Supporting Information

Pirfenidone–flavonoid cocrystals with reduced solubility and dissolution rate

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<th>pH 6.8</th>
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<tr>
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<tr>
<td>PFD–HES</td>
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<td>7.06+/−0.04</td>
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<td>7.09+/−0.04</td>
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Table S1 pH values after solubility tests
**Table S2** Intermolecular interaction energies (kJ mol\(^{-1}\)) of PFD. (PFD as the central molecule)

<table>
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<th>Molecule</th>
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<th>Symop</th>
<th>R</th>
<th>E_ele</th>
<th>E_pol</th>
<th>E_dis</th>
<th>E_rep</th>
<th>E_tot</th>
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<td>x, y, z</td>
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<td>3.5</td>
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Total: −208.0 kJ mol\(^{-1}\)
Table S3  Intermolecular interaction energies (kJ mol\(^{-1}\)) of PFD–HES. (PFD as the central molecule)

<table>
<thead>
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<th>No</th>
<th>Molecule</th>
<th>N</th>
<th>Symop</th>
<th>R</th>
<th>E_ele</th>
<th>E_pol</th>
<th>E_dis</th>
<th>E_rep</th>
<th>E_tot</th>
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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)

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<th>Molecule</th>
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<th>Symop</th>
<th>R</th>
<th>E$_\text{ele}$</th>
<th>E$_\text{pol}$</th>
<th>E$_\text{dis}$</th>
<th>E$_\text{rep}$</th>
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<td>$-4.1$</td>
<td>1.2</td>
<td>$-5.9$</td>
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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)

<table>
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<tr>
<th>No</th>
<th>Molecule</th>
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<th>Symop</th>
<th>R</th>
<th>E_ele</th>
<th>E_pol</th>
<th>E_dis</th>
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<th>E_tot</th>
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<td>0.3</td>
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</table>

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)

<table>
<thead>
<tr>
<th>No</th>
<th>Molecule</th>
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<th>Symop</th>
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<th>E_ele</th>
<th>E_pol</th>
<th>E_dis</th>
<th>E_rep</th>
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<td>-19.3</td>
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Total: -222.2 kJ mol$^{-1}$

PFD$^b$-PFD$^a$: -98.1 kJ mol$^{-1}$
PFD$^a$-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)

<table>
<thead>
<tr>
<th>No</th>
<th>Molecule</th>
<th>N</th>
<th>Symop</th>
<th>R</th>
<th>E(_{\text{ele}})</th>
<th>E(_{\text{pol}})</th>
<th>E(_{\text{dis}})</th>
<th>E(_{\text{rep}})</th>
<th>E(_{\text{tot}})</th>
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<td>x, -y, z+1/2</td>
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<td>x, y, z</td>
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<td>-</td>
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<td>-0.5</td>
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</table>

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·H₂O, (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

<table>
<thead>
<tr>
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<th>pH 1.2</th>
<th>pH 6.8</th>
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<tbody>
<tr>
<td>PFD</td>
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<td>$2.92 \times 10^{-3} \pm 2.89 \times 10^{-5}$</td>
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<td>PFD–HES</td>
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<td>$1.77 \times 10^{-4} \pm 1.62 \times 10^{-6}$</td>
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<tr>
<td>PFD–GEN</td>
<td>$4.14 \times 10^{-5} \pm 1.13 \times 10^{-6}$</td>
<td>$6.71 \times 10^{-5} \pm 2.87 \times 10^{-6}$</td>
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