

was used upstream to generate seed particles. In the second scheme, the wet mill was integrated in a recycle loop. Although the wet mill could not improve start-up dynamics, they demonstrated that a high-quality product and effective disturbance rejection could be achieved in closed-loop mode.

4.8 Conclusions and Perspective

Process control of continuous crystallization has been studied for several decades and remains an active area of research. In the earlier work, existing types of crystallizers were studied, sometimes even on unique pilot-plant scale, mainly for the production of bulk chemicals. Those earlier studies already demonstrated the importance of suitable and flexible process actuators for continuous crystallization as well as the need for robust and reliable process analytical technologies and dynamic process models. More recently, a number of fast-developing branches of research provide the necessary tools to address those fundamental challenges in different ways when all put together. Therefore, it is not surprising that the trend in important industries such as the pharmaceutical industry is towards continuous processing. In particular, new types of crystallizers have become available. For example, a new generation of plug-flow crystallizers allow for more flexible process control and fast learning from the broad literature on advanced process control of batch crystallization due to their conceptual similarity. The rapid advancement of PAT has provided new opportunities to measure process variables *in situ* and in real-time such that they can be used in automated control loops. Regulatory support and knowledge transfer is important to move those PAT tools from the current research and development environment to commercial manufacturing. Furthermore, new types of process actuators have also been developed, which are often based on the principles of process intensification. For example, a whole new generation of methods based on external fields (*e.g.*, ultrasound, electric, microwave, laser) are becoming available to provide targeted and non-invasive actuation. Finally, there has been much progress on the development of reliable dynamic models and numerical methods to optimize dynamic models rapidly such that they can be used for controller design and for real-time model-based control methods. The various combinations of all these recent developments provide ample opportunities to develop new and improved process control strategies for continuous crystallization.

References

1. K. P. Cole, J. M. Groh, M. D. Johnson, C. L. Burcham, B. M. Campbell and W. D. Diseroad, *et al.*, Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions, *Science*, 2017, **356**(6343), 1144–1150.
2. A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison and K. F. Jensen, *et al.*, On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system, *Science*, 2016, **352**(6281), 61–67.