Controlling Crystallisation of Pharmaceutical Ingredients

By Graham Ruecroft, Co-Founder and Director, Prosonix

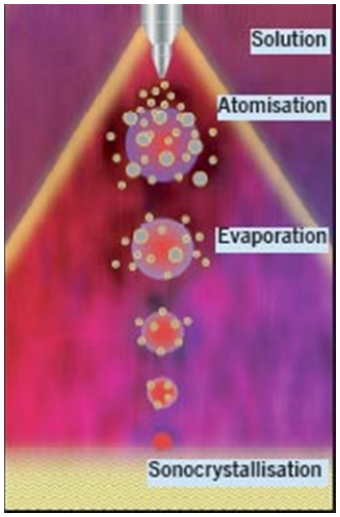
Crystallisation has been described as one of the most difficult unit operations to control.

Prosonix has developed a range of proprietary technologies that use power ultrasound to control the process and allow the precise production of high-purity chemicals, including pharmaceutical intermediates and ingredients.

Prosonix Ltd, a recently-formed UK company, has just established an agreement with the University of Bath for the exclusive commercialisation of the sonocrystallisation particle engineering technology known as Solution Atomisation and Crystallization by Sonication (SAX™).

The agreement was concluded following 18 months of technology evaluation between Prosonix and the University. The limitations of conventional crystallisation techniques in the processing of pharmaceutical ingredients for a number of dosage forms typically requires the need for micronisation.

These low-technology destructive techniques are usually expensive and can adversely affect a range of highly important physicochemical properties of the ingredient.



SAX nanocrystallisation technology is comprised of solution preparation, atomisation, solvent evaporation andsonocrystallisation, leading to isolation of crystals with closely controlled particle size and morphology.

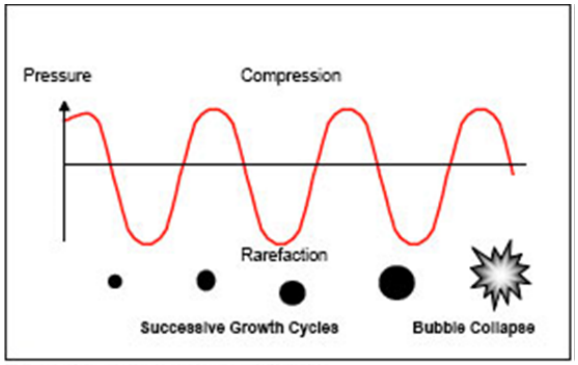
"There is an unmet and pressing need to engineer crystalline particles with an even greater control of the surface characteristics and surface geometry of micron and sub-micron sized particles while maintaining high throughput, low cost and industrial scalability," says Dr Graham Ruecroft, chief technical officer of Prosonix.

"Alternative processes for the production of drug particles within an optimum particle size range, for example by the use of supercritical fluids, have generated significant interest and potential, albeit with limited success to date.

Recent industry announcements raise serious question marks about its scalability and cost-effectiveness as the technique requires extremes of pressure, only delivers minimal volume, and can lead to a high degree of amorphous content."

Discovered by Dr Robert Price from the University of Bath's Department of Pharmacy and Pharmacology, the SAX technology is a single-step, solutionto-particle technology, incorporating solution atomisation and sonocrystallisation, that has shown potential benefits in

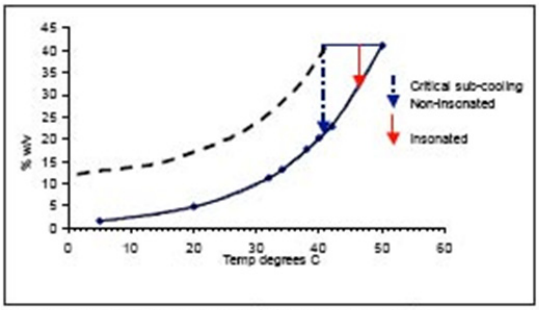
the production of particles, particularly for inhaled therapeutics, but also has potential in the production of nanosuspensions and improved particles for other formulation techniques, including pharmaceutical co-crystals and combination-based therapies:



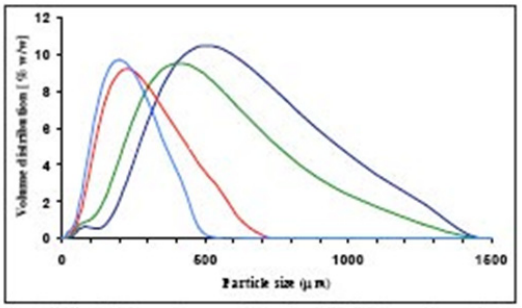
Acoustic cavitation with power ultrasound.

