Organic Process Research & Development **2003**, *7*, 1002−1006

Particle Engineering Using Power Ultrasound[1]

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Abstract:

Particle size control is of great importance to the pharmaceutical industry and is a key factor in product performance. Mechanical size reduction methods have some significant drawbacks. Sonocrystallisation, the use of power ultrasound in crystallisation, is a method of generating particles of controlled size, and this is illustrated with three examples.

The Need for Particle Engineering

The pharmaceutical industry strives to make drug substance of the right quality for formulation, and solid-state properties are a key determinant of product performance. The polymorphic form of a drug can have a direct impact on bioavailability,[2] and the literature contains myriad examples where control of the solid-state form has been accomplished and examples where control has been lost.[3] Besides polymorphic form, the control of particle size is often an important objective in process development. In the case of oral formulations, particle size influences dissolution rate in the stomach,[4] thereby affecting the release of drug into the blood stream and, hence, the therapeutic profile. The situation for inhaled formulations is more complex. Not only does size exert an influence on dissolution, it also influences deposition within the lung, there being an optimum aerodynamic size of 1−5 μm for targeting the alveoli.[5] Aerodynamic size, in turn, is a function of particle volume (a measurement often made using laser light scattering) coupled to density and shape.

As particle size is such an important factor in product performance, GlaxoSmithKline (GSK) is investigating novel methods of size control, of which sonocrystallisation is one.

Size Reduction and Product Quality. With relatively small volumes of high-value products being manufactured, it is unsurprising that batch crystallisers, often in cooling mode, are used almost exclusively in the pharmaceutical industry. Obtaining the necessary nucleation rates to generate particles that are, for example, of respirable size, is difficult if not impossible in such a typical case. Many complex organic molecules nucleate slowly, a property indicated by a wide metastable zone width. Heat transfer in batch crystallisers is inefficient, precluding the generation of high supersaturation which would enhance nucleation. Even if high supersaturation could be obtained, poor mixing in the typical large vessel would produce inhomogeneity in growth and nucleation rates and may produce undesirable effects such as encrustation.[6] Seeding is the common approach to size control in batch crystallisers but is unlikely to provide access to particles of small size and requires a high degree of process control.

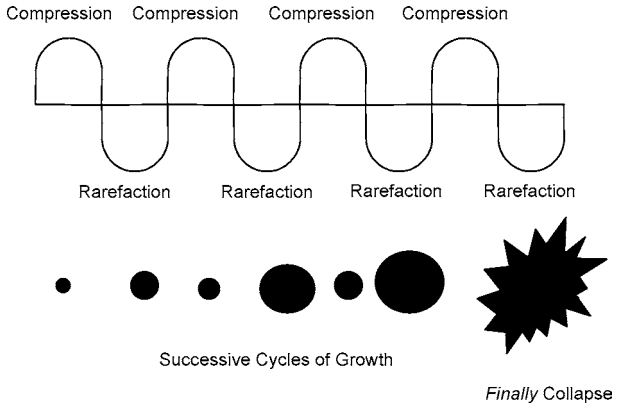

Figure 1.

Batch crystallisation, therefore, produces particles that are often too large to meet a specification, and thus, further mechanical size reduction by milling or micronisation is required. Mechanical size reduction, however, can have significant drawbacks. Most molecular crystals deform plastically, on a molecular level, producing dislocations in the crystal lattice[7] when a mechanical force is applied. In extreme cases, regions of amorphicity are formed, particularly on the crystal surface, which may subsequently recrystallise. The example of albuterol sulphate illustrates how mechanical size reduction can have a negative impact on stability.[8]

Power Ultrasound and Crystallisation. Power ultrasound has long been applied to heterogeneous reactions to enhance reaction rates, but its application to crystallisation, sonocrystallisation, is more limited.[9] Power ultrasound (defined as frequencies from 20 to 100 kHz) exerts alternate cycles of compression and rarefaction within a liquid, creating bubbles during the rarefaction stage (Figure 1).

