

An Overview of Ultrasound-Assisted Food-Grade Nanoemulsions

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Abstract Nanoemulsions are considered a very important tool for the delivery of bioactive compounds to the human body through food systems. Application of low-frequency ultrasound, a high-energy method, facilitates the homogenization and dispersion process under the influence of cavitation phenomena. Frequency, time, power, oil phase and aqueous phase are major parameters governing the cavitation process, concomitantly influencing the size and polydispersity index of nanoemulsion droplet. Additionally, hydrostatic pressure, gas content and temperature may also have profound effects on the process. Present review highlights the principles and production technology of high-intensity ultrasound and discusses the role of acoustic cavitation in the preparation of food-grade O/W nanoemulsions. Finally, it indicates technical hurdles, issues and future prospects of the technology.

Keywords Ultrasonication · Cavitation · Homogenization · Nanoemulsions · Food-grade

Introduction

Emulsion-based delivery systems have been conventionally used in the cosmetics, pharmaceutical and food industry since long. Emulsions are thermodynamically unstable

colloidal dispersions that consist of two immiscible liquids in which one liquid (minor component) is dispersed as a droplet into other liquid (major component) in the presence of surfactant. Although such systems tend to break down overtime, use of surfactants and extreme mechanical forces make it possible to keep emulsions kinetically stable for a certain period of time [1–3]. There are two basic types of emulsions, that is, oil-in-water (O/W) and water-in-oil (W/O). Emulsions are generally recognized as nanoemulsions when the average droplet diameter is in the range of 20–200 nm [4, 5]. Although the range of droplet diameter has been stated as high as 500 nm in the literature, this issue is still open for debate [6, 7]. In case, all the building components of nanoemulsions are safe for human consumption or “generally recognized as safe” (GRAS) materials, such nanoemulsions are considered as food-grade. Food-grade nanoemulsions are increasingly being utilized for encapsulating and delivering functional food ingredients and nutraceuticals because of their potential advantages. Moreover, nanoemulsions-based encapsulation confers stability to droplet against aggregation and gravitational separation besides delivering the protected ingredient to the specific site [8–11]. In particular, translucent or transparent nanoemulsions (droplet diameter: <100 nm) have received much attention by food, pharmaceutical and cosmetics sector, in the recent years [12, 13]. This type of nanoemulsions can be readily incorporated into sports drinks, clear beverages, cosmetics and medicinal formulations. Nanoemulsions systems, by the virtue of their small size droplets and improved solubility and stability properties, offer enhanced oral bioavailability and biological efficacy to the dispersed bioactives [10, 11, 14, 15]. A thin layer of surfactant acts as a barrier between the oil phase and aqueous phase, making O/W nanoemulsions suitable for encapsulating fat-soluble bioactives [16–18]. A wide

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variety of lipophilic food bioactives, including flavors, vitamins, carotenoids, flavonoids, phytosterols and polyunsaturated lipids have been encapsulated [1, 3, 9, 19, 20].

Different emulsification techniques used to prepare nanoemulsions are generally categorized as low-energy or high-energy approaches. Frequently used low-energy emulsification techniques, that is, phase inversion temperature (PIT) method, emulsion inversion point (EIP) method and spontaneous emulsification have been recently reviewed by Mason et al. [5], McClements and Rao [14], McClements [2], Koroleva and Evgenii [21], and Solans and Solé [6]. These techniques facilitate the spontaneous formation of nanoemulsions and are dependent on composition and surrounding environment of the emulsion system [6, 22]. High-energy techniques, that is, high-pressure homogenization [22–32], microfluidization [26, 33–38] and ultrasonication [22, 36, 39–42], have been extensively used to produce nanosize droplets. These methods rely on mechanical devices for the generation of intense disruptive forces needed for the breakdown of macroscopic phases. Generally, sound waves of 20 kHz–100 MHz are generated in physical medium in order to induce the ultrasonic process [43]. Low-frequency (high-intensity) ultrasound has become an important processing tool in the food sector. Currently, this innovating technology is being utilized as a processing aid to develop high-quality food products with the enhanced functional properties. Ultrasonication is found helpful in the inactivation of enzymes and microbes [44–55], modification of food ingredients [56–59], crystallization processes [46, 59, 60], extraction of natural compounds [46, 61–65], homogenization [59, 66] and emulsification to produce nano-scale materials [14, 16, 39, 40, 67–69].

Ultrasound-assisted emulsification has been successfully used to prepare O/W nanoemulsions. Although this approach is being utilized to produce conventional emulsions since long [70], its application to fabricate nanoemulsions in the food sector is a relatively new phenomenon. Cavitation process governs the formation of nanoemulsions in such a way that rapid formation and collapse of micro-bubbles occurs at the interface of two immiscible (continuous and dispersed) phases under the influence of high-intensity acoustic field [5, 71]. Collapse of micro-bubbles produces intense shock waves and localized turbulence, resulting in high-velocity jets in the liquid. These high-velocity jets produce intense shear forces, which facilitate droplet disruption and mixing of phases [14, 39, 40, 72, 73].

At present, this approach is far from being fully developed since scaling-up process is still a major challenge. Additionally, problem of uneven power distribution, contamination

and the chance of formulation deterioration are needed to be addressed [14]. However, a number of potential benefits offered by ultrasonic emulsification over conventional emulsification methods are recognized by several researchers [39, 42, 46, 65, 72, 74–81].

- Emulsions with smaller particle or droplet size and narrow size distribution
- Emulsions are more stable
- Surfactant quantity required is reduced for the given droplet size
- Ultrasonic emulsification is an energy-efficient process
- Low production cost
- Less chances of contamination
- Easy to operate, clean and control the apparatus

Process and formulation variables influence the droplet size, droplet size distribution, concentration of bioactive dissolved into the oily phase and overall stability of emulsion [39, 41, 82]. At present, interest is growing in the production techniques of food-grade nanoemulsions, and ultrasonication method is not an exception. In this article, we will review various food-grade nanoemulsions prepared by this process. Besides, process shortcomings and its effectiveness for producing nanoemulsions with desired characteristics will be discussed. Finally, some latest developments and prospects in the field will be highlighted.

Principles and Production Technology of Ultrasound

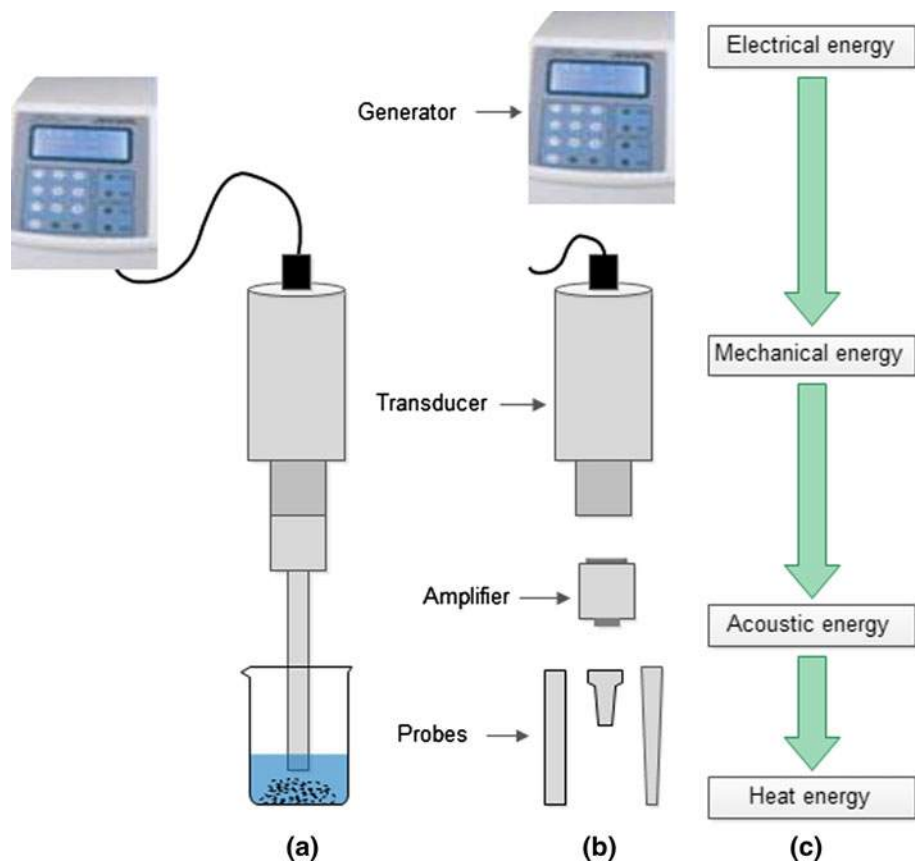
Ultrasound waves in the frequency range of 20–100 kHz, when interact with matter, have an ability to bring about physical and chemical changes. When a planar surface vibrates with certain frequency and amplitude, longitudinal waves are generated and propagate into the surrounding liquid/gas medium. These waves induce a motion in the medium particles through a series of compressions and rarefactions under fluctuating pressure, thus leading to acoustic cavitation phenomena [43, 81]. While passing through the medium, depending upon viscosity and conductivity of medium, sound waves dissipate part of the acoustical energy into heat energy [43].

