



# Nanoemulsions for health, food, and cosmetics: a review

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## Abstract

Nanoemulsions are gaining importance in healthcare and cosmetics sectors as a result of the unique properties of nanosized droplets, such as high surface area. Here we review nanotechnology and nanoemulsions with focus on emulsifiers and nanoemulsifiers, and applications for drugs and vaccines delivery, cancer therapy, inflammation treatment, cosmetics, perfumes, polymers, and food. We discuss nanoemulsion safety and properties, e.g., stability, emulsification, solubility, molecular number and arrangements, ionic strength, pH and temperature.

**Keywords** Nanotechnology · Nanoparticles · Nanoemulsions · Emulsifiers · Applications

## Introduction

Nanotechnology is developing rapidly in many sectors, especially cosmetics, pharmaceuticals, agriculture and food industries (Chowdhury et al. 2017). Most of these interests are geared toward the development of lipophilic substances like fatty acids, flavors, colors, and drugs (Azmi et al. 2019). The need for using nanotechnology/nanoparticles in emulsion fabrication is crucial because emulsions have been produced from numerous ingredients and additives for so many years, creating markets and profitability. Carbohydrates, fats, proteins and other active components such as antioxidants, colorings, acidulants, flavorings, preservatives, benzoic acid, coenzyme-Q10, vitamins A and E, isoflavones, beta-carotene, citric acid, ascorbic acid, lutein, omega-3 fatty acids, minerals, among other bioactive compounds have contributed to improved taste, appearance, texture, fortification and stability, and as such innovatively inspired wide applications of nanoemulsions to foods for enhanced uptake, absorbability and bioavailability (Kumar and Sarkar 2018; McClements and Jafari 2018; Dasgupta et al. 2019a; Walia et al. 2019; Saini et al. 2020).

Research into nanoemulsions is extensive. These emulsions are disequibrated systems of water-in-oil (W/O) or

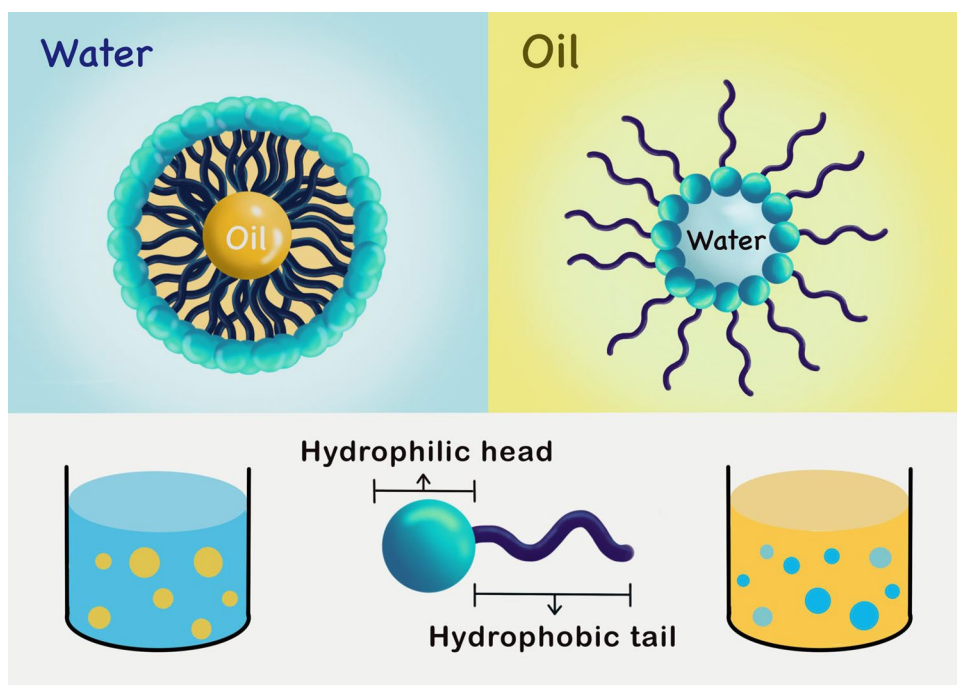
oil-in-water (O/W) emulsions (Fig. 1) within nanometer-range particle sizes and droplet diameters of 50–1000 nm (Yukuyama et al. 2016); otherwise, nanoemulsions are referred to as dispersed systems with  $\leq 100$  nm droplets (Azmi et al. 2019). Nanoemulsions are immiscible liquids consisting of oil and water forming a single phase by an emulsifier such as the surfactants and co-surfactants. The combination of these constituents confers high thermodynamics, stability and other physicochemical properties on the emulsion. Thus, the versatility of nanoemulsions becomes greater than that of conventional emulsions, including microemulsions and macroemulsions.

The Federal Drug Administration (FDA) has utilized molecularity and functions of some emulsifiers as the basis of approval for their use in pharmaceutical and food industries (McClements et al. 2017). Stability, emulsification and solubility of emulsions are inspired by their surface-active nature dovetailed with molecular number and arrangements, ionic strength, pH and temperature of the mixture (McClements et al. 2017). Since the preparations of nanoemulsions and their emulsifiers are crucial and paramount to the interests of key industries, the aim of the present review is to evaluate the concept of nanotechnology, the formation and the applications of nanoemulsions in the healthcare and cosmetics industries, as well as their potentials in foods and other sectors in this present century. Further considerations were also put forward. To conduct the review, web of science (WoS), google and springer search engines were used, using the words and phrases “nano”, “nanosize”, “nanotechnology”, “emulsion”, “nanoemulsion”, “applications of

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**Fig. 1** Oil-in-water and water-in-oil emulsions. Nanoemulsions are disequibrated systems of water-in-oil (W/O) or oil-in-water (O/W) emulsions. They are immiscible liquids consisting of oil and water forming a single phase by an emulsifier such as the surfactants and co-surfactants, the combination of which confers high thermodynamics, stability and other physicochemical properties on the emulsion



nanoemulsions” and “applications of emulsions”, filtering the year range to 2000–2020.

