

The supersaturation ratio  $S$  is defined by the concentration  $C$  and solubility  $C^*$  at the current value of the parameters being adjusted to generate supersaturation (temperature, solvent mixture composition, pH *etc.*). [Note: concentration can have various units (*e.g.*, mole fraction or mg per mL solvent), which will result in different values for  $S$  and therefore it is important that it is clearly specified which units are used]. The supersaturation can be increased by, for instance, a concentration increase through solvent evaporation or a solubility decrease by decreasing the temperature. Crystal growth would reduce the solution concentration and thus the supersaturation.

If the concentration exceeds the solubility, the supersaturation ratio  $S > 1$ , the solution is supersaturated and any crystals present can grow. If the concentration is lower than the solubility ( $S < 1$ ) the solution is undersaturated and any crystals present will tend to dissolve. At thermodynamic equilibrium the solution is saturated, concentration and solubility are equal ( $S = 1$ ), any crystals present will be maintained in equilibrium with the flux of molecules arriving and leaving the collective crystal surface being in balance. Since the supersaturation ratio drives the crystallization process, the solubility of a compound is a crucial parameter in the crystallization process design. For instance, a strongly increasing solubility with temperature and a sufficiently small solubility at a low temperature direct the preferred supersaturation generation method towards cooling. In addition, the difference between the inlet concentration and the end point solubility is strongly associated with the yield and productivity of a crystallization process.

Within an industrial crystallization process, crystals can be formed from an initially clear solution (primary nucleation) or due to the presence of parent crystals (secondary nucleation). In turn, primary nucleation generally is divided into homogeneous and heterogeneous nucleation. In a supersaturated solution new crystals can be formed in the absence of crystalline solids of the same substance, which is termed primary nucleation, or in the presence of crystalline solids of the same substance, which is termed secondary nucleation. Primary and secondary nucleation will be discussed in respectively Sections 1.2.1 and 1.2.2. Both primary and secondary nucleation as well as crystal growth kinetics vary widely under thermodynamically metastable conditions. However, the nucleation rate varies over many orders of magnitude while growth rate has more gentle increase with increasing supersaturation. During heterogeneous primary nucleation, the crystals form at surfaces such as dust particles, crystallizer wall, air–solution interface or deliberately added template particles. Homogeneous primary nucleation takes place in the absence of heterogeneous particles in a clear solution. It is important to note that in the laboratory and more so in large-scale processes on an industrial scale, the presence of many different heterogeneous particles or surfaces is impossible to avoid. Despite their importance, usually no information is available on the amount and kind of heterogeneous particles that are finally responsible for the occurrence of heterogeneous nucleation.