[Sitemap](http://sonomechanics.com/sitemap)



* [Home](http://sonomechanics.com/home/)
* [About ISM](http://sonomechanics.com/about_ism/)
* [Technology](http://sonomechanics.com/technology/)
* [Products & Services](http://sonomechanics.com/products_services/)
* [Applications](http://sonomechanics.com/applications/)
* [Technical Resources](http://sonomechanics.com/technical_resources/)
* [Blog](http://blog.sonomechanics.com/blog/)
* [Home](http://sonomechanics.com/)
* [Applications](http://sonomechanics.com/applications/)
* [Pharmaceutical](http://sonomechanics.com/applications/pharmaceutical/)
* [Drug-Carrier Liposomes and Nanoemulsions](http://sonomechanics.com/applications/pharmaceutical/drug-carrier_liposomes_and_nanoemulsions/)

**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 nanosized 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](http://sonomechanics.com/applications/pharmaceutical/nanoemulsions_for_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](http://sonomechanics.com/products_services/). Furthermore, nanoemulsions can be administered by almost all available routes including parenteral, ocular, nasal, oral, topical, and even aerosilization 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 PFAT5 < 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](http://www.sonomechanics.com)), offers bench and industrial-scale high-power [ultrasonic processors](http://sonomechanics.com/products_services/) for the production of nanoemulsions and liposomes. The processors are based on our [patented](http://sonomechanics.com/technical_resources/intellectual_property/) Barbell Horn Ultrasonic Technology ([BHUT](http://sonomechanics.com/technology/barbell_horn_ultrasonic_technology/)), 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](http://sonomechanics.com/technology/barbell_horn_ultrasonic_technology/), 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](http://sonomechanics.com/technology/barbell_horn_ultrasonic_technology/) inherently forces all processes to run either at a small scale and high amplitude or a large scale and low amplitude. [ISM](http://sonomechanics.com/home/) has successfully overcome this limitation by developing [BHUT](http://sonomechanics.com/technology/barbell_horn_ultrasonic_technology/), which permits constructing industrial-scale [ultrasonic processors](http://sonomechanics.com/products_services/) 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 following nanoemulsion and liposome systems were prepared using Industrial Sonomechanics' ([ISM](http://www.sonomechanics.com)) 1200 W bench-scale flow-through ultrasonic processor, [BSP-1200](http://sonomechanics.com/products_services/1200_w_bench-scale_processor/), equipped with a [piezoelectric transducer](http://sonomechanics.com/technology/ultrasonic_transducers/), flow-through [reactor chamber](http://sonomechanics.com/technology/flow-through_reactor_chambers/) and Full-wave Barbell Horn ([FBH](http://sonomechanics.com/technology/ultrasonic_horn_designs_and_properties/)) operating at the ultrasonic amplitude of 75 microns: 1) Emulsion 1 ([Intralipid-type emulsion](http://sonomechanics.com/applications/pharmaceutical/nanoemulsions_for_parenteral_nutrition/%22%20%5Co%20%22Intralipid-type%20Nanoemulsion%20Prepared%20by%20Industrial%20Sonomechanics%27%20Ultrasonic%20Processor%22%20%5Ct%20%22_blank)): soybean oil-in-water nanoemulsion consisting of soybean oil (10%), L-a-Phosphatilylcholine, 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-Phosphatilylcholine, 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](http://www.allisystems.com)).

