Supplementary Information

The supramolecular self-assembly of 5-fluorouracil and caffeic acid through cocrystallization strategy opens up a new way for the development of synergistic antitumor pharmaceutical cocrystal†

Yue-Ming Yu,‡[a] Ling-Yang Wang,‡[a] Fan-Zhi Bu,[a] Lin-Lin Wang,[a] Yan-Tuan Li,[a,b,*] Cheng Wang[a,*] and Zhi-Yong Wu[a,*]

[a]*School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong 266003, PR China.*

[b]*Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, 266003, PR China.*

* Correspondence to: Yan-Tuan Li, Cheng Wang, and Zhi-Yong Wu.
E-mail addresses: yantuanli@ouc.edu.cn (Yan-Tuan Li), Cheng Wang@ouc.edu.cn (Cheng Wang) and wuzy@ouc.edu.cn (Zhi-Yong Wu)
‡ These authors contributed equally to this work.

*Correspondence to: Yan-Tuan Li, Cheng Wang and Zhi-Yong Wu.
E-mail address: yantuanli@ouc.edu.cn (Yan-Tuan Li), Cheng Wang@ouc.edu.cn (Cheng Wang) and wuzy@ouc.edu.cn (Zhi-Yong Wu).
‡ These authors contributed equally to this work.

Contents

Table S1 HPLC parameters for FL

Parameter	Details
Column	Diamonsil C-18 column (4.6×250 mm, 5 μm)
Mobile phase	methanol-water (5:95)
Flow rate	1.0 mL·min^{-1}
Column temperature	25 ℃
λ_{max}	265 nm
Retention time	6 min
Calibration range	50~2000 ng·mL^{-1}

Table S2 Screenings for the cocrystal of FL with phenolic acid of hydroxy-cinnamic acid group

sample number	system	molar ratio	cocrystal formation
1	FL-caffeic acid	1:1	Yes
2	FL-caffeic acid	1:2	No
3	FL-caffeic acid	2:1	No
4	FL-ferulic acid	1:1	No
5	FL-ferulic acid	1:2	No
6	FL-ferulic acid	2:1	No
7	FL-p-coumaric acid	1:1	No
8	FL-p-coumaric acid	1:2	No
9	FL-p-coumaric acid	2:1	No
10	FL-sinapic acid	1:1	No
11	FL-sinapic acid	1:2	No
12	FL-sinapic acid	2:1	No

Table S3 The MEP values of maxima and minima around relevant atoms in FL and cocrystal

	FL dimer in free FL	FL hydrated tetramer in the cocrystal	FL-CF heterodimer in the cocrystal	FL-CF hydrated tetramer in the cocrystal	FL-CF hydrated trimer in the cocrystal	CF hydrated tetramer in the cocrystal
F1	-31.83, -31.23				-8.73	
O1	-12.27, -12.24		-26.05			
O2	-37.39, -37.40	-57.49, -56.86		-40.74	-33.27	
O4			-23.08			
O5				-32.51		-24.92,-24.94
O7				-49.93		-26.07,-26.06
O8				-40.74	-36.47	
H1	43.17, 43.19			18.39		
H2A	40.60, 40.56		35.35			
H3			7.43			
H5				20.41	-33.47	
H6A						13.67,13.68
H7A				15.85		30.82,31.69
H8A		12.30, 12.33		36.70	18.87	
H8B		2.63, 2.64				
H9					11.07	

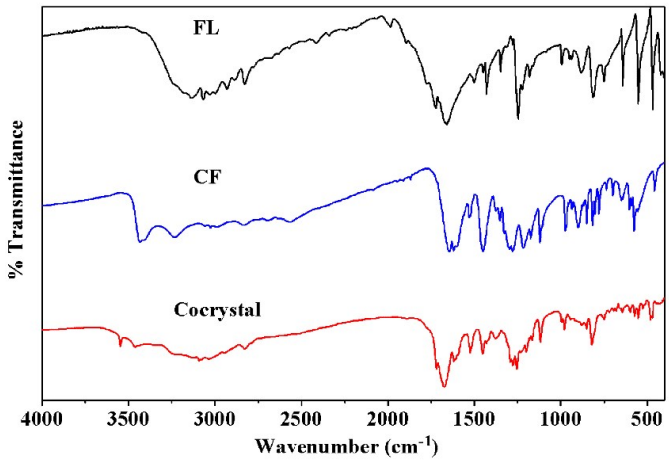

Fig. S1 FT-IR spectra of FL-CF-2H_2O cocrystal compared with the starting materials.