Li and Fogler [73, 83], in their classical work, described the acoustic emulsification as a two-phase phenomena. In the first phase, dispersed phase droplets or gas bubbles are incorporated into aqueous media under the influence of Rayleigh–Taylor instability. Rayleigh–Taylor instability is the acceleration of one fluid into other due to ultrasonic waves at the media surface [84]. In the second phase, larger bubbles/droplets are disrupted into smaller one due to cavitation process (discussed in other section).

Ultrasound Generation

Most commonly used ultrasonic apparatus for the production of sub-micron emulsions is a probe system which consists of generator, ultrasonic converter (transducer), metal horn and probe [85], as shown in Fig. 1. Generator produces electrical waves of certain frequency (normally 20–24 kHz) while ultrasonic transducers consist of piezoelectric (electrostrictive) material which converts electrical oscillations into mechanical vibrations of the similar frequency [85]. Commonly used piezoelectric material includes quartz and ceramics such as barium titanate, lead titanate and lead zirconate titanate, which impart piezoelectric effect, that is, electricity is generated when mechanical stress is applied and vice versa (converse piezoelectric effect) [86]. Generated mechanical vibrations are amplified with the help of metal horn and are further propagated, through a probe attached to the horn, in the form of acoustic waves [85]. When a probe is immersed in the liquid sample, ultrasonic waves are transferred to sample. These sinusoidal waves exert a pressure (P_a), known as acoustic pressure, on the liquid medium and are dependent on time (t), frequency (f) and the maximum pressure amplitude ($P_{a, \max}$) of the wave [80, 87].

Fig. 1 Ultrasonic setup **a** batch-type ultrasonic setup, **b** components of batch-type ultrasonic setup, that is, generator, transducer, amplifiers and probe-types, **c** sequence of energy transformations at different levels of the operation



$$P_a = P_{a, \max} \sin(2\pi ft) \quad (1)$$

As $P_{a, \max}$ of the wave is directly proportional to power input of transducer, acoustic streaming is the predominant phenomena at lower amplitude while acoustic cavitation is initiated at higher amplitudes [80, 88].

Different components of probe-type ultrasound apparatus and scheme of energy transformation at different levels of the operation are shown in Fig. 1b, c, respectively. In the batch-type sonication system, acoustic waves are propagated to liquid sample, either by attaching a transducer to the container walls or through direct immersion of a probe into liquid (Fig. 1a). In the case of most commonly used continuous-type assemblies (Fig. 2), liquid sample flows either through the reactor equipped with probe (Fig. 2a, b), through the tube having single/multiple externally attached transducers (Fig. 2c) or through flow-through cell having internally installed transducer (Fig. 2d).

Acoustic Cavitation

Ultrasound waves, when pass through a liquid medium; induce molecular motion through a series of compression and rarefaction cycles. Preexisting micro-bubbles of gas dissolved into the liquid medium grow in size due to

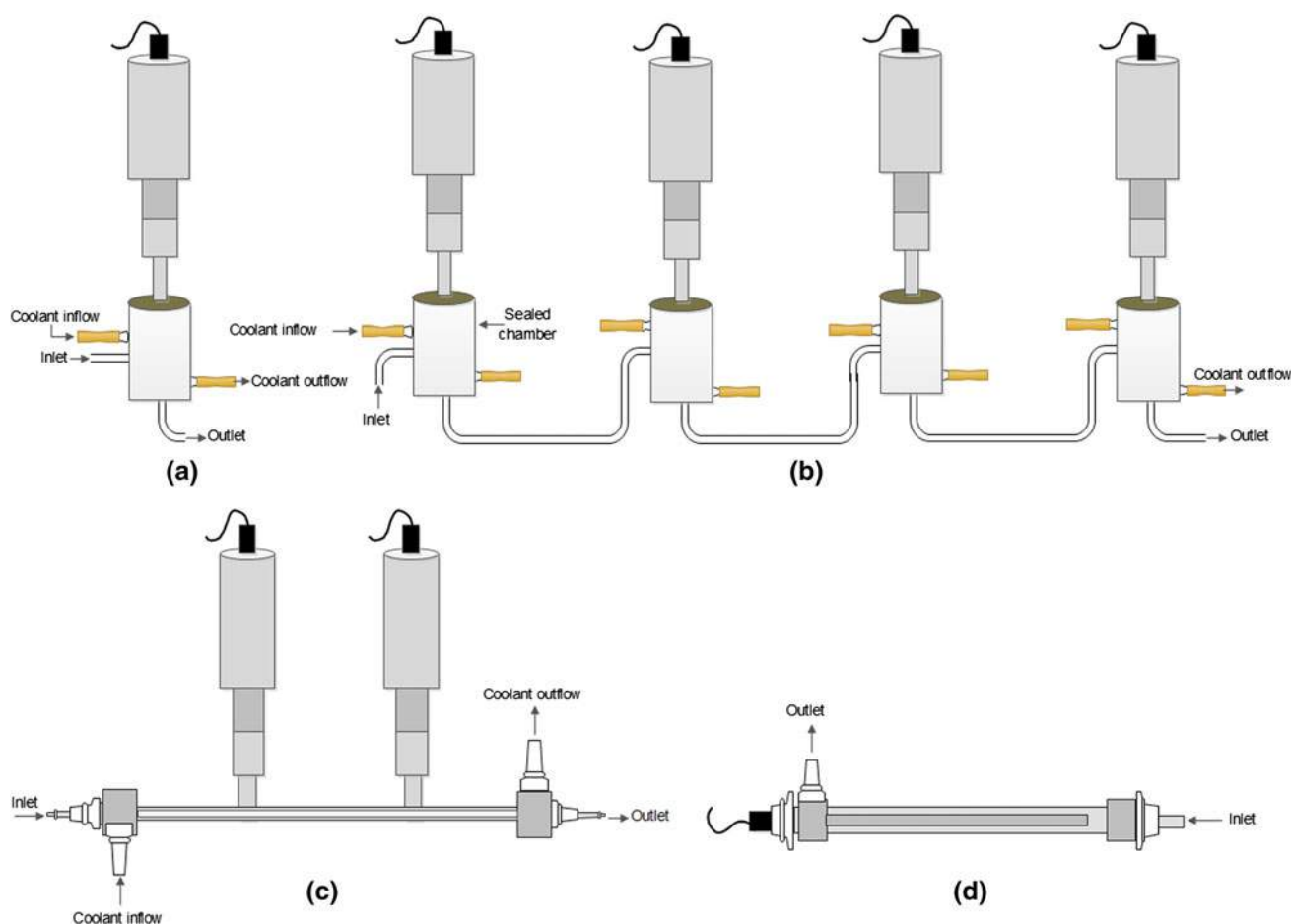


Fig. 2 Continuous flow ultrasonic systems **a** single-unit system, **b** multiple-unit system connected in series, **c** contact- and contamination-free flow-through cell, **d** flow-through cell equipped with internally installed transducer

rectified diffusion with each succeeding expansion and rarefaction half-cycle until they become unstable and violently collapse [89–91] (Fig. 3). Rectified diffusion is phenomena of bubble growth under the influence of increased gas exchange area and larger inward flux during expansion [92]. Briefly, acoustic cavitation is a “growth and collapse of micro-bubbles under an ultrasonic field” [93] as quoted by Ashokkumar [89]. Negative acoustic pressure (Fig. 3) in the liquid medium induces formation of cavitation bubbles. Furthermore, vibration amplitude (see Fig. 3) directly influences the sonication intensity as an increment in the vibration amplitude leads to greater vibration intensity, consequently increasing the cavitation effects. Physical effects produced by acoustic cavitation, that is, shock waves, micro-jets, turbulence, shear forces, temperature, etc., can be employed for a number of applications, including cleaning, extraction, inactivation, modification and emulsification. Applications of ultrasound technology for food processing were a topic of several

reviews [62, 65, 94–102] and book chapters [74, 80, 86, 103, 104] published in the last few years.