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Published on Web 10/25/2003

10.1021/op034124i CCC: $25.00

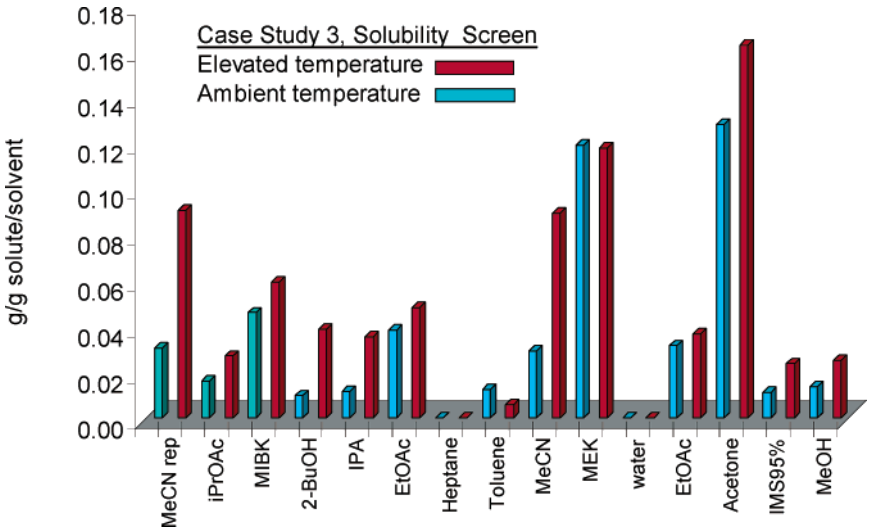

Figure 2.

The bubbles survive repeated cycles of compression and rarefaction until a critical size is reached and collapse occurs, a process known as cavitation. Collapse engenders the creation of high temperatures and pressures within the bubble. Whilst the overall effect is often seen only as a modest rise in temperature, the local effect in the fluid can be energetic enough to result in the sintering of metal powders and the emission of photons. The literature contains examples of sonocrystallisation: in melt crystallisation to control polymorphism,[10] batch crystallisation of an antibiotic,[11] and the continuous crystallisation of barium sulphate.[12] In all of these examples, an increase in nucleation rate is reported when compared to uninsonated or "silent" controls. The effect is not solely due to an enhancement of micromixing resulting from cavitation and acoustic streaming. Indeed, induction time measurements during the crystallisation of potassium sulphate seem to indicate a mechanism akin to secondary nucleation, but the actual mode of action remains elusive.[13]

These literature observations are typical of our own findings. Making a highly supersaturated solution of a drug substance by mixing a saturated solution with an antisolvent, often results in slow crystallisation and sometimes appreciable "oiling out". As nucleation is slow, enhanced micromixing results in no change in the observed rate of nucleation.

Application of ultrasound to such a supersaturated system results in much faster nucleation and a distribution of smaller crystals. Judicious selection of solvent, solution concentration, antisolvent, and temperatures enables this enhancement in nucleation to be maximized. Solvent selection also enables some control over polymorphism to be exerted although metastable polymorphs are sometimes produced in preference to the thermodynamic form.

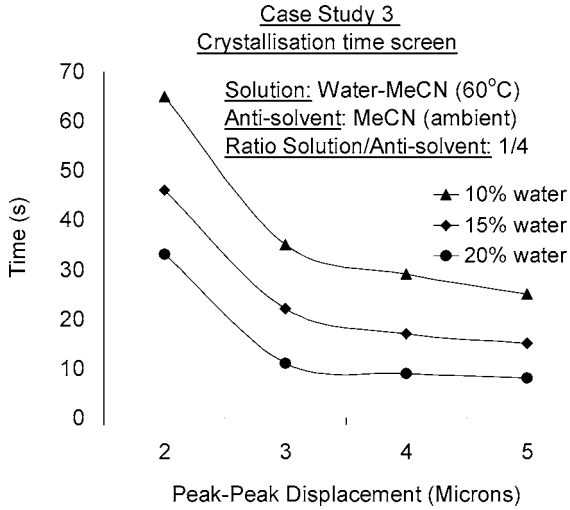

Figure 3.

