Supplementary Materials: Rational Development of a Carrier-Free Dry Powder Inhalation Formulation for Respiratory Viral Infections via Quality by Design: A Drug-Drug Cocrystal of Favipiravir and Theophylline

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Table S1. Experimental outlet temperatures resulted in the DOE.

	F1	F2	F3	F4	F5	F6	F7	F8	CPs
Outlet Temperature (°C)	56	58	54	53	52	54	49	48	54

Table S2. The powder dispersion was performed at various flow rates to obtain 4 L passing air drawn into the next generation impactor (NGI) with designated pressure drops.

Flow rate (L/min)	Pressure difference (kPa)	Time required (s)
30	0.4	8.0
40	0.7	6.0
50	1.1	4.8
60	1.4	4.0

Table S3. Equilibrium solubilities of coformers and cocrystal at 20°C (n=3).

Chemical Species	Aqueous Solubility (mg/mL) (± SD)
Raw FAV	2.29 ± 0.34
Raw THP	7.14 ± 0.47
FAV-THP	FAV: 3.11 ± 0.03 THP: 3.42 ± 0.43

Table S4. Crystal data and structure refinement for THP:FAV.

Identification code	cu_IS_HKU_4FAV_THP_SEBatch2_0m	
Empirical formula	C12 H12 F N7 O4	
Formula weight	337.29	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 13.3490(6) Å	= 90°.
	b = 7.3654(3) Å	= 107.7362(14)°.
	c = 14.7643(6) Å	= 90°.
Volume	1382.64(10) Å3	
Z	4	
Density (calculated)	1.620 Mg/m3	
Absorption coefficient	1.161 mm-1	
F(000)	696	
Crystal size	0.296 x 0.220 x 0.076 mm3	
Theta range for data collection	3.913 to 72.167°.	
Index ranges	-15<=h<=16, -9<=k<=9, -18<=l<=18	
Reflections collected	41916	
Independent reflections	2730 [R(int) = 0.0402]	
Completeness to theta = 67.679°	99.90%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.6120	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2730 / 0 / 269	
Goodness-of-fit on F2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0962	
R indices (all data)	R1 = 0.0368, wR2 = 0.0974	
Extinction coefficient	0.0016(3)	
Largest diff. peak and hole	0.314 and -0.174 e.Å-3	

Table S5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for THP:FAV. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z
C(10)	5685(1)	1279(2)	-7005(1)
O(10)	6137(1)	1101(1)	-3988(1)
N(10)	5528(1)	962(2)	-6166(1)
C(11)	7033(1)	2328(2)	-5975(1)
O(11)	9156(1)	3896(1)	-4104(1)
N(11)	6592(1)	2129(2)	-6930(1)
N(12)	7981(1)	3128(1)	-5519(1)
C(12)	6403(1)	1628(2)	-5482(1)
C(13)	6667(1)	1688(2)	-4477(1)
N(13)	7638(1)	2524(2)	-4062(1)
C(14)	8313(1)	3221(2)	-4542(1)
C(15)	8012(1)	2678(3)	-3023(1)
C(16)	8680(1)	3772(2)	-6049(1)
C(24)	6472(1)	3635(2)	353(1)
C(23)	7839(1)	2181(2)	-265(1)
C(22)	9338(1)	1012(2)	752(1)
O(22)	5960(1)	4116(1)	-474(1)
N(22)	6147(1)	3925(2)	1100(1)
C(21)	8989(1)	1550(2)	1503(1)
N(21)	8757(1)	1327(2)	-138(1)
O(21)	7266(1)	2496(2)	-1163(1)
C(20)	7501(1)	2698(2)	511(1)
N(20)	8098(1)	2361(1)	1407(1)
F(20)	9606(1)	1234(1)	2398(1)

Table S6. Bond lengths [Å] and angles [°] for THP:FAV.

C(10)-N(11)	1.3372(17)
C(10)-N(10)	1.3389(17)
C(10)-H(10)	0.950(17)
O(10)-C(13)	1.2317(15)
N(10)-C(12)	1.3806(15)
N(10)-H(10N)	0.891(18)
C(11)-N(11)	1.3609(15)
C(11)-C(12)	1.3691(17)
C(11)-N(12)	1.3724(15)
O(11)-C(14)	1.2198(15)
N(12)-C(14)	1.3763(15)
N(12)-C(16)	1.4678(15)
C(12)-C(13)	1.4180(16)
C(13)-N(13)	1.3971(16)
N(13)-C(14)	1.4018(15)
N(13)-C(15)	1.4662(16)
C(15)-H(151)	1.00(2)
C(15)-H(152)	1.03(2)
C(15)-H(153)	0.92(2)
C(16)-H(161)	0.92(3)
C(16)-H(162)	0.94(2)
C(16)-H(163)	1.00(2)
C(16)-H(164)	1.0831(14)
C(16)-H(165)	0.9932(14)
C(16)-H(166)	1.0781(14)
C(24)-O(22)	1.2555(15)
C(24)-N(22)	1.3192(16)
C(24)-C(20)	1.4906(18)
C(23)-O(21)	1.3333(17)
C(23)-N(21)	1.3393(18)
C(23)-C(20)	1.4064(18)
C(22)-N(21)	1.328(2)
C(22)-C(21)	1.3845(19)
C(22)-H(22)	0.966(17)
N(22)-H(23N)	0.898(18)
N(22)-H(22N)	0.890(18)
C(21)-N(20)	1.2996(17)
C(21)-F(20)	1.3487(16)
O(21)-H(21O)	0.93(2)
C(20)-N(20)	1.3427(16)
N(11)-C(10)-N(10)	113.50(11)

