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

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ABSTRACT

High-pressure homogenization (HPH, including microfluidization) and high-amplitude ultrasonic processing are currently the leading two methods used to produce nanoemulsions of superior quality. Despite suffering from multiple important drawbacks, HPH is currently the technology of choice for the industrial manufacture of pharmaceutical nanoemulsions. The ultrasonic nanoemulsification technology is free from most of these drawbacks and frequently used in laboratory studies. The challenge for the ultrasonic method, however, has been bridging the gap between laboratory research and its industrial implementation. Due to limitations of conventional ultrasonic technology, scaling up has not been possible without a significant reduction in ultrasonic amplitudes, which compromises product quality. This limitation has been overcome by Barbell Horn Ultrasonic Technology (BHUT), which permits constructing bench and industrial-scale processors capable of operating at high ultrasonic amplitudes. In the present study, a high-quality MF59®-analog pharmaceutical nanoemulsion has been successfully manufactured using laboratory, bench and industrial-scale high-amplitude ultrasonic processors. The overall laboratory-to-industrial scale-up factor achieved by using BHUT was approximately 55. The ultrasonic amplitude and the resulting product quality were maintained identical at all three scales. To our knowledge, this work is the first reported instance of a successful and systematic industrial scale-up of any high-amplitude ultrasonic process.

1. Introduction

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 an important source of fatty acids for pediatric and adult patients, used when oral nutrition is impossible or disadvantageous. Their size and stability are critically important [1]. Lipid nanoemulsions are also 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. Furthermore, nanoemulsions can be administered by almost all available routes including parenteral, ocular, nasal, oral, topical, and even aerosolization to the lungs [2]. There are approximately a dozen commercially available drugs encapsulated into nanoemulsions [2].

Recent years have seen major breakthroughs in how vaccines are formulated, with the approval of three new lipid-based adjuvants, each of which is formulated as a nanoemulsion. The lipid-based adjuvants approved for use in human vaccines include MF59® (Novartis), AS03 and AS04 (GlaxoSmithKline) [3]. MF59® and AS03 are squalene-based adjuvants, while AS04 combines monophosphoryl lipid A (MPL) with alum [3]. AS04 is approved for the use with hepatitis B virus and human papilloma virus in Fendrix and Cervarix vaccines (GlaxoSmithKline), respectively [4]. AS03 has been approved as a component of the pandemic flu vaccine Prepandrix [5]. Squalene nanoemulsion most commonly used in vaccine formulations, MF59®, has already been licensed as a component of an influenza vaccine, Fluad® [6], and pandemic H5N1 vaccine [7]. MF59® has an established safety and efficacy profile: MF59®-based seasonal and pandemic flu vaccines have been distributed to approximately 80 million persons [7]. The global vaccine market is estimated at $32.05 billion in 2013 and is expected to reach $84.44 billion by 2022 [8].

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1.1. Overview of techniques used for the production of nanoemulsions

The industrial production of nanoemulsions requires significant energy deposition and intense shear forces [9]. Although low-energy emulsification methods do exist, they have the disadvantage of requiring high concentrations of surfactants, which must be removed before administration [10,11]. The shear forces necessary for the emulsification process can be provided by mechanical agitation, for example, stirring, high shear mixing, high-pressure homogenization (using a homogenizing valve-based device or a Microfluidizer®) or high-amplitude ultrasound. The latter two methods have been demonstrated to be superior to all others, being able to produce nanoemulsions with droplets much smaller than 500 nm in diameter and narrow size distributions [9,12,13].

High-pressure homogenizers require a coarse dispersion with droplets of about 1–10 μm in diameter to be prepared first, for example by a rotor-stator colloid mill [10], which is a significant limitation of this method. The premix is then pulled into a chamber and forced at an extremely high pressure (over 1000 bar) through a narrow valve (as in a valve homogenizer) or is split into two streams that go through separate micro-channels and subsequently collide with each other at very high velocities, producing droplet shear (as in Microfluidizer® devices). This process is very energy-intensive [10]. In addition, high-pressure homogenization utilizes expensive, large-footprint equipment that requires frequent and costly maintenance, is difficult to clean and service, and needs major redesign in order to enable aseptic processing [9,14].

Presently, high-amplitude ultrasound-based techniques for producing pharmaceutical, food and cosmetics nanoemulsions are being actively developed as an alternative to high-pressure homogenization [9,14–17]. Intense shear forces necessary for nanoemulsification are generated by high-amplitude ultrasound through the associated effect of acoustic cavitation, which produces violently and asymmetrically imploding bubbles and causes micro-jets that impinge one liquid into the other in the form of nano-droplets. This effect has been extensively studied and reviewed [14,15,18–20], and demonstrated to be effective for small-scale preparations of pharmaceutical nanoemulsions [16,17]. It has been shown that high ultrasonic amplitudes, at least 80 μm peak-to-peak (μ_{pp}) [21–24], are required for efficient particle size reduction.

