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Nanoemulsions in Food Industry

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Abstract

A great attention has been received in the last few years for nanotechnology applications in food as well as pharmaceutical industries. People are looking for healthy and safe food worldwide. Therefore, researchers have been currently focusing on nanoemulsion technology that is particularly suited for the production of functional food. This chapter includes an overview about nanoemulsion terminology and formulation, various approaches for production of nanoemulsions which include high energy approaches such as high-pressure valve homogenization, microfluidizers and ultrasonic homogenization, and low energy methods such as spontaneous emulsification, phase inversion composition, phase inversion temperature and emulsion inversion point. In addition, the applications of nanoemulsions in food industry are discussed in detail.

Keywords: nanoemulsions, formulation, production approaches, food industry, applications

1. Introduction

Serious health-related problems contribute to the worldwide distribution of healthier, safer, and cost-effective food products. Additionally, functional foods were introduced as a tool to give an additional function to food. This can be achieved by increasing the production of existing biologically active molecules or adding new bioactive ingredients. Therefore, food products in addition to their nutritional value, they usually have health-promotion or disease prevention values. Nevertheless, it has become evident that the low bioavailability or inefficient long-term stability of these health-promoting products may not sustain their benefits. Subsequently, a great attention has been received in the last few years for nanotechnology in food applications. Nanoemulsions are one of the most interesting delivery systems in food

industry. Nanoemulsion-based delivery systems improve the bioavailability of the encapsulated bioactive components and increase food stability [1].

Nanoemulsions are emulsions that have very small particle size [2]. They have some unique characteristics such as small size, increased surface area and less sensitivity to physical and chemical changes, making them ideal formulas in food industry [3, 4].

Food grade nanoemulsions are being increasingly used in for improving digestibility, efficient encapsulation, increasing bioavailability and targeted delivery [3–5]. The aforementioned advantages of nanoemulsions over the conventional emulsions increased the utility of nanoemulsions in food industry. The kinetic stability of nanoemulsions can be improved by incorporating stabilizers such as emulsifiers, ripening retarders, weighting agents or texture modifiers [3]. Emulsifiers such as small molecule surfactants (Tweens or Spans), amphiphilic polysaccharides (gum Arabic or modified starch), phospholipids (soy, egg or dairy lecithin) and amphiphilic proteins (caseinate or whey protein isolate) can be used in food industry to formulate nanoemulsions. Texture modifiers, substances that increase the viscosity such as proteins (whey protein isolate, gelatin or soy protein isolate), sugars (high-fructose corn syrup or sucrose), polysaccharides (carrageenan, xanthan, pectin, alginate) and polyols (sorbitol or glycerol) can be also used as stabilizers. Dense lipophilic materials such as brominated vegetable oil, sucrose acetate isobutyrate, ester gums can be used as a weighting agent to balance the densities of the liquids nanoemulsions [1, 3, 5–9].

In this chapter, we provide an overview on the terminology used in emulsions, formulation of nanoemulsions and diverse approaches for production of nanoemulsions. Additionally, we summarize the recent applications of nanoemulsions in food industry.

Emulsions are defined by International Union of Pure and Applied Chemistry (IUPAC) as “a fluid colloidal system in which liquid droplets and/or liquid crystals are dispersed in a liquid” [10]. If the continuous phase of the emulsion is an aqueous solution, the emulsion is oil-in-water and denoted by the symbol O/W, whereas, if the continuous phase is oil, the emulsion is referred to W/O (**Figure 1**) [10]. An emulsifier is a surfactant or surface-active agent, a substance that lowers the surface tension and/or the interfacial tension [10].

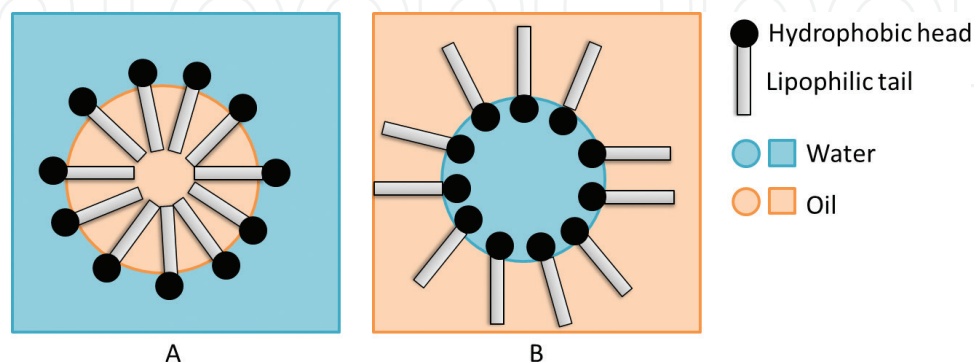


Figure 1. Schematic representation of oil in water (O/W, A) and water in oil (W/O, B) emulsions.

Nanoemulsions are emulsions that have a particle size at the nanometer range (20–500 nm) [2, 5, 6, 11]. Nanoemulsions have major differences in size, shape and stability from the classical macroemulsions and microemulsions [5]. While microemulsions are thermodynamically stable, both macroemulsions and nanoemulsions are thermodynamically unstable [5, 11].

2. Formulation of nanoemulsions

A typical nanoemulsion consists of a water phase, an oil phase and an emulsifier [5]. When present in small amounts, an emulsifier facilitates the formation of emulsions by decreasing the interfacial tension between the oil and water phases [5]. Additionally, emulsifiers aid the stabilization of nanoemulsions [11]. Formation and stabilization of nanoemulsions depend largely on the physico-chemical properties of the three aforementioned constituents.

O/W nanoemulsions have the greatest application in commercial products [9]. The particles in O/W nanoemulsion have a core-shell-type structure with a shell of surface-active amphiphilic material covers a core made of lipophilic material.

