# Sonocrystallization: The use of Ultrasound for Improved Industrial Crystallization

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# Sonocrystallization: The Use of Ultrasound for Improved Industrial Crystallization

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**Abstract:**

**An overview of the application of power ultrasound to crystallization of organic molecules, and the equipment developed in recent years in which sonocrystallization and sonochemistry may be carried out at industrial scale, is presented. It includes both results from the research and development programs carried out by us and a survey of developments in the field more generally. The most important effect of ultrasound on crystallization is the induction of nucleation and the principal benefits derived from an ability to manipulate this effect. The reported effects of ultrasound on crystal nucleation and growth have been briefly reviewed, and examples are given of physical properties of the products having been manipulated by varying and controlling the insonation regime. New applications, directions, and developments have been identified. Developments in scale-up methods and available equipment have also been reviewed. It is the availability of robust large-scale equipment that has been critical to establishing the viability of this technology for industrial use in recent years.**

## Introduction

Ultrasound has been used in many diverse fields such as medical imaging and diagnostics, biological cell-disruption, nondestructive testing of materials, under-water ranging (SONAR) and thermoplastic welding. Large-scale equipment is available for the application of power ultrasound to wastewater treatment (in particular, anaerobic digestion) and to a range of activities in the food processing industry (e.g., emulsification, microbial fermentation, cell disintegration, homogenizing). Many of the devices available use high-power ultrasonic probes and sonotrodes. The application of power ultrasound (20−100 kHz, but can be as high as 2 MHz) to chemical processing is an intensification technology that has undergone serious development over the past 15 years or so. The most widely reported facet of this has been in sonochemistry: the use of ultrasound to promote or modify chemical reactions. Some key references are cited.[1−3] The first application of ultrasound to crystallization (sonocrystallization) in 1927 predates by decades any serious application to chemistry.[4] In addition, there is considerable literature from the former Soviet Union in the 1950s to the 1970s, albeit dealing with small-scale applications.[5−7] However, whilst the concept of ultrasonic processing is not new, the ability to use it on an industrial scale is. Indeed, recent advances in equipment have made its implementation at industrial scale feasible.[8] Interest in the application of ultrasound to crystallization in the pharmaceutical and fine chemicals sectors of industry has received further impetus in recent years with the increased focus on specificity of effect, and the corresponding requirement to prepare and purify complex chemical entities to very exacting standards.

Ultrasound may influence crystallization through the mechanisms of cavitation and acoustic streaming.[9] Cavitation appears to be particularly effective as a means of inducing nucleation, and there is evidence of dramatic improvements in reproducibility obtained through such sononucleation. Furthermore, using ultrasound to generate nuclei in a controlled and reproducible way provides a well-defined starting point for the crystallization process. This allows focus on controlling the crystal growth via the residence time in the crystallizer. We have used this combined approach to influence crystal size distribution, assist in morphological control, elimination of impurities in the crystal, and improve solid−liquid separation behaviour. Sononucleation can also eliminate the requirement to add seed crystals, and this can be particularly advantageous in contained crystallizations.

## Observed Effects of Ultrasound on Crystallization

A number of papers and patents, several of which are shown in Table 1, have been filed/published relating to improving the crystallization of organic compounds of low to medium molecular weight. For example, crystallization improvements have been reported for paroxetine,[10] aspartame,[11] adipic acid,[12] amino acids,[11,13,14] Fenoterol HBr,[15]

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(1) Cains, P. W.; Martin, P. D.; Price, C. J. *Org. Process Res. Dev.* **1998**, *2*, 34.
(2) Luche, J. L. *Synthetic Organic Sonochemistry*; Plenum Press: New York, 1998.
(3) Ley, S. V.; Low, C. M. R. *Ultrasound in Synthesis*; Springer-Verlag: New York, 1989.
(4) Richards, W. T.; Loomis, A. I. *J. Am. Chem. Soc.* **1927**, *49*, 3086.
(5) Kapustin, A. P. *The Effects of Ultrasound on the Kinetics of Crystalization;* U.S. Academy of Sciences Press, English Translation Consultants Bureau: New York, 1963.
(6) Martynovskaya, N. V. *Akust. Ul'trazvuk. Tekh.* **1970**, *6*, 14.
(7) Reshetnyak, I. I. *Akust. Zh.* **1975**, *21*, 99.
(8) McCausland, L. J.; Cains, P. W. *Chem. Ind.* **2002**, *5,* 15
(9) Young, F. R. *Cavitation*; McGraw-Hill: New York, 1989.
(10) Craig, S.; Jones, D. A. World Patent WO 00/32597, 1999.
(11) McCausland, L. J. World Patent WO 03/101577, 2003.

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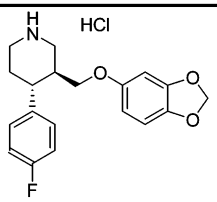
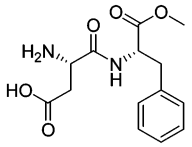
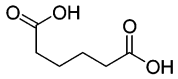
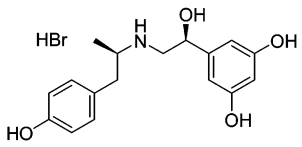
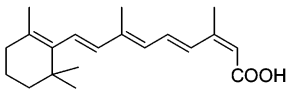
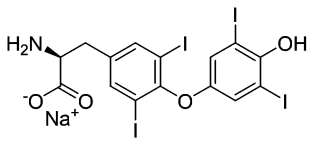
***Table 1.*** **Activity in sonocrystallization from companies and academia**

