Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting Information

Improving Aqueous Solubility of Ciprofloxacin: Three Different Stoichiometric Hydrated Salt Forms with Oxalic acid

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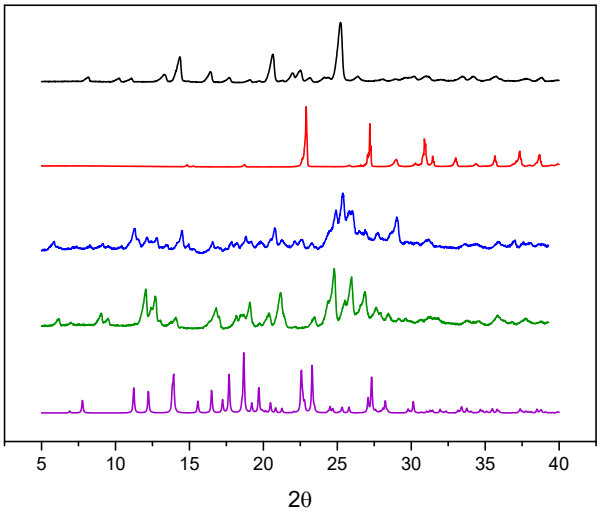


*Figure S**1** The XRPD patterns show pure ciprofloxacin(black), oxalic acid (red), toluene assistance co-grinding (LAG) (blue), methanol assistance co-grinding (LAG) (green, and ciprofloxacin methanol solvate (purple)[27].*

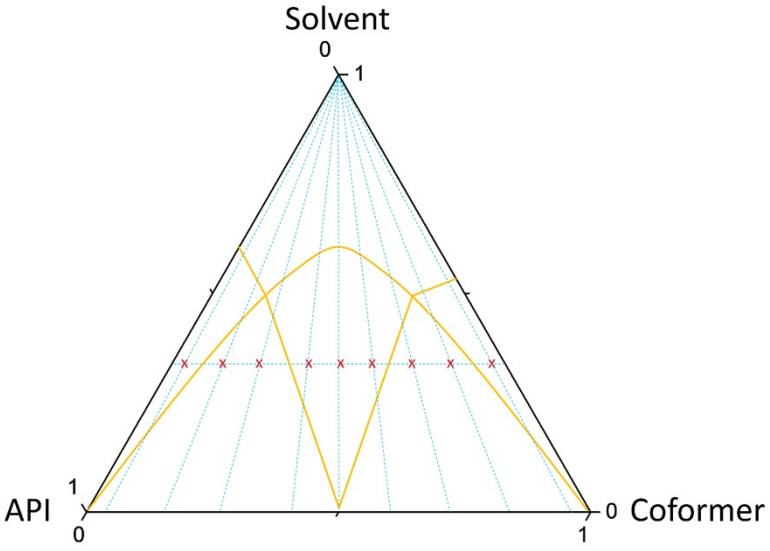


*Figure S**2** The various ratios of API:Coformer in experiments to construct the ternary phase diagram*

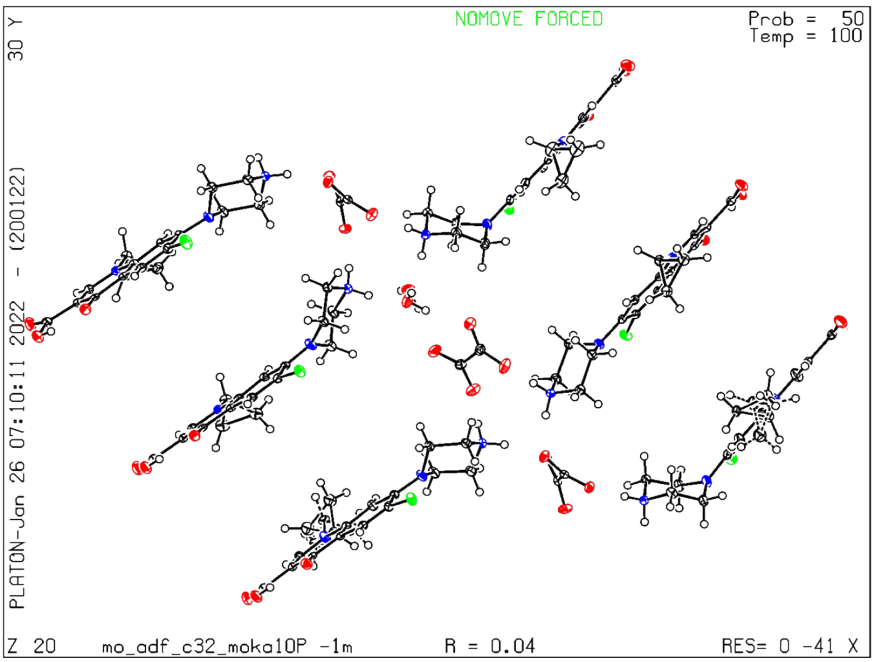


Figure S3 X-ray crystal structure of $CIF\,{}^{+}_{6}\,OXA^{2-}_{3}\cdot 2H_2O$ *(form A).*

