4.3 Measured Variables

Automated process control loops for continuous crystallization rely on the availability of real-time measurements of either controlled variables or process variables from which controlled variables can be inferred. In general, the recent development of more reliable, affordable and high performance PAT along with increased computing power have enabled a shift towards continuous manufacturing even in heavily regulated industries such as the pharmaceutical industry.[1,2,4] A significant number of new and advanced control strategies have been implemented in crystallization processes (and beyond) over the last decade, which have been enabled by PAT.[3,12,33–35]

Many control strategies for solution crystallization processes aim to control the crystal quality attributes indirectly by controlling supersaturation. Therefore, a significant improvement in crystallization process control has been enabled by *in situ* real-time PAT to measure solute concentration, such as attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy[35–41] and attenuated total reflection ultraviolet/visible (ATR-UV/vis) spectroscopy.[42–46] The performance of these spectroscopic methods has further improved over the years *via* rigorous chemometric techniques, the use of multiple wavenumbers and the combination of temperature and absorbance. Various PAT are available for direct measurement of the crystal size. Arguably the most popular *in situ* and real-time measurement of crystal size is the focused beam reflectance measurement (FBRM), which measures the number-based chord length distribution (CLD). The advantages of FBRM are that the method is free of calibration, non-invasive, robust, and relatively affordable. However, the CLD is only a fingerprint of the CSD and mathematical transformations have to be developed if a CLD is to be used within a control method for CSD, which is challenging, but effective demonstrations of such conversion have recently been reported.[47] Laser diffraction is a common bench-top instrument for CSD measurements, which can be integrated with a continuous crystallizer in an on-line fashion using an automated sampling device, a flow cell, and a dilution loop to obtain a slurry density in the required range for laser diffraction.[48] Acoustic methods have also been used for on-line CSD measurements.[35] Neumann and Kramer[49] compared two on-line laser diffraction instruments (Sympatec HELOS and Malvern 2600c) and an acoustic instrument (Sympatec OPUS), which were all implemented on-line for continuous crystallization of ammonium sulphate in an 1100-L draft-tube baffle (DTB) crystallizer. The on-line measurements were compared with off-line measurements and they concluded that the shape of the CSD was measured consistently with all three instruments, but differences in absolute values existed. The latter was attributed to the different measurement principles of the instruments. The on-line implementation of some of these instruments were later used in model-predictive control methods for batch crystallization.[50–52] Such control frameworks could equally well be applied to continuous crystallization. Recently, particle vision measurement (PVM)