Supporting Information

Pirfenidone–flavonoid cocrystals with reduced solubility and dissolution rate

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Table S1 pH values after solubility tests

	pH 1.2	pH 6.8
PFD	1.37+/−0.08	7.02+/−0.11
PFD–HES	1.45+/−0.07	7.06+/−0.04
PFD–GEN	1.43+/−0.16	7.09+/−0.04

Table S2 Intermolecular interaction energies (kJ mol^{-1}) of PFD. (PFD as the central molecule)

	No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
	1	PFD	2	x, y, z	10.59	−1.1	−0.3	−5.8	2.6	−4.8
	2	PFD	2	−x, y+1/2, −z	5.54	−10.1	−2.3	−36.5	22.8	−30.0
	3	PFD	2	x, y, z	6.25	−13.4	−5.0	−19.6	21.3	−21.7
	4	PFD	2	−x, y+1/2, −z	7.92	−10.6	−3.9	−14.8	13.2	−18.7
	5	PFD	2	−x, y+1/2, −z	9.24	−1.0	−0.3	−6.3	1.7	−5.7
	6	PFD	2	−x, y+1/2, −z	6.38	−3.8	−2.5	−21.0	10.4	−17.6
	7	PFD	2	x, y, z	10.28	−0.0	−0.4	−8.5	3.5	−5.5

Total: −208.0 kJ mol^{-1}

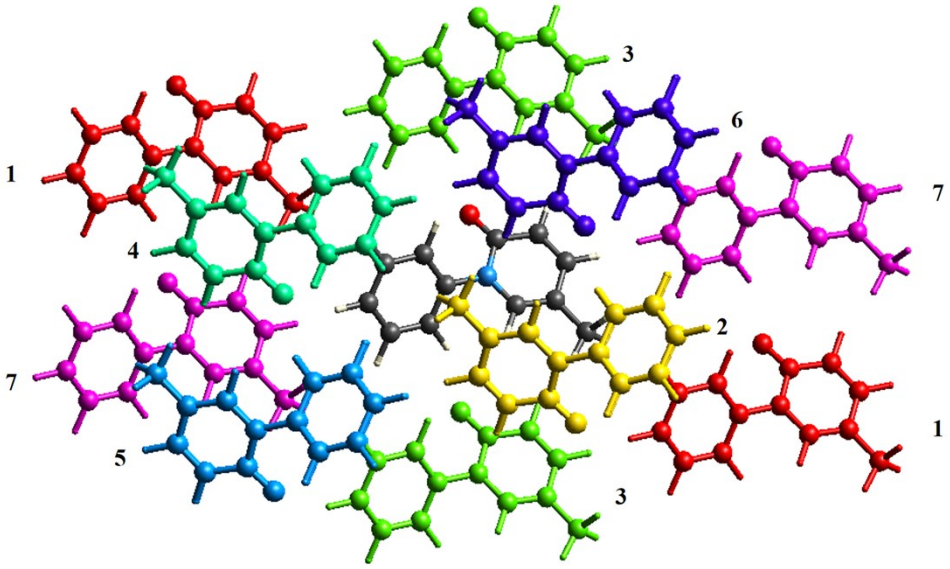


Table S3 Intermolecular interaction energies (kJ mol^{-1}) of PFD–HES. (PFD as the central molecule)

No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
1	HES	1	-	10.65	−4.3	−1.8	−10.2	5.8	−11.2
2	HES	1	-	6.84	−10.6	−5.4	−45.4	24.1	−39.9
3	HES	1	-	11.94	−6.7	−2.4	−11.1	12.3	−10.9
4	HES	1	-	7.97	−62.6	−16.4	−12.3	68.7	−46.6
5	PFD	2	−x+1/2, y+1/2, z	5.74	−1.7	−0.7	−21.5	7.9	−16.1
6	PFD	2	x, y, z	6.64	−2.2	−2.9	−15.0	6.7	−13.3
7	PFD	2	−x, y+1/2, −z+1/2	8.15	−4.4	−1.4	−12.5	6.0	−12.9
8	HES	1	-	12.72	0.8	−0.2	−4.8	1.8	−2.3
9	HES	1	-	11.82	−5.8	−1.2	−10.0	9.4	−9.9
10	HES	1	-	12.46	−2.7	−0.3	−4.1	1.2	−5.9
11	HES	1	-	13.04	−0.4	−0.3	−4.6	1.6	−3.7