"The SAX technology allows production in a well-defined particle size range and controls the macroscopic morphology, including polymorphism and mesoscopic surface topology," says Ruecroft.

"These properties are invaluable in defining aerodynamic properties of particles, shelf life, stability, bioavailability and efficacy. To this end, SAX particles can have unique spherical shape and surface nanotopology providing minimum area for interfacial contact with low surface free energies."



Effects on the metastable zone width (MZW) for a cooling crystallisation: The arrows represent the first observation of crystals.



The effects of ultrasound on particle size distribution and morphology for a small-molecule API.

Applications of ultrasound in crystallisation

Ultrasound has been used in many life science fields such as medical imaging and diagnostics, biological cell disruption and fermentation processes. The application of power ultrasound (20-100 kHz, or even up

to 2 MHz) to chemical processing has seen steady progress over the past 15 years or so, and a widely reported aspect of this is the use of sonochemistry to promote or modify chemical reactions. Ultrasound can also be used to influence crystallisation through the mechanisms of cavitiation and acoustic streaming.

Cavitation is particularly effective in promoting nucleation, and the controlled and reproducible generation of crystal nuclei, or rather nanocrystalline seed crystals, provides the starting point for controlling the crystallisation process, enabling control of crystal size distribution, morphological control, elimination of impurities in the crystal and improved solid-liquid separation behaviour.

Sonocrystallisation can also eliminate the need to use seed crystals, and this can be particularly advantageous in contained crystallisations. In the past, one of the principal barriers to the adoption of power ultrasound technology in pharmaceutical manufacturing was the lack of equipment suitable for using the technology at industrial scale, most discoveries in sonochemistry and sonoprocessing having been at laboratory or milligram to gram scale.

It is now possible to apply the technology at the kilogram to tonne scale required for fine chemical and pharmaceutical manufacture, as demonstrated by Prosonix's application of the technology in bulk alumina production.

There are also potential applications for using the technology at small laboratory scale, ie down to the microgram to milligram scale. These applications include microscale mixing and small-scale pharmaceutical discovery. "Controlling and actively manipulating nucleation and subsequent crystal growth behaviour is fundamental to the improvement of a crystallisation process," says Ruecroft. "Prosonix achieves this through the selective application of ultrasound, via patented scale-out technology and developed procedures.

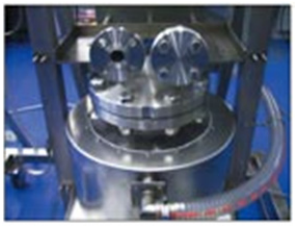
"The value-added benefits arising from the control of physical form are capitalised at production scale because process repeatability is increased as a result of controlling the point of nucleation and the approximate number of nuclei generated," he says. "Significant value-added benefits are capitalised through new process patents that can be created for individual products, thus securing and extending marketing timescales.

"An attractive feature of the Prosonix technology is that it can be applied at any stage in a product pipeline. The technique can be used in early laboratory studies through to full industrialisation. This scale-out feature of the technology ensures that success in the lab can be replicated across scale." Proprietary technologies Almost all chemical processes utilise at least one crystallisation step, either as the key separation mechanism or final polish filtration.

Crystallisation has been described as one of the most difficult unit operations to control, irrespective of whether the process utilises cooling, evaporative, anti-solvent or pH shift. Prosonix has developed a suite of proprietary technologies that use power ultrasound to control the crystallisation process and allow the precise production of high-purity organic and inorganic microcrystalline chemicals including intermediates, excipients, APIs, binders, sugars and colorants.