| Reference | Structure / comments | Comments |
|---|---|---|
| 10 |  | **GlaxoSmithkline - Paroxetine Hydrochloride IPA solvate** used as an antidepressant, anti-Parkinson<br>Poor crystal habit without ultrasound leading to heavily solvated mass<br>Use of ultrasound (20 kHz probe) gives a superior crystal habit (monoclinic) being more readily de-solvated<br>Continuous flux of fresh nuclei advantageous<br>Rapid cooling in a continuous flow apparatus also of benefit (vortex mixer, Y-tube) |
| 11 |  | **C$^3$ Technology - Aspartame and various amino acids**<br>Superior crystal habit and particle size distribution |
| 12 |  | **DuPont - Adipic acid**<br>Small proprietary 1 L vessel with immersed transducers<br>Purer, easily handled product<br>Superior particle size distribution<br>Low power (<1 W/cm$^2$) for crystal definition<br>High power (>1 W/cm$^2$) for prolific seed generation |
| 15 |  | **Boehringer Ingelheim - Fenoterol HBr**<br>Preparation of inhalable medicines - <6 μ particle size<br>Continuous crystallization with microreactor<br>Pass concentrated solution (695 mg/mL) through tube reactor with immiscible separating / segmenting fluid (hydrocarbon) [22 min 'travel'], treat with US, 20-60 kHz, for 14 min 'travel' [tube reactor immersed in ultrasonic bath] |
| 16 |  | **Abbott Pharma - Isotretinoin (Accutane)**<br>Crystallization of carotenoids and retinoids<br>Simple use of ultrasonic probe-in-a-beaker (250 W sonotrode, 20 kHz)<br>Small PSD d(0.5) = 58 μ compared with 227 μ non-ultrasound |
| 17 |  | **Abbott - Sodium L-thyroxine and other α,β L,D-Amino acids -**<br>Crystallization in alcohol / water mixture to achieve < 20 μ particle size<br>2000 W, 20 kHz sonotrode mounted in 1000 L reactor<br>Custom 24 kHz probe used in 22 L reactor<br>Superior particle size distribution |
| 26, 27 | | **GlaxoSmithkline, Bristol Myers Squib**: Crystallization of various drug compounds using batch and anti-solvent addition processes using probe-based flow-cells.<br>Particle size control to avoid of milling.<br>Consistent Particle size distribution |
| 42 | | **GlaxoSmithkline - Inhaled Therapeutics** |
| 43 | | **Astra-Zeneca - Inhaled therapeutics**<br>Novel procedure for production of a high yield of small crystal particles<br>Wide range of inhalable therapeutics requiring < 5 μ particle size<br>Simple equipment set-up: Probe-in-a-jacketed beaker<br>Saturated solution added to anti-solvent with ultrasound |
| 44 | | **University of Bath - Inhaled therapeutics** - SAXS<br>Formation of aerosol of solute in solvent<br>Crystallize 1 μ particles by sononucleation and crystallization in non-solvent<br>Obtain as a slurry or spray dry |

Accutane,[16] and sodium L-thyroxine.[17] Larger molecules, such as proteins and peptides, and highly water-soluble/polar compounds such as sugars,[11,14] are more demanding because of the difficulties in inducing crystal nucleation and the large supersaturation driving forces involved.

Literature reports indicate that ultrasound has been employed increasingly throughout the 1990s and the present decade in the preparation of amorphous and nanostructured materials. Although beyond the scope of this paper, these

(12) Anderson, H. W.; Carbery, J. B.; Staunton, H. F.; Sutradhar, B. C. U.S. Patent 5 471 001, 1995.
(13) McCausland, L. J.; Cains, P. W.; Martin, P. D. *Chem. Eng. Prog.* **2001**, *97* (7), 56.
(14) McCausland, L. J.; Cains, P. W. *Biotechnol. Genet. Eng. Rev.* **2004**, *21*, Chapter 1.
(15) Jongen, N.; Lemaitre, J.; Bowen, P.; Donnet, M.; Schiewe, J.; Zierenberg, B.; Soare, L. C. World Patent WO 04/034943, 2004.
(16) Rauls, M.; van Gelder, R.; Wagner, K.; Bernard, H. U.S. Patent 0051,659 (A1), 2003.
(17) Bechtel, S.; van Gelder, R.; Simpson, S. C. World Patent WO 03/057 717 (A3), 2003.

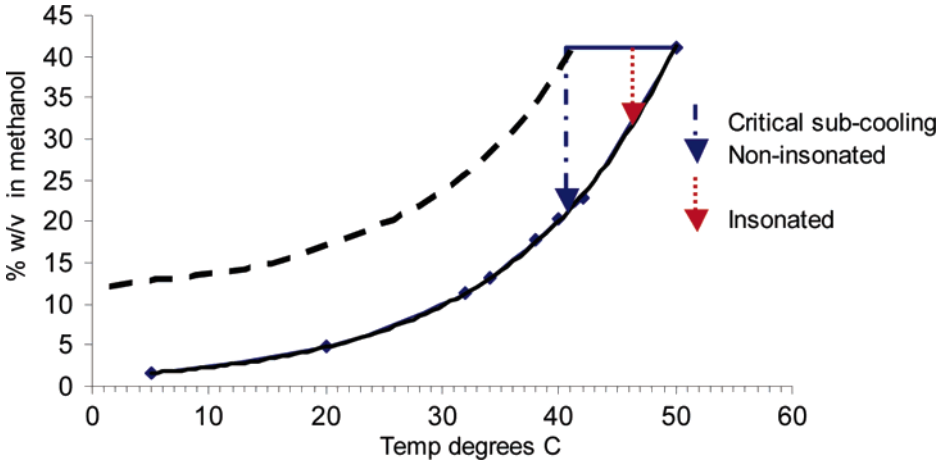



***Figure 1.*** **Effects upon metastable zone width (MZW) for the cooling crystallization of sorbitol hexaacetate in methanol. The arrows represent the first observation of crystals.**

developments are potentially important in showing that ultrasonic technology can be used increasingly in new areas with considerable commercial potential and indeed may lead to a greater understanding of sonocrystallization with respect to the observed effects on product structure and morphology.

## Ultrasound and the Nucleation of Crystals

It is usual to consider crystallization in terms of the fundamental processes of nucleation and crystal growth;[18] whilst such events will occur sequentially in any crystallization process, they can be very difficult to decouple for fundamental investigations. Although nucleation theories have advanced considerably in recent years, the templating or a particular ordering within the solid state via the nucleation process is not fully understood.[19] Work recently reported on the crystallization of organic compounds from solution suggests that pre-ordering of solids in supersaturated solution, in particular via hydrogen bonding motifs, is important in determining what solid forms are produced.[20]

Ultrasound can induce primary nucleation in nominally particle-free solutions and, noteworthy, at much lower supersaturation levels than would otherwise be the case. The application of ultrasound to a liquid induces the phenomenon of cavitation in the process fluid. Indeed, most sonochemical and sonoluminescent effects of ultrasound have been attributed to transient cavitation.[9] This cavitation effect creates bubbles during successive cycles of compression and rarefaction to a point of transient bubble collapse, perhaps after only two acoustic cycles. This bubble collapse produces highly spatially resolved regions of extreme excitation, temperature (5000 K) and pressure (2000 atm), as well as concomitant release of shock waves. The reasons why such local and transient energy concentrations correlate with nucleation events have not yet been fully explained. In one sense, the effect is counter-intuitive, in that a local temperature increase will reduce or eliminate the supersaturation in the immediate vicinity, effectively removing the driving force to nucleation. However, the shock waves may contribute to nucleation in the regions of the supersaturated solution somewhat remote from the cavitation event. Other postulates suggest (i) subsequent rapid local cooling rates, calculated at $10^7 - 10^{10}$ K·s$^{-1}$, play a significant part in increasing supersaturation; (ii) localised pressure increases reduce the crystallization temperature, and (iii) the cavitation events allow the excitation energy barriers associated with nucleation to be surmounted, in which case it should be possible to correlate the numbers of cavitation and nucleation events in a quantitative way. There is clearly a need for further research on the relationship between cavitation and nucleation. Interestingly, it has been suggested that nucleation caused by scratching the walls of a vessel containing a supersaturated solution with a glass rod/spatula could be the result of cavitation.[18]

In many respects, the ease or difficulty of carrying out a crystallization process can be linked to an understanding of the metastable zone (MZ). For a cooling crystallization, the width of this zone (MZW) can be described as the temperature drop below the solubility curve at which the solid starts to separate spontaneously for a given supersaturation level and cooling rate (supersolubilty limit). Figure 1 shows the effect of a short 30 s burst of high-intensity 20 kHz ultrasound on the crystallization of sorbitol hexaacetate from methanol where the MZW has been narrowed by some 5 °C, as indicated by the observation of crystals at lower levels of supersaturation. Very similar effects have been recorded for a variety of small molecules where the MZW is fairly narrow and crystallization occurs quite readily.

