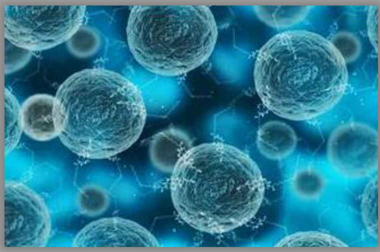
Scaling Up the Production of a Pharmaceutical Nanoemulsion with Barbell Horn Ultrasonic Technology



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Allied Innovative Systems

Recent years have seen major breakthroughs in how vaccines and drugs are formulated. Oil-in-water nanoemulsions are now widely used as drug carriers because they can easily incorporate lipophilic bioactive compounds, stabilize substances that tend to undergo hydrolysis, and reduce side effects of potent drugs. Ultrasonic nanoemulsification is frequently applied in laboratory studies. This process, however, has previously not been possible to scale up due to technological limitation of conventional ultrasonic technology.

Allied Innovative Systems (ALLIS) partnered with Industrial Sonomechanics (ISM) to determine the feasibility of applying ultrasonic nanoemulsification on a large scale with ISM's Barbell Horn® Ultrasonic Technology (BHUT).

Problems

- The industrial production of pharmaceutical-quality nanoemulsions requires intense shear forces to be applied on a large scale.
- Conventional high-amplitude ultrasonic processing is effective only on a laboratory scale. It cannot be scaled up without drastically reducing the ultrasonic amplitudes and, therefore, diminishing the resulting shear force intensities.

Goals

- Confirm the requirement for high ultrasonic amplitudes during the production of pharmaceutical-quality nanoemulsions.
- Demonstrate that the process can be directly scaled-up with BHUT, providing reproducible, high-quality results on all scales of operation.
- Determine the productivity scale-up factors achieved by transferring from ISM laboratory to bench and industrial ultrasonic processors.

Results

- Ultrasonic processing is very effective for the production of pharmaceutical-quality nanoemulsions, as long as high amplitudes are maintained.
- With BHUT, the process is directly scalable, making it possible to implement laboratory accomplishments in an industrial production environment.
- Scale-up factors of about 11 and 55 were achieved when transferring the process from the laboratory to the bench and industrial scales, respectively.

> *Nanoemulsions are used in pharmaceutical applications for a large number of purposes. We had tried conventional ultrasonic processors for their preparation, but it is not something you can use on a large scale. With this study, we were able to show that ISM's Barbell Horn Ultrasonic Technology can be used to transfer this process to a large scale, while maintaining the same processing conditions and achieving the same high quality of the final product. We believe this to be a breakthrough in the pharmaceutical field.*
>
> ***Simon Bystryak, Ph.D.***
> *President, Allied Innovative Systems (ALLIS)*

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BACKGROUND AND SUMMARY

ALLIS partnered with ISM to determine the feasibility of continuous, commercial-scale production of pharmaceutical-quality nanoemulsions using ISM's Barbell Horn® Ultrasonic Technology (BHUT).

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 as well as their clinical validation.

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

Lipid nanoemulsions are complex, kinetically stable oil-in-water dispersions, homogenized with the aid of an emulsifier. In clinical practice, there are three major applications of nanoemulsions: (1) parenteral nutrition, (2) colloidal drug carriers and (3) vaccine preparations.

Intravenous lipid nanoemulsions are important sources of fatty acids for pediatric and adult patients, applied when oral nutrition is impossible or disadvantageous. Lipid nanoemulsions are also widely used as drug carriers because they easily incorporate lipophilic bioactive compounds, stabilize them against hydrolysis, and reduce their side effects. Nanoemulsions are biodegradable and can be administered by almost all available routes, including parenteral, oral, ocular, nasal, topical, and pulmonary. Nano-scale median droplet sizes (< 300 nm) and long-term stability profiles of nanoemulsions are critically important to maintain.

Why Did We Choose the MF59® Nanoemulsion as a Model?

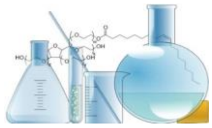
Recent years have seen major breakthroughs in how vaccines and drugs are formulated, with the approval of three new lipid-based adjuvants formulated as nanoemulsions: MF59® (Novartis), AS03 and AS04 (GlaxoSmithKline) [1].

The MF59® squalene oil nanoemulsion is used for most vaccine formulations worldwide. It has, for example, been licensed as a component of an influenza vaccine, Fluad®, and pandemic H5N1 vaccine, which are distributed to millions of people annually. The global vaccine market is estimated at $32.05 billion in 2013 and expected to reach $84.44billion by 2022 [2].

