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Supplementary data for

Intermolecular interactions and permeability of 5-fluorouracil cocrystals with a series of isomeric hydroxybenzoic acids: A combined theoretical and experimental study

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Table S1 Hydrogen bonding distances and angles of **5FU/SA**.

hydrogen bond	H···A (Å)	D···A (Å)	∠D–H···A (°)	symmetry
N2–H2···O1	1.96	2.817(3)	174.7	1.5-x,0.5+y,0.5-z
N1–H1···O1	1.97	2.815(3)	169.6	1.5-x,-0.5+y,0.5-z
O5–H5···O3	1.90	2.633(6)	148.1	
O4–H4···O2	1.98	2.802(4)	175.7	

Table S2 Crystallographic data and refinement parameters for **5FU/3HBA, 5FU/4HBA I** and **5FU/4HBA II.**

	5FU/3HBA	**5FU/4HBA I**	**5FU/4HBA II**
chemical formula	$C_{11}H_9FN_2O_5$	$C_{11}H_9FN_2O_5$	$C_{11}H_9FN_2O_5$
formula wt	268.20	268.20	268.20
temperature (K)	150(2)	150.02(11)	150.00(10)
crystal size (mm^3)	0.10×0.08×0.05	0.20 × 0.1 × 0.1	0.20 × 0.20 × 0.10
crystal system	triclinic	Monoclinic	Triclinic
space group	*P*-1	P21/c	*P*-1
a (Å)	7.0551(4)	7.0356(3)	6.8225(6)
b (Å)	7.5754(6)	14.9022(13)	8.6115(9)
c (Å)	10.7143(7)	10.2665(4)	10.7203(12)
α (deg)	105.869(6)	90	67.906(10)
β (deg)	96.217(5)	99.418(4)	86.057(8)
γ (deg)	97.652(5)	90	78.308(8)
volume ($Å^3$)	539.57(6)	1061.90(11)	571.46(10)
Z	2	4	2
density (g/cm^3)	1.651	1.678	1.559
2*θ* range	4.3367-66.6667	5.28–62.95	4.45–62.94
F (000)	276	552	276
index ranges	-8<=h<=6	-7<=h<=7	-7<=h<=5
	-8<=k<=9	-17<=k<=16	-9<=k<=9
	-12<=l<=12	-10<=l<=11	-10<=l<=12
no. of reflns	4288	3520	3293
no. of unique reflns	1904	1690	1808
no. of params	185	185	182
R_{all}, R_{obs}[a]	0.0607 , 0.0475	0.1014 , 0.0617	0.0630, 0.0456
w$R_{2,all}$, w$R_{2,obs}$[b]	0.1377 , 0.1253	0.1844, 0.1490	0.1266, 0.1106
Goodness-of-fit on F^2	1.056	1.055	1.054

[a] $R_1 = \Sigma \,||F_o| - |F_c||/\Sigma\,|F_o|$. $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma w(F_o^2)^2]^{1/2}$, $w = 1/[\sigma^2 (F_o)^2 + (aP)^2 + bP]$,where $P = [(F_o^2)$

Table S3 Metric and electron density properties in bond critical point of non-covalent interactions in **5FU/4HBA I**[*].

non-covalent interaction	D···A (Å) | H···A (Å)	∠D–H···A (°)	ρ_b (a.u.)	$\nabla^2\rho_b$ (a.u.)	G_b (a.u.)	E_{int} (kJ·mol^{-1})
O4–H4···O2[a]	2.621 | 1.624	172.67	0.053	0.151	0.040	**44.8**
N2–H2···O5[a]	2.765*1.731	172.89	0.042	0.121	0.031	**34.4**
N1–H1···O1[b]	3.018*1.995	173.23	0.023	0.062	0.016	**18.1**
O3–H3···O1[c]	2.948*1.978	170.11	0.023	0.061	0.016	**18.1**
O3···F1[c]	2.649	-	0.012	0.057	0.013	**14.2**
H9···H9[d]	1.869	-	0.014	0.047	0.010	**11.6**
C6–H6···O2[e]	3.215*2.320	138.70	0.013	0.041	0.010	**10.9**
C7–H7···O4[e]	3.277*2.358	141.70	0.011	0.037	0.009	**9.7**
C7–H7···F1[f]	3.261*2.580	120.22	0.006	0.029	0.006	**6.5**
C10–H10···O5[d]	3.479*2.617	136.00	0.007	0.024	0.005	**5.7**
C8···C1[g]	3.261	-	0.006	0.022	0.004	**4.8**
C3···O4[f]	3.231	-	0.006	0.021	0.004	**4.8**
C9···N1[g]	3.342	-	0.006	0.018	0.004	**4.5**
C9···O1[h]	3.329	-	0.005	0.020	0.004	**4.5**
C5···N2[i]	3.343	-	0.006	0.017	0.004	**4.2**
C8···C4[i]	3.345	-	0.006	0.018	0.004	**4.2**
C3···O2[h]	3.344	-	0.004	0.018	0.003	**3.9**
C3···C7[j]	3.395	-	0.006	0.017	0.003	**3.9**
C3–H3A···O3[d]	3.877*2.816	166.53	0.004	0.015	0.003	**3.5**
C9–H9···N1[h]	3.718*2.958	127.72	0.004	0.015	0.003	**3.4**
C6···N2[g]	3.484	-	0.005	0.014	0.003	**3.4**
H6···H10[k]	2.600	-	0.004	0.013	0.002	**2.7**
E_{latt} (kJ·mol^{-1})						**222.0**

[*]The electron density ρ_b, Laplacian of electron density $\nabla^2\rho_b$ and local electronic kinetic energy density G_b at the bond critical point; the energy of the intermolecular noncovalent interaction E_{int}.
Symmetry codes: [a] x,y,z; [b] 1-x,1-y,1-z; [c] x,-1+y,z; [d] -x,-y,-z; [e] 1-x,-y,1-z; [f] x,1/2-y,1/2+z; [g] 1-x,-1/2+y,1/2-z; [h] x,1/2-y,-1/2+z; [i] -x,-1/2+y,1/2-z; [j] -x,1/2+y,1/2-z; [k] x,-1/2-y,1/2+z.