We apply ultrasound to the supersaturated mixture in continuous mode, thus creating a more homogeneous environment for crystallisation and obviating at least some of the problems associated with scaling-up ultrasound in batch mode.

Typical Experimental Procedures and Equipment. Understanding the solubility of a given pharmaceutical is the most important piece of information in evaluating whether sonocrystallisation can be used to control particle size. The solubility of the compound is measured at two points on the solubility curve, at nominal elevated temperature and at ambient temperature (Figure 2 gives an example of this taken from Case Study 3 which will be described later). Analysis of the solid residue after equilibration in the solvent indicates if a solid-state transformation has occurred. The screen is not designed to collect highly accurate solubility data. The limitations can be seen from the anomalous result obtained for toluene although the duplicate determinations for acetonitrile are in relatively good agreement.

Having identified solvents and antisolvents for the pharmaceutical being studied, saturated solutions are prepared and mixed with antisolvents on a vial scale. Ultrasound is

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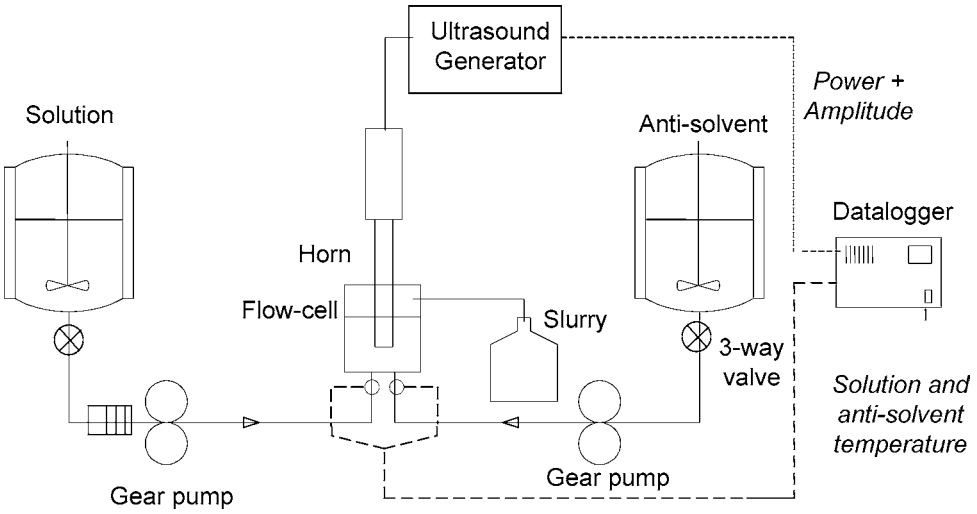

Figure 4.

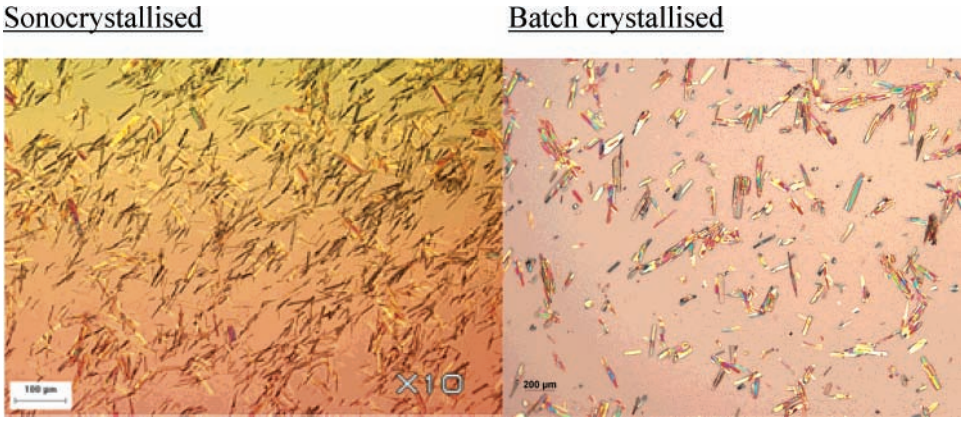

Figure 5.

