

The kind of nucleation occurring depends strongly on the continuous crystallization process configuration chosen. A simple continuous crystallization concept is to use a single continuous agitated vessel with a continuous feed solution and suspension outflow, such as a CST, or MSMPR crystallizer. The various crystallization methods can be performed by either maintaining the crystallizer at a lower temperature than the feed solution, evaporating solvent in the crystallizer or adding an additional antisolvent or solution feed to the crystallizer. It is also possible to combine various crystallization methods, for instance, an antisolvent crystallization or a pH shift with a cooling crystallization, if the product still has a substantial solubility at the higher temperature after the antisolvent addition or pH shift, respectively.

Growth is a bulk average (driven by bulk composition and temperature), while nucleation is a local phenomenon (*e.g.*, mixing zone, impeller, vessel wall, liquid/air interface, temperature heterogeneity, external field) occurring at the locations with highest supersaturation. During mixing of the feed and crystallizer suspension locations with a relatively high concentration and low temperature exist at the feed inlet and/or cooling surfaces. In evaporative crystallization, locally increased concentrations occur in the boiling zone due to the selective evaporation of the solvent. These locations therefore are associated with a high supersaturation at which primary nucleation could occur and be determined. Secondary nucleation can occur for instance due to large crystals colliding with the stirrer so that small crystal fragments (secondary nuclei) are created.

The encrustation in continuous cooling crystallization (MSMPR or oscillatory baffled crystallizer (OBC)) mostly happens at the heat transfer interface that provides a high local supersaturation ratio, which initiates intense and uncontrolled local nucleation. The continuous nucleation on the heat transfer surface is deteriorative to the process stability and longevity of the runs and there have been some control strategies proposed to avoid the rapid nucleation on the surface.^{84,85}

In CST type continuous cooling and evaporative crystallization processes new particles are typically generated through secondary nucleation due to collisions of particles with an agitator. However, there are other types of agitated vessels where secondary nucleation may not be dominant (see below). In case of mixing induced crystallization processes such as antisolvent and reactive crystallization, particles often are generated by primary nucleation due to concentration heterogeneities introduced by the mixing process.

Another continuous crystallization concept is a *plug flow crystallizer* (PFC). A PFC is a long tube in which the crystals are allowed to grow along the length of the tube while they are taken along with the solution flowing through the tube. Use of a PFC allows all crystals to have the same residence time in the tube if the back mixing is sufficiently small. In principle, this allows a tight control over the CSD. In a plug flow type continuous crystallization processes there are 2 routes towards generating particles in the process.