SUPPORTING INFORMATION

Improving Solubility and Pharmacokinetics of Meloxicam via Multiple-Component Crystal Formation

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Section 1: Synthesis of meloxicam cocrystals.

Meloxicam was reacted with 12 selected coformers: 1-hydroxy-2-naphthoic acid, salicylic acid, succinic acid, 4-hydroxybenzoic acid, glutaric acid, maleic acid, L-malic acid, benzoic acid, DL-malic acid, hydrocinnamic acid, glycolic acid, and fumaric acid. Cocrystal formation was achieved either via slurry or ball-mill techniques. Details for the syntheses are provided below.

Synthesis of meloxicam•1-hydroxy-2-naphthoic acid (1:1) cocrystal (1) – 0.700 g (1.99 mmol) meloxicam and 0.391 g (2.07 mmol) of 1-hydroxy-2-naphthoic acid were slurried at ca. 250 rpm in 3mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF. **1** was obtained in ca. 90% yield.

Synthesis of meloxicam•salicylic acid (1:1) cocrystal form III (2) – 0.876 g (2.49 mmol) meloxicam and 0.350 g (2.53 mmol) of salicylic acid were slurried at ca. 250 rpm in 2 mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF. **2** was isolated in ca. 84% yield.

Synthesis of meloxicam•succinic acid (2:1) cocrystal (3) – 0.880 g (2.50 mmol) meloxicam and 0.150 g (1.27 mmol) of succinic acid were slurried at ca. 250 rpm in 3 mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF. **3** was isolated in ca. 78% yield.

Synthesis of meloxicam•4-hydroxybenzoic acid (1:1) cocrystal (4) –0.175 g (0.498 mmol) meloxicam was ball-milled with 0.069 g (0.498 mmol) of 4-hydroxybenzoic acid and 40 μL of THF for 30 minutes, generating **4** in ca. 100% yield.

Synthesis of meloxicam•glutaric acid (1:1) cocrystal (5) – 0.179 g (0.511 mmol) meloxicam was ball-milled with 0.0699 g (0.529 mmol) of glutaric acid and 40 μL of chloroform for 30 minutes, producing **5** in ca. 100% yield.

Synthesis of meloxicam•maleic acid (1:1) cocrystal (6) – 0.750 g (2.13 mmol) meloxicam and 0.248 g (2.13 mmol) of maleic acid were slurried at ca. 250 rpm in 2 mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with the same solvent employed for the slurry. **6** was isolated in ca. 92% yield.

Synthesis of meloxicam•L-malic acid (1:1:1) cocrystal of a salt (7) – 0.897 g (2.55 mmol) meloxicam and 0.182 g (1.36 mmol) of L-malic acid were slurried at ca. 250 rpm in 3mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF and afforded an ca. 92% yield of **7**.

Synthesis of meloxicam•benzoic acid (1:1) cocrystal (8) – 0.176 g (0.501 mmol) meloxicam and 0.061 g (0.500 mmol) of benzoic acid were slurried at ca. 250 rpm in 3 mL of ethyl acetate overnight sealed under ambient conditions. The resulting solid was filtered and washed with ethyl acetate. **8** was isolated in ca. 81% yield.

Synthesis of meloxicam•DL-malic acid (2:1) cocrystal (9) – 0.880 g (2.50 mmol) meloxicam and 0.170 g (1.27 mmol) of DL-malic acid were slurried at ca. 250 rpm in 3 mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF. **9** was isolated in ca. 79% yield.

Synthesis of meloxicam•hydrocinnamic acid (1:1) cocrystal (10) – 0.702 g (2.00 mmol) meloxicam and 0.300 g (1.99 mmol) of hydrocinnamic acid were slurried at ca. 250 rpm in 3 mL of ethyl acetate overnight sealed under ambient conditions. The resulting solid was filtered and washed with ethyl acetate. **10** was isolated in ca. 78% yield.

Synthesis of meloxicam•glycolic acid (1:1) cocrystal (11) – 0.950 g (2.70 mmol) meloxicam and 0.206 g (2.70 mmol) of glycolic acid were slurried at ca. 250 rpm in 2 mL of ethyl acetate overnight sealed under ambient conditions. The resulting solid was filtered and washed with ethyl acetate. **11** was isolated in ca. 92% yield.

Synthesis of meloxicam•fumaric acid (2:1) cocrystal (12) – 0.880 g (2.50 mmol) meloxicam and 0.150 g (1.29 mmol) of fumaric acid were slurried at ca. 250 rpm in 3 mL of THF overnight sealed under ambient conditions. The resulting solid was filtered and washed with THF. **12** was isolated in ca. 81% yield.

Section 2: Solid-state characterization results of the dissolution studies in 25 mM sodium phosphate buffer at pH 6.5 and 37 °C.