Nanoemulsions Production

As mentioned earlier, nanoemulsions are a type of emulsions, which consists of very small droplet size [4, 5] and may be of O/W or W/O types depending upon the nature of dispersed droplets, that is, oil or water, respectively. O/W nanoemulsions are of prime interest in food science for the encapsulation of lipophilic bioactives. Oil, containing such bioactives, is then dispersed into the aqueous medium and is stabilized by applying surfactants. Formation of nanoemulsions is a non-spontaneous process, and the formed system is metastable, and thus, high energy is required to overcome the surface free energy and to increase the interfacial area between the two phases for the dispersion and breakdown of large oil drops into nanosize droplets

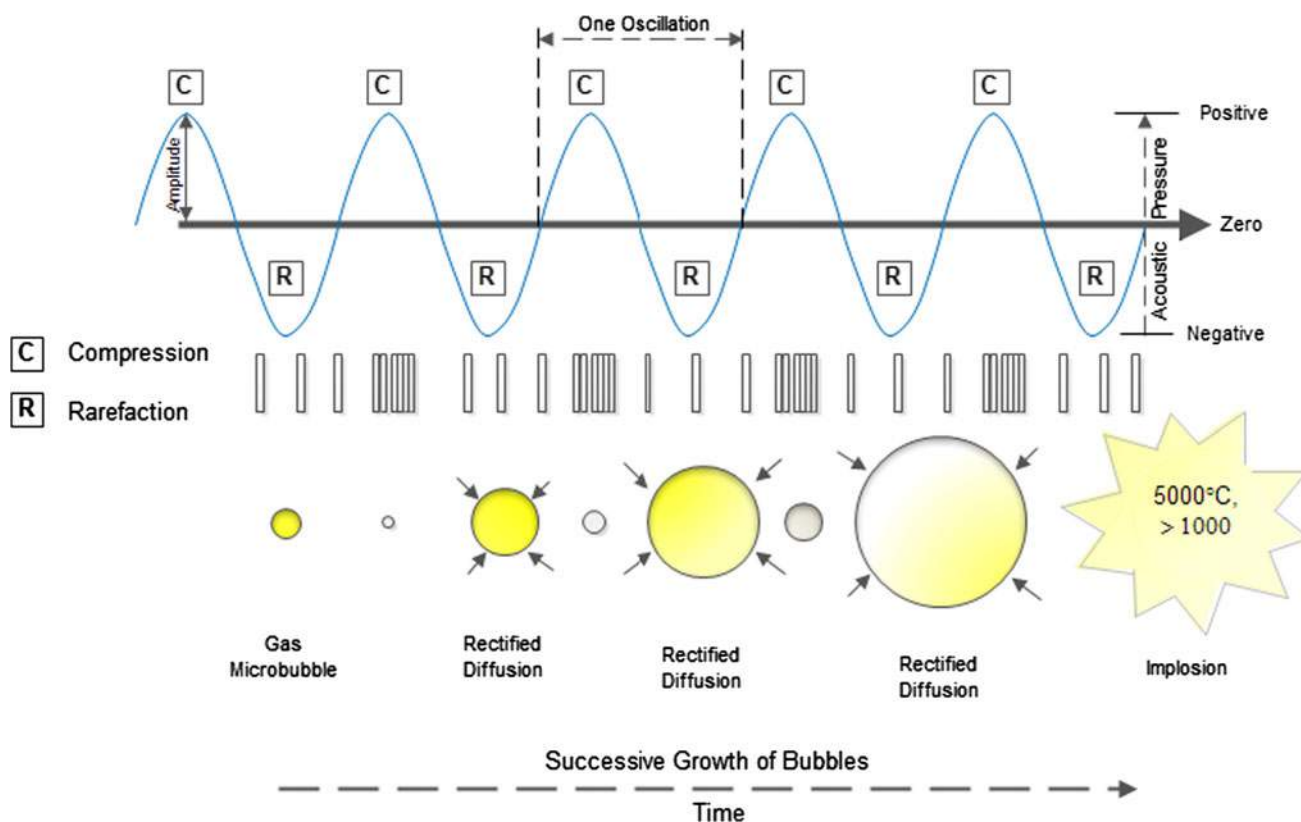


Fig. 3 Schematic depiction of growth and collapse of bubble in acoustic cavitation process

[3, 42]. Energy required by continuous phase in the form of shear to break (deform) droplets of dispersed phase is expressed in terms of Laplace pressure (p) as shown in Eq. 2.

$$p = \gamma \left[\frac{1}{R_1} + \frac{1}{R_2} \right] = \frac{\gamma}{2R} \tag{2}$$

Here, R_1 and R_2 are the radius of curvature of perfectly spherical droplets, thus $R_1 = R_2$, while γ is the interfacial tension of droplets. Emulsions can be created whether the pressure due to applied shear stress is greater than the characteristic Laplace pressure, though extremely high shear stress is required in the case of nanoemulsions [105, 106]. Laplace pressure is the pressure difference between outside and inside of the droplet. Under the effect of this pressure difference, micro-size droplets tend to break up into fine nano-size droplets. Laplace pressure is directly proportional to the surface tension (Eq. 2) which can be lowered by applying emulsifiers. Ultrasonication is categorized as a high-energy emulsification method as it requires intense mechanical forces for the breakdown of droplets into smaller size. Although ultrasonic technique can provide high shear stress due to acoustic cavitation, final size of the nanoemulsion droplet is dependent on the combined effect of shear rate and emulsion rheology [105]. Shear rate and

emulsion rheology are influenced by the design of sonication device, process parameters and the physicochemical properties of nanoemulsion components [39, 41]. Droplet deformation can be expressed in terms of Weber number (We), which is the ratio of external disruptive energy (E_v) over surface energy (E_s), as given below.

$$We = \frac{E_v}{E_s} = \frac{\rho_c (\bar{u})^2 d_{max}}{\gamma} \tag{3}$$

Equation 3 expresses the Weber number for maximum stable droplet diameter (d_{max}) for dilute emulsions where drop coalescence is unlikely. Here, ρ_c is the continuous phase density, \bar{u} is the mean velocity difference across the droplet and γ is the interfacial tension. Droplet disruption increases with increasing Weber number; it is usually assumed that droplet breakup only occurs when the Weber number exceeds a critical value [106, 107]. In Eq. 2, $(\bar{u})^2 d$ is the function of the average power dissipated per mass unit [107, 108] which implies that strong disruption forces (energy) are needed for the production of nano-size droplets.

Role of Coarse Emulsion Preparation

When dispersed phase is added into the continuous phase, a high energy is required to break down planar interfaces

and to initiate the emulsification process. Preferably, coarse emulsion is prepared prior to the ultrasonic treatment in order to increase the sonication process efficiency. A variety of stirrers, blenders and homogenizers have been used for this purpose, as shown in Table 1. Size of coarse emulsion droplets is generally in the range of 1–20 μm , depending upon the type of device used. Final size and distribution of nanoemulsions droplets are directly influenced by the size and PDI of coarse emulsion droplets [36, 109]. Tang et al. [72] studied the influence of coarse emulsion (Ultra-Turrax T18, 9,300 rpm for 30 min) on mean droplet diameter and PDI of Cremophor EL-based O/W nanoemulsions generated by ultrasonication at 60 % amplitude for 100 s. Results showed that lesser energy density, that is, 1.3 J/cm^3 , was needed to produce nanoemulsions of 170 nm from coarse emulsion (average droplet diameter of 1 μm) than that of without coarse emulsion. Reduction in emulsion droplet size was partly attributed to the viscosity decrease in coarse emulsion from 6.23 to 3.98 cP. Additionally, there was slight improvement in the polydispersity of nanoemulsions with the aid of pre-homogenization. Similarly, Tal-Figiel [110] prepared O/W nanoemulsions of size as low as 100 nm, concluded that the preparation of coarse emulsion (stirring at 1,000 rpm) in the first step enabled to generate more stable emulsions with smaller droplets in the final step. Contrary to above discussion, Kentish et al. [39] observed that pre-emulsification had insignificant effect on the droplet size distribution of flaxseed oil nanoemulsion when prepared in the batch cell, however, confirmed that pre-mixing is a vital step in the flow-through ultrasonic arrangements (continuous mode) as it helps develop an emulsion with consistent formulation and facilitates its smooth flow through the cell. Although Takegami et al. [111] managed to prepare ultrasonic-assisted nanoemulsion having a very small mean droplet diameter (50 nm), without pre-emulsification step, ultrasonic treatment time (1 h) was remarkably high. Prolonged ultrasonic treatment is considered detrimental for the stability of nanoemulsion components.

