Supplementary Information

Cocrystallization-driven self-assembly with vanillic acid offers a new chance for surmounting fast and excessive absorption issues of antifungal drug 5-fluorocytosine: A combined theoretical and experimental research†

Fan-Zhi Bu,[1,+] Yue-Ming Yu,[1,+] Yu-Li Shen,[1] Lu Liu,[1] Cui-Wei Yan,*[,1] Zhi-Yong Wu,[1,2] Yan-Tuan Li,*[,1,2]

1. *School of Medicine and Pharmacy, College of Marine Life Science, Ocean University of China, Qingdao, Shandong 266003, P.R. China.*
2. *Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science, Qingdao, Shandong, P.R. China.*

*Corresponding authors

[+]These authors contributed equally to this work

Contents

Section 1. The data calibration method used for solubility/IDR measurements

Section 2. Supplementary figures and tables

Section 1. The data calibration method used for solubility/IDR measurements

Based on the linear absorption and constant proportion (1:1) of the two components in the present cocrystal, the Lambert-Beer's law is still applicable. We present the conversion process as the following equations:

$$A_{FCY} = \varepsilon_{FCY} \times C_{FCY} \times L \quad (1)$$

$$A_{VAA} = \varepsilon_{VAA} \times C_{VAA} \times L \quad (2)$$

In addition, because the proportion of the two components FCY and VAA in the present cocrystal, as well as the optical path length L, are constantly equal, then, the following relationship can be established:

$$C_{FCY} \times L = C_{VAA} \times L \quad (3)$$

Based on the above equations, it can obtain equation (4):

$$A_{FCY}/(A_{FCY} + A_{VAA}) = \varepsilon_{FCY}/(\varepsilon_{FCY} + \varepsilon_{VAA}) = k \quad (4)$$

Where k is a constant, and also, because of the additive property of absorption, the $A_{FCY} + A_{VAA}$ is usually the read absorption in the experiments. Therefore, the actual absorption value of FCY is determined by substituting the measured values of FCY and VAA into the subsequently obtained equation (5). From the **Fig. S1**, it can be seen that the measured A_{FCY} and A_{VAA} are respectively 0.468 and 0.301, thus, the constant k value is calculated to 0.609. According to the result above, the actual absorption value of FCY in our experiments (denoted as A'_{FCY}) is obtained by multiplying the coefficient k with the read absorption value (denoted as A'_{read}) as follows:

$$A'_{FCY} = 0.609 \times A'_{read} \quad (5)$$

Section 2. Supplementary figures and tables.