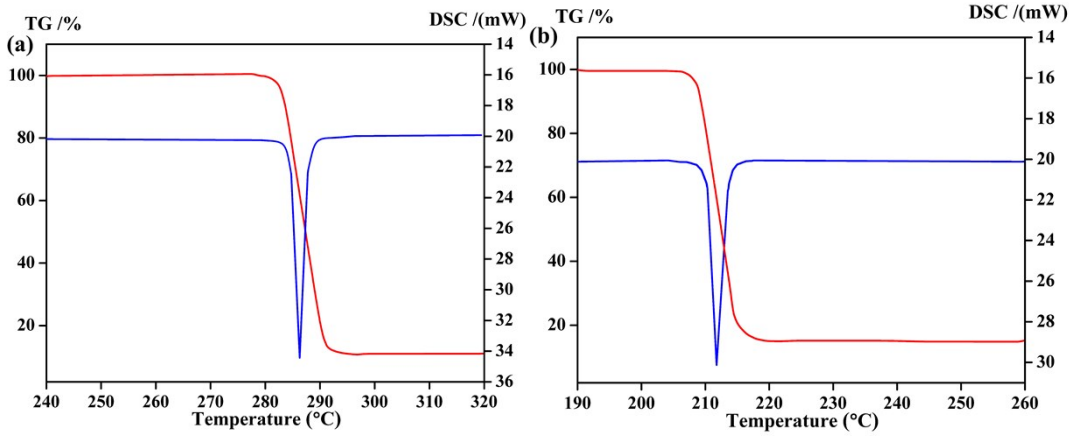

Fig. S2 DSC (blue line) and TGA (red line) profiles of pure FL (a) and CF (b).

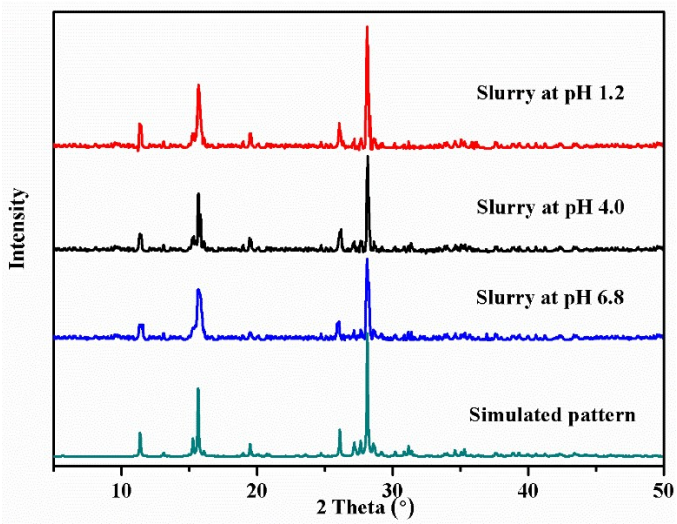

Fig. S3 PXRD comparison of simulated pattern and experimental pattern for remaining solids after the powder dissolution measurements.

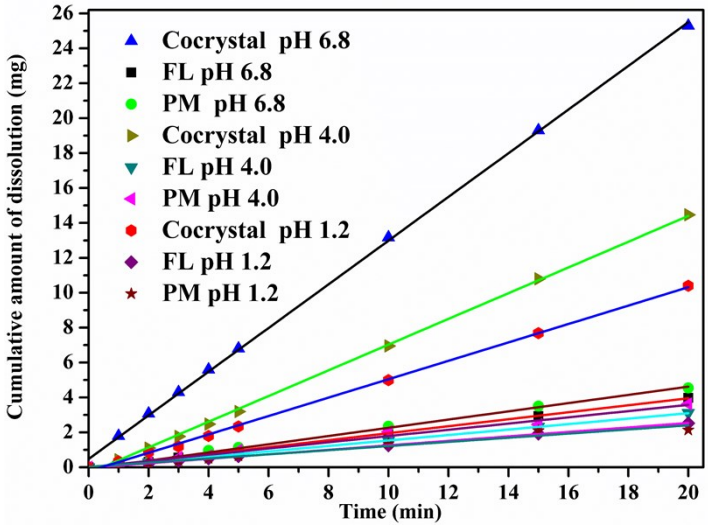

Fig. S4 IDR profiles of FL and FL-CF-2H_2O cocrystal at pH 1.2, 4.0, and 6.8 buffers.