INDUSTRIAL SONOMECHANICS™

NANOEMULSIONS USED FOR PARENTERAL NUTRITION

BACKGROUND

Lipid nano-sized emulsions (nanoemulsions) are complex, kinetically stable oil-in-water dispersions, homogenized with the aid of one or several surfactants (emulsifiers). In clinical practice, one major application of lipid nanoemulsions is parenteral nutrition, with such products as Intralipid® used for patients who are unable to get nutrition via an oral diet.

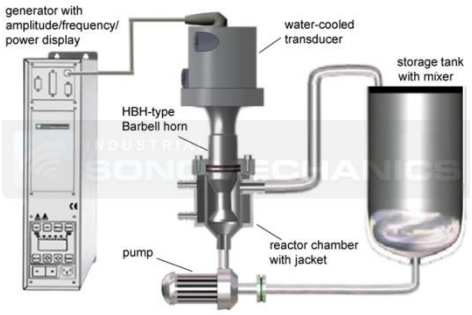
Traditional nanoemulsions used for parenteral nutrition are made of safflower and/or soybean oils using egg-derived phospholipids as emulsifiers. These nanoemulsions are known as long-chain triglyceride emulsions and are composed of omega-6 polyunsaturated fatty acids (linoleic and linolenic acids) and long-chain non-essential saturated fatty acids. New types of lipid nanoemulsions used for parenteral nutrition consist of physical mixtures of soybean or safflower oil with oils that are rich in medium-chain triglycerides, such as olive and coconut oils and/or omega-3 long-chain polyunsaturated fatty acids found in fish oil. These lipid formulations have clinical benefits over traditional soybean and safflower nanoemulsions and offer improvements in stability and safety when combined with new multi-chamber bags. Omega-3 fatty acids laden nanoemulsions made from fish oil are likely to be increasingly used not only for nutrition but also for the modification of biological and pathological processes.

Two parameters are measured to check toxicity and physical stability of nanoemulsions: 1) lipid globule 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 used for parenteral nutrition: 1) MDS < 500 nanometers (nm); 2) percent of lipid globules > 5 microns (um) or $PFAT_5$ < 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

Industrial Sonomechanics, LLC (ISM), offers bench and industrial-scale high-power ultrasonic processors for the production of nanoemulsions. 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 vibration amplitudes are required for efficient oil droplet size reduction. 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 droplets 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.).



Number of passes	Ultrasonic amplitude (μ_{pp})	SLS, MDS (nm)	DLS, MDS (nm)	$PFAT_5$ (%)
1	75	319.7		
3	75	308.7		
5	75	200.2	199.23	0.024
5	25		527.7	0.384

Table 1. $PFAT_5$ is percentage (volume-weighted) of oil droplets > 5 μm, determined by LE/SPOS, MDS is mean droplet size (intensity-weighted) determined by Static (SLS) and Dynamic Light Scattering (DLS). Color coding refers to pass and fail, according to USP recommendations.

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 nanoemulsions 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 Intralipid-Type Nanoemulsions Produced Using ISM's Ultrasonic Technology

Intralipid-type nanoemulsion consisting of soybean oil (10%), L-a-Phosphatilylcholine, Type IV-S (1.2%), glycerol (2.25%) and water (86.55%) was 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. The results are presented on the left. The obtained Intralipid-type nanoemulsion's quality exceeds USP standards. It should be emphasized that decreasing the ultrasonic amplitude to 25 microns (as in conventional industrial ultrasonic systems) results in a significant increase of MDS and PFAT5, both of which are well outside of the acceptable levels. This result clearly shows that ultrasonic amplitude plays a crucial role in the process of preparing high-quality nanoemulsions and justifies the importance of being able to scale up without sacrificing the amplitude.

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

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