frac{\mathrm{K_{sp}}}{[\mathrm{A}]_{\mathrm{T}}}\left(1 + \frac{[\mathrm{H^+}]}{\mathrm{K_a^B}} + \mathrm{K_s^B}[\mathrm{M}] + \frac{[\mathrm{H^+}]}{\mathrm{K_a^B}}\mathrm{K_s^{BH^+}}[\mathrm{M}]\right)\left(1 + \frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]} + \mathrm{K_s^{HA}}[\mathrm{M}] + \frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]}\mathrm{K_s^{A^-}}[\mathrm{M}]\right) \tag{93}$$

Where $[B]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^B >> K_s^{BH+}$ and $K_s^{HA} >> K_s^{A-}$, then Equation (54) can be simplified to

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

Eutectic solution concentrations of drug and coformer of cocrystal BHA

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

$$BHA_{solid} + B_{solid} \rightleftharpoons B_{aq} + HA_{aq} \qquad (95)$$

$[B]_{eu,T}$ 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

$$[B]_T = S_{B,T} \qquad (96)$$

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

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

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

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

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

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

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

$$[B]_{eu,aq} = S_{B,aq}\left(1 + \frac{[H^+]}{K_a^B}\right) \qquad (101)$$

$$[\mathrm{A}]_{\mathrm{eu,aq}} = \frac{\mathrm{K_{sp}}}{\mathrm{S_{B,aq}}}\left(1+\frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]}\right) \tag{102}$$

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

$$[\mathrm{B}]_{\mathrm{eu,T}} = [\mathrm{B}]_{\mathrm{eu,aq}}\left(\frac{1+\dfrac{[\mathrm{H^+}]_{\mathrm{T}}}{\mathrm{K_a^B}}+\mathrm{K_s^B}[\mathrm{M}]}{1+\dfrac{[\mathrm{H^+}]_{\mathrm{aq}}}{\mathrm{K_a^B}}}\right) \tag{103}$$

$$[\mathrm{A}]_{\mathrm{eu,T}} = [\mathrm{A}]_{\mathrm{eu,aq}}\left(\frac{1+\dfrac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]_{\mathrm{T}}}+\mathrm{K_s^{HA}}[\mathrm{M}]}{1+\dfrac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]_{\mathrm{aq}}}}\right) \tag{104}$$

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

$$\mathrm{BHA_{solid}} + \mathrm{HA_{solid}} \rightleftharpoons \mathrm{B_{aq}} + \mathrm{HA_{aq}} \tag{105}$$

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

$$[\mathrm{A}]_{\mathrm{T}} = \mathrm{S_{A,T}} \tag{106}$$

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

$$\mathrm{S_{A,T}} = [\mathrm{A}]_{\mathrm{T}} = [\mathrm{HA}]_{\mathrm{aq}} + [\mathrm{A^-}]_{\mathrm{aq}} + [\mathrm{HA}]_{\mathrm{m}} \tag{107}$$

$$\mathrm{S_{A,T}} = \mathrm{S_{HA,aq}}\left(1+\frac{\mathrm{K_a^{HA}}}{[\mathrm{H^+}]}+\mathrm{K_s^{HA}}[\mathrm{M}]\right) \tag{108}$$

where $\mathrm{S_{HA,aq}}$ is the coformer intrinsic solubility. Solving for $[\mathrm{B}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ according to Equation (55) for E_2 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

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

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

$$[M]_{CSC} = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\dfrac{1+\dfrac{[H^+]_T}{K_a^B}}{1+\dfrac{[H^+]_{aq}}{K_a^B}}\right)}{\dfrac{K_s^B}{\left(1+\dfrac{[H^+]_{aq}}{K_a^B}\right)}-\dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}} \tag{112}$$

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

$$\mathrm{CSC} = \frac{K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{HA}}{[H^+]_T}}{1+\dfrac{K_a^{HA}}{[H^+]_{aq}}}\right)-\left(\dfrac{1+\dfrac{[H^+]_T}{K_a^{B}}}{1+\dfrac{[H^+]_{aq}}{K_a^{B}}}\right)}{\dfrac{K_s^{B}}{\left(1+\dfrac{[H^+]_{aq}}{K_a^{B}}\right)}-\dfrac{K_{eu,aq}K_s^{HA}}{\left(1+\dfrac{K_a^{HA}}{[H^+]_{aq}}\right)}}+\mathrm{CMC} \tag{113}$$

R_2H_2A (2:1 monoprotic weakly basic drug R, diprotic weakly acidic coformer H_2A)

