7.5.1 Ultrasound

Ultrasound is the most studied alternative form of energy to be used for solution crystallization processes with dedicated literature spanning several decades. The ability of ultrasound to discharge metastable systems was already reported in 1927.[270] Since then many more studies have been conducted on so-called sonocrystallization and there is broad consensus that ultrasound can have a significant impact on crystallization kinetics for a wide variety of systems. However, the precise mechanism is still a topic of debate.[271] The general understanding is that ultrasound can induce the formation of cavitational bubbles, which can implode when instable and thereby locally create high temperature and pressure. There are several mechanisms through which the crystallization kinetics can be affected as a result of such cavitation: (i) acoustic streaming, (ii) microjets,[272] (iii) heterogeneous primary nucleation,[273–275] (iv) heat, and (v) pressure.[276] The observed effects of ultrasound on crystallization systems vary and include (i) enhanced or (apparent) inhibited primary nucleation, (ii) enhanced secondary nucleation (*e.g.*, attrition), (iii) breakage, (iv) reduced fouling, and (v) de-agglomeration.[277,278]

Different crystallization configurations and hardware to induce ultrasound into continuous crystallization have been reported (Table 7.3). A typical objective is to supply sufficient energy to overcome the threshold for cavitation but avoid excessive heating of the solution. In addition, the equipment should facilitate a uniform cavitation field to obtain a predictable influence when scaling up. For instance, Eder *et al.*[34] combined sonocrystallization for seed generation with a segmented flow crystallizer as dedicated growth compartment for continuous cooling crystallization of acetylsalicylic acid from solution. Specifically, a segmented flow crystallizer was placed inside an ultrasonic bath to induce nucleation for seed generation, which allowed control over the final CSD.[34,43] Jiang and coworkers[279,280] made a variation to that concept by replacing the ultrasonic bath with an ultrasonic probe that was pressed against the outside of the tube, which enabled a more localized generation of the ultrasound field. Furuta *et al.*[281] placed an ultrasonic generator inside a temperature-controlled tank that contained a tubular crystallizer (20 m to 40 m long) for the crystallization of a commercial API. This PI approach helped to mitigate fouling issues while achieving a desired particle size (1–7 μm), which was not possible when using a conventional fed-batch system. Siddique *et al.*[127] describe how the crystallization of α-lactose monohydrate in an OBC can be intensified by applying sonocrystallization for seed generation. Although, the CSD of the final product was bimodal in the OBC, similar to a batch crystallization process, the CSD was narrower with an adjustable mean crystal size and higher yield.

Sonocrystallization has also been applied in continuous milli- and microfluidic settings. Hattoria *et al.*[282] demonstrated sonocrystallization in a continuous microfluidic channel leading to precipitation of