## Nanotechnology and nanoemulsions

Nanotechnology is a global concept that entails the manipulation of particles within the range of 10–1000 nm using scientific, innovative and well-characterized techniques, for improved productivity and applications in agriculture, healthcare, cosmetics, defense, energy and food sectors (Kaul et al. 2018; Feng et al. 2018; Aziz et al. 2019). The world’s nanotechnology industry could worth 80 billion US dollars and could be reaching 17% growth rate by 2024. Therefore, the potential benefits and profits are huge in this emerging market (Research and Market 2018). Application of the technology to the food industry has always been towards emulsions, encapsulation and packaging technologies, of which nanoemulsions are of utmost economic importance (Dasgupta et al. 2019b).

Nanoemulsions are formed when an emulsifier is involved in the mixture of two immiscible liquids to form stable but kinetic dispersions with droplet sizes and diameters of  $\leq 100$  nm and 20–200 nm, respectively. The kinetic stability is achieved when nanoparticles Brownian motion surpasses the emulsions’ gravitational forces, which then stop the particles from aggregating (Wani et al. 2018). Being very minuscule in size, nanoemulsions offer great functional potentials such as enhanced stability, surface area, optical transparency, rheology and other functions associated with innovative technologies and fortification of many

aqueous-based food and beverage products (Dasgupta et al. 2019b). Regarding nanoemulsions production, common methods used include high-pressure homogenization, phase-inversion temperature, ultrasonication, high-shear mixing, solvent displacement, emulsion inversion point, bubble bursting and spontaneous emulsification—all falling under the categories of low- and high-energy techniques (Mohammadi et al. 2016; O’Sullivan et al. 2018; Azmi et al. 2019; Dasgupta et al. 2019a, b).

Increasing rate of consumption of processed foods and beverages has led to increased use of food additives and processing aids such as emulsifiers, which are meant to enhance the texture, flavor, stability and shelf-life of foods (Roca-Saavedra et al. 2018; Vo et al. 2019). The hydrophilic and hydrophobic molecular groups in emulsifiers contribute to immiscibility of the formulated liquids, which then lead to much enhanced homogeneity and stability in the final products as found in butter, mayonnaise, dressings, chocolates, ketchups and yogurts (Shah et al. 2017; Vo et al. 2019). Emulsifiers have been estimated to constitute more than 70% of the world’s approved food ingredients (Shah et al. 2017), necessitating the importance and use of nanosized emulsifiers in this century.

## Emulsifiers and nanoemulsifiers for nanoemulsions

Emulsifiers are surface-active molecules widely applied in the breakage of droplets into tiny and very small droplets. Emulsifiers concentration must reach the right amounts

so as to overcome the interfacial forces, and to ensure that the coating rate is rapid (Artiga-Artigas et al., 2018). This phenomenon prevents the particles from aggregating whilst enabling longer storage time and better stability. Fabricating nanoemulsions implies that the emulsifiers are well absorbed at the oil–water interface and subsequently reduce the interfacial tension in order to loosen up the particles and easily disrupt the droplets. The emulsifiers then protectively coat the oil droplets to prevent aggregation and coagulation (Dasgupta et al. 2019a).

The mixture of oil and water in the process of emulsion formulation creates two immiscible phases based on the segregation caused by coalescing globules in dispersion. The use of emulsifiers or nanoemulsifiers from the generally regarded as safe (GRAS) agents and components, such as peptides, proteins, phospholipids, micro-molecular surfactants, and polysaccharides, for the production of emulsion systems in the appropriate ratios would contribute to their efficiency and stability. Table 1 illustrates some emulsifier-stabilized nanoemulsions. This stability results from circumnavigation of processes like Oswald ripening, especially when the surfactants/emulsifiers are mixed with oil and other components in the right ratio (Gordon et al. 2003).

Over time, the formulated emulsions exhibit droplet coalescence characterized with various behavioral patterns such as heterogeneous or homogeneous growths, in which droplet sizes decrease and create early phase separation, or increase with time, respectively. Indeed, microparticulated emulsions will exhibit a higher degree of aggregation than nanoparticulated emulsions because of the irreversible droplets coalescence taking place with the former's bigger particle size (An et al. 2014). Moreover, the properties of emulsifier used, such as functional, sensory and physicochemical characteristics, can positively or negatively affect the rheology of the nanoemulsion droplets.

The hydrophile–lipophile balance (HLB) system (hydrophilic range  $> 10$ , lipophilic range = 1–10) should be considered when determining the right nano(emulsifiers) for nanoemulsions fabrication because the HLB system has been in use for more than half of the last century to prove optimum conditions of surfactants required for emulsions fabrication with desired characteristics (Macedo et al. 2006; Azmi et al. 2019).

