

( $V = 40$  mL) with a customized suspension transfer pumping system, utilizing a dip tube for the slurry handling, controlled only by the generation of head pressure within the MSMPR using a small scale diaphragm metering pump. The total footprint of a two-stage MSMPR (each 40 mL) with introduced pressure-driven transfer scheme is only  $4800\text{ cm}^3$ , including valves and pumps. In comparison, the volume of a commonly used single Masterflex peristaltic pump (Cole-Parmer, Masterflex L/S Digital Drive 600 rpm) for intermittent withdrawal is  $7360\text{ cm}^3$ .<sup>26</sup> In addition, this compact system has been demonstrated to operate on the bench scale for at least  $24\text{ h}$ <sup>26</sup> and was integrated into a continuous flow platform for on-demand pharmaceutical manufacturing.<sup>14</sup>

While all previous examples were driven to enable representative and isokinetic withdrawal of product crystals from a MSMPR without blocking the transfer lines, Nagy and coworkers<sup>73,74</sup> studied the effect of periodic flow operation applied also to the feed stream. The periodic addition and withdrawal of solution and slurry (synchronous or asynchronous)<sup>74</sup> is followed by an equilibration or pause period without any material transfer, which allows the system to stay undisturbed until the next cycle begins. Consequently, this concept of MSMPR operation is a hybrid of continuous and batch operations leading to periodically oscillating supersaturation between an upper and lower limit compared to a fixed supersaturation in true continuous MSMPR. Moreover, the mean residence time of crystals in the periodic operating MSMPR is extended by the period of batch operation, which can be manipulated by the holding time in between the cycles. Thus, higher yield and larger product crystals can be achieved compared to truly continuous operating MSMPR at steady-state given that the oscillations of the supersaturation are kept small by a “controlled state of operation” (periodic steady-state).<sup>73,74</sup> In addition, periodic operation of the feed stream aids in the mitigation of fouling issues in the transfer lines due to much higher flow rates.<sup>73</sup> The concept of an OBC (Chapter 3) intrinsically applies periodic flow to provide enhanced mixing at low flow rates resulting in enhanced heat and mass transfer and particle mixing with reduced particle settling by providing structures (see Section 7.3 for further details on the structure).<sup>52</sup>

### 7.3 Space Domain

In general, spatial randomness (inhomogeneity) in crystallizers needs to be avoided for the sake of process control (*e.g.*, supersaturation, nucleation, growth) and robust operation (*e.g.*, no process fluctuation beyond the process design under steady state operation condition<sup>75</sup>). For instance, homogenization through mixing during the addition of reactants and antisolvents is crucial to obtain desired CQAs of the resulting crystalline material (*e.g.* CSD, size, morphology, purity, polymorph, solvate). Although mixing is the manipulation of time, PI methods applied to intensify the mixing process for crystallization are typically based on the introduction of structures in the