Total: −215.0 kJ mol^{-1}
PFD-HES: −130.4 kJ mol^{-1}
PFD-PFD: −84.6 kJ mol^{-1}

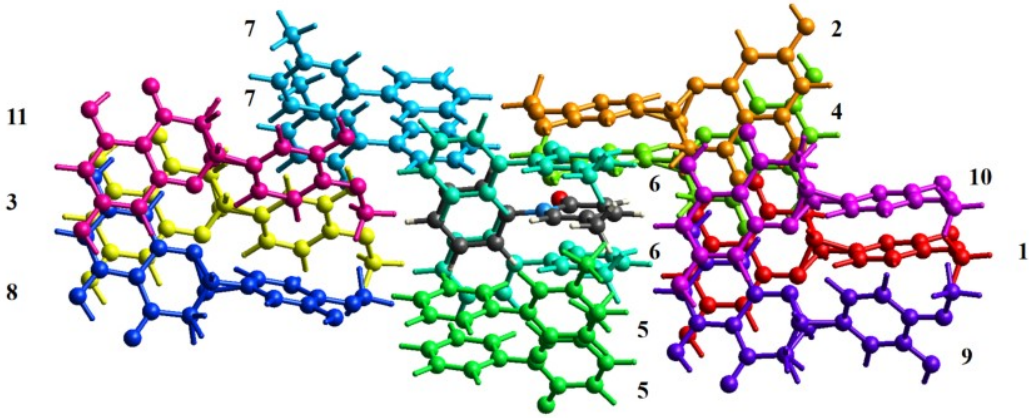


Table S4 Intermolecular interaction energies (kJ mol^{-1}) of PFD–HES. (HES as the central molecule)

No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
1	HES	2	−x+1/2, y+1/2, z	4.83	−14.3	−5.0	−78.8	55.0	−53.4
2	HES	1	−x, −y, −z	7.40	−14.3	−3.4	−31.7	41.7	−19.5
3	HES	2	x, y, z	6.64	2.8	−2.1	−13.9	3.4	−8.6
4	PFD	1	-	6.84	−10.6	−5.4	−45.4	24.1	−39.9
5	PFD	1	-	13.04	−0.4	−0.3	−4.6	1.6	−3.7
6	PFD	1	-	12.72	−0.8	−0.2	−4.8	1.8	−2.3
7	HES	2	x+1/2, −y+1/2, −z	9.74	−70.6	−19.3	−19.1	93.1	−48.1
8	HES	1	−x, −y, −z	8.32	−19.3	−8.1	−27.8	11.7	−43.4
9	PFD	1	-	7.97	−62.6	−16.4	−12.3	68.7	−46.6
10	PFD	1	-	10.65	−4.3	−1.8	−10.2	5.8	−11.2
11	PFD	1	-	11.82	−5.8	−1.2	−10.0	9.4	−9.9
12	PFD	1	-	11.94	−6.7	−2.4	−11.1	12.3	−10.9
13	PFD	1	-	12.46	−2.7	−0.3	−4.1	1.2	−5.9