The technology is already validated across scale in GMP environments. It can be used in in-line continuous flow mode, or batch mode for in situ generation of seed crystals using the process liquid itself as the source for the seeds, thus overcoming one of the major limitations of classical seeded processes.

Prosonix sonocrystallisation technology works by controlling and actively manipulating nucleation and subsequent crystal growth behaviour that is fundamental to the control of physical form and the improvement of a crystallisation process.



A Prosonix Prosonitron sonocrystallisation reactor system approved for pharmaceutical use.

This provides control of crystal habit, amorphous state, polymorphs, manipulation of crystal size distribution, and the prevention and reversal of troublesome agglomerations. Additional value-adding improvements in related product properties such as purity, filtration rate and bulk density are seen at production scale.

Extended agreement Prosonix has also just announced the extension of its co-development and licensing agreement with UCB for its proprietary sonocrystallisation technology across a range of UCB's pharmaceutical products.

The renewal of the agreement follows the completion of Proof of Concept, and Initial Proof of Process studies and is the result of almost three years of collaborative research and development effort by the two companies.

To enable further scale-up and clinical development activities to be undertaken by UCB, Prosonix has provided a bespoke multipurpose Prosonitron™ sonocrystallisation reactor system that will be utilised in the cGMP manufacturing facilities at UCB's Braine l'Alleud site in Belgium.

Technologies for scale-up of ultrasonic processing include the use of probes, ie small-scale devices that provide very high local ultrasound intensities, in flow cells or large-volume reactors; or the use of opposing parallel transducers arranged around a duct in which the process solution or suspension flows.

A Prosonitron system installed for processing in the alumina industry.

An alternative approach to the design of larger-scale units for industrial processing is the use of systems that avoid coherent wave relationships. There are a number of advantages in using non-coherent ultrasound, not least the more even distribution of the ultrasound through the working fluid.

Prosonix adopted this approach following the company's early experience with multiple transducer systems that gave rise to difficulties such as transducers tuning into each other and mechanical resonance occurring between system components.

Micrometre-sized Particles

There have also been a number of developments in the preparation of micrometre-sized particles for drug inhalation. One such development is that of a vortex mixing system that provides high transient supersaturation and rapid vortex mixing to give fine, micrometre-sized crystals with very narrow size distributions.

Prosonix's SAX technology in conjunction with sononucleation has been shown to be very useful for the production of nano- and micrometre-sized particles formulated for drug inhalation as nanosuspensions. The technology allows the reproducible production of regular spherical particles that have unique nanotopologies with improved absorption characteristics.

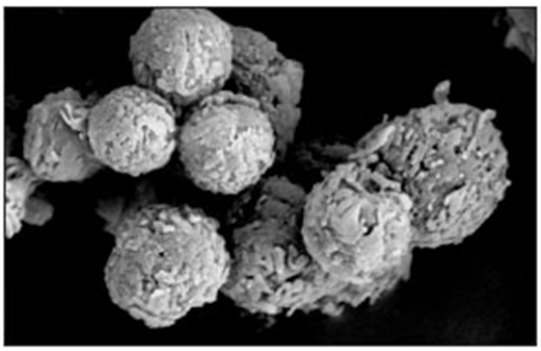
"The application of ultrasound to initiate and control crystallisation has been attracting more attention from potential users than has sonochemistry," says Ruecroft. "This is because the effects of ultrasound are more clearly defined from a processing perspective and more easily

demonstrated, and also because conventional Crystallisation processes can sometimes be difficult to nucleate and make particle size control difficult.

Ultrasound can be applied at a pre-defined level of supersaturation, and then continued until online monitoring indicates otherwise.

Ultrasound also provides control over the nucleation regime and allows the nucleation-crystal growth balance to be controlled in order to optimise product and particle properties. "Recent developments have enabled the application of ultrasound technologies at larger scale, and there is major potential for ultrasonic processing for crystallisation and in turn sonocrystallisation to be more extensively used in producing micrometre-sized particles for drug inhalation.

There may also be further applications in biotechnology, such as enhancing biocatalytic processes and in crystallisation of proteins, but these are areas that remain to be researched more fully," concludes Ruecroft.



SAX crystals of Budesonide (a synthetic steroid and potent anti-inflammatory).