can either be applied to a low supersaturated solution where nucleation would not otherwise take place (which can be considered as increase of supersaturation locally) or to a highly supersaturated solution to promote nucleation further and better control particle size. However, the multi-effects of grinding and particle breakage by ultrasound, combination of secondary nucleation, high supersaturation, cavitation and so on could initiate some complexity. In addition to primary nucleation there has been specific research into triggering continuous secondary nucleation in a controllable manner by means of contact secondary nucleation where the generated secondary nuclei are directly fed into a tubular crystallizer. In this way the secondary nucleation process and the subsequent crystal growth process are decoupled. The differences in operating windows for the different subprocesses in crystallization and the need for specific conditions for local nucleation have been framed before.[109]

The continuous nucleation process can be undertaken in a variety of equipment utilizing a variety of crystallization modes. Rapid mixing is typically employed in a range of static mixers including standard T and Y shaped mixers, Rushton-type mixers, co-axial mixers, radial mixers and pipes with inserts. Cooling and simple solution addition are usually employed in either a standard tubular device, a glass channel, an OBC or a cascade of MSMPR Crystallizers of one or more stages. Each piece of equipment has a set of advantages and disadvantages with regards to mixing intensity, capacity, temperature control and heat transfer characteristics. This equipment can be used in conjunction with novel technologies such as the wet mill and ultrasound. Furthermore, the crystallization modes can be combined with novel operation strategies including slug flow and periodic flow.

1.4.4 Supersaturation Control by Rapid or Non-rapid Mixing

One method of generating local high supersaturation is to rapidly mix solutions in a static mixer in an effort to reach a target supersaturation level instantaneously. The rapid mixing should result in a crystallization process which is dominated by primary nucleation with minimal crystal growth which leads to the creation of a seed suspension with a narrow particle size distribution (PSD) and a small mean particle size. Many studies which utilize rapid mixing strategies have applied these to antisolvent,[91,110–114] reactive[92–94] and cooling[111,115,116] crystallizations with a specific desire to control PSD and/or mean particle size. Some of this research[91–94] has compared continuous mixing processes in static mixers with conventional batch processes and shown that the more controlled mixing environment in the static mixer does result in a narrower PSD with a smaller mean particle size. Furthermore, when using a static mixer the PSD and mean particle size can be controlled by changing the initial supersaturation and the flow velocity.[91,93,94,110,111,113] Sometimes ultrasound is applied even to rapidly mixed, highly supersaturated solutions in an effort to further decrease particle size