Total: −413.5 kJ mol^{-1}

HES-PFD: −130.4 kJ mol^{-1}

HES-HES: −283.1 kJ mol^{-1}

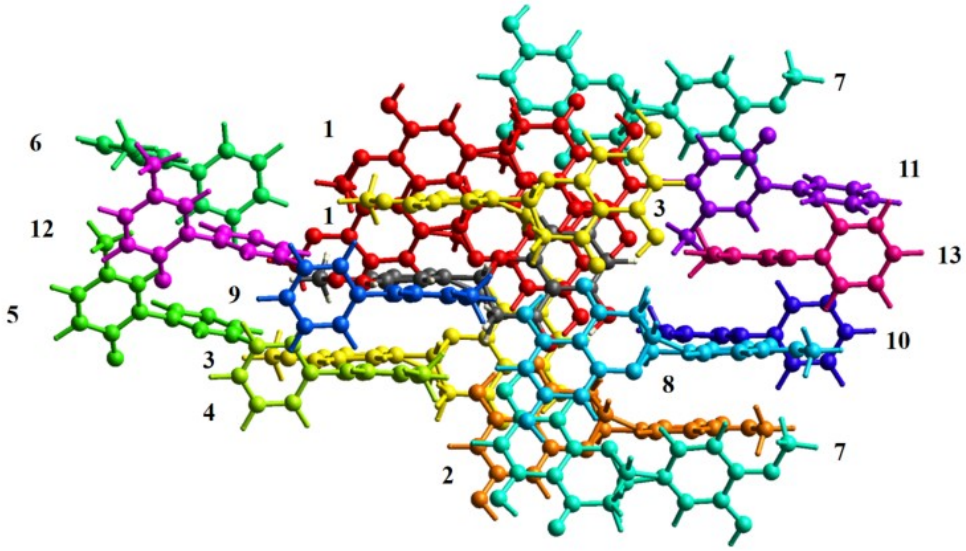


Table S5 Intermolecular interaction energies (kJ mol^{-1}) of PFD–GEN. (PFD^{a} as the central molecule)

No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
1	GEN	1	-	7.80	−3.4	−1.1	−12.5	6.2	−11.4
2	GEN	1	-	9.18	2.6	−0.9	−7.6	1.5	−3.6
3	PFD^{a}	2	x, −y, z+1/2	11.08	−0.2	−0.2	−4.1	1.9	−2.8
4	PFD^{b}	1	-	4.42	−18.7	−5.3	−50.0	37.5	−44.0
5	GEN	1	-	6.06	−21.9	−6.0	−28.2	28.7	−34.5
6	GEN	1	-	8.93	−3.7	−0.8	−13.1	11.4	−8.9
7	PFD^{b}	1	-	11.18	0.2	−0.2	−4.4	3.8	−1.5
8	PFD^{b}	1	-	4.33	−13.0	−4.6	−47.6	27.2	−41.8
9	GEN	1	-	7.10	−7.8	−1.6	−20.3	12.6	−19.3
10	GEN	1	-	7.77	−1.3	−0.2	−10.2	4.8	−7.4
11	GEN	1	-	9.76	−66.0	−17.8	−11.6	67.1	−51.6
12	PFD^{b}	1	-	8.12	−0.2	−1.1	−3.1	0.1	−3.3
13	PFD^{b}	1	-	9.95	−3.4	−0.5	−4.2	0.3	−7.5

