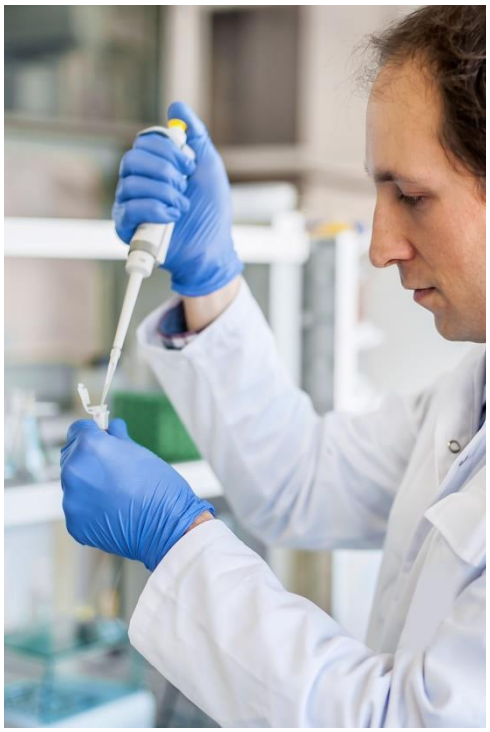
Ultrasonic Nanocrystallization of Nifedipine for Improved Drug Delivery

INDUSTRIAL SONOMECHANICS™

Allied Innovative Systems

Many biologically active compounds (e.g., drugs and nutraceuticals) exhibit poor water solubility, which complicates their delivery to the blood stream and reduces the associated bioavailability. Top-down nanocrystallization (particle size reduction to the nanometer range) of these substances increases their aqueous dissolution rate and solubility, which results in improved bioavailability, accelerated onset of action, and decreased potential of harmful side-effects.

Allied Innovative Systems (ALLIS) partnered with Industrial Sonomechanics (ISM) in order to determine the effectiveness of the high-amplitude ultrasonic nanocrystallization process and the feasibility of applying it on a production scale by using ISM's Barbell Horn® Ultrasonic Technology (BHUT).



Problem

- Drugs with poor water solubility exhibit low bioavailability and present challenges in delivery.
- Wet Media Milling and High Pressure Homogenization, as particle reduction methods, are scalable but have many disadvantages (high cost, complexity, large footprint, extensive maintenance).
- Ultrasonic nanocrystallization is potentially attractive, but scalability has previously been a problem.

Goal

- To evaluate the effectiveness and scalability of top-down ultrasonic nanocrystallization with ISM technology and equipment.
- To determine post-scale-up productivity gain factors and confirm that the process can be directly transferred from the laboratory to the production environment.

Results

- ISM ultrasonic processors are very simple to operate and effective for the production of high-quality drug nanocrystals.
- High ultrasonic amplitudes are necessary for efficient nanocrystallization.
- With BHUT, the process is directly scalable and can be implemented in the industrial production environment.

> *Our company has extensive experience with the preparation and characterization of colloidal systems, including nanocrystal suspensions, nanoemulsions, liposomes, and protein particles. During this nanocrystallization study, we concluded that ISM ultrasonic processors can be successfully employed for the preparation and scaled-up production of very small-sized (<200 nm) nanocrystals of one of the most difficult active pharmaceutical ingredients to fracture, nifedipine.*
>
> ***Simon Bystryak, Ph.D.***
> *President, Allied Innovative Systems (ALLIS)*

(646) 580-4676
contact@sonomechanics.com

BACKGROUND AND SUMMARY

Allied Innovative Systems (ALLIS) engaged in this project to evaluate the effectiveness and scalability of Industrial Sonomechanics (ISM) high-intensity ultrasonic equipment and technology for the process of top-down nanocrystallization of active pharmaceutical ingredients (APIs), using nifedipine as an example.

ABOUT Allied Innovative Systems

ALLIS has extensive experience in developing and implementing new biomedical technologies.

