Edible Nanoemulsions as Carriers of Active Ingredients: A Review

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Abstract

There has been growing interest in the use of edible nanoemulsions as delivery systems for lipophilic active substances, such as oil-soluble vitamins, antimicrobials, flavors, and nutraceuticals, because of their unique physicochemical properties. Oil-in-water nanoemulsions consist of oil droplets with diameters typically between approximately 30 and 200 nm that are dispersed within an aqueous medium. The small droplet size usually leads to an improvement in stability, gravitational separation, and aggregation. Moreover, the high droplet surface area associated with the small droplet size often leads to a high reactivity with biological cells and macromolecules. As a result, lipid digestibility and bioactive bioavailability are usually higher in nanoemulsions than conventional emulsions, which is an advantage for the development of bioactive delivery systems. In this review, the most important factors affecting nanoemulsion formation and stability are highlighted, and a critical analysis of the potential benefits of using nanoemulsions in food systems is presented.

INTRODUCTION

Consumers are increasingly demanding food products that promote human health and well-being. The food industry is therefore trying to fortify foods with health-promoting ingredients (such as nutraceuticals and vitamins) while removing undesirable ingredients (such as saturated fats, sugar, and salt). In addition, consumers are demanding foods that are more natural and sustainable, which has promoted the food industry to remove or replace synthetic additives (such as many antimicrobials, colors, and flavors) with label-friendly alternatives. To achieve these goals, there has been great interest in the development of food-grade delivery systems to incorporate active ingredients, such as nutraceuticals, vitamins, antimicrobials, colors, and flavors, into foods. Nanotechnology has been a key technology in the development of these kinds of delivery systems (Chaudhry et al. 2008, Durán & Marcato 2013, Sozer & Kokini 2009). Nanoscale control of food structure allows the modification of macroscale characteristics such as processability, texture, sensory attributes, shelf life, and functionality (Moraru et al. 2003). In particular, the scientific and industrial communities are putting a lot of attention on the development of nanosized delivery systems for active compounds. For instance, the United States Department of Agriculture (USDA) forecasted that the global impact of nanoproducts would be around a trillion dollars annually by 2015 (Kumari & Yadav 2014).

The use of many synthetic and natural antimicrobials, antioxidants, vitamins, flavorings, and colorants in the food industry still presents a challenge because they have poor water solubility and stability in food formulations (Weiss et al. 2006). Nanosized structures such as oil-in-water (o/w) nanoemulsions are regarded as useful tools with great potential in the food sector for the delivery of food ingredients. Oil-in-water nanoemulsions consist of oil droplets (typically with radii between 10 and 100 nm) that are dispersed in water (Mason et al. 2006, McClements & Rao 2011, Tadros et al. 2004). Thus far, several advantages have been attributed to nanoemulsions over conventional emulsions. Owing to their reduced droplet size, they are considered to be more stable in terms of gravitational separation and particle aggregation (Mason et al. 2006). Moreover, when the droplet size is sufficiently small (radius < 20 nm), they are nearly transparent systems because of weak light scattering, which makes them suitable for incorporation into clear drinks and foods (McClements 2002). Commercial products with a wide range of textures and rheological properties can be created by adding biopolymers or by controlling the concentration, size, and interactions of the oil droplets. The reduction in droplet size, and the associated increase in droplet surface area, may increase the functionality of bioactive compounds encapsulated in nanoemulsions. Even though many studies have highlighted the potential benefits of nanoemulsions as delivery systems, most of the information has been generated using simple model systems. These model systems simply consist of small emulsifier-coated oil droplets dispersed in water and therefore do not take into account the compositional and structural complexity of most commercial food products. However, their application in foodstuffs remains limited because of the lack of scientific evidence about whether or not they preserve their stability and functionality once incorporated into formulated products. Therefore, in this review, we aim to provide a perspective of the main factors affecting the formation and stability of food-grade nanoemulsions, as well as to provide an insight into their potential applications in food products.

FORMULATION

Nanoemulsions are formulated by mixing at least three components: oil, water, and an emulsifier. However, both the oil and water can contain multiple other components, and more than one type of emulsifier can be used. The characteristics and concentration of the major components in a nanoemulsion determine its final properties.

Lipid Phase

The lipid phase of nanoemulsions may consist entirely of the bioactive lipid (such as a fish, essential, or flavor oil), or it may consist of a bioactive lipid (such as a vitamin or nutraceutical) dissolved in a carrier oil (such as corn, soybean, sunflower, or olive oil) (McClements & Rao 2011). Minor lipophilic active compounds are usually solubilized in the carrier oil prior to emulsification. One potential advantage of reducing the oil droplet size into the nanometric range is the resulting increase in the solubility of the bioactive lipids in the surrounding water phase (McClements 2011). This thermodynamic phenomenon is a result of the increase in oil solubility that occurs when the droplet size is reduced due to curvature effects. The ability of active lipids to interact with biological membranes is also enhanced when the droplet size is decreased, thereby boosting their biological activity. A summary of some lipophilic active compounds that are encapsulated in nanoemulsion systems is presented in **Table 1**.

The oil phase can be formulated using different nonpolar compounds, such as triglycerides, mineral oils, flavor oils, or essential oils (McClements 2011, McClements & Rao 2011). The bulk physicochemical characteristics of the oil, such as viscosity, density, refractive index, and interfacial tension, impact the formation and stability of emulsions and nanoemulsions (McClements 2005). As reported by several authors, the lower the viscosity and interfacial tension of the oil phase, the smaller the droplet size produced, because droplet disruption within the homogenizer is facilitated (Jafari et al. 2008, Qian & McClements 2011, Seekkuarachchi et al. 2006, Wooster et al. 2008). Droplets with lower viscosities need a shorter residence time inside the homogenizer to become deformed and disrupted, and are thus easier to break down during emulsification (Walstra 1993). Droplets with lower interfacial tensions require less energy to become deformed and disrupted, and are therefore also easier to break down. For this reason, essential oils and flavor oils tend to produce nanoemulsions with small droplet sizes because of their low viscosity and interfacial tension, whereas long-chain triglycerides (LCTs) tend to produce nanoemulsions with larger droplet sizes. However, nanoemulsions containing flavor oils may have lower long-term stability because of destabilization phenomena, such as Ostwald ripening or coalescence (McClements & Rao 2011). Consequently, the oil phase must be carefully formulated to ensure the production of small droplets during homogenization that are stable during storage and application.

Table 1 Lipophilic active ingredients that can be incorporated in nanoemulsions

Compound	Types	Functionality
Antimicrobials		
Plant essential oils	Oregano, sage, clove, mint, limonene, etc.	Flavorings and antimicrobial activity
Bioactive compounds		
Fatty acids	ω-3 fatty acids, conjugated linoleic acid, butyric acid	Prevention of coronary heart disease, immune response disorders, stroke, and cancer; improvement of visual acuity, bone health, and mental health
Carotenoids	β-Carotene, lycopene, lutein, and zeaxanthin	Prevention of cancer, coronary heart disease, macular degeneration, and cataracts
Antioxidants	Tocopherols, flavonoids, and polyphenols	Prevention of coronary heart disease, cancer, and urinary tract disease
Phytosterols	Stigmasterol, β-sitosterol, and campesterol	Prevention of coronary heart disease
Quinones	Coenzyme Q_{10}	Antioxidant activity

Adapted from McClements et al. (2007).

Oil type also influences the nutritional profile of food-grade nanoemulsions. Flavor and mineral oils are nondigestible and pass through the gastrointestinal tract (GIT) without being hydrolyzed, whereas triglyceride oils tend to be converted into monoglycerides and free fatty acids (Salvia-Trujillo et al. 2015). As a result of the ability of lipid digestion products to increase the solubilization capacity of the intestinal fluids, the utilization of digestible triglycerides as carrier oils for hydrophobic nutraceuticals and vitamins may increase their bioavailability. However, this effect also depends on the nature of the triglycerides used. For instance, the bioaccessibility of carotenoids has been shown to be much greater when delivered with LCTs than with medium-chain triglycerides (MCTs) because the hydrophobic domains within the mixed micelles formed by LCTs are sufficiently large to accommodate these long hydrophobic molecules, whereas those formed by MCTs are not (Qian et al. 2012a, Salvia-Trujillo et al. 2013a).

