NANOCRYSTALLIZATION FOR IMPROVED DRUG DELIVERY

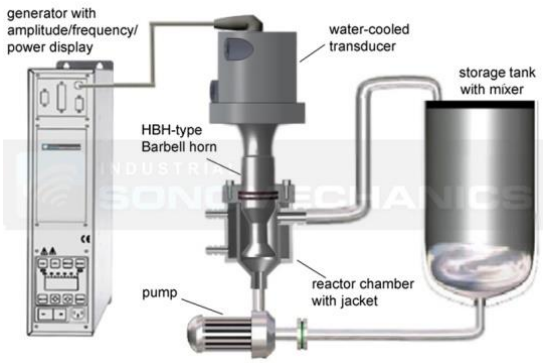
BACKGROUND

Up to 40% of currently available drug substances and up to 70% of those under investigation by the pharmaceutical industry exhibit poor water solubility, leading to reduced bioavailability and increased the potential for adverse effects. Furthermore, fears of problems with future launch preclude many otherwise promising water-insoluble compounds from being taken beyond early R&D stages. Particle size reduction down to the nano-scale (nanocrystallization) has been shown to increase the bioavailability and reduce the required dose frequency, thereby improving patient compliance and decreasing drug side-effects.

PRODUCTION WITH HIGH-AMPLITUDE ULTRASOUND

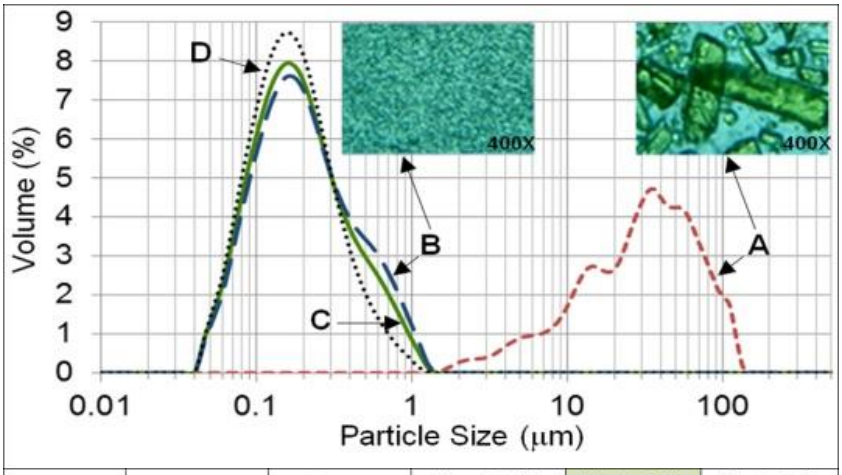
Industrial Sonomechanics, LLC (ISM), offers bench and industrial-scale high-power ultrasonic processors for the production of nano-sized drug crystals. This procedure may be called op-down ultrasonic nanocrystallization, nanomilling, wet milling, particle size reduction or nano-sizing, among other names. 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 nanocrystallization 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 up the original drug particles down to the nano-size range. However, prior to the introduction of BHUT, none of the existing ultrasonic liquid processors could generate the required high amplitudes on the industrial scale.



Why ISM's Ultrasonic Technology?

Conventional high-power ultrasonic technology inherently forces all processes to run either at a small scale and high amplitude or a large scale and low amplitude, which is why commercial implementation of high-power ultrasound has been limited to processes for which low amplitudes are sufficient (cleaning, simple deagglomeration, mixing, macro-emulsification, etc.) ISM has successfully overcome this limitation by developing BHUT, which permits constructing 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 high-quality drug 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.



Sample	Processing	Rate (ml/min)	d(vol;0.1) (μm)	d(vol;0.5) (μm)	d(vol;0.9) (μm)
A	NONE	NA	8.090	33.29	82.71
B	CH	0.84	0.088	0.203	0.625
C	FBH	4.2	0.085	0.191	0.554
D	C, filtered	4.2	0.083	0.176	0.421

Examples of Produced Drug Nanocrystals

The experiments were conducted using ISM's 1200 W bench-scale flow-through ultrasonic processor, BSP-1200, equipped with a piezoelectric transducer, flow-through reactor chamber and either a Conventional Horn (CH) with the output tip diameter of 15.7 mm or a Full-wave Barbell Horn (FBH) with the output tip diameter of 35 mm. A 100 ml beaker, used in conjunction with the CH, was placed into an ice bath. The FBH was used with a water-cooled jacketed 500 ml beaker. Both horns operated at the ultrasonic amplitude of 100 μ_{pp}. Nifedipine was chosen as the model drug for this study because it has very poor water solubility and is composed of hard, difficult to fracture crystals.

Nifedipine powder was stirred into an aqueous solution of HPMC surfactant. The initial mixture (sample **A**) was split into 50 ml and 250 ml volumes, which were processed for 60 min using the CH (sample **B**) and the FBH (sample **C**), resulting in processing rates of 0.84 ml/min and 4.2 ml/min, respectively. A portion of sample **C** was passed through a 450 nm filter (sample **D**). The data demonstrates that high-intensity ultrasound exposure yields very small nifedipine nanocrystals, with d(vol;0.5)<200 nm. FBH permitted processing 5 times more material per unit of time than CH, demonstrating the direct scalability of the BHUT-based nanocrystallization process. No pre-processing of precursor materials was required. The obtained nanosuspension was able to pass through the 450 nm filter almost unperturbed, which is essential for the post-processing effectiveness, resulting in efficient decontamination and sterilization.

Ultrasound is a simple and effective technique for producing drug 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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