N(11)-C(10)-H(10)	123.0(10)
N(10)-C(10)-H(10)	123.5(10)
C(10)-N(10)-C(12)	106.14(10)
C(10)-N(10)-H(10N)	127.5(11)
C(12)-N(10)-H(10N)	126.3(11)
N(11)-C(11)-C(12)	111.61(11)
N(11)-C(11)-N(12)	126.70(11)
C(12)-C(11)-N(12)	121.69(11)
C(10)-N(11)-C(11)	103.34(10)
C(11)-N(12)-C(14)	119.32(10)
C(11)-N(12)-C(16)	121.24(10)
C(14)-N(12)-C(16)	119.30(10)
C(11)-C(12)-N(10)	105.40(10)
C(11)-C(12)-C(13)	123.21(11)
N(10)-C(12)-C(13)	131.37(11)
O(10)-C(13)-N(13)	121.30(11)
O(10)-C(13)-C(12)	126.77(11)
N(13)-C(13)-C(12)	111.93(10)
C(13)-N(13)-C(14)	126.43(10)
C(13)-N(13)-C(15)	117.85(10)
C(14)-N(13)-C(15)	115.70(10)
O(11)-C(14)-N(12)	121.73(11)
O(11)-C(14)-N(13)	120.88(11)
N(12)-C(14)-N(13)	117.39(10)
N(13)-C(15)-H(151)	107.5(11)
N(13)-C(15)-H(152)	108.6(13)
H(151)-C(15)-H(152)	109.4(18)
N(13)-C(15)-H(153)	107.7(13)
H(151)-C(15)-H(153)	111.6(18)
H(152)-C(15)-H(153)	111.9(19)
N(12)-C(16)-H(161)	109.6(15)
N(12)-C(16)-H(162)	110.5(13)
H(161)-C(16)-H(162)	103(2)
N(12)-C(16)-H(163)	108.3(12)
H(161)-C(16)-H(163)	111.8(19)
H(162)-C(16)-H(163)	113.9(17)
N(12)-C(16)-H(164)	108.14(10)
N(12)-C(16)-H(165)	110.58(11)
H(164)-C(16)-H(165)	116.02(12)
N(12)-C(16)-H(166)	112.38(11)
H(164)-C(16)-H(166)	105.77(11)
H(165)-C(16)-H(166)	103.89(11)
O(22)-C(24)-N(22)	123.21(12)
O(22)-C(24)-C(20)	119.05(11)

N(22)-C(24)-C(20)	117.73(11)
O(21)-C(23)-N(21)	116.32(12)
O(21)-C(23)-C(20)	122.33(13)
N(21)-C(23)-C(20)	121.34(12)
N(21)-C(22)-C(21)	120.29(13)
N(21)-C(22)-H(22)	119.0(9)
C(21)-C(22)-H(22)	120.7(9)
C(24)-N(22)-H(23N)	116.8(11)
C(24)-N(22)-H(22N)	121.0(11)
H(23N)-N(22)-H(22N)	121.5(15)
N(20)-C(21)-F(20)	116.86(12)
N(20)-C(21)-C(22)	124.42(13)
F(20)-C(21)-C(22)	118.71(12)
C(22)-N(21)-C(23)	117.02(12)
C(23)-O(21)-H(21O)	102.8(14)
N(20)-C(20)-C(23)	120.78(12)
N(20)-C(20)-C(24)	118.80(11)
C(23)-C(20)-C(24)	120.42(12)
C(21)-N(20)-C(20)	116.14(11)

Table S7. Anisotropic displacement parameters ($\text{Å}^2\text{x }10^3$) for THP:FAV.   The anisotropic

