

conditions, while avoiding secondary nucleation by providing mild crystallization conditions, to achieve required performance of purification and particle product attributes.

A suspension of seed crystals can be added as a feed so that the continuous crystallizer is used to grow the seeds. In this case it is important to prevent any kind of nucleation in order to control the final product size. Therefore, relatively mild supersaturation conditions will have to be used. In case of a continuous cooling crystallization in a plug flow crystallizer, for instance, the temperature of the suspension will have to be reduced along the length of the crystallizer. This can be done in a way equivalent to cooling profiles used in batch cooling crystallization processes. The seed suspension feed stock will have to be made in a nucleation or seeding unit. One way of doing this is by using a continuous nucleator, or to introduce seed crystals to invoke crystal nucleation in the clear solution right at the start of the plug flow crystallizer. This can be achieved, for example, by mixing with an antisolvent or by performing reactive crystallization to create a relatively high supersaturation. While a high supersaturation is needed for the local nucleation to take place, a mild supersaturation is needed to create the conditions under which only growth occurs. Therefore, in the remainder of the crystallizer, it is difficult to control the supersaturation to only grow crystals. Since the mixing in an industrial scale crystallizer has some intrinsic locality, the mixing time could be lower than the reaction time (the Damköhler number), and scaling issues might arise. It is therefore preferable to locally induce nucleation by other means, for instance by external energies such as ultrasound, laser light and electric fields.

1.4.2 Decoupling Nucleation and Growth in Continuous Crystallization

As discussed above, in the context of continuous crystallization, there are several general scenarios of how nucleation can be employed to obtain the required crystalline product quality attributes (see Figure. 1.12):

1. secondary nucleation, *e.g.*, under mechanical impact, typically in MSMRP.
2. primary nucleation under conditions where supersaturation is mixing-induced, *e.g.*, in antisolvent or reactive crystallization, in MSMRP or PFC.
3. primary nucleation under conditions where the driving force for nucleation is localized and induced by shear or external fields, *e.g.*, ultrasound or laser, typically in PFC but could also be MSMRP bypass.

There are 2 approaches to follow in order to get a crystal product with a narrow size distribution: (1) seeding, or (2) nucleation zone/nucleator approach.