

of the lack of fundamental measurements linking the underlying physics of ultrasound with measured intensity maps is that the approaches to process development are structured but empirically based.

Early pharmaceutical applications of ultrasound in crystallization include Pfizer's patent to reduce the crystal size of procaine penicillin.³⁶ Principe and Skauen (1962) report the use of ultrasound in the preparation of micro-crystalline particles of the hormone progesterone as an alternative to size reduction by milling.³⁷ They report the effect of intensity on particle size and size distribution, reporting smaller particles formed at higher intensities. Wyeth's Hem (1967) investigated mechanisms by which ultrasound might be effective in producing small uniform crystals and suggested that the beneficial effects of ultrasound on crystallization are linked to cavitation arising from the passage of ultrasound thorough the solution.³⁸ He was the first to suggest that cavitation bubbles act as nucleation sites.

Three key examples indicate the benefits of controlled ultrasound induced nucleation.

Howard Anderson *et al.* (1995) obtained US5471001A, the first patent for continuous sonocrystallization. It relates to evaporative crystallization of adipic acid from aqueous solution and significantly was applied at manufacturing scale.³⁹ Whilst the patent makes no explicit reference to nucleation, the claimed benefits are consistent with manipulation of the nucleation rate allowing the process to operate at reduced supersaturation to deliver crystals with improved powder flow characteristics.

Michael Midler secured US3892539A in 1971 for Merck & Co. Inc., which relates to the use of ultrasound to break up large crystals at the base of a continuous fluidized bed crystallizer effectively both managing the upper particle size and generating new nuclei at a controlled rate whilst operating at a modest supersaturation.⁴⁰ The technology was applied to facilitate continuous resolution of an API.

Whilst not typically a continuous process, a particularly attractive application for the pharmaceutical industry is reliably triggering nucleation in a sterile environment.⁴¹ Insonation substantially reduces the induction time even at modest levels of supersaturation generated by addition of an antisolvent. The resulting controlled nucleation was shown to deliver more consistent particles than in the equivalent unseeded process and since conventional seeding is not favored in sterile manufacture, due to the risk of introducing biological contamination, this is clearly beneficial.

1.2.1.3.2 Laser-induced Nucleation. Application of continuous wave^{42,43} or pulsed lasers^{44,45} can dramatically shorten induction times in a wide range of solutions. In principle, this provides an intriguing opportunity for accurate spatial and temporal control of nucleation in both batch and continuous systems. Furthermore, laser-induced nucleation can lead to different polymorphs being nucleated compared to identical solutions in the absence of lasers.⁴⁶