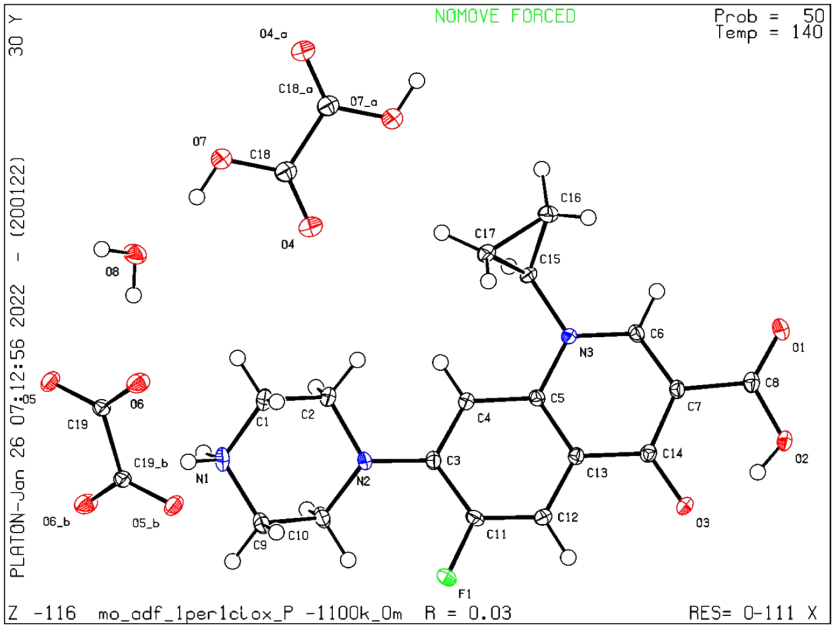


Figure S4 X-ray crystal structure of $CIF\,{}^{+}_{2}\,OXA_1OXA^{2-}_{1}\cdot 2H_2O$ *(form B).*

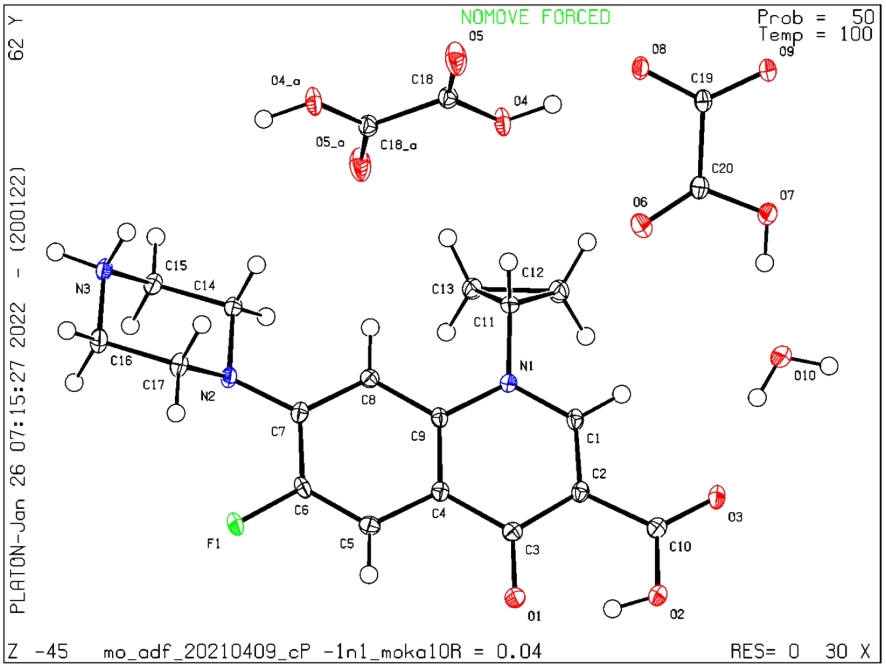


Figure S5 X-ray crystal structure of $CIF_2^+ OXA_1 OXA_2^- \cdot 2H_2O$ *(form C).*

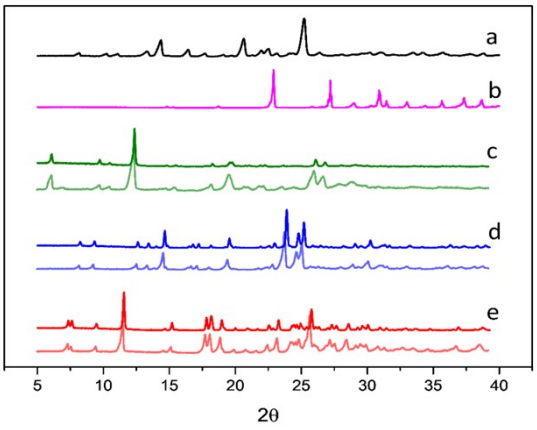


Figure S6 Comparing the x-ray diffraction patterns between experimental patterns (solid line) and patterns calculated from SC-XRD (faded lines) of (a) ciprofloxacin(CIF), (b) oxalic acid(OXA), (c) (form A), (d) (form B), and (e) (form C)

