

is the “may not take place” part, while the “may take place” part contains a significant amount of uncertainties where dusts, impurity or any residual left behind from a previous batch could lead to heterogeneous primary nucleation.

What has been overlooked is the primary nucleation caused by variations of local temperature, *i.e.* local supersaturation, within an industrial scale crystalliser, which can vary from a few to 10 s of degrees depending on scales. The added practical difficulty is that it is not feasible to measure such variations in large vessels as most thermocouples can only be located near to the walls of crystallizers. When dealing with organic compounds with narrow metastable zone width, the local temperature variations can readily overshoot the metastable zone, and lead to spontaneous nucleation. Because of the local and random nature of such temperature variations, it is impossible to forecast and prevent these unwanted nucleation moments.

Seeding can readily be adopted in COBC, as illustrated earlier in Section 3.4. Some research works of both public and confidential nature have been undertaken in OBC/COBC,^{16,147,148} *e.g.* cooling crystallisation of paracetamol,^{149–152} L-glutamic acid,^{16,147,153–155} aspirin,¹⁵⁶ a pharmaceutical API,¹⁵⁷ sodium chlorate,^{65,69,70,158} adipic acid,¹⁵⁹ urea,^{160,161} mannitol,⁶⁷ α -lipoic acid:nicotinamide co-crystal,¹⁶² palm oil¹⁶³ and cyclopentane hydrate.¹⁶⁴ Seeded cooling crystallisation in NiTech DN15 crystallisers has successfully been running¹⁶⁵ for 8 h,¹⁶⁶ 10 h¹⁴⁷ and 4 weeks in CMAC at the time of writing this chapter.

As the nucleation process is too fast to be captured, nucleation and growth are often lumped together. To be able to separate and control nucleation from growth has been at the heart of crystallisation research worldwide. When tubular crystallisers are used, this presents new possibilities and feasibilities of investigating this subject,^{167,168} *e.g.* nucleation was generated by adding two streams in a “Y” shaped tube, which was fed to a continuous device for growth,⁶⁶ the challenges were from encrustation in the nucleator due to the unquantified amount of nuclei generated. More research on separating nucleation from growth are needed.

3.5.2 Antisolvent Crystallisation and Seed Generator

3.5.2.1 Antisolvent Crystallisation

Tubular plug flow crystallisers enable multi inputs and hence are well suited for antisolvent crystallisation operation. There are a few of ways to initiate the meeting of solvent and antisolvent, *e.g.* a “Y” shaped tube, an “L” shaped nozzle or a lantern ring within the COBC. The degree of supersaturation within COBC can be adjusted by the flow rates of solvent and antisolvent, which effectively controls the sizes of crystals. Generally speaking, the higher the initial supersaturation, the smaller the crystal size. Supersaturation increases significantly once the two streams meet, then drops sharply; efficient mixing is