Total: −240.4 kJ mol^{-1}

PFD^{a}-PFD^{a}: −5.6 kJ mol^{-1}

PFD^{a}-PFD^{b}: −98.1 kJ mol^{-1}

PFD^{a}-GEN: −136.7 kJ mol^{-1}

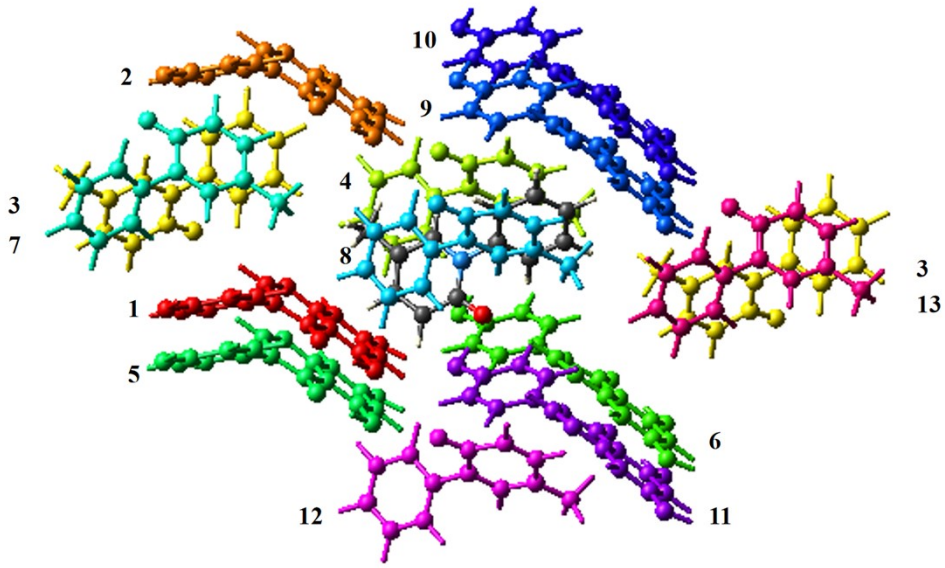


Table S6 Intermolecular interaction energies (kJ mol^{-1}) of PFD–GEN. (PFD^{b} as the central molecule)

No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
1	GEN	1	-	10.34	−0.6	−0.1	−1.7	0.0	−2.1
2	GEN	1	-	7.62	−3.3	−0.5	−17.9	10.4	−13.0
3	PFD^{a}	1	x, −y, z+1/2	4.33	−13.0	−4.6	−47.6	27.2	−41.8
4	PFD^{b}	2	-	11.04	−0.1	−0.2	−5.7	3.8	−3.0
5	PFD^{a}	1	-	4.42	−18.7	−5.3	−50.0	37.5	−44.0
6	PFD^{a}	1	-	9.95	−3.4	−0.5	−4.2	0.3	−7.5
7	GEN	1	-	8.18	−2.8	−1.1	−19.3	10.7	−14.0
8	PFD^{a}	1	-	11.18	0.2	−0.2	−4.4	3.8	−1.5
9	GEN	1	-	8.43	−2.3	−1.6	−8.8	6.2	−7.4
10	GEN	1	-	5.53	−8.4	−1.3	−35.6	21.6	−27.5
11	GEN	1	-	9.53	−66.9	−17.6	−12.3	71.1	−50.5
12	GEN	1	-	9.48	1.3	−1.0	−5.7	1.0	−3.6
13	PFD^{a}	1	-	8.12	0.2	−1.1	−3.1	0.1	−3.3

