INDUSTRIAL SONOMECHANICS™

SONOFRAGMENTATION OF EXCIPIENT CRYSTALS

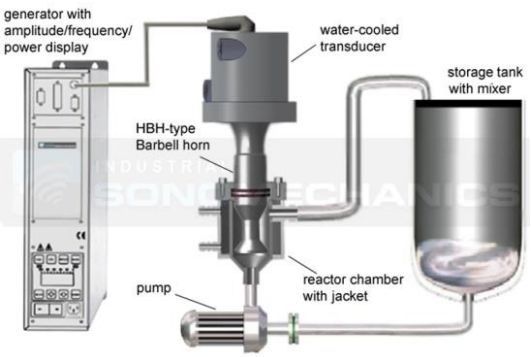
BACKGROUND

Excipients are additives included in drug formulations to enhance their stability, delivery, and manufacturability. There are many cases when excipients incorporated in, for example, inhalation therapy products need to have predetermined particle diameters, narrowly distributed around several microns, in order to positively affect pharmaceutical properties of the drugs. When prepared by conventional methods, however, excipient particles have much larger diameters (several tens or even hundreds of microns) as well as wide and inconsistent particle size distributions. It is, therefore, important to have the methodology and equipment allowing the manufacture of excipient particles with a specified median diameter and a consistent, narrow particle size distribution.

The method most successfully employed for this purpose involves the production of nanosized excipient particles in the form of a slurry and using these particles as seeds for controlled crystallization, for example, by a solvent/anti-solvent technique. This method results in the formation of final excipient particles with target median diameters, narrow size distributions and smooth surfaces, undamaged by milling. The mean diameter of the seed particles most commonly needs to be about 400 nanometers. The production of such small excipient particles is quite challenging and requires extensive nano-milling.

PRODUCTION WITH HIGH-AMPLITUDE ULTRASOUND

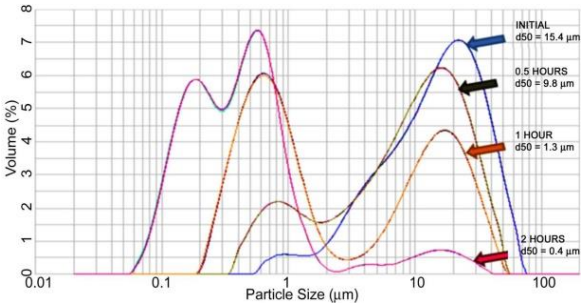
Industrial Sonomechanics, LLC (ISM), offers bench and industrial-scale high-power ultrasonic processors for the production of excipient nanocrystals.ISM's processors are based on patented Barbell Horn Ultrasonic Technology (BHUT), which, as explained below, makes it possible to directly implement laboratory accomplishments in a production environment, guaranteeing reproducible and predictable results at any scale. The process of ultrasonic top-down sonofragmentation (nanocrystallization with ultrasound) requires extremely high ultrasonic amplitudes to be applied to particle suspensions, producing extreme shear forces. The shear forces are the result of intense ultrasonic cavitation, which creates violently and asymmetrically imploding vacuum bubbles and causes micro-jets that break the original crystals down to nanocrystals.



Why ISM's Ultrasonic Technology?

Conventional ultrasonic liquid processing systems comprise acoustic horns that reduce their diameters in the output direction and can only provide high ultrasonic amplitudes when their output tips are small. Process scale-up requires switching to horns with larger output tip diameters, able to output the ultrasonic energy into greater volumes of processed liquids while still maintaining high amplitudes. If, however, the output tip diameter of a conventional horn is increased, its maximum vibration amplitude becomes significantly lower and insufficient for most processes. The use of conventional high-amplitude ultrasonic processors is, therefore, limited to laboratory investigations that cannot be scaled-up without sacrificing the quality of the final product. ISM has successfully overcome this limitation by developing BHUT, which permits constructing bench and industrial-scale ultrasonic processors able to operate at extremely high amplitudes. The processors are directly scalable and can be used in the commercial production of excipient nanocrystals for the pharmaceutical industry. Our equipment is compact and relatively low-cost, needs little technical support,

includes very few wetted parts, generally requires no special pre-treatment of precursors, and is potentially self-sterilizing due to antibacterial properties of high-intensity ultrasound.



Sonofragmentation of Excipient Crystals

In order to illustrate the ability of BHUT-based processors to produce excipient nanocrystals, a sonofragmentation experiment was conducted using our bench-scale ultrasonic liquid processor, BSP-1200. The processor was configured in the flow-through arrangement, as shown in the above schematic.

The initial excipient crystals with the mean particle size diameter (d50) of 15.4 micrometers were suspended in 1 L of an organic solvent at the concentration of 5 % by mass. No surfactants or any other agents were used. The suspension was stirred in the storage tank as it recirculated through the reactor chamber at the rate of 4 L/min for 2 hours. The reactor chamber was equipped with an HBH-type Barbell horn having the diameter of 32 mm and vibrating at the amplitude of 90 microns. The temperature of the suspension was maintained at 25 C throughout the procedure by running chilled water through the temperature control jacket on the reactor chamber.

The results presented above show that after 2 hours of ultrasonic exposure, the required mean particle size of about 0.4 micrometers (400 nanometers) was obtained. For commercial-scale production, the procedure can be transferred to the ISP-3000 industrial ultrasonic processor, which would allow productivity to increase by a factor of 5.

Ultrasound is a simple and effective technique for producing excipient nanocrystals. With the use of BHUT, the process is directly scalable, making it possible to implement laboratory accomplishments in an industrial production environment.

The data presented above was collected in collaboration with Allied Innovative Systems, LLC (ALLIS).

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