It is possible to "tailor" a crystal size distribution between the extreme cases of a short burst of ultrasound to nucleate at lower levels of supersaturation and allow growth to large crystals, and the production of small crystals via continuous (or perhaps a longer single burst) insonation throughout the duration of the process, which can facilitate prolific nucleation at higher levels of supersaturation at the expense of some crystal growth. Pulsed or intermittent application of ultrasound can give intermediate effects. In any event, the optimum needs to be determined by experimental investiga-

(18) Mullin, J. W. *Crystallization,* 4th. ed.; Butterworth−Heinemann: Woburn, MA, 2001.
(19) *Nucleation Control*; Royal Society Discussion Meeting, London, 2002.
(20) Davey, R. J.; Allen, K.; Blagden, N.; Cross, W. I.; Lieberman, H. F.; Quayle, M. J.; Righini, S.; Seton, L.; Tiddy, G. J. T. *Cryst. Eng. Commun.* **2002**, *4*, 1.

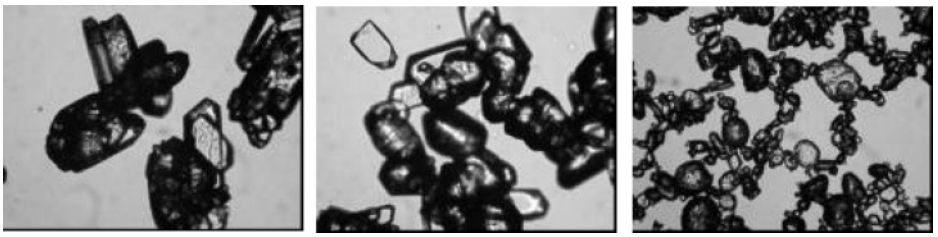


***Figure 2.*** **Cooling crystallization of adipic acid from water: (left) noninsonated control experiment; (center) short ultrasound burst at 48 °C; (right) continuous insonation.**

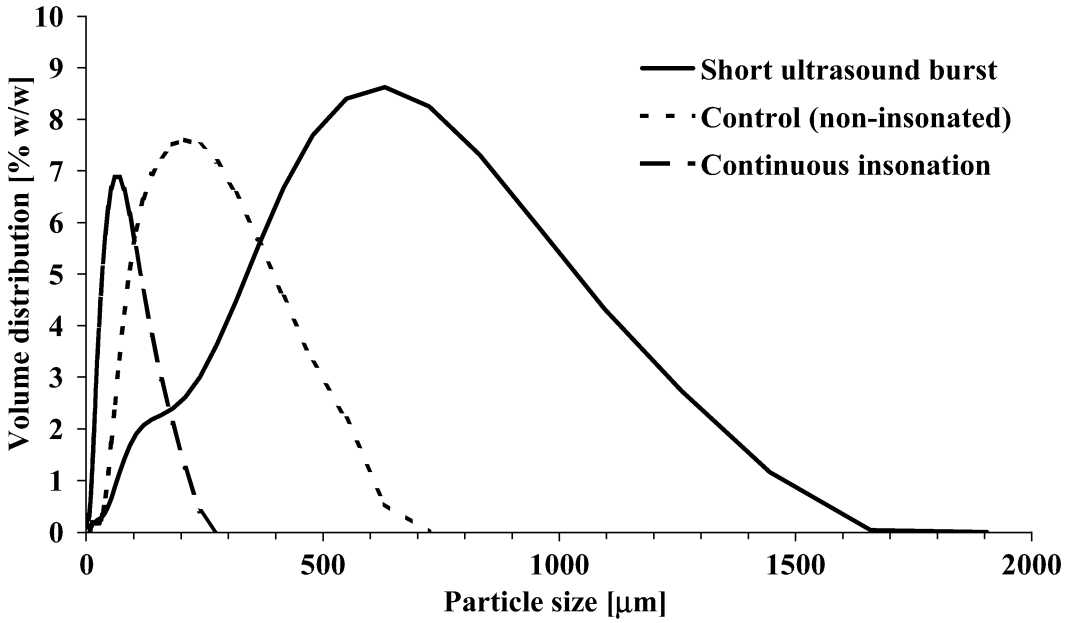



***Figure 3.*** **Crystal size distribution of sorbitol hexaacetate produced using different ultrasonic process conditions.**

