Computational scheme for design of ionic liquid in extraction of pharmaceutical intermediate

Madakashira Harini[†], Shanu Jain[†], Jhumpa Adhikari[†], Santosh B. Noronha[†] and K. Yamuna Rani[*]

[†]*Department of Chemical Engineering, Indian Institute of Technology Bombay, Mumbai-400076*
[*]*Chemical Engineering Division, Indian Institute of Chemical Technology, Hyderabad-500007*

Ionic liquids (ILs) are green solvents that have tuneable properties and are considered as potential alternatives to volatile organic compounds in many industrial applications. Whenever, there is a need for replacement of a non-green solvent in a process due to environmental, health and toxicological concerns; ILs can be an alternative. The properties of ILs can be optimized for a specific task by the combination various cations and anions; and also by varying alkyl chain length or by addition of a functional group on the cation/anion. As it is tedious and uneconomical to conduct experiments on various ILs to find its suitability for specific process, computer aided molecular design[1] (CAMD) methodology has been adopted to design an IL for efficient extraction of R-phenylacetylcarbinol (PAC), from aqueous phase. PAC is an intermediate in the manufacture of several pharmaceutical products and is currently produced by means of whole cell biocatalysis.

The properties that are of interest, for extraction of PAC, include solvent power, selectivity, distribution coefficient, solvent loss, octanol-water partition coefficient, melting point (T_m), viscosity and thermal decomposition temperature (T_d). These properties, except the T_m, visosity and T_d, are ratios of infinite dilution activity coefficient values and are estimated using the universal functional activity coefficients (UNIFAC) method;[2] while the T_m and T_d are estimated using a group contribution model. A basis set of 16 ILs has been chosen, to which an alkyl chain or a functional group (with a maximum of four groups) can be attached at two or three different positions, based on the structure of the IL. A total of 23 groups (including repetitions) have been chosen, whose combinations lead to an attachment of hydroxyl, alkyl, vinyl and ketone based ILs.

A variant of the genetic algorithm, namely, non-dominated sorting genetic algorithm (NSGA-II)[3], and the direct search method, have been employed to arrive at list of feasible ILs that can extract PAC efficiently. The structural constraints have been incorporated to generate a viable ionic liquid. The bounds on all the target properties are specified based on the property values of toluene; as current industrial practice employs toluene as the solvent. A multi objective function that minimizes solvent loss and maximizes selectivity, distribution coefficient and solvent power, has been utilized in optimization to generate the list of feasible ILs. Among the ILs considered in this study, the ILs containing anions Tf_2N^- and FAP^- have been determined as the best solvents for extraction of PAC. The resultant molecules obtained from the direct search method and NSGA-II are in excellent agreement and yielded 2-methyl 2-butenyl [N-C3OHPY][FAP]

(1-(3-hydroxypropyl) pyridinium tri(pentafluoroethyl) trifluorophosphate) as the best solvent. The order of extraction capability for the side chain attachment in this case study suggests, vinyl > alkyl > ketone > alcohol; and among alkyls, butyl > propyl > ethyl > methyl. This observation on alkyl groups is in agreement with the experimental trend of increase in hydrophobicity with chain length. In addition, some of the experimental findings on specific ILs (with Tf_2N^- and FAP^- anions) reported in literature[4] are in agreement with our CAMD findings.

References:

1. Karunanithi, A. T. & Mehrkesh, A. *AIChE J.* **59,** 4627-4640 (2013).
2. Lei, Z., Dai, C., Liu, X., Xiao, L. & Chen, B. *Ind. Eng. Chem. Res* .**51**, 12135-12144 (2012).
3. Deb, K., Pratap, A., Agarwal, S. & Meyarivan, T. *IEEE Trans.Evolutionary Computation* **6,** 182–197 (2002).
4. Marciniak, A. & Karczemna, E. *Fluid Phase Equilib.* **304,** 121–124 (2011).