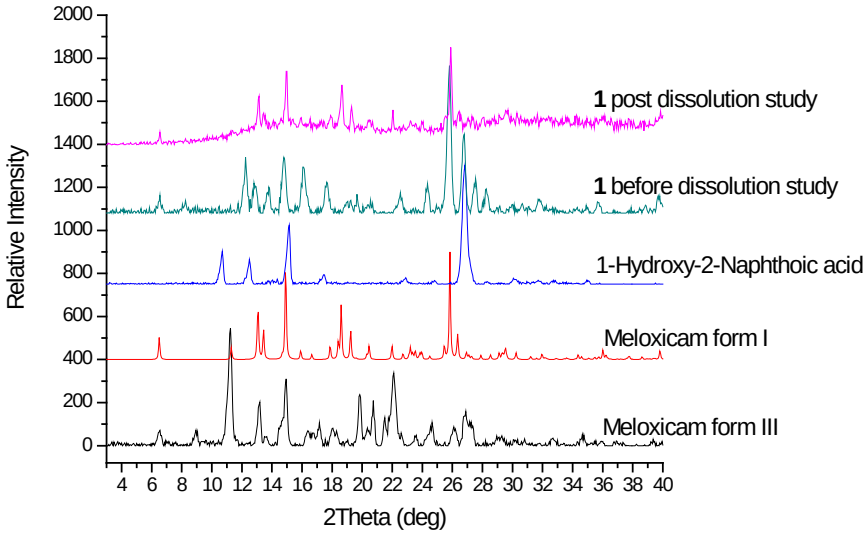

Figure S1. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, 1-hydroxy-2-naphthoic acid, **1** prior to dissolution study and **1** post dissolution study.

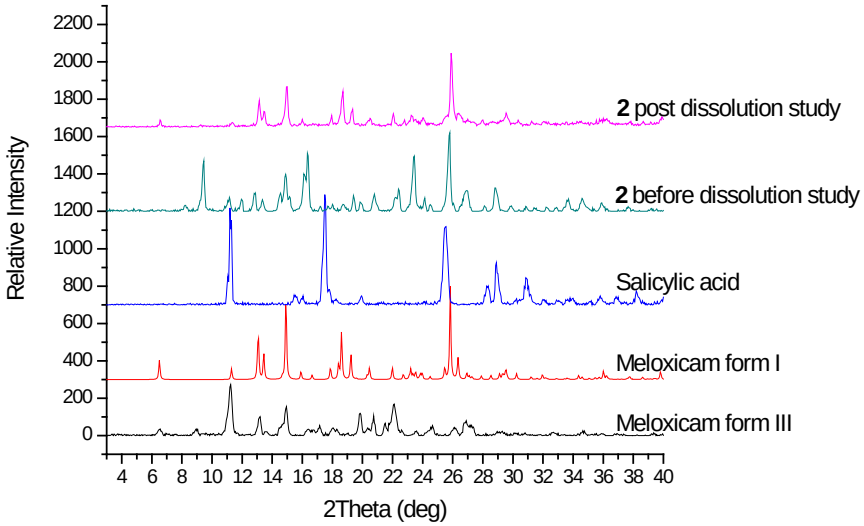

Figure S2. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, salicylic acid, **2** prior to dissolution study and **2** post dissolution study.

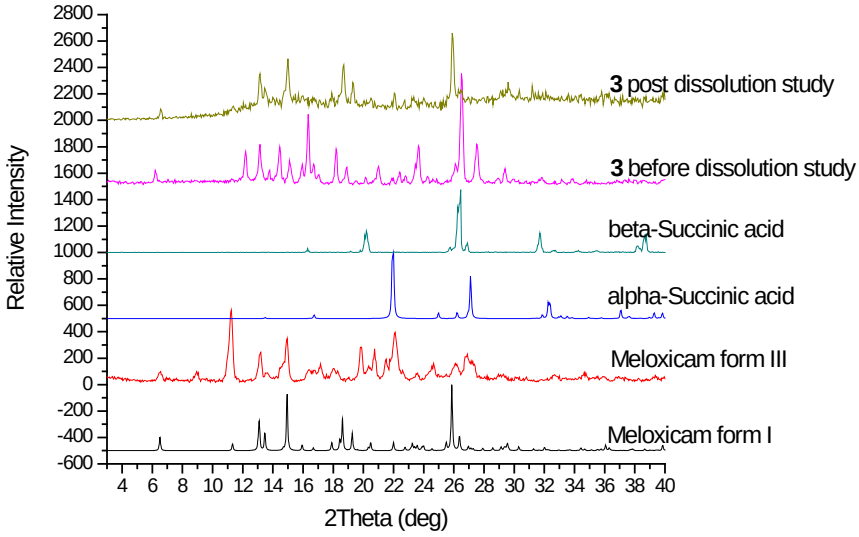

Figure S3. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, succinic acid, **3** prior to dissolution study and **3** post dissolution study