displacement factor exponent takes the form: -2 $^2[\,h^2\,a^{*2}U^{11} + \dots$ $+ 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(10)	22(1)	33(1)	21(1)	-1(1)	4(1)	0(1)
O(10)	26(1)	41(1)	26(1)	1(1)	12(1)	-9(1)
N(10)	16(1)	30(1)	23(1)	-1(1)	5(1)	-3(1)
C(11)	18(1)	20(1)	21(1)	1(1)	6(1)	3(1)
O(11)	23(1)	44(1)	26(1)	-3(1)	6(1)	-12(1)
N(11)	22(1)	31(1)	20(1)	1(1)	6(1)	1(1)
N(12)	20(1)	25(1)	20(1)	1(1)	8(1)	-2(1)
C(12)	17(1)	22(1)	22(1)	0(1)	5(1)	1(1)
C(13)	18(1)	24(1)	24(1)	0(1)	8(1)	0(1)
N(13)	21(1)	34(1)	18(1)	-1(1)	6(1)	-6(1)
C(14)	19(1)	26(1)	23(1)	1(1)	7(1)	-2(1)
C(15)	39(1)	70(1)	20(1)	-4(1)	10(1)	-23(1)
C(16)	22(1)	30(1)	28(1)	2(1)	12(1)	-2(1)
C(24)	26(1)	21(1)	24(1)	0(1)	10(1)	-4(1)
C(23)	33(1)	26(1)	28(1)	-2(1)	16(1)	-4(1)
C(22)	28(1)	27(1)	43(1)	-2(1)	18(1)	0(1)
O(22)	33(1)	35(1)	24(1)	3(1)	10(1)	4(1)
N(22)	24(1)	30(1)	25(1)	1(1)	10(1)	3(1)
C(21)	26(1)	27(1)	32(1)	0(1)	11(1)	-1(1)
N(21)	35(1)	33(1)	39(1)	-4(1)	22(1)	0(1)
O(21)	44(1)	53(1)	25(1)	-2(1)	17(1)	4(1)
C(20)	27(1)	20(1)	26(1)	-1(1)	13(1)	-4(1)
N(20)	25(1)	24(1)	27(1)	-1(1)	11(1)	-2(1)
F(20)	31(1)	51(1)	35(1)	3(1)	7(1)	9(1)

Table S8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10^3) for THP:FAV.

	x	y	z	U(eq)
H(10N)	4987(14)	390(20)	-6060(12)	36(4)
H(151)	8192(16)	3980(30)	-2865(14)	55(6)
H(152)	8680(20)	1900(30)	-2770(16)	71(7)
H(153)	7476(18)	2290(30)	-2794(15)	65(7)
H(161)	9240(20)	2970(30)	-5963(16)	27(6)
H(162)	9017(17)	4850(30)	-5782(14)	16(5)
H(163)	8258(17)	3890(30)	-6738(16)	18(5)
H(164)	9465	3906	-5555	58(17)
H(165)	8385	4875	-6423	40(13)
H(166)	8747	2812	-6579	14(9)
H(10)	5197(13)	950(20)	-7599(12)	34(4)
H(23N)	5506(14)	4420(20)	989(11)	37(4)
H(22N)	6507(14)	3500(20)	1671(13)	35(4)
H(22)	10012(13)	420(20)	868(11)	33(4)
H(21O)	6678(19)	3080(30)	-1096(16)	67(7)

