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*Editorial*

# Anti-Solvent Crystallization

**Zai-Qun Yu [1,*] and Reginald Beng Hee Tan [2,*]**

[1] Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore 627833, Singapore

[2] Department of Chemical & Biomolecular Engineering, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore

* Correspondence: yu_zaiqun@ices.a-star.edu.sg (Z.-Q.Y.); reginald@nus.edu.sg (R.B.H.T.)

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This Special Issue collects six studies on different aspects of anti-solvent crystallization development, with a particular focus on pharmaceutical crystallization. In the first contribution, continuous crystallization of glycine was developed in slug flow crystallizer [1]. A crash cooling stage was introduced in the entry section to induce nucleation. Secondary nucleation was suppressed, and millimeter-sized crystals were produced. Slug flow crystallizer exhibits its potential, but engineering challenges still remain for industrial application. More studies are needed on continuous crystallization, as it is lagging behind in the transition from batch to continuous manufacture of pharmaceuticals.

The evolution of crystal habits has been an intriguing research puzzle for many years. Crystallization media have larger impacts on habit modification than other process parameters, as demonstrated by the contribution from Zhou et al. [2]. The crystals of LLM-105, an energetic material, can have very different habits depending on the kind of anti-solvent used, including X-shaped, spherical cluster-like, rod-like, needle-like, and dendritic. The authors attributed habit modification to differences in polarity and functional groups of anti-solvent. Up to now, most studies of solvent effects on crystal habit are descriptive, and this one is no exception. Predictive studies of solvent effects are needed to facilitate solvent screening efforts.

Solvate screening is an essential step in pre-formulation study and crystallization development of pharmaceuticals. Yang et al. presented a rather comprehensive case study of solvate screening for sorafenib tosylate [3]. New solvates were obtained and characterized by thermal analysis, hot stage microscopy, FTIR spectroscopy, powder XRD, and single-crystal XRD. In particular, it was found that two NMP solvates exist with different stoichiometries. Their stability depends on the content of NMP in solvent mixture. The critical activity of a solvent is a key factor to determine in crystallization development when solvate formation can take place.

Micron-sized or even nano-sized particles exhibit a favorable dissolution profile and higher solubility for poor water-soluble APIs. In their contribution, Tari et al. demonstrated that mixing of an anti-solvent and cilostazol solution through an impinging jet can consistently produce micron-sized crystals when combined with cooling crystallization [4]. A few attributes of crystal products were characterized in this study to assess the influences of process parameters via a factorial design. Indeed, anti-solvent crystallization should be considered as a prime option among various techniques for micronization process development of particles due to its simplicity and efficiency.

Polymorphic transformation is frequently encountered in crystallization development. Zhu et al. displayed a methodology to understand transformation processes [5]. Probe-based Raman spectroscopy and ATR-FTIR spectroscopy were used to monitor the polymorphic transformation of theophylline in different solvents at different temperatures using a simplified process model that was constructed to fit experimental data. The limiting steps in transformation were identified, and effects of

process parameters were analysed, which constitutes the basis to formulate a control strategy of transformation processes.

Some crystal habits, including thin needles and plates, often cause flowability and filtration problems. Spherical crystallization can be attempted to agglomerate primary particles and thus mitigate problems in downstream operations. An and co-workers developed a spherical crystallization process for clopidogrel bisulfate via anti-solvent addition [6]. They found that anti-solvent kind, supersaturation, agitation intensity, and temperature influence agglomerate size and size distribution. A bridging agent was not used in this study, and it seems that the primary particles have the tendency to agglomerate. This brings about a few general questions that need to be answered for the spherical crystallization study, i.e., are surface properties of primary crystals the key for agglomeration to proceed? Is it feasible to modify surface properties for successful agglomeration, and how to do it?

In summary, this Special Issue represents the latest advances in anti-solvent crystallization research. At the same time, many challenges still remain in areas of development such as continuous crystallization, habit prediction, and agglomeration control. We are looking forward to more studies in this area.

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