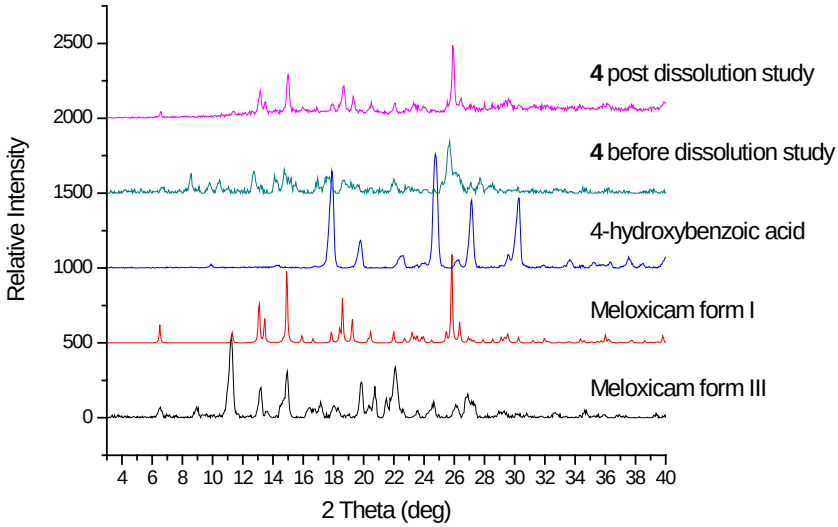

Figure S4. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, 4-hydroxybenzoic acid, **4** prior to dissolution study and **4** post dissolution study.

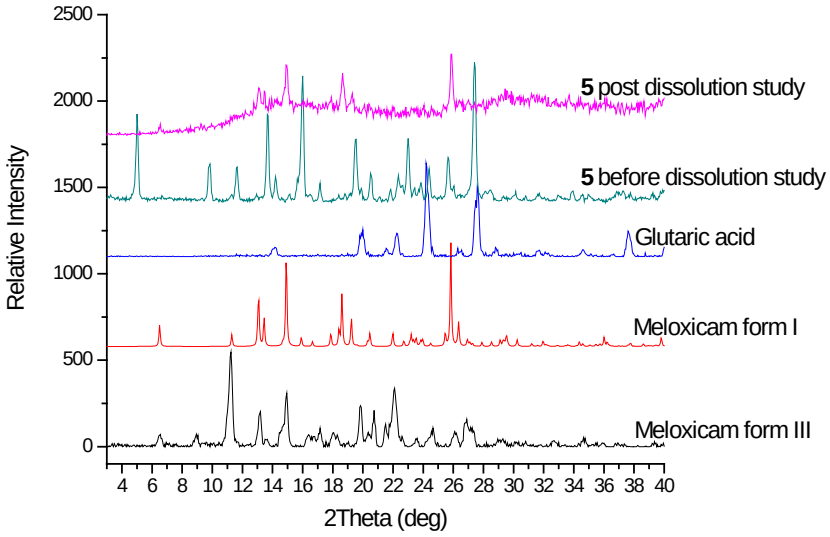

Figure S5. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, glutaric acid, **5** prior to dissolution study and **5** post dissolution study.

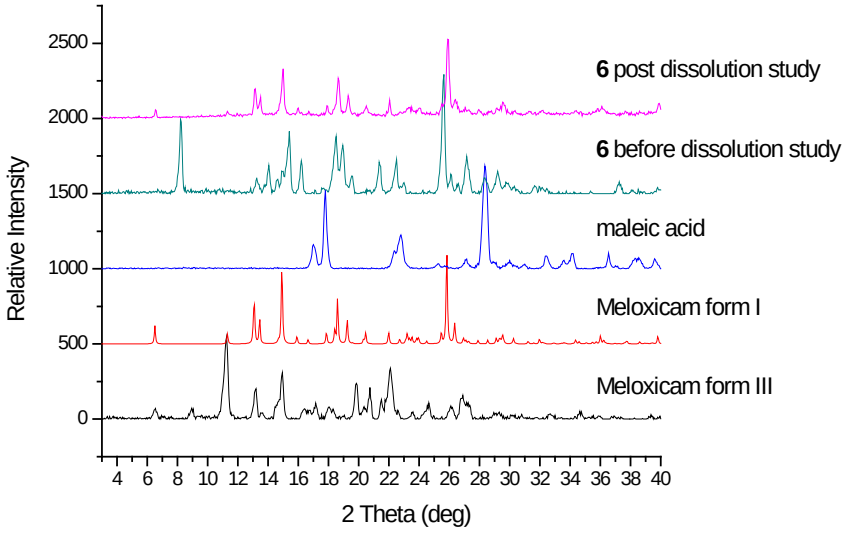

Figure S6. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, maleic acid, **6** prior to dissolution study and **6** post dissolution study.

