

## DRUG-CARRIER LIPOSOMES AND NANOEMULSIONS



### BACKGROUND

Liposomes are spherical, self-closed structures formed by one or several concentric lipid bilayers with an aqueous phase inside and in between the lipid bilayers, having droplet diameters from about 50 to 5000 nm. Some attractive properties of liposomes include their biocompatibility and ability to entrap water-soluble (hydrophilic) pharmaceutical agents in their internal water compartment and water-insoluble (hydrophobic) pharmaceuticals in their membrane. There are approximately a dozen liposomal drugs currently on the market, including anticancer agent doxorubicin, in both polyethylene glycol (PEG) liposomes (Doxil) and in non-pegylated liposomes (Myocet). This agent is used widely off-label and is approved for the treatment of solid tumors in patients with breast-carcinoma metastases.

Lipid nano-sized emulsions or nanoemulsions are complex, kinetically stable oil-in-water dispersions, homogenized with the aid of an emulsifier. In clinical practice, there are two major applications of lipid nanoemulsions: 1) [parenteral nutrition](#) and 2) colloidal drug carriers.

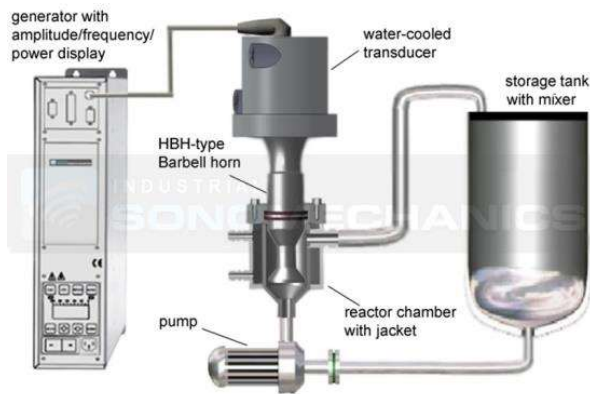
Lipid nanoemulsions are widely used as drug carriers because they easily incorporate lipophilic bioactive compounds, stabilize bioactive compounds that tend to undergo hydrolysis, and reduce side effects of potent drugs. Additionally, lipid nanoemulsions are biodegradable and can be produced on a large scale using ISM's [ultrasonic processors](#). Furthermore, nanoemulsions can be administered by almost all available routes including parenteral, ocular, nasal, oral, topical, and even aerosolization to the lungs. Examples of commercially available drugs encapsulated into nanoemulsions include Diprivan (Propofol) from AstraZeneca, Etomidat-Lipuro (Etomidate) from B. Braun Melsungen, Lipotalon (Limethason, Dexamethasone Palmitate) from Merckle, Restasis (Cyclosporin A) from Allergan, and Gengraf (Cyclosporin A) and Norvir (Ritonavir) both from Abbott.

Two parameters are measured to check toxicity and physical stability of liposomes and nanoemulsions: 1) mean droplet size (MDS) and 2) particle size distribution (PSD). United States Pharmacopeia (USP) adopted Chapter 729, entitled "Globule Size Distribution in Lipid Injectable Emulsions", which sets two physical limits for nanoemulsions: 1) MDS < 500 nanometers (nm); 2) percent of lipid globules > 5 microns (um) or PFAT<sub>s</sub> < 0.05%. This is of great significance for infusion safety: higher amounts (> 0.05%) of outsized (> 5 um) lipid droplets are associated with instability; moreover, intravenously administered lipid droplets exceeding 5 um have been shown to cause adverse effects, in particular emboli in the lungs.

### PRODUCTION WITH HIGH-AMPLITUDE ULTRASOUND

The formation of nanoemulsions and liposomes requires intense shear forces and significant energy deposition in order to break the original particles down to the nanometer scale. Industrial Sonomechanics, LLC ([ISM](#)), offers bench and industrial-scale high-power [ultrasonic processors](#) for the production of nanoemulsions and liposomes. The processors are based on our [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.