2.1. Oil phase

The oil phase used to prepare food-grade nanoemulsions can be formulated from a variety of nonpolar molecules, such as free fatty acids (FFA), monoacylglycerols (MAG), diacylglycerols (DAG), triacylglycerols (TAG), waxes, mineral oils or various lipophilic nutraceuticals [9]. TAG oils extracted from soybean, safflower, corn, flaxseed, sunflower, olive, algae or fish are the most commonly used in nanoemulsions primarily due to their low cost and nutritional value [9]. Physical and chemical characteristics of the oil phase such as viscosity, water solubility, density, polarity, refractive index and interfacial tension and chemical stability greatly influence the properties of nanoemulsions [1, 3, 5–8].

2.2. Aqueous phase

The aqueous phase used to prepare food-grade nanoemulsions can be formulated from water with a variety of polar molecules, carbohydrates, proteins, acids, minerals or alcoholic cosolvents [9]. The selection of the aqueous phase has a great impact on the physicochemical properties of the produced nanoemulsion.

2.3. Stabilizers

Stabilizers influence the long-term stability of nanoemulsions; therefore, the selection of the appropriate stabilizer is one of the most important factors to consider for the proper production of nanoemulsions. Various kinds of stabilizers are added to improve the long-term stability of nanoemulsions, and they are summarized in **Table 1** [1, 3, 5–9]. Stabilizers can be emulsifiers, ripening retarders, texture modifiers and weighting agents. Emulsifiers are

Stabilizers	Function	Examples
Emulsifiers	Single emulsifier or combination of emulsifiers are added to stabilize emulsions by increasing their kinetic stability	<ol style="list-style-type: none">1. Small molecule surfactants (Table 2)2. Amphiphilic polysaccharides (gum Arabic or modified starch)3. Phospholipids (soy, egg or dairy lecithin)4. Amphiphilic proteins (caseinate or whey protein isolate)
Ripening retarders	Hydrophobic substances that stabilize nanoemulsions by retarding or inhibiting Ostwald ripening	<ol style="list-style-type: none">1. Mineral oil2. Ester gum3. Long-chain triglyceride
Texture modifiers	Substances that increase the viscosity of nanoemulsions	<ol style="list-style-type: none">1. Proteins (whey protein isolate, gelatin or soy protein isolate)2. Sugars (high-fructose corn syrup or sucrose)3. Polysaccharides (carrageenan, xanthan, pectin, alginate)4. Polyols (sorbitol or glycerol)
Weighting agents	Substances that balance the densities of the liquids nanoemulsions	<ol style="list-style-type: none">1. Brominated vegetable oil2. Sucrose acetate isobutyrate

Table 1. Kinds of stabilizers added to improve long-term stability of nanoemulsions.

Small molecule surfactants	Type	Examples	Remarks
Ionic surfactants	Negatively charged	Sodium lauryl sulfate (SLS) Diacetyl tartaric acid ester of mono- and diglycerides (DATEM) Citric acid esters of mono and diglycerides (CITREM)	<ul style="list-style-type: none">• Used with low- and high-energy approaches.• They can cause irritation.
	Positively charged	Lauric arginate	
	Sugar esters	Sucrose monopalmitate Sorbitan monooleate	
	Polyoxyethylene alkyl ethers (POE)	Brij-97	
	Ethoxylated sorbitan esters	Tweens 20 and 80 Spans 20, 40, 60 and 80	
Nonionic surfactants			<ul style="list-style-type: none">• Used with low- and high-energy approaches.• They have low toxicity.• No irritability.
Zwitterionic surfactants	Positively and negatively charged groups	Phospholipids (lecithin)	pH influences the net positive, negative or neutral charge

Table 2. Examples of small molecule surfactants added to nanoemulsions.

the most common stabilizers added in nanoemulsions. Emulsifiers of different kinds may be added such as phospholipids, small molecule surfactants, polysaccharides, and proteins. Examples of small molecule surfactants are listed in **Table 2**.

3. Approaches for production of nanoemulsions

Nanoemulsion is a nonequilibrium system which needs external or internal energy source to be successfully formed [12]. Nanoemulsions can be fabricated using many approaches that can be classified as high-energy or low-energy approaches.

The used techniques for the production of nanoemulsion has a great effect on the droplet size and consequently affect the stability mechanisms of the emulsion system through operating conditions and composition. Generally, preparation of nanoemulsions applies lower concentrations of surfactant (5–10%) than the microemulsion (20% and higher) [13].

Mechanical devices which can produce strong disruptive forces are used in high-energy approaches to mix and disrupt oil and water phases allowing the formation of tiny oil droplets [2, 14–16]. On the other hand, low energy approaches depend on the spontaneous formation of tiny oil droplets in the oil-water-emulsifier mixed systems when either the solution or the environmental conditions such as temperature and composition are changed [14, 17–21]. The used approach in nanoemulsion formation, together with the operating conditions, and the composition of the system affect the size of the formed droplets. In this section, we have a brief overview on the most commonly used high-energy and low-energy approaches for nanoemulsion formation.

3.1. High-energy emulsification

The preparation of nanoemulsions by high-energy methods is strongly dependent on the surfactants used as well as the functional compounds in addition to the quantity of energy applied [1]. Accordingly, the nanoemulsions formed by high-energy approaches constitute a natural method for the preservation of the nanoemulsions against formulation modification such as addition of monomer, surfactant, cosurfactants [17].