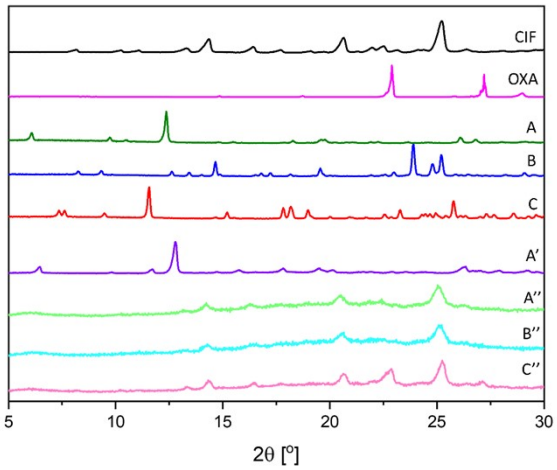


Figure S7 The x-ray diffraction patterns show (CIF) ciprofloxacin, (OXA) oxalic acid, (A) form A, (B) form B, (C) form C, (A') the anhydrous form of form A by annealed form A at 150-200 ℃ for 15 min under Ar gas, (A'') neat grinding of 2 mole CIF: 1mole OXA (at composition of form A) at 25 Hz for 40 min under Ar gas, (B'') neat grinding of 1 mole CIF: 1mole OXA (at composition of form B) at 25 Hz for 40 min under Ar gas, and (C'') neat grinding of 1 mole CIF: 2mole OXA (at composition of form C) at 25 Hz for 40 min under Ar gas.

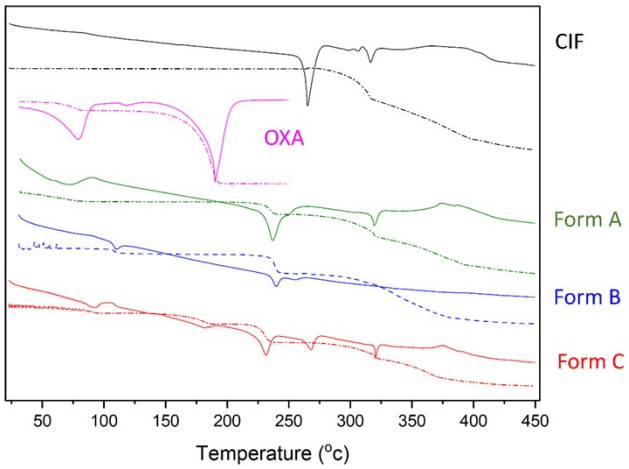


Figure S8 TGA thermal diagram of ciprofloxacin (black), oxalic acid (pink), form A (green), form B (blue), and form C (red). The solid lines represent the normalized DTA and the dashes line represent the normalized mass loss.

Calculated precent mass loss up to 150°C by TGA

The percent mass loss of form A is 4.12%

$$\frac{2294\ g\ Form\ A}{1\ mol\ Form\ A} \times \frac{4.12}{100} = \frac{94.51\ g\ H_2O}{1\ mol\ Form\ A}$$

The percent mass loss of form B is 3.92%

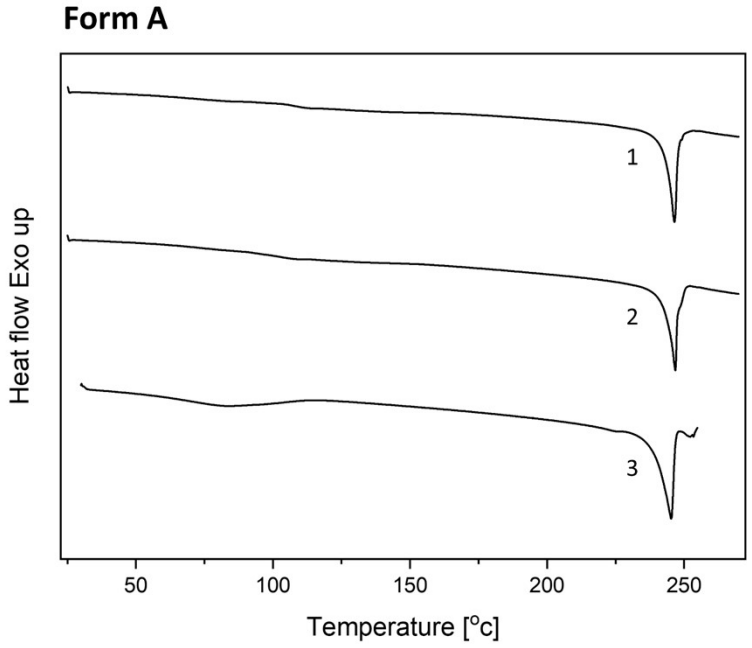
$$\frac{878\ g\ Form\ A}{1\ mol\ Form\ A} \times \frac{3.92}{100} = \frac{34.42\ g\ H_2O}{1\ mol\ Form\ A}$$