High ultrasonic amplitudes are required for efficient nanoemulsion and nanoliposome production. The necessary shear forces are created by ultrasonic cavitation, which produces violently and asymmetrically imploding vacuum bubbles and causes micro-jets that disperse and break up the original oil droplets and liposomes down to the nanometer scale. Known for many decades, this effect of high-amplitude ultrasound has been extensively studied and successfully used in laboratory-scale research. However, prior to the introduction of [BHUT](#), none of the existing ultrasonic liquid processors could generate the required amplitudes on the industrial scale. Commercial implementation of high-power ultrasound has, therefore, been limited to processes for which low-amplitudes are sufficient (cleaning, simple deagglomeration, mixing, macro-emulsification, etc.).



### 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. [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-containing nanoemulsions and liposomes 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.

### Examples of Drug-Containing Nanoemulsions and Liposomes Produced by High-Intensity Ultrasound

The table on the left demonstrates that nanoemulsions and liposomes prepared using our ultrasonic technology are effective for the delivery of one of the most promising hydrophobic drugs widely used for the treatment of a variety of solid tumors, [Zn-Phtalocyanine \(ZnPC\)](#). The

Sample type	SLS, MDS (nm)	DLS, MDS (nm)	PFAT <sub>5</sub> (%)
Emulsion 1	215	190	0.007
Emulsion 1+ ZnPC	210	177	0.001
Emulsion 2	60		
Emulsion 2+ ZnPC	84	70	0.026
Liposomes	101		

PFAT<sub>5</sub> is the percentage (volume-weighted) of oil droplets > 5 μm, determined by LE/SPOS. MDS is the mean droplet size (intensity-weighted) determined by Static (SLS) and Dynamic Light Scattering (DLS).

following nanoemulsion and liposome systems were prepared using Industrial Sonomechanics' ([ISM](#)) 1200 W bench-scale flow-through ultrasonic processor, [BSP-1200](#), equipped with a [piezoelectric transducer](#), flow-through [reactor chamber](#) and Full-wave Barbell Horn ([FBH](#)) operating at the ultrasonic amplitude of 75 microns: 1) [Emulsion 1 \(Intralipid-type emulsion\)](#): soybean oil-in-water nanoemulsion consisting of soybean oil (10%), L-a-[Phosphatilycholine](#), Type IV-S (1.2%), glycerol (2.25%), water (86.55%) 2) [Emulsion 2](#): soybean oil-in-water nanoemulsion consisting of Soybean oil (10%), Tween 80 (8.7%), Span 80 (1.3%), water (80%); 3) [Liposomes](#): L-a-[Phosphatilycholine](#), Type IV-S (2.4%), phosphate buffer saline (97.6%). We also prepared Emulsions 1 and 2 containing 0.05 mg/ml ZnPC with and without preliminary dissolution of ZnPC in ethanol (final ethanol concentration did not exceed 2%). In this case, either ZnPC powder or its ethanol solution was added to the oil phase. In order to examine the effect of filtration on the size of the droplets, Emulsion 2 was also filtered using a 0.45 mm filter.

As can be seen from the table, all parameters of the prepared nanoemulsions and liposomes are well within USP requirements. Other most significant results obtained for Emulsions 1, 2 and Liposomes include: 1) The addition of ethanol to Emulsions 1 and 2 does not significantly change the droplet size; 2) The droplet sizes for filtered (through a 0.45 mm filter) and unfiltered Emulsion 2 are practically the same; 3) The absorbance and fluorescence spectra obtained for ZnPC-containing Emulsions 1 and 2 coincide with those for solutions of ZnPC in pure soybean oil; 4) Absorbance and fluorescence spectroscopy measurements showed that the ZnPC incorporation coefficient is close to 100% (results were confirmed by scanning electronic images showing no ZnPC crystals in the water phase).

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

## HAVE QUESTIONS?

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with a process specialist

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**Industrial Sonomechanics, LLC**  
560 W 144 Street, Suite 6  
New York, NY 10031