Sono-Crystallization:

Publicity materials taken from Internet.

Constant frequency ultrasound is already producing extraordinary effects in chemistry. Here is also the place to apply MMM, sonic & ultrasonic, broad band, multifrequency systems in order to optimize state of the art technologies for orders of magnitudes. See how others are explaining effects of constant frequency ultrasound in Sonochemistry, and imagine how you would benefit if you repeat similar experience using MMM technology (just by replacing constant frequency transducers and generators with MMM components).

Feature

AEA TECHNOLOGY
THE INNOVATION BUSINESS

Ultrasound - The key to better crystals for the **Pharmaceutical** industry

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Introduction

Sonochemistry, the sum of the chemical effects of power ultrasound, has been recognised and

studied for many years. Some effects of power ultrasound in crystallization have been known for more than 30 years and are well summarised by Hem. However, it is only recently that it has been the subject of industrial scale interest.

The combination of the two technologies of sonoprocessing and crystallization is known as 'sonocrystallization' Previously this has only been available at Laboratory scale, where it is normally achieved either by immersing the reaction flask in an ultrasonic bath or by placing the tip of an ultrasonic probe directly into the reagents.

Investigative research has led to the development of the sonochemical reactor, or sonocrystallizer. This is capable of operation at laboratory, pilot plant and industrial scales typical of those for many pharmaceutical products, and it can be used in a range of configurations. This article takes a detailed look at the use of sonocrystallization and the benefits that it can bring to the pharmaceutical industry.

The benefits of ultrasound

Many of the useful effects of insonation are due to cavitation, the opening and subsequent implosion of gas or vapour bubbles with a typical diameter of 10-50 μm.(3) For a further discussion of cavitation and the effects of ultrasound, see Suslick.(4) The full potential for sonochemistry has been demonstrated by frequent discoveries in the laboratory, particularly in the fine chemicals sector. Examples range from subtle switching of reaction pathways (5) to dramatic improvements in rate or yield,6 to the ability to operate under milder conditions.(7) Ultrasound can be used beneficially in several key areas of crystallization, such as

- initiation of primary nucleation, narrowing the metastable zone width
- secondary nucleation
- crystal habit and perfection
- crystal size distribution
- reduced agglomeration
- improved product handling.

Sonocrystallization can be used to impart a variety of desirable characteristics to high-value products. By using ultrasound to initiate nucleation in a controlled manner, crystal growth occurs at a modest supersaturation level. The improvement in product size distribution and reduced agglomeration results in fewer inclusions of impurities and a number of advantages in mechanical handling.

The sonocrystallizer is particularly appropriate for pharmaceuticals which, because they often comprise high-molecular-weight organics, are among the hardest materials to crystallize well. They are often difficult to nucleate and exhibit extreme crystal habits. In addition, they tend to be produced batch-wise on a small scale with a tight specification on bulk-solid properties.

Potential applications and design strategies

A range of pharmaceutical materials has been studied and a series of potential applications and design strategies identified. Examples include

- insonation at modest supersaturation to initiate controlled nucleation
- a non-invasive alternative to the addition of seed crystals (seeding) in sterile environment
- continuous or prolonged insonation
- manipulation of crystal distribution by controlled nucleation.

Insonation to initiate controlled nucleation.

Without seeds, nucleation occurs when the metastable limit is exceeded. At such relatively high

supersaturation levels vast numbers of nuclei form and grow rapidly, resulting in the initially formed crystals having extreme crystal habits and low perfection. Insonation can initiate nucleation at lower supersaturations, as illustrated in Figure 1,(8) where initial growth is less rapid and the number of nuclei formed can be lower, giving larger, more perfect crystals with increased purity. This is demonstrated in Figure 2.

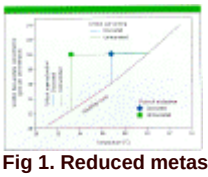

Fig 1. Reduced metastable zone width induced by insonation for sorbitol hexa-acetate in solution in methanol

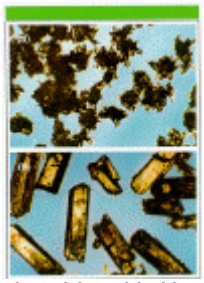

Fig 2. (a) Sorbitol hexa-acetate crystals generated by conventional cooling crystallization. (b) Sorbitol hexa-acetate crystals produced under the same conditions but with nucleation initiated by ultrasonic cavitation.