Table S4 Metric and electron density properties in bond critical point of non-covalent interactions in **5FU/4HBA II**[*].

non-covalent interaction	D···A (Å) | H···A (Å)	∠D–H···A (°)	ρ_b (a.u.)	$\nabla^2\rho_b$ (a.u.)	G_b (a.u.)	E_{int} (kJ·mol^{-1})
O4–H4···O5[a]	2.598*1.588	177.13	0.058	0.157	0.044	**49.3**
O3–H3···O1[b]	2.619*1.731	148.30	0.039	0.132	0.031	**35.4**
N1–H1···O2[c]	2.808*1.776	175.15	0.037	0.111	0.027	**30.9**
N2–H2···O2[d]	2.840*1.851	160.81	0.031	0.093	0.023	**26.0**
C3–H3A···O1[e]	3.344*2.388	146.59	0.010	0.035	0.008	**8.9**
C3–H3A···O3[f]	3.234*2.468	126.85	0.009	0.033	0.007	**8.1**
C3–H3A···O4[g]	3.281*2.558	123.49	0.008	0.029	0.006	**6.9**
N1···O4[h]	3.126	-	0.008	0.024	0.006	**6.5**
C6–H6···F1[b]	3.563*2.510	163.26	0.006	0.027	0.006	**6.4**
O1···O4[i]	3.140	-	0.006	0.024	0.005	**6.1**
C2···C9[j]	3.178	-	0.007	0.024	0.005	**5.2**
N2···O5[k]	3.228	-	0.005	0.021	0.005	**5.1**
C4···O5[i]	3.213	-	0.006	0.022	0.004	**5.0**
C10–H10···F1[l]	3.455*2.667	129.09	0.005	0.022	0.004	**4.8**
O3···F1[l]	3.226	-	0.004	0.021	0.004	**4.7**
C6···C7[i]	3.428	-	0.006	0.017	0.004	**4.0**
C5···C1	3.305	-	0.005	0.018	0.003	**3.9**
E_{latt} (kJ·mol^{-1})						**216.9**

[*]The electron density ρ_b, Laplacian of electron density $\nabla^2\rho_b$ and local electronic kinetic energy density G_b at the bond critical point; the energy of the intermolecular noncovalent interaction E_{int}.
Symmetry codes: [a] -x,-y,1-z; [b] x,y,z; [c] -x,2-y,-1-z; [d] 1-x,2-y,-1-z; [e] 1+x,1+y,z; [f] 1+x,y,z; [g] 1-x,1-y,-z; [h] x,1+y,1+z; [i] -x,1-y,-z; [j] -x,2-y,-z; [k] 1+x,1+y,-1+z; [l] -1+x,1+y,z.

Table S5 Metric and electron density properties in bond critical point of non-covalent interactions in **5FU/3HBA**[*].

non-covalent interaction	D···A (Å) | H···A (Å)	∠D–H···A (°)	ρ_b (a.u.)	$\nabla^2\rho_b$ (a.u.)	G_b (a.u.)	E_{int} (kJ·mol^{-1})
O2–H2···O3[a]	2.597*1.588	174.84	0.059	0.156	0.044	**49.2**
N2–H2A···O5[b]	2.818*1.789	174.30	0.036	0.106	0.026	**29.8**
N1–H1B···O5[c]	2.888*1.862	173.57	0.030	0.088	0.022	**24.7**
O1–H1···O4[d]	2.801*1.852	162.65	0.028	0.092	0.022	**24.7**
C4–H4···F1[d]	3.217*2.154	167.04	0.015	0.051	0.013	**14.4**
C6–H6···O3[e]	3.261*2.355	140.02	0.012	0.038	0.009	**10.2**
C1–H1A···O2[f]	3.381*2.352	158.54	0.011	0.036	0.008	**9.4**
C3–H3···O1[g]	3.411*2.636	127.96	0.007	0.026	0.006	**6.2**
C4···C4[h]	3.152	-	0.008	0.024	0.005	**5.6**
C11-H11···O4[e]	3.601*2.593	154.51	0.006	0.023	0.005	**5.6**
F1···O1[e]	3.155	-	0.004	0.023	0.005	**5.2**
C11–H11···O1[e]	3.455*2.666	129.27	0.005	0.021	0.004	**4.9**
N2···O2[h]	3.291	-	0.005	0.020	0.004	**4.9**
C7···O5[i]	3.186	-	0.006	0.022	0.004	**4.8**
C11–H11···F1[j]	3.254*2.734	109.12	0.004	0.023	0.004	**4.8**
F1···F1[j]	3.162	-	0.003	0.022	0.004	**4.7**
C6···O5[k]	3.300	-	0.006	0.019	0.004	**4.5**
C5···N1[i]	3.444	-	0.006	0.019	0.004	**4.5**
C2···C9[i]	3.274	-	0.006	0.020	0.004	**4.3**
C11···C7[h]	3.368	-	0.005	0.017	0.003	**3.7**
C8···C5[h]	3.408	-	0.005	0.015	0.003	**3.4**
C6···O1[h]	3.450	-	0.004	0.015	0.003	**3.3**
C1···O4[h]	3.470	-	0.004	0.014	0.003	**3.1**
C1–H1A···N1[k]	3.737*3.144	115.39	0.003	0.012	0.002	**2.6**
E_{latt} (kJ·mol^{-1})						**238.6**

[*]The electron density ρ_b, Laplacian of electron density $\nabla^2\rho_b$ and local electronic kinetic energy density G_b at the bond critical point; the energy of the intermolecular noncovalent interaction E_{int}.

