Efficient, Reliable and Predictive Solvent Design for Pharmaceutical Processes

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Solvents play a very important role in the processing of pharmaceutical products. For example, use of pure solvents and antisolvents for crystallization and in organic synthesis steps are critical in pharmaceutical process design. In fact, the identity of the solvent or antisolvent is a key issue for efficient solute recovery in the case of crystallization and solid reactant conversion in the case of reaction. From an environmental point of view, the solvents also need to be “green” and improve process sustainability. Also, in pharmaceutical formulations, solvents are needed. In many situations, solvent blends could enhance the solubility of the active pharmaceutical ingredient (API) and show a ‘solubility peak’ (solubility higher than the solubility in the two pure solvents). Therefore, it is important to have a method for solvent design method that is able to cover pure solvents as well as solvent blends.

In this presentation a systematic method to identify/design pure solvents, solvent blends that show solubility peaks and antisolvents that cause a large decrease in solubility when added to the API-solvent system is presented.

The method is based on the theory of the conceptual segments introduced by Chau-Chyun and Song (2004) with the NRTL-SAC model: hydrophobic, polar and hydrophilic segments. First, a Marrero and Gani (Marrero and Gani, 2001) type of group contribution model is developed and applied to estimate the conceptual segment values in the absence of experimental data. The advantage here is that the procedure is now independent of the need for experimental data. Next, the API solubility in *apriori* generated list of pure solvent candidates is evaluated and the pure solvents are ranked according to their performance (for example, solvent power). Once the most promising candidates have been identified, mixture (blend) design is performed to identify the solvents that mixed with the best candidates give the solubility peaks. This is done by identifying the combination of conceptual segments that maximizes the excess (mixing) properties. The same procedure is also applicable for design of antisolvents and blends of solvents-antisolvents. In this case, however, a solubility valley is desired. That is, the method uses the excess properties of mixing to identify an enhancement of the API solubility for solvent-solvent blends (the formation of a solubility peak) or a reduction of the API solubility for solvent-antisolvent blends (the formation of a solubility valley). For organic synthesis or API solubility, the same procedure is also applicable.

A case study dealing with the crystallization of a well-known pharmaceutical product, ibuprofen, is highlighted to illustrate the application of method for identifying solvents, antisolvents and to design solvent-antisolvent blends for use in cooling crystallization followed by drop-down crystallization. Other examples involving paracetamol and hydrocortisone are also briefly presented.

References

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Marrero J. and Gani R. Group contribution based estimation of pure component properties. *Fluid Phase Equilibr.* 2001, 183-184, 183-208.

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