Table S9. Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg for THP:FAV.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N10-H10N	0.891	1.877	169.77	2.758	O10 [-x+1, -y, -z-1]
C15-H153	0.924	2.27	110.4	2.733	O10
C15-H153	0.924	2.512	131.07	3.196	O21
C16-H164^b	1.083	2.613	121.32	3.308	O11 [-x+2, -y+1, -z-1]
C16-H166^b	1.078	2.45	156.35	3.464	F20 [x, y, z-1]
C10-H10	0.95	2.237	161.37	3.152	O11 [x-1/2, -y+1/2, z-1/2]
N22-H23N	0.898	2.161	167.78	3.044	O22 [-x+1, -y+1, -z]
N22-H22N	0.89	2.27	151.79	3.083	N11 [x, y, z+1]
C22-H22	0.966	2.569	146.28	3.414	N21 [-x+2, -y, -z]
O21-H21O	0.925	1.699	154.55	2.565	O22
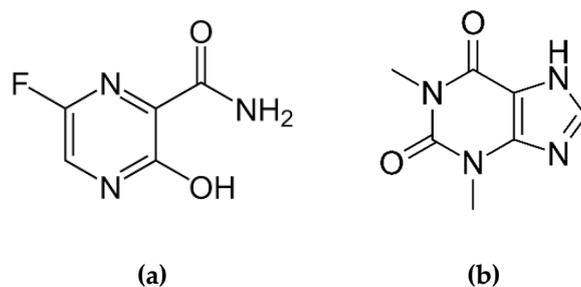
Figure S1. Chemical structures of the two APIs **(a)** Favipiravir and **(b)** Theophylline.
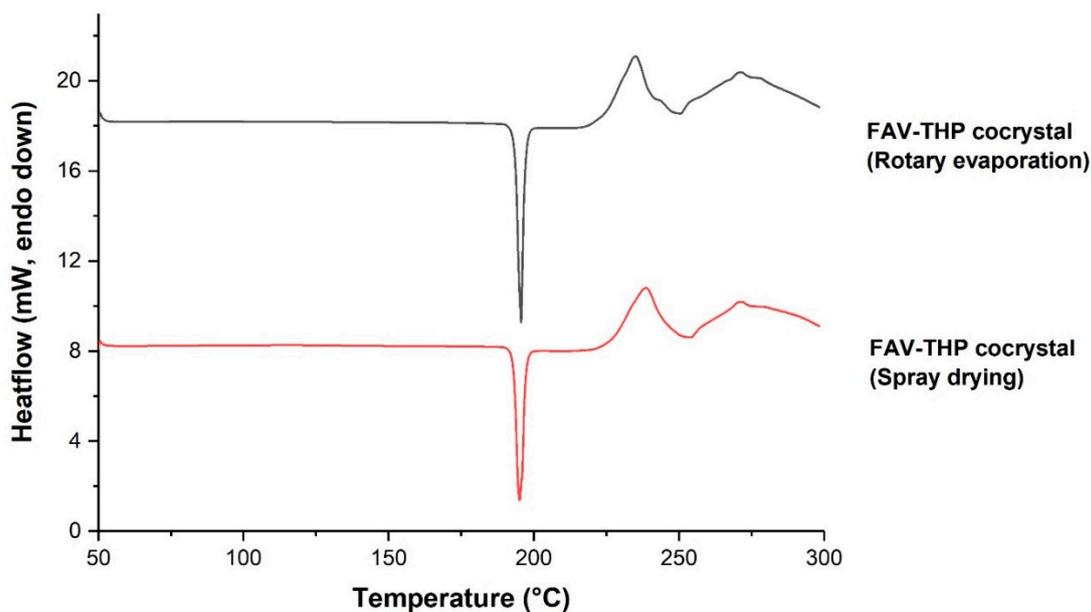