[1]. S.L. Baldwin, S. Bertholet, V.A. Reese, L.K. Ching, S.G. Reed, R.N. Coler, The importance of adjuvant formulation in the development of a tuberculosis vaccine, J.Immunol. 188 (2012) 2189–2197.

[2]. ASD Reports, Vaccine Market – by Technology & Types, Trend Analysis by Various Classes – Live/Attenuated, Subunit, Toxoid, Conjugate, DNA, Recombinant Vector, Synthetic Dentritic Vaccines and by Indications with Market Landscape Analysis – Global Forecasts to 2022, Viruses Market Research Reports, 2013.

MATERIALS & METHODS



Materials and Methods

For the preparation of squalene-based nanoemulsions, high-purity squalene oil, Na-citrate buffer, Tween 80 and Span 85 were purchased from Sigma–Aldrich (St. Louis, MO). The formulation was identical to that of the commercially produced MF59® nanoemulsion used for vaccine preparations: squalene oil (4.3%), Tween 80 (0.5%), Span 85 (0.5%), water (94.7%), 10 mM Na-citrate buffer. All components were vigorously stirred together in the pre-mix tank for 30 min, with no additional processing prior to sonication.

Median droplet sizes (MDS) were measured by dynamic light scattering (DLS) using a Beckman Coulter N4 Plus analyzer. The target MDS value for the nanoemulsions produced at the laboratory, bench and industrial scales was 250 nm. The ability to reach this value at progressively larger scales of operation was used to demonstrate process scale-up success achieved with BHUT.

Ultrasonic Processors and Experimental Setup

The experiments were conducted using three ultrasonic liquid processors obtained from Industrial Sonomechanics (ISM):

1. LSP-500 laboratory-scale processor configured in the batch mode (Fig. 1a).
2. BSP-1200 bench-scale processor configured in the flow-through mode (Fig. 1b).
3. ISP-3000 industrial-scale processor configured in the flow-through mode (Fig. 1c).

All three processors were able to provide the ultrasonic amplitudes in the range of 20 to 100 microns peak-to-peak (μ_{pp}). The average sample temperature in all experiments was maintained at 45 ^{o}C. All processed samples were passed through a 0.45 μm filter.

Figure 1a. LSP-500 in batch mode using a conventional horn (CH).

Figure 1b. BSP-1200 in flow-through mode using a Half-wave Barbell horn (HBH).

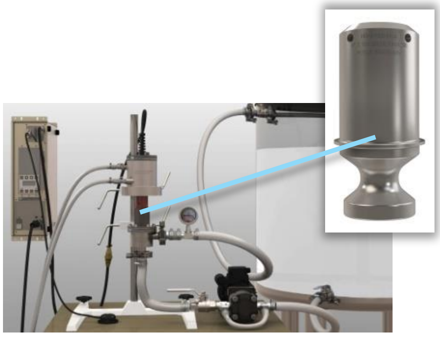


Figure 1c. ISP-3000 in flow-through mode using a Half-wave Barbell horn (HBH).

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Continuous-flow production of a pharmaceutical nanoemulsion by high-amplitude ultrasound: Process scale-up.

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RESULTS & CONCLUSIONS

The Importance of High Ultrasonic Amplitudes.

The effect of the ultrasonic amplitude on the MDS values was evaluated by conducting the nano-emulsification process at 90 μ_{pp} and 20 μ_{pp} with the LSP-500 processor. The results presented in Fig. 2 show that the MDS values for the nanoemulsion obtained at 20 μ_{pp} amplitude are significantly higher. Even at dramatically increased processing times (decreased processing rates), the target MDS value of 250 nm cannot be achieved at this low amplitude.