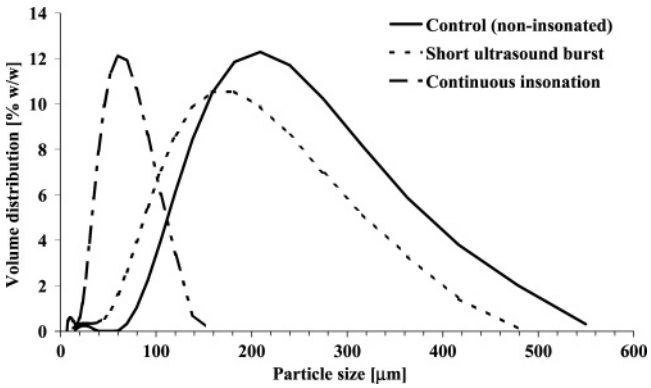



***Figure 4.*** **Crystal size distribution of adipic acid using different ultrasonic process conditions.**

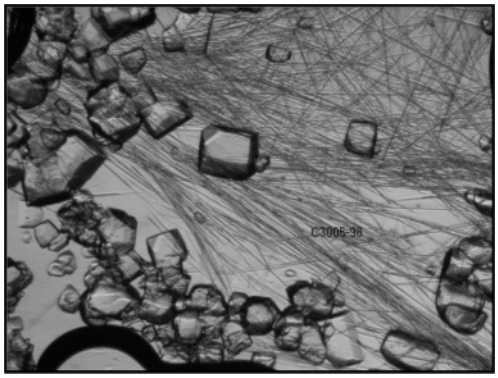


***Figure 5.*** **Growth of two different crystal habits of a small-molecule API at labile levels of supersaturation.**

tion. Particle size control has been demonstrated for a number of molecules including sorbitol hexaacetate, where more regularly shaped crystals can be formed, and adipic acid.[12] Figure 2 illustrates the effects of ultrasound on the overall shape and size of crystals of adipic acid. The effects of ultrasound on the particle size distribution for sorbitol hexaacetate and adipic acid are shown in Figures 3 and 4, respectively. It is possible that ultrasound may also induce secondary nucleation by mechanically disrupting crystals or loosely bound agglomerates that have already formed. A number of new active pharmaceutical ingredients (APIs) have also been examined; one particular small molecule has been shown to exhibit troublesome behaviour in terms of crystal habit. When high (labile) levels of supersaturation were reached in a standard cooling crystallization, high nucleation rates, along with concomitant poorly controlled crystallization, led to the proliferation of a distinct needle habit (Figure 5), manifesting itself in poorly stirred slurries and variable product bulk density. Conversely, when a solution was treated with ultrasound at much lower levels of supersaturation, a highly desired rhombic-/plate-type habit was easily produced. In addition to controlling the habit, careful insonation regimes allowed the particle size to be controlled consistently as shown in Figure 6. Importantly, large particles and agglomerates >1 mm in size were avoided.

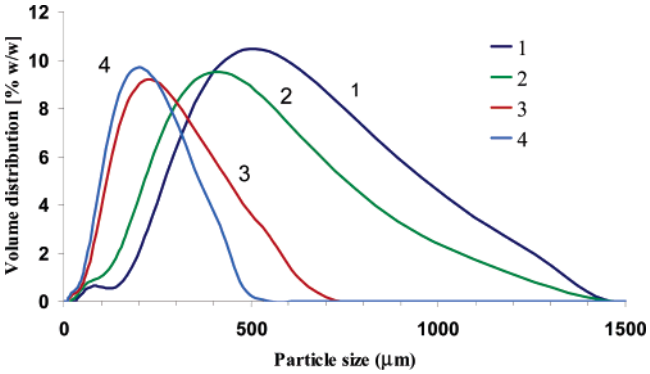



***Figure 6.*** **The effects of ultrasound on particle size distribution for a small-molecule API: (1) single burst at *low* supersaturation, (2) multiple bursts with cooling at *low* supersaturation, (3) multiple bursts with cooling commencing at *medium*-high levels of supersaturation, (4) as (3) but with improved stirring with baffles.**

***Table 2.*** **Ultrasonic crystallization of mono- and disaccharides from aqueous solutions[a]**

| solute | quantity dissolved in 10 mL water (g) | temp (°C) at which solid appeared: without ultrasound | temp (°C) at which solid appeared: with ultrasound |
|---|---|---|---|
| D-xylose | 25.0 | 36 | 43 |
| D-sucrose | 18.0 | <40 | 47 |
| D-lactose | 5.5 | 41 | 43 |
| D-maltose | 13.0 | <20[b] | 40 |
| D-glucose | 100.0[c] | <30 | 75 |
| D-cellubiose | 2.0 | <20[b] | 42 |

[a] Saturated solutions are prepared at 50 °C and cooled at 0.2 °C/min; 20 kHz ultrasound applied for 30 s for every degree drop in temperature at power input density ~35 $W \cdot L^{-1}$. [b] No crystals appeared at 20 °C. [c] Solution prepared at 85 °C.

Controlling the crystal properties of substances such as carbohydrates and proteins under conventional conditions can be troublesome because the crystallizations are very difficult to carry out and control.[21] As part of a progressive development towards more challenging applications, ultrasound has been successfully applied to the crystallization of sugars and amino acids.[11,13,14] The crystallization of sugars from water exhibit MZWs of tens of K under conventional conditions. Table 2 shows the reduction in MZW observed in laboratory-scale experiments for a range of sugars. For D-lactose, where the MZW reduction was small, the crystals obtained with ultrasound were smaller and more uniform in appearance than those in the noninsonated control. For D-glucose a broad MZW was usually observed; anhydrous glucose was isolated above 52 °C, which was achieved by sononucleation around 70 °C and managing the growth to 55 °C. Similarly, well-defined crystals of D-glucose monohydrate were obtained by sononucleation at 70 °C and managing the growth process accordingly whilst cooling to ambient temperature as shown in Figure 7. Noteworthy, if ultrasound was not used, the solution remained metastable down to 22 °C or less. As a general point, frequency, intensity, power, and pulsing can all yield different effects in sonocrystallization.

Polymorphism is common amongst organic materials, and given that small-molecule drugs can be flexible and exhibit significant internal freedom, it is no surprise that such entities can exist as two or more crystalline phases with different packing in the crystal lattice. Indeed, isolation of the "wrong" polymorph brings substantial problems in pharmaceutical applications. Judicious application of ultrasound to a polymorphic system at the right level of supersaturation can assist in isolating the ground-state polymorph (the most thermodynamically favoured and least soluble) or one near the ground state. Conversely, without ultrasound (or careful seeding) one may expect to generate a kinetically favoured and more soluble metastable polymorph. Narrowing of the MZW for the more stable polymorph can lead to nucleation at lower levels of supersaturation than would otherwise be the case and, ideally, undersaturated with respect to the less stable polymorph. Supersaturation can then be managed over the process cycle, such as with slow or exponential cooling, so as to avoid indiscriminate nucleation.

In crystallization processes induced by the addition of an antisolvent, where high supersaturation levels may be produced very rapidly, it has been shown that the application of ultrasound reduces not only the induction times of nucleation but also the spread of variability in induction times at a given level of supersaturation.[8,13] Typically in antisolvent-based crystallizations the antisolvent is added to the point of precipitation, which can lead to high supersaturation levels. For a number of molecules it has been shown that significantly less antisolvent can be used in conjunction with ultrasound to induce crystallization in a controlled manner.

(21) Chayen, N. E. *Acta Crystallogr., Section D*. **2002**, *58*, 921.

