12.2 Phase Equilibria of Chiral Systems

The specific solid–liquid phase equilibria (SLE) and the corresponding phase diagrams of a system form the fundamental thermodynamic basis to design crystallization processes. Detailed SLE data provide the information necessary to answer the question of which solid-state form of a target product can be crystallized under certain conditions (*i.e.* a certain polymorph or solvate) together with information regarding yields and purities achievable.

In binary systems one can distinguish between two groups of phase diagrams regarding solid–liquid equilibria: systems showing (1) immiscibility and (2) miscibility in the solid state. The first group can be further divided into systems exhibiting eutectic behaviour or the formation of intermediate molecular compounds. It is by far the most prominent group, representing about 86% of the organic systems, with the majority (*ca.* 54%) being simple eutectic systems.[23] The second group, systems with full miscibility in the solid state, is less frequently observed within organic systems (about 14%).[23] In addition, limited (partial) miscibility can occur in all types of group (1) systems. Concerning chiral systems, the frequency at which different phase diagrams occur is influenced by the unique similarity of the two chiral molecules and their mirror-image symmetry in particular. Eutectic systems are found in only 5 to 10% of the cases.[15] In 90 to 95% of the systems the two enantiomers form a 1 : 1 racemic compound, represented by an additional two-phase domain in the corresponding ternary solubility phase diagrams (Figure 12.1). Although full miscibility in the solid state is rare for chiral systems, limited miscibility can occur and is increasingly reported and analysed within the last years.[24–30] Figure 12.1 illustrates ternary solubility phase diagrams of a eutectic and a racemic compound-forming chiral system in a certain solvent as well as a eutectic system with limited miscibility in the solid state. An example of the latter case is described for the ethanolamine salt of 3-chloromandelic acid.[25] It should be noted that the phase equilibria depicted above can be much more diverse due to, for example, solid–solid or liquid–liquid equilibria that interfere with the SLE (*e.g.* polymorphy,[31] liquid–liquid demixing[32]) and the formation of non-equimolar discrete compounds of the enantiomers.[33]

The separation of enantiomers can be considered as a special case of purification by crystallization, because the counter-enantiomer can occur in the same amount as the target enantiomer and the two molecules to be separated show extraordinary similarity. In fact, thermodynamic and kinetic properties are identical, *e.g.* the melting points, the solubility and crystallization characteristics.

Due to these similarities, resolution of the racemates by crystallization under equilibrium conditions is not feasible. Resolution is possible, however, through the aforementioned preferential crystallization (PC) method: a kinetically controlled separation process relying on the