Ultrasonic Process Parameters

Frequency

Appropriate frequency is an important extrinsic-control parameter for the production of ultrasonic-assisted nanoemulsions. Recent literature indicates (Table 1) that a frequency range of 20–24 kHz is frequently used (as it is found effective) for the initiation of cavitation. Low frequencies are preferred for the production of high-power waves [104], and the power generated is inversely related to the square of the frequency, as given in Eq. 4.

$$P \propto \frac{1}{f^2} \quad (4)$$

Above relation indicates that the ultrasonic waves of high power can be produced at lower frequencies. With a frequency increase, time available for the expansion and collapse of bubbles is reduced [86], consequently decreasing the extent of cavitation. Additionally, at higher frequency (~ 100 kHz), cavitation threshold increases, thereby making the sonication process less efficient as additional power will be required to initiate the cavitation process [85, 112].

Treatment Time

The ultrasonication treatment time (ranges from few seconds to several minutes, as shown in Table 1) has a profound effect on the nano-droplet size and PDI. Increasing treatment time means a greater amount of energy available for droplet's disruption, thus decreasing the mean droplet diameter and PDI of emulsion. Salvia-Trujillo et al. [68] studied the effect of sonication time on an average droplet diameter of lemongrass oil–alginate nanoemulsions. Results revealed that increasing treatment time gradually decreased the droplet diameter, showing a final average droplet diameter of 4.31 ± 0.18 nm after being treated for 180 s. Ghosh et al. [113] formulated basil oil (*Ocimum basilicum*) nanoemulsion (oil–surfactant ratio of 1:1) at different ultrasonic treatment times. Results showed that droplet diameter decreased from 57.75 to 41.15 nm, when sonication time increased from 5 to 15 min, respectively. Similarly, Leong et al. [41] prepared 15 wt% sunflower oil nanoemulsions with 5.6 wt% sodium dodecyl sulfate and 13.6 wt% polyethylene glycol using glass batch cell at 5-, 10-, 15- and 20-min residence time. There was a gradual decrease in the average droplet diameter with the increase in time, from around 100 nm at 5 min to 40 nm after 20 min. Tang et al. [72] studied the effect of sonication treatment time (10–100 s) at 50, 60 and 70 % amplitude on the size of aspirin nanoemulsions; it was documented that the mean droplet diameter decreased as sonication time was increased up to 60 s, after which it remained constant. Up to a certain limit, increasing the residence time decreases the emulsion droplet diameter. Above that optimum limit (equilibrium/leveling-off state), further increase in ultrasonic residence time (energy) has an insignificant effect on the droplet diameter [39, 109].

Ultrasonic Power

Sonication power is another important factor, which is taken into account while preparing nanoemulsions. For a

Table 1 Ultrasonic process conditions for O/W food-grade nanoemulsions

| CE ^a preparation | Frequency (kHz) | Energy (W/mL) | Sample volume (mL) | Treatment time (min) | Probe Ø/Amp | Droplet size (nm) | References |
|--|-----------------|---|-----------------------------|----------------------|--------------------------------|-------------------------------|--------------------------------------|
| Ultra-Turrax T25 at 6,500 rpm for 4 min | 20–24 kHz | 1.04 | 100 | 4 | 13 mm/119 and 173 μ m amp | 615 | Kaltsa et al. [141] |
| High-speed blender at 3,400 rpm for 2 min | 24 kHz | 400 W ^b | 100 mL/ min ^c | 3 | 22 mm | 4.31 \pm 0.18 | Salvia-Trujillo et al. [68] |
| Magnetic stirrer | 20 kHz | 750 W ^b | | 15 | 13 mm | 29.3 | Ghosh et al. [113] |
| Ultra-Turrax T25 at 8,000 rpm for 30 min | | 200 W ^b | 200 | 30 | – | 76.02–94.20 | Dey et al. [142] |
| High-speed stirrer | 20 kHz | 15 | 10 | – | 3 mm microtip, 20 % amp | 225.83 \pm 1.52 | Chalothorn and Warisnoicharoen [130] |
| Polytron (PT-MR 3000) rotar–stator system | 20 kHz | 2,160 J | – | 2 | 20 mm | <100 | Li and Chiang [40] |
| Magnetic stirring for 30 min | – | – | – | 1 | 70 % amp | <200 | Rao and McClements [22] |
| CE not necessary | 20 kHz | – | 5 | 20 | 13 mm, microtip 3 mm, 20 % amp | 300 | Camino and Pilosof [143] |
| Not indicated | – | 4,500 J | 20 | – | – | 20–60 | Amani et al. [32] |
| Not prepared | 20 kHz | 5.71 | 7 | 1 | – | \leq 380 | Wulff-Perez et al. [131] |
| Ultra-Turrax mixer at low shear rate for 1–2 min | – | 2.3 | 15 | <5 | 12-mm horn and 30- μ m amp | 50 | Leong et al. [41] |
| Not prepared | – | 500W ^b | \sim 30 | 60 | – | 58.2 | Takegami et al. [111] |
| Ultra-Turrax, at 13,500 rpm for 2 min | 20/24 kHz | 1.1 | 50 | 5 | 19/22 mm | 120 | Kentish et al. [39] |
| Silverson, UK, rotor–stator system | 24 kHz | 80.5 \times 10 ⁶ Joules/m ³ | 400 | 1.6 | 22 mm, | \sim 500 100 μ m amp | Jafari et al. [36] |
| Magnetic stirring, 150 rpm for 30 min at 25 °C | – | – | 10 | 2 | 3 mm | \sim 200 | de Araújo et al. [144] |
| High-speed IKA blender | 24 kHz | 400 W ^b | \sim 500 | 0.3–1 | 22 mm, 100 μ m amp | 243/298 | Jafari et al. [79] |
| Premixing by magnetic stirrer | 24 kHz | 10 ⁹ J/m ³ | 1.27 ^c | 0.42 | 100 % of maximum amp | \sim 500 | Freitas et al. [40] |
| Silverson homogenizer, at 6,000 rpm for 2 min | 20 kHz | 500 W ^b | 5 | 5 | 13 mm, 21 % amp | 132 \pm 1.7 | Ganta and Amiji [145] |
| Stirred for 10 min | 20 kHz | 0.5 | 60 | 5 | – | 700 | Cucheval and Chow [116] |

Table 1 continued

| CE ^a preparation | Frequency (kHz) | Energy (W/mL) | Sample volume (mL) | Treatment time (min) | Probe Ø/Amp | Droplet size (nm) | References |
|---|-----------------|---------------|--------------------|----------------------|-----------------------------------|-------------------|------------------------|
| Magnetically stirred for 2 min at 500 rpm | — | 800 J/mL | 10 ^c | — | 15.6 mm, 90 µm amp (peak to peak) | 79 | Peshkovsky et al. [13] |

^a Coarse emulsion

^b Applied power

^c Flow rate (mL/min)

given sample, it is likely to achieve an acoustic cavitation threshold at any power by varying the residence time. In order to achieve droplets of desired diameter in shortest possible time, ultrasonic power is usually set at a reasonable level through optimization. In other words, increasing sonication power significantly reduces the sonication time until it reaches to the point where no further effect is noted [42]. Instead of discussing the nominal applied or generated power alone, it is more meaningful to consider the power delivered from the surface of probe tip (ultrasonic intensity) and the actual amount of energy dissipated (energy density) into the sample. Total energy delivered (E_{total}), expressed in Joules (J) or kilojoules (kJ), and is the product of delivered power (P) of sonication and time (t) of sonication, as given below (Eq. 5).