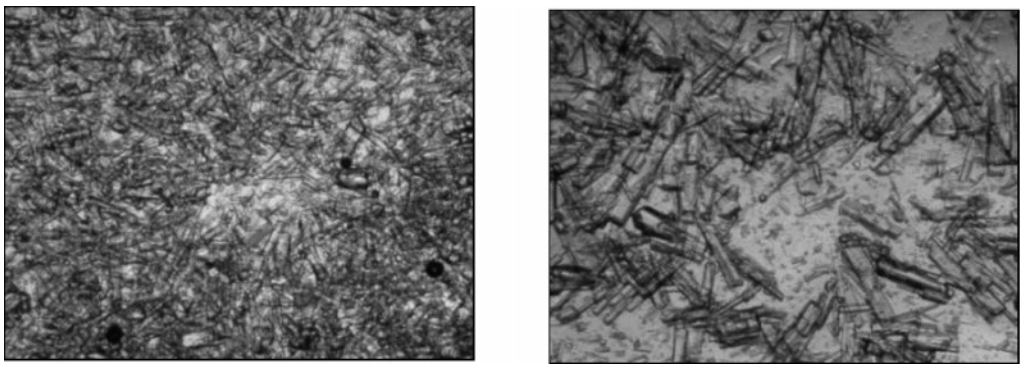


***Figure 7.*** **Crystals (50× magnification) of D-glucose obtained without ultrasound (left) with nucleation/crystallization ~30 °C and with sononucleation (right) at 70 °C. Both samples taken at 30 °C.**

## Ultrasonic Nucleation and Seeding

The ultrasonic induction of crystal nucleation invites comparison with seeding. Intentional seeding is common in industrial crystallization processes, including the crystallization of APIs, but they usually require operator intervention to add the seeds, which may entail additional engineering to control the seed addition whilst maintaining containment. The effects of intentional seeding include narrowing of the MZW, shortening of induction times, and control of particle size and distribution. In a batch process, seeds have to be added at precisely the correct time during the development of the supersaturation profile. Addition too soon to a solution that is undersaturated will result in the seeds dissolving. Seeding too late will also be ineffective because the solute material may already have rapidly (and possibly disastrously) crystallized as a result of high supersaturation levels with ensuing high nucleation rates, giving a product of inferior physical characteristics. Extremely small seed crystals generated by insonation offer all the advantages of conventional seeding without many of the drawbacks such as handling, actual physical size of the seeds, when to add to a batch process, and cGMP quality of the seed. The exact point of nucleation (in terms of supersaturation) can be well controlled, and to a degree the number of nuclei generated as a result of the prevailing supersaturation level.

The application of ultrasound to nucleate contained cGMP and/or sterile processes in place of deliberate seeding may have been viewed as niche technology in the past. However, with the arrival of scale-up and affordable equipment, sonocrystallization could very well become a method of choice since many of the difficulties of intentional seeding in such environments may be avoided. Sterile solutions can often be difficult to crystallize in any case, because the conditions exclude a significant fraction of the minute particulate material that brings about heterogeneous primary nucleation in conventional crystallizations. Ultrasonic equipment can be easily engineered into the process plant, and the application of ultrasound can be started and stopped at the flick of a switch. If the ultrasound is applied too early (i.e., undersaturated), there will be no effect (except possibly slight heating of the solution), and a further burst may be applied subsequently at the correct stage of the process.

## Ultrasound and Crystal Growth

The effects of ultrasound on crystal growth have not appeared as dramatic as those on nucleation and arise largely from enhanced bulk-phase mass transfer. Insonation of a liquid creates mechanical disturbances via both cavitation and acoustic streaming. Such effects will alter the fluid dynamics and increase bulk-phase mass transfer of solute to the surface of the growing crystal. In most cases, however, the surface nucleation and integration effects at the crystal faces will determine the growth rate of each individual face and, hence, the habit of the crystal.

A theoretical study along these lines has suggested that the effects of ultrasound on crystal growth rate will depend on the magnitude of the supersaturation driving force.[22] At low supersaturation, with growth velocities at the crystal faces around $10^{-10}$ m·s$^{-1}$, the application of ultrasound doubled the growth rate, while at higher supersaturation with growth velocity around $10^{-7}$ m·s$^{-1}$ there appeared to be no effect. The classical Burton−Cabrera−Frank (BCF) theory of crystal growth without insonation postulates that growth rate is limited by the formation of new surface layers at defect sites and predicts that the growth rate will exhibit approximately quadratic dependence on supersaturation at low supersaturation levels, while at higher levels the dependence becomes closer to linear.[23] The ultrasonic effect is explained by the hypothesis that, at low supersaturation, the quantity of available growth units in the vicinity of the crystal surface is small. Under these conditions, bulk-phase mass transfer becomes rate limiting in supplying growth units to the crystal surface, and its ultrasonic enhancement will enhance the growth rate.

## Scale-Up and Equipment Development

One of the most important barriers to the adoption of power ultrasound technology in manufacturing has been the lack of suitable equipment for use in industrial environments at the scale required. Most discoveries in sonochemistry and sonoprocessing have been carried out in laboratories on the milligram−gram scale using either high-intensity probe or bath systems. There is a fundamental requirement for equipment that may be operated simply and reliably at the kilogram−tonne scale in the small-volume manufacturing of fine chemicals and pharmaceuticals and importantly in an explosion-proof environment. For bulk-commodity chemicals manufacturing, scales of at least an order of magnitude larger than this would be required. Although the cost−benefit basis of the technology makes it less attractive for this type of application, all processes should be examined on a case-by-case basis, as evidenced by our work in bulk alumina production.[24] There are also potential applications for power ultrasound technology that are scaled down from the conventional laboratory to the microgram−milligram scale.[25] These consist mainly of applications to microscale mixing, and to work close to the discovery phase of pharmaceutical development where only very small quantities of material will be available. Some recent literature illustrates the utility of sonocrystallization and how relatively simple probe systems can be used to improve crystallization processes and become new tools for the process chemist.[26,27] A simple system incorporates a crystallizing jacketed vessel and a process flow loop with glass flow cell containing an ultrasonic probe. That said, laboratory probe and bath systems are usually built with a single ultrasonic transducer attached either to a delivery tip (probe) or to the base of a cylindrical or rectilinear vessel (bath). The size of these devices limits the scale at which they may be operated. In addition they also suffer further disadvantages with respect to the distribu-

(22) Arakelyan, V. S. *Acta Phys. Hung.* **1987**, *61*, 185.

(23) Burton, W. K.; Cabrera, N.; Frank, F. C. *Philos. Trans.* **1951**, *A243*, 299.

(24) Ruecroft, G.; Hipkiss, D.; Fennel, M. *TMS 2005*, *TMS Light Metals*, 2005

(25) McCausland, L. J.; Cains, P. W.; Maxwell, M. *Chem.-Ing.-Tech.* **2001**, *73*, 717.

(26) Dennehy, R. D. *Org. Process Res. Dev.* **2003**, *7*, 1002.

(27) Kim, S.; Wei, C.; Kiang, S. *Org. Process Res. Dev.* **2003**, *7*, 997.

tion of the energy intensity that they deliver. A bath will deliver nonhomogeneous acoustic fields throughout the medium with maximum amplitude at multiples of the half-wavelength of sound.[28,29] The nonhomogeneity of the acoustic field means that one must be careful with the positioning of the reaction/crystallizing vessel (depth, positioning with respect to where the transducers are mounted) if direct comparison is to made for a series of experiments. In addition, the higher power levels will be at points closest to the base and will dissipate with increasing distance from the transducer.

