The pharmaceutical industry is beginning to adopt continuous manufacturing.[1] Although crystallization has been identified as one of the bottlenecks for full adoption of continuous manufacturing as it is considerably slower than the upstream continuous synthesis,[2–4] a number of principal drivers for switching from batch to continuous crystallization have been identified.[5]

Continuous crystallization is a collection of sub-processes such as solution feeding, supersaturation generation, heat transfer, evaporation, primary nucleation, secondary nucleation, crystal growth, agglomeration and particle suspension. While it sets the rate of formation of new crystalline particles over which the crystallizing mass is distributed in a continuous crystallization process, the sub-process of crystal nucleation is poorly understood and controlled.[6] Once a supersaturation is created crystallization can commence. Crystallization is a collection of the subprocesses of crystal primary nucleation, crystal growth, secondary nucleation and agglomeration, which are all governed by the prevailing supersaturation as well as other parameters. The rates of these subprocesses determine the crystalline product quality.

In order to achieve enhanced control over the crystal nucleation and growth in a continuous crystallization processes, a higher level of nucleation understanding and control is needed. Nucleation can be circumvented by seeding which is especially useful during start-up to minimize the peak of supersaturation associated with conventional unseeded crystallization and along with this reduce the risk of encrustation forming, as once formed this ultimately limits the duration of a continuous crystallization process. Seed suspension can also be continuously fed into a crystallizer operating at a steady state as an additional input. Continuous nucleators also have been proposed as a workaround technique, as well as *in situ* milling, or the inherent *in situ* secondary nucleation in mixed suspension mixed product removal (MSMPR) due to particle–particle or particle–impeller attrition.

1.2 Crystal Nucleation

Industrial crystallization involves the formation of a particulate crystalline phase from a thermodynamically metastable solution.[7,8] A continuous crystallization process will have a clear (particle free) undersaturated solution as an input and a slightly supersaturated suspension as an output. The product crystals will need to be generated in the crystallizer by creating the supersaturation driving force for crystallization using an external action.

One of the ways to define the driving force for crystallization is by the supersaturation ratio S:

$$S = C/C^* \tag{1.1}$$