Electronic Supplementary Information

Solid-state characterization and solubility enhancement of apremilast drug-drug cocrystals

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Methods

Materials. AP was purchased from Shanghai Demo Biological Technological Co., Ltd. with purity greater than 98%. All analytical grade organic solvents were purchased from the Sinopharm Chemical Reagent Company and used without further purification.

Preparation of cocrystals. Slow evaporation experiments were performed by dissolving each component in 2 mL of solvent according to Table S2. Crystals for physicochemical characterization were harvested after slow evaporation.

Characterization. PXRD patterns were measured at ambient temperature on a Bruker D8 Advance diffractometer using copper radiation (Cu-Kα). Data over the range 3-40° 2θ were collected with a scan speed of 0.02°·step^{-1}. The voltage and current were 40 kV and 40 mA, respectively. The data were imaged and integrated with RINT Rapid and peak-analyzed with Jade 6.0 from Rigaku.

Yellow prismatic single crystals of the cocrystals were collected for diffractions. X-ray diffractions of all single crystals were performed at 170 or 50 K on a Bruker Apex II CCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å). The data integration and scaling were processed with SAINT software, and absorption corrections were performed using the SADABS program. The structures were solved by direct method and refined on F^2 by the full-matrix least-squares technique using SHELXL-2014 program package. All non-hydrogen atoms were refined with anisotropic displacement parameters. The remaining hydrogen atoms were placed in calculated positions and refined with a riding model. CCDC 1838819 and 1838924 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Thermogravimetric analysis was carried out on a Netzsch TG 209F3 using nitrogen as the purge gas at 20 mL·min^{-1}. The samples were placed in open aluminum oxide pans and heated at 10 °C·min^{-1} to 400 °C. DSC experiments were performed on a DSC TA Q2000 instrument under a nitrogen gas flow of 50 mL·min^{-1} purge. Ground samples weighing 2-3 mg were heated in sealed aluminum pans from 40 to 200 °C with a scan rate of 10 °C·min^{-1}. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment. PLM examinations were performed on an XPV-400E polarizing microscope equipped with a JVC TK-C9201 EC digital video recorder (Shanghai Chang Fang Optical instrument Co., Ltd.).

Solubility and dissolution experiments. Equilibrium solubility was determined by suspending an excess amount of each sample in 1 mL of pH 2.0 glycine-hydrochloric acid buffer, pH 4.6 NaH_2PO_4-citric acid buffer, pH 6.8 NaH_2PO_4-citric acid buffer, and pH 2.0 buffers with the presence of 1% PEG2000, HPC, PVPK30, Tween 80, TBAB, respectively at ambient temperature for 48 h. Upon equilibration, the solutions were centrifuged at 14000 rpm for 5 min, and the supernatants were subjected to HPLC analysis. Intrinsic dissolution rate (IDR) experiments were conducted by a Mini-Bath dissolution apparatus. Approximately 3 mg of each sample was compressed into a 0.07 cm^2 disk in an intrinsic dissolution die. Only one side of the disk was exposed to the dissolution media. The intrinsic attachment was placed in a dissolution vessel containing 10 mL of pH 2.0 buffer with the presence of 1% HPC preheated at 37 °C and stirred at 75 rpm. Sampling was performed at 10, 20, 30, 45, and 60 min. 200 μL of each sample was assayed for AP concentration using HPLC.

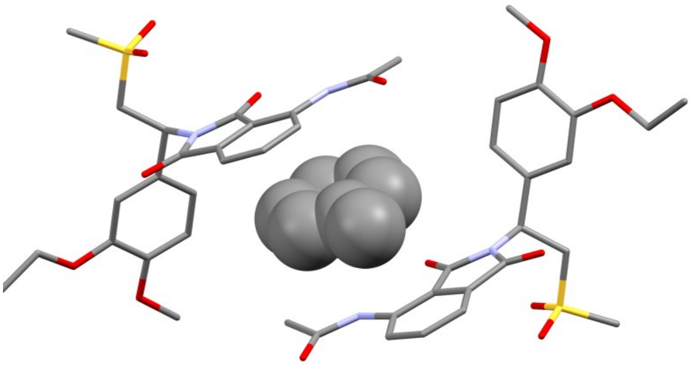


Fig. S1 A “sandwich” fashion in AP toluene solvate (CCDC Refcode MAWSOV).[1]