Dr. Simon Bystryak, the company's President, has developed, validated and marketed many new technologies in the field of life sciences. The company works with the government as well as with private organizations such as ISM.

ALLIS has assembled a group of highly skilled scientists and engineers with expertise in key scientific disciplines that are vital to the success of its development efforts. These disciplines include biochemistry and organic chemistry, biomedical engineering and optics, medicine, computational methods, software development, developing new technologies and products, and performing clinical validation reviews.

Some of ALLIS' target customers include research labs, university labs and hospitals.

Company headquarters: Chatham, NJ

Industry: Pharma, biotechnology, healthcare, clinical diagnostics.

Website: http://www.allisystems.com/

Significance of the study

Poor water solubility of many APIs is a major hurdle for pharmaceutical companies because it lowers drug bioavailability and results in formulation and delivery challenges. The most promising solution is to fracture the drug particles into nanocrystals.

Two technologies are commonly used commercially for drug nanocrystallization - Wet Media Milling (WMM) and High Pressure Homogenization (HPH). Both techniques have significant drawbacks. WMM suffers from long milling times, scale-up limitations, product contamination by the media, large equipment footprint, drug adhesion to the media, and substantial support requirements (cleaning, set up, extracting the media, etc.). HPH cannot consistently produce sufficient particle size reduction, requires extensive pre-milling of the original crystals, and is very complex in terms of cleaning and servicing (high maintenance costs).

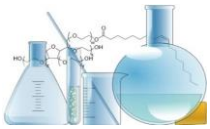
In this study, BHUT-based high-amplitude ultrasonic nanocrystallization has shown to be an effective alternative to WMM and HPH, providing high-quality results while being free from most of the abovementioned limitations.

The efficiency of ultrasonic nanocrystallization was tested at the laboratory and pilot scales in order to evaluate the scalability of the process with BHUT and to determine the productivity gain factor.

Why did we choose nifedipine?

Nifedipine was chosen for this study because it has very poor water solubility and is composed of hard, difficult to fracture crystals. The reduction of the crystal sizes to below 200 nm is known to greatly enhance this drug's efficacy, particularly in topical formulations widely used in the treatment of Raynaud phenomenon, chilblains, keloids, burn scars, calcinosis cutis, burn wounds, skin grafting, and chronic anal fissures.

MATERIALS & METHODS



Materials and analysis equipment

Nifedipine and Methocel 15 (hydroxy-propyl-methylcellulose, HPMC) were obtained from Sigma-Aldrich (St. Louis, MO) and DuPont (Wilmington, DE), respectively. Particle size distributions (PSD) in nifedipine suspensions were measured by laser diffraction using MasterSizer 2000 (Malvern Instruments, Worcestershire, UK). The metal content analysis was carried out by the FDA-recommended ICP-MS method for the determination of contaminants in pharmaceutical preparations, using Agilent 7500 (Agilent Technologies, Santa Clara, CA, USA).

Ultrasonic processors and experimental setup

The experiments were conducted using two ultrasonic liquid processors obtained from Industrial Sonomechanics (New York, NY):

- LSP-500 laboratory-scale processor (Fig. 1a) equipped with a 15.7 mm tip diameter CH-type horn.
- BSP-1200 pilot-scale processor (Fig. 1c) equipped with a 35 mm tip diameter FBH-type horn.

Both processors were configured in the batch mode. The LSP-500 to BSP-1200 productivity scale-up factor (SF) was expected to be equal to the ratio of high-amplitude areas under the tips of the incorporated horns:

- $SF = (D_{fbh}/D_{ch})^2 = 5$, where D_{fbh} and D_{ch} are the output tip diameters of the FBH-type and CH-type horns, respectively.

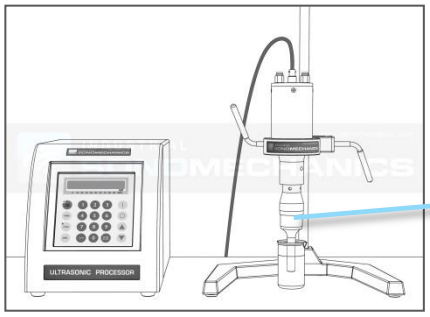


Figure 1a. LSP-500 configured in the batch mode using a Conventional Horn (CH).