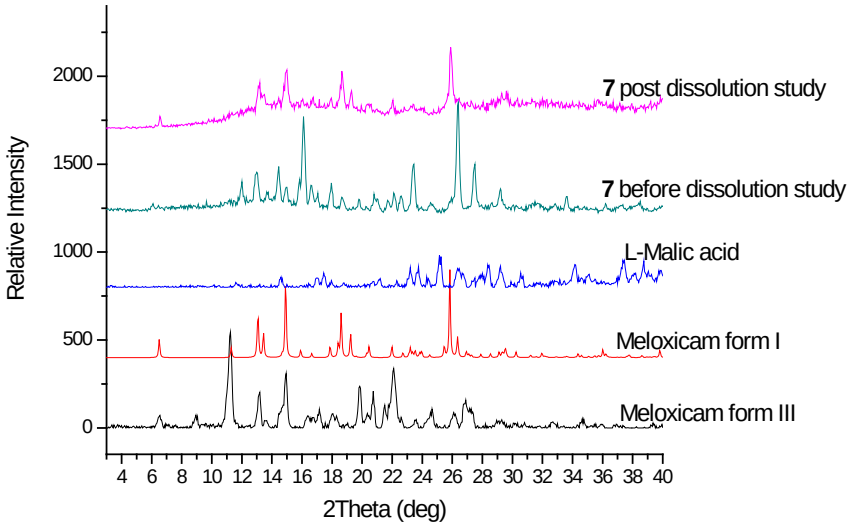

Figure S7. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, L-malic acid, **7** prior to dissolution study and **7** post dissolution study.

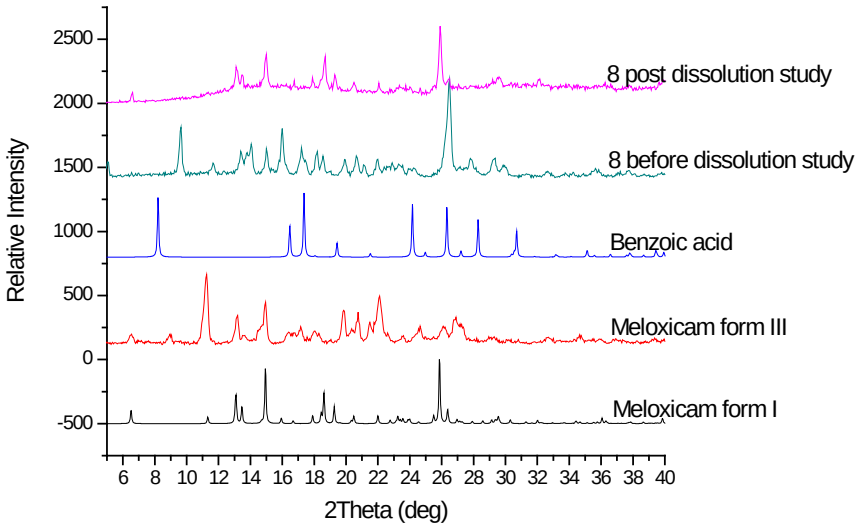

Figure S8. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, benzoic acid, **8** prior to dissolution study and **8** post dissolution study.

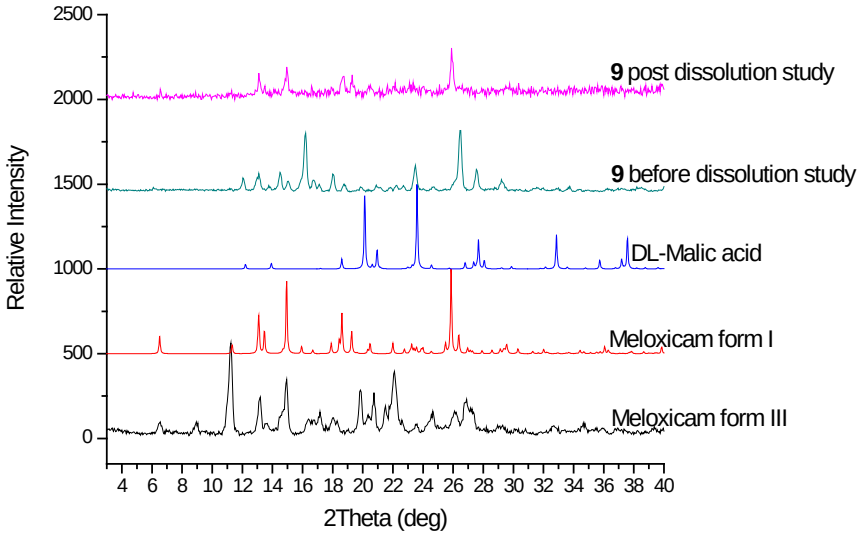

Figure S9. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, DL-malic acid, **9** prior to dissolution study and **9** post dissolution study.

