

Particle Engineering in Crystallization of Drug Substances

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Crystallization is a primary unit operation to separate and purify drug substances in pharmaceutical production. It defines the solid-states attributes of drug substances such as purity, polymorphs, particle size distribution (PSD), morphology etc., which have immediate impacts on the performance of downstream operations, e.g., washing, filtration, drying, conveyance and packaging. Moreover, these solid-state attributes may extend their influences throughout to the therapeutic and toxicological properties of medicines. In this sense, particle engineering in crystallization units plays a pivotal role in delivering satisfactory overall process efficiency and quality consistency.

Particle engineering in crystallization should be approached from four aspects during process development: solvent system, operation mode, design of crystallizers and auxiliaries, and operating variables. Operating variables stand out in setting the dynamics of crystallization and thus the attributes of crystals. Major operating variables include seeding protocol and generation rate of supersaturation. In commercial production stage when the first three aspects have already been unchangeable, dynamic adjustment of operating variables is the only resort to tailor crystal attributes and ensure quality integrity which is otherwise subject to operating fluctuations.

In this work, particle engineering has been carried out in the framework of process analytical technology (PAT). A multi-purpose experimental platform has been constructed in our lab with feedback loop and important PAT sensor technologies in place, e.g. FBRM, PVM, ATR-FTIR, as shown in Fig. 1. The structure of feedback loop can be modified as per the particle attributes to be engineered. Data-mining software tools are also at hand to search definite linkages between certain particle attributes and process variables.

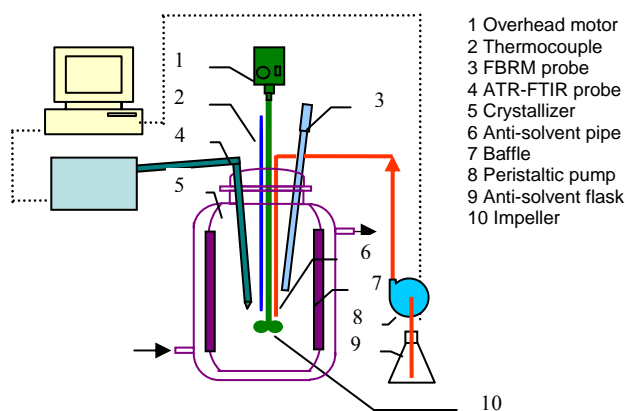


Fig.1 Experimental setup for particle engineering

Case study - PSD engineering in anti-solvent crystallization of paracetamol from acetone-water mixtures

Control targets: To ensure a narrow PSD even with certain operation fluctuations from upstream.

Methodology: Optimal seeding protocol and dynamic adjustment of addition rate of anti-solvent to maintain a constant supersaturation via ATR-FTIR technique.

Outcome: Seeds of two size fractions were applied - 212-250 and 150-180 μm respectively. The profile of accumulated mass of anti-solvent and batch time varied with different combinations of seed mass and size as shown in Fig. 2 (a). Unimodal PSD was ensured with different seed mass-size couples as shown in Fig. 2 (b).

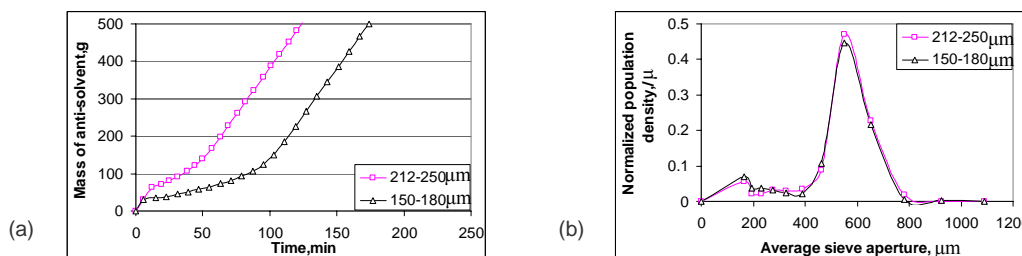


Fig. 2 (a) Profiles of accumulated mass of anti-solvent with seeds of two sizes, (b) PSD of resulting crystals

Publications:

Yu, Z. Q.; Chow, P. S.; Tan, R. B. H., Seeding and constant-supersaturation control by ATR-FTIR in anti-solvent crystallization. *Organic Process Research & Development* **2006**, 10, (4), 717-722.

Yu, Z. Q.; Chow, P. S.; Tan, R. B. H., Application of attenuated total reflectance-Fourier transform infrared (ATR-FTIR) technique in the monitoring and control of anti-solvent crystallization. *Industrial & Engineering Chemistry Research* **2006**, 45, (1), 438-444.

Yu, Z. Q.; Tan, R. B. H.; Chow, P. S., Effects of operating conditions on agglomeration and habit of paracetamol crystals in anti-solvent crystallization. *Journal of Crystal Growth* **2005**, 279, (3-4), 477-488.