The A Priori Design and Selection of Ionic Liquids as Solvents for Active Pharmaceutical Ingredients

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In this paper we derive a straightforward computational approach to predict the optimal ionic liquid (IL) solvent for a given compound, based on COSMO-RS calculations. These calculations were performed on 18 different active pharmaceutical ingredients (APIs) using a matrix of 210 hypothetical ILs. These results indicated that the 18 APIs could be classified into three distinct categories based on their relative hydrogen bond donating or accepting ability, with similar optimal IL solvent predictions within each class. Informed by these results, a family of strongly hydrogen bond donating ILs based on the N-alkylguanidinium cation were prepared and characterized. The solubility of the APIs in each of these classes was found to be qualitatively consistent with the predictions of the COSMO-RS model. The suitability of these novel guanidinium salts as crystallization solvents was demonstrated by the use of N-butylguanidinium bis(trifluoromethanesulfonyl)imide for the purification of crude fenofibrate using dimethylsulfoxide as an antisolvent, which resulted in good yields and excellent purities. Finally, a simple descriptor based model is proposed to suggest the best IL solvent for arbitrary APIs.

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Contributors: Kunov-Kruse, A. J., Weber, C. C., Rogers, R. D., Myerson, A. S.
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