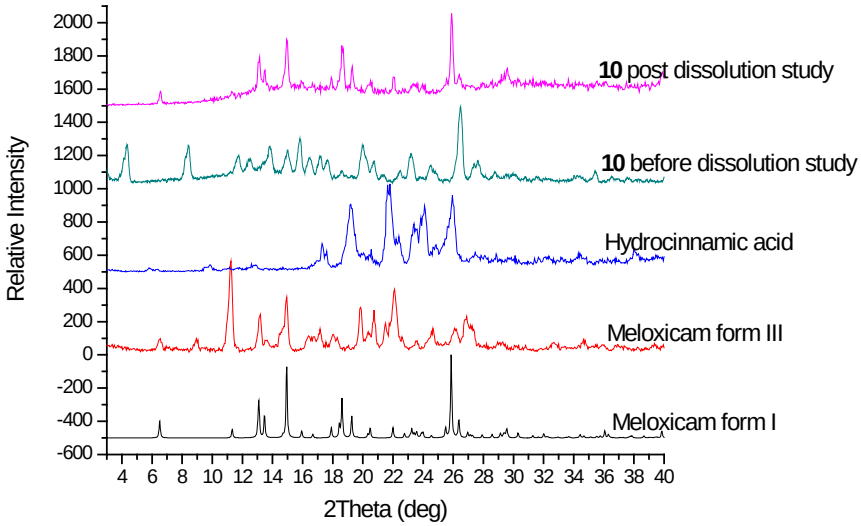

Figure S10. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, hydrocinnamic acid, **10** prior to dissolution study and **10** post dissolution study.

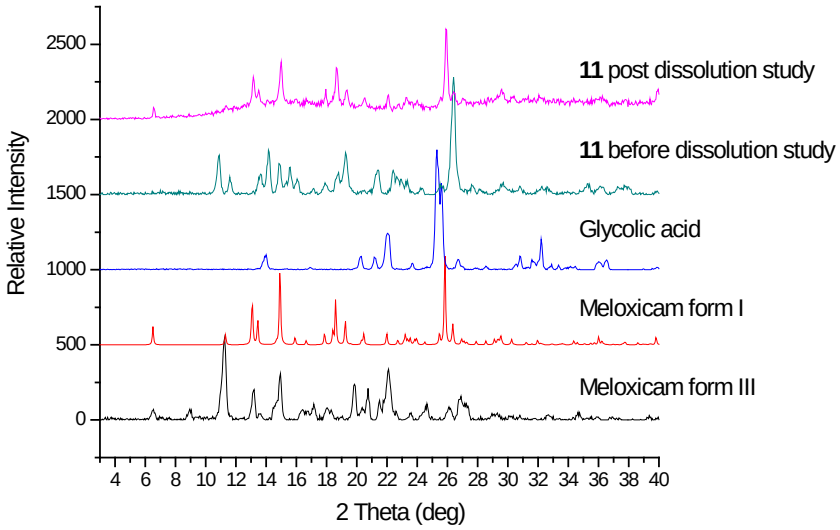

Figure S11. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, glycolic acid, **11** prior to dissolution study and **11** post dissolution study.

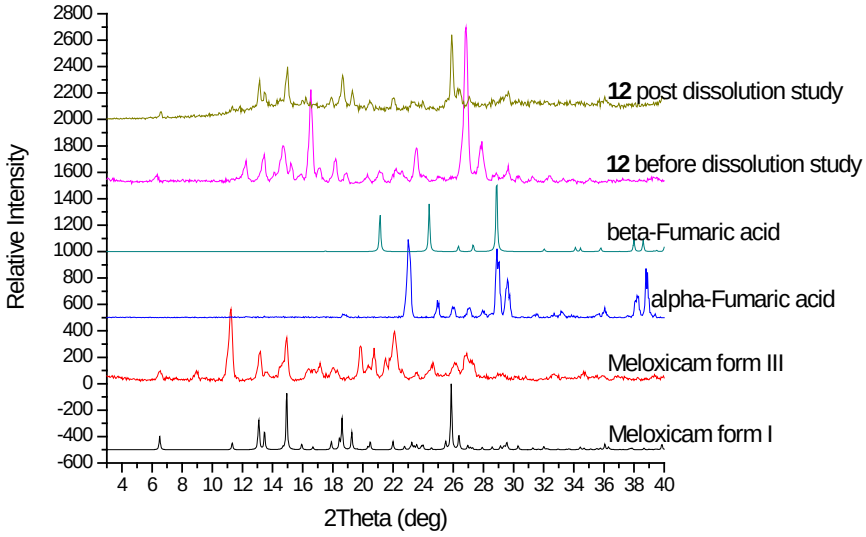

Figure S12. Comparison of PXRD profiles of meloxicam form III, meloxicam form I, fumaric acid, **12** prior to dissolution study and **12** post dissolution study.

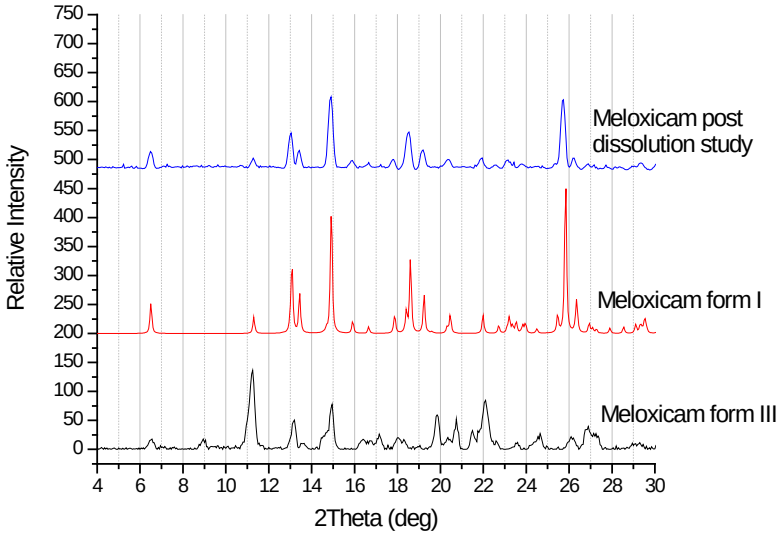

Figure S13. Comparison of PXRD profiles of meloxicam form III, meloxicam form I prior to dissolution study and meloxicam form I post dissolution study.