Several studies on colloidal and nanoemulsion systems used emulsifiers due to their better interfacial diffusive properties compared to larger biopolymers, such as proteins and polysaccharides, but their metabolism and safety are of concern in the food industry (Adjonu et al. 2014). For protein and peptide-based emulsifiers, both plant and dairy sources have been widely investigated and applied in foods because they form a protectively strong film

in the formed emulsions. They later become employed in nanoemulsions (Table 1d), with the most important of them being whey proteins. These proteins comprise 20% whey and 80% caseins with very high nutritional contents based on their essential amino acids composition. The whey proteins are basically  $\alpha$ -lactalbumin,  $\beta$ -lactoglobulin, bovine serum albumin, lactoferrins, and immunoglobulins, and possess amphiphilic properties that make them crucial emulsifiers in foods (Foegeding et al. 2002; Adjonu et al. 2014; Zhao and Ashaolu 2020). Under optimal control, hydrolyzation of the proteins will yield shorter peptides with fewer secondary and tertiary structures, to expose the hidden hydrophobic core (Christiansen et al. 2004; Ashaolu 2020a, b). These outcomes increase their diffusion rate and interfacial capacity when compared to their native parent proteins. Both hydrophilic and hydrophobic mixed groups generated further increase their absorption tendencies to the oil droplets surfaces, which ensure much better stability (van der Ven et al. 2001).

In brief, the advantages of nanoemulsifiers/nanoemulsions above emulsifiers include: they are small-sized droplets that have larger surface area for enhanced absorption, with much less energy requirement (Gurpreet and Singh 2018); they play active role in solubilization of lipophilic drugs and suppression of off-flavors of the drugs (Yu et al. 2012); they are considered non-toxic and non-irritant in nature (Jaiswal et al. 2015); they stabilize chemically unstable compounds by protecting them from oxidative and light degradation (Kim et al. 2001); they can substitute liposomes with vesicles (Bouchemal et al. 2004) and improve the bio-availability of a drug (Lovelyn and Attama 2011; Yu et al. 2012), while several types of nanoemulsions can be formed in the likes of creams, liquids, and sprays. On the flip side, in order to stabilize the nanodroplets, higher concentration of surfactant and cosurfactant may be required by nanoemulsifiers (Lovelyn and Attama 2011); solubilization of high-melting substances could be limited (Azmi et al. 2019); environmental parameters such as temperature and pH could affect the stability of nanoemulsifiers (Mishra et al. 2014); and the surfactants used pharmaceutical applications must be non-toxic (Mishra et al. 2014).

Moreover, the use of nanoemulsifiers is currently limited. Adjonu et al. (2014) quite well noted certain potentials of whey protein hydrolysates as emulsifying agents in nanoemulsions. Other than protein- or peptide-based nanoemulsifiers, other groups of molecules are described in Table 1. The continuous studies on nanoemulsions and its use in food applications require a whole lot of further in-depth analyses and critical evaluations, especially for their safety validation.

**Table 1** Emulsifiers in nanoemulsion systems

Type of emulsifier	Homogenization technique	Percentage of oil used	Percentage of emulsifier used	Oil phase used	Droplet size diameter (nm)	Citation
<i>a. Non-ionic</i>						
Polyoxyethylene sorbitan monolaurate	Microfluidization/ high-pressure valve homogenizer	0.03, 1	1, 10	Sunflower oil	117–280	Mao et al. (2009, 2010)
	Microfluidization	4	1.5	Corn oil, Miglyol 812 and orange oil	140–170	Qian et al. (2012)
	Microfluidization	5	1–10	Corn oil	113–143	Qian and McClements (2011)
	Microfluidization/ solvent evaporation	0.3	0.5	$\beta$ -Carotene in hexane	40–260	Tan and Nakajima (2005)
	Microfluidization	10	1	Thyme oil/Miglyol 812 oil	160–176	Chang et al. (2012)
				Thyme oil/corn oil	170–196	
	Sonication	15	5.6	Flaxseed oil	135	Kentish et al. (2008)
	High-pressure valve homogenizer	3	4–12	$\beta$ -Carotene in MCT oil	160–184	Yuan et al. (2008)
Polyoxyethylene sorbitan monooleate	Catastrophic phase inversion	20	10–20	Acetem 90–50 K	100–200	Bilbao-Sáinz et al. (2010)
	High-pressure valve homogenizer	3	4–12	$\beta$ -Carotene in MCT oil	161–174	Yuan et al. (2008)
	Microfluidization	5	0.5	Thyme oil/corn oil	164–196	Ziani et al. (2011)
Polyoxyethylene sorbitan monooleate	Ultrasonication	6	6–24	Basil oil	29–41	Ghosh et al. (2013)
	High-pressure valve homogenizer	20/4/1	1	PCL-liquid/ Lipoid S-75/ $\alpha$ -tocopherol	170	Hoeller et al. (2009)
	High-pressure valve homogenizer	3	4–12	MCT oil	157–178	Yuan et al. (2008)
	Microfluidization	10	1	Lemon oil	217–296	Rao and McClements (2011)
Polyoxyethylene lauryl ether	Emulsification with low energy	40–80	4–10	Isohexadecane	26–1277	Peng et al. (2010)
Decaglycerol monolaurate	Microfluidization/ high-pressure valve homogenizer	0.03, 1	1, 10	$\beta$ -Carotene in sunflower oil	115–279	Mao et al. (2009, 2010)
Sucrose palmitate	Ultra-high-pressure homogenization	8/2, 10	1	D-limonene, trans-cinnamaldehyde, carvacrol in sunflower oil	130–168	Donsì et al. (2012)
Sucrose laureate	High-pressure valve homogenizer	20/4/1	1	PCL-liquid/ lipoid S-75/ $\alpha$ -tocopherol	161	Hoeller et al. (2009)
Sucrose monopalmitate	Microfluidization	10	1–20	Lemon oil	15–120	Rao and McClements (2011)