Symmetry codes: [a] 2-x,-y,-1-z; [b] -x,-1-y,1-z; [c] 1-x,-1-y,1-z; [d] x,y,z; [e] -1+x,y,z; [f] 1-x,-y,-1-z; [g] 2-x,-y,-z; [h] 1-x,-y,-z; [i] 1-x,-1-y,-z ; [j] -x,-1-y,-z; [k] x,y,-1+z.

Table S6 Metric and electron density properties in bond critical point of non-covalent interactions in **5FU/SA**[*].

non-covalent interaction	D···A (Å) | H···A (Å)	∠D—H···A (°)	ρ_b (a.u.)	$\nabla^2\rho_b$ (a.u.)	G_b (a.u.)	E_{int} (kJ·mol^{-1})
O5–H5···O6[a]	2.570*1.673	147.69	0.051	0.145	0.039	**43.6**
N2–H2···O4[b]	2.787*1.760	173.12	0.038	0.116	0.029	**32.3**
O7–H7···O1[a]	2.745*1.750	176.05	0.039	0.111	0.028	**31.2**
N4–H4···O2[a]	2.801*1.773	174.07	0.037	0.112	0.028	**31.0**
N1–H1···O4[a]	2.815*1.784	174.71	0.036	0.108	0.027	**30.3**
N3–H3···O2[c]	2.833*1.805	173.67	0.035	0.103	0.025	**28.7**
F001···O7[a]	2.687	-	0.011	0.055	0.012	**13.5**
F001···O6[b]	2.696	-	0.011	0.050	0.011	**12.8**
C13–H13···F1[d]	3.20*2.288	143.06	0.011	0.043	0.010	**11.1**
C11–H11···F1[e]	3.396*2.343	163.48	0.010	0.037	0.008	**9.5**
C10–H10···O5[b]	3.429*2.386	160.85	0.011	0.034	0.008	**9.1**
C12–H12···O3[e]	3.375*2.439	143.79	0.009	0.033	0.007	**8.3**
C5–H5A···O3[b]	3.433*2.414	156.12	0.009	0.032	0.007	**8.1**
C1–H1A···O1[b]	3.438*2.412	157.22	0.009	0.031	0.007	**8.1**
C7···O1[f]	3.029	-	0.008	0.029	0.006	**6.8**
C15···O4[g]	3.067	-	0.007	0.027	0.006	**6.4**
C3···O3[g]	3.090	-	0.007	0.026	0.005	**6.1**
C7···O5[h]	3.133	-	0.007	0.026	0.005	**6.0**
N1···O5[f]	3.252	-	0.006	0.023	0.005	**5.7**
C14···N3[i]	3.232	-	0.007	0.022	0.005	**5.4**
O2···F001[j]	3.107	-	0.004	0.023	0.005	**5.2**
N4···O6[f]	3.212	-	0.006	0.020	0.005	**5.2**
C15···O3[i]	3.153	-	0.006	0.023	0.005	**5.2**
C1–H1A···O6[b]	3.385*2.695	121.09	0.006	0.022	0.005	**5.1**
C5–H5A···O7[k]	3.331*2.821	108.72	0.005	0.022	0.004	**4.8**
C10···N4[l]	3.336	-	0.006	0.017	0.004	**4.1**
C12···O2[m]	3.427	-	0.005	0.018	0.004	**4.1**
N3···O7[f]	3.382	-	0.004	0.016	0.003	**3.9**
C3···C13[f]	3.408	-	0.005	0.016	0.003	**3.6**
C10···N2[n]	3.413	-	0.005	0.015	0.003	**3.6**
H12···H5A[d]	2.434	-	0.004	0.014	0.002	**2.8**
C1···C11[f]	3.559	-	0.004	0.012	0.002	**2.6**
C5···C1[n]	3.638	-	0.003	0.009	0.002	**2.1**
E_{latt} (kJ·mol^{-1})						**322.3**

[*]The electron density ρ_b, Laplacian of electron density $\nabla^2\rho_b$ and local electronic kinetic energy density G_b at the bond critical point; the energy of the intermolecular noncovalent interaction E_{int}.

Symmetry codes: [a] x,y,z; [b] x,1+y,z; [c] x,-1+y,z; [d] -1/2+x,-1/2+y,1+z; [e] -1/2+x,1/2+y,1+z; [f] x,-y,-1/2+z; [g] x,-y,1/2+z; [h] 1/2+x,-1/2-y,-1/2+z; [i] -1/2+x,-1/2-y,1/2+z; [j] x,1-y,-1/2+z; [k] 1/2+x,1/2-y,-1/2+z; [l] 1/2+x,1/2-y,-1/2+z; [m] -1/2+x,1/2-y,1/2+z; [n] x,1-y,1/2+z.