High-energy methods employ mechanical devices to produce disruptive forces that can mix and disrupt oil and water phases leading to the formation of the tiny oil droplets, such devices as high-pressure valve homogenizers, microfluidizers, and sonication methods [14, 16]. To keep the droplets in spherical shapes, intense energies are applied in order to generate disruptive forces that exceed the restoring forces, and these restoring forces could be calculated by the Laplace Pressure: $\Delta P = \gamma / 2r$, which increases by reducing droplet radius (r) and increasing interfacial tension (γ) [22]. Generally, the droplet size produced by high-energy approaches is controlled by a balance between two opposing processes that occur within the homogenizer, which are the droplet disruption and droplet coalescence [23]. Smaller droplets can be obtained by increasing the homogenization intensity or duration, increasing the

concentration of the used emulsifier or by controlling the viscosity ratio [14, 22, 24]. The smallest droplet size that can be obtained using certain high-energy device is governed by the flow and force profiles of the homogenizer, the operating conditions such as the energy intensity and duration of the process, the environmental conditions meaning the applied temperature, the sample composition which includes the oil type, emulsifier type and concentrations, and the physicochemical properties of the phases which means the interfacial tension and viscosity [14, 25, 26]. In more clear words, the droplet size decreases as the intensity or duration of energy increases, the interfacial tension decreases, the emulsifier adsorption rate increases, and the disperse-to-continuous phase viscosity ratio falls within a certain range ($0.05 < \eta D / \eta C < 5$) [12, 13, 27]. Production of small droplets depends on the extent of the $\eta D / \eta C$ range and the nature of the disruptive forces produced by the particular homogenizer used, that is, simple shear versus extensional flow. Thus, the smaller the droplet radius, the more difficult is to break them up further.

High-energy approaches are the most suitable methods for the production of food-grade nanoemulsions as they can be applied to various types of oils such as triacylglycerol oils, flavor oils, and essential oils as the oil phase as well as different emulsifier types such as proteins, polysaccharides, phospholipids, and surfactants. Even so, the size of the formed particles is strongly dependent on the oil characteristics and the used emulsifier. For instance, it is easier to produce very small droplets when flavor oils, essential oils or alkanes are used as the oil phase because they have low viscosity and/or interfacial tension [9]. Now we present the most commonly used devices in high-energy approaches.

3.1.1. High-pressure valve homogenization

In high-pressure valve homogenization, first a very high pressure is applied on the mixture and then it is pumped through a restrictive valve (**Figure 2**). The very fine emulsion droplets are generated by the very high shear stress [28, 29]. High-pressure and multiple passes are necessary to produce the required droplet size [9]. The combination of intensive disruptive forces such as shear stress, cavitation, and turbulent flow conditions can break the large droplets into smaller ones [30]. Production of conventional emulsions with small droplet sizes in food industry is commonly done using high-pressure valve homogenizers [22, 31]. Some of the food nanoemulsions prepared by high-pressure valve homogenization technique is β -carotene, thyme oil, and curcumin nanoemulsions [32–34].

These devices are more suitable for reducing the size of the droplets in preexisting coarse emulsions than in making emulsions directly from two separate liquids [9]. To describe the operation in the high-pressure valve homogenizer, the coarse emulsion is produced by the high shear mixer and is then passed into a chamber by the pump through the inlet of the high-pressure valve homogenizer and then forced through a narrow valve at the end of the chamber on its forward stroke. The coarse emulsion particles are broken down into smaller ones by a combination of intense disruptive forces when it passes through the valve. Different nozzle designs are available to increase the efficiency of droplet disruption [9].

The droplet size produced using a high-pressure valve homogenizer usually decreases as the number of passes and/or the homogenization pressure increases. It also depends on the

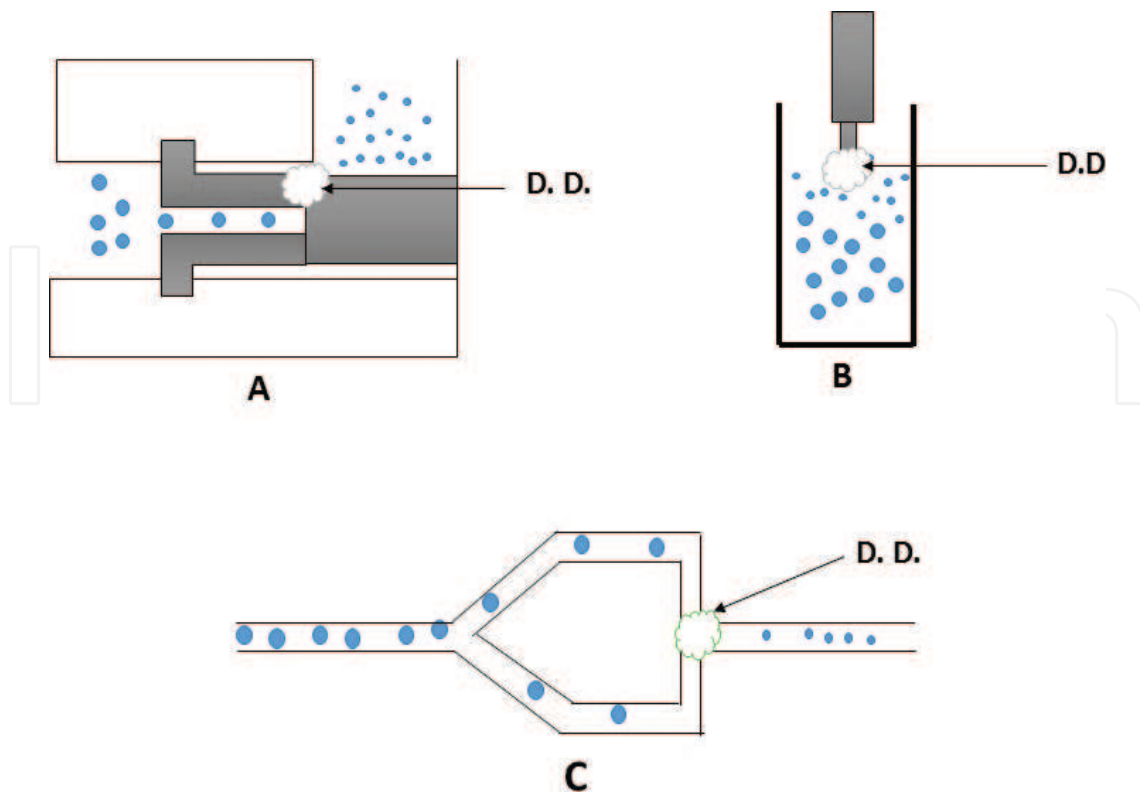


Figure 2. Schematic representation of three devices utilized in high-energy approach for production of food-grade nanoemulsions: A. high-pressure valve homogenization; B. ultrasonic homogenization; C. microfluidizer; and D.D. droplet disruption.

