Impurity-Coformer Cocrystals and/or Complexes and their Use in Separations

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TECHNICAL SUMMARY
Separation processes are of great importance in many industries, especially in those that produce highly regulated products. Crystallization is commonly used as a purification technique in many industries, but can have two drawbacks: the first is the reduced selectivity when a structurally similar impurity is incorporated into the crystal lattice of the target being crystallized; the second is increased process time and cost related to filtration and drying, a particular issue for intermediates that are crystallized and need to be re-dissolved in a subsequent step. The aim of this thesis is to develop separation processes to enhance the selectivity along with minimization of solids handling. Three different approaches were studied: (1) the separation of impurities from solution by selective impurity cocrystal formation where the cocrystal has a lower solubility than that of the impurity alone; (2) the use of coformers to form impurity-coformer complexes in solution followed by the crystallization of the desired compound; and (3) the selective adsorption of the impurity in solution using functionalized self-assembled monolayers on gold surfaces.

All three approaches were built on the concept of “molecular recognition”. In the first approach, the impurity was crystallized in its cocrystal form by the addition of a coformer while the target remained solubilized for downstream processing. The feasibility of this process was assessed using ketoprofen/ibuprofen as the model target/impurity system. A strategy was established for selecting the optimal coformer, concentration of the coformer, and solvent for the separation process. The amount of ibuprofen was decreased from 6 wt% to 2.5 wt%.

In the second approach, impurity-coformer complexes that could no longer fit into the crystal lattice of the target compound were formed by the addition of coformers. The feasibility of this process was examined using three systems: benzamide/benzoic acid, cinnamamide/cinnamic acid, and amoxicillin trihydrate/4-hydroxyphenylglycine system. Using the two model systems (benzamide/benzoic acid and cinnamamide/cinnamic acid), we demonstrated the feasibility of reducing the amount of the impurity substituting into the target crystal lattice by adding coformers that could form cocrystal with the impurity but not with the target compound. In these cases we knew in advance that cocrystals of the impurity with particular coformers would form. The impurity content in the target crystals was approximately 20% less using the coformer than without the coformer. We then tested this method using the amoxicillin trihydrate (AMCT)/4-hydroxyphenylglycine (4HPG) system for which we had no advance knowledge of coformers that could form cocrystals with 4HPG. In this case we were able to identify coformers that substantially reduced the impurity content in amoxicillin crystals. Their purities were even superior to the purity that would be obtained from two crystallizations of the initial solution. A clear correlation between the level of complexation and the purification results was shown in this system.
The goal of the third method was to adsorb the impurity in solution selectively using functionalized self-assembled monolayers on gold surfaces. Gold surfaces were functionalized using thiols with different tail groups that could form hydrogen bonds with a functional group on the impurity. Three target/impurity systems and two thiols were studied using this approach. Despite the reasonable concept and experimental design, large standard deviation between the experiments performed under same conditions was observed. No significant separation results were obtained.