1.2. Scale-up limitations of conventional ultrasonic technology

Despite its potential, the high-amplitude ultrasonic method for producing nanoemulsions has been restricted to the laboratory scale. As explained below, when conventional ultrasonic liquid processors are scaled-up, their ultrasonic amplitudes are always reduced to levels insufficient for producing most types of pharmaceutical nanoemulsions [22,24]. Ultrasonic transducers, which convert the electrical energy supplied by an ultrasonic generator into mechanical vibrations, provide low displacement amplitudes: 20–25 μm peak-to-peak (μ_{pp}). In order to amplify the amplitudes and deliver the ultrasonic energy to the processed liquids, high-gain ultrasonic horns (sonotrodes) are used. Conventional ultrasonic horns (CH), however, do not allow independent design of amplitude amplification and output surface area. Only small-surface, large-amplification or large-surface, zero or negative-amplification horns are possible. The use of conventional high-amplitude ultrasonic processors is, therefore, limited to small-scale investigations, for which horn tip diameters of 10–20 mm are sufficient (Fig. 1a) [25,26]. Since industrial-scale ultrasonic processors require large-diameter horns, they are forced to run at low amplitudes and cannot produce high cavitation intensities.

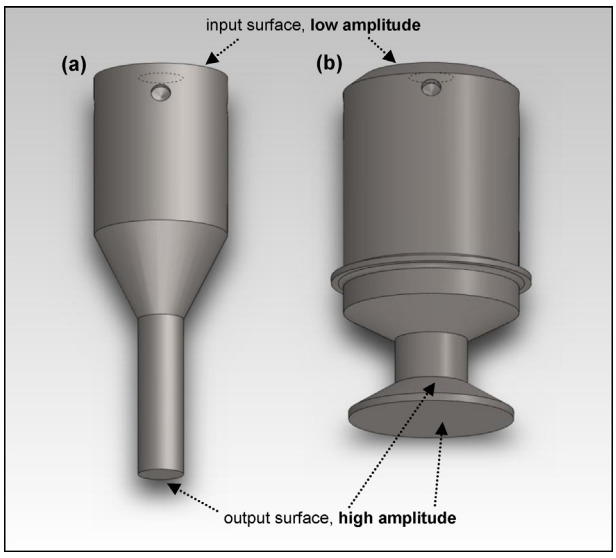

Fig. 1. High gain ultrasonic horns: (a) conventional horn (CH); (b) half-wave Barbell Horn (HBH). HBH is able to provide similar amplitude amplification as CH, while providing two high-amplitude radiating zones with a significantly larger cumulative output surface area.

High-power industrial-scale ultrasonic processors incorporating conventional sonotrodes (horns) are available [27]. However, these industrial processors cannot generate ultrasonic amplitudes above about 20 μ_{pp}. As a result, high power levels can only be attained by utilizing very large sonotrodes, which provide low power densities (due to low amplitudes), but high total powers (due to large radiating surfaces). It is important to point out that it is the amplitude of ultrasound, not the total power of the processor that determines its usefulness for many physical or chemical processes. For the production of high-quality nanoemulsions, the ultrasonic amplitude must be at least 80 μ_{pp} [21–24].

In order to successfully transfer a process from the laboratory to a production environment, one must maintain all processing parameters (amplitude, temperature, etc.) at the same level. Only if the amplitude can be maintained should the horn size (along with the corresponding power and productivity rate of the processor) be increased. The inability to scale up without sacrificing ultrasonic amplitudes has, therefore, been the most important limitation of conventional ultrasonic technology and the reason why it has not been able to compete with high-pressure homogenization in the industries requiring high-quality nanoemulsions.

1.3. High-amplitude processor scale-up with Barbell Horn Ultrasonic Technology

The scale-up limitation of conventional ultrasound has been successfully overcome by Barbell Horn Ultrasonic Technology (BHUT), which enables horn designs where amplification and output surface are independent variables, and permits constructing large-scale industrial processors that operate at high amplitudes [28–31]. BHUT-based processors have been used for the production of nanocrystals, liposomes and nanoemulsions, yielding high-quality products [22–24].

Fig. 1b illustrates a Half-wave Barbell Horn (HBH) having an output tip with the diameter of about 50 mm and two radiating surfaces that can generate ultrasonic amplitudes over 100 μ_{pp}. When a process is scaled-up by switching from a CH to a HBH-type horn, the processing capacity increases by a factor of about $2(D_{hbh}/D_{ch})^2$, where D_{ch} and D_{hbh} and are the respective output tip diameters of the two horns [22]. This relationship is based on the approximate