viscosity ratio of the two phases (usually oil and water) being homogenized. As mentioned before, small droplets can only usually be produced when the disperse-to-continuous phase viscosity ratio falls within a certain range ($0.05 < \eta_D/\eta_C < 5$) [12, 13, 27]. Moreover, sufficient emulsifier is required to cover the surfaces of the new droplet formed during homogenization, and the emulsifier should be rapidly adsorbed on the droplet surfaces to prevent re-coalescence [23].

As a summary, to obtain the required droplet size in nanoemulsions, we need to operate at extremely high pressures and to use multiple passes through the homogenizer. Even then, high emulsifier levels, low interfacial tensions, and appropriate viscosity ratios are required to obtain droplets less than 100 nm in radius [9].

3.1.2. Microfluidizer

This device is similar in design to high-pressure valve homogenizer in that it employs high pressure to force the premix of emulsion through a narrow orifice to facilitate the disruption of droplet but differs only in the channels in which the emulsion flows (**Figure 2**). The emulsion flowing in a microfluidizer is divided through a channel into two streams, each passes through a separate fine channel, and then both streams are redirected into interaction chamber, in which they are exposed to intense disruptive forces leading to highly efficient droplet disruption [3]. Increasing the homogenization pressure, number of passes, and

emulsifier concentration can efficiently reduce the droplet size formed. McClements and Rao have practically proved that the logarithm of the mean droplet diameter decreased linearly as the logarithm of the homogenization pressure increased for both ionic surfactant and a globular protein (β -lactoglobulin). But it could be noticed that this relation was appreciably steeper for the surfactant than for the protein, and this could be explained by the slow rate of the protein to adsorption to the droplet surfaces, with the formation of a viscoelastic coating which inhibits further droplet disruption [9].

In addition, there is an optimum range of disperse-to-continuous phase viscosity ratio, which facilitates the formation of small droplets [14]. But this relation is highly affected by the surfactant used, for the ionic surfactant mean droplet diameter decreases when the viscosity ratio decreases. On the other hand, the mean droplet size is hardly affected by viscosity ratio when a globular protein was used as an emulsifier, which may be also attributed to the relatively slow adsorption of the protein and its ability to form a coating that inhibits further droplet disruption [9].

Microfluidizers have been extensively used for the preparation of pharmaceutical products as nutraceutical emulsions, food and beverages such as homogenized milk in addition to the production of flavor emulsion [9]. Nanoemulsions of various bioactive compounds such as β -carotene and lemon grass essential oil were prepared using microfluidization technique [35–37].

3.1.3. *Ultrasound homogenizer*

When two immiscible liquids in the presence of a surfactant are subjected to high-frequency sound waves (frequency > 20 kHz) using sonicator probes that contain piezoelectric quartz crystals that expand and contract in response to an alternating electrical voltage, this causes strong shock waves produced in the surrounding liquid by the tip of the sonicator placed within the liquid (**Figure 2**). The mechanical vibrations lead to the formation of liquid jets at high speed, the collapse of the micro-bubbles formed by cavitation generates intense disruptive forces that lead to droplet disruption and the formation of emulsion droplets of nano size (70 nm). The emulsion should spend sufficient time within the region where droplet disruption occurs to ensure efficient and uniform homogenization [9, 16, 25, 38]. Practically, the droplet size decreases when the intensity of ultrasonic waves, sonication time, power level, and emulsifier concentration increase [25, 39, 40]. The type and amount of the emulsifier used, as well as the viscosity of the oil and aqueous phases affect the homogenization efficiency [16, 23, 25, 40]. All the above parameters should be first optimized to produce nanoemulsions of the right droplet size. It is noteworthy to mention that sonication methods may lead to protein denaturation, polysaccharide depolymerization, or lipid oxidation during homogenization. Thus, this technology has not yet been proved as efficient for industrial-scale applications [3].

3.1.4. *High-speed devices*

Rotor/stator devices (such as Ultra-Turrax) do not provide a good dispersion in terms of droplet sizes when compared to other high-energy techniques. The efficiency of such devices when calculated was 0.1%, where 99.9% is dissipated as heat during the homogenization process, so the energy provided mostly being dissipated, generating heat [12, 13, 17].

3.2. Low-energy emulsification

The low-energy methods are dependent on the internal chemical energy of the system [13, 41]. The nanoemulsions here are formed as a result of phase transitions that occur during the emulsification process due to the change in the environmental conditions such as temperature or composition [20], applying constant temperature and changing the composition or using constant composition and changing the temperature [42–44]. The composition of the emulsion such as surfactant-oil-water ratio, surfactant type and ionic strength in addition to the environmental conditions temperature, time history and stirring speeds greatly affect the droplet size [17, 44].

Low-energy approaches can produce smaller droplet sizes than high-energy approaches; however, low-energy approaches can be applied to limited types of oils and emulsifiers. For example, proteins or polysaccharides cannot be used as emulsifiers; alternatively, high concentrations of synthetic surfactants should be used to form nanoemulsions by low-energy approaches. This factor limits the use of such approaches in many food applications [4, 9]. The low-energy methods are listed in the next section and represented in **Figure 3**.