Most desired effects of ultrasound are mediated by cavitation, which occurs at a threshold energy density.[9] Above this threshold, the number density of cavitational events increases, but the increase is less than proportional to the increase in energy input, and the effect levels off at very high input levels. The cavitational threshold varies with the conditions of operation, including the physical properties of the liquid being insonated. We have found an energy input density of around 35 $W \cdot L^{-1}$ is a reasonable rule-of-thumb to exceed the cavitational threshold for most common solvents operating at room temperature.

Probe systems deliver very high intensity at the tip of the probe, the point of delivery, but the energy density is concentrated in the axial direction, away from the tip, and falls away rapidly with distance according to an inverse square law. Indeed, it is not possible to transmit an intense cavitation field more than 2−5 cm beyond the end of the probe, nor is it a suitable means to transmit the acoustic energy into large process volume, thus precluding scale-up. Probe systems only work effectively if operated in a geometry where most of the working liquid is constrained within the longitudinal high-intensity region or where the liquid is stirred vigorously. In addition, they suffer from erosion and particle shedding at the delivery tip surface, they may also be subject to cavitational blocking (acoustic decoupling), and the large transducer displacement increases stress on the material of construction, resulting in the possibility of failure. Whilst good for laboratory studies, they cannot be used at large commercial scale. We have attempted to create uniform fields of ultrasonic energy density above the cavitational threshold, using multitransducer systems to extend the volume of the cavitating region. Early scale-up designs extended to two or three transducers,[30,31] but more recent developments in both transducer design and bonding technology have allowed the number of transducers fitted to an installation to be increased well beyond this.[32]

Another aspect of scale-up is that it is effect specific. Different applications depend on different effects arising from ultrasound, and systematic scaling requires that the effect that is important for the particular application be identified, measured, and subsequently used as the basis for scaling. Crystallization effects will be determined principally by the enhancement of the nucleation rates, which as a first approximation may be assumed roughly proportional to the number density of cavitation events. Thus, the measurement of acoustic intensity is a major point of consideration, and indeed several methods are available.[2] These include the calorimetric method (whilst simple, this can be rather inaccurate), radiometric method (measurement of a force exerted on a surface by a radiation pressure/parallel sound beam), and measurement of the acoustic pressure using calibrated hydrophones. Acoustic pressure measurement can be very useful due the ease of use of the hydrophones and the fact that fast Fourier transform analysis can be performed which provides information on the type of cavitation taking place.

## Large-Scale Processing Equipment

Technologies for the scale-up of ultrasonic processing have been developed in many different ways, which may be classified generally as (1) probes, i.e., tips or other small-area devices delivering very high local intensities, in a flow cell or large volume, (2) opposing parallel transducers arranged around a duct, through which the process solution or suspension flows.

Probe systems have been developed that employ a high-intensity probe operating in a flow cell,[26,27,33] or immersed in a large volume.[34] The probe is in direct contact with the process fluid, but in such systems the acoustic energy is not particularly well focused other than at the tip. Systems where opposing parallel plate transducers are used to insonate a fluid flowing through a duct contain the acoustic energy to a greater extent than a probe system; however, the energy is still not particularly well focused to a central volume. Devices where an annular duct is employed through which the process fluid flows and around which transducers are placed may be considered to be similar to an opposing parallel plate arrangement where limited focusing of ultrasound occurs.[35]

In terms of energy efficiency, the optimum design of equipment would deliver ultrasonic energy intensity slightly above the cavitational threshold throughout its working volume. For this reason, we have concentrated our development on innovative distributed transducer systems that aim to deliver moderate energy densities dispersed as uniformly as possible throughout the working volume.

A number of developments have concentrated on utilising a central resonating duct through which the process fluid flows; one such system uses only one transducer,[34] whilst others, such as the Sodeva Sonitube, use several.[37,38] The essential feature of this device is that the dimensions of the tube are designed to give standing waves along its length. Resonating systems essentially set up standing waves using coherent ultrasound within the working liquid and will therefore give rise to spatially inhomogeneous and very often high power densities. Although a resonating tube will result in acoustic energy being transmitted into the fluid from the

(28) Leighton, T. G. *The Acoustic Bubble*; Academic Press: New York, 1994; p 31.
(29) Mason, T. J. *Sonochemistry;* NATO Advanced Study Institute Series C524; Kluwer Academic Publishers: Boston, Dordrecht, 1999; p 42.
(30) Martin, P. D.; Ward, L. D. *Trans. Inst. Chem. Eng.* **1992**, *70A*, 296.
(31) Desborough, C. L.; Pike, R. B.; Ward, L. D. U.S. Patent 5,658,534, 1997; GB 2 243 092 A, 1991; EP 0 449 008 B1, 1994.
(32) Perkins, J. P. World Patent WO 00/35579 B1, 2000.
(33) Sonics & Materials Inc. http://www.sonicsmaterials.thomasregister.com.
(34) Hielscher GmbH. http://www.hielscher.com.
(35) Sawyer, H. T. U.S. Patent 4,369,100, 1983.

entire inner surface of the tube, the focusing effect is limited as is the achievable power.

Alternatively, transducers have been placed radially around a resonating duct, which has the effect of focusing the acoustic energy into the duct. In one such design, four transducers are mounted at 90° to each other around a cylinder as two sets of facing pairs, which are operated at the same amplitude and frequency but 180° out of phase with each other.[39] This arrangement results in coherent interference with inverting nodes/antinodes every half cycle. It is claimed that this insonation pattern allows a more efficient coupling of acoustic energy with the fluid than a simple standing-wave arrangement. In another development by Sonertec Inc., a cylindrical duct made of a nonresonant material (e.g., polymeric/PTFE) is specified, around which are placed several transducers in the form of longitudinal bars.[38] The transducers, acoustically coupled to the wall by a thin layer of lubricant, taper inwards, thereby increasing the power intensity at the face. It is claimed that cavitation does not occur at the wall. The design envisages converging cylindrical acoustic waves that can induce cavitation in a cylindrical zone concentric to the tube, whilst maintaining the cavitation away from the inner wall of the tube. It also specifies that the inner wall of the tube has a diameter equal to or greater than the wavelength of sound in the liquid flowing in the tube at the operating frequency of the reactor. The transducers are operated in phase and potentially at up to 4 $kW \cdot L^{-1}$ in a pilot unit. It is possible that this power level may have been calculated for the centre of the reaction vessel, where cavitation is occurring, or that it is the quoted power output of the generators. The transducers may also be operated out of phase, which has the effect of inducing mixing but no cavitation.

