Predicting the Phase Behaviour and Ph-Solubility Profiles of Active Pharmaceutical Ingredients Using the SAFT-Γ Mie Group-Contribution Approach

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The pharmaceutical industry is facing a constantly rising demand for drugs of growing complexity and more efficient manufacturing processes. The solubility of pharmaceuticals is a key property during the drug formulation and the subsequent design of the processes involved in the manufacturing of the drug. Common challenges in these manufacturing processes include: the large number of experiments required and the extremely low solubilities of active pharmaceutical ingredients (APIs) in water for which experiments are difficult to perform. Computer-aided approaches provide an attractive alternative to performing time-consuming and costly experiments. Specifically, molecular modelling approaches can deliver physical properties predictively, including phase equilibria and solubility.

The SAFT-γ Mie group-contribution (GC) equation of state (EoS) [1, 2] is such a predictive thermodynamic modelling technique. In the SAFT-γ Mie framework, molecules are modelled as heteronuclear chains formed from fused spherical segments, which represent the distinct functional groups comprising the molecule. In this framework, it is assumed that the properties of a molecule or a mixture can be determined from the weighted contributions of the functional groups present in the system of interest, with the assumption that the parameters characterizing the functional groups are fully transferable across molecules.

We demonstrate the validity of the SAFT-γ Mie EoS in the prediction of thermodynamic equilibrium properties of neutral APIs including solubilities. We then develop the phase diagrams of the APIs in water, outlining the solid-liquid, liquid-liquid and vapour-liquid equilibria for these mixtures. We expand on these findings and use the SAFT-γ Mie GC approach for the solubility prediction of ionisable APIs, and their salts, under changing pH. The model accounts for the complex speciation phenomena that take place under pH changes including fully ionised (strong electrolyte) and partially ionised (weak electrolyte) systems. We investigate in particular, the solubility of the acidic APIs, ibuprofen and ketoprofen, their speciation and salt formation, to develop the pH-solubility profiles for these drugs. This is followed by considering the application of predicted pH-solubility profiles for optimal salt selection.

References

[1] Papaioannou, V. et al. Group contribution methodology based on the statistical associating fluid theory for heteronuclear molecules formed from Mie segments. *Chem. Phys.* **140**, (2014).

[2] Dufal, S. et al. Prediction of thermodynamic properties and phase behavior of fluids and mixtures with the SAFT-γ mie group-contribution equation of state. *J. Chem. Eng. Data* **59**, 3272–3288 (2014).