Aqueous Phase

The composition of the aqueous phase plays a major role in determining the physicochemical properties of nanoemulsions. A variety of water-soluble constituents, including minerals, acids, bases, flavors, preservatives, vitamins, sugars, surfactants, proteins, and polysaccharides, can be added to the aqueous phase to change its properties (McClements 2005). The pH and ionic strength of the aqueous phase impact the electrostatic interactions between the oil droplets, which may alter the stability to droplet aggregation. The addition of viscosity enhancers prior to homogenization has been reported to decrease the size of the oil droplets produced by increasing the disruptive shear stresses generated inside the homogenizer (Qian & McClements 2011). In addition, the incorporation of viscosity enhancers in the aqueous phase of nanoemulsions alters their long-term stability by slowing down gravitational separation and droplet collisions. The addition of water-soluble antioxidants (such as chelating agents) to the aqueous phase decreases the rate of lipid oxidation in nanoemulsions (McClements & Decker 2000). Consequently, there is considerable scope for controlling the formation, stability, and functional properties of nanoemulsions by controlling their aqueous phase composition.

Stabilizers

Nanoemulsions are thermodynamically unstable systems and so appropriate stabilizers are required to form and stabilize them (Tadros et al. 2004, Wooster et al. 2008). Emulsifiers are needed to facilitate the formation of small droplets during homogenization and to prevent their aggregation during and after homogenization. Other types of stabilizers may also be incorporated into nanoemulsions to prevent their breakdown due to gravitational separation droplet aggregation, and Ostwald ripening, such as weighting agents, texture modifiers, and ripening inhibitors (McClements & Rao 2011).

Emulsifiers. Emulsifiers are surface-active amphiphilic molecules that have both hydrophilic and lipophilic parts in their molecular structure. Thus, one part has an affinity for nonpolar media (such as oil) and another part has an affinity for polar media (such as water). A good indicator of the relative affinity of an emulsifier for the water and oil phases is the hydrophilic-lipophilic balance (HLB), which describes the ratio of hydrophilic to lipophilic groups on a molecule. Emulsifiers with HLB numbers greater than 10 have a higher affinity for water (hydrophilic), whereas those with HLB numbers less than 10 have a higher relative affinity for oil (lipophilic) (Hasenhuettl & Hartel 2008). Emulsifiers adsorb to the oil-water interface during emulsification, thus protecting oil droplets against aggregation (Kralova & Sjöblom 2009, McClements 2005). Moreover,

emulsifiers lower the interfacial tension and thereby facilitate droplet disruption during homogenization. Emulsifier concentration is an important factor to consider in the development of nanoemulsions because of their large surface area. Typically, a higher concentration of emulsifier is used when formulating nanoemulsions than conventional emulsions for this reason. It has been reported that oil droplet size decreases in nanoemulsions with increasing surfactant concentration in both high-energy (Qian & McClements 2011) and low-energy (Rao & McClements 2011) homogenization methods. Also, the type of emulsifier to be used must be carefully selected according to the lipid phase characteristics. Proteins and small molecule surfactants are widely used for food emulsion and nanoemulsion stabilization because of their ability to adsorb at the oil-water interface (Bos & Van Vliet 2001). Among proteins, casein and β-lactoglobulin are reported to be suitable for nanoemulsion fabrication, leading to nanoemulsions with oil droplet diameters of approximately 100–200 nm (Qian & McClements 2011). Nevertheless, proteins tend to produce larger droplets than surfactants because they adsorb more slowly during homogenization and are less effective at reducing the interfacial tension (Karbstein & Schubert 1995, Stang et al. 1994). Emulsifiers can be classified according to their electrical characteristics, as cationic (positive), anionic (negative), non-ionic (neutral), or zwitterionic (both positive and negative). The electrical properties of an emulsifier have a major impact on the formation, stability, and functional properties of nanoemulsions (McClements 2005). Anionic surfactants include sodium dodecyl sulfate (SDS), sodium lauryl sulfate (SLS), citric acid esters of monoglycerides (CITREM), and diacetyl tartaric acid esters of monoglycerides (DATEM) (Leong et al. 2009, Qian & McClements 2011, Wooster et al. 2008). Nonionic surfactants include sucrose esters, such as sorbitan monooleate or sucrose monopalmitate, polyoxyethylene sorbitan esters of monoglycerides (Tweens), and polyoxyethylene ether surfactants (Brij). Nonionic surfactants would not be expected to lead to an electrical charge on oil droplets, but they may cause a charge due to preferential adsorption of ions from the water phase or if they contain charged impurities (Hsu & Nacu 2003). Nonionic surfactants are commonly used for nanoemulsion production (Choi et al. 2009, Salvia-Trujillo et al. 2013c). Cationic surfactants are rarely used in the food industry, with the exception of lauric arginate (LAE), which has strong antimicrobial properties (Ziani et al. 2011). Finally, the last group corresponds to the zwitterionic emulsifiers, which are molecules with two or more ionizable groups with opposite charges on the same molecule. Lecithins and proteins are the two most commonly used types of zwitterionic emulsifiers for food applications (Hoeller et al. 2009, Trotta et al. 1996). Along with the capability of emulsifiers to form and stabilize nanoemulsions, their compositions and characteristics also have important implications for the loading and protection of active compounds. For example, β-carotene degradation in β-lactoglobulin-stabilized nanoemulsions was significantly slower than in Tween 20–stabilized nanoemulsions (Qian et al. 2012b). Moreover, certain surfactants such as SDS or LAE have been shown to exhibit antimicrobial activity when used to stabilize nanoemulsions (Ziani et al. 2011). Certain types of surface-active polysaccharides (such as gum arabic and modified starch) may also be used as emulsifiers to form nanoemulsions, but they tend to be less efficient than proteins or small molecule surfactants because they adsorb more slowly and reduce the interfacial tension less (McClements 2011). Indeed, small molecule surfactants are usually the most suitable emulsifiers for producing nanoemulsions because of their low surface load, rapid adsorption kinetics, and low interfacial tension (McClements 2011). Nevertheless, most small molecule surfactants are synthetic ingredients and may therefore be unsuitable for some commercial applications.

Texture modifiers. Hydrocolloids have been extensively used in food formulations for their thickening or gelling properties when incorporated into aqueous solutions (Saha & Bhattacharya 2010). In nanoemulsions, they may be utilized to modify the texture of the product or to improve

the stability to gravitational separation. Modifying the rheology of the aqueous phase changes the texture and mouth-feel of a nanoemulsion, as well as retarding droplet movement (McClements 2005). Polysaccharides with highly extended and hydrated structures are widely used as texture modifiers because of their ability to thicken solutions or form gels (Dickinson 2009, Garti & Leser 2001). Conversely, polysaccharides with amphiphilic structures tend to be used as emulsifiers, such as gum arabic, modified starch, modified celluloses, modified alginate, pectins, and some galactomannans or cellulose derivatives (Dickinson 2003). The surface activity of these polysaccharides has been attributed to the presence of nonpolar chemical groups or protein components attached to the hydrophilic polysaccharide backbone (Dickinson 2009). It should be noted that the addition of polysaccharides to nanoemulsions may also destabilize them because of bridging or depletion flocculation (Dickinson 2003). Also, hydrocolloids might interact with previously adsorbed species depending on their electrical characteristics, thus creating multilayers at the oil-water interface (Dickinson 2003, Goddard 2002, Guzey & McClements 2006). Hydrocolloid properties have been used to design emulsion-based delivery systems for food ingredients (McClements et al. 2007). However, their effect on the digestibility and bioactivity of the encapsulated lipophilic compound is highly dependent on the type of biopolymer used. It has been reported that the digestibility of emulsified oil droplets was retarded or inhibited depending on the composition of the interfacial layer (Li et al. 2010). Moreover, the presence of hydrocolloids in nanoemulsions may influence their gastrointestinal fate, which may impact the nutritional properties of any encapsulated lipophilic active ingredients (Dickinson & Leser 2013, Gidley 2013).