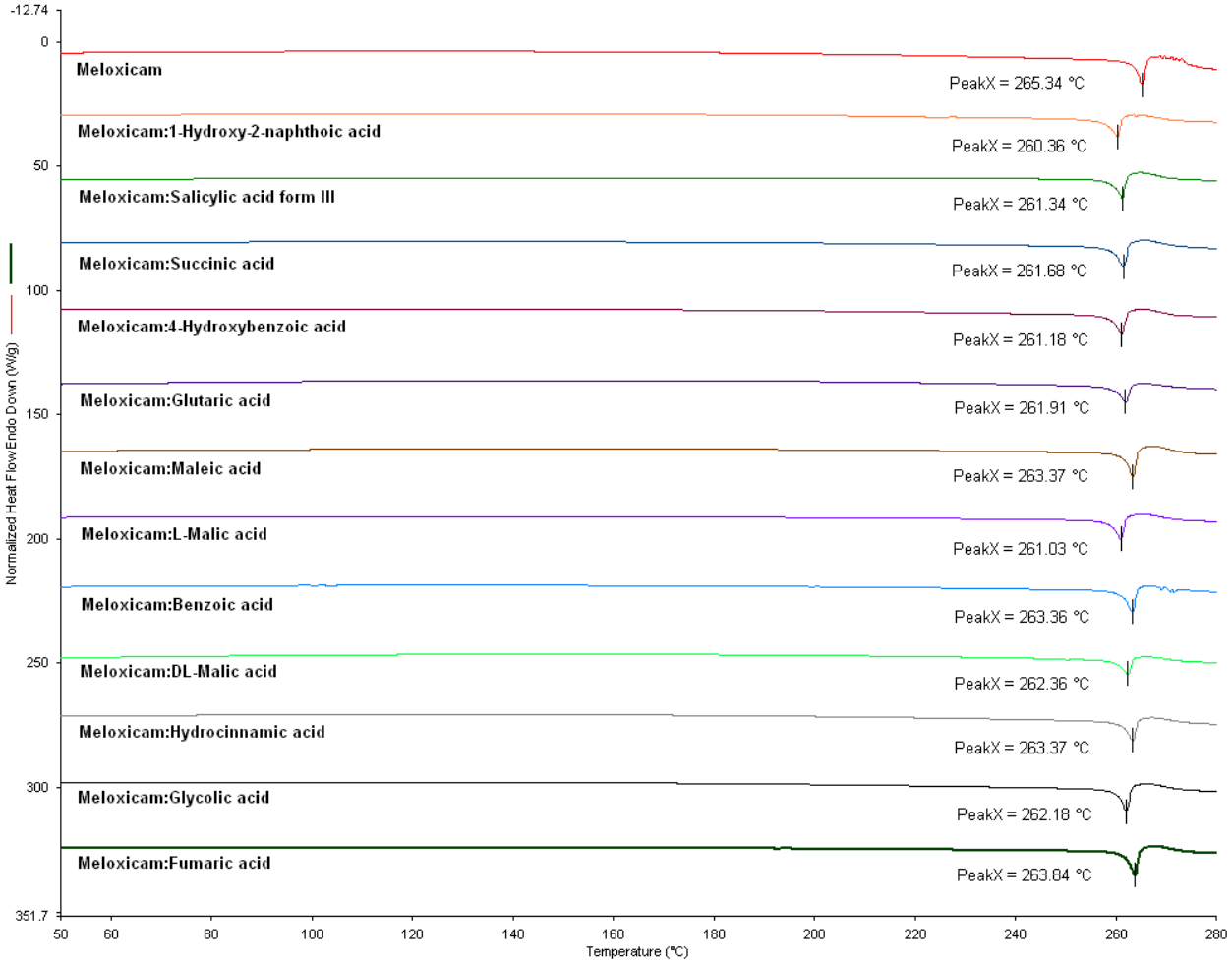

Figure S14. Comparison of DSC profiles of remaining solids from meloxicam form I and all cocrystals at the end of dissolution studies.

Section 3: Dissolution profiles of meloxicam form I and 1-12 over 72 hours.