Relevant equilibria are given by

$$R_2H_2A_{solid} \xrightleftharpoons{K_{sp}} 2R_{aq} + H_2A_{aq} \tag{114}$$

$$H_2A_{aq} \xrightleftharpoons{K_a^{H_2A}} HA^-{}_{aq} + H^+{}_{aq} \tag{115}$$

$$HA^-{}_{aq} \xrightleftharpoons{K_a^{HA^-}} A^{2-}{}_{aq} + H^+{}_{aq} \tag{116}$$

$$R_{aq} + M \xrightleftharpoons{K_s^{R}} R_m \tag{117}$$

$$H_2A_{aq} + M \xrightleftharpoons{K_s^{H_2A}} H_2A_m \tag{118}$$

$$HA^-{}_{aq} + M \xrightleftharpoons{K_s^{HA^-}} HA^-{}_m \tag{119}$$

$$A^{2-}{}_{aq} + M \xrightleftharpoons{K_s^{A^{2-}}} A^{2-}{}_m \tag{120}$$

Associated equilibrium constants are given by

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

$$K_a^{H_2A} = \frac{[HA^-]_{aq}[H^+]_{aq}}{[H_2A]_{aq}} \tag{122}$$

$$K_a^{HA^-} = \frac{[A^{2-}]_{aq}[H^+]_{aq}}{[HA^-]_{aq}} \tag{123}$$

$$K_s^{R} = \frac{[R]_m}{[R]_{aq}[M]} \tag{124}$$

$$K_s^{H_2A} = \frac{[H_2A]_m}{[H_2A]_{aq}[M]} \tag{125}$$

$$K_s^{HA^-} = \frac{[HA^-]_m}{[HA^-]_{aq}[M]} \tag{126}$$

$$K_s^{A^{2-}} = \frac{[A^{2-}]_m}{[A^{2-}]_{aq}[M]} \tag{127}$$

Solubility of cocrystal R_2H_2A

Mass balance on R is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{128}$$

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

$$[R]_T^{\ 2} = \frac{K_{sp}}{[H_2A]_{aq}}\left(1 + K_s^R[M]\right)^2 \tag{129}$$

Mass balance on A is given by

$$[A]_T = [H_2A]_{aq} + [HA^-]_{aq} + [A^{2-}]_{aq} + [H_2A]_m + [HA^-]_m + [A^{2-}]_m \tag{130}$$

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

$$[A]_T = [H_2A]_{aq}\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M] + \frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M] + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \tag{131}$$

Combining (129) and (131) gives

$$[R]_T^{\ 2} = \frac{K_{sp}}{[A]_T}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{K_a^{H_2A}}{[H^+]} + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2} + K_s^{H_2A}[M] + \frac{K_a^{H_2A}}{[H^+]}K_s^{HA^-}[M] + \frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}K_s^{A^{2-}}[M]\right) \tag{132}$$

where $[R]_T$ and $[A]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^{H_2A} >> K_s^{HA^-}$ and $K_s^{H_2A} >> K_s^{A^{2-}}$, (132) can be simplified to

$$[R]_T^{\,2} = \frac{K_{sp}}{[A]_T}\left(1+K_s^R[M]\right)^2\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]\right) \qquad (133)$$

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.

$$R_2H_2A_{solid} + R_{solid} \rightleftharpoons R_{aq} + HA_{aq} \qquad (134)$$

$[R]_{eu,T}$ 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

$$[R]_T = S_{R,T} \qquad (135)$$

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

$$S_{R,T} = [R]_T = [R]_{aq} + [R]_m \qquad (136)$$

$$S_{R,T} = S_{R,aq}\left(1+K_s^R[M]\right) \qquad (137)$$

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

$$[R]_{eu,T} = S_{R,aq}\left(1+K_s^R[M]\right) \qquad (138)$$

$$[A]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^{\;2}}\left(1+\frac{K_a^{H_2A}}{[H^+]}+\frac{K_a^{H_2A}K_a^{HA^-}}{[H^+]^2}+K_s^{H_2A}[M]\right) \qquad (139)$$

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

$$[R]_{eu,aq} = S_{R,aq} \qquad (140)$$

$$[\mathrm{A}]_{\mathrm{eu,aq}} = \frac{\mathrm{K_{sp}}}{\mathrm{S_{R,aq}}^2}\left(1+\frac{\mathrm{K_a^{H_2A}}}{[\mathrm{H^+}]}+\frac{\mathrm{K_a^{H_2A}K_a^{HA^-}}}{[\mathrm{H^+}]^2}\right) \tag{141}$$