FABRICATION METHODS

The approaches used to form nanoemulsions are typically classified as either high-energy or low-energy methods (McClements & Rao 2011, Tadros et al. 2004). High-energy methods consist of applying high disruptive forces with mechanical devices capable of causing the breakup of oil droplets and dispersing them into the water phase, such as high-pressure homogenizers, microfluidizers, and sonicators. Low-energy approaches rely on the formation of tiny oil droplets within mixed oil-water-surfactant systems when the solution or environmental conditions are altered, such as spontaneous emulsification and phase inversion temperature methods (Anton & Vandamme 2009, Solans et al. 2005). Both approaches can form small droplets, but high-energy methods are more suitable for most applications in the food industry for a number of reasons: (*a*) Natural emulsifiers can be used, (*b*) lower emulsifier levels are required, (*c*) large scale production is easier, and (*d*) the equipment is already widely available and utilized. Therefore, this review only focuses on high-energy approaches to fabricate nanoemulsions.

When two immiscible liquids are placed together, they tend to adopt their most thermodynamically stable state, which is a layer of oil on the top of a layer of water (McClements 2005). To form a nanoemulsion, mechanical stress must therefore be applied to disrupt and mix the oil and water phases. Typically, the energy density required to break down oil droplets increases as their droplet size decreases, which means that a high-energy input is required to form nanoemulsions. There must also be sufficient emulsifier present to cover the surfaces of all the oil droplets generated and prevent coalescence. The most commonly used mechanical devices to form nanoemulsions are high-pressure homogenizers and sonicators because they are capable of generating the high-energy densities required to form small droplets. **Table 2** provides an overview of studies where high-energy emulsification has been used to form nanoemulsions.

Table 2 Review of the published works reporting nanoemulsions produced by high-energy methods (high-pressure homogenization or ultrasonication)

Fabrication method	Processing conditions	Lipid carrier	Functional compound	Emulsifier	Droplet diameter	Reference
High-pressure homogenization	50–150 MPa; 1–10 cycles	Not applicable (NA)	Lemongrass essential oil	Tween 80 and sodium alginate	53–57 nm	Salvia-Trujillo et al. 2013c
	50–150 MPa; 1–5 cycles	Silicon oil	NA	Tween 20, sodium caseinate, or sodium dodecyl sulfate (SDS)	110–140 nm	Lee & Norton 2013
	150 MPa; 10 cycles	Medium-chain triacylglycerides (MCTs)	β-carotene	Octenylsuccinic anhydride–modified starch	150 nm	Liang et al. 2013
	10 KPa; 10 cycles	MCTs and corn oil	Thyme oil	Tween 80	<200 nm	Chang et al. 2012
	15,000 psi; 5 cycles	Corn oil:hexane	NA	β-lactoglobulin	radius <100 nm	Troncoso et al. 2012b
	70–280 MPa; 1–10 cycles	Sunflower oil	NA	Tween 80, SDS, sucrose palmitate, soy lecithin, or modified starch	90–190	Donsì et al. 2012
	9,000 psi; 3 cycles	Orange oil	β-carotene	β-lactoglobulin	79 nm (radius)	Qian et al. 2012c
	12,000 psi; 5 cycles	Corn oil, MCTs, orange oil	Polymethoxy flavones	β-lactoglobulin, lyso-lecithin, Tween, and dodecyl trimethyl ammonium bromide	<100 nm	Li et al. 2012
	200–500 bar; 3 cycles	Palm oil	Vitamin E	Tween 40	200 nm	El Kinawy et al. 2012
	300, 800, or 1,200 bar; 12 cycles	Palm oil	α-Tocopherol	Whey proteins and/or lecithin	201–431 nm	Shukat & Relkin 2011
	9,000 psi; 3 cycles	NA	Lemon oil	Sucrose monopalmitate	radius <100 nm	Rao & McClements 2011
	4–14 Kbar; 1–8 cycles	Corn oil	NA	β-Lactoglobulin, sodium caseinate, Tween 20, or SDS	146–231 nm	Qian & McClements 2011

(*Continued*)

Table 2 (*Continued*)

Fabrication method	Processing conditions	Lipid carrier	Functional compound	Emulsifier	Droplet diameter	Reference
	300 MPa; 5 cycles	Sunflower oil	Carvacrol, limonene, and cinnamaldehyde	Lecithin, pea proteins, sugar ester, and a combination of Tween 20 and glycerol monooleate	123–293 nm	Donsì et al. 2011a
	1,000 bar; 5 cycles	Hexadecane or peanut oil	NA	SDS and Tween 80	80–120 nm	Wooster et al. 2008
	20 MPa; 1 cycle	NA	D-limonene	Maltodextrin and modified starch	570 nm	Jafari et al. 2007a
Ultrasounds	750 W; 15 min	NA	Basil essential oil	Tween 80	29–41 nm	Ghosh et al. 2013a
	750 W; 30 min	NA	Cinnamon oil	Tween 80	65 nm	Ghosh et al. 2013b
	12–28.1 W; 70–170 s	NA	D-limonene	Sorbitan trioleate and polyoxyethylene (20) oleyl ether	24–444 nm	Li & Chiang 2012
	30–100 μm; 30–180 s	NA	Lemongrass essential oil	Tween 80 and sodium alginate	5–35 nm	Salvia-Trujillo et al. 2012
	20–40% of the acoustic power (W); 20 min (pulses of 10 s sonication/30 s without sonication)	Soybean oil and wax	NA	Lipoid s75 and polyethylene glycol (PEG)-surfactants	50–180 nm	Delmas et al. 2011
	30 μm; 5–20 min	Sunflower oil and canola oil	NA	Tween 80, Span 80, and SDS, PEG	40–180 nm	Leong et al. 2009
	40 W; 4 pulses (15 s sonication/15 s without sonication)	Soybean, sesame, and olive oils	NA	Pluronic F68	368–380 nm	Wulff-Pérez et al. 2009
	340 W; 17–119 s	Flaxseed oil	NA	Tween 40	130–140 nm	Kentish et al. 2008
	100 μm; 20 s	NA	D-limonene	Maltodextrin and modified starch	680 nm	Jafari et al. 2007b

Abbreviation: NA, not applicable.

High-Pressure Homogenization

High-pressure homogenization is widely used in industry to form emulsions and nanoemulsions because of its versatility and the possibility of scaling up. Nevertheless, only certain types of high-pressure homogenizers are able to produce nanoemulsions containing droplets in the nanometer range. There are several types of high-pressure homogenizers, with the most common being high-pressure valve homogenizers and microfluidizers. In the case of high-pressure valve homogenizers, a coarse emulsion is pumped through a narrow valve at the end of a chamber (McClements & Rao 2011). The intense disruptive forces that the liquid experiences as it passes through the valve cause the breakdown of larger droplets into smaller ones. The geometry of the high-pressure valve homogenizer used has a significant impact on the droplet size distribution of nanoemulsions produced (Donsì et al. 2012). In addition, the operating pressure and number of passes through the chamber are important factors determining droplet size distribution produced: typically, the higher the pressure and number of cycles, the smaller the droplet size (Donsì et al. 2012).