Total: −222.2 kJ mol^{-1}

PFD^{b}-PFD^{a}: −98.1 kJ mol^{-1}

PFD^{b}-PFD^{b}: −6.0 kJ mol^{-1}

PFD^{b}-GEN: −118.1 kJ mol^{-1}

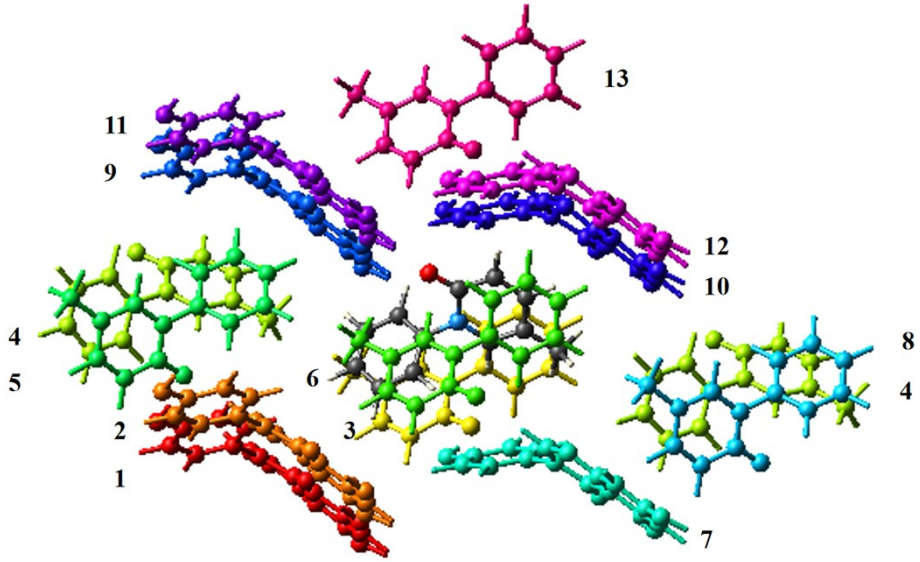


Table S7 Intermolecular interaction energies (kJ mol^{-1}) of PFD–GEN. (GEN as the central molecule)

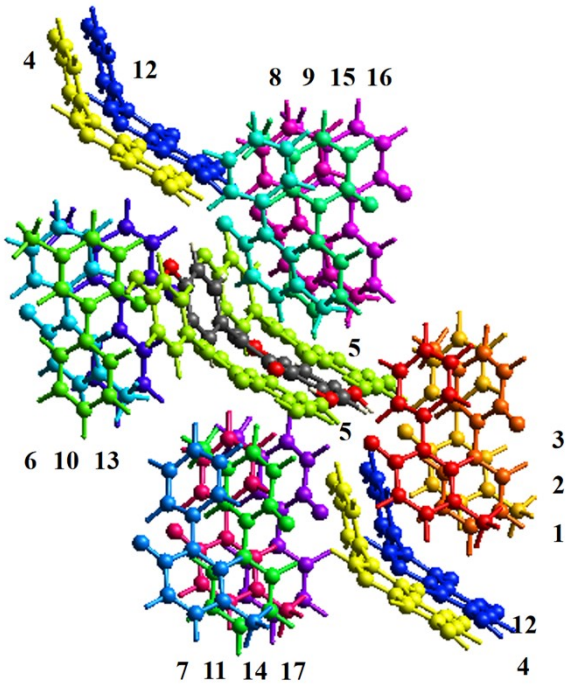
No	Molecule	N	Symop	R	E_ele	E_pol	E_dis	E_rep	E_tot
1	PFD[b]	1	-	8.43	−2.3	−1.6	−8.8	6.2	−7.4
2	PFD[a]	1	-	9.18	2.6	−0.9	−7.6	1.5	−3.6
3	PFD[b]	1	-	9.53	−66.9	−17.6	−12.3	71.1	−50.5
4	GEN	2	x, −y, z+1/2	10.74	−4.1	−1.5	−9.7	6.7	−9.7
5	GEN	2	x, y, z	8.28	−1.4	−2.6	−17.1	10.7	−11.7
6	PFD[a]	1	-	9.76	−66.0	−17.8	−11.6	67.1	−51.6
7	PFD[a]	1	-	7.80	−3.4	−1.1	−12.5	6.2	−11.4
8	PFD[a]	1	-	7.10	−7.8	−1.6	−20.3	12.6	−19.3
9	PFD[b]	1	-	9.48	−1.3	−1.0	−5.7	1.0	−3.6
10	PFD[b]	1	-	8.18	−2.8	−1.1	−19.3	10.7	−14.0
11	PFD[b]	1	-	10.34	−0.6	−0.1	−1.7	0.0	−2.1
12	GEN	2	x, −y, z+1/2	12.01	1.0	−0.2	−1.4	0.0	−0.3
13	PFD[a]	1	-	6.06	−21.9	−6.0	−28.2	28.7	−34.5
14	PFD[a]	1	-	8.93	−3.7	−0.8	−13.1	11.4	−8.9
15	PFD[a]	1	-	7.77	−1.3	−0.2	−10.2	4.8	−7.4
16	PFD[b]	1	-	5.53	−8.4	−1.3	−35.6	21.6	−27.5
17	PFD[b]	1	-	7.62	−3.3	−0.5	−17.9	10.4	−13.0