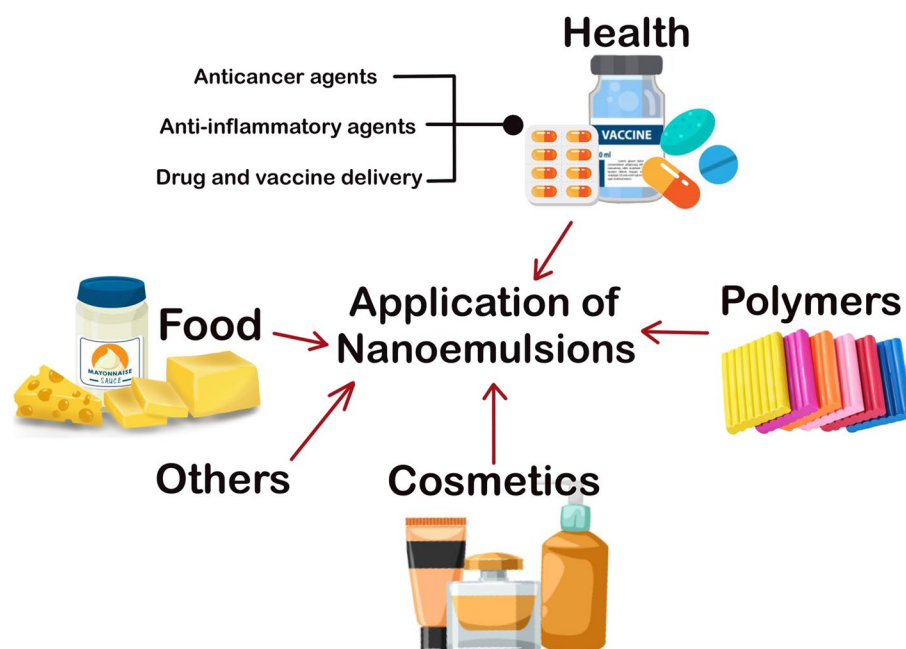
**Table 1** (continued)

Type of emulsifier	Homogenization technique	Percentage of oil used	Percentage of emulsifier used	Oil phase used	Droplet size diameter (nm)	Citation
<i>b. Ionic</i>						
Pluronic F-68	Ultrasonication	25	1–2.5	Olive oil	379	Wulff-Pérez et al. (2009)
				Sesame oil	368	
				Soybean oil	380	
Sodium dodecyl sulfate	Microfluidization	5	1–10	Silicone oil	150	Graves et al. (2005)
	Microfluidization			Corn oil/octadecane	92–131	
<i>c. Polysaccharide</i>						
Low-methoxyl pectin, amidated low-methoxyl pectin, high-methoxyl pectin	Ultra-Turrax	20	0.5–3	Itraconazole in chloroform	200–900	Burapapadh et al. (2010)
				Itraconazole in Miglyol® 812	> 2000	
Succinylated waxy maize starch/octenyl succinate starch	High-pressure valve homogenizer	10	15	Neobee 1053	140	Donsì et al. (2011)
	Microfluidization/high-pressure valve homogenizer	1	10	Neobee 1095 $\beta$ -Carotene in sunflower oil	130 262–674	Mao et al. (2010)
	High-pressure valve homogenizer	12	12	Peppermint oil/ MCT oil	184–228	Liang et al. (2012)
Maltodextrin/H-Cap	Microfluidization/sonication	5, 10, 15	30/10 (40)	Fish oil	174–274	Jafari et al. (2007a,b)
<i>d. Protein</i>						
Pea protein	High-pressure valve homogenizer	8, 10	3	Sunflower oil	184–218	Donsì et al. (2012)
Whey protein isolate-maltodextrin conjugate	Emulsification with high energy/evaporation	10, 15, 20, 30	1	Thymol in hexane	67–420	Shah et al. (2012)
Soy protein	Microfluidization	0.1	1	$\beta$ -Carotene in hexane	196	Chu et al. (2007)
Whey protein concentrate	Microfluidization; microfluidization/sonication	0.1; 20, 25	1; 10	$\beta$ -Carotene in hexane; <i>D</i> -limonene	145; 125–387	Chu et al. (2007), Jafari et al. (2006)
Whey protein isolate	High-pressure valve homogenizer	15, 30, 45	4.3	Pea nut oil	146–236	Cortés-Muñoz et al. (2009)
	High-energy emulsification/solvent evaporation	10	1	Corn oil	75–121	Lee and McClements (2010)
	High-pressure valve homogenizer	0.03, 1	1, 10	$\beta$ -Carotene in sunflower oil	160–373	Mao et al. (2010)
	High-pressure valve homogenizer	20	4.5	$\alpha$ -Tocopherol in palm oil	200–500	Relkin et al. (2011)

