these domains are distinguished based on the most dominant PI principle for crystallization processes.[11] The chapter is not intended to provide an exhaustive list of PI examples that have been documented, but rather will draw attention to the recent developments in PI concepts applied in continuous crystallization. Finally, some perspectives on these PI approaches in terms of their readiness for implementation in industrial settings are discussed.

## 7.2 Time Domain

The currently ongoing paradigm shift from batch to continuous processing for the manufacture of pharmaceuticals to improve the manufacturing efficiency is a PI approach within the time domain.[3,11–18] Continuous processing has the potential to improve product quality, process efficiency and safety as well as aid in minimizing waste and maintenance. In addition, it can reduce the number of unit operations, size of equipment, and plant footprint allowing for the process development and manufacturing at the laboratory scale ranging from grams to kilograms per day, which aids to reduce the time to market.[14,19–21] Generally, the PI principle time follows two common strategies (i) the manipulation of process time scales at which different process steps proceed and (ii) the introduction of dynamic states within a process, typically in the form of periodicity.[7] To comply with these two strategies different crystallizer designs have been developed, periodic operations are applied, and mixers for faster mixing (mass transfer) of process streams have been invented.

### 7.2.1 Crystallizer Designs

A continuous crystallizer is an apparatus that enables the creation of a suitable environment for the nucleation and growth of the crystalline material with the desired CSD and operates with continuous feed and continuous withdrawal of crystallized product (contained in mother liquor). It requires the ability (i) to generate supersaturation at a desired temperature, (ii) to provide sufficient residence time for the crystals to nucleate and grow, and (iii) to provide some extent of mixing that allows ideally a uniform environment throughout the entire crystallizer volume (temperature, concentration, slurry density), which ensures that the composition in the crystallizer is the same as that of the effluent (slurry). Such a continuous crystallizer is called a mixed suspension, mixed product removal crystallizer (MSMPR).[22]

A wide variety of continuous crystallizer designs exist and even more of specialized crystallizers. The two main designs currently studied for PI, especially for fine chemicals and pharmaceuticals, are the MSMPR[23–27] and the tubular crystallizer.[28–34] The choice of whether to use a MSMPR or a tubular crystallizer is primarily driven by the kinetics and slurry density