Figure S2. DSC thermograms of the FAV-THP cocrystal produced by rotary evaporation and spray drying after stability test.
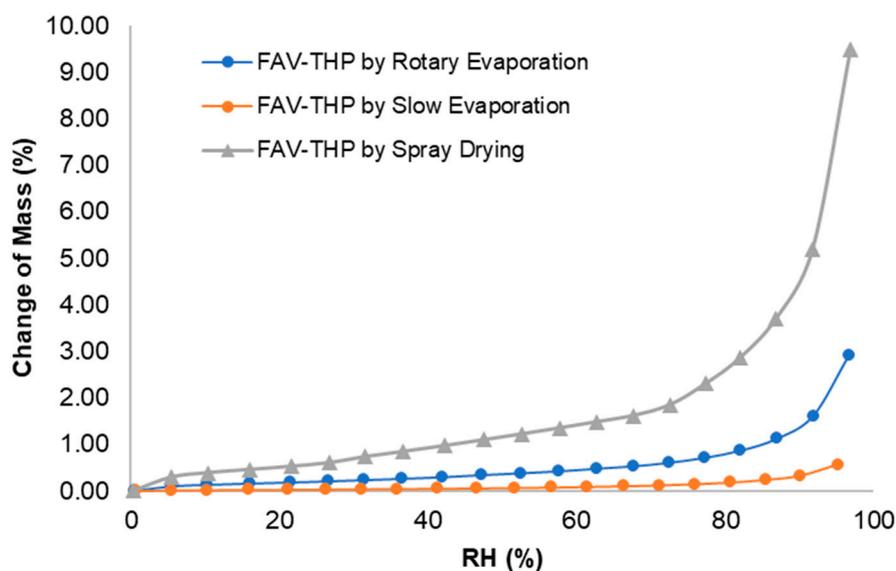
Figure S3. Water sorption isotherms at 25 °C of the FAV-THP cocrystals produced by different methods.
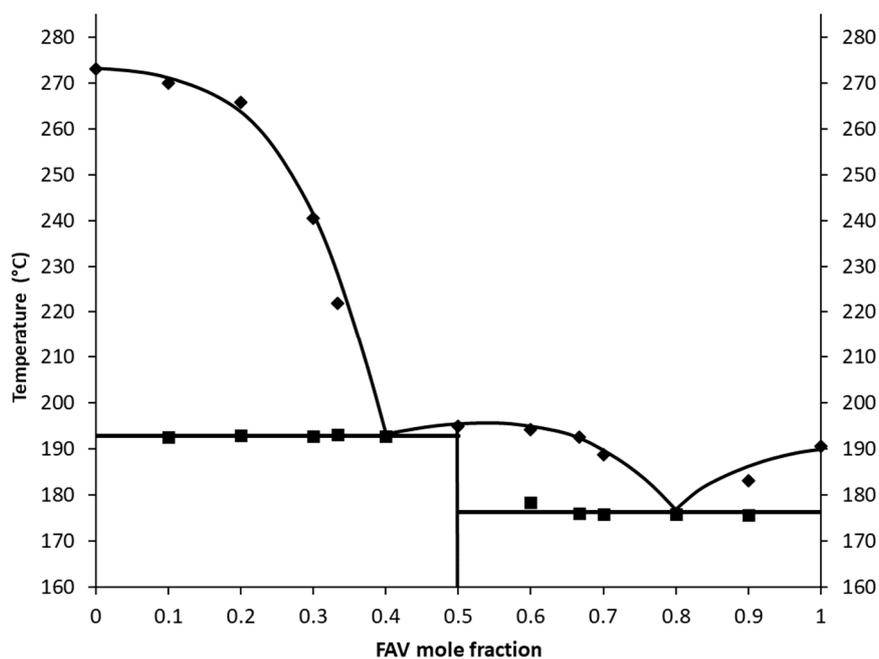
Figure S4. Temperature−composition phase diagram of the FAV-THP cocrystal system.
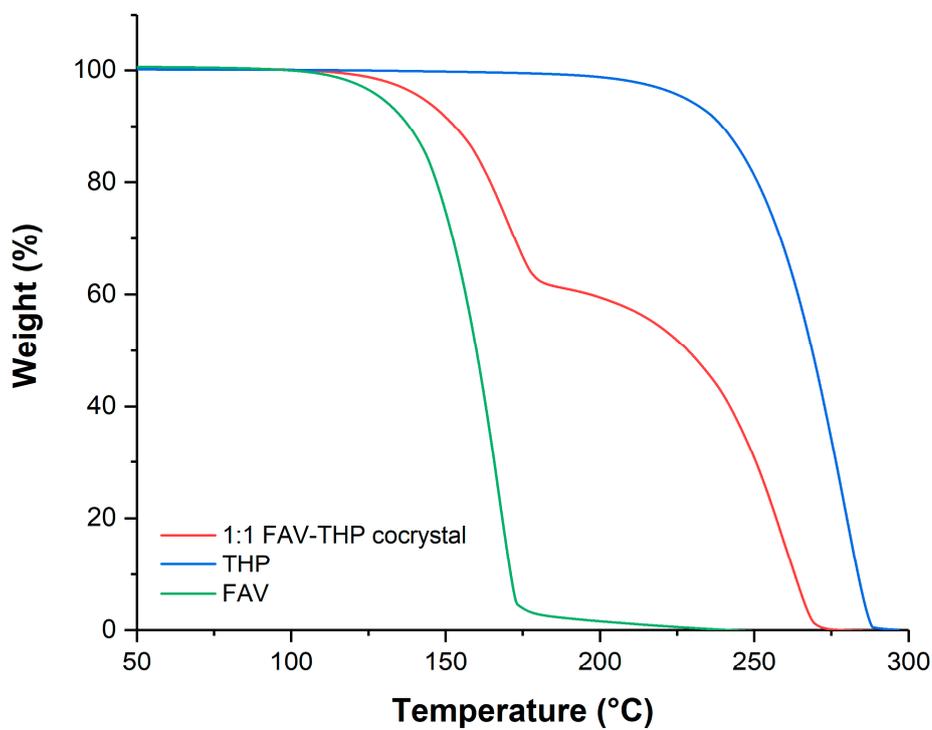
Figure S5. TGA profiles of the FAV-THP cocrystal system.
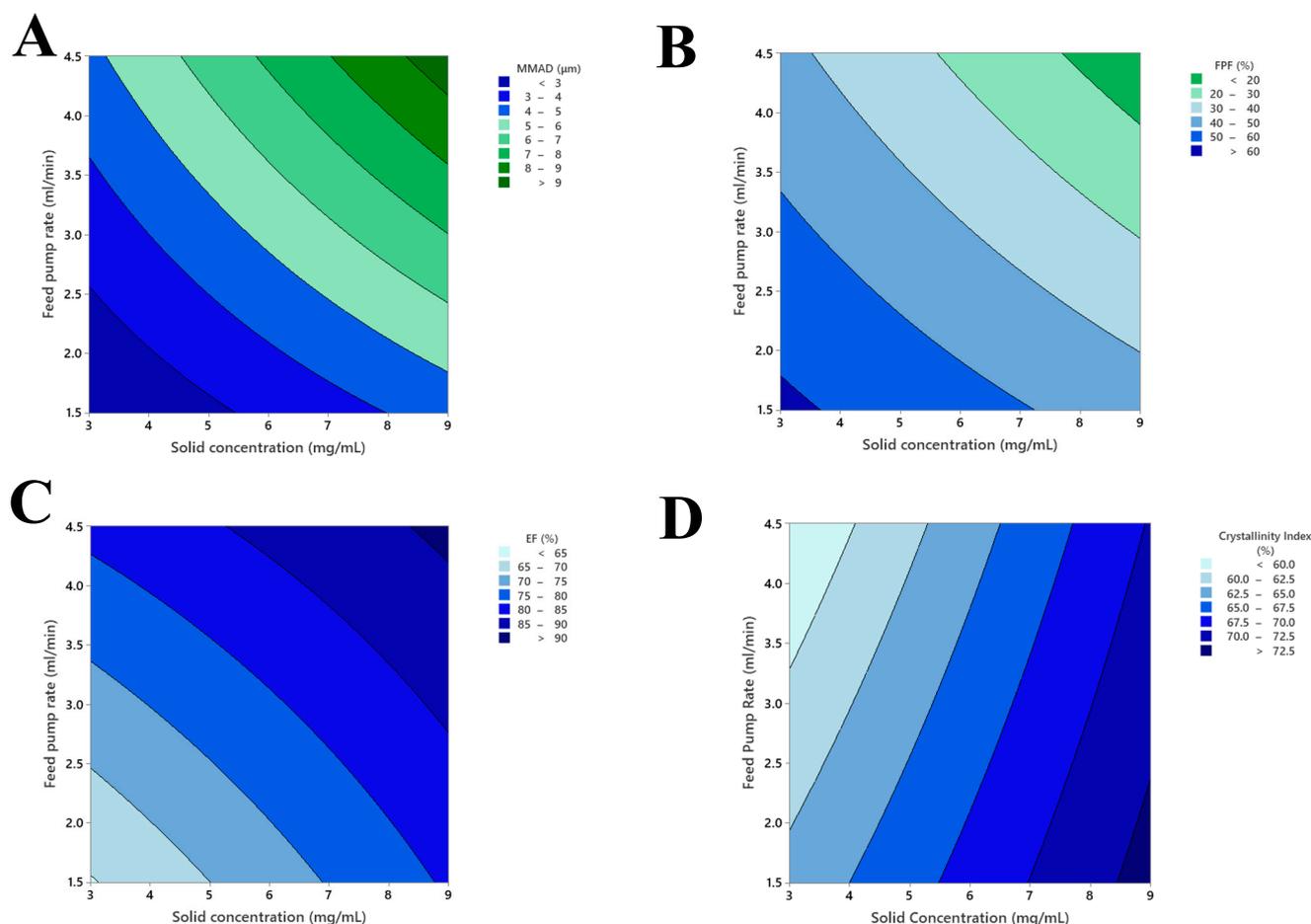
Figure S6. 2D contour plots for the (A) MMAD, (B) FPF, (C) EF, and (D) CI as projections of the total solute concentration (x-axis) and the feed pump rate (y-axis), holding a high level atomizing gas flow. The blue color represents areas within the design space where the defined limits, MMAD of <5 µm, FPF of ≥30%, EF of ≥60% and CI of ≥50%, are fulfilled.