Non-invasive seeding in sterile environments.

Sterile crystallization processes can pose problems. Particle-free solutions support very high supersaturation levels and seeding is often required, but special care is required to prevent biological contamination. Insonation can be used to initiate nucleation, eliminating the need for both seed addition (which brings the danger of contamination) and seed preparation. The value of insonation as a reliable tool to initiate nucleation is illustrated in Figure 3.

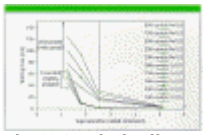

Fig 3. Statistically controlled reduction in waiting time for nucleation. Data for a pharmaceutical product driven out of solution by addition of an antisolvent (drowning out crystallization). (U/S = Ultrasound)

The figure shows a tight grouping of waiting times for nucleation even at quite modest supersaturation levels when ultrasound is used. By contrast, there is wide scatter amongst the waiting times for nucleation under comparable conditions without the use of ultrasound. In addition, nucleation by insonation allows greater control of the crystallization and the resulting product quality.(10),(11)

Continuous or prolonged insonation.

Prolonged insonation results in a small product with a wide crystal size distribution, which has a relatively high bulk density and surface area

per unit mass. The large surface area favours more complete de-supersaturation and hence improved yield. However, the penalty for these improvements is poor filtration performance.

Manipulation of the crystal size distribution.

Control of the level of supersaturation at the point of initial insonation to initiate nuclei, the power and duration of this insonation and the subsequent supersaturation generation profile allow the crystal size distribution to be manipulated. The mean product size can be shifted upwards or

downwards and the width broadened or narrowed. This is illustrated in Table I at scales of two litres and 1000 litres for a complex organometallic product. Additional bursts of insonation during the crystallization can be used to generate secondary nuclei, resulting in a polymodal size distribution. Insonation at the end of the crystallization can be used to de-agglomerate crystals in some cases. It is this kind of manipulation of crystallization conditions that is the basis of the patent claim11 of DuPont relating to improved crystal purity and handling characteristics of adipic acid, which has now been exploited in commercial scale manufacture.

Industrial scale insonation

Neither the ultrasonic bath nor the immersed probe tip used for laboratory insonation experiments lend themselves to larger scale applications. The transmitted intensity in a bath is low and although ultrasonic probes provide a far higher intensity, it is over a smaller and poorly defined volume. In addition, the probe tip, normally of titanium, suffers from pitting and erosion after several hours of use.

Process scale insonation therefore requires different equipment. The range of ultrasound, even in homogenous liquids, is limited, and attenuation is further increased by scattering in heterogeneous media, that is, when crystals are present. The cavitation bubbles themselves also act as scattering centres, so that the cavitation range is, to some extent, self-limiting. Good cavitation extends to a few, or at best a few tens of, centimetres, depending on the medium.

In practice, industrial scale insonation is best achieved by configuring the sonochemical reactor as a pumped loop or flow through device, which can insonate a portion of liquid intensely in a duct of defined diameter (Figure 4).

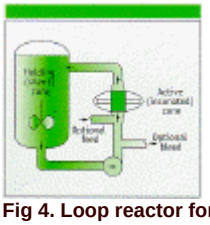

Fig 4. Loop reactor for industrial sonochemistry for use in batch, semi-batch or continuous flow operation

A pumped-loop crystallization plant therefore comprises two defined zones: an 'active zone; where insonation takes place, and a 'holding' or 'silent' zone. The effects of cavitational self-shielding in the active zone are minimized and can be further reduced by insonating the liquid from more than one direction. This configuration is easily adaptable for semi-batch or in-line processes, where, in the latter case, a cascade of feed and bleed loop reactors is optimal. Additional advantages of this pumped-loop configuration are

- good control of residence time in the active zone
- easy retrofit to conventional reactors
- modularity of the active region, making scale-up straightforward
- the ability to use the same type of active zone module at pilot scale, greatly reducing the uncertainty normally associated with the scale-up of crystallization processes.

At this point it is useful to focus on the design of the insonator itself. However, it is also important to consider the complete loop, with particular reference to the interaction between the insonated volume and the rest of the loop.