$$E_{\text{total}} = P \times t \quad (5)$$

$$E_v = \frac{\text{energy input}}{\text{dispersing volume}} \quad (6)$$

Equation 6 shows volumetric acoustic energy density (E_v) expressed in W/cm^3 or W/mL , is the energy (power) dissipated per unit volume of sample for a given period of time. Above relations (Eq. 5, 6) indicate that emulsification efficiency can be increased by manipulating the total amount of energy delivered into the system. Calorimetry is a commonly used technique to determine the dissipated ultrasonic power [39, 62, 114, 115] in which the change in temperature of sample over time due to ultrasound is measured, as given below:

$$P = mC_p \left(\frac{\Delta T}{\Delta t} \right)_{t=0} \quad (7)$$

Here, m is the mass (kg), C_p is the specific heat ($3.73 \text{ kJ}/\text{kg}/^\circ\text{C}$) and $\Delta T/\Delta t$ is the change in temperature over time ($^\circ\text{C}/\text{s}$), of the sample. After the determination of P value in Eq. 7, it is possible to estimate the ultrasonic intensity (UI) distributed over surface area A for particular probe of a circular area. At a given frequency and applied power, UI can be calculated as follows:

$$UI = \frac{P}{A} = \frac{P}{\pi r^2} \quad (8)$$

Where, r is the mean radius of probe microtip (cm). Ultrasonic intensity, expressed in W/cm^2 , helps measure the power transmitted through the surface of a probe tip into medium. Ultrasonic intensity is proportional to vibration amplitude of ultrasonic source, consequently increasing the intensity of vibration and cavitation. In order to achieve cavitation threshold, a minimum intensity is required, as higher amplitudes may deteriorate the ultrasonic transducer, resulting in reduced cavitation and poor transmission of ultrasound through the sample [85]. However, authors suggested the use of higher amplitude (ultrasonic intensity) to initiate a cavitation process in high viscosity samples as it helps overcome resistance offered to the movement of a probe tip.

Kentish et al. [39] demonstrated that the conversion of applied power to delivered power was less efficient at higher power levels which imply that with the increase in ultrasonic intensity, the conversion rate of applied power into delivered power reduces. Possible reason for power transmission decrease, as explained by researchers, is the increased production of acoustic bubbles in horn vicinity, which shield the remainder of solution from ultrasonic energy source.

Although ultrasonic intensity provides a fair assessment of power delivered and the power dissipated into system, it is challenging to compare and reproduce results due to the geometric variation of ultrasonic reactors. In order to avoid these problems, estimation of dissipated energy in terms of power density (W/cm^3) is a more realistic approach [62]. For accurate results, energy dissipated into the container walls should be considered also, for the calculation of energy density.

Delmas et al. [42] studied the effect of different sonication energy inputs (J/mL) on nanoemulsion droplet size (formulation: 272 mg of NC75; 276 mg of Myrj s40; 52 mg of Lipoid s75; 1,400 mg of NaCl 154 mM, dispersed phase weight fraction: $\Phi = 0.3$, sample size: 2 mL)

and found that increasing energy input from 6,250 to 50,000 J/mL significantly reduced the droplets size from ~ 125 to ~ 50 nm until it reached a plateau for large energy inputs (energy input $>50,000$ J/mL). It was concluded that, for a constant composition, saturated size is reached whatever the sonication power is, if sonication is performed at sufficient energy inputs, and indicated that the energy provided to the system is the major control parameter to be considered. Similar conclusions are presented by other researchers [116]. Briefly, accurate measurement of local distributions of acoustic power (energy) in the sample may provide better assistance to optimize other process parameters as well, to prepare ultrasound-assisted emulsions without adversely affecting the formulation.

Hydrostatic Pressure

The pressure exerted by a liquid in its state of rest is known as hydrostatic pressure. Hydrostatic pressure is known to affect both the onset and intensity of cavitation for liquid sample, consequently affecting the power dissipation capacity of ultrasound device [43, 117]. Hydrostatic pressure (p_h) is a part of the total external applied pressure (p_m) at the time of bubble implosion, that is, $p_m = p_h + p_A$, where p_A is the acoustic pressure [112, 118]. Normally, increasing hydrostatic pressure results in the increase in cavitation intensity and cavitation threshold [43, 118].

Behrend and Schubert [117] used flow-through unit to prepare emulsion at different hydrostatic pressures for a constant flow rate and noted that there was an increase in the size of droplets with increasing pressure and attributed this behavior to a partial suppression of the cavitation process. They also found that cavitation intensities peaked at a moderate pressure ($\Delta p \leq 1.5 \times 10^5$ Pa), as highest energy densities were obtained at that pressure level.

Leong et al. [41] studied the effect of increasing overpressure (pressure above the ambient pressure) in the continuous flow-through cell on the droplet diameter of 15 wt% sunflower oil emulsions. About 20 mL samples of SDS-PEG, stabilized emulsions were sonicated for 1 min under varying overpressures; overpressure of 300 kPa resulted in a significant reduction in particle size to 57 nm at a delivered power of 2.3 W/mL while no emulsification was achieved above 450 kPa. It is evident in the studies discussed; although hydrostatic pressure has no significant effect on the constant energy density, it increases the cavitation threshold and causes more violent collapse of bubbles. Consequently, fine emulsion droplets can be produced at lower level energy density under overpressure conditions.

Dissolved Gas Concentration

Effect of dispersed/dissolved gas concentration in liquid sample is well established on the cavitation process. Gas/air present in the liquid sample act as nuclei for the formation and growth of micro-bubbles, thus necessary for the cavitation onset. Although dissolved gas tends to lower the cavitation threshold, further increase in gas concentration increases the gas-vapor ratio inside bubbles. Increase in gas-vapor ratio reduces the intensity of shock wave by cushioning the collapse of bubbles (dampening), thereby negatively affecting the cavitation phenomena [43, 117, 119]. However, cavitation threshold increases with decreasing the gas concentration. Behrend and Schubert [117] using a flow-through unit for emulsion preparation also studied the effect of gas content on droplet size and found that mean droplet size was the function of the energy density. No clear effect of gas content was observed on droplet disruption at the constant energy density.

More recently, the influence of dissolved gas type and concentration on ultrasonic cavitation processes, focused on sonoluminescence and sonochemistry, is reviewed by Rooze et al. [120]. Authors concluded that gas and vapors define the thermal properties of bubble during collapse, and addition of gas to liquid lowers its surface tension, thereby increasing nucleation. More research is needed to determine the effects of gas type and concentration (dissolved/dispersed into the liquid sample) on the preparation process of ultrasonically assisted nanoemulsions, droplet size and PDI.

Temperature and Viscosity

Series of explosions and implosions in sample during the cavitation process generate high temperature and pressure. Based on the thermodynamic model for a bubble collapse (assuming adiabatic compression), the maximum theoretical temperature within the bubble (T_{\max}) can be calculated as follows [89];

$$T_{\max} = T_o \left(\frac{P_m(\gamma - 1)}{P_v} \right) \quad (9)$$

Here, T_o is the ambient temperature of solution, P_m is the external applied pressure in the liquid, γ is the specific heat ratio of the gas/vapor mixture and P_v is the pressure in the bubble at its maximum size. Heating cycles that take place at the micro-scale bubble interface (due to cavitation) increase the overall temperature of the liquid over time. Temperature increase due to cavitation results in reducing the viscosities of dispersed and continuous phases of emulsion, thereby lowering the interfacial tension and Laplace pressure [43, 121]. Consequently, less energy is needed for emulsification and production of nanoemulsions. Although cavitation

process increases with the elevation of temperature (as the number of nuclei increase), vapor pressure also increases, thereby reducing the intensity of the acoustic shock waves [43, 121]. Additionally, temperature increase during ultrasonic treatment may damage the formulation components of nanoemulsion [4] including heat-sensitive bioactives. Therefore, it is very important to control the temperature of sample being emulsified, either by manipulating the ultrasonic process parameters such as treatment time and amplitude or by using assembly equipped with a cooling system.

Formulation Related Parameters

Dispersed Phase (oil)

Oil phase plays a major role for the solubility of lipophilic bioactives. A variety of vegetable oils have been used in the production of O/W nanoemulsions, as shown in the Table 2. Physicochemical characteristics of oil significantly influence the formation, stability and properties of nanoemulsions [14, 38]. Viscosity, ability to solubilize bioactives and bioaccessibility of oils are critical factors to be considered while selecting the oil type. Triacylglycerols are frequently used oils for the preparation of food-grade nanoemulsions due to low-cost and better functional and nutritional properties [14]. Generally, choice of oil type determines the energy required for the breakdown of large-size oil droplets into nanosize. For instance, medium- and short-chain triglycerides (MCT and SCT)-based oils exhibit high interfacial tension and viscosity, and strong hydrophobicity, thus requires high-energy approaches. However, oils with less hydrophobicity and viscosity (essential/flavor oils) are considered suitable for low-energy methods because of their low interfacial tension.