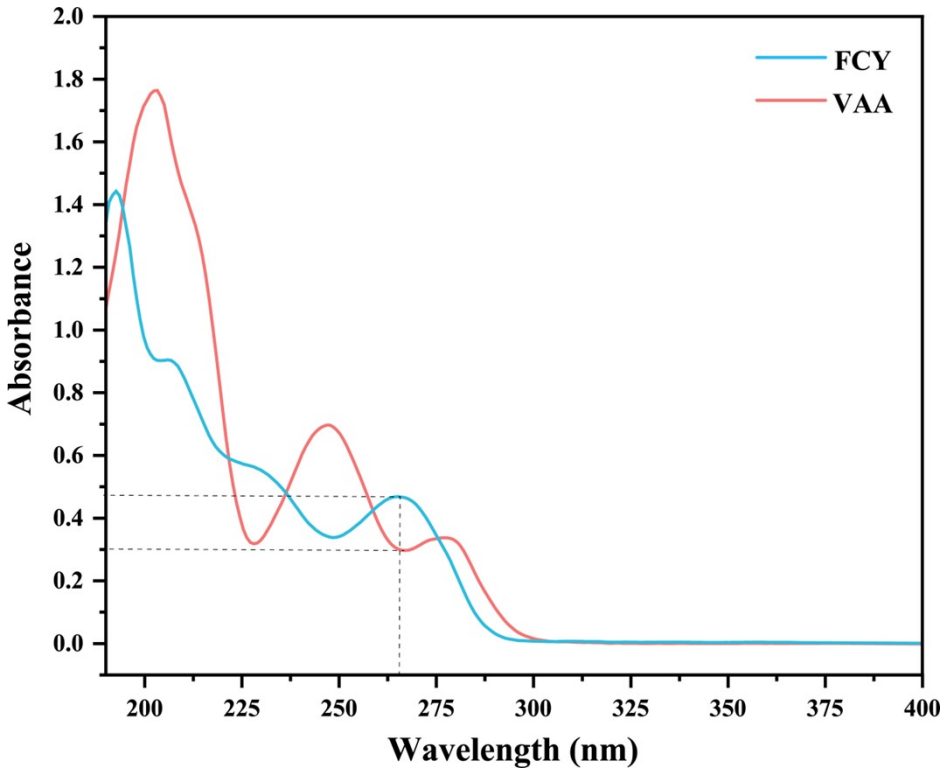

Fig. S1 UV absorption spectra of FCY and VAA.