Total:

GEN-PFD[a]: −136.7 kJ mol^{-1}

GEN-PFD[b]: −118.1 kJ mol^{-1}

GEN-GEN: −43.4 kJ mol^{-1}



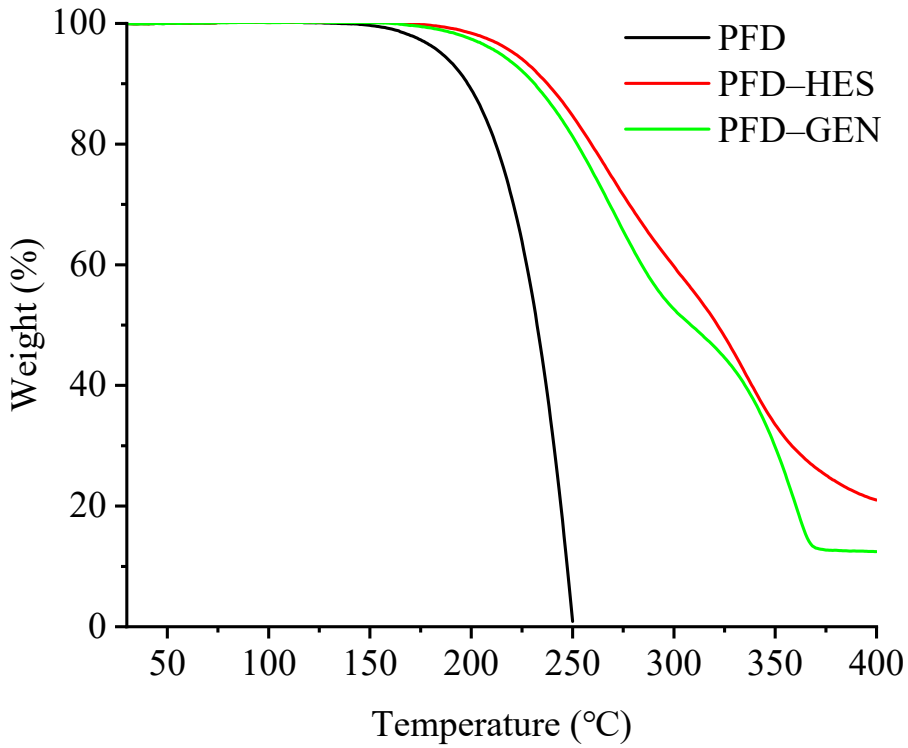


Fig. S1 TGA curves of PFD, PFD–HES, and PFD–GEN.

