2.6.1 Modeling Solvent Mediated Polymorphic Transformation

Numerous APIs have multiple polymorphic forms that can be obtained under similar process conditions, however, it is of primary importance to ensure that the end-product contains only the desired polymorph. Therefore, the mathematical modeling of polymorphic crystallization has great interest in pharmaceutical crystallization.

2.6.1.1 Model Equations for a MSMPR Crystallizer

To keep the simplicity without losing generality, the polymorphic crystallization modeling is presented through the example of the crystallization of a substance with two polymorphic forms (form I and form II). The fundamental difference that is related to the crystal lattice structure is that each polymorphic form has individual solubility. Typical solubility curves of the two polymorphs are presented in Figure 2.13 through the example of ortho-amino benzoic acid in 90% water 10% isopropyl-alcohol, adapted from the literature.[33]

The form I and form II crystals in the suspension can be treated as individuals belonging to two separate populations. In this context, two population density functions can be distinguished within all the solids, one for the form I $n_{\mathrm{I}}(L,t)$ and another for form II $n_{\mathrm{II}}(L,t)$. The population density function of all solids in the crystallizer is represented by the sum $n_{\mathrm{I}}(L,t) + n_{\mathrm{II}}(L,t)$. Given the actual concentration and temperature conditions in the crystallizer, three cases can occur with respect to solubility conditions:

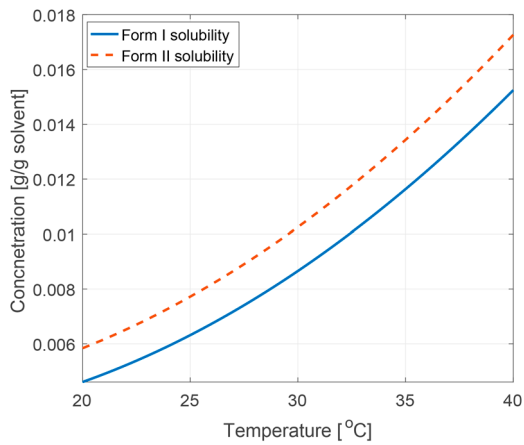

Figure 2.13 Typical polymorphic solubility curves – case of ortho-amino benzoic acid solubility in 90% water – 10% isopropyl alcohol.