Insonator design

In practice, sonoprocessing equipment must be designed so that the maximum number of cavitation events occurs per unit time within the defined active volume. Some measure of the intensity of the cavitation in the insonated zone is required and this must be related to the number

of nuclei generated or to the chemical performance if undertaking sonochemistry.

The transducer

The most important element in any ultrasonic reactor is the transducer. This typically consists of a piezoelectric 'sandwich' with titanium end masses leading, often through a coupler, to the face radiating the ultrasound. The transducer has three important features:

- The piezoelectric elements are cylindrical, making the emitting face approximately circular.
- Practical equipment runs at a constant frequency, as the mechanically determined frequency of the transducer is fixed within the limits imposed by thermal expansion.
- The fragility of the piezoelectric sandwich under its pre-stressing bolt dictates a maximum amplitude in transducer operation.

Sonic intensity

The radiating face of the transducer creates a sonic intensity in the local liquid medium. This is defined in terms of the power transmitted per unit area perpendicular to the direction of propagation. This intensity must exceed a critical value to ensure cavitation of the medium and, therefore, successful insonation. The potential to generate nuclei, or the chemical reactivity, of the insonated zone will therefore depend on the

volume of the liquid across which the required intensity is achieved and the degree to which it is exceeded. This cavitation threshold intensity typically varies between 0.5 Wcm^{-2} and 1.5-2.0 Wcm^{-2}. For high viscosity liquids this figure can be tens of Wcm^{-2}

To translate sonocrystallizer design from laboratory to industrial scale, a relationship must be drawn between sonic intensity and the required cavitation per unit volume necessary to define nucleation performance at a specific supersaturation level.

Mechanical design of a sonocrystallizer module

The main challenges addressed in the mechanical design of sonoprocessing equipment concern the interaction of multiple transducers with each other and the rest of the hardware and the provision for maintenance of the equipment. A number of duct insonators, superficially suitable for sonoprocessing are commercially available. However, in practice these have been found to be most appropriate for application of lower power densities. The intensity levels required for sonocrystallization and sonochemistry are such that equipment must be designed empirically. This is mainly because the mathematics appropriate to low power ultrasound, for example, in diagnostic applications, become non-linear and no longer apply at higher power levels.

The sonoprocessing module, developed by AEA Technology (Didcot,UK(12)) consists of a cylindrical duct, of 13 cm diameter, insonated by three transducers and couplers situated radially about the mid-plane. The couplers terminate in a buffer fluid selected for its high cavitation threshold. In this way the couplers are not eroded and erosion in the reactor itself is minimized by properly selecting the distance between the coupler and the wall. In addition, an individual

transducer can be removed while the others are running. Process scale sonocrystallization equipment is shown in Figure 5.

Fig 5. Process scale sonochemical reactor

Conclusion

Scaling-up from laboratory to industrial operations has been addressed by means of an understanding of conventional crystallization, chemical reaction engineering, sound physical principles and ultrasonic engineering innovation. The use of a loop

configuration, comprising active and silent zones, has enabled the problems associated with the limited penetration of ultrasound to be overcome. The sonoprocessing units permit retrofit, modularity and residence time control and are well suited to batch, semi-batch or continuous processes. Insonation, therefore, is now commercially viable on an industrial scale and provides a practical route to improved crystals and all the attendant benefits that this brings to pharmaceutical manufacturing.

References

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Sonocrystallization

Frequently Asked Questions

- What is sonocrystallization?
- What are the benefits of sonocrystallization?
- How does it work?
- Will ultrasound affect the size and shape of my crystals?
- Can crystal purity be influenced by sonoprocessing?
- Can I use sonocrystallization to replace conventional seeding?
- Can sonocrystallization improve downstream processing?
- What sonocrystallization equipment can AEA Technology supply?
- Can sonoprocessing equipment be fitted to existing plant?
- Can I use sonoprocessing in a sterile environment?
- Do Sonocrystallizers™ conform to GMP and CIP standards?
- Are Sonocrystallizers™ safe in flameproof areas?
- Will retrofitting sonocrystallization bring regulatory problems?
- Can AEA Technology develop my process for me?
- What about sonochemistry?

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Q What is sonocrystallization?

