

## 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:



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:

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

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



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



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

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

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

Equation 2.7A can be expressed in terms of pH and pK<sub>a</sub>

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

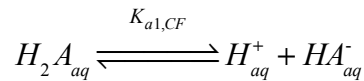
#### *Acidic cofomer ionization*

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

$$CF_T = H_2A_{aq} + HA_{aq}^- + A_{aq}^{2-} \quad (S9)$$

where H<sub>2</sub>A represents the non-ionized form of cofomer. HA<sup>-</sup> and A<sup>2-</sup> are the two ionized species of the cofomer.

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



(S10)

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

(S11)



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

(S13)

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

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

(S14)

Equation 2.14A can be expressed in terms of pH and pK<sub>a</sub>:

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

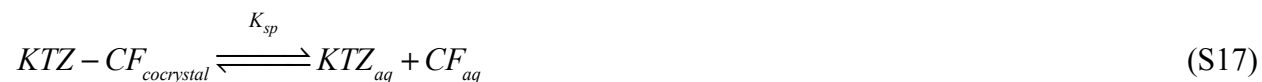
*Cocrystal Solubility as a function of pH, pK<sub>a</sub>, and K<sub>sp</sub>*

For 1:1 cocrystals of KTZ and dicarboxylic acid, the cocrystal solubility (S<sub>cc</sub>) under stoichiometric condition can be described as:

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

(S16)

Cocrystal dissociates in solution according to its solubility product, K<sub>sp</sub>



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

(S18)

where [B]<sub>aq</sub> and [H<sub>2</sub>A]<sub>aq</sub> 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:

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

(S19)

Equation S19 can be rewritten in terms of pH and pK<sub>a</sub>:

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

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	1.75	1.65	1.72	1.65
± 0.01	± 0.01	± 0.01	± 0.01	± 0.01
5.00	5.01	4.94	4.94	4.99
± 0.03	± 0.02	± 0.02	± 0.06	± 0.02
6.50	6.48	6.23	6.30	6.24
± 0.04	± 0.01	± 0.02	± 0.09	± 0.05