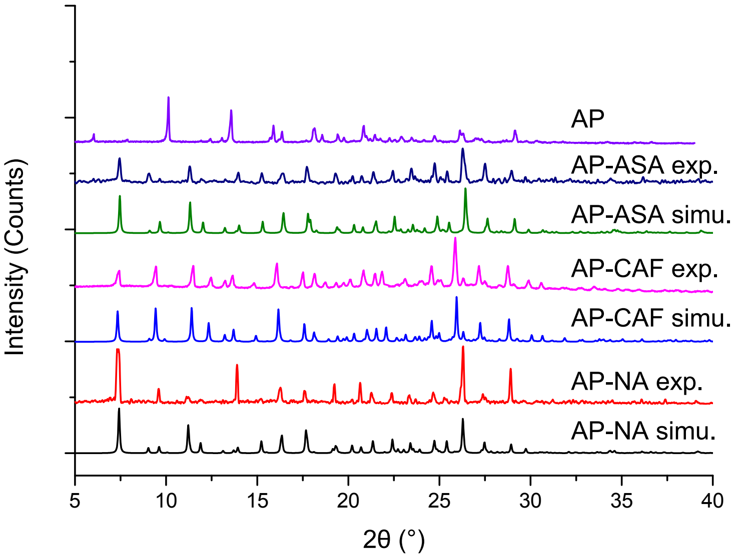


Fig. S2 PXRD patterns comparison for AP-NA, AP-CAF, and AP-ASA with their simulated patterns.

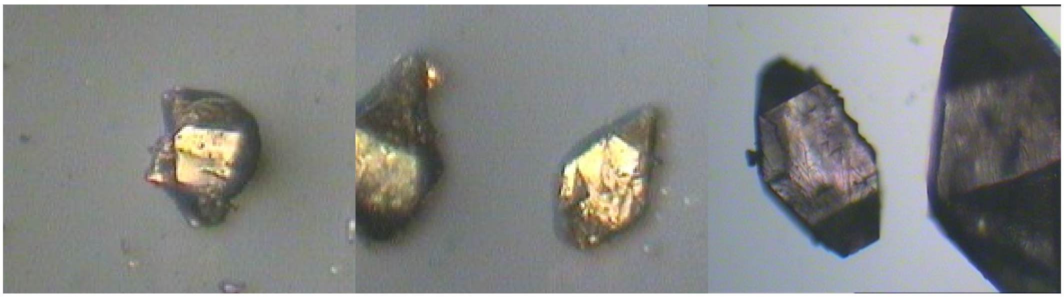
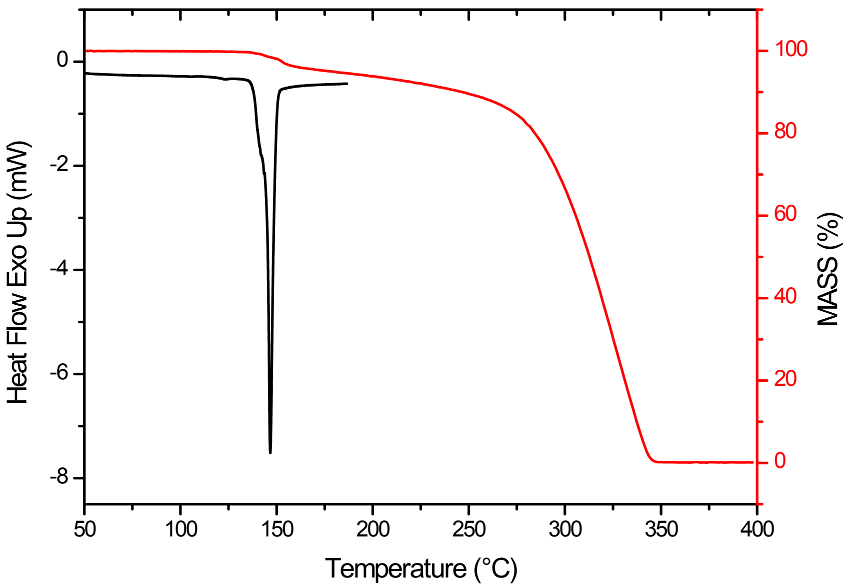
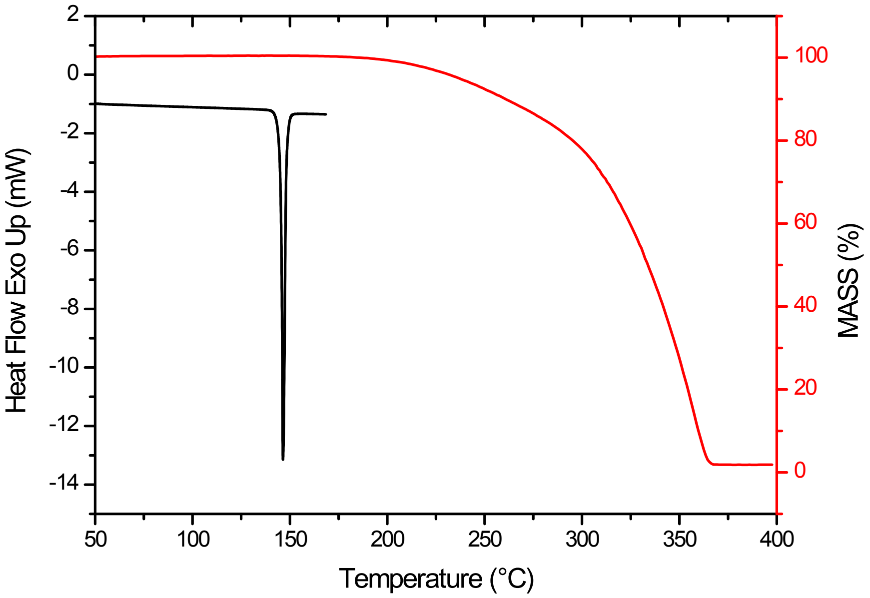