Sonocrystallization is the use of power ultrasound to control the course of an industrial crystallization process. Crystallization is a complex process, the control of which can be difficult, and this is especially the case for organic compounds. Ultrasound is used principally to influence the nucleation process, thus giving the engineer or chemist a level of process control and product tailoring previously unobtainable.

AEA Technology has been active in the field of sonoprocessing since 1986, and now offers a complete package from product screening to supply of process plant.

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Q What are the benefits of sonocrystallization?

The use of ultrasound provides a non-invasive way of improving crystal properties and process controllability, chiefly by controlling the size distribution and habit of the crystals. The following benefits accrue:

- **Improved product and process consistency;**

- **Improved crystal purity;**
- **Improved product secondary physical properties;**
- **Shorter crystallization cycle times and less frequent rework;**
- **Shorter and more reliable downstream processes.**

Additionally, ultrasound can be used to replace seeding as a nucleator in difficult-to-nucleate systems.

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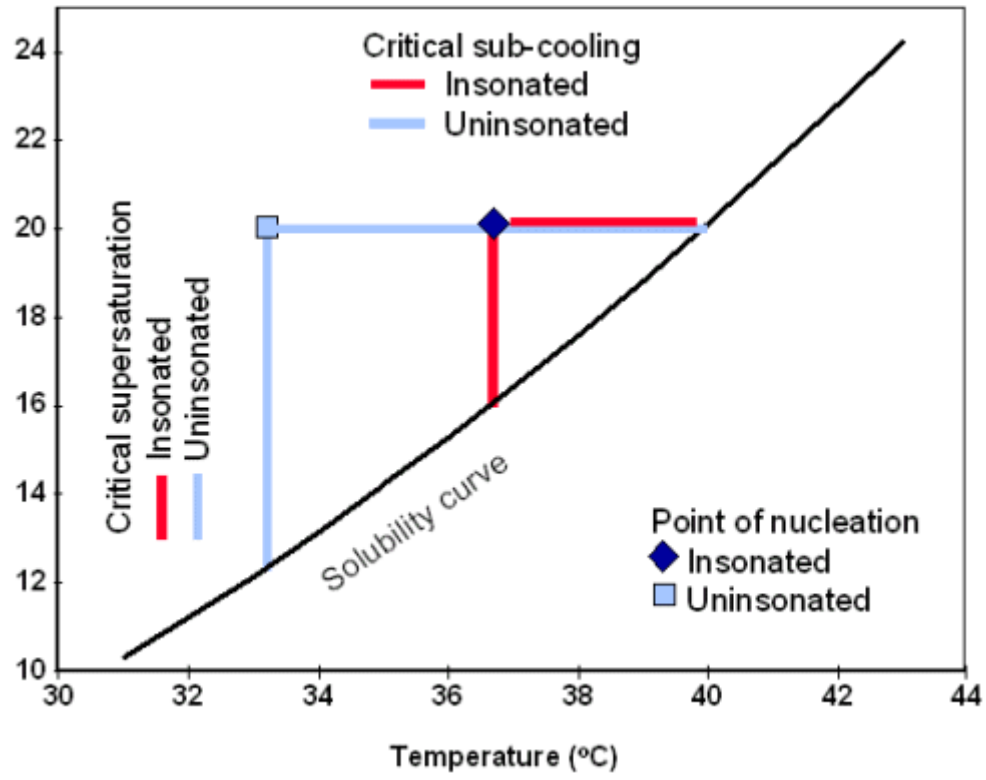
How does sonocrystallization work?

Power ultrasound creates *cavitation* in liquid media, each cavitation event comprising the opening of a small (a few tens of microns) gas or vapour void followed by its violent collapse. Cavitation events serve as nuclei for new crystals to form and grow. At high intensities ultrasound can be used instead of seed crystals, and/or to start nucleation at a lesser degree of supersaturation than would normally be the case.

This reduction of the metastable zone width, shown in the illustration, has many significant benefits to the control of crystal size and habit. These are described below under 'How will ultrasound affect the size and shape of my crystals?'



The effect is most beneficial with large organic molecules, where normally very high supersaturation levels may be required for primary nucleation.

