

demonstrated a dynamic continuous reactive crystallization case, where a temperature shift in reactor temperature had a nonlinear effect on reaction rate and solubility.<sup>80</sup> In this case, the higher temperature increases the reaction rate, hence the solute concentration, by generating more solute from the reaction. However, the solubility of the solute increases as the temperature ramps up. Therefore, the supersaturation ratio decreases at higher temperature. The dynamic effect and nonlinearity were modelled in Aspen Plus and bi-direction effects of temperature on crystal size, nucleation rate, and steady-state crystal chord length were demonstrated. The transition time (unsteady-state period) and amount of residence time required for reaching the steady state, are important aspects in controlling the process and defining control strategies. Another crucial aspect of the reactive crystallization in a dynamic case is to monitor and model impurity inclusion and the effect of the concentration of unreacted reagents on the crystal's purity, shape, and yield.<sup>80,81</sup> Continuous reactive crystallization also could be challenging with concentration PAT tools if a change in concentration of reagents affects the reflective index of the solution or generates water that shifts the Raman/FTIR base line or creates noise and significant peaks that mask the solution/solute characteristic peaks. Further discussion on PAT tools are provided in Chapter 9.

Both antisolvent and reactive crystallization use mixing-induced supersaturation to enable crystallization. Here by mixing we mean bringing together two fluids resulting in a molecularly homogeneous/isotropic solution mixture on a molecular scale, while agitation refers to the process of keeping contents of a vessel from developing segregation in terms of composition, temperature or dispersion homogeneity (*e.g.*, suspension of solids). Depending on the reaction rate magnitude of difference to crystallization rate, the Damköhler number and mixing *vs.* reaction rate study could be useful in designing an efficient continuous reactive crystallization. Some intense mixing, such as impinging jet mixing and adding the reagent/antisolvent inside an *in situ* high shear mixer have been proposed to overcome these challenges.<sup>82,83</sup>

Assuming that agglomeration and breakage (“mass fracture”) are negligible, the CSD developing in a steady state is then a function of the prevailing nucleation rate  $B$  and growth rate  $G$  in the crystallizer as well of the residence time  $\tau = V_{cr}/\varphi$ . Under the further assumptions that the crystallizer is perfectly mixed (composition, temperature and solids uniformly distributed within the crystallizer volume, the feed stream instantly mixed with the crystallizer volume and the outlet stream identical to the crystallizer contents; *i.e.*, MSMPR conditions), growth rate  $G$  of the equally shaped crystals is independent of crystal size and constant, the number-based size distribution  $n(L)$  can be shown to be function of only the nucleation rate  $B$  in the crystallizer, the growth rate  $G$  of the crystals and the residence time  $\tau$ :

$$n(L) = (B/G) \exp(-L/G\tau) \quad (1.9)$$