Microfluidizers are similar to high-pressure valve homogenizers, but the design of the chamber where droplet disruption occurs is substantially different. In this case, a coarse emulsion is also passed through an interaction chamber using a high-pressure pumping device (Jafari et al. 2007a). However, the interaction chamber consists of two flow channels, which are designed so that they cause two streams of the coarse emulsion to impinge on each other at high velocity, thereby creating a very high shearing action that provides an exceptionally fine emulsion (Mahdi Jafari et al. 2006). Several shapes of microfluidization channel are available to create nanoemulsions, with the Y-shaped channel being most common. The successful application of microfluidization to produce nanoemulsions has been reported by several authors (Qian & McClements 2011, Salvia-Trujillo et al. 2013c), with the droplet size decreasing with increasing operating pressure and number of cycles. However, overprocessing during microfluidization can lead to an increase in oil droplet size due to rapid droplet recoalescence (Jafari et al. 2008). This phenomenon might be related to a low surfactant concentration or an inefficient adsorption rate, which is also a crucial factor when forming nanoemulsions. Researchers have reported that microfluidizers are more efficient than high-pressure valve homogenizers at forming small droplets with a single pass at the same operating pressure (Lee & Norton 2013). Controlling the viscosity of both the oil and water phases has also been shown to be crucial to the formation of nanoemulsions (Wooster et al. 2008), with the droplet size decreasing with the viscosity ratio (Qian & McClements 2011). Theoretical predictions can be used to predict the particle size distribution produced under different conditions (McClements 2005).

During emulsification by high-pressure homogenization there is an intrinsic increase in the temperature of the sample, which must be taken into account, especially when it comes to the production of nanoemulsions incorporating heat-sensitive active compounds. High-pressure valve homogenizers and microfluidizers are usually equipped with a cooling coil at the outlet of the treatment chamber; the product can otherwise reach temperatures as high as 70°C. For example, Shukat and coworkers (Shukat & Relkin 2011) observed a substantial degradation of α-tocopherol in palm oil nanoemulsions produced with high-pressure homogenization. Similarly, Donsì and coworkers (Donsì et al. 2011b) reported a degradation of certain volatile compounds after high-pressure homogenization of nanoemulsions containing essential oils. Therefore, the temperature of the process is a critical factor to consider when producing nanoemulsions as carriers of active ingredients.

Sonication

Sonication utilizes high-intensity ultrasonic waves (frequency typically higher than 20 kHz) to break down a mixture of oil and water into a nanoemulsion. Sonication of liquid food products has been described as a method for microbial inactivation (Knorr et al. 2004, Piyasena et al. 2003)

and food extraction (Vilkhu et al. 2008) as well as for emulsification (McClements 1995). The production of nanoemulsions by sonication has been described in several research papers (see **Table 3**). Emulsification with sonication is mainly caused by cavitation effects. Sonication treatments produce pressure fluctuations in the fluid, which cause the cyclical growth and compression of air bubbles within the fluid. Eventually, the air bubbles reach a critical size, become unstable, and violently collapse (Barbosa-Cánovas & Rodríguez 2002, Soria & Villamiel 2010). The implosion of cavitation bubbles leads to the generation of high shear forces, hot spots, and turbulence in the cavitation zone (Soria & Villamiel 2010). This effect causes the breakup of oil droplets, leading to particle sizes in the nanometric range.

The main factors affecting the final droplet size in ultrasonically generated nanoemulsions are the treatment time and intensity, which is directly related to the amplitude of the sonication wave. Several studies report a reduction in the droplet size of nanoemulsions after increasing the sonication amplitude and treatment time (Leong et al. 2009, Li & Chiang 2012, Salvia-Trujillo et al. 2012). Sonication can be conducted in a batch or continuous mode depending on the design of the operating chamber. However, it has been reported that broader particle-size distributions are produced when using a continuous mode than when using a batch mode, which was attributed to nonhomogeneous treatment of the fluids in the flow chamber (Kentish et al. 2008). The minimum droplet size of nanoemulsions is independent of the design of the flow cell, whereas using overpressure in the flow cell leads to a more efficient process (Leong et al. 2009).

There are several potential drawbacks to using sonication to produce nanoemulsions. First, the hot spots generated by bubble implosion and high shear rates may cause a temperature increase in the emulsion (up to 80°C), which can have a detrimental effect on heat-sensitive compounds. Moreover, it has been observed that cavitation can lead to the hydrolysis or oxidation of triglycerides and therefore the degradation of lipids (Chemat et al. 2004), which is caused by the appearance of reactive species in the sonicated fluid (Riesz et al. 1985). Another limitation for the commercial application of sonication is that metal ions or particles from the sonication probe may be released into the product due to cavitational abrasion (Freitas et al. 2006).

POTENTIAL ADVANTAGES OVER CONVENTIONAL EMULSIONS

Antimicrobial Nanoemulsions

Many of the currently approved chemicals used as antimicrobials in foods are water soluble; thus, they are unsuitable for incorporation in the lipid droplets in nanoemulsions. Nevertheless, there are some types of antimicrobial agents that are oil soluble and are therefore suitable for encapsulation in nanoemulsions, such as natural essential oils. In this case, encapsulation of the antimicrobials in nanoemulsions may increase their usability and effectiveness. Antimicrobial agents may be encapsulated within the hydrophobic interior or amphiphilic exterior of oil droplets, or both (**Figure 1**) (Weiss et al. 2009). The transport of the antimicrobial compounds from the nanoemulsion droplets to the microorganism surfaces is a major factor impacting their activity. This process may occur through two different mechanisms: (*a*) molecular diffusion through the intervening aqueous phase or (*b*) direct droplet-microorganism interactions. The small size of the oil droplets in nanoemulsions may enhance their antimicrobial activity in a number of ways. First, it leads to a greater local concentration of antimicrobial agents at the droplet surfaces due to the Laplace effect, which may increase their efficacy by increasing their mass transport through the aqueous phase (McClements 2005). Second, it leads to more rapid droplet-microorganism encounters due to the

Table 3 Review of the most relevant results of antimicrobial nanoemulsions in comparison with conventional emulsions

Antimicrobial compounds	Lipid carrier	Emulsifier	Functionality	Droplet diameter	Fabrication method	Processing conditions	Reference
Thyme oil	NA	Soluble soybean polysaccharide	Same or slight increase of nanoemulsions compared with thyme oil predissolved in ethanol	300 nm	Homogenization	15,000 rpm for 3 min	Wu et al. 2014
Thyme oil	NA	Sodium caseinate and lecithin	Nanoemulsified thyme oil exhibited quicker initial reductions of bacteria than free thyme oil	82.5 nm	Homogenization	15,000 rpm for 3 min	Xue et al. 2015
Clove oil	Canola oil	Maize starch	Negatively charged nanoemulsion showed prolonged antibacterial activities against Gram-positive bacterial strains	170–400 nm	High-pressure homogenization	50–150 MPa for 1–20 cycles	Majeed et al. 2016
Achillea essential oils	NA	Tween 20	Dramatically increased antimicrobial activity of nanoemulsions compared with bulk oils against several food-borne pathogens	65.6–144.8 nm	High-pressure homogenization	300 MPa for 5 cycles	Almadiy et al. 2016
Anise oil	NA	Soy lecithin	Nanoemulsions presented a higher antimicrobial activity against *Escherichia coli* O157:H7 and *Listeria monocytogenes* compared with coarse emulsions or bulk oil	<200 nm	High-pressure homogenization	150 MPa for 8 cycles	Topuz et al. 2016
Thyme oil and lauric arginate (LAE)	Corn oil	Tween 80	The addition of LAE enhanced the antimicrobial activity of thyme oil nanoemulsions	<250 nm	High-pressure homogenization	10 kPa for 5 cycles	Chang et al. 2015
Lemongrass essential oil	NA	Tween 80	Nanoemulsions produced by microfluidization showed a faster inactivation kinetics against *E. coli*	<10 nm	High-pressure homogenization	50–150 MPa for 1–10 cycles	Salvia-Trujillo et al. 2014

(*Continued*)

Table 3 *(Continued)*

Antimicrobial compounds	Lipid carrier	Emulsifier	Functionality	Droplet diameter	Fabrication method	Processing conditions	Reference
Carvacrol, limonene, and cinnamaldehyde	Sunflower oil	Lecithin, pea proteins, sugar ester, and a combination of Tween 20 and glycerol monooleate	The antimicrobial activity was determined by the solubilization of the essential oils on the aqueous phase of nanoemulsions	123–293nm	High-pressure homogenization	300 MPa	Donsì et al. 2011b
Peppermint essential oil	Medium-chain triacylglycerides (MCTs)	Modified starch	Nanoemulsions with a prolonged long-term antimicrobial activity in comparison with unformulated oil	146–550 nm	High-pressure homogenization	50–150 MPa for 1–20 cycles	Liang et al. 2012
Thyme essential oil	Corn oil (as ripening inhibitor)	Tween 80, LAE, or sodium dodecyl sulfate (SDS)	Impact of the nanoemulsions' interfacial properties on microbial membranes. Combination of thyme oil and antimicrobial surfactants (SDS or LAE) decreased the overall antimicrobial efficacy	≈200 nm	High-pressure homogenization	9 kPa for 5 cycles	Ziani et al. 2011
A mixture of terpenes and D-limonene	Sunflower oil and palm oil	Soy lecithin, Tween 20, glycerol monooleate, and modified starch	Delayed microbial growth in orange or pear juices with the use of nanoemulsions	365–74 nm	High-pressure homogenization	350 MPa for 10 cycles	Donsì et al. 2011a

Abbreviation: NA, not applicable.

