Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting information

Solution chemistry and phase solubility diagram of CL-20/MTNP energetic cocrystal

Table of contents

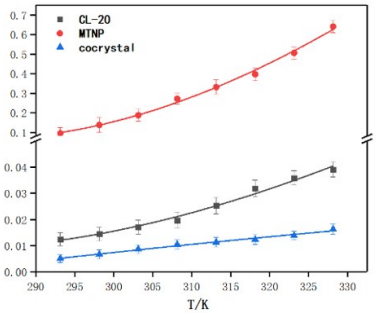
Section 1:Solubilities determinations:

The solubilities of CL-20, MTNP and CL-20/MTNP co-crystal were determined by HPLC measurements in ethanol, ethyl acetate and acetonitrile. The solubilities of CL-20, MTNP and co-crystal were modeled by the Apelblat equation and the curves were shown in figure 1 (a) to (c) respectively. Every examining point was determined by three parallel samples so that these solubilities were given with error bars in figure 1.

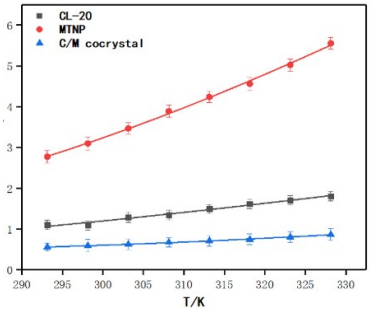
The modified Apelblat models derived from Clausius-Claperyron equation can be utilized to describe the trends of solubility as the equation would be given：

$$lnx = A_1 + \frac{B_1}{T} + c_1 lnT \quad \text{(T/K)} \qquad (1)$$

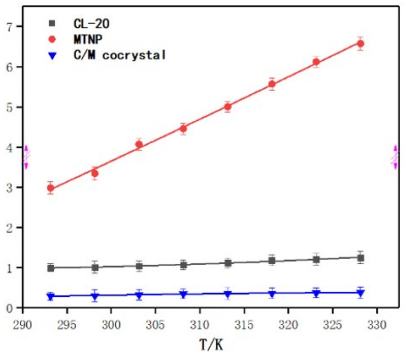
Where the x refers to the mole fraction solubility of CL-20 or MTNP; The solubilties x were given in mol/L. The A_1,B_1,C_1 were all empirical parameters and can be acquired through the calculation of a non-liner least-square method. A_1, B_1 gave a quantification of the variation of the activity coefficient and the solubility of solute in a non-ideal solution respectively while the effect of temperature on fusion enthalpy can be indicated via C1.



(a)



(b)



(c)

Figure 1 (a) to (c) exhibited the solubilities and solubility curves modeled by Apelblat equation in three solvents for CL-20, MTNP and CL-20/MTNP cocrystal in each fiure.

The concentrations of sample 1,2,3 in figure 1 were actually the same with samples in figure 2. The differences are the x-axis in figure 2 were the reciprocal of MTNP concentrations (1/[MTNP]total). The various concentrations of MTNP were controlled and these correspond CL-20 concentrations were determined by HPLC as below. The samples were taken for 1ml to HPLC analysis. And these correspond CL-20 concentrations were determined by HPLC as below. Concentration order 1 to 4 are the test points in 'figure 1(a) to (c)'.

Table 1. Exhibits the various concentrations of CL-20 (mol/L) at different concentrations of MTNP (mol/L) in ethanol (EtoH) at 308.15K.