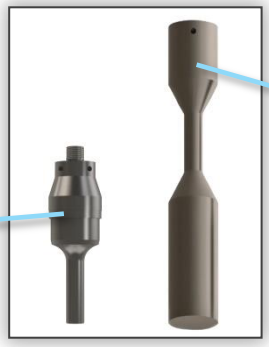


Figure 1b. Conventional Horn (left) and Full-wave Barbell Horn (right).

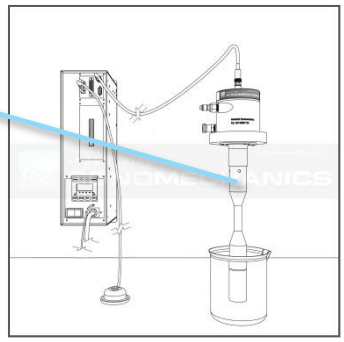


Figure 1c. BSP-1200 configured in the batch mode using a Full-wave Barbell Horn (FBH).

The initial suspension was prepared by mixing 5% nifedipine powder into a 1% solution of HPMC in deionized water using a magnetic stirrer at 500 rpm for 5 min. This suspension (Fig. 2, Sample A) was split into 50 ml and 250 ml samples. The samples were then processed for 60 minutes using the LSP-500 and the BSP-1200 ultrasonic processors, resulting in the processing rates of 0.84 ml/min (Fig. 2, Sample B) and 4.2 ml/min (Fig. 2, Sample C), respectively. In all experiments presented in Fig. 2 and Table 1, the ultrasonic amplitude was maintained at 100 microns peak-to-peak (µpp). At the end of the experiment conducted with the BSP-1200 processor, a portion of the resulting Sample C was passed through a 450 nm filter (Fig. 2, Sample D).

RESULTS & CONCLUSIONS

The results are presented in Figure 2 and Table 1. We arrived at the following conclusions:

1. **Efficient particle size reduction.**

   High-amplitude ultrasonic exposure led to efficient particle size reduction of nifedipine crystals from approximately 33 microns to 200 nanometers. The resulting nano-suspension was able to pass through the 450 nm filter almost unperturbed (Fig. 2, Sample D). Analysis of metal content in Sample D showed only 1.6 ppm of Ti and much lower quantities of any other contaminants, which is well within FDA acceptance parameters for pharmaceutical formulations (<10 ppm) [1], [2].

2. **High ultrasonic amplitudes are needed for efficient nanocrystallization.**

   In our preliminary study conducted with the LSP-500 processor at the ultrasonic amplitude of 50 µpp (data not shown), we were unable to reduce the size of nifedipine crystals to the nanometer range. This strongly supports the importance of high ultrasonic amplitudes in the nanocrystallization process.

3. **The sonication process can be directly scaled up with BHUT.**

   As expected, the BSP-1200 (FBH horn) permitted processing approximately 5 times more material per unit of time than the LSP-500 (CH horn) and produced slightly smaller nifedipine particles. This confirms the ability of BHUT to directly scale up the process of ultrasonic nanocrystallization. Further scale-up from the BSP-1200 is possible with ISM industrial-scale ultrasonic processor, ISP-3000.