applied using a probe, and the time taken to deposit appreciable solid (visually) is measured. Figure 3 shows data on a crystallisation screen, again taken from Case Study 3, saturated solutions being prepared from various mixtures of water in acetonitrile expressed on a w/w basis.

In most instances, the thermodynamic polymorph is required, and the crystals are analysed to confirm this. Provided that the desired solid-state form is produced and that the crystallisation time is reasonably short (in the region of 10 s or less) the crystallisation is operated continuously (Figure 4). The residence time in the flow cell is generally at least 3 multiples of the determined crystallisation time.

Typical flow rates and temperatures for the solution range from 15 to 50 mL min^{-1} at ambient to 80 °C. For the anti-solvent these ranges are 40−150 mL min^{-1} at ambient to −20 °C. The flow cell volume is in the range of 10−50 mL, with ultrasound powers of 10−80 W (0−15 μm peak to peak displacement at 20 kHz) using a 32 mm diameter probe.

Case Study 1. Batch crystallisation of this drug substance from 2-propanol and water produces crystals of large size which require milling to reach the desired particle size specification. Manipulating the solvent ratios enabled this to be turned into a continuous crystallisation using approximately the same ratio of 2-propanol and water at volume efficiency similar to that used in batch mode. Sonocrystallisation produced considerably smaller crystals. Microscopy (Figure 5) shows the impact of sonocrystallisation compared to a batch-crystallised control. There appears to be a threshold power density; no crystallisation is observed at less than 10 W. Increasing the ultrasound power from 10 W appears, at least microscopically, to produce little change in particle size (Table 1).

Table 1

solution temp. (°C)	2-propanol temp. (°C)	power (W)	power (W cm^{-2})	microscopy (length, μm)
72.0	−16.7	10	1.24	5−30
73.0	−15.7	25	3.11	5−50
72.7	−16.2	50	6.22	5−40
72.6 replicate	−16.2	25	3.11	5−40

Case Study 2. This drug was poorly bioavailable, and required two stages of size reduction. The batch crystallisation was performed using *n*-propyl acetate and heptane as the antisolvent and, thus, was amenable to continuous sonocrystallisation. Applying ultrasound (50 W) gave particles of the desired size for the final size reduction, thus at least removing the initial milling step. The effect of manipulating antisolvent ratio, and hence supersaturation, was also investigated (Figure 6). This clearly shows how increasing supersaturation (defined here as c/c^*) leads to a decrease in particle size as measured by laser light scattering.

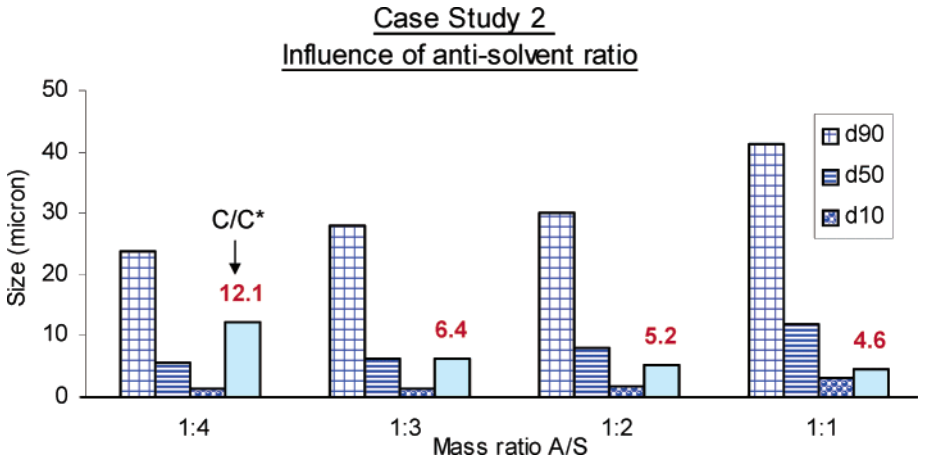

Figure 6.

