THERMODYNAMIC MODELING OF DRUG CRYSTALLIZATION PHENOMENA

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Crystallization processes of drugs (APIs) depend to a great extent on the API solubility in the applied solvent or solvent mixtures. Thus, the first step in optimizing crystallization conditions is usually a solvent screening which includes pure solvents as well as solvent mixtures.
Another important phenomenon of API crystallization processes is the co-called oiling out: upon cooling, crystallization is preceded by the formation of a second liquid phase in the metastable, supersaturated solution. This often disturbs the crystallization process and deteriorates the product properties.
The talk discusses the thermodynamic modeling of both, solubility as well as oiling out in API solutions. Nowadays, one of the most-successful thermodynamic models is the so-called PC-SAFT (Perturbed-Chain Statistical Associating Fluid Theory) model[1]. It expresses the Helmholtz energy of an API solution based on the structure and physical properties of the API as well as of the solvent(s). Knowing this quantity subsequently allows the calculation of all other thermodynamic properties like density, enthalpy or solubility.
PC-SAFT is able to correlate and to predict the solubility of API's in pure solvents and based on only a small amount of experimental data.

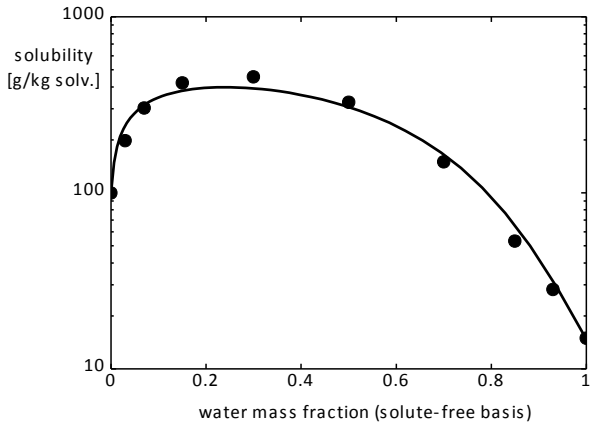

Figure 1. Solubility of paracetamol in water/acetone mixture at 25°C as function of the water content in the solute-free system. Symbols is experimental data, the line is a prediction with PC-SAFT.

Once the solubility in pure solvents is known, the one in solvent mixtures can even be predicted in almost quantitative agreement with experimental data without fitting any additional parameters (Figure 1) [2].
Figure 2 shows an example for the prediction of pH influence on the solubility of DL-Methionine based only on the knowledge of the solubility at the isoelectric point (at pI) and the two acid constants.

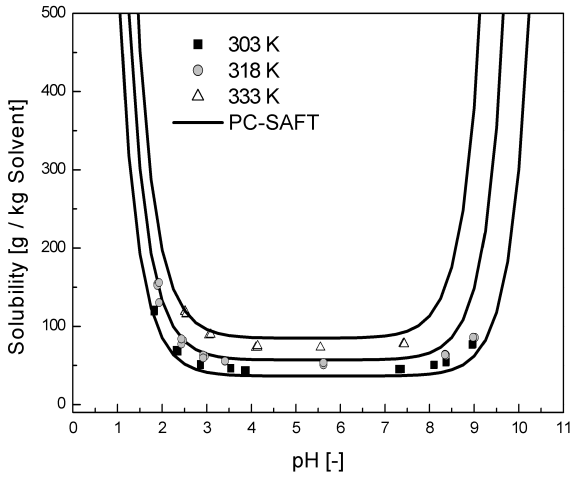

Figure 2. pH-dependence of DL-methionine solubility at different temperatures. Symbols are experimental data. Lines are calculations with PC-SAFT.

Finally, it possible to predict whether the solution tends to demix and to form a liquid-liquid miscibility gap in the stable or even metastable liquid which is causing the oiling out[4],[5]. Thus, thermodynamic modeling allows drastically reducing the number of screening experiments and supports an appropriate choice of solvents or solvent mixtures for preventing oiling out.

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