

of the process. Generally, the MSMPR can be used for low conversions, long residence times, and high slurry density, while the tubular crystallizer is favored for higher conversions with short residence times and low slurry density at any residence time due to settling of crystals. The MSMPR provides a robust operation with intensive mechanical mixing at a small surface-to-volume ratio, which reduces fouling and settling. Moreover, the MSMPR permits the relatively simple conversion of existing batch capacity to continuous capacity to obtain PI.<sup>35</sup> However, the residence time distribution (RTD) is broader in a single MSMPR compared to a tubular crystallizer, which leads to a broader crystal size distribution (CSD) and thus non-uniform product quality. To produce narrower CSDs, MSMPRs can be connected in series, also known as cascade, which offers the ability to gain degrees of freedom for process design and operation. Although leading to increased equipment costs, a MSMPR cascade allows for flexible process temperatures, targeted supersaturation profiles over the sequence of MSMPRs in the cascade, increased yield, and economies of energy consumption.<sup>36–38</sup> MSMPRs, single or cascade, represent the classic workhorse for continuous crystallization (cooling,<sup>39</sup> antisolvent,<sup>14,21,40,41</sup> reactive<sup>20,42</sup>) in academia and industry. Tubular crystallizer strategies have also been employed but their examples remain mostly in the academic literature.<sup>28,30–32,43,44</sup> A tubular crystallizer has the advantage of a narrower CSD at a typically higher efficiency compared to a MSMPR of the same volume due to the narrower RTD.<sup>31,45–47</sup> This is important as it may aid in avoiding additional downstream operations such as milling to reduce the crystal size, which contributes to PI.<sup>48,49</sup> In addition, the tubular crystallizer enables (i) supersaturation profile manipulation along the tube through temperature control<sup>33,43</sup> or multiple antisolvent additions<sup>32</sup> in different segments of the tube and (ii) a more rapid approach to steady state simplifying process dynamics. The tubular crystallizer concept can be distinguished in (i) plug flow crystallizers (PFC),<sup>28–34</sup> (ii) segmented flow crystallizer,<sup>28,46,50,51</sup> and (iii) oscillatory baffled crystallizers (OBC),<sup>49,52,53</sup> illustrated in Figure 7.1a–c, respectively. Further discussions are provided within the PI principle space domain (Section 7.3).

The crystallizer designs introduced can include advanced control strategies such as mother liquid recycling,<sup>27,54</sup> solids recycling,<sup>36</sup> and fines destruction (fines dissolution)<sup>33,34</sup> to reduce waste and increase crystal yields<sup>22,55–57</sup> or be combined with other technologies, such as membranes<sup>23,58,59</sup> for further PI (see function domain in Section 7.4).

## 7.2.2 Periodic Operation

Periodic operation (*e.g.*, temperature cycling, solvent cycling, flow cycling) is a common operation strategy for PI of continuous crystallization processes. This periodic operation is aimed at controlling critical quality attributes (CQA) of the crystalline products (*e.g.*, CSD, morphology, polymorphism, and chirality) or process performance (prevention of