

due to enhanced primary nucleation rates.^{92,112} Sonication may also help reduce the extent of fouling and blockages in a tubular device. With rapid mixing there is the issue of what happens to the seed suspension immediately after it is created. An attractive answer to this is to employ slug flow in the tubular device to allow for the seeds to grow to a larger size while maintaining a narrow PSD.¹¹⁵

In addition to controlling particle size, other studies^{117–119} have used rapid mixing to demonstrate the control of solid form in antisolvent and reactive crystallization processes. The polymorphic outcome of a single component system was shown to be controlled *via* the solution concentration and antisolvent mass fraction.¹¹⁹ It has also been demonstrated that a solid solution can be produced continuously by means of a rapid mixing process.¹¹⁸ Being able to produce these solid solutions rapidly and at steady state for extended periods of time is a marked improvement over the small batch crystallizations which were previously performed.

Some studies have shown high supersaturation generation with non-rapid cooling or simple addition leads to a crystallization process in which primary nucleation is still dominant but crystal growth plays a larger role. This has been shown for antisolvent and cooling crystallizations in standard tubular devices^{120,121} and in OBCs.^{122–124} It was demonstrated that for a continuous crystallization process in a standard tubular device it is crucial that the flow rate, residence time and temperature profile are well controlled so that seeds are continuously produced from the crystallizer rather than a clear solution.¹²¹ This essentially comes down to ensuring the supersaturation profile along the tubular crystallizer is suitable for the crystallization process being performed. Supersaturation profile control for an antisolvent crystallization process has also been shown in a standard tubular device with inserts.¹²⁰ In this process the crystal size distribution was controlled by varying the number of antisolvent addition points along the length of the tube showing that the final PSD depends on the relative nucleation and growth rates of the compound being crystallized. OBCs have the advantage over standard tubular devices that they provide good mass and heat transfer even at low flow rates due to the fluid oscillation. This advantage has been applied successfully to continuous seed generation *via* antisolvent crystallization where it has been shown that crystal size can be decreased by increasing the initial supersaturation level.^{122,123} Continuous seed generation *via* cooling crystallization has also been demonstrated in the OBC where increasing initial supersaturation and mixing intensity reduces particle size due to the increased nucleation rate.¹²⁴

1.4.5 Ultrasound Induced Nucleation

By using ultrasound (whether in the form of a bath, probe or transducer) primary nucleation can be triggered at relatively low supersaturation levels. Many studies have demonstrated this phenomenon for cooling crystallization processes in standard tubular devices,^{125–127} glass channels^{128,129} and