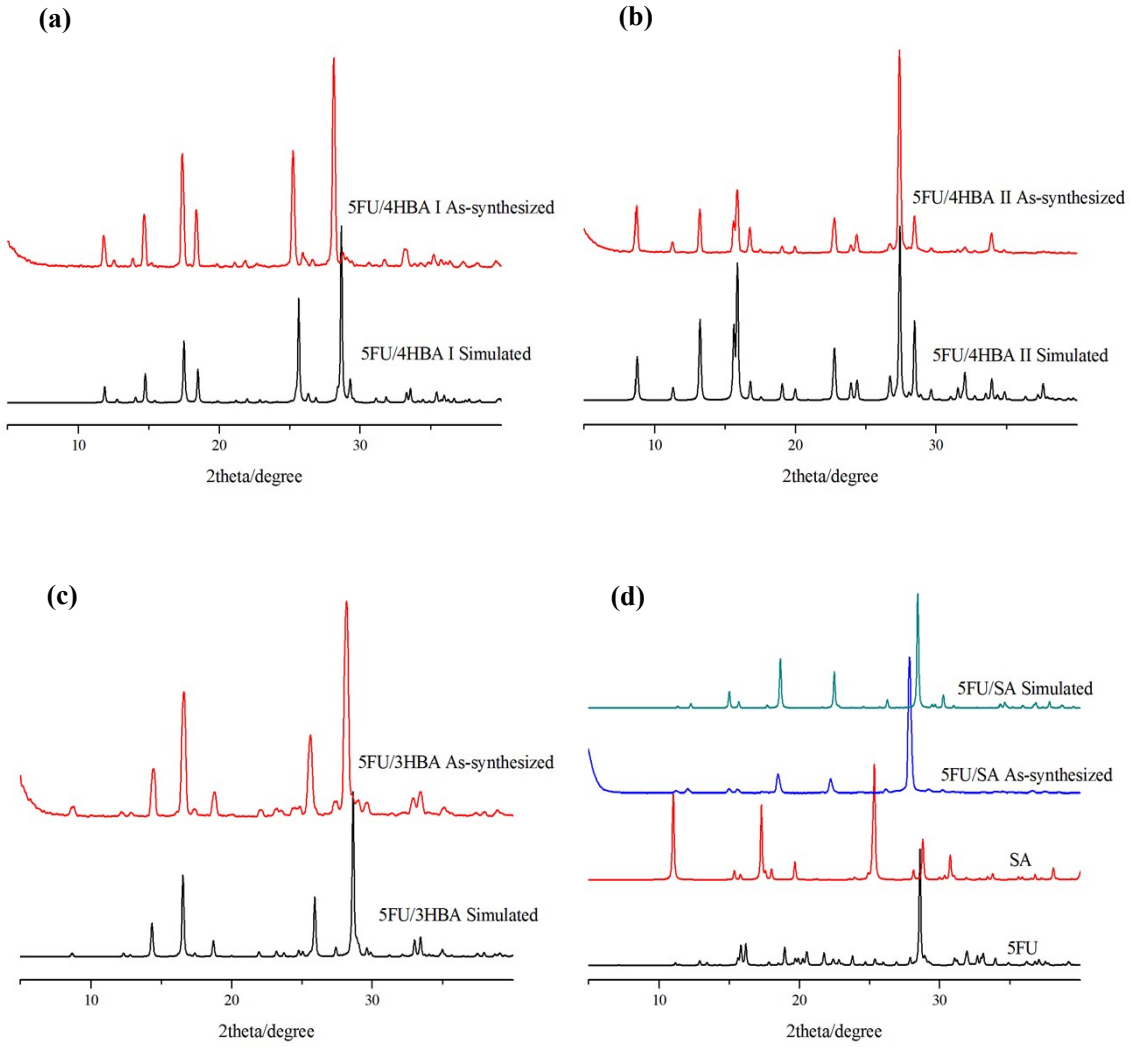

Fig. S1 XRPD patterns of as-synthesized samples and simulated from the single crystal data for (a) **5FU/4HBA I**, (b) **5FU/4HBA II**, (c) **5FU/3HBA** and (d) **5FU/SA**.

