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Thermodynamic Modeling of Drug-Like Molecules

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Solubility is the most important phase equilibrium property for solvent selection and design in the pharmaceutical industry.[1] Its experimental measurement, although desirable is not recommended, as this is expensive and time-consuming, and not practical for the early stages of drug development, where a large set of solute-solvent systems needs to be screened. Thermodynamic models have been classical tools to describe it, but the complexity of pharmaceuticals has hampered their use in the pharmaceutical industry, where empirical correlations, lacking from a strong theoretical basis, have been predominantly employed. In this work our aim is to identify strengths, weaknesses and opportunities of some classical thermodynamic models, such as activity coefficient models and equations of state, to perform solubility calculations of pharmaceutical molecules. The solubility of different complex solutes, like benzoic, salicylic, acetylsalicylic, terephthalic, nicotinic and stearic acids, ibuprofen, hydroquinone, estriol, estradiol, resveratrol, paracetamol and piperazine were studied in a wide variety of solvents. For that purpose, NRTL-SAC,[2] UNIFAC [3] and A-UNIFAC,[4] and the CPA equation of state,[5,6] were used to correlate and predict the solubilities in pure and mixed solvents. If possible, the Reference Solvent Approach was also applied.[1] Generally, A-UNIFAC and NRTL-SAC are able to satisfactorily represent the data. For the mixed solvent systems, A-UNIFAC proved to be better and in general, there is a clear improvement with A-UNIFAC over the UNIFAC model. The results obtained when applying the Reference Solvent Approach were significantly improved. CPA was tested for describing aqueous solubilities, being able to correlate the data, using a binary interaction parameter, which may have to be high because the model cannot yet represent all the possible functional groups interactions.

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