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

$$[\mathrm{R}]_{\mathrm{eu,T}} = [\mathrm{R}]_{\mathrm{eu,aq}}\left(1+\mathrm{K_s^R}[\mathrm{M}]\right) \tag{142}$$

$$[\mathrm{A}]_{\mathrm{eu,T}} = [\mathrm{A}]_{\mathrm{eu,aq}}\left(\frac{1+\dfrac{\mathrm{K_a^{H_2A}}}{[\mathrm{H^+}]_{\mathrm{T}}}+\dfrac{\mathrm{K_a^{H_2A}K_a^{HA^-}}}{[\mathrm{H^+}]_{\mathrm{T}}^2}+\mathrm{K_s^{H_2A}}[\mathrm{M}]}{1+\dfrac{\mathrm{K_a^{H_2A}}}{[\mathrm{H^+}]_{\mathrm{aq}}}+\dfrac{\mathrm{K_a^{H_2A}K_a^{HA^-}}}{[\mathrm{H^+}]_{\mathrm{aq}}^2}}\right) \tag{143}$$

$\mathrm{E_2}$, the eutectic between solid coformer, cocrystal, and solution, is described by

$$\mathrm{R_2H_2A_{solid}} + \mathrm{HA_{solid}} \rightleftharpoons \mathrm{R_{aq}} + \mathrm{HA_{aq}} \tag{144}$$

At $\mathrm{E_2}$, $[\mathrm{R}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ are special solutions to Equation (133) when the following condition is satisfied

$$[\mathrm{A}]_{\mathrm{T}} = \mathrm{S_{A,T}} \tag{145}$$

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

$$\mathrm{S_{A,T}} = [\mathrm{A}]_{\mathrm{T}} = [\mathrm{H_2A}]_{\mathrm{aq}} + [\mathrm{HA^-}]_{\mathrm{aq}} + [\mathrm{A^{2-}}]_{\mathrm{aq}} + [\mathrm{H_2A}]_{\mathrm{m}} \tag{146}$$

$$\mathrm{S_{A,T}} = \mathrm{S_{HA,aq}}\left(1+\frac{\mathrm{K_a^{H_2A}}}{[\mathrm{H^+}]}+\frac{\mathrm{K_a^{H_2A}K_a^{HA^-}}}{[\mathrm{H^+}]^2}+\mathrm{K_s^{H_2A}}[\mathrm{M}]\right) \tag{147}$$

where $\mathrm{S_{H_2A,aq}}$ is the coformer intrinsic solubility. Solving for $[\mathrm{R}]_{\mathrm{eu,T}}$ and $[\mathrm{A}]_{\mathrm{eu,T}}$ according to Equation (133) for $\mathrm{E_2}$ yields the same expressions as (142) and (143).

Eutectic constant K_{eu} of cocrystal R_2H_2A

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

$$K_{eu} = \frac{a_{A,eu}}{a_{R,eu}} \tag{148}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[A]_{eu,T}}{[R]_{eu,T}} \tag{149}$$

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

$$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1+K_s^R[M]}\right)\left(\frac{1+\dfrac{K_a^{H_2A}}{[H^+]_T}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^{\,2}}+K_s^{H_2A}[M]}{1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}}\right) \tag{150}$$

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],

$$[M]_{CSC} = \frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{H_2A}}{[H^+]_T}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T^{\,2}}}{1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}}\right)-1}{K_s^R-\dfrac{2K_{eu,aq}K_s^{H_2A}}{\left(1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}^{\,2}}\right)}} \tag{151}$$

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

$$\mathrm{CSC}=\frac{2K_{eu,aq}\left(\dfrac{1+\dfrac{K_a^{H_2A}}{[H^+]_T}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_T{}^2}}{1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}{}^2}}\right)-1}{K_s^R-\dfrac{2K_{eu,aq}K_s^{H_2A}}{\left(1+\dfrac{K_a^{H_2A}}{[H^+]_{aq}}+\dfrac{K_a^{H_2A}K_a^{HA^-}}{[H^+]_{aq}{}^2}\right)}}+\mathrm{CMC} \tag{152}$$