The percent mass loss of form C is 4.22%

$$\frac{968\ g\ Form\ A}{1\ mol\ Form\ A} \times \frac{4.22}{100} = \frac{40.85\ g\ H_2O}{1\ mol\ Form\ A}$$

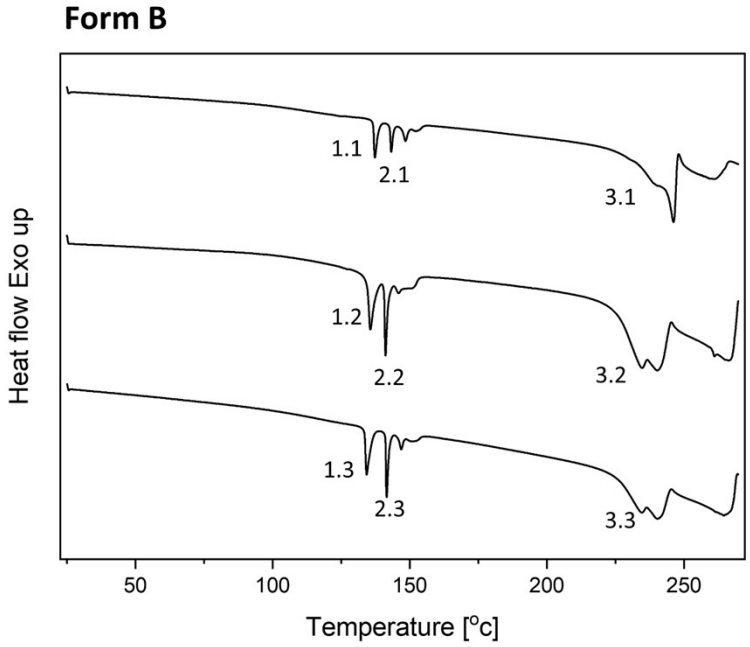
All three stoichiometric hydrated salts contain 2 mol of water per 1 mol of stoichiometric hydrated salt. Thus, the theoretical mass of water is

$$\frac{18\ g\ H_2O}{1\ mol\ H_2O} \times 2mol = 36\ g\ of\ H_2O\ loss$$



Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
1	243.68	246.45	247.86	128.14
2	243.3	246.78	247.72	154.97
3	239.63	245.28	246.79	141.08

Figure S9 DSC thermogram and the thermal parameters of stoichiometric forms A of hydrated salt.

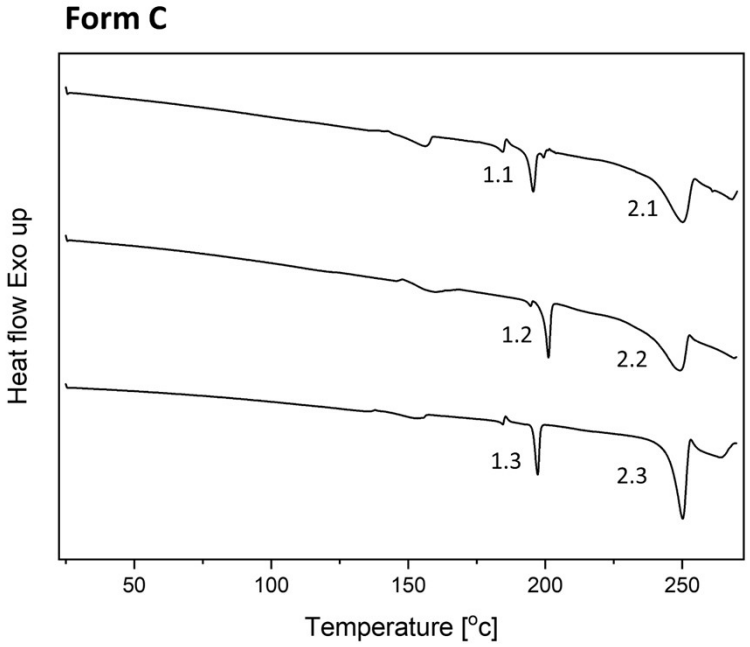


Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
1.1	136.65	137.31	-	-
1.2	134.50	135.65	-	-
1.3	133.58	134.28	-	-

Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
2.1	-	143.24	-	-
2.2	-	141.17	-	-
2.3	-	141.59	-	-

Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
3.1	229.75	-	-	-
3.2	225.72	-	-	-
3.3	229.58	-	-	-

Figure S10 DSC thermogram and the thermal parameters of stoichiometric forms B of hydrated salt.



Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
1.1	199.22	201.17	202.33	42.51
1.2	193.21	195.59	197.15	43.03
1.3	195.44	197.25	198.23	39.15

Peak	T_{Onset} [°C]	T_{Peak} [°C]	T_{Endset} [°C]	ΔH [J/mol]
2.1	238.72	248.92	252.12	125.89
2.2	240.03	250.10	253.72	115.95
2.3	245.32	250.16	252.40	180.96

Figure S11 DSC thermogram and the thermal parameters of stoichiometric forms C of hydrated salt.

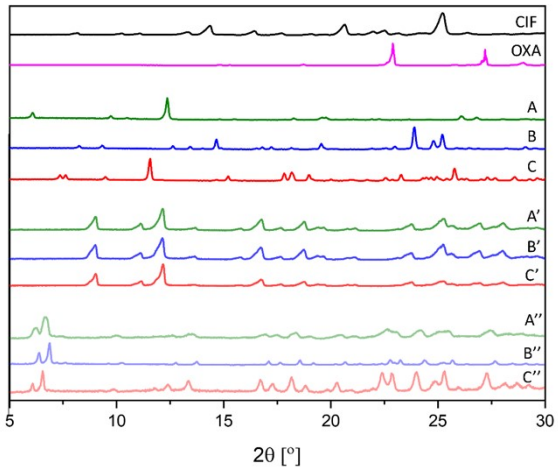


Figure S12 The x-ray diffraction patterns show (CIF) ciprofloxacin, (OXA) oxalic acid, (A) form A, (B) form B, and (C) form C. A', B', and C' are stable solid phases at the equilibrium in pH 4 when dissolving form A, B, C, respectively. A'', B'', and C'' are stable solid phases at the equilibrium in pH 7 when dissolving form A, B, C, respectively.

