feedback control loop with the mean crystal size of the product as controlled variable. In general, seeding is an important manipulated variable for continuous plug-flow crystallization due to various reasons. First, seeding provides control over the solid-state form of the final product. Second, seeding can minimize primary nucleation, which is often unpredictable and exhibits high variation, which makes control and reproducibility difficult. Third, seeding allows for a certain degree of control over the final CSD. In particular, if the seed surface area is sufficient to consume supersaturation at a sufficiently fast rate such that secondary nucleation is minimized, the final mean product size can be predicted from the so-called ideal growth expression,[87] which is derived from a mass balance over the seed population assuming a narrow CSD of the seeds, negligible nucleation, agglomeration, and no residual supersaturation at the end of the tubular crystallizer:

$$\frac{L_P}{L_S} = \left(\frac{C_S + 1}{C_S} \right)^{1/3} \tag{4.2}$$

where L_P is the product mean size, L_S is the seed mean size, and C_S is the seed load defined as the ratio of the seed mass over the product yield. Since the seed size and seed mass can be controlled and product yield can be estimated from solubility data, the final product size can be predicted and controlled without any feedback control. In the case where nucleation is not negligible, a product with a smaller mean can be expected, as the number of crystals increases. Since tubular crystallizers do not have moving mechanical parts, attrition may be small, which would improve the predictability of a seeded continuous plug-flow crystallizer.

4.4.3 Quality-by-design

Modern model-free process control strategies for pharmaceutical crystallization are often aligned with the concepts of so-called quality-by-design (QbD), which is a robust control strategy that ensures a built-in quality (*e.g.* safety and efficacy) for a drug product. QbD may involve control of the crystallization process within a so-called design space, which is defined as the range of critical process parameters (CPPs) that has been demonstrated to provide assurance of quality, described by a targeted range of critical quality attributes (CQAs).[88] Most of the published work has focussed on monitoring the CQAs using an array of PAT.[89] Since pharmaceutical manufacturing is currently almost exclusively conducted in batch mode of operation, most literature examples of QbD involve batch crystallization. For example, the QbD approach proved effective when operating a batch crystallization process within the design space to achieve the desired polymorphic form of tolbutamide using a combination of ATR-FTIR and Raman spectroscopy.[90] However, the QbD approach is also attractive for continuous crystallization by identifying those process parameters that have a significant impact on the steady-state behaviour of the continuous crystallization.