3.2.1. Membrane emulsification method

This technique involves the formation of a dispersed phase (droplets) through a membrane into a continuous phase (**Figure 3**). It requires less surfactant and produces emulsions with a narrow size distribution range than the high-energy techniques. Unfortunately, the low flux of the dispersed phase through the membrane is a strong limitation during scale-up of this method [29].

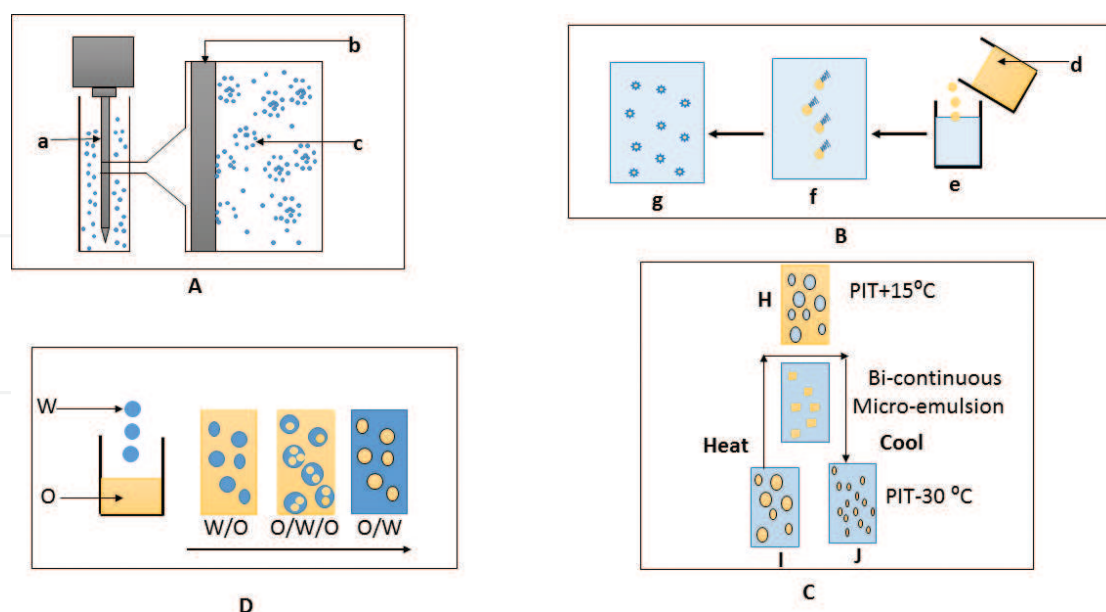


Figure 3. Schematic representation of four devices utilized in low-energy approach for production of food-grade nanoemulsions: A. membrane emulsification method; B. spontaneous emulsification method; C. phase inversion temperature method; D. emulsion inversion point method; a, rotating membrane; b, disperse phase; stabilized droplets of colloidal particles; d, surfactant and oil phase; e, aqueous phase; f, surfactant moves to water phase; g, oil in water emulsion; H. W/O emulsion; I. O/W emulsion; and J. O/W nanoemulsion.

3.2.2. *Spontaneous emulsification method*

This technique involves spontaneous formation of nanoemulsion as a result of the movement of a water miscible component from the organic phase into the aqueous phase when the two phases are mixed together (**Figure 3**) [17]. The organic phase is usually a homogeneous solution of oil, lipophilic surfactant and water-miscible solvent, and the aqueous phase consists of water and hydrophilic surfactant [19]. The spontaneous characteristic of this technique results from the initial nonequilibrium states when the two liquids are mixed without stirring. Accordingly, spontaneous emulsification is brought about by various methods such as diffusion of solutes between two phases, interfacial turbulence, surface tension gradient, dispersion mechanism or condensation mechanism. These mechanisms are highly influenced by the systems' compositions and their physicochemical features such as the physical properties of the oily phase and nature of the surfactants [19]. The size of the droplets produced can be controlled by varying the compositions of the two initial phases, as well as the mixing conditions [9].

There are many physicochemical mechanisms that can be utilized for spontaneous emulsification [45]. When two immiscible phases like water and oil are brought into contact with each other, and one of the phases contains a component that is partially miscible with both phases such as amphiphilic alcohol or surfactant. In this case, some of the components that are partially miscible with both phases will move from its original phase into the other one causing an increase in oil-water interfacial area, interfacial turbulence, and spontaneous formation of droplets. In this method, the variation in the compositions of the two initial phases, and the mixing conditions can control the size of the droplets produced.

McClements and Rao [9] compared the spontaneous emulsification method of producing nanoemulsions with the high-energy method named the microfluidizer. The surfactant-oil-water system used consisted of 15.4 wt% nonionic surfactant, 23.1 wt% medium-chain triglycerides (MCT), and 61.5% water, with the surfactant containing a 50:50 mixture of a hydrophilic (Tween 80) and lipophilic (Tween 85) surfactant. The microfluidization method produced droplets with a diameter of about 110 nm, whereas the spontaneous emulsification method could produce droplets with diameters around 140 nm. This simple experiment demonstrated that nanoemulsions could be produced using the spontaneous emulsification method, provided that the system composition was optimized, that is, surfactant, oil, and water contents.

This process itself increases entropy and thus decreases the Gibbs free energy of the system [17]. In pharmaceutical industry, the systems prepared by spontaneous emulsification method are referred to either as self-emulsifying drug-delivery systems (SEDDS) or as self-nano-emulsifying drug delivery systems (SNEDDS).

3.2.3. *Solvent displacement*

This method depends on the rapid diffusion of a water-miscible organic solvent that contains a lipophilic functional compound in the aqueous phase promoting the formation of nanoemulsions. This rapid diffusion enables the one-step preparation of nanoemulsion at low-energy input with high yield of encapsulation. At the end, the organic solvent is evaporated from the nanodispersion under vacuum [20, 21]. However, the use of this technique is limited to water-miscible solvents [21].

