

Interestingly, for a continuous crystallization process under MSMPR conditions, valuable kinetic data therefore can be extracted from a measured number-based CSD of a product by fitting a straight line to the log-normal CSD plot of  $\ln(n)$  against crystal size  $L$ . The slope and intercept then are equal to respectively  $(-G\tau)^{-1}$  and  $\ln(B/G)$ . It is important to note that the nucleation rate determined in this way is an average over the entire crystallizer volume: if the nucleation rate is locally occurring, the volume in which this occurs has to be known in order to determine the true nucleation rate. The relation for the number-based CSD  $n(L)$  is also valid for other crystallization methods under MSMPR conditions.

If, for instance, the secondary nucleation rate due to attrition with the stirrer is the dominant nucleation mechanism, the stirrer speed influences the attrition. After an increase in the stirrer speed for a suspension in a steady state continuous process, the nucleation rate  $B$  would increase and with it an increased total crystal surface area would be available for growth. This would decrease the prevailing average supersaturation in the crystallizer and decrease the growth rate  $G$ . The newly developing CSD  $n(L)$  would be characterized by a larger intercept  $\ln(B/G)$  and a more negative slope  $(-G\tau)^{-1}$ : the average number-based crystal size would decrease.

Although MSMPR conditions often do not hold, the model is useful and helps understanding of continuous crystallization processes in agitated vessels. Generally, increasing the value of  $B/G$  and decreasing the value of  $G\tau$ , *i.e.*, increasing the nucleation rate  $B$  and decreasing the growth rate  $G$  as well as the residence time  $\tau$ , will result in smaller crystals. These are general criteria for design of any seed generation/nucleator units.

### 1.3.1 Crystalline Product Quality Attributes

All continuous crystallization processes result in a suspension flow with a certain suspension density of the crystalline product having a certain solid form, CSD, shape and purity. These represent the crystalline product quality attributes, which determine performance in downstream processing steps (isolation, formulation) and of the final product.

Control of crystal nucleation in a continuous crystallization process is crucial to control the final product quality attributes. In continuously seeded crystallization processes for instance, crystal nucleation has to be avoided to allow control over the particle size, however, continuously seeded, continuous crystallizers are quite rare. Moreover, in unseeded continuous crystallization the (secondary) nucleation process has to continuously produce small crystals with a constant rate to remain in the steady state allowing control over the product size. The nucleation process thus directly influences the resulting crystal size distribution. It can furthermore cause significant issues with solid form control if nucleation of undesired polymorphs occurs. Fouling and encrustation are other significant issues in the continuous crystallization which are covered in Chapter 3.