Hielscher - Ultrasound Technology logo Hielscher – Ultrasound Technology +49 (3328) 437-420 info@hielscher.com Home Devices Processes Industries Contact DE Ultrasonic Liposome Preparation Ultrasonic Liposome Preparation for Pharmaceuticals and Cosmetics Liposomes (liposome-lipid based vesicles), transferosomes (ultradeformable liposomes), ethosomes (ultradeformable vesicles with high alcohol content), and niosomes (synthetic vesicles) are microscopic vesicles, which can be artificially prepared as globular carriers into which active molecules can be encapsulated. These vesicles with diameters between 25 and 5000 nm are often used as drug carriers for topical purposes in the pharmaceutical and cosmetic industry, such as drug delivery, genetherapy, and immunization. Ultrasound is a proven method of liposome preparation and the encapsulation of active agents into these vesicles. Liposomes are made from Phosphatidyl Choline (PC) Liposomes are not only carriers of active agents, also without encapsulated agents, the vacant vesicles, are potent actives for the skin, as the phosphatidylcholin incorporates two essentials, which the human organism cannot produce by itself: linoleic acid and choline. Liposomes Liposomes are unilamellar, oligolamellar or multilamellar vesicular systems and are composed of the same material as a cell membrane (lipid bilayer). Regarding to their composition and size, one differs between multi-lamellar vesicles (MLV, 0.1-10μm) and unilamellar vesicles, which are distinguished between small (SUV, <100 nm), large (LUV, 100–500 nm) or giant (GUV, ≥1 μm) vesicles. The composite structure of liposomes consists of phospholipids. Phospholipids have a hydrophilic head group and a hydrophobic tail group, which consists of a long hydrocarbon chain. The liposome membrane has a very similar composition as the skin barrier, so that they can be easily integrated into the human skin. As the liposomes fusionate with the skin, they can unload the entrapped agents directly to the destination, where the actives can fulfill their functions. Thus, the liposomes create an enhancement of skin penetrability/ permeability for the entrapped pharmaceutical and cosmetical agents. Also liposomes without encapsulated agents, the vacant vesicles, are potent actives for the skin, as the phosphatidylcholin incorporates two essentials, which the human organism cannot produce by itself: linoleic acid and choline. Liposomes are used as biocompatible carriers of drugs, peptides, proteins, plasmic DNA, antisense oligonucleotides or ribozymes, for pharmaceutical, cosmetic, and biochemical purposes. The enormous versatility in particle size and in physical parameters of the lipids affords an attractive potential for constructing tailor-made vehicles for a wide range of applications. (Ulrich 2002) Ultrasonic Liposomes Formation Liposomes can be formed by the use of ultrasonics. The basic material for liposome preperation are amphilic molecules derived or based on biological membrane lipids. For the formation of small unilamellar vesicles (SUV), the lipid dispersion is sonicated gently – e.g. with the handheld ultrasonic device UP50H (50W, 30kHz), the VialTweeter or the ultrasonic reactor UTR200 – in an ice bath. The duration of such an ultrasonic treatment lasts approx. 5 – 15 minutes. Another method to produce small unilamellar vesicles is the sonication of the multi-lamellar vesicles liposomes. Dinu-Pirvu et al. (2010) reports the obtaining of transferosomes by sonicating MLVs at room temperature. Hielscher Ultrasonics offers various ultrasonic devices, sonotrodes and accessories to provide the appropriate sonicator regarding power Ultrasonic encapsulation of agents into liposomes Liposomes works as carriers for active agents. Ultrasound is an effective tool to prepare and form the liposomes for the entrapment of active agents. Before encapsulation, the liposomes tend to form clusters due to the surface charge-charge interaction of phospholipid polar heads (Míckova et al. 2008), furthermore they have to be opened. By way of example, Zhu et al. (2003) describe the encapsulation of biotin powder in liposomes by ultrasonication. As the biotin powder was added into the vesicle suspension solution, the solution has been sonicated for approx. 1 hour. After this treatment, biotin was entrapped in the liposomes. High power ultrasonicators from Hielscher Ultrasonics enable for targeted liposome preparation, emulsification and dispersing. Pic. 1: 1kW ultrasonic processor for continuous inline processing Liposomal Emulsions To enhance the nurturing effect of moisturizing or anti-aging cremes, lotions, gels and other cosmeceutical formulations, emulsifier are added to the liposomal dispersions to stabilize higher amounts of lipids. But investigations had shown that the capability of liposomes is generally limited. With the addition of emulsifiers, this effect will appear earlier and the additional emulsifiers cause a weakening on the barrier affinity of phosphatidylcholine. Nanoparticles – composed of phosphatidylcholine and lipids – are the answer to this problem. These nanoparticles are formed by an oil droplet which is covered by a monolayer of phosphatidylcholine. The use of nanoparticles allows formulations which are capable to absorb more lipids and remain stable, so that additional emulsifiers are not needed. Ultrasonication is a proven method for the production of nanoemulsions and nanodispersions. Highly intensive ultrasound supplies the power needed to disperse a liquid phase (dispersed phase) in small droplets in a second phase (continuous phase). In the dispersing zone, imploding cavitation bubbles cause intensive shock waves in the surrounding liquid and result in the formation of liquid jets of high liquid velocity. In order to stabilize the newly formed droplets of the disperse phase against coalescence, emulsifiers (surface active substances, surfactants) and stabilizers are added to the emulsion. As coalescence of the droplets after disruption influences the final droplet size distribution, efficiently stabilizing emulsifiers are used to maintain the final droplet size distribution at a level that is equal to the distribution immediately after the droplet disruption in the ultrasonic dispersing zone. Liposomal Dispersions Liposomal dispersions, which are based on unsaturated phosphatidylchlorine, lack in stability against oxidation. The stabilization of the dispersion can be achieved by antioxidants, such as by a complex of vitamins C and E. Ortan et al. (2002) achieved in their study concerning the ultrasonic preparation of Anethum graveolens essential oil in liposomes good results. After sonication, the dimension of liposomes were between 70-150 nm, and for MLV between 230-475 nm; these values were approximately constant also after 2 month, but inceased after 12 month, especially in SUV dispersion (see histograms below). The stability measurement, concerning essential oil loss and size distribution, also showed that liposomal dispersions maintained the content of volatile oil. This suggests that the entrapment of the essential oil in liposomes increased the oil stability. Long-time stability of ultrasonically prepared multilamellar (MLV) and small unilamellar (SUV) vesicle dispersion. Fig.1+2: Ortan et al. (2009): Stability of MLV and SUV dispersions after 1 year. Liposomal formulations were stored at 4±1 ºC. Hielscher ultrasonic processors are the ideal devices for applications in the cosmetic and pharmaceutical industry. Systems consisting of several ultrasonic processors of up to 16,000 watts each, provide the capacity needed to translate this lab application into an efficient production method to obtain finely dispersed emulsions in continuous flow or in a batch – achieving results comparable to that of today’s best high-pressure homogenizers available, such as the new orifice valve. In addition to this high efficiency in the continuous emulsification, Hielscher ultrasonic devices require very low maintenance and are very easy to operate and to clean. The ultrasound does actually support the cleaning and rinsing. The ultrasonic power is adjustable and can be adapted to particular products and emulsification requirements. Special flow cell reactors meeting the advanced CIP (clean-in-place) and SIP (sterilize-in-place) requirements are available, too. Contact Us / Ask for more Information Talk to us about your processing requirements. We will recommend the most suitable setup and processing parameters for your project. your name your email (\*required) your phone number product or area of interest Related Posts Ultrasonic Treatment of Nanoparticles for Pharmaceuticals Ultrasonic Production of Stable Nanoemulsions Surfactant-Free Cosmetic Emulsions by Power Ultrasonics Power Ultrasound for the Production of Cosmetics Sonochemical Synthesis of Latex Terms of use and legal information, imprint, © copyright 1999-2017, by hielscher ultrasonics gmbh

Read more: https://www.hielscher.com/ultrasonic-liposome-preparation.htm#94069