the intrinsic baffles are fixed.[123–125] The oscillatory fluid flow leads to the generation and decay of eddies around the baffles that provide enhanced mixing at low flow rates resulting in enhanced heat and mass transfer, particle mixing with reduced particle settling compared to other tubular crystallizer strategies and at lower slurry densities compared to MSMPRs at any residence time.[52,87] However, this improvement comes at the cost of significantly greater mechanical complexity.[126] In addition, the oscillation amplitude and frequency should be selected carefully as the oscillation can introduce axial back mixing, broaden the residence time distribution,[86] and can increase the secondary nucleation due to the high shearing of the oscillation flow.[49] Recent studies have demonstrated the capabilities of OBC in continuous operation to produce salicylic acid by anti-solvent/cooling,[124] as well as α-lactose monohydrate[127] and β-L-glutamic acid[123] by cooling crystallization. For technical details and the design consideration of OBCs, the interested reader is referred to Chapter 3 of this book and to specialist literature.[52,87]

In conclusion to the concept of spatial structures, this approach can be employed to realize any of the four PI principles (Table 7.2)[7] and will be included in further discussions within this chapter.

7.3.2 Miniaturization

The PI concept of miniaturization considers the crystallization in confined spaces to create well-defined environments that allow controlling the solution properties as a function of spatial coordinates. For instance, as the volume of solution containing droplets decreases, the evaporation rate increases and the droplets become highly supersaturated favouring the nucleation of high energy metastable polymorphic forms, while low levels of supersaturation lead typically to the thermodynamically stable forms.[128,129] Moreover, crystallization in confined spaces (physical barrier, *e.g.*, nanopores) is a concept where polymorph selectivity can be directed by suppressing the nucleation of polymorphic forms whose critical nucleus size is larger than the pore volume dimensions. As a consequence, nucleation of polymorphic forms with critical sizes less than the pore volume can be achieved.[130–132] It is also well known that nucleation becomes more difficult as the volume of the crystallization environment decreases due to the suppression of primary homogeneous nucleation.[133] This provides the opportunity to exploit the heterogeneous nucleation mechanism through templating effects (substrate-solute interactions), which allows control of the formation of polymorphic form.[128,134–138] In addition, confining the crystallization environment using, for instance, porous materials,[139–143] patterned surfaces, or emulsions[144] is a common approach to produce nano-sized particles to enhance the physicochemical properties of substances with poor aqueous solubility (*e.g.*, APIs).[145–147] Although nano-sized crystals can also be obtained using top-down methods such as milling and high pressure homogenization to break large crystals into smaller ones,