

this approach is that the post-crystallization operations (filtration, drying, dissolution) can be operated within the same customized setup once the crystallization is finalized. The results using diphenhydramine hydrochloride, fluoxetine hydrochloride, and ibuprofen as model systems demonstrated satisfying operation (yields between 78 and 99%) with reduced loss of material, due to the fact that slurry and/or solid transport to the next unit operation is not needed. However, similar to the filtration avoidance approach, it comes with the expenses of consecutive batch operation for each unit operation within the setup. To maintain an overall continuous operation and to boost the production capacity of the innovative crystallization system, multiple units might operate in parallel in a semi-continuous mode.

7.5 Energy Domain

The focus of PI approaches in the energy domain is on the development of novel concepts that deliver energy from the source to the intended place of action in the required form and amount.⁷ Transfer of energy for crystallization processes may be needed (i) to generate supersaturation (*e.g.*, in case of cooling or evaporative crystallization), (ii) to dissolve crystals, (iii) to overcome the energy threshold for primary nucleation, or (iv) to induce secondary nucleation *via* crystal breakage or attrition. A significant number of studies exist in which alternative forms of energy such as ultrasound, electric, and magnetic fields are applied to crystallization processes. In general, by varying the properties of such fields, additional control over the crystallization process can be obtained.

Although the majority of studies on the effect of alternative energy forms involve batch crystallization, PI methods in the energy domain can typically benefit from the inherent scale-up advantages of continuous crystallization when conducted in flow channels. In particular, batch crystallization requires by definition all material to be processed at the same time, which may pose inherent limitations for transfer of alternative forms of energy to larger volumes due to, for example, rapid energy dissipation (*e.g.*, ultrasound) or impracticality of establishing potential energy fields of high strength (*e.g.*, in case of electric fields or microwaves). In contrast, energy can be transferred during the complete operational time to a smaller volume when operating in continuous mode. Furthermore, when batch crystallization is conducted in a well-mixed tank, the area-to-volume ratio will decrease with increasing scale, which may also pose limitations in terms of effective transfer of alternative energy forms in contrast to continuous crystallization (*e.g.*, in a flow channel), where a larger surface-to-volume ratio is available for the energy transfer. This difference in the surface-to-volume ratio can be exploited to intensify the energy transfer, for instance, by using multiple transducers for ultrasound or electrodes for electric fields.