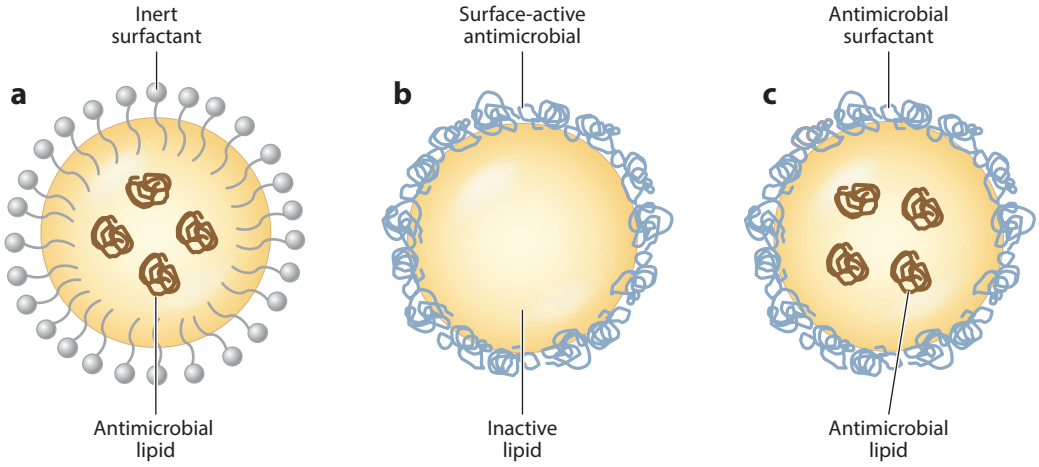

Figure 1

Different structures of antimicrobial nanoemulsions. (*a*) Nanoemulsions with antimicrobial lipid and inert surfactant. (*b*) Nanoemulsions with surface-active antimicrobials and inactive lipids. (*c*) Nanoemulsions with antimicrobial surfactants and lipids.

higher Brownian motion of smaller particles. Third, it may facilitate the penetration of the oil droplets through the biological membranes coating bacterial surfaces. Along with incorporating antimicrobials into the oil phase of a nanoemulsion, it is also possible to incorporate surface-active antimicrobial agents at the interface, such as lysozyme, nisin, LAE, and SDS. Despite the potential applications of nanoemulsions as delivery systems of antimicrobials, there is a lack of consistent data on that topic, and the actual benefits over conventional emulsions remain unclear. In some cases, reducing the particle size may actually reduce the efficacy of an emulsion-based delivery system for surface-active antimicrobials because they tend to adsorb to the droplet surfaces rather than the microbial ones.

Some researchers have focused on elucidating the mechanism of interaction between antimicrobial nanoemulsions and food-borne microorganisms. **Table 3** presents some of the most relevant research papers concerning the delivery of antimicrobials using nanoemulsions with a potential for application in foods. Ziani and coworkers studied the impact of particle charge on the interaction between thyme oil nanodroplets and microbial cells by using different types of surfactants (cationic, anionic, and nonionic) to coat the oil droplets (Ziani et al. 2011). They hypothesized that because the surfaces of microorganisms are typically negatively charged, oil droplets with a positively charged surface are electrostatically attracted and therefore should exhibit an enhanced antimicrobial activity. However, the conclusion of their study was that the partitioning of the cationic or anionic surfactant molecules between the oil droplets and the microbial surface reduced the efficacy of the nanoemulsions. Therefore, it would be more suitable to use nonionic surfactants to formulate delivery systems of essential oils to inactivate microorganisms. Donsí and coworkers (Donsì et al. 2011a) as well Liang and coworkers (Liang et al. 2012) studied the antimicrobial properties of nanoemulsions containing aromatic compounds. In both studies, a higher antimicrobial activity of nanoemulsions was reported compared to the same concentration of nonemulsified essential oils. Salvia-Trujillo and coworkers (Salvia-Trujillo et al. 2014) reported a faster inactivation of *Escherichia coli* in contact with lemongrass oil nanoemulsions than conventional emulsions. An increased efficacy of antimicrobial compounds against microorganisms in nanoemulsion-based delivery systems would allow a reduction in the concentration of essential

oils required to ensure food preservation. However, it has been reported that the concentration of aromatic compounds in nanoemulsions may be reduced during homogenization due to volatilization, which should be taken into account when formulating this kind of delivery system (Donsì et al. 2011a).

Bioactive Nanoemulsions

Many bioactive compounds, such as several types of vitamins and nutraceuticals used in food fortification are lipophilic; thus, they are typically emulsified prior to incorporation into foods. Consequently, understanding the gastrointestinal fate of bioactive-fortified nanoemulsions is therefore important. It is known that oil droplet size and interfacial properties are key factors determining the digestibility of lipid droplets within the GIT as well as the release of encapsulated bioactive compounds.

The digestion of lipids is a complex physicochemical and biochemical process that occurs within the GIT (Golding & Wooster 2010, McClements & Li 2010, Singh et al. 2009) (**Figure 2**). In the mouth, the presence of salts may alter the ionic strength of the system and induce changes in nanoemulsion stability. Also, the mucin in the saliva can cause aggregation of nanodroplets by bridging or depletion flocculation. When the oil droplets reach the stomach, their aggregation state may further be changed because of the low pH and high ionic strength and shear conditions there (Salvia-Trujillo et al. 2013a). A small amount of hydrolysis of the lipid droplets occurs in the stomach due to the presence of a gastric lipase, but the majority occurs in the small intestine due to the presence of pancreatic lipase. Bile salts present in the gastrointestinal fluids may displace the original emulsifier molecules from the oil-water interface, allowing the binding of the enzyme (Reis et al. 2009). As lipolysis takes place, free fatty acids (FFAs) and monoacylglycerols (MGs) are generated and accumulate on the oil surface. Owing to their high surface activity, long-chain FFAs and MGs can displace the lipase and interrupt the lipolysis reaction. Bile salts remove these digestion products from the oil droplet surface by solubilizing them in mixed micelles, thus facilitating complete digestion. Moreover, calcium ions can form insoluble soaps with long-chain FFAs and remove them from the droplet surfaces. Finally, products from lipolysis as well as the encapsulated lipophilic compounds, if any, are solubilized in mixed micelles or unilamellar phospholipid vesicles, enabling them to be adsorbed across the intestinal lumen.