The alternative approach to the design of scaled-up units for industrial application is to avoid resonance and standing waves and to develop systems that avoid coherent wave relationships. This equipment designed and manufactured by $C^3$ Technology for sonoprocessing has followed this course. There are a number of advantages in using noncoherent ultrasound; the more even distribution of the ultrasound through the working fluid is a key benefit. In addition one can design equipment with greater flexibility in terms of dimensions, frequency, and configuration. We embarked on noncoherent designs after our early experience with multitransducer systems gave rise to difficulties with transducers tuning in to each other and of mechanical resonance in system components. Such difficulties can undoubtedly be more easily overcome with modern transducers and system designs.

The original multitransducer designs were based on a 4−5-L insonated volume as a cylindrical duct, 120 mm in diameter, fitted with three radially mounted transducers.[30,31] To reduce surface erosion and mechanical stresses at the point of contact, a liquid barrier was employed between the transducer and the (thinned) duct wall. This unit was designed for noncoherent ultrasonic operation with a nominal frequency of 20 kHz. Experience of operating the unit showed that the three transducers, tuned to slightly different frequencies between 19 and 21 kHz, and spot tests with aluminium foils and hydrophones indicated that the power input densities were reasonably uniform throughout the 4−5 L working volume.

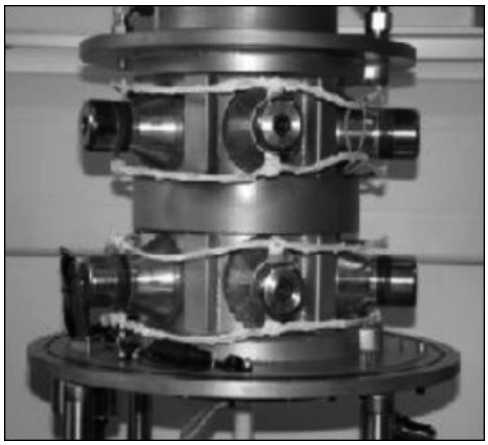


***Figure 8.*** **$C^3$ Technology ultrasonic flow cell: 5-L cell in stainless steel with bonded transducers shown with acoustic shield removed for clarity.**

More recent developments have employed direct bonding of the transducer to the surface of the vessel.[32] Improvements in the bonding method, and a move to transducers with lower individual outputs, have enabled the move to systems with large numbers of transducers to give an acoustic pattern that is uniform and noncoherent above the cavitational threshold throughout the working volume. The use of low-output transducers gives the additional advantage of avoiding the phenomenon of cavitational blocking (acoustic decoupling), which arises where power densities close to the delivery point are very high. In addition these multitransducer units very effectively concentrate ultrasonic intensity towards the central axis of the cylinder and away from the vessel walls, thus reducing problems of erosion and particle shedding. This vessel can be operated in batch mode or, for larger-scale work, in continuous mode whereby units can be combined in a modular fashion for "scale-out" and increased residence time. In summary, a plurality of low electrical and acoustic power (~1−3 $W \cdot cm^{-2}$) transducers produces 25−150 $W \cdot L^{-1}$, but ideally 40−80 $W \cdot L^{-1}$. The power can be applied continuously or pulsed. A typical example of the flow cell is shown in Figure 8.

This fundamental design and supporting patent has been crucial in developing more advanced flow cells. One such device is the Hastelloy explosion-proof cell (for use with flammable solvents in a zoned process area) used for the manufacture of pharmaceuticals (Figure 9). Scaling out the fundamental flow cell design in one dimension facilitated the design and manufacture of the 1.2 m flow cell used in the bulk-scale alumina production at Aughinish Alumina in Ireland—Europe's largest production site (Figure 10). This flow cell, with 40 bonded transducers, is manufactured from 316 stainless steel with a hard chrome internal surface for added corrosion resistance. To provide the desired residence

(36) Asai, K.; Takeuchi, A. U.S. Patent 4,074,152, 1978.
(37) Vaxelaire, P. U.S. Patent 5,384,508, 1995.
(38) Boursier, G.; Devidal, P.; Dubruque, D.; Vaxelaire, P. World Patent WO 02/072229, 2002.
(39) Hall, M. N. U.S. Patent 4,433,916, 1984.

***Figure 9.*** **C³ Technology ultrasonic flow cell: 5-L cell fabricated in Hastelloy for pharmaceutical use with two inputs and two output flanges for flexible hose attachment.**

time in this continuous system six of these 1.2-m cells were joined together in a modular fashion.

For the preparation of micrometer-sized particles for drug inhalation a novel device for preparation of micrometer-sized particles using a vortex-mixing device (Figure 11) has been developed.[41] Vortex mixing utilizes vortex-flow dynamics to promote efficient mixing of a liquid with a second phase, which may be a solid, liquid, or gas, on time scales down to 10 ms. The combination of high transient supersaturation, arising from the rapid vortex mixing along with ultrasonic nucleation can produce fine, micrometer-sized crystalline solids with a very narrow size distribution. Such rapid and efficient mixing can be used in precipitation, reaction, and antisolvent crystallizations to bring about high product yields. On a related point, *Solution Atomization and XtalliSation* (SAXS) technology in conjunction with sononucleation[44] has been shown to be extremely useful for the production of nano- and micrometer-sized particles formulated for drug inhalation and as nanosuspensions. The process involves (i) formation of a drug-substance solution, (ii) generation of an aerosol, (iii) collection of the aerosol droplets in a vessel containing nonsolvent, and (iv) application of ultrasound to induce crystallization. The use of this technology facilitates the production of regular spherical particles in a reproducible fashion. These particles, when used in an aerosol-based formulation, appear to have aerodynamic properties superior to those of particles produced by other techniques, resist flocculation and settling, when in suspension, and have a unique nanotopology with improved absorption characteristics.

## Summary Conclusions and Future Directions

The application of ultrasound to initiate and control crystallization has attracted more attention from potential users in recent years than sonochemistry. This has been partly because the effects are better defined and easier to demonstrate, and partly because conventional crystallization processes can sometimes be difficult to nucleate and control the particle size distribution, although seeding can help in both these areas. Usually the process operator has direct control over (i) the rate at which supersaturation is generated (via cooling or antisolvent addition), (ii) the point at which seed crystals are added if required and, to a lesser extent, (iii) the mixing regime in the crystallizer. Ultrasound allows an additional dimension of control over the nucleation regime, and may allow the nucleation−crystal growth balance to be regulated to optimize the product and particle properties.