C

EF (%)

Feed pump rate (ml/min)

Solid concentration (mg/mL)

D

CI (%)

Feed Pump Rate (ml/min)

Solid Concentration (mg/mL)
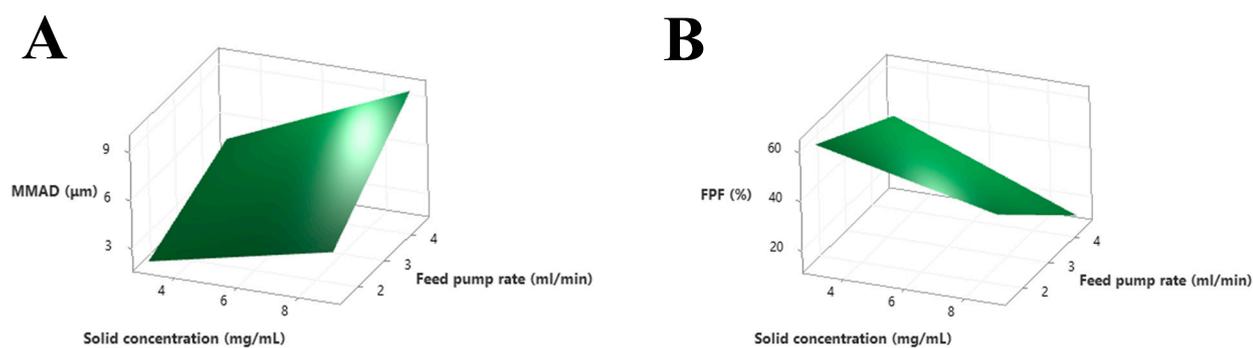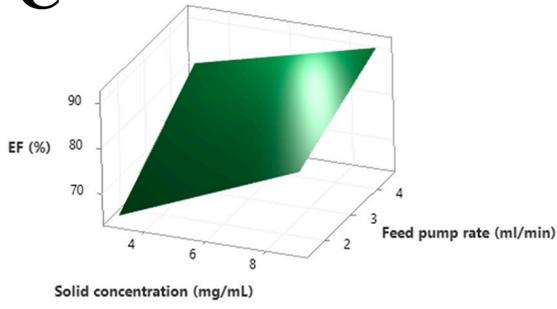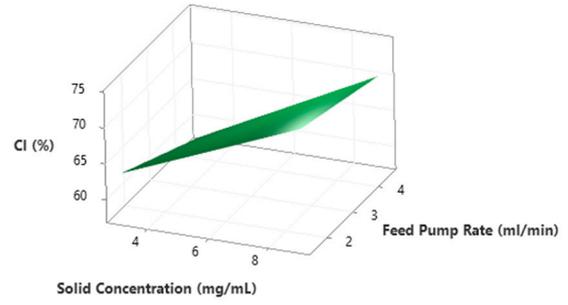
Figure S7. 3D surface plots for the (A) MMAD, (B) FPF, (C) EF, and (D) CI at high level atomizing gas flow.