An understanding of gastrointestinal processes is important for designing nanoemulsions to improve the bioaccessibility and bioavailability of bioactive compounds. A number of research studies on the potential benefits of incorporating active lipophilic compounds in nanoemulsions are summarized in **Table 4**. On one hand, it seems clear that the coadministration of hydrophobic bioactive compounds with a lipid phase facilitates their absorption after digestion (Pouton & Porter 2008). For instance, Yu and coworkers (Yu & Huang 2012) found that the bioavailability of curcumin-loaded nanoemulsions was increased ninefold compared with the crystalline form. In addition, the droplet size and lipid carrier type of nanoemulsions are also important. Several authors (Salvia-Trujillo et al. 2013a; Troncoso et al. 2012a,b) have reported that the smaller the droplet size of nanoemulsions, the higher the bioaccessibility of encapsulated bioactive compounds, which could be attributed to the higher digestibility of the lipid phase. Salvia-Trujillo and coworkers (Salvia-Trujillo et al. 2013a) reported a β-carotene bioaccessibility of 60% after in vitro digestion of nanoemulsions, but only 34% after digestion of conventional emulsions. The lower bioaccessibility of carotenoids in emulsions containing large droplets can be attributed to (*a*) a higher amount of nondigested oil that retained the β-carotene and (*b*) a lower amount of mixed micelles to solubilize the β-carotene. A reduction in the droplet size therefore typically increases the bioavailability of hydrophobic bioactive agents. However, one study reported lower

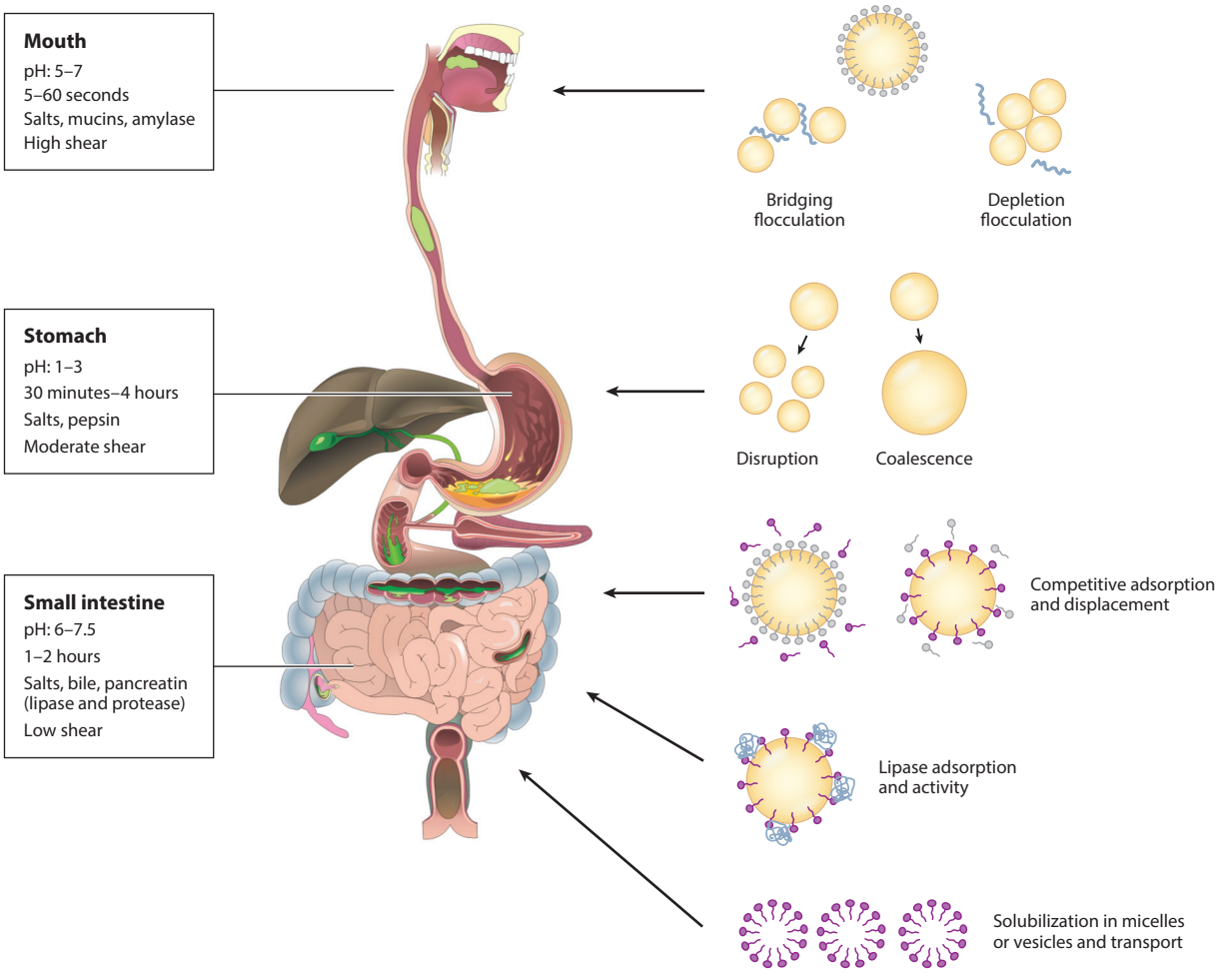

Figure 2

Representation of the possible changes in nanoemulsion structure during their journey through the gastrointestinal tract. Adapted from Singh et al. (2009) and McClements & Li (2010).

bioavailability of curcumin in nanoemulsions than in conventional emulsions (Ahmed et al. 2012), which may have been because the larger oil-water interface led to faster chemical degradation of the curcumin. Therefore, the precise nature of the bioactive compound used has to be taken into account. Second, the composition of the lipid carrier, in terms of the length and unsaturation of the free fatty acids, also determines the bioaccessibility of the bioactive compounds in a nanoemulsion. For instance, it has been reported that the bioaccessibility of carotenoids delivered using nanoemulsions is higher when the lipid phase consists of LCTs than when it consists of MCTs (Ahmed et al. 2012, Qian et al. 2012a, Salvia-Trujillo et al. 2013a). This effect can be attributed to the fact that the long carotenoid molecules can be incorporated into the large hydrophobic core of mixed micelles containing long-chain FFAs, but not in the small hydrophobic core of mixed micelles containing medium-chain FFAs. These results were further confirmed by Salvia-Trujillo and coworkers (Salvia-Trujillo et al. 2013b), who observed a higher β-carotene bioaccessibility in nanoemulsions at increasing ratios of LCTs in the lipid phase.

Table 4 Review of the most relevant results concerning nanoemulsions containing bioactive compounds in comparison with conventional emulsions

Bioactive compounds	Lipid carrier	Emulsifier	Functionality	Droplet diameter	Fabrication method	Processing conditions	Reference
Quercetin	Medium-chain triglycerides (MCTs)	Tween 80 and Span 20	A maximum bioaccessibility of quercetin was observed with nanoemulsions or nanostructured lipid carriers (>60%) compared with solid lipid nanoparticles or free quercetin (7%)	34–83 nm	High-pressure homogenization	17,000 psi for 10 cycles	Aditya et al. 2014
Fucoxanthin	MCTs and corn oil as long-chain triglycerides (LCTs) and undigestible oil (orange oil)	Tween 80	MCT or LCT nanoemulsions presented a higher in vitro fucoxanthin incorporation in mixed micelles and also accumulation in rat tissues	<250 nm	High-pressure homogenization	12,000 psi for 3 cycles	Salvia-Trujillo et al. 2015
Curcumin	Corn oil	Tween 80	Nanoemulsions presented a higher stability than protein or phospholipid nanoparticles as well as higher curcumin solubilization in intestinal fluids	<200 nm	High-pressure homogenization	12,000 psi for 3 cycles	Zou et al. 2016
β-Carotene	Mixtures of MCTs and corn oil as LCTs	Tween 20	The bioaccessibility of β-carotene was enhanced in low-fat nanoemulsions by increasing the percentage of LCTs in the lipid phase	146–415 nm	High-pressure homogenization	9,000 psi for 3 cycles	Salvia-Trujillo et al. 2013a
β-Carotene	Corn oil	Tween 20	Enhanced β-carotene bioaccessibility in nanoemulsions with smaller droplet size in comparison with conventional emulsions	23 μm to 200 nm	High-speed homogenization or high-pressure homogenization	10,000 rpm for 2 min, 4 kpsi for 3 cycles, or 9 kpsi for 5 cycles	Salvia-Trujillo et al. 2013b