**Table 1** (continued)

Type of emulsifier	Homogenization technique	Percentage of oil used	Percentage of emulsifier used	Oil phase used	Droplet size diameter (nm)	Citation
$\beta$ -Lactoglobulin ( $\beta$ -lg)	Microfluidization	5	1–10	Corn oil/octadecane	162	Qian and McClements (2011)
	High-pressure valve homogenizer	20	1	Soy oil	350	Sarkar et al. (2009)
	Microfluidization	10	1	Corn oil Miglyol® 812 Tributyrin	181 174 1981	Ahmed et al. (2012)
Maize germ protein	Combined aqueous extraction–ultrafiltration method	5	3	Maize germ oil bodies	155	Nikiforidis et al. (2011)
Sodium caseinate	Microfluidization	0.05–0.3	0.5–5	$\beta$ -Carotene in hexane	17	Chu et al. (2007)
	Microfluidization	5	1–10	Corn oil/octadecane	179	Qian and McClements (2011)
	High-pressure valve homogenizer	40	3.6	$\alpha$ -Tocopherol/low melting triacylglycerols	255–416, 293–304	Relkin et al. (2008, 2009)

**Fig. 2** An overview of nanoemulsions applications. Nanoemulsions are not only used in foods, they are now potent targets in healthcare delivery, cosmetics, polymers, among others. The physicochemical properties of nanoemulsions like stability, emulsification, solubility, ionic strength, pH and temperature are indicative of their functional purposes and utilization in several sectors other than the food industry



## Nanoemulsion applications

Recent studies on the applications of nanoemulsions are described below, schematically presented in Fig. 2 and captured in Tables 2 and 3. The present coronavirus disease (COVID-19) pandemic has called for a more robust and holistic approach to solving health-related issues, the highest priority of the modern human civilization.

## Health

### Drugs

Nanoemulsions have the ability to dissolve nonpolar active compounds, a characteristic paramount to being choice of use as drug and bioactive compounds delivery systems. Both oral and parenteral delivery routes are employable, as the



**Table 2** Composition, fabrication methods and applications of nanoemulsions

Citation	Composition	Fabrication method	Application/activity
Arredondo-Ochoa et al. (2017)	Beeswax–starch nanoemulsions; oil-in-water	Microfluidization with Tween-80	Antimicrobial (against <i>R. stolonifer</i> , <i>C. gloeosporioides</i> , <i>B. cinerea</i> , and <i>S. saintpauli</i> ); applied as edible coatings for food preservation
Bakshi et al. (2018)	Non-irritant topical formulation for topical delivery of heparinoid	Homogenization with high pressure	Therapeutic agent for superficial thrombophlebitis
Gharibzadeh and Mohammadhabi (2017)	Jujube gum with nettle essential oil; oil-in-water	Homogenization with Tween-40	Antimicrobial; fabrication of jujube gum edible coating for Beluga sturgeon filets
Salim et al. (2018)	Ibuprofen nanoemulsions	Phase inversion composition	Good stability; topical uses
Nirmal et al. (2018)	Lemon myrtle and anise myrtle essential oil in water	Ultrasonication	Antibacterial; good stability
Noori et al. (2018)	Sodium caseinate and ginger essential oil; oil-in-water	Ultrasonication with Tween-80	Antimicrobial ( <i>L. monocytogenes</i> and <i>S. typhimurium</i> ); chicken breast fillet coating
Prakash et al. (2019)	Linalool-based nanoemulsions; oil-in-water	Ultrasonication with Tween-80	Antibacterial (against <i>S. typhimurium</i> ), antibacterial agent
Zhang et al. (2019)	Docosahexaenoic acid and eicosapentaenoic acid; oil-in-water	Emulsion phase inversion with Tween-80 and 85	Antioxidant effect from tea polyphenols and good stability; applications in food fortification meant for commercial purpose
Lu et al. (2018)	Citral essential oil	Ultrasonication	Antimicrobial; utilizable in cosmetics, pharmaceuticals and agrochemicals
Park et al. (2019)	Nanoemulsion powder consisting turmeric extract; oil-in-water	High-speed homogenization, ultrasonication and spray drying with Tween-80	Antioxidant effect and good stability in gastric model; enhanced shelf-life of fortified milk for 3 weeks
Teo et al. (2017)	Phenytoloin-loaded alkyl	Phase inversion method	Applied to topical wound healing
Farshi et al. (2019)	Cumin seed oil, corn oil, whey protein isolate-guar gum; oil-in-water	Ultrasonication and homogenization with Tween-80	Antifungal (against <i>A. flavus</i> ); food preservative
Kaci et al. (2018)	Coenzyme Q10	Sonication	Topical uses
Pongsumpun et al. (2020)	Cinnamon essential oil; oil-in-water	Ultrasonication with Tween-80	Antifungal (against <i>A. niger</i> , <i>R. arrhizus</i> , <i>C. gloeosporioides</i> and <i>Penicillium</i> sp.); food and agricultural uses
Sari et al. (2015)	Curcumin and medium chain triglyceride oil	Ultrasonication	Improved bioaccessibility and stability; applicable in functional foods
Majeed et al. (2016)	Purity gum ultra. canola and clove oil; water-in-oil	High speed homogenization	Antibacterial against Gram-positive strains; antimicrobial agent
Rebolledo et al. (2015)	Wheat bran oil-based nanoemulsions	Ultrasonication with Span-80 and Tween-80	Good stability; antioxidant and tyrosinase inhibitory activities; Usable in functional foods
Gundewadi et al. (2018)	Sapindus extract and basil oil; oil-in-water	Ultrasonication with saponin	Antimicrobial (against <i>P. chrysogenum</i> and <i>A. flavus</i> ); applied in food safety against food spoilage pathogens
Anjali et al. (2012)	Neem oil from <i>A. indica</i> and non-ionic surfactant (Tween 20)	Ultrasonication with Tween 20	Active against <i>Culex quinquefasciatus</i> ; usable as a larvicidal agent

