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Sonocrystallization: For Better Pharmaceutical Crystals

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In recent years crystallization using ultrasound has received greater impetus in the pharmaceutical field. It provides an effective, versatile and non-invasive way of improving crystal properties. This technique can be used to crystallize complex organic molecules (most of them are drugs) that are difficult to crystallize by conventional techniques. Sonocrystallization can also eliminate the need to add seed crystals, which can be more advantageous in sterile operations. A combination of ultrasound and vortex mixing can be used to form micro particles, ideal for cost effective production of inhaled therapeutic agents. This article takes a detailed look at the sonocrystallization and the benefits that it can bring to the pharmaceutical industry.

Key Words: Sonocrystallization, Ultrasound, Pharmaceuticals.

INTRODUCTION

Crystallization is a process commonly used for the isolation of active drug substances from the final stage of a synthesis. It is used for product purification and consolidation as a convenient solid form. If crystallization is carried out efficiently will consistently yield a product with specified crystal morphology, size distribution and habit (shape). In practice however the ideal specifications often cannot be achieved and pharmaceutical substances can be among the most difficult substances to crystallize efficiently. Large and complex organic molecules are often difficult to crystallize, because of the conformational limitations on the orientation of the molecules with in the unit cell of the crystal, which are expressed as large energy barriers that impede nucleation and growth. So for nucleation and growth, high super saturation driving forces are often required. Crystallization under these conditions often produces a mass of small crystals with unfavourable needle like habits, by virtue of the fact that nucleation and

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crystal growth occur in a very rapid and uncontrolled way. Morphological problems may also occur, because the use of extreme conditions to overcome the high activation energy barriers and this may leads to formation of polymorphs with different configurations.

For controlling all the above problems ultrasound is applied to the crystallization process. This is called sonocrystallization. Applying ultrasound to crystallizing systems offers a significant potential for modifying[1] and improving products in terms of their crystal habit, size distribution, purity and possibly their morphological form as well. For example crystallization of β-form of PABA[2]. The most important mechanism by which ultrasonic irradiation or insonation, can influence crystallization is ultrasonic cavitation. Cavitation is particularly effective for inducing nucleation and dramatic improvements in reproducibility *via* sononucleation. Using ultrasound to generate nuclei in a relatively reproducible way offers a well-defined starting point for the crystallization process and allows the focus to be on controlling the crystal growth for the remainder of the residence time in the crystallizer. This approach has been used successfully to manipulate crystal size distribution and hence, to modify solid / liquid separation behaviour, washing and product purity, product bulk density and powder flow characteristics. Sononucleation can also eliminate the need to add seed crystals, which can be advantageous in contained sterile operations. This technique is particularly useful in pharmaceuticals. Ultrasound can also be used to carry out reactions[3] at milder conditions[4] with improvement in yield[5] and minimizing the production of waste[6].

Benefits of sonocrystallization

The use of ultrasound for crystallization provides the following benefits: (i) Improved product and process consistency, (ii) Improved crystal purity, (iii) Improved product secondary physical properties, (iv) Shorter crystallization cycle times and less frequent work, (v) A non-invasive alternative to the addition of seed crystals in sterile environment and (vi) Shorter and more reliable drown stream processes.

Mechanisams involved in sonocrystallization

Ultrasonic cavitation

The most important effect of ultrasound in crystallizing systems is the cavitation, the opening and subsequent implosion of gas or vapour bubbles with a typical diameter of 10-15 μm. The primary effect of ultrasound on a continuum fluid is to impose an oscillatry pressure on it. At low intensity this pressure wave will induce motion and mixing with in the fluid, this process is known as acoustic streaming. At higher intensities, the local pressure in the expansion phase of the cycle falls below the vapour pressure of the fluid, causing minute bubbles or cavities to grow. A further

increase generates negative transient pressures with in the fluid, enhancing bubble growth and producing new cavities by the tensioning effect on the fluid[7]. Ultrasonic or accoustic cavitation[8] in continuous liquid phase can be analyzed mathematically using bubble dynamics.

The voids or cavities can be stable or transient. Stable cavities exists overtime scales of a number of sonic pressure cycles, while transient ones exists for a single cycle. They may enlarge to many times their original size during expansion and collapse violently during compression. Experimentally cavitation is observed to occur above a definite threshold in ultrasonic intensities and cavitation can be easily detected by the pitting of a coupon (*i.e.* small test plate) of metal foil in the liquid.

Cavitation and nucleation

Nucleation occurs at high super saturation levels, without seeds when metastable limit is exceeded. Under such high levels, reversible clustering occurs. Beyond the clustering stage, a point is reached at which the cluster is able to template further accretion of material into the solid matrix and the nucleus can be considered to have formed. At such high super saturation levels vast number of nuclei form and grow rapidly, resulting in the formation of crystals having extreme crystal habits, low perfection and poor reproducibility.

Insonation or applying ultrasound to the crystallization process not only induces nucleation but also increases reproducibility. A short burst of ultrasound at intensity or energy density, above the cavitational threshold, will induce nucleation of crystallization at significantly lower saturation levels than those required where no ultrasound is applied[9]. For a cooling crystallization sorbitol hexacetate from methanol[10], a short burst of ultrasound reduced the metastable zone width from 6.8 to 3.5 K and yielded a product with better quality in terms of purity, size and habit[11] and a lesser propensity for the solute[12,13], to crash out with the extensive formation of fines.