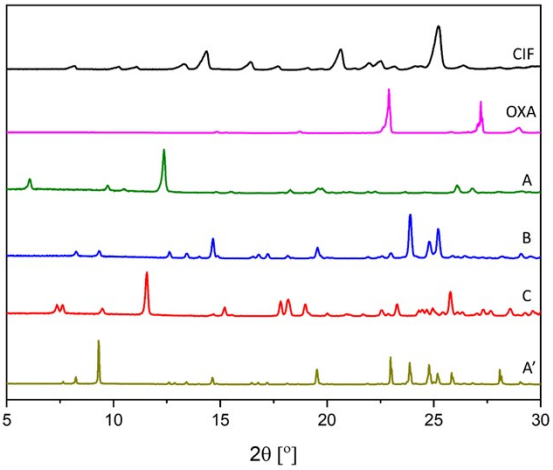
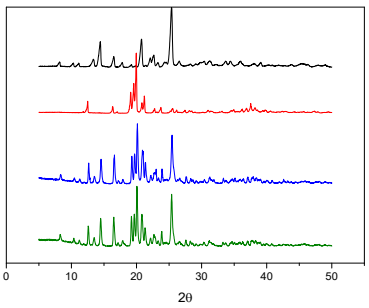
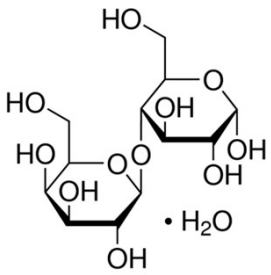
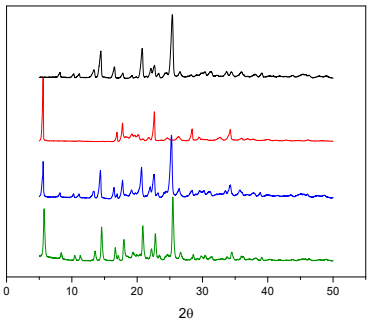
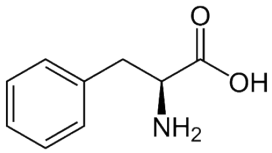
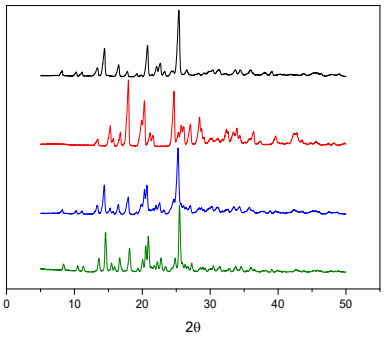
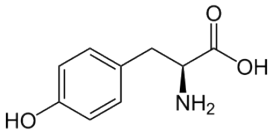
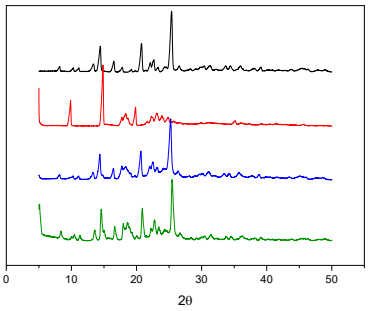
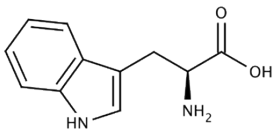
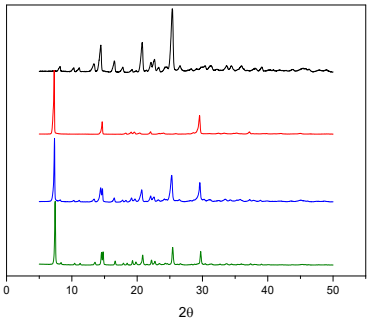
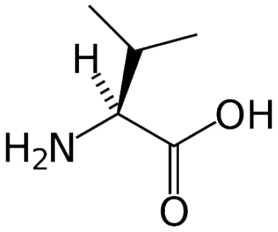
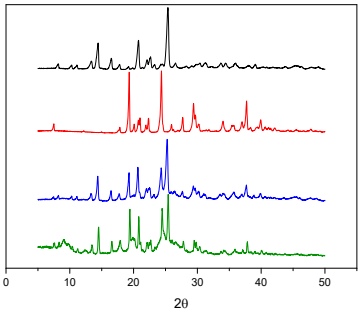
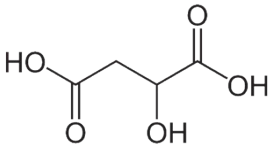
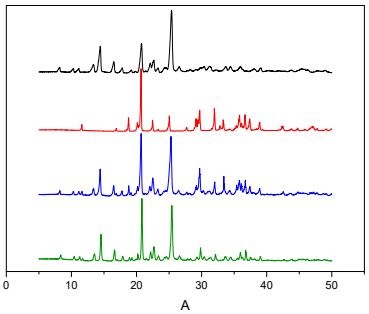
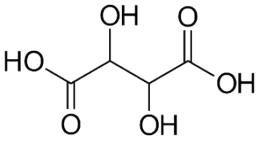
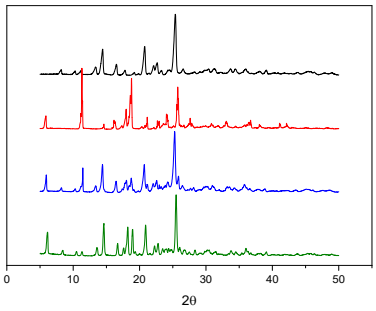
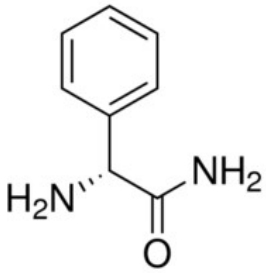
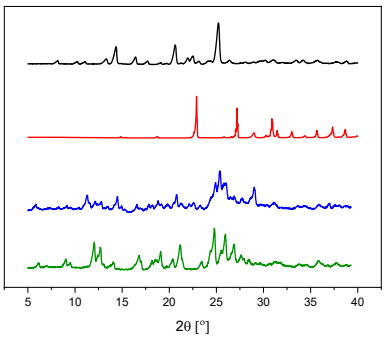
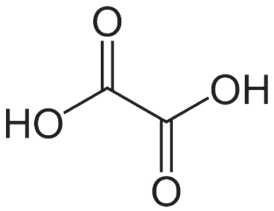


Figure S13 The x-ray diffraction patterns show (CIF) ciprofloxacin, (OXA) oxalic acid, (A) form A, (B) form B, (C) form C, and (A') is the stable solid phase at equilibrium when suspended form C in deionized water.

Table S1 XRPD patterns of multi-component screening section of all candidates. The XRPD patterns show pure ciprofloxacin(black), coformer(red), liquid assistance co-grinding (LAG) with a few drop of toluene(blue), and reusing LAG to slurry cocrystallization in toluene (green).

Screening XRPD patterns	Coformer name and structure	LAG result	Slurry result
	lactose monohydrate 	-	-
	*L*-phenylalanine 	-	-
	*L*-tyrosine 	-	-

	*L*-tryptophan 	-	-
	*L*-valine 	-	-
	*L*-malic acid 	-	-
	*D*-tartaric acid 	-	-

	*Rac*-phenyl glycinamide 	-	-
 *Blue pattern is LAG with toluene *Green pattern is LAG with MeOH	oxalic acid 	+	+