**Table 3** Composition, fabrication methods and applications of nanoemulsions in foods

Citation	Composition	Fabrication method	Application/activity
Arredondo-Ochoa et al. (2017)	Beeswax–starch nanoemulsions; oil-in-water	Microfluidization with Tween-80	Antimicrobial (against <i>R. stolonifer</i> , <i>C. gloeosporioides</i> , <i>B. cinerea</i> , and <i>S. saintpauli</i> ); applied as edible coatings for food preservation
Gharibzadeh and Mohammadhadi (2017)	Jujube gum with nettle essential oil; oil-in-water	Homogenization with Tween-40	Antimicrobial; fabrication of jujube gum edible coating for Beluga sturgeon filets
Nirmal et al. (2018)	Lemon myrtle and anise myrtle essential oil in water	Ultrasonication	Antibacterial; good stability
Noori et al. (2018)	Sodium caseinate and ginger essential oil; oil-in-water	Ultrasonication with Tween-80	Antimicrobial ( <i>L. monocytogenes</i> and <i>S. typhimurium</i> ); chicken breast fillet coating
Prakash et al. (2019)	Linalool-based nanoemulsions; oil-in-water	Ultrasonication with Tween-80	Antibacterial (against <i>S. typhimurium</i> ); antibacterial agent
Zhang et al. (2019)	Docosahexaenoic acid and eicosapentaenoic acid; oil-in-water	Emulsion phase inversion with Tween-80 and 85	Antioxidant effect from tea polyphenols and good stability; applications in food fortification meant for commercial purpose
Park et al. (2019)	Nanoemulsion powder consisting turmeric extract; oil-in-water	High-speed homogenization, ultrasonication and spray drying with Tween-80	Antioxidant effect and good stability in gastric model; enhanced shelf-life of fortified milk for 3 weeks
Farshi et al. (2019)	Cumin seed oil, corn oil, whey protein isolate-guar gum; oil-in-water	Ultrasonication and homogenization with Tween-80	Antifungal (against <i>A. flavus</i> ); food preservative
Pongsumpun et al. (2020)	Cinnamon essential oil; oil-in-water	Ultrasonication with Tween-80	Antifungal (against <i>A. niger</i> , <i>R. arrhizus</i> , <i>C. gloeosporioides</i> and <i>Penicillium</i> sp.); food and agricultural uses
Sari et al. (2015)	Curcumin and medium chain triglyceride oil	Ultrasonication	Improved bioaccessibility and stability; applicable in functional foods
Majeed et al. (2016)	Purity gum ultra. canola and clove oil; water-in-oil	High speed homogenization	Antibacterial against Gram-positive strains; antimicrobial agent
Rebolledo et al. (2015)	Wheat bran oil-based nanoemulsions	Ultrasonication with Span-80 and Tween-80	Good stability, antioxidant and tyrosinase inhibitory activities; Usable in functional foods
Gundewadi et al. (2018)	Sapindus extract and basil oil; oil-in-water	Ultrasonication with saponin	Antimicrobial (against <i>P. chrysogenum</i> and <i>A. flavus</i> ); applied in food safety against food spoilage pathogens



latter has been utilized in supplying required nutrients, controlled drug release, and vaccine delivery. Systemic antibacterial, antifungal, antiparasitic and antimicrobial activities of nanoemulsions have been reported on *E. coli*, *S. aureus*, *Candida* spp., *Dermatophytes* spp., *Plasmodium bergheii*, among others (Singh and Vingkar 2008; Mansour et al. 2009).

Nanoemulsions are more advantageous than the conventional emulsions and other systems since their droplet sizes are below the micrometers range, and thus they easily pass the stringency of intravenous administration of drugs. The parenteral administration of nanoemulsions employed in nutrition of vitamins and other bioactive substances, attest to the merits they possess over other systems as their transit time, absorption, and efficacy are highly improved, while drug toxicity is reduced. Therefore, they are perfect drug delivery systems for antimicrobials, diuretics, steroids, and hormones (Sonneville-Aubrun et al. 2004; Singh and Vingkar 2008; Quintão et al. 2013).

### Vaccines

Of equal importance is the delivery of vaccines by nanoemulsions because it is gaining much wider attention from researchers. An attenuated organism is delivered onto the surface of a mucosal in order to elicit an immune response. Nanoemulsions are used in this case as adjuvants to deliver proteins onto the mucosal surface in order to instigate rapid absorption of antigen presenting cells. Physical adsorption, encapsulation (with or without coating and targeting), and conjugation (with chemical or targeting) mechanisms are often used to load antigens into nanocarriers. In any of the mechanisms, antigens are encapsulated in nanocarriers, while the nanoparticles degrade in vivo (Zhao et al. 2014). The vaccines can be very effective and spontaneous, irrespective of the site they are introduced to in the body. For instance, the immunity of genital mucosa might be guaranteed by administering the vaccines to the nasal mucosal (Berkowitz and Goddard 2009).