Fig. S3 PLM photographs of AP cocrystals. (left) AP-NA, (middle) AP-CAF, (right) AP-ASA.


Heat Flow Exo Up (mW)
0
-2
-4
-6
-8
MASS (%)
100
80
60
40
20
0
50
100
150
200
250
300
350
400
Temperature (°C)

(a)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-4
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-12
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MASS (%)
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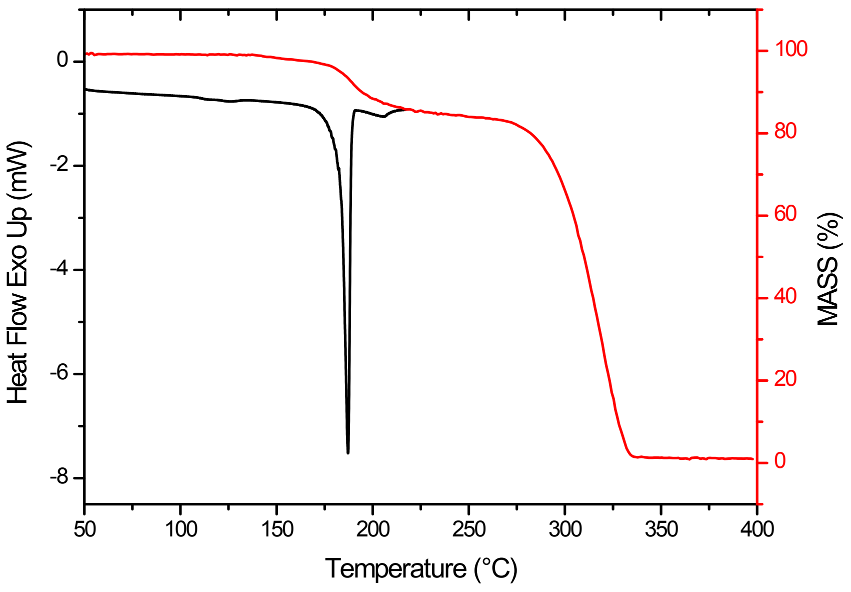
20
0
50
100
150
200
250
300
350
400
Temperature (°C)

(b)



(c)

Fig. S4 Overlaid DSC (black) and TGA (red) profiles of (a) AP-NA, (b) AP-CAF and (c) AP-ASA.