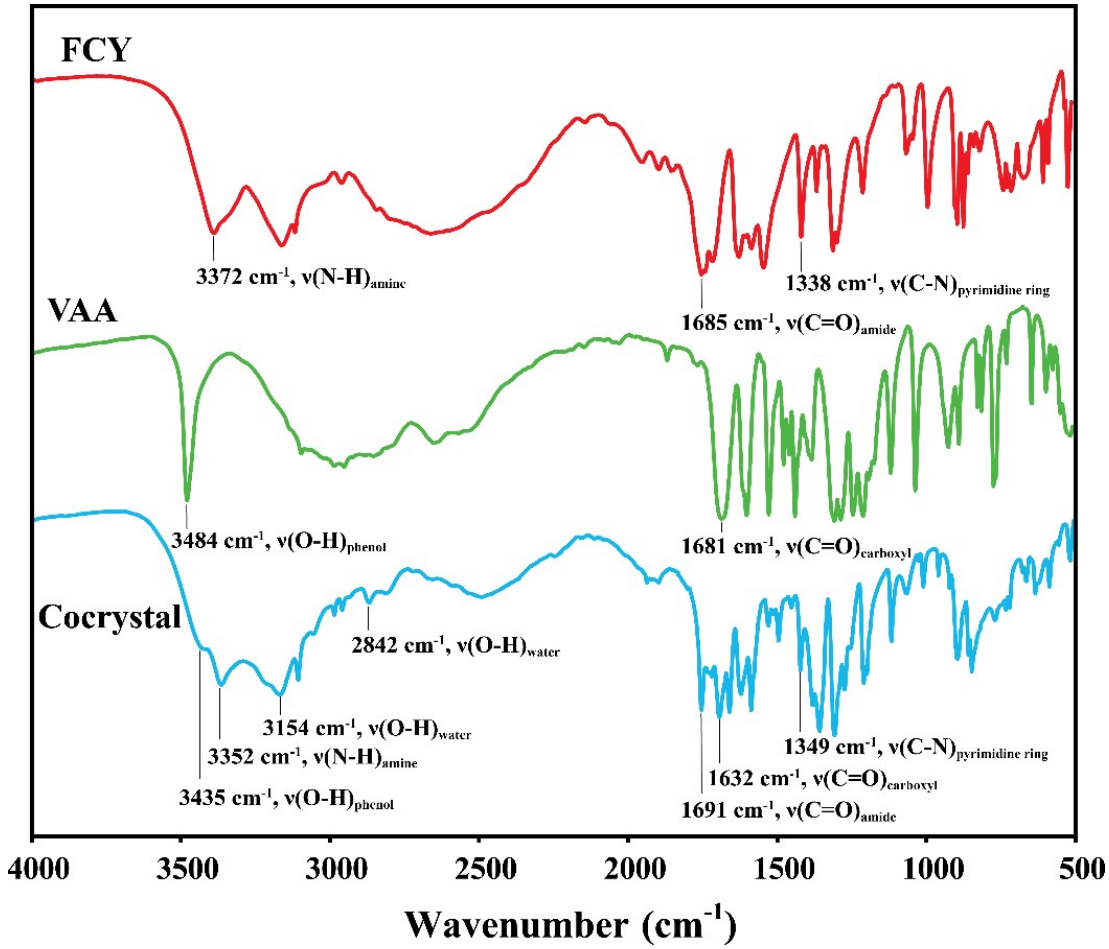

Fig. S2 FT-IR spectra of FCY, VAA and cocrystal FCY-VAA-H_2O.

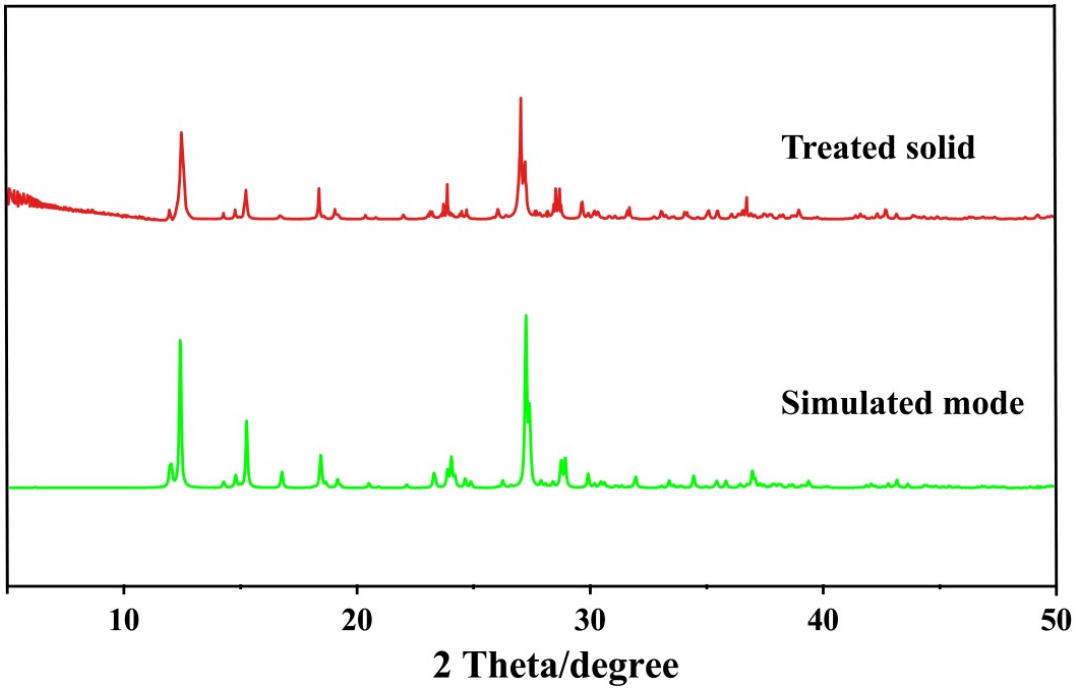

Fig. S3 PXRD comparison for the cocrystal's simulated pattern and the treated solid obtained from above 140 °C to cooling room temperature.