(*Continued*)

Table 4 (*Continued*)

Bioactive compounds	Lipid carrier	Emulsifier	Functionality	Droplet diameter	Fabrication method	Processing conditions	Reference
Not applicable (NA)	MCTs	Modified starch, Tween 20 and whey protein isolate	No cytotoxicity of nanoemulsions on Caco-2 cell monolayers	155–172 nm	Ultrasounds	175 W for 5 min	Yu & Huang 2013
NA	Corn oil:hexane	Tween 20	Increased oil digestibility at decreasing emulsion droplet size	30–85 nm (radius)	High-pressure homogenization and solvent displacement	15,000 psi for 5 cycles	Troncoso et al. 2012a
β-carotene	Corn oil as LCTs, MCTs, or orange oil	Tween 20	β-carotene bioaccessibility is highly dependent on the lipid carrier: LCTs > MCTs > orange oil	<200 nm	High-pressure homogenization	9,000 psi for 3 cycles	Qian et al. 2012a
Curcumin	Corn oil	Tween 20, sodium dodecyl sulfate (SDS), and dodecylTrimethylAmmonium bromide (DTAB)	The bioaccessibility of curcumin is affected by the surfactant charge. Tween 20 and SDS presented a higher curcumin solubility compared with DTAB under simulated intestinal conditions	120–153 nm	High-pressure homogenization	20,000 psi for 5 cycles	Pinheiro et al. 2013
Curcumin	MCTs	Modified starch, Tween 20, and whey protein isolate	Oral bioavailability of curcumin loaded in nanoemulsions enhanced ninefold in comparison with the crystalline form	218 nm	Ultrasounds	175 W for 5 min	Yu & Huang 2012

(*Continued*)

Table 4 (*Continued*)

Bioactive compounds	Lipid carrier	Emulsifier	Functionality	Droplet diameter	Fabrication method	Processing conditions	Reference
Curcumin	Long-, medium-, and short-chain triacylglycerides (LCTs, MCTs, and SCTs)	β-Lactoglobulin	Curcumin bioaccessibility was highly dependent on the lipid carrier: the higher the chain length, the higher the bioaccessibility. Nanoemulsions presented lower bioaccessibility than conventional emulsions	<100 nm (radius)	High-pressure homogenization	9,000 psi for 5 cycles	Ahmed et al. 2012
Resveratrol	Peanut oil	Soy lecithin or Tween20	Resveratrol presented a higher chemical and cellular antioxidant activity. Nanoencapsulated resveratrol nonmetabolized is potentially absorbable in the intestinal wall	<180 nm	High-pressure homogenization	300 MPa for 10 cycles	Sessa et al. 2011
Coenzyme Q_{10}	Corn oil and mineral oil	Tween80	Nanoemulsions formulated with digestible oil and the smallest droplet size showed an enhanced in vitro and in vivo bioavailability	2.27 μm to 210 nm	High-pressure homogenization	12,000 psi for 3–4 cycles	Cho et al. 2014
Vitamin E	MCTs	Tween 80	Very high bioaccessibility of vitamin E (>95%) regardless of the surfactant concentration or the nanoemulsion fabrication method	<40 nm	High-pressure homogenization versus low-energy method	12,000 psi for 4 cycles; titration of the water phase into the oil phase	Mayer et al. 2013
Quercetin	MCTs	β-Lactoglobulin	Quercetin incorporated in nanoemulsions showed higher bioaccessibility than quercetin dissolved in bulk oils or in bulk water	<200 nm	High-pressure homogenization	12,000 psi for 5 cycles	Pool et al. 2013

Nanoemulsions are likely to be rapidly digested within the GIT when they are formulated from digestible lipids (such as triglycerides). However, they may behave differently if they are formulated from indigestible lipids (such as mineral or flavor oils). In this case, the small lipid droplets themselves may be absorbed by the epithelium cells within the GIT (Carey et al. 1983, Mu & Høy 2004). To our knowledge, there is only one recently published work dealing with in vivo toxicity testing of nanoemulsions (Yu & Huang 2013). The authors reported no toxicity of nanoemulsions with droplet diameters below 200 nm in Caco-2 cells (small intestine cells). However, they detected a greater loss of viability in HepG2 cells (liver cells) after exposure to nanoemulsions compared with conventional emulsions. These results indicate that despite the potential use of nanoemulsions to enhance the bioavailability of certain food ingredients more information about the biological fate and potential toxicity of ingested nanoemulsions is required. In future studies, it would be useful to use both cell culture and animal models to track the potential GIT fate of both digestible and nondigestible nanoemulsions.

APPLICATIONS IN FOOD PRODUCTS

Nanoemulsions have considerable potential as delivery systems for active compounds in food applications. A number of basic research studies have highlighted the potential advantages of using nanoemulsions in foods. Oregano oil nanoemulsions ($d = 150$ nm) have been recently described to effectively control the growth of food-borne pathogens in fresh lettuce during refrigerated storage (Bhargava et al. 2015). Cinnamaldehyde nanoemulsions ($d < 200$ nm) have been reported to deactivate bacteria in melon juice (Jo et al. 2015). Moreover, soaking mung bean, alfalfa, or radish seeds in carvacrol nanoemulsions has been reported to inactivate *Salmonella enterica* Enteritidis and *Escherichia coli* O157:H7 without compromising sprout yield (Landry et al. 2014, 2015). Donsì and coworkers (Donsì et al. 2011a) incorporated terpene nanoemulsions ($d < 200$ nm) in orange and pear juices and evaluated the inactivation of inoculated *Lactobacillus delbrueckii* as well as their physicochemical characteristics during 16 days of storage at 32°C. The addition of low concentrations of the nanoencapsulated terpenes delayed microbial growth (1.0 g/l terpenes) or completely inactivated the microorganisms (5.0 g/l terpenes) while minimally altering the organoleptic properties of the fruit juices. Joe and coworkers (Joe et al. 2012) used a sunflower oil–based nanoemulsion to extend the shelf life of fish steaks. They observed a significant reduction in the heterotrophic, H_2S, and lactic acid bacteria populations as well as a significant shelf-life extension during storage compared with the nontreated samples. Likewise, Maté and others (Mate et al. 2016) reported a significant reduction of *Listeria monocytogenes* in chicken broth and vegetable cream treated with D-limonene and nisin nanoemulsions. Ma and coworkers (Ma et al. 2016) reported a similar antimicrobial activity of thymol or eugenol nanoemulsions ($d < 100$ nm) emulsified with lecithin and LAE in low-fat milk compared to the free LAE form. However, the nanoemulsion form was more suitable for application in commercial food products.

Examples of the incorporation of nanoemulsions loaded with bioactive compounds into commercial food products are currently limited. However, a number of studies have shown that excipient nanoemulsions can improve the bioavailability of bioactive compounds in real foods. An excipient nanoemulsion does not contain any bioactive compounds itself, but it improves the bioavailability of any bioactive compounds in foods ingested with it (McClements et al. 2015). For instance, several recent studies revealed that excipient nanoemulsions improve carotenoid bioaccessibility from carrots (Zhang et al. 2016), tomato juice (Salvia-Trujillo & McClements 2016), mangoes (Liu et al. 2016), and yellow peppers (Liu et al. 2015). Despite the proven efficiency of nanoemulsions as model delivery systems with improved oral bioavailability, more research is

Table 5 Products available in the market consisting or containing active nanoemulsions

