Amgen Seminar Series in Chemical Engineering

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Control of Molecular Purity, Crystal Structure, and Particle Size Distribution in Pharmaceutical Crystallization

By

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An overview is provided on advances in the design and operation of pharmaceutical crystallizations to control polymorphic identity, shape, and size distribution. A systematic methodology is described for the selective crystallization of metastable and stable polymorphic and solvatamorphic forms based on the feedback control of solution concentration measured in process using Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy calibrated using chemometrics methods. The methodology enables the design and operation of seeded batch crystallizers to manufacture large crystals of uniform size by suppressing secondary nucleation. A modification of the methodology is able to achieve a target size distribution in semi-batch crystallization by employing continual seeds manufactured by a spatially localized zone of highly intense mixing such as occurs in a dual-impinging jet crystallizer. The methodology has been evaluated in theoretical, simulation, and experimental studies for a large variety of pharmaceutical compounds. The maximum supersaturation to allow during the crystallizer operations is determined by employing in-situ laser backscattering (focused beam reflectance measurement, FBRM) during a semi-automated initial experiment design, and FBRM is also employed to confirm that secondary nucleation is suppressed during pharmaceutical production runs. A methodology is proposed for the manipulation of crystal shape, by employing in-situ fines dissolution. The presentation ends with a discussion of directions towards control of multiple properties of the crystal product.

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