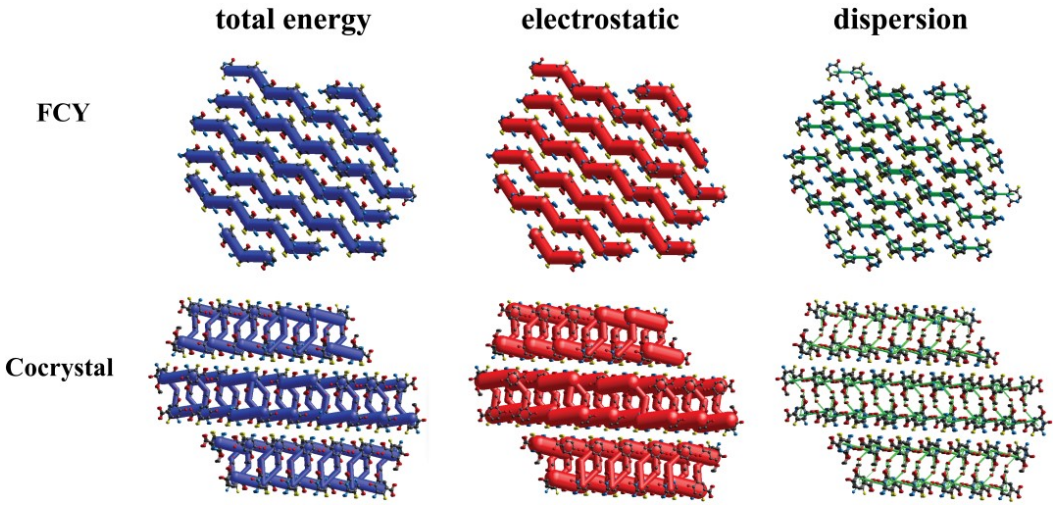

Fig. S4 FCY and cocrystal: energy-frameworks for total interaction energies (blue) with the component of electrostatic (red) and dispersion (green). All drawings adopt the same cylinder scale and H atoms have been omitted for clarity.

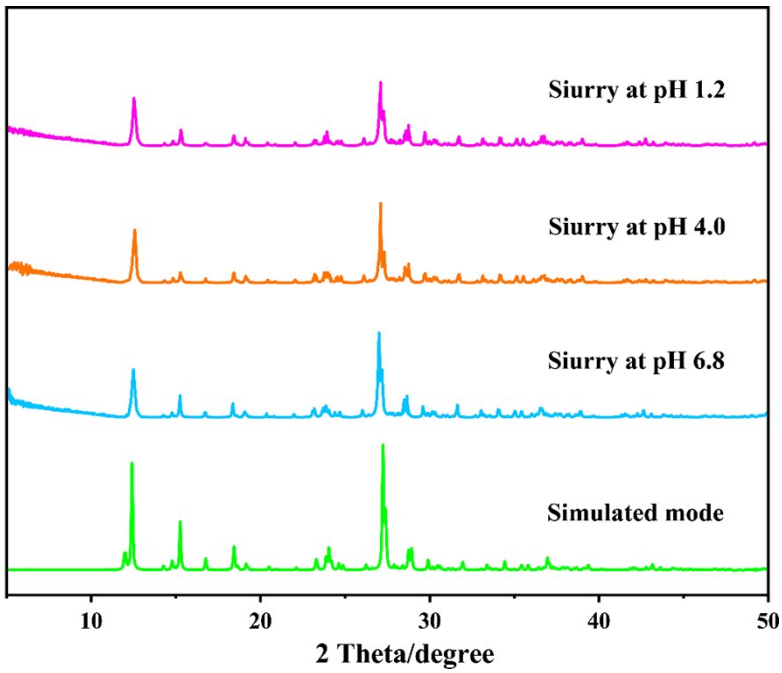

Fig. S5 PXRD comparison of the cocrystal's simulated pattern and the residual solids after the powder dissolution measurements.

Table S1. pH values measured in different media after solubility tests.

Solution	pH (dissolution media)		
	1.20	4.00	6.80
pH (FCY solution)	1.92	4.11	6.91
pH (cocrystal solution)	1.27	4.09	6.85

Table S2. pH values measured in different media after IDR tests.

Solution	pH (dissolution media)		
	1.20	4.00	6.80
pH (FCY solution)	1.28	4.07	6.84
pH (PM solution)	1.22	4.01	6.79
pH (cocrystal solution)	1.25	4.04	6.81