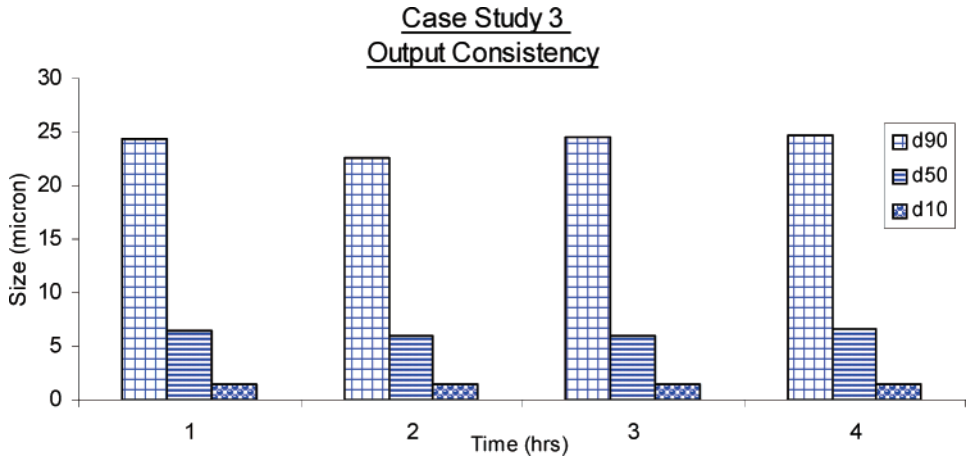

Figure 7.

Case Study 3. In this example, a hydrate, micronisation produced appreciable amorphicity, and it was anticipated that this would have a negative impact on product performance when formulated into an inhaler. The batch crystallisation uses a mixture of acetonitrile and water in antisolvent and cooling mode. Manipulating the solvent ratios enabled the crystallisation to be operated in continuous mode in the laboratory producing ca. 5% slurry in a throughput of ca. 600 mL h^{-1}. The expected hydrate was also produced. Furthermore, sampling during the course of the crystallisation and performing analysis off-line using laser light-scattering measurement, (Figure 7) shows how consistent the particle size distribution is with time. Power ultrasound is of sufficient intensity to break chemical bonds, hence, its application in reactive chemistry. To test if any degradation occurs, a solution of hydrate at ambient temperature was insonated at high power for 1 h. No change in impurity profile was detected.

Particle isolation. Cake filtration can be applied to effect the isolation of relatively large particles. As particle size decreases, however, cake resistance increases, and cake filtration can result in prohibitively long filtration times.[14]

Since small particles that filter poorly are often the desired outcome, methods other than cake filtration must be applied. In our experience, direct *slurry* spray drying provides the best access to a free-flowing powder after sonocrystallisation. Without mother liquor removal, however, no improvement in purity is anticipated although limited impurity purging may be possible using techniques such as cross-flow filtration prior to spray drying. Slurry spray drying is further complicated by the presence of product in solution which may not crystallise during the drying process and present a risk of contamination with the amorphous form. In case study 3, however, slurry spray drying from acetonitrile was applied, and no amorphous character was detected by XRPD.

Cavitation Erosion. The key technical drawback associated with the use of power ultrasound is cavitation erosion. Cavitation bubbles collapse unsymmetrically when in close proximity to the emitting probe face (or another solid surface). A microjet forms which impacts the solid surface, resulting in surface pitting, and metal is released into the medium, the major component being titanium from the probe tip. To understand the magnitude of this, deionised water was sonicated for a standard period of time at 25 °C, the water was filtered, and the amount of titanium released was measured by ICP (Figure 8).