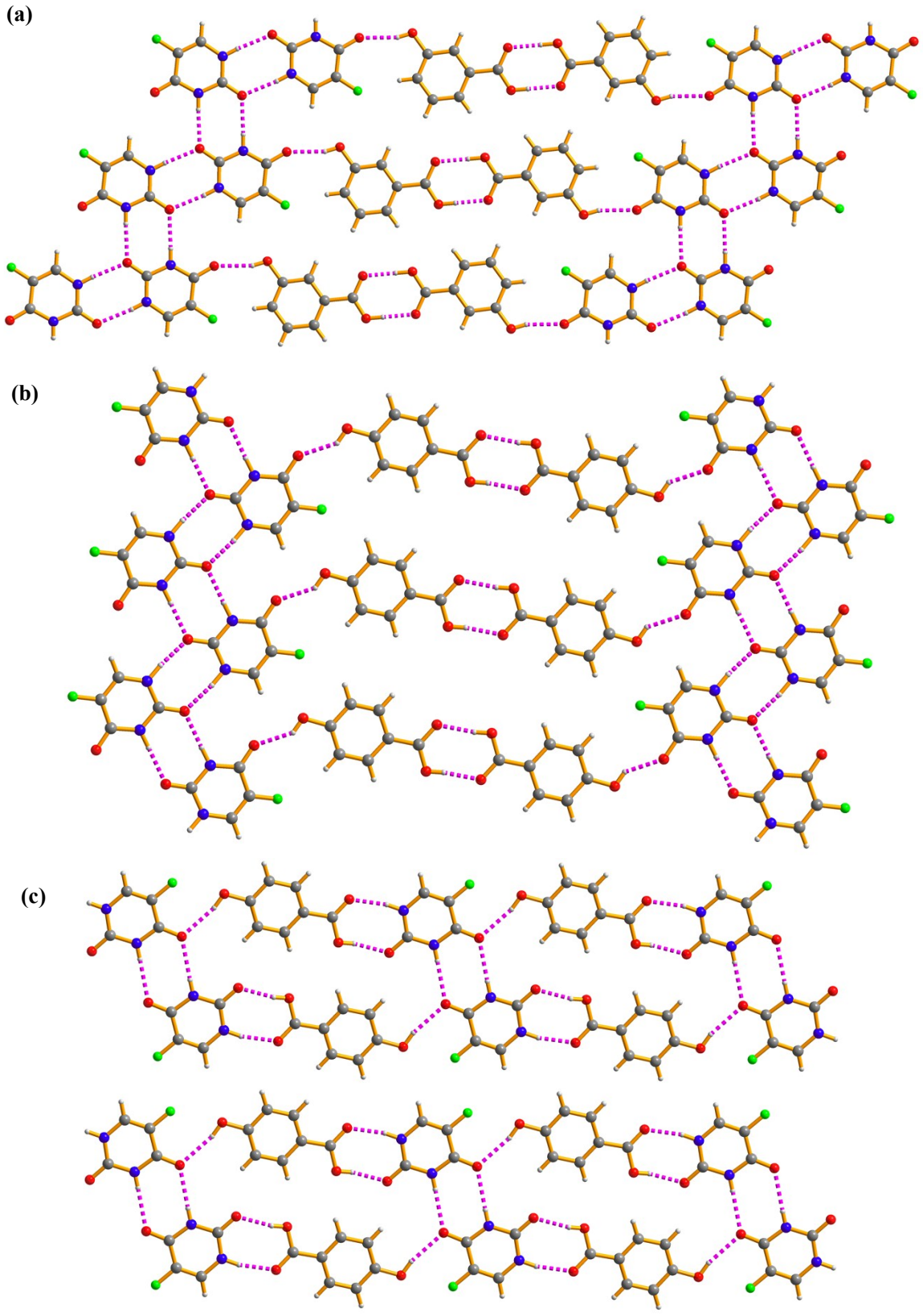

Fig. S2 2D sheet structures of (a) **5FU/3HBA**, (b) **5FU/4HBA II** and (c) **5FU/4HBA I**.

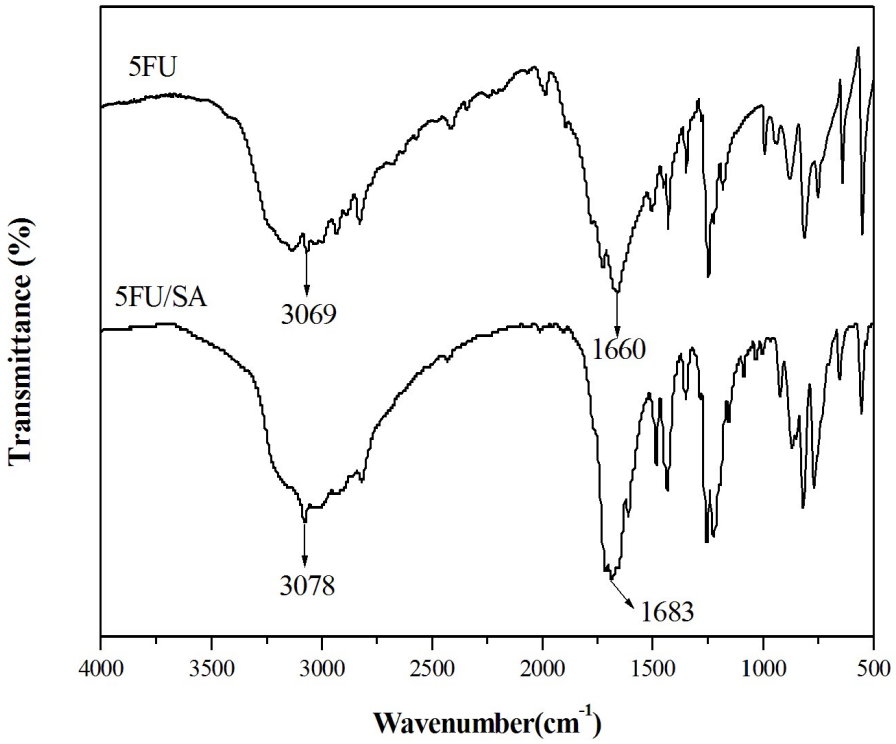

Fig. S3 IR spectra of 5FU and **5FU/SA**.