Concentration order	MTNP (sample1)	CL-20 (sample1)	MTNP (sample 2)	CL-20 (sample 2)	MTNP (sample 3)	CL-20 (sample 3)
1	0.00917	0.00836	0.00904	0.00925	0.00872	0.00885
2	0.01272	0.00667	0.0135	0.00606	0.01243	0.00552
3	0.02408	0.00347	0.0272	0.0037	0.0258	0.0035
4	0.0317	0.00272	0.03301	0.00299	0.03091	0.00262

Table 2. Exhibits the various concentrations of CL-20 (mol/L) at different concentrations of MTNP (mol/L) in ethyl acetate (EtoAc) 308.15K

Concentration order	MTNP (sample1)	CL-20 (sample1)	MTNP (sample 2)	CL-20 (sample 2)	MTNP (sample 3)	CL-20 (sample 3)
1	0.35192	0.35081	0.35249	0.37012	0.35916	0.31204
2	0.66	0.16515	0.6769	0.19986	0.64822	0.16943
3	0.99	0.1101	0.9855	0.12915	1.01497	0.13525
4	1.32	0.08258	1.30565	0.10772	1.33958	0.09243

Table 3. Exhibits the various concentrations of CL-20 (mol/L) at different concentrations of MTNP (mol/L) in acetonitrile (AN) 308.15K.

Concentration order	MTNP (sample1)	CL-20 (sample1)	MTNP (sample 2)	CL-20 (sample 2)	MTNP (sample 3)	CL-20 (sample 3)
1	0.57857	0.58771	0.60566	0.5911	0.56566	0.54577
2	1.17	0.28889	1.12902	0.31299	1.198	0.25689
3	1.73595	0.17259	1.78255	0.19259	1.755	0.19259
4	2.314	0.14971	2.294	0.1551	2.35322	0.13914

Section 2:Calculated eutectic constants:

In order to calculate the eutectic constants for CL-20/MTNP co-crystal, the general equations of co-crystal dissolution process are necessary to discuss here. Drug A and cocrystal A_xB_y, equations and definitions of equilibrium constants can be given as equation (2) to (4),Where the $[A]_{eu}$ and $[B]_{eu}$ stands for the total concentrations in equilibrium condition at eutectic points with solutions[3] :

$$A_{solid} \leftrightarrow A_{soln} \qquad S_{drug} = a_{drug} \tag{2}$$

$$A_x B_{ysolid} \leftrightarrow xA_{soln} + yB_{soln} \qquad K_{sp} = a_{drug}^{x} a_{coformer}^{y} \tag{3}$$

$$A_{soln} + B_{soln} = AB_{soln} \qquad K_{11} = \frac{a_{complex}}{a_{drug} a_{coformer}} \tag{4}$$

Where slon stands for solute in solutions; K_{sp} and K_{11} are the solubility product constant and complexation constant in solution respectively.

While the $[AB]_{soln}$ can be expressed combining with K_{11}, K_{sp} and S_{drug}:

$$[AB]_{soln} = K_{11}(K_{sp} s_{drug}^{(y-x)})^{\frac{1}{y}} \tag{5}$$

The eutectic constant (Keu) is defined by the concentration ratio of conformer to drug:

$$K_{eu} = \frac{[B]_{eu}}{[A]_{eu}} = \frac{[B] + [AB]}{[A] + [AB]} = [\frac{\left(\frac{K_{sp}}{S_{drug}^{x}}\right)^{\frac{1}{y}} + K_{11}\left(K_{sp} S_{drug}^{y-x}\right)^{\frac{1}{y}}}{S_{drug} + K_{11}\left(K_{sp} S_{drug}^{y-x}\right)^{\frac{1}{y}}}] \tag{6}$$

The cocrystal to drug solubility ratio is used to determine the eutectic constants and defined as:

$$\alpha = \frac{S_{co-crystal}}{S_d} \tag{7}$$

Base on equations (1) to (3), another calculation of K_{eu1} via the solubility ratio of co-crystal and CL-20 in pure solvents can be shown as :

$$K_{eu1} = xy^{y/x} \alpha^{(y+x)/x} \tag{8}$$

While for 1:1 co-crystal, the co-crystal to CL-20 solubility ratio (α) is shown to determine the excess eutectic co-former concentration and the eutectic constant (K_{eu}), which is the ratio of solution concentrations of co-crystal components at the eutectic. Equation (8) also can be simplified as equation (9) below, by which the calculated K_{eu1} thus we can make comparisons about the calculative and observed K_{eu} values in Table 3:

$$K_{eu1} = \left(\frac{S_{co\text{ - }crystal}}{S_d}\right)^2 = \alpha^2 \tag{9}$$

Base on equation (9), the K_{eu1}(c) can be obtained from the solubilities that were determined previously.