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

Relevant equilibria are given by

$$R_2HAB_{solid}\overset{K_{sp}}{\rightleftharpoons}2R_{aq}+HAB_{aq} \tag{153}$$

$$H_2AB^+{}_{aq}\overset{K_a^{H_2AB^+}}{\rightleftharpoons}HAB_{aq}+H^+{}_{aq} \tag{154}$$

$$HAB_{aq}\overset{K_a^{HAB}}{\rightleftharpoons}AB^-{}_{aq}+H^+{}_{aq} \tag{155}$$

$$R_{aq}+M\overset{K_s^R}{\rightleftharpoons}R_m \tag{156}$$

$$H_2AB^+{}_{aq}+M\overset{K_s^{H_2AB^+}}{\rightleftharpoons}H_2AB^+{}_m \tag{157}$$

$$HAB_{aq}+M\overset{K_s^{HAB}}{\rightleftharpoons}HAB_m \tag{158}$$

$$AB^-{}_{aq}+M\overset{K_s^{AB^-}}{\rightleftharpoons}AB^-{}_m \tag{159}$$

Associated equilibrium constants are given by

$$K_{sp}=[R]_{aq}{}^2[HAB]_{aq} \tag{160}$$

$$K_a^{H_2AB^+}=\frac{[HAB]_{aq}[H^+]_{aq}}{[H_2AB^+]_{aq}} \tag{161}$$

$$K_a^{HAB} = \frac{[AB^-]_{aq}[H^+]_{aq}}{[HAB]_{aq}} \tag{162}$$

$$K_s^{R} = \frac{[R]_m}{[R]_{aq}[M]} \tag{163}$$

$$K_s^{H_2AB^+} = \frac{[H_2AB^+]_m}{[H_2AB^+]_{aq}[M]} \tag{164}$$

$$K_s^{HAB} = \frac{[HAB]_m}{[HAB]_{aq}[M]} \tag{165}$$

$$K_s^{AB^-} = \frac{[AB^-]_m}{[AB^-]_{aq}[M]} \tag{166}$$

Solubility of cocrystal R_2HAB

Mass balance on B is given by

$$[R]_T = [R]_{aq} + [R]_m \tag{167}$$

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

$$[R]_T{}^2 = \frac{K_{sp}}{[HAB]_{aq}}\left(1 + K_s^R[M]\right)^2 \tag{168}$$

Mass balance on AB is given by

$$[AB]_T = [HAB]_{aq} + [H_2AB^+]_{aq} + [AB^-]_{aq} + [HAB]_m + [H_2AB^+]_m + [AB^-]_m \tag{169}$$

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

$$[AB]_T = [HAB]_{aq}\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{170}$$

Combining (168) and (170) gives

$$[R]_T{}^2 = \frac{K_{sp}}{[AB]_T}\left(1 + K_s^R[M]\right)^2\left(1 + \frac{[H^+]}{K_a^{H_2AB^+}} + \frac{K_a^{HAB}}{[H^+]} + K_s^{HAB}[M] + \frac{[H^+]}{K_a^{H_2AB^+}}K_s^{H_2AB^+}[M] + \frac{K_a^{HAB}}{[H^+]}K_s^{AB^-}[M]\right) \tag{171}$$

where $[R]_T$ and $[AB]_T$ are the total concentrations of drug and coformer when cocrystal and solution are in equilibrium. When $K_s^{HAB} >> K_s^{H_2AB^+}$ and $K_s^{HAB} >> K_s^{AB^-}$, (171) can be simplified to

$$[R]_T^{\ 2} = \frac{K_{sp}}{[AB]_T}\left(1+K_s^R[M]\right)^2\left(1+\frac{[H^+]}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]}+K_s^{HAB}[M]\right) \qquad (172)$$

Eutectic solution concentrations of drug and coformer of cocrystal R_2HAB

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

$$R_2HAB_{solid} + R_{solid} \rightleftharpoons R_{aq} + HAB_{aq} \qquad (173)$$

$[R]_{eu,T}$ 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

$$[R]_T = S_{R,T} \qquad (174)$$

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

$$S_{R,T} = [R]_T = [R]_{aq} + [R]_m \qquad (175)$$

$$S_{R,T} = S_{R,aq}\left(1+K_s^R[M]\right) \qquad (176)$$

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

$$[R]_{eu,T} = S_{R,aq}\left(1+K_s^R[M]\right) \qquad (177)$$

$$[AB]_{eu,T} = \frac{K_{sp}}{S_{R,aq}^{\ \ 2}}\left(1+\frac{[H^+]}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]}+K_s^{HAB}[M]\right) \qquad (178)$$

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

$$[R]_{eu,aq} = S_{R,aq} \qquad (179)$$

$$[\mathrm{AB}]_{\mathrm{eu,aq}} = \frac{\mathrm{K_{sp}}}{\mathrm{S_{R,aq}}^2}\left(1 + \frac{[\mathrm{H^+}]}{\mathrm{K_a^{H_2AB^+}}} + \frac{\mathrm{K_a^{HAB}}}{[\mathrm{H^+}]}\right) \tag{180}$$