Another important effect of ultrasound on nucleation is shortening the induction time between the establishment of supersaturation and the onset of nucleation and crystallization. Extended induction times represent the relaxation times required for the large and complex molecular units of the solutes (drugs) to organize themselves in to the geometric conformations that are favourable to crystal formation. The effect of ultrasound on induction times has been demonstrated for the crystallization of a drug substance from acetone-water, with supersaturation induced by the addition of ethyl acetate as an anti solvent[11], nucleation appeared virtually, instantaneously at high supersaturation levels, with and without ultrasound. This is the situation of crash crystallization, where dissolved material is forced out of solution very rapidly, and the crystals produced are usually of poor and

variable quality because of the extreme conditions. As the supersaturation levels are reduced, the induction time gradually increased and shows an increase in variability that arises from the stochastic nature of nucleation. With ultrasound, there are not only marked reductions in the induction times, but also much improved reproducibility.

Modification and control of crystal size and shape

Control of crystal size

Controlled ultrasound (by varying the power and duration of insonation) at the various stages of crystallization may be used to modify and tailor product properties to meet requirements and also to optimize downstream processing. A more extensive or continuous application of ultrasound will induce continuing nucleation and result in small and less perfect crystals. Insonation to induce primary nucleation will produce large and well-formed crystals with minimum fines. Ultrasound may also be applied in the final stages to break up agglomerates. This kind of manipulation of crystallization conditions are the basis of improved crystal purity and handling characterstics of adipic acid[13].

The specification of crystal size is usually determined by the physical properties needed for the product in either further processing or end use where the later involves dissolution. For example an orally ingested pharmaceutical active, crystal size will determine how quickly such dissolution occurs and of bioavailability.

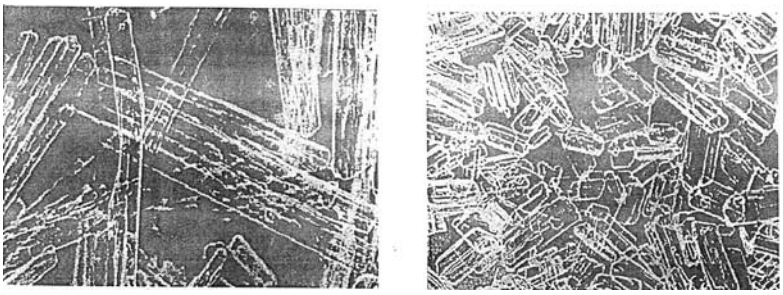
Control of crystal habit (shape)

Control of crystal shape or habit is a requirement for size, crystals with extreme habits, particularly needles are difficult to filter and to handle on account of their susceptibility to fracture. On the other hand, a needle will have a higher surface to volume ratio than an equivalent acicular form and will therefore dissolve more rapidly.

Crystal growth does not occur isotropically and the faces that are exhibited by a crystal are those, which grow more slowly. Extreme crystal habits form when the growth rate at a particular crystal face (or faces) occurs significantly more rapidly than the growth at other faces. These anisotropic effects are most marked when the driving force for growth *i.e.* the supersaturation is high. Crystals produced with ultrasound usually exhibit moderate and regular habits because the process operates under conditions of low or moderate supersaturation.

The shape of a drug substance without ultradound or seeding and with ultrasound is shown in Fig. 1. Without ultrasound or seeding, the product crystals were in the form of needles that are formed by rapid growth in the longitudinal direction under high super saturation. A more regular crystal

shape (platelets) was obtained where a short burst of ultrasound was applied to initiate nucleation at a more moderate supersaturation level.



Needles (without Ultrasound) Platelets (with Ultrasound)

Fig. 1

Manipulating the size and habit of the product crystals can be made to achieve the following benefits: (a) 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 (b) Similarly, better access to the inter crystal voids greatly improved the speed of washing and drying, as well as the decontamination level achievable (c) 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 and (d) 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.

Sonocrystallization and vortex mixing

For the production of micro-scale crystalline particles, a unit-combining vortex mixing with ultrasonic cavitation was recently developed. 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, over time scales of between 10 milli seconds and 3 h. Such rapid and efficient mixing can be used in precipitation, reaction and anti solvent crystallization, to bring about high product yields. The combination of high transient supersaturation produced in this way with ultrasonic nucleation can produce fine crystalline solids with a very narrow size distribution. These properties are ideal for pharmaceuticals which are required to be administered by inhalation.

Conclusion

Crystallization using ultrasound offers a non-invasive, effective and versatile means of controlling batch crystallization processes for the purification and isolation of pharmaceutically active substances and other

organic compounds. Sonocrystallization is particularly appropriate for pharmaceuticals which, because they often comprise high molecular weight organics and are the hardest materials to crystallize well. Controlled ultrasound at the various stages of crystallization may be used to modify and tailor the product properties (crystal size and shape) to meet the requirements and also to optimize the down stream processing. Conventional methods for crystallization of many organic compounds require high supersaturation levels; this leads to formation of poor quality crystals in terms of morphology, size and shape. Ultrasound often enables such systems to be nucleated at much lower supersaturation levels and thus provides some means of control over the final product quality.

Sonocrystallization is an ideal technique for sterile processing *i.e.*, injectable drugs. Sterile solutions are very clean and so very deifficult to nucleate. Traditional methods of producing seed crystals can compromise sterility, so insonation can be used to initiate nucleation, eliminating the need for both seed addition (which brings the danger of contamination) and seed preparation. A combination of ultrasound and vortex mixing can be used to form micro (< 5 μm) crystalline particles, ideal and administered by inhalation. Therefore sonocrystallization provides a non-invasive route to improve the crystal properties and all the attendant benefits that brings to pharmaceutical manufacturing.

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