Another low-energy approaches are the phase inversion methods that use the chemical energy released as a result of phase transitions that occur during the emulsification. Nanoemulsions have been formed by inducing phase inversion in emulsion from a W/O to O/W form or vice versa by either changing the temperature in the phase-inversion temperature (PIT), the composition in phase-inversion composition (PIC) or emulsion-inversion point (EIP) [6].

3.2.4. Phase inversion temperature method

This method depends on that at a fixed composition and by changing temperature, the non-ionic surfactants changes their affinities to water and oil through the changes in the optimum curvature (molecular geometry) or relative solubility of nonionic surfactants [46, 47]. Using the PIT method, nanoemulsions are spontaneously formed by varying the temperature-time profile of certain mixtures of oil, water, and nonionic surfactant, thus nanoemulsions are formed by suddenly breaking-up the microemulsions maintained at the phase inversion point by a rapid cooling [48] or by a dilution in water or oil [17] the formed nanoemulsions are kinetically stable and can be considered as irreversible [3]. PIT also involves the controlled transformation of W/O emulsion to O/W emulsion or vice versa through an intermediate liquid crystalline or bicontinuous microemulsion phase [9].

The key for this phase inversion is the temperature-induced changes in the physicochemical properties of the surfactant (**Figure 3**). Here the molecular geometry of a surfactant is dependent on the packing parameter, $p = aT / aH$, where, aT is the cross-sectional area of the lipophilic tail-group and aH is the cross-sectional areas of the hydrophilic head-group [49].

In water, the surfactant molecules tend to associate with each other forming a monolayer due to the hydrophobic effects, and these monolayers have an optimum curvature that causes the most efficient packing of the molecules [49]. The packing parameter p determines the optimum curvature of the surfactant monolayer, when $p < 1$, the optimum curvature is convex and the surfactant favors the formation of O/W emulsions, for $p > 1$ the optimum curvature is concave favoring W/O emulsions, while for $p = 1$, monolayers have zero curvature, where surfactants do not favor either O/W or W/O systems and instead lead to the formation of form liquid crystalline or bicontinuous systems (**Figure 3**).

The relative solubility of surfactants in oil and water phases usually changes with temperature due to the physicochemical properties and packing parameter (p) of nonionic surfactants [50, 51]. At a particular temperature, the solubility of the surfactant in the oil and water phases is approximately equal, and this is known as phase inversion temperature or PIT at which an oil-water-surfactant system changes from an O/W emulsion to a W/O emulsion as the packing parameter equals unity ($p = 1$). At temperatures greater than the PIT ($\approx T > \text{PIT} + 20^\circ\text{C}$), the head group becomes progressively dehydrated and the solubility of the surfactant in water decreases, it becomes more soluble in oil, its $p > 1$, and the formation of a W/O emulsion is favored. When the temperature is decreased ($\approx T < \text{PIT} - 30^\circ\text{C}$), the head group of a nonionic surfactant becomes highly hydrated and tends to be more water soluble ($p < 1$), favoring the formation of O/W emulsions [9].

Above PIT, the surfactant molecules are being present predominantly within the oil droplets as they are more oil-soluble at this temperature. When this system is quench-cooled below the

PIT, the surfactant molecules rapidly move from the oil phase into the aqueous phase just like the movement of water-miscible solvent in the spontaneous-emulsification method, which leads to the spontaneous formation of small oil droplets because of the increase in interfacial area and interfacial turbulent flow generated. For this reason, Anton et al. [51] proposed that the formation of nanoemulsions by the PIT method has a similar physicochemical basis to the spontaneous emulsification method.

This process is characterized by being simple, prevents the encapsulated drug being degraded during processing, consumes low amounts of energy, and allows an easy industrial scale-up [17].

3.2.5. *Phase inversion composition method*

PIC method is very close to PIT method, but here the optimum curvature of the surfactant is altered by changing the formulation of the system, rather than the temperature [51]. For example, an O/W emulsion can be phase inverted to a W/O emulsion by adding salt as in this case the packing parameter increased and becomes greater than unity ($p > 1$) due to the ability of the salt ions to screen the electrical charge on the surfactant head groups [52]. Alternatively, a W/O emulsion containing a high salt concentration can be phase inverted to O/W emulsion by dilution with water in order to reduce the ionic strength below some critical level. Another PIC method for preparation of nanoemulsions is to change the electrical charge and stability of emulsions by changing the pH. The carboxyl groups of fatty acids are uncharged at low pH ($\text{pH} < \text{pK}_a$) and have a relatively high oil solubility ($p > 1$), so they could stabilize W/O emulsions, but at high pH, they become ionized so they become more water-soluble ($p < 1$) and stabilize O/W emulsions. Consequently, nanoemulsions can be formed by increasing the pH of a fatty acid-oil-water mixture from below to above the pK_a value of the carboxyl groups [41, 52].

3.2.6. *Emulsion inversion point*

This method involves changing the composition of the system at a constant temperature. In order to create kinetically stable nanoemulsions, the structures are formed through a progressive dilution with water or oil [17]. In EIP methods, the change from W/O to O/W or vice versa needs a catastrophic-phase inversion, rather than a transitional-phase inversion as with the PIC or PIT methods [53]. A transitional-phase inversion occurs when the characteristics of a surfactant are changed through adjusting one of the formulation variables, such as the temperature, pH, or ionic strength. A catastrophic-phase inversion occurs by changing the ratio of the oil-to-water phases while the surfactant properties remain constant. The emulsifiers used in catastrophic-phase inversion are usually limited to small molecule surfactants that can stabilize both W/O emulsions (at least over the short term) and O/W emulsions (over the long term) [9].