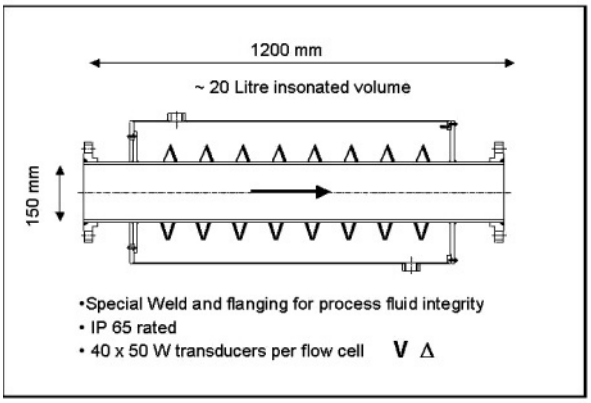



***Figure 10.*** **C³ Technology 20-L flow cell fabricated in hard chrome-plated stainless steel with 40 bonded transducers for use in the alumina industry; shown with acoustic shield removed.**

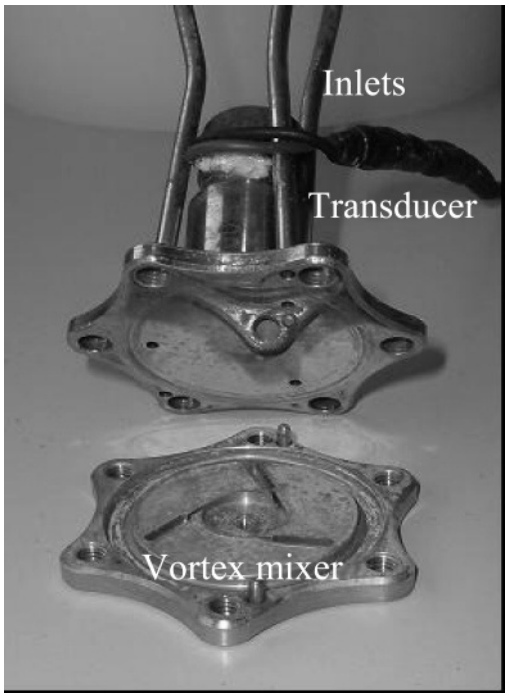



***Figure 11.*** **C³ Technology vortex mixer fitted with a bonded ultrasonic transducer.**

Developments in equipment in recent years, in particular the availability of large insonation cells fitted with multiple transducers, has increased the possibilities of using ultrasound in larger-scale processes. As for most sonochemical applications, the ideal arrangement would insonate a large process volume at an energy input density slightly above the cavitational threshold. Systems developed recently aim to achieve this by combining a large number of transducers, each of which delivers a relatively low power output. Distributing the energy input in this way also helps to minimize particle shedding from the power sources.

There is serious potential for ultrasonic processing and sonocrystallization to be more extensively used in producing micrometer-sized particles for drug inhalation[42−44] and in the developing areas of nanotechnology. The use of ultrasound to nucleate nanophases, either amorphous or partially ordered, has been demonstrated in practical applications. Indeed, this may also point a way forward to developing an improved general understanding of the relationship between ultrasonically induced cavitation and nucleation. There may also be further applications in biotechnology, such as the isolation and crystallization of proteins, that remain to be researched more fully.

(40) Dion, J.-L.; Agbossou, K. U.S. Patent 6,361,747 B1, 2002.
(41) McCausland, L. J.; Bowe, M.; Stairmand, J. World Patent WO 02/089942, 2003.
(42) Lancaster, R. W.; Singh, H.; Theophilus, A. L. World Patents WO 02/00199 A1, 2002; WO 02/00200 A1, 2002; WO 02/38811, 2000.
(43) Rogueda, P. World Patent WO 05/004847 A1, 2005.
(44) Price, R.; Kaerger, J. S. World Patent WO 05/073827, 2005.
(45) The amplitude of vibration relates to the displacement of the piezoelectric ceramic discs and correlates to approximately 2−35 W. The P100 maintains constant amplitude and varies the power consumption accordingly, depending upon load at the probe tip, viscosity changes, and mechanical losses. The energy is transferred along a titanium probe with a face surface area of either 0.5 $cm^2$ or 7.0 $cm^2$, depending upon the volume of liquid requiring insonation.

## Example Experimental Protocols

Experimental procedures were carried out using a Sonic Systems P100 ultrasonic processor with ancillary probe. The probe was used either as an immersable device in the bulk of the experimental liquor or in a secondary flow cell where flow was controlled by means of a Prominent diaphragm pump with maximum flow of 19 $L \cdot h^{-1}$. The ultrasound intensity was controlled between 1 and 16 $\mu$m amplitude peak-to-peak.[45] The crystallization experiments were carried out in two identical jacketed vessels (150 mL) controlled by a Julabo F32. An overhead stirrer with a two-blade agitator maintained at 100 rpm was used in each vessel. A P100 small-diameter probe[45] was fitted to one of the two vessels with the titanium horn submersed to 10 mm into the solution. Vessel A, fitted with the probe, was used for the insonated samples, whilst vessel B was used as the control. Particle size measurements were carried out using a Malvern Mastersizer fitted with nonsolvent dispersion chamber.

**Crystallization of Sorbitol Hexaacetate.** Sorbitol hexaacetate (20 g) and methanol (63 mL) were transferred into each crystallization vessel. The slurry in each vessel was then fully dissolved at 60 °C for 1 h. The solutions were then cooled from 60 °C to the equilibrium solubility temperature of 50 °C followed by linear cooling at 0.2 °C/min to 20 °C. The solution in vessel A, fitted with the P100 probe, was treated with ultrasound using a 2−4 $\mu$m displacement[45] for 30 s at every 1 °C drop in temperature until turbidity was observed. Turbidity typically became noticeable from 46 °C in vessel A and 42 °C in control vessel B.

**Crystallization of Adipic Acid.** Adipic acid (9 g) and deionized water (100 mL) were transferred into each crystallization vessel. The slurry in each vessel was then fully dissolved at 65 °C for 1 h. The solutions were then cooled from 65 °C to the equilibrium solubility temperature at 50 °C followed by linear cooling at 0.2 $°C \cdot min^{-1}$ to 20 °C. The solution in vessel A, fitted with the P100 probe, was treated with ultrasound using a 4−7 $\mu$m displacement[45] for 30 s at every 1 °C drop in temperature until turbidity was observed. Turbidity typically became noticeable from 49 °C in vessel A and 48.2 °C in control vessel B.

**Crystallization of D-Glucose.** D-Glucose monohydrate (100 g) and deionized water (10 mL) were transferred into each crystallization vessel. The thick slurry in each vessel was then fully dissolved at 95 °C for 1 h. The solutions were then cooled from 95 °C to the equilibrium solubility temperature of 85 °C followed by linear cooling at 0.2 °C/min to 60 °C. The solution in vessel A, fitted with the P100 probe, was treated with ultrasound using a 7 $\mu$m displacement[45] for 30 s at every 1 °C drop in temperature until turbidity was observed. Turbidity typically became noticeable from 75 °C in vessel A, whilst the control vessel B still remained a clear solution at 60 °C. This solution exhibited a broad MZW with solution clarity being observed as low as 22 °C.

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