Whilst detectable amounts of titanium are released, solid loadings in a typical slurry mean that the proportion of titanium is significantly less than 1 ppm. This is well within most specifications for metal contamination.

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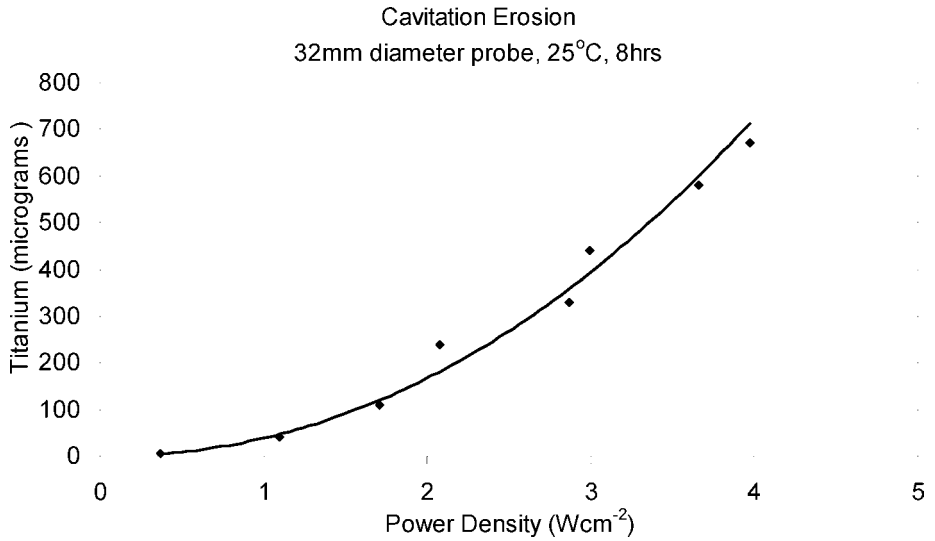

Figure 8.

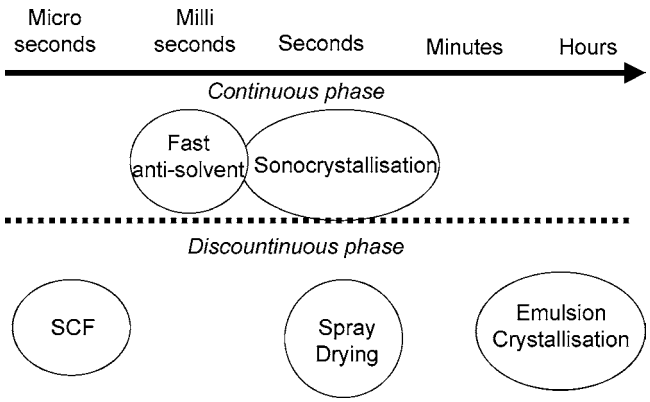

Figure 9.

Conclusions

Sonocrystallisation is one technique that can be be used to form small particles of controlled size. There are a number of others (Figure 9) which can be classified in terms of those that operate discontinuous phases (aerosols or emulsions) and those that operate in essentially a continuous phase. The observed kinetics for a process are a function of the solute, the solvent *and* the mode of supersaturation generation, and a time axis allows further comparison between techniques. Applying different techniques to the same substrate may produce crystals that are similar in size but very different when other physical properties are measured. In this case, product performance and cost are the most important factors in deciding which technique to advance.

Where nucleation is slow, small particle formation becomes particularly difficult with only emulsion crystallisation being applicable. Sonocrystallisation is clearly a central technique within the 'Toolbox' and one of the few methods available to chemists and engineers for exerting control over particle size.

Acknowledgment

I thank all of the collaborators involved in this work at GSK, specifically from the Particle Sciences and Synthetic Chemistry groups in Chemical Development and the World Wide Physical Properties in Pharmaceutical Development.

Received for review August 29, 2003.

OP034124I