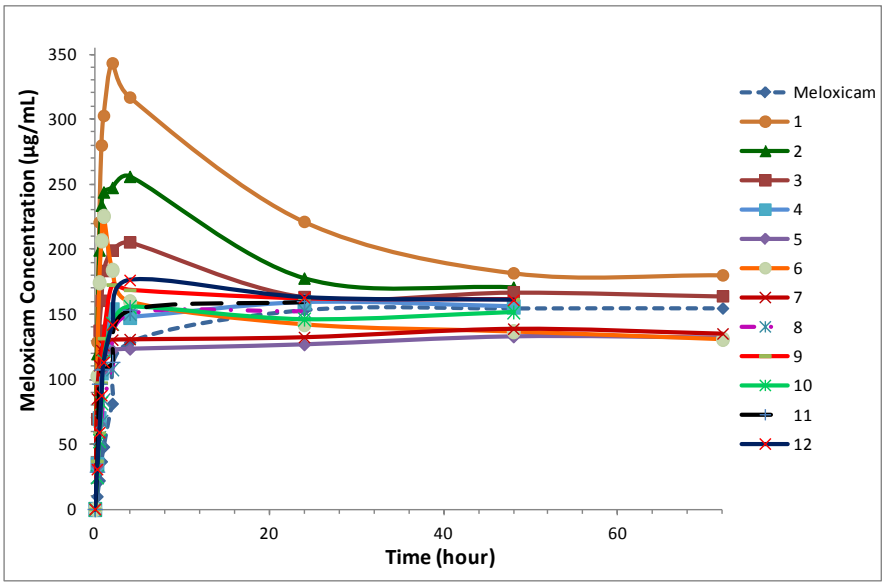

Figure S15. Dissolution profiles of meloxicam form I and **1-12** over 72 hours.

Section 4: Correlation coefficients (R^2) generated from linear regression analyses between *in vitro* mean dissolution and *in vivo* mean serum concentration data (time-point-by-time-point) on an individual crystal form basis.

Crystal form	R^2
Meloxicam Form I	0.9218
1	0.9562
2	0.7638
3	0.9743
4	0.8761
5	0.7347
6	0.7488
7	0.9605
8	0.8415
9	0.8571
10	0.822
11	0.9461
12	0.9505

Section 5: Correlations of S_{max} vs solubility data and S_{max} vs melting point data.

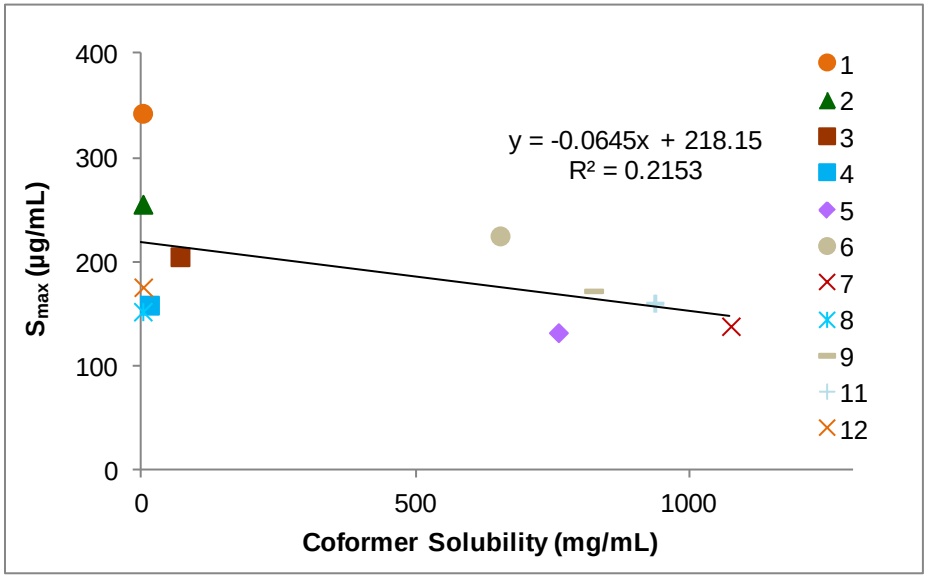

Figure S16. Correlation of coformer solubility and cocrystal S_{max} at pH 6.5 and 37 °C.

