A Comparison of Slow Evaporation and Reaction Crystallization Methods to Generate Cocrystals of Piroxicam, a BCS Class II Drug
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Purpose
Pharmaceutical co-crystals are promising solid forms for improving drug substance properties such as solubility, dissolution rate, and bioavailability. Piroxicam, a BCS Class II drug, was used as a model compound to investigate the feasibility and scalability of two co-crystallization methods: slow evaporation and reaction crystallization.

Methods
Seven slow evaporation experiments were performed in organic solvents using 1:1 or 2:1 stoichiometric amounts of piroxicam and 10 carboxylic acid coformers. Reaction crystallization experiments were designed using organic solubility data for piroxicam and the same coformers. In this method, solutions of the components were made so that the co-crystal forms were supersaturated and precipitated out of solution. Co-crystals were characterized by DSC, HPLC, and XRPD. Co-crystal solubility was measured using equilibrium solubility measurement techniques. Intrinsic dissolution rates were measured using a Wood's Apparatus in biorelevant media. Piroxicam and co-crystals were dosed orally in capsules in rats to determine oral bioavailability.

Results
Pure co-crystals could not be obtained by slow evaporation, but reaction crystallization yielded six piroxicam co-crystals on both 15-30 mg and 1-15 g scales. The co-crystals that were isolated were found to be 300 – 2000 times more soluble than piroxicam. Thirty-minute dissolution rates for two co-crystals were greater than that of piroxicam, but oral bioavailabilities were comparable to that of piroxicam.

Conclusion
Reaction crystallization was shown to be more effective than slow evaporation in producing pure batches of co-crystals. A small boost in dissolution rate was observed for two co-crystals, but it did not translate to increased oral bioavailability.