Vaccine adjuvants of oil/water emulsions have notable prospects, as found in AS03 pandemic flu and recombinant HIV gp 120 nanoemulsion-mixed vaccines (Akhter et al. 2008; Reed et al. 2009). The validation of these studies are still warranted. Moreover, the composition of emulsion, antigenicity and adjuvant specificity are paramount factors to consider when designing nanoemulsion-based vaccines. The essence of this is to ensure safety and effective immunological benefits.

### Inflammation

Nanoemulsions could also be employed in anti-inflammatory functions. Free radicals are released by enzymes, toxic

metabolites of pathogens, and inflammation mediators such as polymorphonuclear lymphocytes, leading to chronic inflammation. These same enzymes and metabolites deprive host cells of their required nutrients for growth. However, the mix of emulsifiers and oils was reportedly significant in phytochemicals absorption and treatment of inflammatory bowel disease (IBD), *i.e.*, Crohn's disease and ulcerative colitis (Yen et al. 2018) and periodontitis, a chronic inflammatory disease that erodes teeth's supporting structures (Aithal et al. 2018).

Inflammatory bowel disease (IBD) is often characterized with inflamed intestinal wall where the colonic and rectal mucosa are impacted. This is continuous for ulcerative colitis while it may be transmural and discontinuous in Crohn's disease. Host's lifestyle, genetic make-up, oxidative stress, pathogenic attack, immune responses, and drastic changes of inflammatory mediator levels are factors associated with IBD (Head and Jurenka 2003). Meanwhile, some studies have shown the usefulness of phytochemicals in treating periodontitis and IBD, including diterpenoid and quercetin, respectively (Geoghegan et al. 2010). Due to their low water solubility, they are less bio-available and are poorly absorbed orally. To increase their absorbability, both phytochemicals were improved with emulsions (Azuma et al. 2002).

### Cancer

Abnormal cell proliferation due to genetic coding errors generate cancer cells. Active angiogenesis and vascular density occur in order to utilize the blood supply for tumor tissues growth, and is supported by a microenvironment of the extracellular matrix, adipocytes, pericytes, immune cells, and others (Ganta et al. 2014). The use of anticancer drugs may result in inadequate solubility, toxicity to non-cancer cells, and poor selectivity of target cancer cells, while chemotherapy drugs may not be ideal in the long run due to their action on every form of proliferative cells, including hair follicles, bone marrow, red blood cells, gut epithelial cells, and lymphatic cells (Qiao et al. 2010; Mahato 2017).

Poor solubility and hydrophobicity of most anticancer drugs connote their inability to reach or effect their action on cancer cells (Sareen et al. 2012). This is where nanoemulsions are essential, as they proffer solubility to hydrophobic drugs and their stability. The resultant effect is that cancerous cells are selectively targeted earlier, leading to a high rate of successful cancer treatment. For instance, nanoemulsions could be engineered using specific ligands to target cells, tissues, or organs, all to improve the status quo in cancer therapy (Mahato 2017). Nanoparticles easily conjugate with multifunctional moieties, as found in nanoemulsions, aimed at drug delivery for cancer therapy via diagnostic means and imaging. Indeed, Tiwari et al. (2006) studied and used lipid-rich nanoemulsions containing fatty

acids (omega-3 and omega-6 fatty acids, linoleic acid), non-glucose-based calories, and vitamins E and K as colloidal carriers for chemotherapeutic drugs, whilst using diagnostic and imaging techniques. Although the *in vitro* study was promising, the need for a validation and safety studies cannot be undermined. Table 2 offers more examples of nanoemulsion applications in healthcare delivery.

## Cosmetics and others

Nanoemulsions could be traced to other applications such as complex matter developments and cosmetics, based on their liquid–liquid affinity to macromolecular moieties, minute size and large surface area. As building blocks of polymers, nanoemulsions could use their hydrophobic monomeric units in the droplets to generate polymers, with vast examples demonstrated in the studies of Asua (2002), Landfester (2006) and Gupta et al. (2016). Interestingly, from the development of varying protein shell structures with silicone oil-based nanoemulsions (Chang et al. 2008), amphiphilic photoreactive surfactants (de Oliveira et al. 2011), silica nanospheres (Wu et al. 2013), photoinduced and thermoreactive polymers or organogels (Helgeson et al. 2012), essential oils-based products (Barradas and e Silva 2020), suspended magnetic nanoparticles (Primo et al. 2007), to erythrocyte-like composite hydrogels (An et al. 2013), nanoemulsions have been studied or applied.

Moreover, nanoemulsions could be used in composite and crystal formulations on the premise of size specificity and accuracy of active pharmaceutical ingredients and other products, involving a low energy-requiring process (Eral et al. 2014). Indeed, nanosized oil-loaded droplets ensure penetration of the stratum corneum, making them highly useful in alcohol-free perfume formulations (Rai et al. 2018; Barradas and e Silva 2020). Noteworthy to mention is that some oils used in nanoemulsions proffer some benefits that should not be undermined, and could be useful in the encapsulation of volatile components like aromatic compounds and essential oils.

On another note, the surface area and small size of nanoemulsion droplets increase their propensity to lesser viscosity, making them utilizable in the cosmetics sector as they could more efficiently deliver active substances to the skin. They are no flocculants, coalescing or creaming agents, and demonstrate little or no sediments, making their applications far more important than conventional emulsions in cosmetology. In this regard, *Vellozia squamata* and *Opuntia ficusindica* (L.) Mill hydroglycolic extracts were studied and applied to fabricate nanoemulsion-based moisturizers, creams, anti-ageing agents (Quintão et al. 2013; Ribeiro et al. 2015). Similarly, oils like coconut, polyethylene glycol octyl phenyl ether and polyethylene glycol hydrogenated

castor oil were included in nanoemulsions for cosmeceutical applications (Pengon et al. 2018).