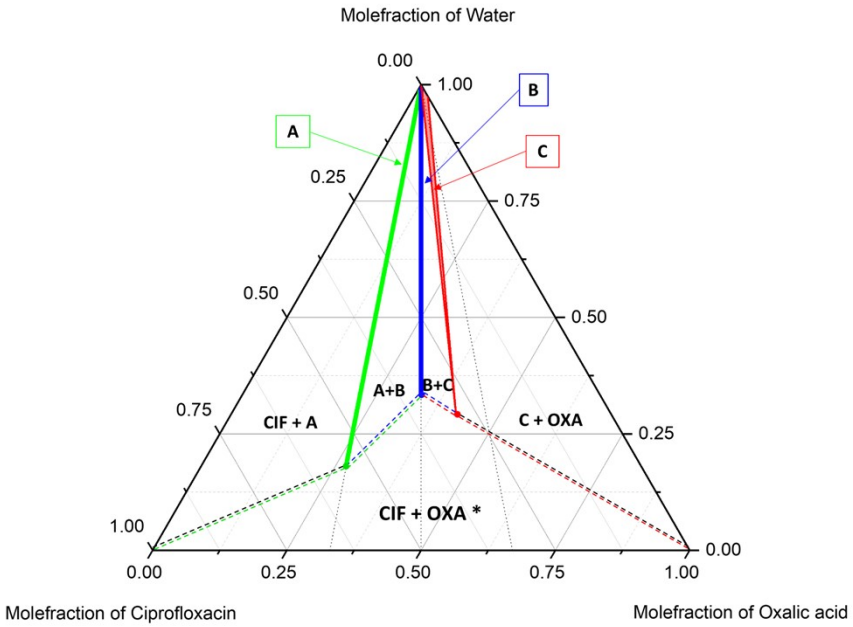


Figure S14 The full scale of ternary phase diagram of CIF-OXA system; product form A (green, A), product form B (blue, B), and product form C (red, C)

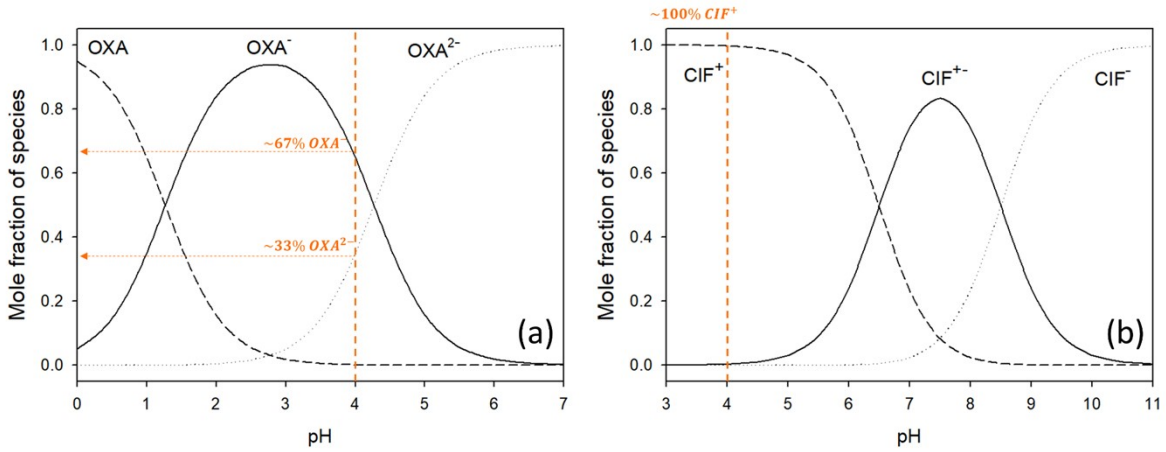


Figure S15 Percentages speciation diagram of CIF (a) and OXA (b) at pH 4 of buffer solution. [7,24,25].

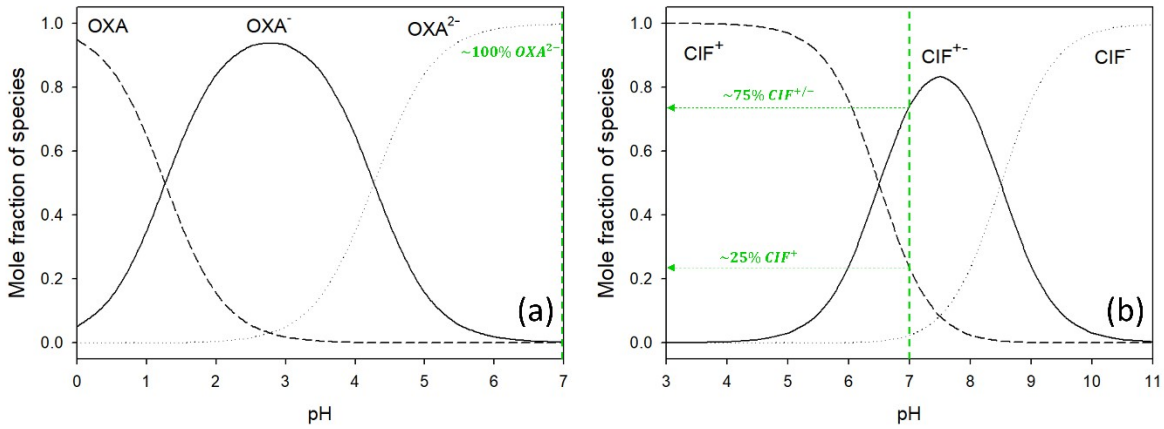


Figure S16 Percentages speciation diagram of CIF (a) and OXA (b) at pH 7 of buffer solution. [7,24,25]