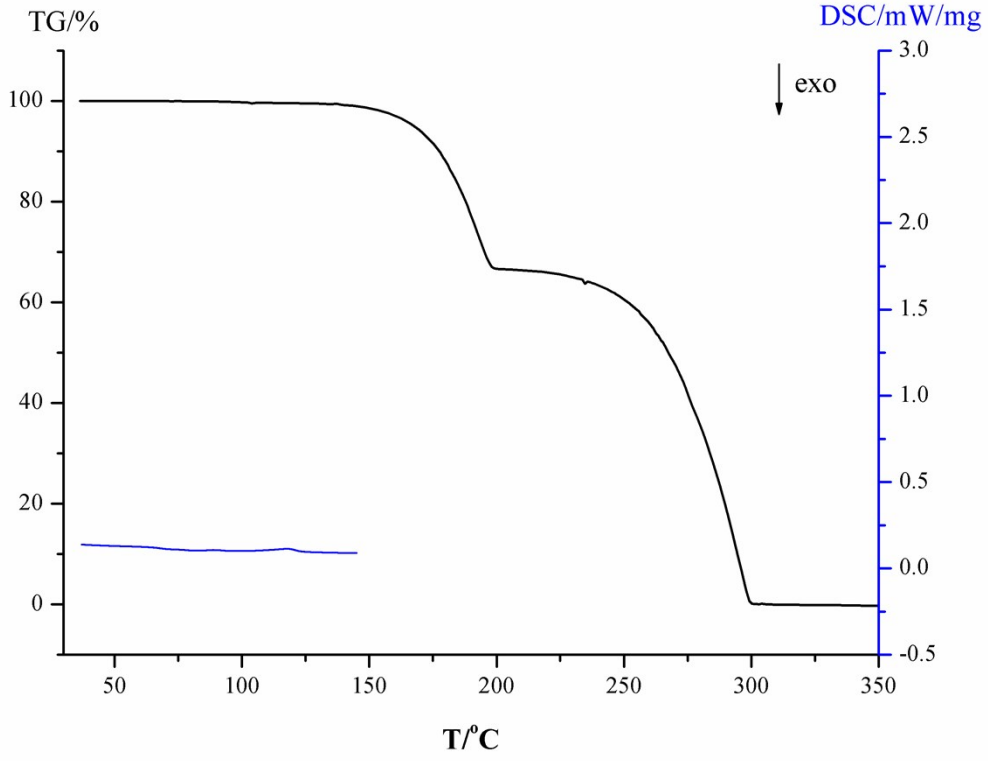

Fig. S4 TG/DSC curve of **5FU/SA**.

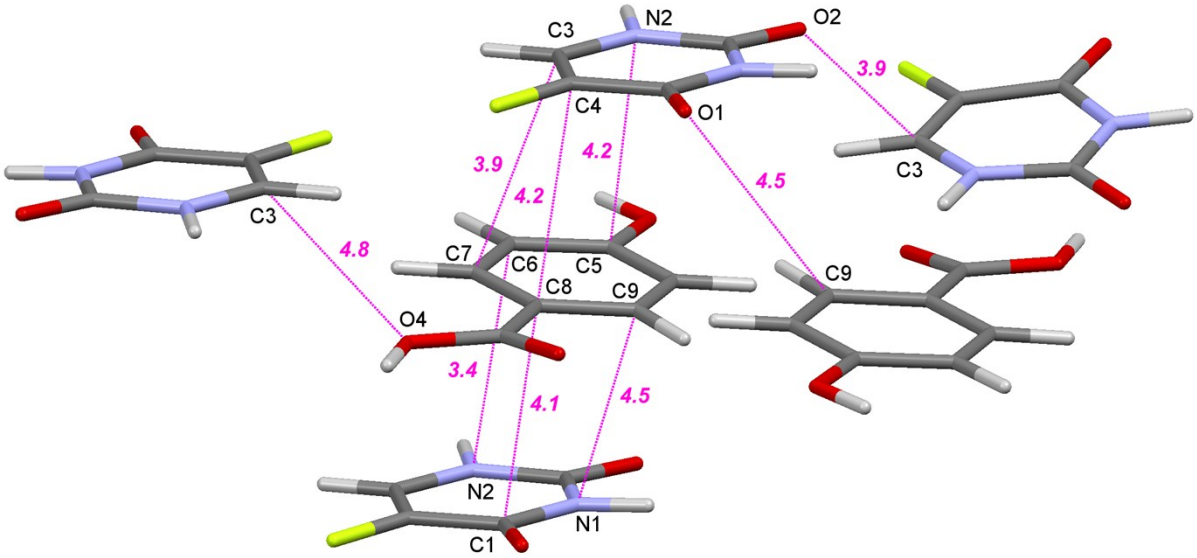

Fig. S5 The π-stacking and van der Waals interactions in **5FU/4HBA I**. The interaction energies are given in kJ·mol^{-1}.