Company	Product	Product properties
Tip Top®	Tip Top UP® Omega-3 DHA	Fortified beverage with nanocapsules containing omega-3 DHA-rich tuna fish oil
Shemen Industries	Canola Active oil	Fortified with nonesterified phytosterols encapsulated via a new nanoencapsulation technology [nanosized self-assembled liquid structures (NSSL) for optimizing the absorption and bioavailability of target nutrients, developed by NutraLease (Israel)]
RBC Life Sciences®, Inc.	Nanoceuticals™ Slim Shake Chocolate	Nanoscale ingredients that scavenge more free radicals, increase hydration, balance the body's pH, reduce lactic acid during exercise, reduce the surface tension of foods, and supplements to increase wetness and absorption of nutrients
Shenzhen Become Industry & Trade Co., Ltd.	Nanotea	Nanofine powder produced using nanotechnologies
Aquanova	NovaSOL sustain	Nanocarrier that introduces coenzyme Q1O to address fat reduction and alpha-lipoic acid for satiety
NutraLease	Nanosized self-assembled liquid structures (NSSL) supplements	Beverages containing encapsulated functional compounds such as coenzyme Q_{10}, lycopene, lutein, β-carotene, omega-3, vitamins A, D3, and E, phytosterols, and isoflavones are available. It is claimed that nanoemulsions can capture the flavor and protect it from temperature, oxidation, enzymatic reactions, and hydrolysis and are thermodynamically stable at a wide range of pH values
LivOn Labs	Lypo-Spheric™ Vitamin C	The smart liposomal Nanospheres® that encapsulate Lypo-Spheric™ Vitamin C gently slip across the intestinal wall and into the blood. That is because they are able to completely bypass a very restrictive nutrient transport system that radically limits the bioavailability of all nonliposome encapsulated forms of vitamin C

Adapted from the Project on Emerging Technologies (**http://www.nanotechproject.org**).

necessary to provide strong evidence about the real advantages of using nanoemulsions to improve the bioavailability of micronutrients from complex food matrices.

From the industrial point of view, despite the lack of strong scientific evidence for the advantages of such antimicrobial and bioactive delivery systems, a number of food products containing functional lipid nanoparticles are already available in the food market. **Table 5** presents a list of commercial food or supplement products that contain bioactive compounds loaded into nanoemulsions or related nanoscale delivery systems, including coenzyme Q_{10}, lycopene, lutein, β-carotene, omega-3, vitamins A, D_3, and E, phytosterols, and isoflavones. In these cases, the manufacturers claim a protection of the active compound during food processing operations and/or enhanced bioavailability of the nutrients after digestion.

Even though numerous research studies have demonstrated that the encapsulation of lipophilic active ingredients in nanoemulsions increases their bioavailability, the real benefits after being incorporated into complex food matrices and after food handling operations have yet to be confirmed. Therefore, the future research trends in this topic need to be directed toward the elucidation of the actual advantages of foods containing lipid nanoparticles in a more comprehensive approach, considering the potential loss of functionality due to food matrix effects, food processing, or storage.

Moreover, evaluation of the relationship between the additional cost of production of nanoemulsions due to the higher energy input and equipment investment, and their effective advantages needs consideration.

REGULATION

The potential benefits of using engineered nanoparticles in foods are many, with high expectations for the food industry; yet the associated risks are still unknown. Nanomaterials may have a wide range of potential toxic effects, depending on their chemical nature (organic or inorganic), particle size distribution, particle shape, surface state (e.g., surface area, surface functionalization, and surface treatment), state of aggregation/agglomeration, etc. There is a need to elucidate the potential toxicology and biological fate of nanoparticles after digestion, to determine their behavior within the GIT, and to determine their possible bioaccumulation in human cells and tissues. The efforts of the scientific community are oriented toward this purpose, but the analytical techniques need validation, and experiments with mice or human are expensive and tedious. Despite this lack of knowledge, the presence of food products containing nanoparticles in the market is growing. This has driven authorities worldwide to release guidelines and regulations dealing with the use of nanomaterials in foods. A number of papers have reviewed the situation related to the regulation of nanoparticles in foods (Card et al. 2011, Chau et al. 2007, Cushen et al. 2012, Magnuson et al. 2013, Sandoval 2009).

Concerning the European Union regulations, efforts have been made to control the use of nanomaterials in foods, and there are several regulations in operation at present. Generally, the incorporation of engineered nanomaterials in foods must fulfill the current regulation for food additives (EU 1333/2008), as they are considered new food ingredients. In February 2009, the European Food Safety Authority (EFSA) adopted a scientific opinion on the potential risks arising from nanoscience and nanotechnologies in food and feed safety. More recently, the European Parliament Commission published the Regulatory Review on Nanomaterials, which compiled an inventory of nanomaterial types and uses, including safety aspects. As a conclusion, it is suggested that there is limited scientific evidence for whether nanoparticles pose a risk for human health. The available toxicological knowledge on nanomaterials suggests that, despite the particle size, their toxicity relies on their nature and their reactivity with biological tissues. As a consequence, some nanomaterials might be hazardous and others not; thus, there is a need for a more focused risk assessment of nanomaterials on a case-by-case basis. Moreover, owing to the need for specific guidelines for nanoparticles, in May 2011, the EFSA published a guide for the risk assessment of engineered nanomaterials in foods as well as consumer exposure, considering their characterization, potential toxicity, and biological fate. In this document, guidance is provided for the characterization of hazards as well as the testing approaches to identify hazards arising from nanoparticles in foods. In this report, it is stated that if the full digestion of a nanoparticle in the GIT can be proven, meaning there is no risk of potentially absorbed species and bioaccumulation in the human gut, the toxicology evidence and regulation of the non-nano form can be used for commercial purposes. This statement is specifically relevant in the case of digestible nanoemulsions, which are typically fully digested within the GIT and therefore are exempt from special toxicological studies before being placed in the food market. Nevertheless, special attention should be paid to nanoemulsions fabricated from nondigestible oils, which could be prone to bioaccumulation in intestinal or liver cells.

In October 2011, the European Parliament and the Council of the European Union published EU Regulation 1169/2011 on the provision of food information to consumers, where it is stated that the presence of engineered nanomaterials in foods must be properly labeled. In September

2013, an amendment to EU 1169/2011 was submitted in order to distinguish between naturally occurring and manufactured nanoparticles. Consumer acceptance of nanoemulsions in foods depends on the scientific community providing reliable information about the real risks associated with consuming this type of engineered nanoparticle.

In the United States, there is a lack of specific regulation with respect to nanomaterials in food products. So far, the Food and Drug Administration (FDA) has released two guides regarding the application of nanomaterials in foods. In June 2011, they published a guide for food manufacturers to take into account possible considerations when incorporating nanoparticles in foods. In April 2012, the FDA also released a guide to assess the effect of manufacturing processes, including emerging technologies, which may cause significant changes in food ingredients already placed in the market and therefore may have an impact on their safety.

CONCLUDING REMARKS

The results of research conducted so far indicate the potential benefits of nanoemulsions as delivery systems of active food ingredients, such as antimicrobials or bioactive compounds. In general, a higher functionality is observed because of their small size and high surface area, leading to a greater interaction with microbial cells in the case of antimicrobial nanoemulsions or a higher digestibility and resulting bioavailability in the case of nanoemulsions containing bioactive compounds. Nevertheless, the promising expectations arising from the recently published data are based on few research papers with concluding results that merit scrutiny and verification. On one hand, there is a need for further studies including a wide range of bioactive compounds or other food ingredients loaded in nanoemulsions to give a more comprehensive overview of the behavior and functionality of different kinds of lipid nanoparticles. On the other hand, most of the research studying the functionality of lipid nanoparticles is conducted in simple model solutions. Therefore, the possible interactions between lipid nanoparticles and other macromolecules present in food formulations, such as proteins, carbohydrates, or fibers, must be elucidated to present reliable data to the producers and consumers about the real benefits of nanoemulsions. Therefore, an important step in establishing the real advantages of using nanoemulsions in foods is to carry out experiments in which they are incorporated into real food matrices to study their functionality and biological fate. Moreover, despite the fact that lipid nanoparticles are usually formulated with edible ingredients and show a similar pattern compared with the digestibility of conventionally emulsified lipids, their toxicological safety cannot be assured. Therefore, it should be noted that the gastrointestinal fate of lipid nanoparticles once they enter the human gut should be described in order to assess their biological fate, tissue location, and possible bioaccumulation. For this purpose, complementary in vivo studies to the already established in vitro methodologies should be carried out to compare and verify the existing information.

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