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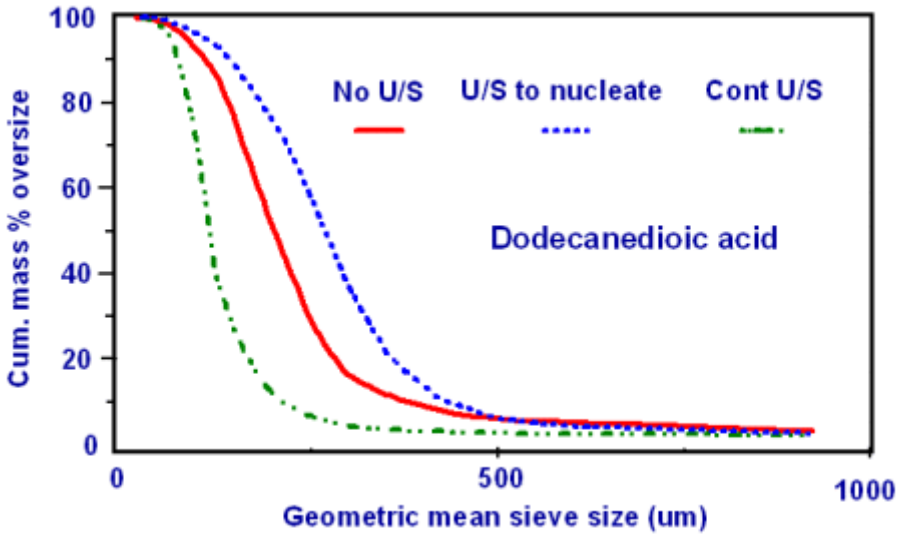
How will ultrasound affect the size and shape of my crystals?

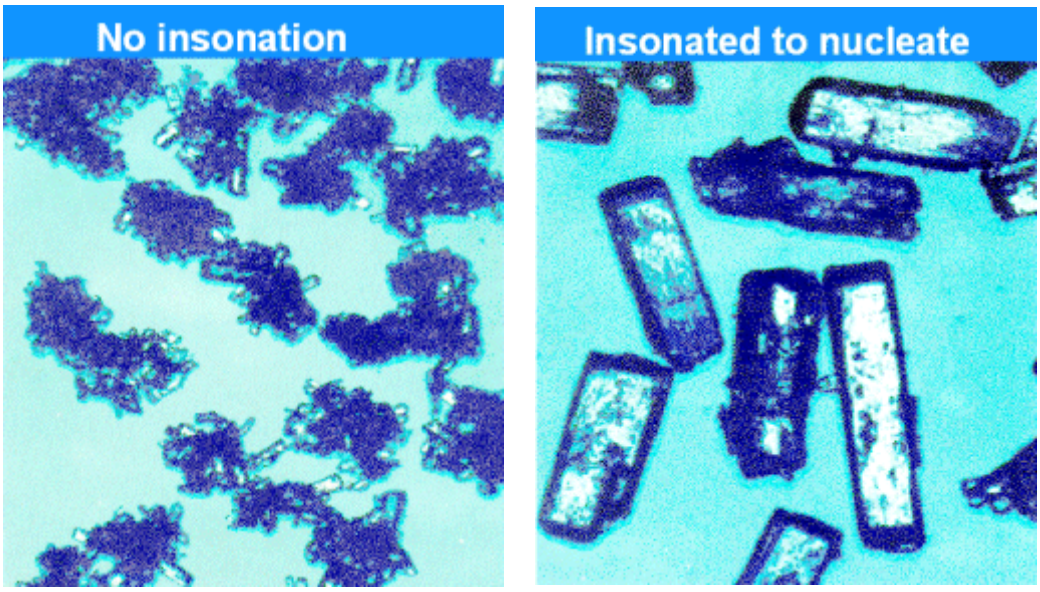
By varying the power and duration of insonation the crystal size distribution can be tailored to optimize downstream processing. The graph below shows how ultrasound was used to control the crystal size distribution of dodecanedioic acid. The solid line shows the base case where no ultrasound was used; the dashed line shows where ultrasound was used to nucleate the solution; and the chain linked line shows where ultrasound was used continuously throughout the crystallization. Insonation to nucleate shows a marked increase in the mean crystal size, whereas continuous insonation has dramatically reduced the mean size.