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

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

$$[\mathrm{AB}]_{\mathrm{eu,T}} = [\mathrm{AB}]_{\mathrm{eu,aq}}\left(\frac{1 + \dfrac{[\mathrm{H^+}]_\mathrm{T}}{\mathrm{K_a^{H_2AB^+}}} + \dfrac{\mathrm{K_a^{HAB}}}{[\mathrm{H^+}]_\mathrm{T}} + \mathrm{K_s^{HAB}}[\mathrm{M}]}{1 + \dfrac{[\mathrm{H^+}]_{\mathrm{aq}}}{\mathrm{K_a^{H_2AB^+}}} + \dfrac{\mathrm{K_a^{HAB}}}{[\mathrm{H^+}]_{\mathrm{aq}}}}\right) \tag{182}$$

$\mathrm{E_2}$, the eutectic between solid coformer, cocrystal, and solution, is described by

$$\mathrm{R_2HAB_{solid}} + \mathrm{HAB_{solid}} \rightleftharpoons \mathrm{R_{aq}} + \mathrm{HAB_{aq}} \tag{183}$$

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

$$[\mathrm{AB}]_\mathrm{T} = \mathrm{S_{AB,T}} \tag{184}$$

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

$$\mathrm{S_{AB,T}} = [\mathrm{AB}]_\mathrm{T} = [\mathrm{HAB}]_{\mathrm{aq}} + [\mathrm{H_2AB^+}]_{\mathrm{aq}} + [\mathrm{AB^-}]_{\mathrm{aq}} + [\mathrm{HAB}]_\mathrm{m} \tag{185}$$

$$\mathrm{S_{AB,T}} = \mathrm{S_{HAB,aq}}\left(1 + \frac{[\mathrm{H^+}]}{\mathrm{K_a^{H_2AB^+}}} + \frac{\mathrm{K_a^{HAB}}}{[\mathrm{H^+}]} + \mathrm{K_s^{HAB}}[\mathrm{M}]\right) \tag{186}$$

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

Eutectic constant K_{eu} of cocrystal R_2HAB

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

$$K_{eu} = \frac{a_{AB,eu}}{a_{R,eu}} \tag{187}$$

Assuming dilute conditions where concentrations replace activities,

$$K_{eu} = \frac{[AB]_{eu,T}}{[R]_{eu,T}} \tag{188}$$

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

$$K_{eu,T} = K_{eu,aq}\left(\frac{1}{1+K_s^R[M]}\right)\left(\frac{1+\frac{[H^+]_T}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]_T}+K_s^{HAB}[M]}{1+\frac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]_{aq}}}\right) \tag{189}$$

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 R_2HAB

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],

$$[M]_{CSC} = \frac{2K_{eu,aq}\left(\frac{1+\frac{[H^+]_T}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]_T}}{1+\frac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]_{aq}}}\right)-1}{K_s^R-\frac{2K_{eu,aq}K_s^{HAB}}{\left(1+\frac{[H^+]_{aq}}{K_a^{H_2AB^+}}+\frac{K_a^{HAB}}{[H^+]_{aq}}\right)}} \tag{190}$$

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

$$\mathrm{CSC}=\frac{2\mathrm{K}_{\mathrm{eu,aq}}\left(\dfrac{1+\dfrac{[\mathrm{H}^+]_{\mathrm{T}}}{\mathrm{K}_{\mathrm{a}}^{\mathrm{H_2AB^+}}}+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HAB}}}{[\mathrm{H}^+]_{\mathrm{T}}}}{1+\dfrac{[\mathrm{H}^+]_{\mathrm{aq}}}{\mathrm{K}_{\mathrm{a}}^{\mathrm{H_2AB^+}}}+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HAB}}}{[\mathrm{H}^+]_{\mathrm{aq}}}}\right)-1}{\mathrm{K}_{\mathrm{s}}^{\mathrm{R}}-\dfrac{2\mathrm{K}_{\mathrm{eu,aq}}\mathrm{K}_{\mathrm{s}}^{\mathrm{HAB}}}{\left(1+\dfrac{[\mathrm{H}^+]_{\mathrm{aq}}}{\mathrm{K}_{\mathrm{a}}^{\mathrm{H_2AB^+}}}+\dfrac{\mathrm{K}_{\mathrm{a}}^{\mathrm{HAB}}}{[\mathrm{H}^+]_{\mathrm{aq}}}\right)}}+\mathrm{CMC} \qquad (191)$$

Table 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 ($K_s < 0.010$).