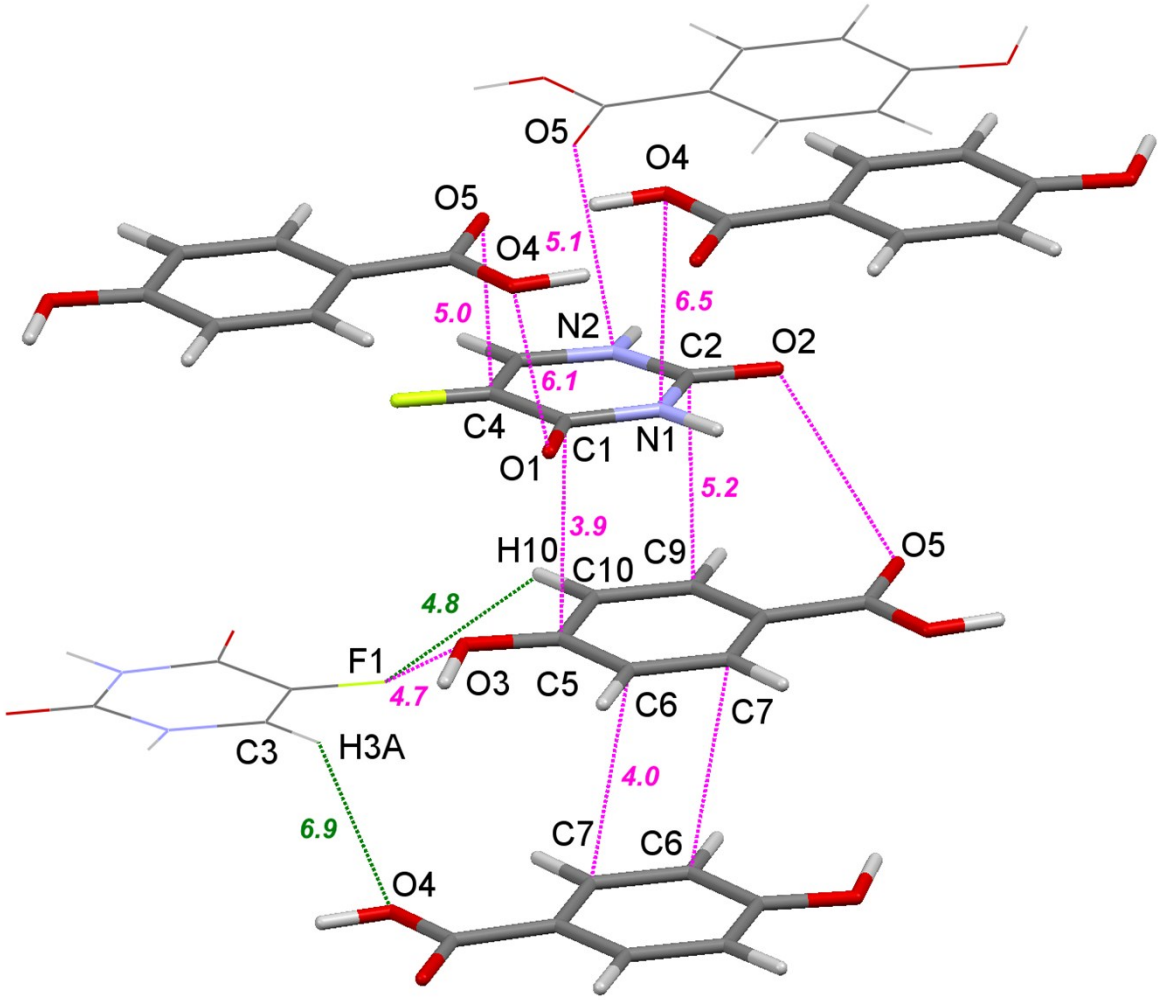

Fig. S6 The C–H···O contacts (green) and π-stacking interactions (magenta) in **5FU/4HBA II**. The interaction energies are given in kJ·mol^{-1}.

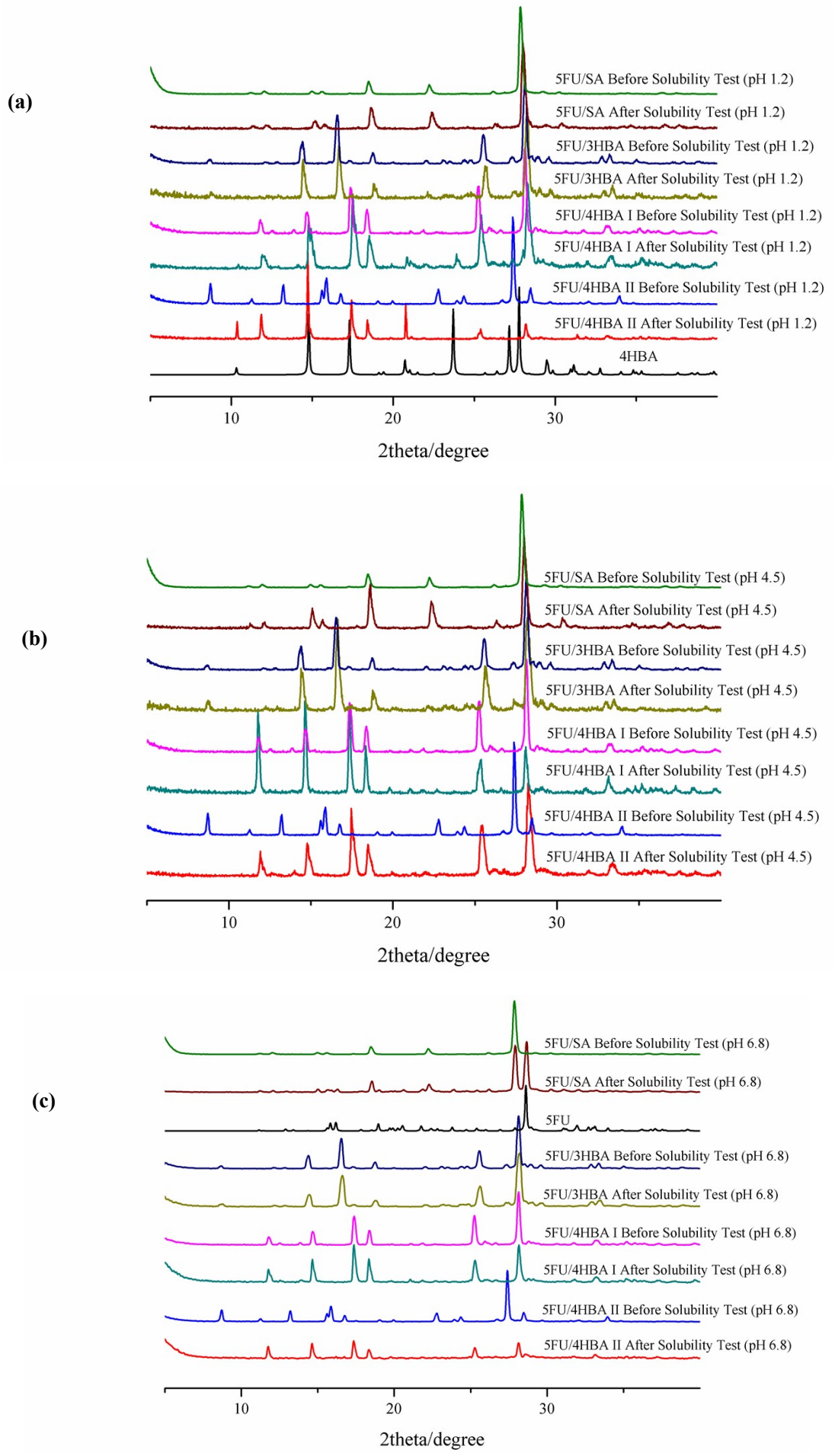

Fig. S7 XRPD patterns of 5FU cocrystals before and after solubility test in different pH buffers.