Crystal size, habit and yield are a function of the growth rate and the supersaturation history. Low supersaturation favours modest rates of nucleation and relatively slow growth at similar rates over the crystal surfaces, leading to a crystal with a compact habit which flows well. In the absence of further nucleation, and with controlled maintenance of supersaturation, these crystals will grow to a large uniform size which is easy to process downstream.

At high supersaturation, on the other hand, both nucleation and growth rates are high, favouring a low mean size and in some cases extreme habits (needly or platy).

The photographs show the dramatic affect of ultrasound on the habit and perfection of sorbitol hexaacetate crystals.



There may also be scope to use ultrasound to generate bursts of secondary nuclei, and so manipulate the width of the size distribution and the product properties.

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Q Can crystal purity be influenced by sonoprocessing?

By controlling the supersaturation level at the point of nucleation and the subsequent growth rate there is less tendency to produce multiple or agglomerated crystals which contain occlusions of the mother liquor. This significantly increases the degree of purification achievable in the crystallization step. Ultrasound can also be used to deagglomerate.

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Q Can sonocrystallization replace conventional seeding?

Yes. A sonocrystallization device can be used for non-invasive seeding of hard-to-nucleate systems, replacing the conventional cycle of seed making, milling and hygienic seed introduction.

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Q Can sonocrystallization improve downstream processing?

Improving or debottlenecking downstream processes is one of the major drivers for employing sonocrystallization. Manipulating the size and habit of the product crystals can be made to achieve the following benefits:

- More rapid filtration: crystals of a more uniform size and compact habit can be filtered much more rapidly, with filter cycle times several times less than for 'conventional' crystals.
- Similarly, better access to the intercrystal voids greatly improves the speed of both washing and drying, as well as the decontamination level achievable.
- The milling of crystals is a messy process which risks mutual contamination of product and environment. By sonically tailoring crystal size distribution, the milling step may be eliminated altogether.
- Powder filling operations can be made much more reliable and trouble-free because sonically nucleated crystals usually flow much better than those produced conventionally. The bulk density of the product may also be improved; doubling of bulk density is not unknown.

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Q What sonocrystallization equipment can AEA Technology supply?

We supply laboratory probe insonators, specialist insonators for customers' plant and our patented Sonocrystallizer ™ , available in modular increments of 1.5 kW. The Sonocrystallizer ™ can be provided in a number of configurations to suit the duty, from a batch 'pot' to a through-flow duct.

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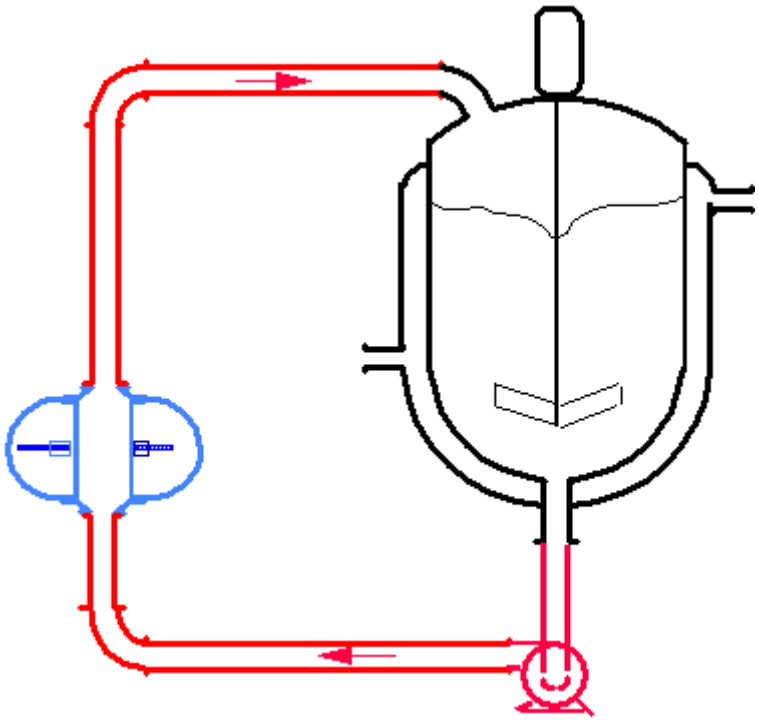
Q Can sonoprocessing equipment be fitted to existing plant?

