Process Intensification Techniques for Continuous Spherical Crystallization in an Oscillatory Baffled Crystallizer with Online Process Monitoring

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Guided by the continuous manufacturing paradigm shift in the pharmaceutical industry, the proposed thesis focuses on the implementation of an integrated continuous crystallization platform, the oscillatory baffled crystallizer (OBC), with real time process monitoring. First, by defining an appropriate operating regime with residence time distribution (RTD) measurements, a system can be defined that allows for plug flow operation while also maintaining solid suspension in a two-phase system. The aim of modern crystallization processes, narrow crystal size distributions (CSDs), is a direct result of narrow RTDs. Using a USB microscope camera and principal component analysis (PCA) in pulse tracer experiments, a novel non-contact RTD measurement method was developed using methylene blue. After defining an operating region, this work focuses on a specific process intensification technique, namely spherical crystallization.

Used mainly to tailor the size of a final dosage form, spherical crystallization removes the need for downstream size-control based unit operations (grinding, milling, and granulation), while maintaining drug efficacy by tailoring the size of the primary crystals in the agglomerate. The approach for generating spherical agglomerates is evaluated for both small and large molecules, as there are major distinctions in process kinetics and mechanisms. To monitor the spherical agglomeration process, a variety of Process Analytical Technology (PAT) tools were used and the data was implemented for scale-up applications.