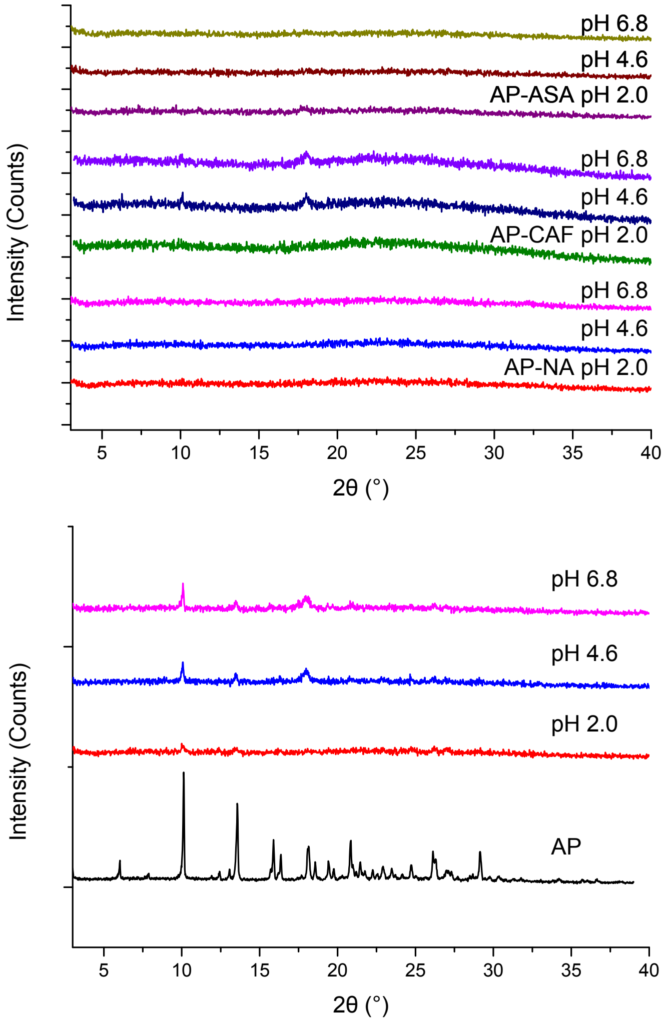


Fig. S5 PXRD patterns for residual solids recovered after AP solubility experiments.

Table S1 Crystallographic data for two cocrystals of AP.

	AP-NA	**AP-CAF**
CCDC No.	1838819	1838924
Formula	$C_{50}H_{54}N_6O_{15}S_2$	$C_{51}H_{55}N_8O_{16}S_2$
Formula weight	1043.11	1100.15
Temperature/K	170(2)	50(2)
Crystal system	tetragonal	tetragonal
Space group	$P4_12_12$	$P4_12_12$
a/Å	12.9994(8)	13.1300(3)
b/Å	12.9994(8)	13.1300(3)
c/Å	29.744(2)	28.8287(6)
α/°	90	90
β/°	90	90
γ/°	90	90
Volume/Å^3	5026.3(7)	4970.0(2)
Z	4	4
ρ_{calc}/g·cm^{-3}	1.378	1.470
R_{int}	0.0671	0.0363
GOF	1.060	1.050
Final R indexes	$R_1 = 0.0600$	$R_1 = 0.1209$
[I>=2σ (I)]	$wR_2 = 0.1552$	$wR_2 = 0.2959$
Flack parameter	-0.01(4)	0.08(3)

Table S2 Summary of components in the crystallization experiments.

cocrystal	amount of API (mg, mmol)	amount of CCF (mg, mmol)	solvent
AP-NA	46.0, 0.1	6.1, 0.05	methanol-ethyl acetate (v/v, 1/1)
AP-CAF	46.0, 0.1	9.7, 0.05	methanol-ethyl acetate (v/v, 1/1)
AP-ASA	18.4, 0.04	3.6, 0.02	methanol

References:

1 Y.-D. Wu, X.-L. Zhang, X.-H. Liu, J. Xu, M. Zhang, K. Shen, S.-H. Zhang, Y.-M. He, Y. Ma and A.-H. Zhang, *Acta Crystallogr. Sect. C*, 2017, **73**, 305–313.