McClements and Rao [9] showed practically that increasing the amount of water in a W/O emulsion consisting of water droplets dispersed in oil with continuous stirring can cause the formation of additional water droplets within the oil phase at low amounts of added water;

however, once a critical water content is exceeded, the coalescence rate of water droplets exceeds the coalescence rate of oil droplets, and so phase inversion occurs from a W/O to an O/W system (**Figure 3**). Thus, the catastrophic-phase inversion is usually induced by either increasing (or decreasing) the volume fraction of the dispersed phase in an emulsion above (or below) some critical level.

The value of the critical concentration where phase inversion occurs, as well as the size of the oil droplets produced, depends on process variables, such as the stirring speed, the rate of water addition, and the emulsifier concentration [53].

4. Applications of nanoemulsions in food industry

Nanoemulsions have diverse applications such as drug delivery, pharmaceuticals, cosmetics, and food [5]. In this section, we focus on the applications of nanoemulsions in food industry. Nanoemulsions have been used as a suitable form to improve the digestibility of food, bioavailability of active components, pharmacological activities of certain compounds, and solubilization of drugs. Some applications are listed below.

4.1. Nanoemulsions and encapsulation of lipophilic components

One of the most important applications of nanoemulsions in food industries is the encapsulation of lipophilic components such as vitamins, flavors, and nutraceuticals [9]. Encapsulation is a useful tool to entrap a bioactive ingredient in a core or a fill within a carrier (coating, matrix, membrane, capsule, or shell) for improving the delivery of bioactive molecules within living cells [54].

This technology has many applications in food industry for masking the unpleasant taste or smell of some bioactive materials, increasing the bioavailability of some components, improving the stability of food ingredients, decreasing air-induced food degradation or decreasing the evaporation of food aroma [54]. One of the most interesting applications of encapsulation in food industry is probiotics. Probiotics are defined as microorganisms that provide health benefits when consumed in adequate amounts [55, 56]. Encapsulation of bioactive compounds in nanoemulsion-based delivery system was achieved for resveratrol (**Figure 4**) [57].

Nanoemulsions from food-grade ingredients are being increasingly utilized to encapsulate biologically active lipids such as Omega-3 fatty acids, polyunsaturated fatty acids (PUFAs) [9]. Omega-3 fatty acid supplementation may be protective effect against cancer, cardiac death, sudden death, cognitive aging, asthma, inflammation and myocardial infarction. α -Linolenic acid (ALA), an Omega-3 fatty acid, is one of two essential fatty acids together with linoleic acid (**Figure 4**). ALA is necessary for health and cannot be synthesized within the human body.

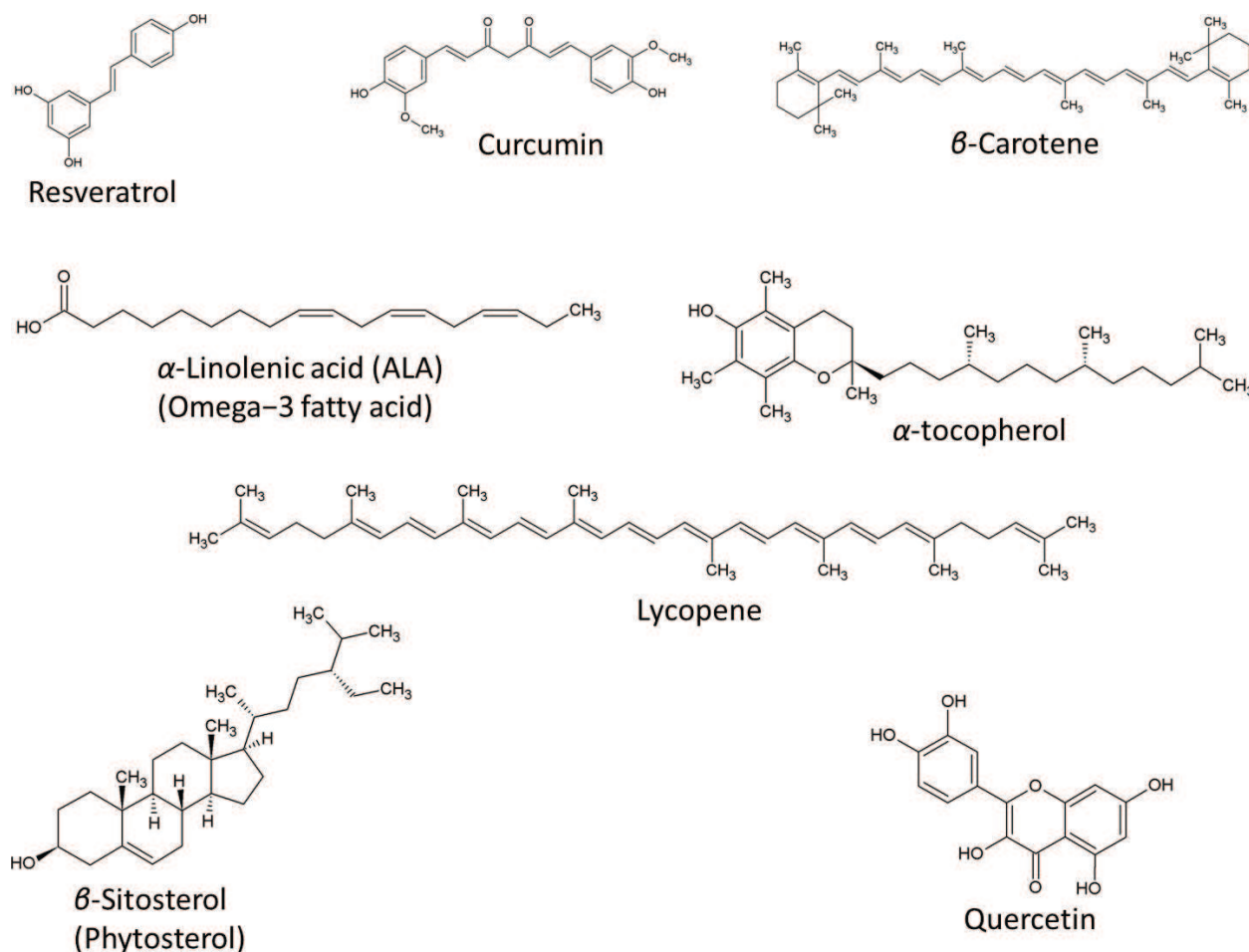


Figure 4. Applications of nanoemulsions-based delivery systems in food industry.