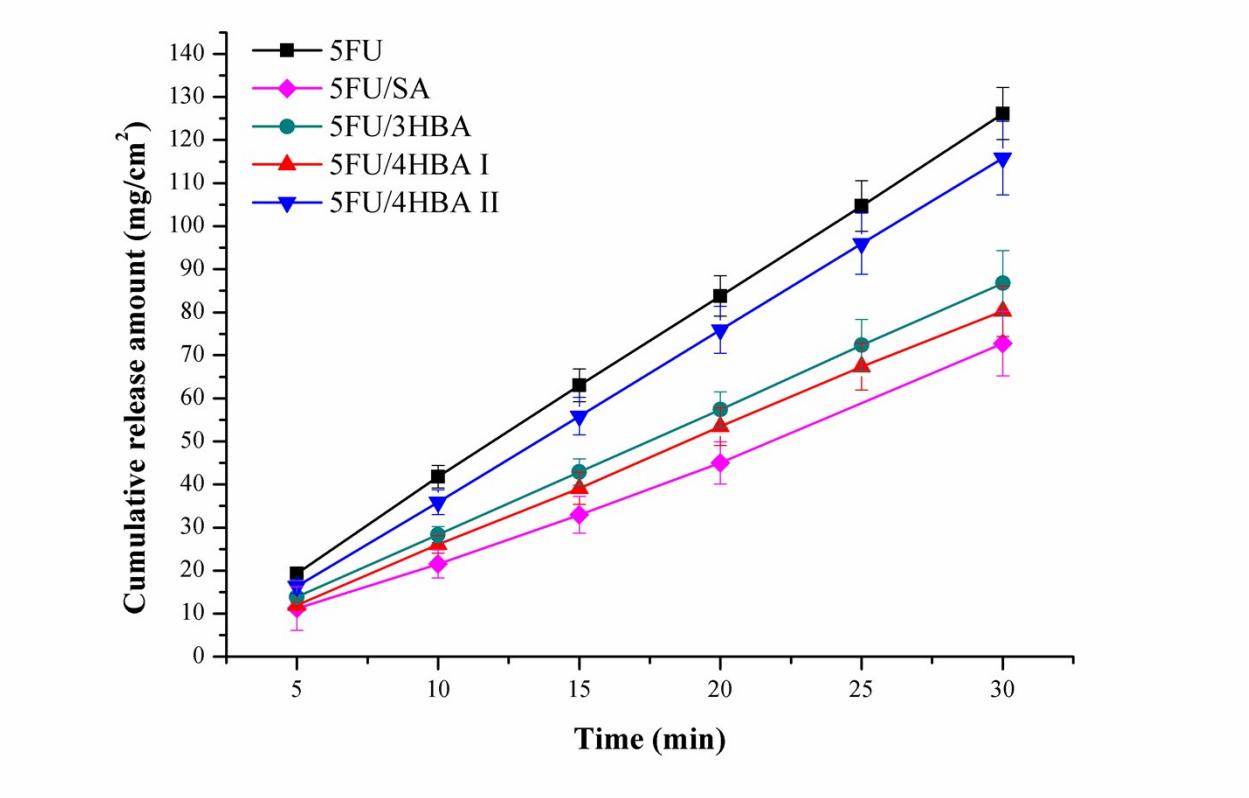

Fig. S8 IDR comparisons of 5FU and its cocrystals in pH 6.8 buffer at 37 ℃.

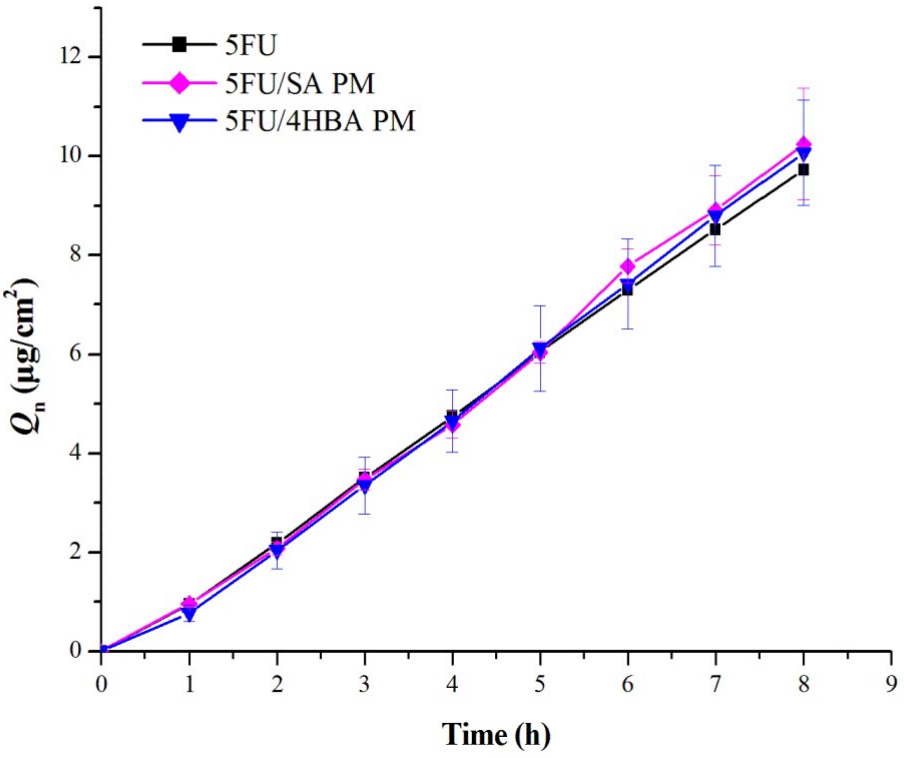

Fig. S9 Cumulative amount per unit area permeated (Q_n) 5FU and physical mixtures *vs* time plot.