:

Section 3: Characterization

The simulated PXRD patterns of CL-20/MTNP cocrystal was given here as comparisons with the experimental PXRD patterns in figure 2.

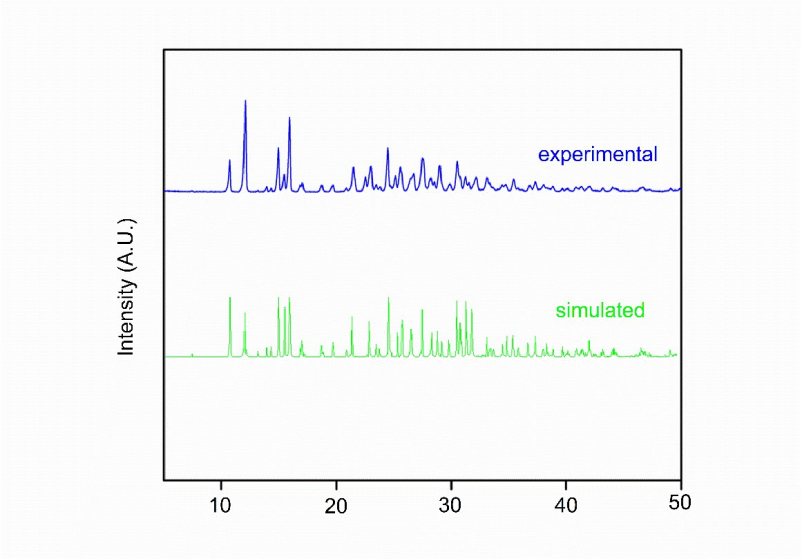


Figure 2. The experimental and simulated PXRD patterns of CL-20/MTNP cocrystal

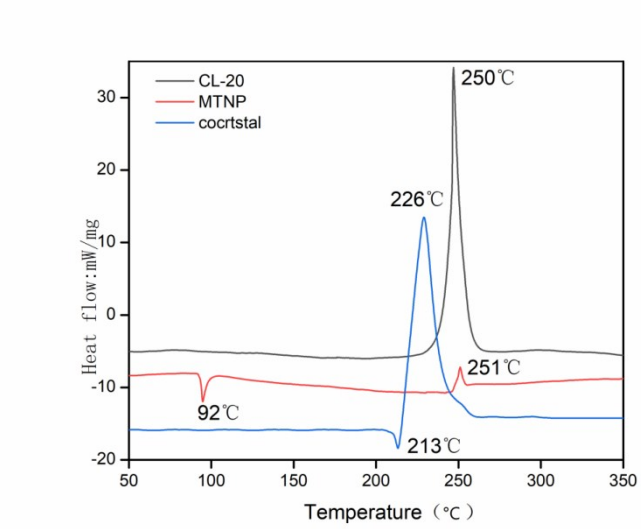


Figure 3. The results of DSC analysis of CL-20/MTNP cocrystal

The thermal analysis of CL-20/MTNP showed the melting point of this cocrystal was improved to be 213℃ comparing with 92℃ of MTNP. While exothermic decomposition peak was 226℃, lower than 250℃ for CL-20 and 251℃ for MTNP.

1. A. Alhalaweh, A. Sokolowski, N. Rodriguezhornedo and S. P. Velaga, Crystal Growth & Design, 2011, 11, 3923-3929.
2. S. J. Nehm, B. Rodriguezspong and N. Rodriguezhornedo, Crystal Growth & Design, 2006, 6, 592-600.
3. D. J. Good and N. Rodriguezhornedo, Crystal Growth & Design, 2010, 10, 1028-1032.