Ternary Solid-Liquid Equilibria for Crystallization of Pharmaceutical Components

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The present study takes place in the general approach regarding the design and the development of methods useful for the acquisition of thermodynamic data on phase equilibria in crystallization engineering. Crystallization is of particular interest since it constitutes very often the final step of the purification of solids. The construction of a phase diagram containing a solid solute and a liquid solvent is simply based on the determination of the solubility of the solid solute in the solvent. The solvent can be a pure liquid component or a liquid mixture for efficient solvent-antisolvent selective capability. Effectively, in such ternary systems the crystallization of the solute can be obtained in adding the antisolvent to a concentred solution of the solute in the other ("good") solvent. Thus, the choice of selected solvents in crystallization processes rests on the knowledge of the solid phase contour of the product to precipitate in the presence of the solvent-antisovent mixture. Since theoretical calculations are not available so far to provide accurate prediction of the solubility limits of a solid component in binary mixtures, experimental determinations are necessary to establish solid-liquid phase equilibria in ternary systems. When the solute is an organic component the solvent is generally a binary mixture water + a hydrophilic organic component. The aqueous mixed solvent behaves as an homogeneous phase over its entire mole fraction range. Then the thermodynamic study of the whole system will be focused on the determination of the maximum of solubility of the solid solute that is to say all along the solid-liquid line of the ternary system; in this way, this line which is the locus of the maximum solubility data points is readily obtained as of plot of those points.

An original technique and associated methodology have been developed to obtain ternary solid-liquid equilibria. For this purpose a Setaram titration calorimeter, Titrys, has been used to construct the solid-liquid equilibrium line in ternary systems consisting of the solute to precipitate and of an aqueous mixed solvent. The method consists in measuring the heat of dissolution of a known mass of the solid component during successive additions of the liquid solvent. The cumulated heat, resulting from the successive heat peaks obtained for the different injections of known volumes of solvent, plotted versus the ratio of the numbers of moles $n_{solvent}$ / n_{solute} is represented by two straight lines. The intercept of the two lines gives the solubility limit (*i.e.* the maximum solubility data point) and the corresponding enthalpy of dissolution of the solute in the solvent. Performances of the technique and methodology will be illustrated by different ternary systems, at 303 K, where the solid components are vanillin, nicotinamide, nicotinic acid, caffeine or salicyaldehyde and the binary liquid solvent being water + methanol, + ethanol or + propanol