Equilibrium moving at Buffer pH4;

Form A ($CIF_6^+ OXA_3^{2-} \cdot 2H_2O$) ;

$$CIF_6^+ OXA_3^{2-} \cdot 2H_2O \overset{Ksp,A}{\leftrightarrow} 6CIF^+ + 3OXA^{2-} + 2H_2O$$

$$2OXA^{2-} + 2H^+ \overset{1/Ka2(OXA)}{\leftrightarrow} 2OXA^-$$

$\therefore \Sigma H^+ = +2H^+$ (To be 67% of OXA^-, 33% of OXA^{2-}, and 100% of CIF^+ at equilibrium base on speciation diagram at pH4)

Form B ($CIF_2^+ OXA_1 OXA_1^{2-} \cdot 2H_2O$) ;

$$CIF_2^+ OXA_1 OXA_1^{2-} \cdot 2H_2O \overset{Ksp,B}{\leftrightarrow} 2CIF^+ + OXA + OXA^{2-} + 2H_2O$$

$$OXA \overset{Ka1(OXA)}{\leftrightarrow} OXA^- + H^+$$

$$0.17OXA^{2-} + 0.17H^+ \overset{1/Ka2(OXA)}{\leftrightarrow} 0.17OXA^-$$

$\therefore \Sigma H^+ = -0.83H^+$ (To be 67% of OXA^-, 33% of OXA^{2-}, and 100% of CIF^+ at equilibrium base on speciation diagram at pH4)

Form C ($CIF_2^+ OXA_1 OXA_2^- \cdot 2H_2O$) ;

$$CIF_2^+ OXA_1 OXA_2^- \cdot 2H_2O \overset{Ksp,C}{\leftrightarrow} 2CIF^+ + OXA + 2OXA^- + 2H_2O$$

$$OXA \overset{Ka1(OXA)}{\leftrightarrow} OXA^- + H^+$$

$$OXA^- \overset{Ka2(OXA)}{\leftrightarrow} OXA^{2-} + H^+$$

$\therefore \Sigma H^+ = -2H^+$ (To be 67% of OXA^-, 33% of OXA^{2-}, and 100% of CIF^+ at equilibrium base on speciation diagram at pH4)

Equilibrium moving at Buffer pH7;

Form A ($CIF_6^+ OXA_3^{2-} \cdot 2H_2O$) ;

$$CIF_6^+ OXA_3^{2-} \cdot 2H_2O \overset{Ksp,A}{\leftrightarrow} 6CIF^+ + 3OXA^{2-} + 2H_2O$$

$$4.5CIF^+ \overset{Ka1(CIF)}{\leftrightarrow} 4.5CIF^{+/-} + + 4.5H^+$$

$\therefore \Sigma H^+ = -4.5H^+$ (To be 100% of OXA^{2-}, 75% of $CIF^{+/-}$, and 25% of CIF^+ at equilibrium base on speciation diagram at pH7)

Form B ($CIF_2^+ OXA_1 OXA_1^{2-} \cdot 2H_2O$) ;

$$CIF_2^+ OXA_1 OXA_1^{2-} \cdot 2H_2O \overset{Ksp,B}{\leftrightarrow} 2CIF^+ + OXA + OXA^{2-} + 2H_2O$$

$$1.5CIF^+ \overset{Ka1(CIF)}{\leftrightarrow} 1.5CIF^{+/-} + + 1.5H^+$$

$$OXA \overset{Ka1 \cdot Ka2(OXA)}{\leftrightarrow} OXA^{2-} + 2H^+$$

$\therefore \Sigma H^+ = -3.5H^+$ (To be 100% of OXA^{2-}, 75% of $CIF^{+/-}$, and 25% of CIF^+ at equilibrium base on speciation diagram at pH7)

Form C ($CIF_2^+ OXA_1 OXA_2^- \cdot 2H_2O$) ;

$$CIF_2^+ OXA_1 OXA_2^- \cdot 2H_2O \overset{Ksp,C}{\leftrightarrow} 2CIF^+ + OXA + 2OXA^- + 2H_2O$$

$$1.5CIF^+ \overset{Ka1(CIF)}{\leftrightarrow} 1.5CIF^{+/-} + + 1.5H^+$$

$$OXA \overset{Ka1(OXA).Ka2(OXA)}{\leftrightarrow} OXA^{2-} + 2H^+$$

$$2OXA^- \overset{Ka2(OXA)}{\leftrightarrow} 2OXA^{2-} + 2H^+$$

$\therefore \Sigma H^+ = -5.5H^+$ (To be 100% of OXA^{2-}, 75% of $CIF^{+/-}$, and 25% of CIF^+ at equilibrium base on speciation diagram at pH7)