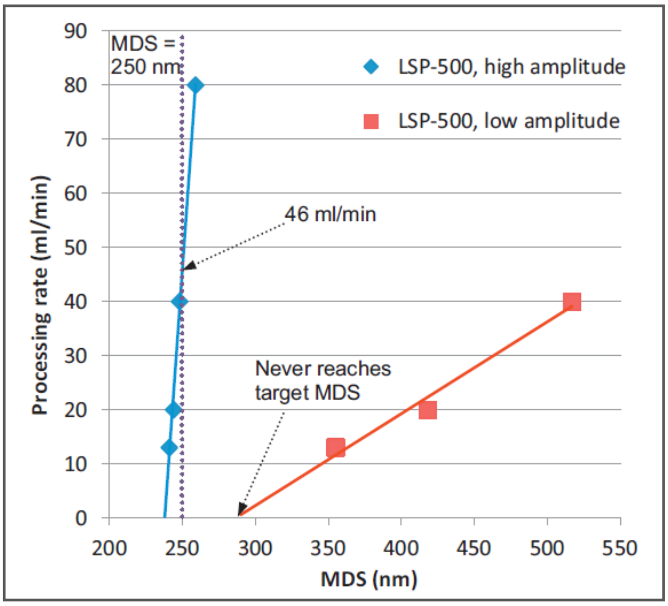

Figure 2. Relationships between processing rates and nanoemulsion MDS values achieved with LSP-500 ultrasonic processor, operating at the ultrasonic amplitudes of 90 μ_{pp} (high amplitude) and 20 μ_{pp} (low amplitude). Target MDS value is shown to be impossible to achieve at the low amplitude.

The Direct High-Amplitude Process Scale-Up

Fig. 3 shows that the target MDS value was possible to obtain at all three scales, laboratory, bench and industrial. The plots were used to identify the optimum processing rates corresponding to the target MDS at each scale (intersection with the vertical line at MDS = 250 nm). Comparing the optimum processing rates demonstrates that laboratory-to-bench and bench-to-industrial scale-up factors were 11.2 and 4.8, respectively. The overall process scale-up factor (laboratory-to-industrial scale productivity rate increase) achieved by utilizing BHUT instead of conventional ultrasonic technology was, therefore, 53.7.

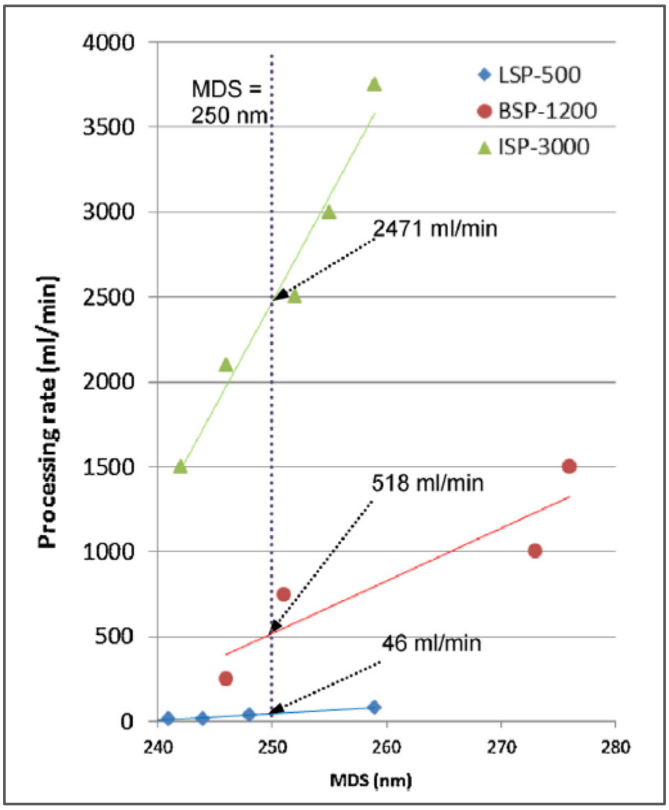

Figure 3. Relationships between processing rates and product nanoemulsion's MDS values achieved with LSP-500, BSP-1200 and ISP-3000 ultrasonic processors. All experiments were performed at the ultrasonic amplitude of 90 μ_{pp}. The arrows point to the processing rates corresponding to the target MDS for each scale of operation (intersection with the vertical line at MDS = 250 nm).

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.

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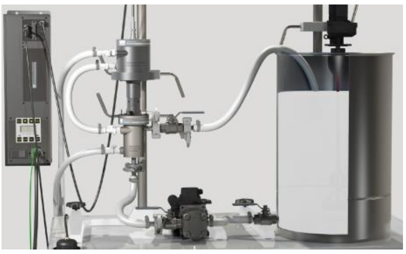
INDUSTRIAL SONOMECHANICS ULTRASONIC PROCESSORS

LSP-600
Laboratory-Scale Processor



BSP-1200
Bench-Scale Processor

ISP-3000
Industrial-Scale Processor

HAVE QUESTIONS?

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