Yes. The schematic shows an example of a pumped loop installation around an existing batch crystallizer. This configuration is favoured by ease of installation and the effective range of the ultrasound in solution. Other, pumpless, configurations are possible: liquid may be transferred by pressure or vacuum or circulated using a top-mounted impeller.



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Can I use sonocrystallization in a sterile environment?

Yes. Sonocrystallization is an ideal technique for sterile processing. Sterile solutions are very clean and so difficult to nucleate. Traditional methods of producing seed crystals can compromise sterility, so non-invasive seeding using insonation overcomes this. Unlike competing ultrasonic technologies, our insonator design meets the standards for the low levels of particle shedding essential for injectable drugs.

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Do Sonocrystallizers ™ conform to GMP and CIP standards?

Yes. The sonocrystallizer™ is constructed with an unobstructed crevice-free 13 cm duct which can be polished to the customer's specification, hygienic flanges and polished stainless steel covers. AEA Technology's patented design provides for the duct to be subjected to steam cleaning temperatures indefinitely without detriment to ultrasonic performance.

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Are Sonocrystallizers™ safe in flameproof areas?

Yes. The ultrasonic transducers which drive the sonocrystallizer can be supplied with enclosures certified to EN 50 014/50 018.

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Will retrofitting sonocrystallization bring regulatory problems?

Most companies find that there are no regulatory problems with retrofitting sonocrystallization to registered processes, largely because crystal morphology is not usually changed, only habit. Similarly, the replacement of an invasive seeding technique with a non-invasive one is unlikely to present difficulties.

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Can AEA Technology develop my process for me?

Yes; AEA Technology offers a complete service based around standard proven hardware but tailored to your needs and opportunities. A typical development cycle for a typical batch process of up to 5,000 litre scale would include:

- **Small scale scoping trials, often of more than one compound or process;**
- **Small-scale trials on one or more promising or most urgent cases, to find optimal crystallization and ultrasonic parameters;**

- **Small pilot trials to provide material for test, replicate the optimal strategy and obtain scale-up parameters;**
- **Supply of fully-engineered Sonocrystallizer ™ plant for integration into customer's product line.**

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What about sonochemistry?

AEA Technology's unique processing equipment can be equally well applied to enhancing chemical reactions, especially in the fine chemicals and pharmaceuticals intermediates sectors. Power ultrasound is especially valuable in two-phase systems, where it can be used (for instance) to give rapid predictable initiation and control of organometallic reactions.

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New Reactor to Improve Crystal Production in Pharmaceutical and Fine Chemical Industries

The AEA Technology Sonocrystallizer™ is a new reactor which helps the pharmaceutical, fine chemicals, and bio-technical products industries produce purer products through the production of better crystals. The Sonocrystallizerä was developed and is now supplied by AEA Technology, the international science and engineering services business.

Sonocrystallization is a non-invasive method of using ultrasound to control the point of nucleation and the number of nuclei formed. Combining technologies of sonochemistry and crystallization sonocrystallization provides "a route to better crystals".

Benefits of sonocrystallization can include controlled initiation of nucleation, enhanced yield, improved crystal habit, improved filtration characteristics, improved product properties including, handling, bulk density and appearance, reduced agglomeration crystals with fewer imperfections and increased process reproducibility.

Sonocrystallization can be used to give a variety of desirable characteristics to high-value products. By using ultrasound to induce nucleation, crystal growth can be achieved in a more controlled manner at a lower supersaturation. Improved product size distribution and reduced agglomeration lead to fewer inclusions of impurities and a number of advantages in secondary processing and

formulation.

This technology is particularly appropriate for pharmaceuticals and fine chemicals which are amongst the hardest materials to crystallize well because they tend to be high molecular weight organics. These molecules can be difficult to nucleate and often exhibit extreme crystal habits.

To support sales of the Sonocrystallizer™ AEA Technology has set up a team which offers a complete service of product screening, process development, scale-up and process equipment supply. A typical laboratory screening programme for a single compound can cost a little as £3,500 and can be performed on the customer's site if necessary.

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'The AEA Technology Pressure Tube Sonoreactor'

AEA Technology have developed a high pressure flow cell for sonocrystallization and sonochemical applications.

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