Additionally, selection of oil type for nanoemulsion preparation is a compromise between the size and stability of oil droplets, that is, more stable emulsions can be prepared from MCT and SCT. On the other hand, essential/flavor oils (more polar) facilitate the formation of fine emulsion droplets, but their stabilization over time is challenging due to Ostwald ripening. Ostwald ripening is a process in which very finer droplets of emulsion dissolved into continuous phase, diffuse and redeposit upon larger droplets, thus increasing the average size of emulsion droplets [122]. This problem should be tackled by using food-grade oils of fine-tuned hydrophobicity to achieve the desired size and stability of dispersed droplets. Hydrophobicity of oils can be enhanced by employing mixed oil systems in the nanoemulsions. For instance, Wooster et al. [38] managed to stabilize nanoemulsions containing soluble oil, that is, tricaprillin, against Ostwald ripening by adding peanut oil (insoluble oil).

Another issue is the oil stability, as there is some concern that the high local intensities in cavitation process may trigger lipids oxidation during homogenization [14, 65]. Chemat et al. [123] used low-frequency ultrasonic treatment (20 kHz; 450 W or 47 kHz; 450 W for 1 h) during food emulsification and processing of sunflower, olive and soybean oils. Metallic and rancid odor was detected in the treated samples which were attributed to the oxidation process induced by cavitation. In another study [124], similar conclusions were drawn for ultrasonically treated (20 kHz and 150 W for 0.5–2 min) sunflower oils. Cavitation was considered as a major factor responsible for oxidation/deterioration of flavor and composition of oils, besides the suspected role of copper for the formation of oxy radical species. Recently, Pingret et al. [125] studied the effects of ultrasound treatment on sunflower oil using two different horns (Titanium and Pyrex). Identification and quantification of formed radicals and assessment of physicochemical parameters revealed that there was an increase in radicals in addition to the modification of physicochemical parameters in sonicated oils due to oxidation. Furthermore, nature of the horn material contributed to oil degradation either by increased temperature (for Titanium) or by radical formation (for Pyrex). In a recently published review, authors [126] have discussed the potential factors, that is, metals, light, high temperatures, radicals and minor compounds present in oils, and underlying mechanisms involved in the degradation of sonicated edible oils. They divided the whole process into initiation, propagation and termination phase. In the first phase, alkyl radicals are formed from unsaturated lipids. In the next phase, formed radicals, when react with hydrogen from other lipid molecules, hydroperoxides and lipid alkyl radicals are produced. In the final phase, decomposition of hydroperoxides leads to the formation of a range of radical products including hydroxyl, peroxy-free and hydroxyl-free radicals, consequently triggering the rate of oxidation and propagating chain reaction until the termination phase is reached. Contrary to above discussion, Leong et al. [41] prepared sunflower oil-based nanoemulsions at energy input levels of around 1,000 J/mL and found that oil stability was unaffected by the sonication process.

By properly addressing the oxidation initiation factors, that is, preparing O/W emulsions by ultrasonic cavitation induced at lowest possible energy levels ($P \times t$; Eq. 5) and avoiding the prolonged exposure of emulsions to light and high temperatures during processing and storage, extent of oil degradation can be controlled to some extent. In addition, reducing the erosion of ultrasonic horn (by lowering amplitude and treatment time) and selecting the oils having minimum concentration of radicals or other trace compounds are also critical in this regard. Further research in this area is needed for the better elucidation of ultrasound-

induced degradation and its pathways and to establish the clear relationship between oil type and its stability as affected by the ultrasonic process parameters.

Aqueous Phase (surfactants)

Surfactants or emulsifiers are considered indispensable for the formation and/or stability of emulsions. For O/W emulsions, emulsifiers are usually dissolved into the aqueous phase. As mentioned earlier, emulsifiers help reduce interfacial tension, consequently less external pressure is required for droplet disruption. Disruption process and the formation of new droplets are followed by adsorption of emulsifiers to the interface of freshly prepared droplets. Adsorption kinetics vary from emulsifier to emulsifier, which determines their ability to prevent droplet re-coalescence [38, 127]. Re-coalescence is a process of fusion of two or more droplets after thinning and disruption of the liquid film, which results in the formation of larger droplets and ultimately, emulsion completely separates into its phases [128]. In case the concentration of emulsifier is high enough, it will cover the interface completely, thus offering stability to nano-droplet by preventing the re-coalescence [121].

It is generally expected that nanoemulsions show better stability against droplet aggregation than conventional emulsions, as their small droplet size influences the Brownian motion and colloidal interactions [2, 128]. Minimum size of emulsion droplet during emulsification (d_{\min}) can be calculated (see Eq. 9) depending upon the type (Γ_{sat}) and concentration of emulsifier (C_s) used [121, 129].

$$d_{\min} = \frac{6\Gamma_{\text{sat}}\varphi}{C_s} \quad (10)$$

Here, φ is the volume fraction of dispersed phase while Γ_{sat} (expressed in mg/m^2) is the surfactant load at saturation and defined as mass of emulsifier adsorbed per unit surface area of an interface when the surfactant concentration is in excess. Above relation (complemented by the turbulence phenomena) shows that droplets with small size can be produced by increasing C_s , decreasing φ , or using an emulsifier with a lower Γ_{sat} .

Varieties of food-grade emulsifiers/stabilizers are available for the formulation of nanoemulsions. Some commonly used emulsifiers in the fabrication of ultrasonic-assisted food nanoemulsions include small-molecule surfactants (e.g., Tweens, Spans, Brijs), amphiphilic proteins (e.g., whey proteins), phospholipids (e.g., egg-, soy- and dairy-based lecithins), amphiphilic polysaccharides (e.g., modified starches, gums) and block copolymers (e.g., Pluronics) as shown in Table 2.

Emulsifier concentration in the solution can play a decisive role to estimate the saturation radius of droplets

resulting from emulsification, provided that, all other parameters are kept constant. Abismail et al. [76] studied the variations in droplet size (preparation conditions: $t = 30$ s, $\varphi = 0.25$, power = 130 W) as a function of surfactant concentration and observed that diameter decreased from micron to sub-micron range when surfactant concentration increased from 1 to 10 g/L. Chalothorn and Warisnoicharoen [130] studied the effect of whey protein isolate (WPI) concentration (1–20 % w/v) on droplet size and PDI of the *Echium plantagineum* L. seed oil (5 % w/v)-based nanoemulsions prepared by using 750 W/1,750 J of delivered energy at 20 % amplitude. There was a gradual and significant decrease in the droplet diameter and PDI with increased WPI concentration; minimum diameter and PDI were found at 20 % w/v WPI concentration. Rao and McClements [22] observed similar trend in the formation of Tween 80-stabilized lemon oil (10 wt%) nanoemulsions. Droplet diameter of ~ 50 nm was achieved when the concentration of Tween 80 increased from 7 to 13 %. Wulff-Perez et al. [131] successfully prepared olive, sesame and soybean oil (25 % v/v) nanoemulsions stabilized by a small amount (1 %) of surfactant (Pluronic F68), and the droplet size (~ 380 nm) was found stable against coalescence after 9-h storage. In another study [41], influence of increasing Span 80 (co-surfactant) content to stabilize 15 wt% O/W nanoemulsions, initially stabilized by 5.3 wt% Tween 80, was noted on the droplet diameter. Increase in Span 80 content up to 6 % steadily reduced the average diameter. Above 6 wt%, steady increase in average droplet diameter was recorded, suggesting that the optimum ratio between Tween 80 and Span 80, required for synergetic effect, was disturbed. Takegami et al. [111] employed two co-surfactants, sodium palmitate and sucrose palmitate for reduced droplet size and for stability enhancement, respectively, besides the main emulsifier (egg yolk Phosphatidylcholine), to prepare lipid nanoemulsions. Obtained nanoemulsions had an average droplet diameter of 50 nm and found highly stable during 1-year storage period.