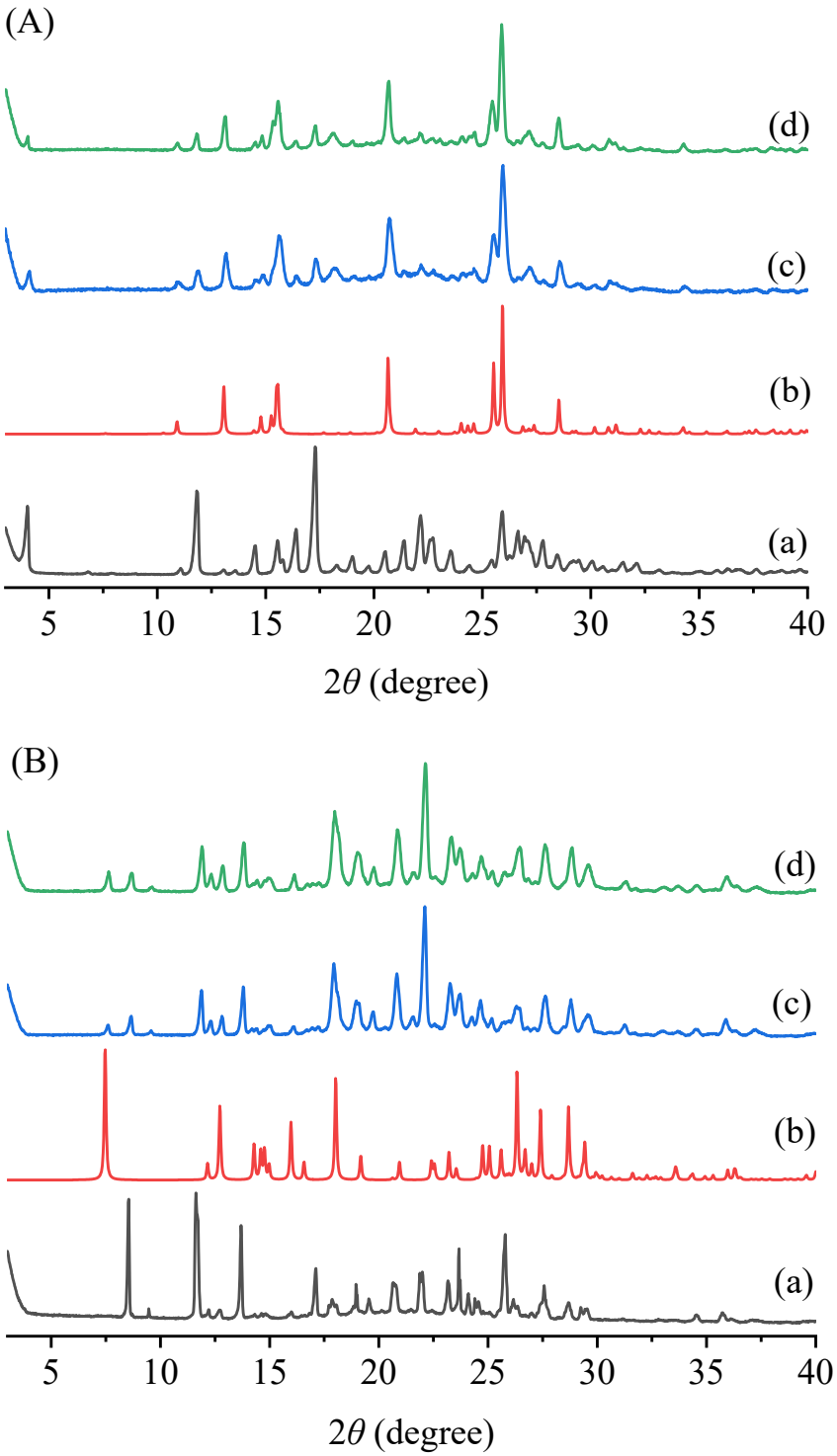


Fig. S2 Powder XRD patterns of the residual materials after equilibrium solubility tests. (A) PFD–HES: (a) experimental XRD pattern of PFD–HES, (b) simulated XRD pattern of HES·H_2O, (c) experimental XRD pattern of residue in pH 1.2 solution, and (d) experimental XRD pattern of residue in pH 6.8 buffer. (B) PFD–GEN: (a) experimental XRD pattern of PFD–GEN, (b) simulated XRD pattern of GEN, (c) experimental XRD pattern of residue in pH 1.2 solution, and (d) experimental XRD pattern of residue in pH 6.8 buffer.

Table S8 IDR values (mg mL^{-1} cm^{-2} min^{-1}) of PFD, PFD–HES, and PFD–GEN

	pH 1.2	pH 6.8
PFD	$2.57\times10^{-3}\pm2.16\times10^{-5}$	$2.92\times10^{-3}\pm2.89\times10^{-5}$
PFD–HES	$1.77\times10^{-4}\pm2.72\times10^{-6}$	$1.77\times10^{-4}\pm1.62\times10^{-6}$
PFD–GEN	$4.14\times10^{-5}\pm1.13\times10^{-6}$	$6.71\times10^{-5}\pm2.87\times10^{-6}$