

ABSTRACT

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Title: Process Intensification through Spherical Crystallization: Novel Experimental and Modeling Approaches

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Process intensification is defined as the use of innovative techniques and technologies to create sustainable solutions to industrial production difficulties. Continuous spherical crystallization is a process intensification technique that could resolve production issues for pharmaceutical and solids processing industries, consequently, allowing for the integration of upstream and downstream manufacturing units. Spherical crystallization is carried out through emulsion based crystallization and/or agglomeration in suspension of fine crystals to produce aggregates of improved bulk and micromeritic properties. The advantages of spherical crystallization include: (i) replacing downstream particle correction units (*i.e.*, milling, granulation), (ii) providing control of crystalline properties by decoupling crystallization and agglomeration mechanisms, and (iii) reducing plant foot print and allowing for reconfigurable units. The overall aim of the thesis is to further develop the scientific understanding of spherical crystallization mechanisms and introduce a systematic approach for implementing continuous spherical crystallization as a smart manufacturing platform enabled by a quality-by-design framework.

Experimentally, the thesis achieves: (i) better mechanistic understanding of spherical crystallization in semi-batch systems using process analytical technologies (PAT); and (ii) the assessment of the feasibility of continuous spherical crystallization in mixed suspension mixed product removal (MSMPR) and oscillatory flow baffled crystallizer (OFBC) systems. Computationally, a coupled population balance model is developed that leads to an optimization framework for bioavailability and manufacturability through spherical crystallization. Together the experimental and modeling approaches deliver a model-based framework for process intensification that can lead to adaptive manufacturing systems for high value-added particulate products.