Besides concentration, physicochemical characteristics of emulsifiers are also critical for the formation and stability of nanoemulsions. Low molecular weight nonionic emulsifiers (Tweens, Spans) facilitate preparing the droplets of very small size [41, 68, 111, 113, 132]. However, it is challenging to fabricate fine droplets from food biopolymers (proteins, modified starches, gums) due to their high molecular weight. Recently published research in this area indicates that the application of food biopolymers to prepare and stabilize food-grade nanoemulsions is increasing. Although protein-based emulsifiers have an ability to produce smaller emulsion droplets when used at lower concentrations than that of polysaccharides, high local intensities of ultrasonic treatment may denature the

Table 2 An overview of food-grade O/W nanoemulsions assisted by ultrasonication

| Oil phase | Surfactant/co-surfactant | Functionality | Storage stability studies | References |
|--|---|---|--|--------------------------------------|
| Olive oil | Lacprodan 80(WPC ^a) XG ^b , GG ^c , LBG ^d | Delivery vehicle | Emulsions were stable after 10 days storage at 5 °C for 0.5 wt% stabilizers concentration | Kaltsa et al. [141] |
| Lemon grass essential oil | Tween 80 | Flavor/ antimicrobial | Not reported | Salvia-Trujillo et al. [68] |
| Basil oil | Tween 80 | Antioxidant/ antimicrobial | After 1 month storage, no changes observed in droplet size and phase characteristics | Ghosh et al. [113] |
| Fish oil | Tween 80, Span 80 | Antioxidant/ delivery vehicle | After 48 h, stable against heating–cooling and freeze–thaw cycles, and centrifugation tests | Dey et al. [142] |
| <i>Echium plantagineum</i> L. seed oil | Whey protein isolate | Antioxidant/ delivery vehicle | Size and phase stability observed up to 60 days of storage | Chalothorn and Warisnoicharoen [130] |
| D-limonene | Span 85, Brij 98/ethylene glycol | Flavor/ antioxidant/ delivery vehicle | Droplet size increased after 14 weeks storage at 4 and 25 °C to 99.1 and 58.8 nm, respectively | Li and Chiang [40] |
| Lemon oil | Tween 80, PG8 | Flavor/delivery vehicle | Phase separated and cream layer formed after overnight storage | Rao and McClements [22] |
| Sunflower oil | HPMC ^e (E5LV) | Delivery vehicle | Droplet size remained almost unchanged after 20 days storage at ambient temperature | Camino and Pilosof [143] |
| MCT ^f | Tween 80/ethanol | Delivery vehicle | Emulsion stored at 30 °C for 30 days Exhibited a very small growth of droplet size | Amani et al. [132] |
| Olive, Sesame or Soybean oil | Pluronic F68 | Delivery vehicle | Stable emulsions prepared with oil % age as high as 25 % after 9 h storage time | Wulff-Perez et al. [131] |
| Sunflower, Canola oil. | Tween 80, Span 80, SDS ^g | Delivery vehicle | Expected storage stability up to several weeks at room temperature | Leong et al. [41] |
| Oleoresin capsicum | Tween 80, PG ^h , Sucrose monostearate | Capsaicin delivery | Droplet size remained stable during storage | Choi et al. [146] |
| Soybean oil | PC ⁱ /sodium palmitate, sucrose palmitate | Delivery vehicle | No significant change in droplet size and size distribution, after 12 months at room temperature | Takegami et al. [111] |
| Flax seed oil | Tween 40 | Delivery vehicle | Not reported | Kentish et al. [39] |
| D-limonene oil | Hi-Cap 100/maltodextrin (DE = 16–20) | Flavor | Not reported | Jafari et al. [36] |
| MCT | Tween 80/Span 80 or lecithin or Pluronic F68 | Drug delivery | Stored at 4 °C for 60 days, no significant | de Araújo et al. [144] |
| D-limonene oil | WPC/Hi-Cap 100 | Flavor | Not reported | Jafari et al. [79] |
| Linseed oil | Tween 40 | Drug delivery | Not reported | Freitas et al. [140] |
| Flaxseed oil | Egg lecithin, ethanol | Paclitaxel and Curcumin delivery | After 3 months storage, no phase separation observed, slight increase in the particle size | Ganta and Amiji [145] |
| Soybean oil | Tween 80 | – | Stored at 5 °C for 24 h, no change in the droplet size observed | Cucheval and Chow [116] |
| Soybean oil | Tween 80, Span 80 | Delivery vehicle | Stable for almost 1 year at 25 °C | Peshkovsky et al. [13] |

^a Whey protein concentrates^b Xanthan gum^c Guar gum^d Locust bean gum^e Hydroxypropylmethylcellulose^f Medium-chain triglyceride^g Sodium dodecyl sulfate^h Propylene glycolⁱ Phosphatidylcholine

protein as they are sensitive to higher temperatures. On the other hand, OSA starches could be a better choice due to their stability against high temperature and a wide range of pH and ionic strength [129, 133]. Sodium caseinate–lactose conjugates, collected at early stages of glycation during Maillard reaction, have also been successfully used as emulsifier to prepare fine (droplet diameter: 421.49 ± 2.11 nm) and stable O/W emulsions from sunflower oil by the ultrasonic method [134].

Further research may assist to find the influence of ultrasonic process parameters on the performance of emulsifiers. Additionally, selection of appropriate emulsifiers becomes easier if the adsorption rate of surfactant molecules or macromolecules at the oil–water interface during homogenization is established.

Aqueous and Dispersed Phase Viscosity

Although several researchers have investigated the influence of continuous and dispersed phase viscosities on droplet disruption and/or size for ultrasound-assisted emulsions [135, 136], data on the viscosity effects in emulsification at nanoscale are scarce in the literature. For O/W systems, type of stabilizer dissolved in the aqueous medium determines the continuous phase viscosity. Behrend et al. [135] used glycerol or polyethylene glycol-stabilized emulsions with sodium dodecylsulfate as an emulsifier to study the influence of continuous phase viscosity on the droplet size. Results revealed that increased continuous phase viscosity due to the addition of stabilizer formed smaller droplets. Similar results were reported for protein-stabilized oil-in-water emulsions prepared using microfluidizer [137]. Due to increased continuous phase viscosity, drainage time of liquid out of the region between two approaching droplets increases, concomitantly increasing the coalescence time or decreasing coalescence frequency.

As already mentioned somewhere, comparatively, it is easier to prepare O/W emulsions of fine droplet size and low PDI from low-viscosity dispersed phases. Furthermore, loading of the carrier oils with bioactives may modify the viscosity of dispersed phases. For instance, addition of vitamin E acetate into the MCT oil increased the viscosity and interfacial tension of oil phase [33]. Consequently, mean droplet diameter (d_{32}) of 10 wt% O/W emulsions (produced by high-pressure homogenization using either Q-Naturale or Tween 80 as surfactant) was also increased. Apparently, similar behavior is expected in the case of other high-energy emulsification methods, including high-intensity ultrasonication. Gaikwad and Pandit [136] investigated the influence of dispersed phase (soybean oil, groundnut oil, paraffin oils) viscosity on the droplet size of O/W emulsions; noticed that the droplet size of emulsion produced from low-viscosity oil (soybean oil) was smaller

as compared to other oils. Reason behind this phenomenon was explained by the fact that cavitation threshold level dropped with decrease in the oil viscosity and interfacial tension. More recently, Nazarzadeh and Sajjadi [106] studied the effect of dispersed phase viscosity on droplet size of O/W nanoemulsions, prepared from silicone oils of varying viscosities in the presence of SDS (surfactant) at 4-min ultrasonic treatment time. Results showed that increasing viscosity of dispersed phase significantly reduced the droplet size till midrange viscosities, followed by a sharp increase at higher viscosities. It was concluded that drop rupturing mechanism appeared to change with the change of phase viscosity ratio.

Besides viscosity, disperse-to-continuous phase viscosity ratio (ξ) is an important factor for preparing stable nanoemulsions [38, 106].

$$\xi = \left(\frac{\eta_d}{\eta_c} \right) \quad (11)$$

In Eq. 11, η_d is the viscosity of dispersed phase while η_c is the viscosity of continuous phase. Braginsky et al. [138] found that, for a turbulent shear, there was an optimal range for ξ (0.5–5) where droplet disruption was most efficient. It is clear from the above relation (Eq. 11) that too high value of ξ can be brought down within the optimal range either by using low-viscosity oils or by increasing continuous phase viscosity. Wooster et al. [38] added PEG- to SDS-stabilized triglyceride nanoemulsions in order to increase the continuous phase viscosity, which resulted in enhanced droplet deformation and reduction in nanoemulsion size. In fact, addition of PEG lowered the ξ value from 56 to 4.2, which was within the optimal range (0.5–5) for the efficient disruption of oil droplets.

