Supporting Information

Basic drug solubility as a function of pH

Ketoconazole (KTZ) was used as a model drug for this study. Drug solubility can be described by the equilibrium of the solid drug KTZ with solution according to the following equilibrium expression:

$$KTZ_{crystal} \rightleftharpoons KTZ_{aq} \quad \text{(S1)}$$

where the dissolved drug, or the KTZ present in the aqueous phase, is expressed as KTZ_{aq}. KTZ is a dibasic drug, and can become ionized under certain aqueous conditions. Therefore, the total KTZ concentration (KTZ_T) in aqueous solution can be described by the sum of its non-ionized and ionized species in solution:

$$KTZ_T = B_{aq} + BH^+_{aq} + BH^{2+}_{2,aq} \quad \text{(S2)}$$

Where B, BH^+, and BH_2^{2+} are KTZ in its non-ionized, first protonated, and second protonated states. The subscripts T and aq denote the total solubility and drug species in the aqueous phase, respectively. The non-ionized KTZ in solution, B_{aq}, is also the intrinsic solubility of KTZ, which is expressed in later equations as $S_{KTZ,0}$.

The conjugate acids of the dibasic drug, KTZ, dissociate in solution according to their corresponding ionization constants

$$BH^{2+}_{2,aq} \overset{K_{a1,KTZ}}{\rightleftharpoons} H^+_{aq} + BH^+_{aq} \quad \text{(S3)}$$

$$K_{a1,KTZ} = \frac{[H^+]_{aq}[BH^+]_{aq}}{[BH_2^{2+}]_{aq}} \quad \text{(S4)}$$

$$BH^+_{aq} \overset{K_{a2,KTZ}}{\rightleftharpoons} H^+_{aq} + B_{aq} \quad \text{(S5)}$$

$$K_{a2,KTZ} = \frac{[H^+]_{aq}[B]_{aq}}{[BH^+]_{aq}} \quad \text{(S6)}$$

Substituting in relevant equilibria into the mass balance equation, KTZ solubility can be described by the equation:

$$S_{drug,T} = [KTZ]_T = S_{KTZ,0}(1 + \frac{[H^+]_{aq}}{K_{a2,KTZ}} + \frac{[H^+]_{aq}^2}{K_{a1,KTZ}K_{a2,KTZ}}) \quad \text{(S7)}$$

Equation 2.7A can be expressed in terms of pH and pK_a

$$S_{drug,T} = S_{KTZ,0}(1 + 10^{pK_{a2,KTZ} - pH} + 10^{pK_{a1,KTZ} + pK_{a2,KTZ} - 2pH}) \quad \text{(S8)}$$

Acidic coformer ionization

Total concentration of diprotic acid coformer ($[CF]_T$) in aqueous solution can be described by the sum of its non-ionized and ionized species in solution (mass balance).

$$CF_T = H_2A_{aq} + HA^-_{aq} + A^{2-}_{aq} \quad \text{(S9)}$$

where H_2A represents the non-ionized form of coformer. HA^- and A^{2-} are the two ionized species of the coformer.

The dicarboxylic acid coformer dissociates in solution according to its ionization constants:

$$H_2A_{aq} \overset{K_{a1,CF}}{\rightleftharpoons} H^+_{aq} + HA^-_{aq}$$

(S10)

$$K_{a1,CF} = \frac{[H^+]_{aq}[HA^-]_{aq}}{[H_2A]_{aq}}$$

(S11)

$$HA^-_{aq} \overset{K_{a2.CF}}{\rightleftharpoons} H^+_{aq} + A^{2-}_{aq} \quad \text{(S12)}$$

$$K_{a2,CF} = \frac{[H^+]_{aq}[A^{2-}]_{aq}}{[HA^-]_{aq}}$$

(S13)

Substituting in relevant equilibria into the mass balance equation, total coformer concentration in solution can be described by the equation:

$$CF_T = [H_2A]_{aq}(1 + \frac{K_{a1,CF}}{[H^+]_{aq}} + \frac{K_{a1,CF}K_{a2,CF}}{[H^+]_{aq}^2})$$

(S14)

Equation 2.14A can be expressed in terms of pH and pK_a:

$$CF_T = [H_2A]_{aq}(1 + 10^{pH-pK_{a1,CF}} + 10^{2pH-pK_{a1,CF}-pK_{a2,CF}}) \quad \text{(S15)}$$

Cocrystal Solubility as a function of pH, pK_a, and K_{sp}

For 1:1 cocrystals of KTZ and dicarboxylic acid, the cocrystal solubility (S_{cc}) under stoichiometric condition can be described as:

$$S_{cc} = KTZ_T = CF_T$$

(S16)

Cocrystal dissociates in solution according to its solubility product, K_{sp}

$$KTZ - CF_{cocrystal} \rightleftharpoons^{K_{sp}} KTZ_{aq} + CF_{aq} \quad \text{(S17)}$$

$$K_{sp} = [KTZ][CF] = [B]_{aq}[H_2A]_{aq}$$

(S18)

where $[B]_{aq}$ and $[H_2A]_{aq}$ refers to the non-ionized species of drug (KTZ) and coformer (CF). Considering cocrystal component mass balance (Equations S2 and S9) and substituting in relevant equilibria, cocrystal solubility can be obtained:

$$S_{cc,T} = \sqrt{K_{sp}(1+\frac{[H^+]_{aq}}{K_{a2,KTZ}}+\frac{[H^+]_{aq}^2}{K_{a1,KTZ}K_{a2,KTZ}})(1+\frac{K_{a1,CF}}{[H^+]_{aq}}+\frac{K_{a1,CF}K_{a2,CF}}{[H^+]_{aq}^2})}$$

(S19)

Equation S19 can be rewritten in terms of pH and pK_a:

$$S_{cc,T} = \sqrt{K_{sp}(1+10^{pK_{a2,KTZ}-pH}+10^{pK_{a1,KTZ}+pK_{a2,KTZ}-2pH})(1+10^{pH-pK_{a1,CF}}+10^{2pH-pK_{a1,CF}-pK_{a2,CF}})} \quad \text{(S20)}$$

Final pH values for cocrystal and drug dissolution are listed in Table S1. Dissolution in pH 1.6 buffer caused the bulk pH to elevate slightly, and dissolution in pH 5 and 6.5 buffers caused small decrease in pH. All pH changes are less than 0.3 pH unit.

Table S1. Final pH values of cocrystal and drug dissolution media

Initial pH	**Final pH**			
	KTZ drug	KTZ-ADP	KTZ-FUM	KTZ-SUC
1.60 ± 0.01	1.75 ± 0.01	1.65 ± 0.01	1.72 ± 0.01	1.65 ± 0.01
5.00 ± 0.03	5.01 ± 0.02	4.94 ± 0.02	4.94 ± 0.06	4.99 ± 0.02
6.50 ± 0.04	6.48 ± 0.01	6.23 ± 0.02	6.30 ± 0.09	6.24 ± 0.05