

OBCs.¹³⁰ In the standard tubular devices ultrasound assisted continuous seed generation is combined with slug flow in order to better control the PSD after the initial nucleation step. This has been demonstrated by first applying ultrasound during cooling to generate the seed suspension followed by the addition of air slugs to create the slug flow.^{125,126} However, this has also been demonstrated by firstly combining a solution with immiscible liquid slugs to create the slug flow followed by the application of ultrasound during cooling to generate the seeds within the slugs.¹²⁷ With either procedure the result is that the ultrasound directly produces small seeds with a narrow PSD and the slug flow allows for a narrow PSD to be maintained as the crystals grow because the slugs minimize the axial dispersion in the tube. In the work which uses glass channels, continuous seed generation was performed by firstly cooling the clear solution inside a length of tubing to generate supersaturation before exposing this solution to ultrasound inside the glass channel by means of an ultrasonic transducer.^{128,129} These studies show that the mean particle size can be controlled with both supersaturation and ultrasonic power, with increasing supersaturation and ultrasonic power leading to a smaller mean particle size. Inserting an ultrasound probe in a OBC demonstrated that ultrasound assisted continuous seed generation could be implemented reliably at a larger scale.¹³⁰ It was shown that using sonication allowed for the mean particle size to be controlled with a narrower PSD than in the equivalent batch process. In addition, the product had consistent quality for 12 hours with no fouling or agglomeration issues being observed.

1.4.6 Fully Continuous Crystallization in an MSMPR Cascade

Continuous seed generation can also be the first step in a cascade of MSMPRs of one or more stages. Studies have demonstrated this for processes which use any combination of antisolvent,¹³¹⁻¹³⁴ reactive¹³⁵ and cooling^{132,133,135-141} crystallization. Some studies have looked at single stage MSMPR configurations which utilize continuous flow with a recycle loop in an effort to better control the product quality and minimize waste.^{132,140} It was shown that the recycle ratio and crystallizer temperature could be used to control purity and yield while the use of additives could control the particle size and shape. Other work has investigated single stage MSMPRs without recycle loops. One study looked at feeding solution and antisolvent into the MSMPR where nucleation takes place followed by continuously feeding the seed suspension into an agglomeration vessel.¹³¹ Conditions were found that allowed the nucleation and agglomeration stages to be decoupled. Another study looked at feeding solution through a membrane into an MSMPR filled with well stirred antisolvent.¹³⁴ By using the membrane the particle size was controlled by the solution concentration, the antisolvent/solvent volume ratio and the type of antisolvent. These studies show that antisolvent crystallization is typically employed to continuously generate seeds in a single stage MSMPR, but ultrasound assisted cooling crystallization has also been employed.¹³⁸ It