F1

S4800-9528 5.0kV 5.9mm x5.00k SE(U)   10.0um

F2

S4800-9525 5.0kV 5.9mm x5.00k SE(U)   10.0um

F3

S4800-9536 5.0kV 6.2mm x5.00k SE(U)   10.0um

F4

S4800-9543 5.0kV 6.2mm x5.00k SE(U)   10.0um
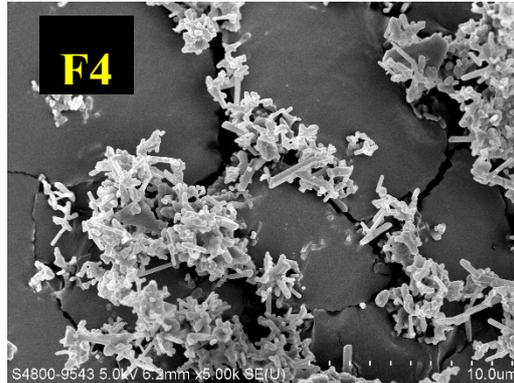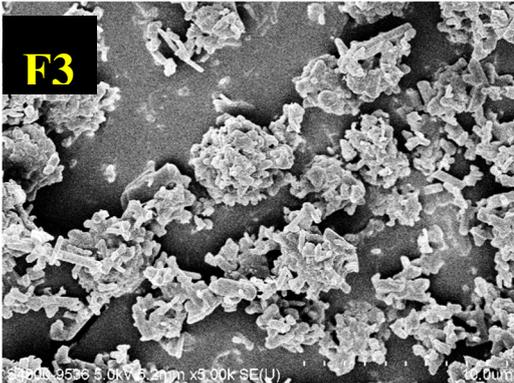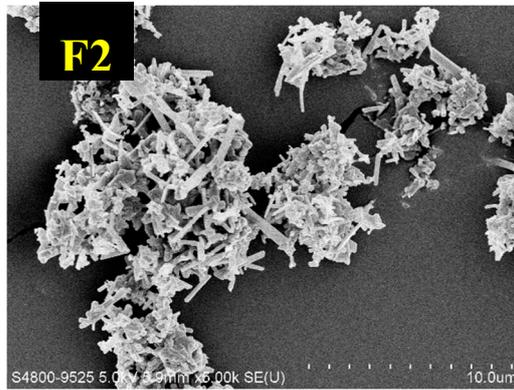