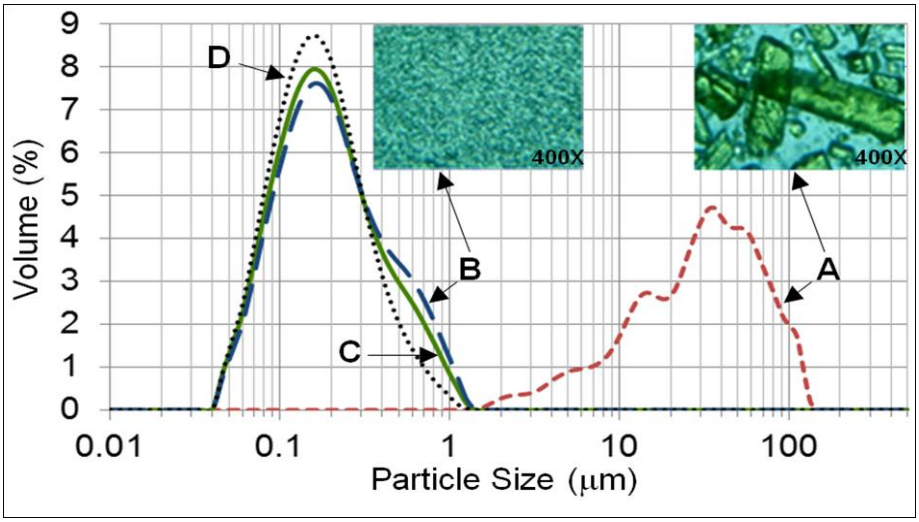


Figure 2. Nifedipine particle size distributions before processing (Sample A), after processing with LSP-500 (Sample B), after scaling up and processing with BSP-1200 (Sample C), and after filtering sample C (Sample D).

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

Table 1. Nifedipine particle sizes before processing (Sample A), after processing with LSP-500 (Sample B), after scaling up and processing with BSP-1200 (Sample C), and after filtering sample C (Sample D).

[1]. FDA: Guidance for Industry Q3A Impurities in New Drug Substances. 2008.

[2]. Keck CM, Rainer HM: smartCrystals – Review of the Second Generation of Drug Nanocrystals; in Torchilin V, Amiji MM, (eds) Handbook of Materials for Nanomedicine. Singapore, Pan Stanford Publishing Pte. Ltd., 2010.

ABOUT INDUSTRIAL SONOMECHANICS

Industrial Sonomechanics, LLC, (ISM) is a research & development, equipment design and process consulting firm, specializing in high-intensity ultrasonic technology for liquid treatment by acoustic cavitation. Our patented Barbell Horn Ultrasonic Technology (BHUT) allows generating extremely high ultrasonic amplitudes and cavitation intensities at any scale, making it possible to directly apply laboratory optimization results in an industrial production environment.

ISM ultrasonic liquid processors (homogenizers, sonicators, mixers) are ideal for the production of nanoemulsions, nanocrystals and liposomes. Other common applications are cell disruption, plant oil extraction, degassing, dispersing, transesterification, desulphurization, and sterilization. Industries utilizing ISM technology include pharmaceutical, medical cannabis, cosmetic, nutraceutical, food & beverage, printer ink, paint, adhesive, pesticide, chemical and alternative fuel.

Contact information:

www.sonomechanics.com
7440 SW 50th Terrace #110, Miami, FL 33155
Sales & Technical Support: (646) 580-4676
General Inquiries: (786) 332-3652
contact@sonomechanics.com

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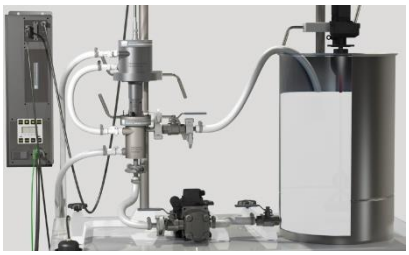
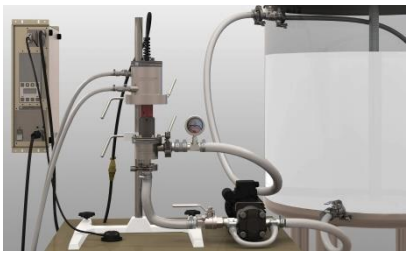
INDUSTRIAL SONOMECHANICS ULTRASONIC PROCESSORS

LSP-600
Laboratory-Scale Processor



BSP-1200
Bench-Scale Processor



ISP-3000
Industrial-Scale Processor

HAVE QUESTIONS?

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