Dispersed Phase Volume Fraction

The volume fraction of dispersed phase (ϕ) is directly related to the minimum diameter (d_{min}) of droplet. It is already shown (see Eq. 10) that the increase in disperse phase (oil) volume fraction results in the increase in droplet size (at constant process variables), as confirmed by Abismail et al. [76]. Possible reasons could be the increase in emulsion viscosity, depletion of emulsifier and coalescence due to the increased rate of collision frequency [121].

Optimization and Operation Considerations

As discussed in the previous sections, number of process and formulation variables may affect the preparation process of ultrasound-assisted nanoemulsions. In high-energy methods, instead of formulation parameters, preparation variables predominantly influence the nanoemulsion characteristics

[139]. Hence, the preparation parameters involved should be optimized to prepare stable nanoemulsions of smallest droplet size and narrow PDI values by using minimum energy input (power and time). Another purpose of the optimization is to enhance the functionality of nanoemulsions as a delivery vehicle for food bioactives. Additionally, it should be ensured that the processing conditions do not damage the formulation components of nanoemulsion, including the bioactive material.

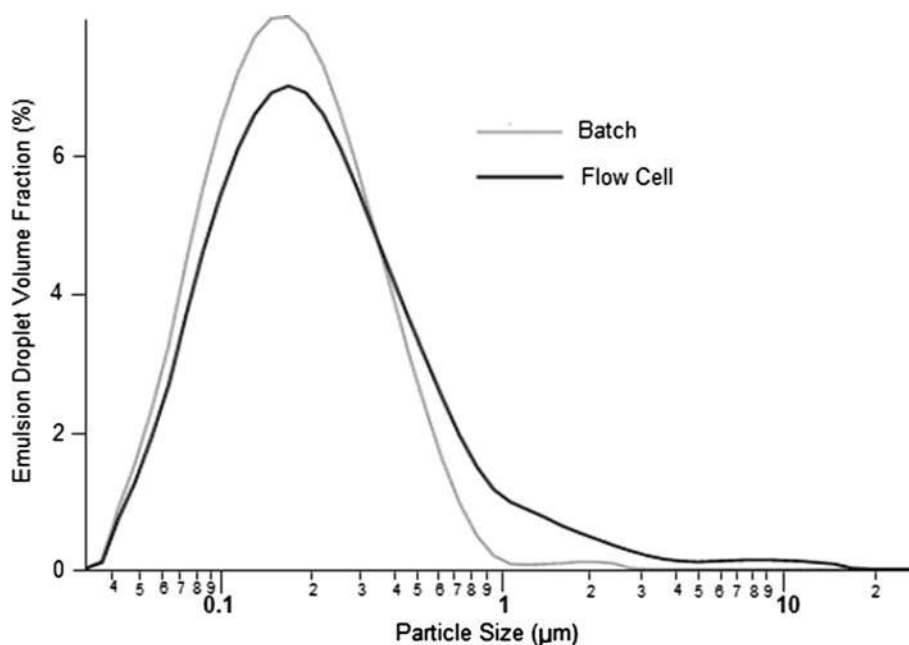
Certain operation-related issues may also adversely affect the cavitation process, thus limiting the potential efficiency of the apparatus. For instance, immersion of the ultrasonic probe should be deep enough to start cavitation. Otherwise, agitation will be the predominant phenomena, resulting in the production of potentially harmful aerosols besides poor emulsification. Another issue is the erosion of probe tip, which results in the contamination of sample with metal particles [39, 79, 140]. These particles may trigger the oxidation and induce the development of off-flavors in the prepared emulsions. Additionally, output energy of the probe with an eroded tip is decreased, thereby reducing the system efficiency. Frequent maintenance checks and the replacement of severely eroded tips may resolve this problem. Alternatively, flow-through cell can be introduced in order to avoid the direct contact of sample with the ultrasonic probe [79]. Furthermore, design of vessel may influence the distribution of ultrasonic energy into the sample [39, 85]. Ultrasonic intensity attenuates both radially and axially in the liquids [112]; containers with a narrow diameter are preferred to ensure a maximum sample-probe contact area in batch systems [85]. Noise produced by the cavitation process is harmful to humans as

it can cause hearing loss. Installation of cabinets insulated with acoustic-shock absorbing material is necessary to reduce the harmful impact of generated noise.

Scaling-Up: Challenges and Future Perspectives

High-intensity ultrasound has been successfully employed for years in several food process operations on the laboratory scale. Only recently, researchers have tried to harness the full potential of this technology by making it operational on industrial scale. Transition from small to large-scale production requires specially designed equipment, ensuring the continuous/uninterrupted flow of liquid material. Researchers have developed flow-through cells to prepare food-grade nanoemulsions. However, there is a consensus that the current technology is far from being developed for industrial-scale applications [10]. A major issue with the flow-through equipment is the uneven distribution of ultrasonic power intensity to the emulsions. Kentish et al. [39] compared the particle distributions of O/W emulsions prepared from flax seed oil (15 vol.%) and stabilized by Tween 40 (5.6 vol.%), using acoustic cavitation in a batch and flow-through cell. Particle distributions from the batch process (obtained at 280 W nominal input power for 25 min) were found superior compared to flow-through cell results (single pass, nominal power: 350 W, pump speed: 20 mL/min, residence time: 17 s), as shown in Fig. 4. Mason et al. [105] suggested that re-circulating the emulsion mixtures through the region of highest shear rate in continuous operations may result in the uniform droplet size distributions. Improved design of

Fig. 4 A comparison of particle distributions for 15 vol.% flax seed O/W emulsions stabilized by 5.6 vol.% Tween 40, in batch (25 min sonication at 280 W) and flow-through cell (one pass, 350 W, pump speed 20 mL/min, residence time 17 s). Reproduced with permission from Ref. [39]



ultrasonic flow-through cell presented by Freitas et al. [140] was an important development toward the production of nanoemulsions on industrial scale. New design enabled the preparation of food-grade emulsions in continuous, contact-free and contamination-free manner using ultrasound treatment. More recently, Peshkovsky et al. [13] have successfully scaled up the laboratory process into a pilot-scale system for the production of soybean oil-based translucent O/W nanoemulsions (79 nm) by high-amplitude power ultrasound. Briefly, Barbell horn (35 mm output diameter, two cavitation zones) was used to scale up the process by a factor of 10 without reducing the amplitude (90 μm peak to peak). Furthermore, possible scale-up of a pilot plant to an industrial-scale system by a factor of ~ 5 was also anticipated by using half-wave Barbell horns (output diameters up to 75 mm). Such developments will trigger the transformation of pilot-scale systems into a full-fledge industrial process.

As high-intensity ultrasound is considered an emerging technology, further research and development is needed to standardize and scale up the technology for food processing in general and nanoemulsions production in particular. Interest to manufacture continuous flow cells with improved design is increasing, which will promote the application of high-intensity ultrasound for large-scale production. Patist and Bates [80] have indicated that the availability of high-power ultrasonic generators (~ 32 kW) and cells of increased flow rate capacity (>7 m^3/h) and the feasibility to integrate them smoothly into the already existing industrial setup are positive developments in the technology. Additionally, successful attempts to improve the efficiency ($\sim 85\%$) of transducers, competitive energy cost, low maintenance costs and increased chances to get patent protection [80, 97] will make it a preferable homogenizing technology among food processors in the near future.

Concluding Remarks

Nanoemulsions are well-known vehicles for the stabilization and controlled delivery of active ingredients in the food and pharmaceutical industry. Furthermore, O/W nanoemulsions have potential to improve the rate of dissolution of poorly water-soluble bioactives, thereby enhancing their bioavailability. Though the application of ultrasound for food processing is not new, potential of high-intensity ultrasound as an efficient tool to prepare nanoemulsions have been recognized by several researchers, only recently. Acoustic cavitation phenomena in liquids induce the rupture of the liquid and the formation of bubbles, leading to the process of emulsification/homogenization. Emulsification process is needed to be optimized by controlling the ultrasonication process

parameters (energy, intensity, temperature and pressure) along with formulation variables (medium viscosity, surface tension and dissolved gas) to obtain stable nanoemulsions with fine droplets size and low polydispersity index. Ultrasound-emulsification is considered as a laboratory-based prototype process, and further research to improve the efficiency of ultrasonic generators and transducers is needed to transform this technology into a large-scale and economically profitable application for nanoemulsions production. In this context, designing the continuous flow-through cells and their comparatively easier integration into the already existing commercial units are positive developments. Additionally, improved control of factors influencing the acoustic cavitation and better understanding of its effects on the nanoemulsions quality could make ultrasonication an efficient and reliable alternative to the traditional emulsification methods.

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