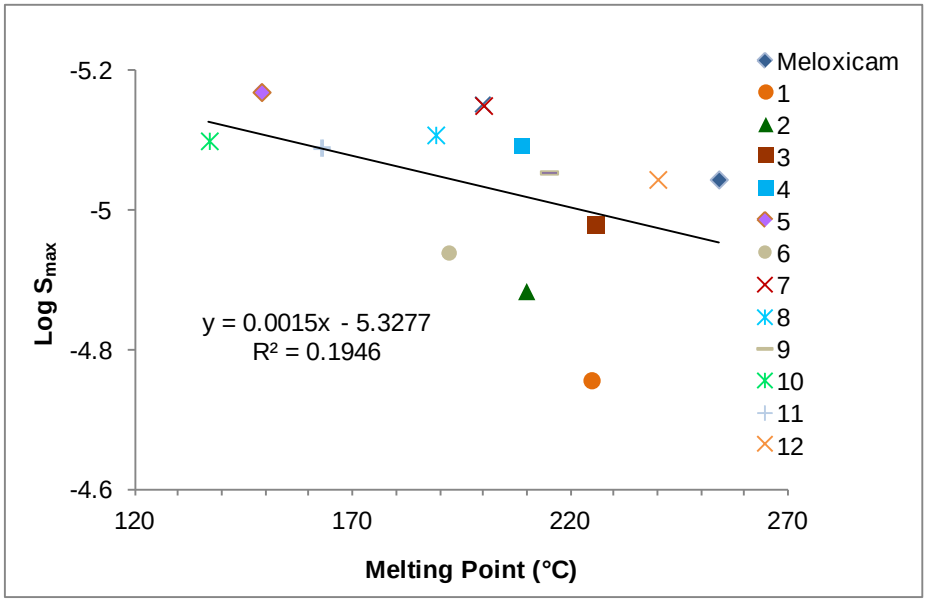

Figure S17. Correlation of melting point and S_{max} data for meloxicam form I and **1-12**.

Section 6. Dissolution and pharmacokinetic profiles of meloxicam and selected cocrystals with error bars.

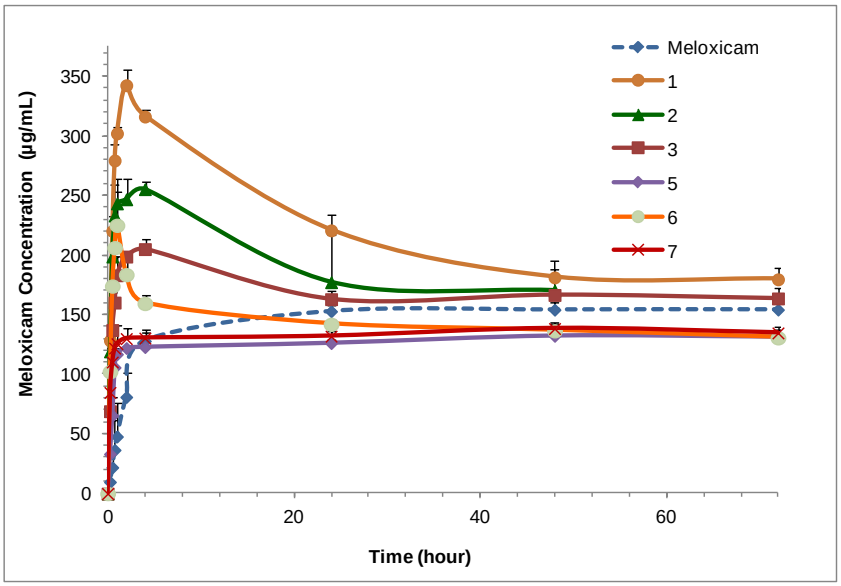

Figure S18. Dissolution profiles of meloxicam form I and selected cocrystals from 0 to 72 hours (pH 6.5, 37 °C).

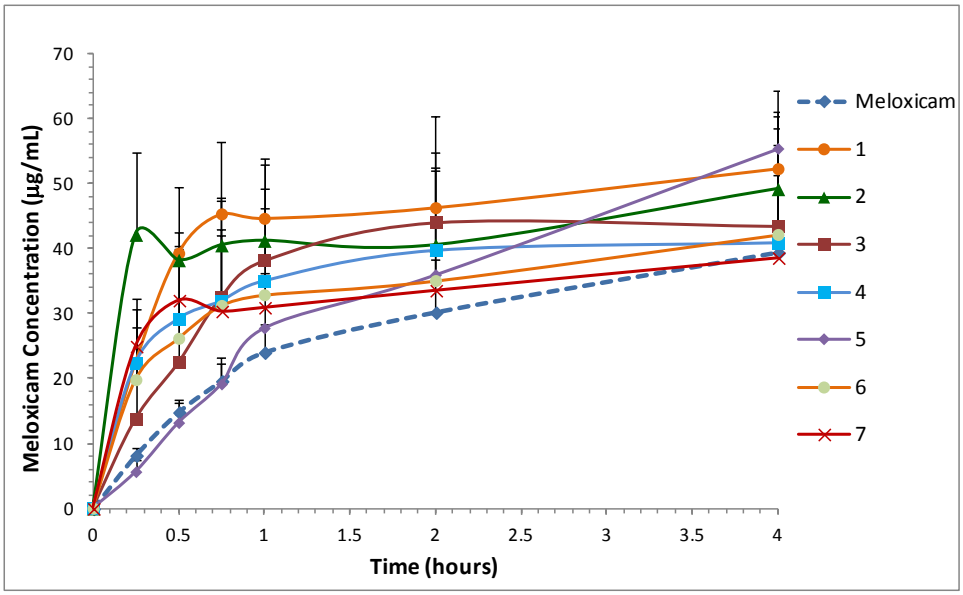

Figure S19. PK profiles over 4 hours following 10 mg/kg (meloxicam equivalent) single-dose oral administration of meloxicam form I and selected cocrystals in rats.