4.2. Nanoemulsions to improve drug bioavailability and pharmacological effects

Low bioavailability of some naturally occurring active compounds hinders their efficient pharmacological activities. Nanoemulsions have been used as a suitable form to increase bioavailability of natural extracts. Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (**Figure 4**), is a yellow-colored polyphenolic compound isolated from the rhizomes of turmeric (*Curcuma longa*, family Zingiberaceae) [58]. Curcumin has been used as a natural coloring agent health benefits such as anticarcinogenic, antioxidant, anti-inflammatory, and antimicrobial [59]. Curcumin nanoemulsions showed significant inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation [60]. However, low bioavailability hinders the efficiency of orally administered curcumin. Flavored nanoemulsions have been prepared with improved curcumin digestibility compared to directly taken curcumin [60, 61].

Additionally, nanoemulsion formulation of oil-soluble vitamins such as alpha-tocopherol enhanced their oral bioavailability and pharmacological effects [62, 63]. α-Tocopherol, a type of vitamin E, is mainly present in olive and sunflower oils (**Figure 4**). Vitamin E supplements have important antioxidant, anticancer as well as cardiovascular protective activities.

Moreover, nanoemulsion preparations improved the bioavailability quercetin or methylquercetin [64]. Quercetin, a polyphenol from the flavonoid group of, has been found in many fruits, vegetables, leaves, and grains (**Figure 4**). Quercetin supplements have been promoted as antioxidant and anticancer.

4.3. Nanoemulsions to improve digestibility characters

Food digestibility is a measure of how much of food is absorbed by the gastro-intestinal tract into the bloodstream. Nanoemulsions have been used as a suitable form to improve digestibility characters of food and natural extracts.

β -Carotene is a red-orange pigment that is found in plants such as carrots and colorful vegetables. β -Carotene is a member of the carotenes, which are terpenoids (isoprenoids), biosynthesized from geranylgeranyl pyrophosphate (**Figure 4**). β -Carotene is the best-known provitamin A carotenoid. β -Carotene flavored nanoemulsion with improved digestibility has been applied [20, 33, 65].

4.4. Nanoemulsions to improve drug solubilization

Nanoemulsion formulation has been applied to increase the solubilization of phytosterols [66]. Phytosterols have been shown to lower the blood cholesterol, and therefore, they reduce the risk of coronary heart diseases. Among phytosterols, β -sitosterol has been isolated from many vegetables and fruits (**Figure 4**). Moreover, nanoemulsions formulas increased also the solubilization of lycopene [66]. Lycopene, a carotenoid pigment and phytochemical, has been found in tomatoes, other red fruits and vegetables (**Figure 4**). Lycopene has potential effects on prostate cancer and cardiovascular diseases.

5. Conclusion and future perspectives

Nanoemulsions have gained great attention and popularity during the last decade due to their exceptional properties such as high surface area, transparent appearance, robust stability, and tunable rheology. The most commonly known preparation approaches for nanoemulsions include high-energy approaches such as high-pressure valve homogenization, microfluidizers and ultrasonic homogenization, and low energy methods such as spontaneous emulsification, phase inversion composition, phase inversion temperature and emulsion inversion point. There is little understanding of the possible industrial relevance of many of these approaches as the physics of nanoemulsion formation is still semi-empirical and rational scale-up procedure have not been widely explored. The interest in nano-emulsion preparation and application is growing, but few of the numerous ideas reported become commercial final applications. Nanoemulsions are considered one of the most promising systems to improve solubility, bioavailability, and functionality of nonpolar active compounds. Food industry seeks to use these systems for the incorporation of the lipophilic functional compounds for the development of innovative food products. The application of nanoemulsions

to food systems still poses challenges that need to be addressed both in terms of the production process, especially their cost, and of the characterization of both the resulting nanoemulsions and the food systems to which they will be applied in terms of product safety and acceptance.

Although nanoemulsions have potential advantages over conventional emulsions such as the preparation of transparent foods and beverages, their improved bioavailability, and physical stability. However, there are a number of regulatory aspects that should be overcome first to allow the wide applications of nanoemulsions.

First of all, most of the components used in formulation of nanoemulsions either in low-energy or high-energy approaches are unsuitable for widespread utilization within the food industry such as synthetic surfactants, synthetic polymers, synthetic oils, or organic solvents. Thus, food-grade ingredients such as flavor oils, triglyceride oils, proteins, and polysaccharides must be utilized in the formulation of food nanoemulsions as these ingredients are legally accepted, label-friendly and economically viable.

Second, in order to fabricate food-grade nanoemulsions on the industrial scale, suitable processing operations should be employed to obtain economic and robust products. Accordingly, many of the identified approaches which were developed in the research laboratories are not suitable for industrial production especially the low-intensity approaches, which could not be yet investigated in industrial scale production. At present, the high-intensity approaches only are utilized for production of nanoemulsions in the food industry.

Finally, there are certain safety concerns associated with the utilization of very small lipid droplets in foods. For example, the route of absorption, the bioavailability or potential toxicity of a lipophilic component encapsulated within nanometer-sized lipid droplets are considerably different from those dispersed within a bulk lipid phase. For these reasons, extensive studies are strongly needed in the area of nanoemulsion safety.

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