was demonstrated that utilizing ultrasound led to a shorter time until steady state with a lower supersaturation level being reached at steady state. In addition, sonication resulted in significantly smaller particle sizes, reduced agglomeration and improved crystal habit.

Continuous cooling crystallization is usually employed in a cascade of MSMPRs rather than a single MSMPR because residence time is increased and the flow becomes closer to plug flow. These processes commonly involve continuous seed generation in the first MSMPR stage followed by crystal growth.[136,137,139,141] Some studies show that process yield and purity can be controlled by changing the temperature and residence time of each stage of the MSMPR as this changes the supersaturation profile.[136,137] In addition, the mean particle size can be controlled by changing the number of stages in the MSMPR cascade. Another study shows that the PSD can be controlled in a two stage MSMPR cascade by implementing a nucleation control strategy where particle chord count information from the FBRM (see Chapter 9) is used to implement heating or cooling rates to maintain particle chord counts in a desired setpoint range during the crystallization process.[141] This allows for greater control over nucleation and growth in an MSMPR cascade without adding additional stages. In addition to controlling particle size in an MSMPR cascade, a study has demonstrated that the polymorphic outcome of a co-crystallization can be controlled when continuous periodic flow is utilized.[139] It was found that the polymorphic outcome of the co-crystallization depended on the feeding regime employed for combining the two components of the co-crystal in the first MSMPR in addition to the initial operating temperature.

A cascade of MSMPRs can also be utilized to employ a combination of crystallization modes. This is typically achieved by combining cooling crystallization with either antisolvent or reactive crystallization.[133,135] In the combined cooling and antisolvent process it was shown that adding antisolvent in a later stage lead to the entire process operating at a lower supersaturation level which resulted in crystals which were less agglomerated with better crystallinity.[133] On the other hand the purity and yield of the crystals were unaffected by the antisolvent addition. In the combined cooling and reactive process it was demonstrated that the reactant molar ratio and temperature of each stage must be well controlled in order to maximize the yield of the reaction as well as the yield of the crystallization.[135] In addition, the temperature profile had to be well controlled so that supersaturation was not generated too rapidly and a high crystal purity was obtained.

1.4.7 Continuous MSMPR Cascade with Batch Crystallization Start Up

Sometimes it is not possible to achieve fully continuous seed generation within a series of one or more MSMPRs. In these cases[142–146] a crystal seed suspension is generated in batch mode before continuous flow is implemented.