Modelling Solid-Liquid Equilibrium Properties of Amino-acid and Oligopeptide Solutions Using the SAFT-γ Mie Group-Contribution Framework

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Peptides are gaining increasing attention as active pharmaceutical ingredients (APIs) due to their therapeutic specificity, potency, and low toxicity [1], and the robust modelling of their properties in solution is central in the screening, development, and design of the drug product and its manufacturing process. The SAFT-γ Mie GC approach is used in this work to model the solubility of peptides and their constituent amino acids in several pure and mixed solvent media and at a wide range of temperatures and solvent compositions. Additionally, the speciation of amino acids under changing pH is modelled by solving the phase- and chemical-equilibrium equations simultaneously. This is made possible by the ability of the model to account explicitly for the zwitterionic nature of amino acids. With minimal use of experimental data, especially that of solubility, the model produces accurate solubility predictions for many binary, ternary, and multicomponent systems containing a variety of amino acids and oligopeptides.

The SAFT-γ Mie group-contribution (GC) approach is a model based on the statistical associating fluid theory (SAFT) in which molecules are treated as heteronuclear chains of interacting spherical segments. Thermodynamic properties of the system of interest are derived from the Helmholtz free-energy expression, which combines terms describing the dispersion, chain, association, and electrostatic interactions between the segments [2]. In the context of pharmaceutical applications, this approach has been used to model the solid–liquid solubility of small APIs such as valproic acid, azelaic acid, and phenlyalkanoic acids [4], ibuprofen and procaine [5], and mefenamic acid [6]. The advantage of using such a model for peptides and amino acids lies in the transferability of its parameters, since peptides are made up of repeating units of amino-acid residues. Hence, this allows for accurate solubility predictions for the amino acids and peptides of interest at a wide range of thermodynamic conditions and in various kinds of solvent media while maintaining the generic applicability of the model.

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