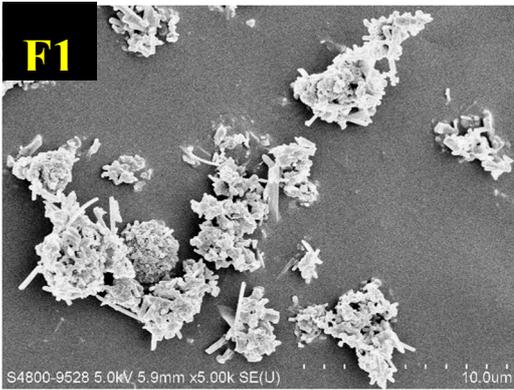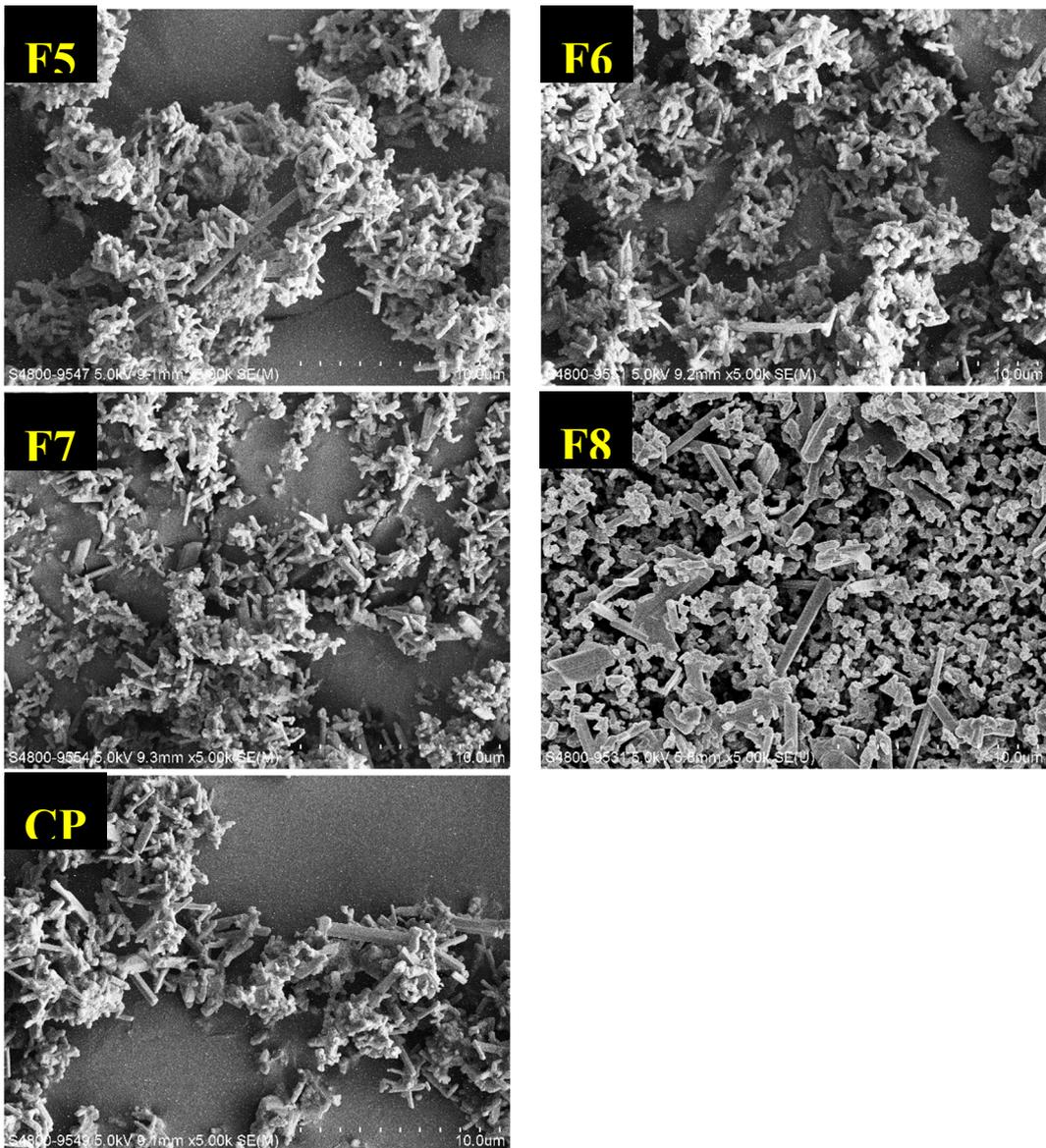
Figure S8. Scanning electron micrographs of different spray-dried cocrystal dry powder formulations at 5000× magnification.
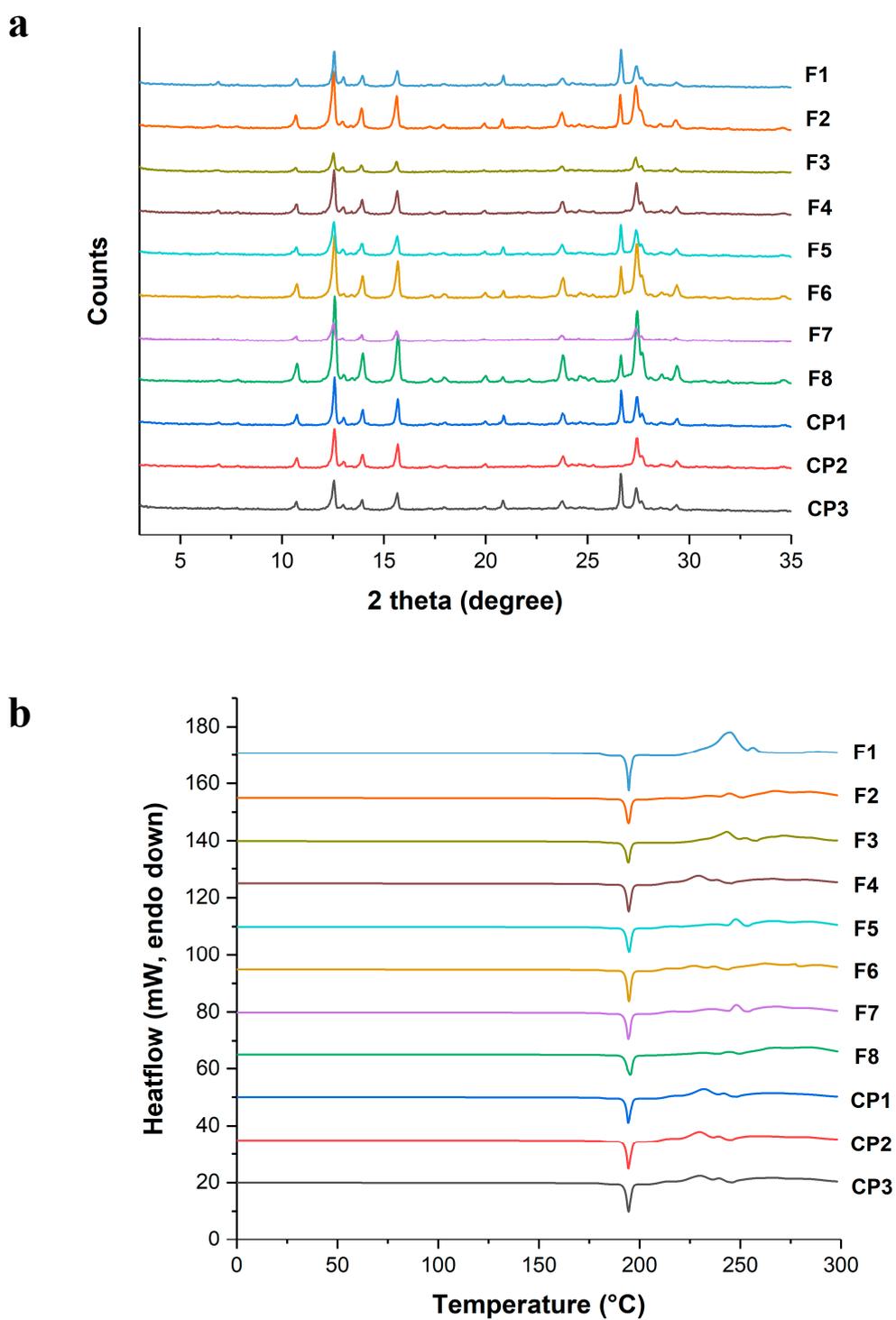
**Figure S9.** PXRD (**a**) and DSC (**b**) profiles of different spray-dried FAV-THP formulations.