Furthermore, the use of nano-gel technique for trans-epidermal water loss minimization, dermal protection, and efficacious active ingredients penetration has been suggested for inclusion in moisteners, anti-ageing creams and various sun care formulations (Mansour et al. 2009). For instance, Kemira nano-gel is a nanoemulsion-based patented cosmetics system meant to attain skin smoothness by enhancing high penetrative capacity of active ingredients and dermal cells production (Guglielmini 2008). Another patented example is that of L'Oreal (Paris, France), using nanoemulsion-based phosphoric acid fatty acid esters in cosmetics and pharmaceutical products, among others (Shah et al. 2010). Table 2 presents more on the overview of use of nanoemulsions in cosmetics and other non-food applications.

## Food

Nanoemulsions have proven quite useful in bioavailability, bioactivity, digestibility, stability, safety, quality, and sensory enhancements of food components and natural extracts, such as lycopene-solubilized and  $\beta$ -carotene-based nanoemulsions (Nedovic et al. 2011; Bakshi et al. 2018), based on their wide surface area and small droplets. To remain stable, formulation of nanoemulsions requires the presence of an emulsifier, often acting as not only an additive but a preservative of the food products and/or the active components. As an example, surface-active molecules were introduced during the fabrication of basil oil nanoemulsions, and were found to exert antimicrobial activity against certain food spoiling fungi, including *Aspergillus flavus* and *Penicillium chrysogenum* (Gundewadi et al. 2018). A similar study was carried out on avocado oil-based nanoemulsions stabilized with Quillaja saponins (QS) where thermal stability was reportedly increased as QS was incorporated in the emulsions, a merit in the cause of safe and sterile emulsion-based food products development (Teo et al. 2017; Riquelme et al. 2019).

The use of nanoemulsions to stabilize essential oils in foods also assist with overcoming their high volatility, hydrophobicity, and reactivity with other food components, which could reduce their applications in the food sector. The stabilized oils or nanoemulsions thus improve the antioxidant and antimicrobial activities of the processed essential oils, enhancing their compatibility, solubility, stability, physicochemical equilibrium, and behaviors (Lawrence and Rees 2000; Bai et al. 2016; Ghasemi et al. 2018; Prakash et al. 2019). Other studies that have applied nanoemulsions in foods include corn oil-based  $\beta$ -carotene nanoemulsions at 300 nm (Borba et al. 2019), sensory efficient nanoemulsions constituted with Brazilian propolis extracts (Seibert et al. 2019), improved digestible curcumin nanoemulsions, and

nanoemulsion-based fortified beverages with vitamin D3 (Golfomitsou et al. 2018; Maurya and Aggarwal 2019). The possibilities of nanoemulsions in foods and food products seem limitless. More examples are presented in Table 3.

## Conclusion

Based on their physicochemical and functional properties, nanoemulsions have very promising multisectorial uses in healthcare, food, polymer manufacturing and cosmetics industries. Therefore, they have gained prominent attention in the scientific community. Recent uses of beeswax-starch, jujube gum, sodium caseinate, turmeric extract, linalool, docosahexaenoic and eicosapentaenoic acid, cumin seed oil, whey protein isolate, and oils like cinnamon, lemon and anise myrtle essential oils in nanoemulsion formulations (Arredondo-Ochoa et al. 2017; Gharibzahedi and Mohammadnabi 2017; Nirmal et al. 2018; Noori et al. 2018; Prakash et al. 2019; Zhang et al. 2019; Park et al. 2019; Farshi et al. 2019; Pongsumpun et al. 2020) have shown high potentials in the food industry and for the general well being. They can also deliver phytochemicals and other bioactive components in the food industry (Mahmood et al. 2017). In addition, nanoemulsions also have multifarious prospects in non-food applications shown recently in inflammatory and periodontitis treatment, agrochemical, cosmetics and pharmaceuticals, texturizing agents and creams, non-steroidal anti-inflammatory drug, drug and vaccine delivery, cosmetic applications and alcohol-free perfume formulations (Aithal et al. 2018; Teo et al. 2017; Bakshi et al. 2018; Lu et al. 2018; Kaci et al. 2018; Salim et al. 2018; Pengon et al. 2018; Rai et al. 2018; Shaker et al. 2019; Kumar et al. 2019; Barradas and e Silva 2020).

Formulating nanoemulsions often employ emulsifiers/surfactants and nanoparticles, which have raised eyebrows regarding their safety because they accumulate both in the environment and in the human body (Bajpai et al. 2018). Any engineered nanoparticulates or materials attract some degree of attention due to limited comprehension of their mechanisms and health consequences, a major reason to delay further implementation of nanotechnology in the food industry (Loira et al. 2020). For instance, long-term exposure to silver nanoparticles could lead to cell damage and inflammation via oxidative stress reactions (Gaillet and Rouanet 2015; Smolkova et al. 2015). Thus, it is required that the safety of nanoparticles-based systems such as nanoemulsions must be ascertained, along with their physicochemical characteristics in order to help with tactile conclusions and policies of regulatory bodies.

In addition, the methods and conditions associated with nanoemulsions production will affect their stability and other physicochemical properties, with corresponding impacts on

their applications. Hence, specificity is key. Solubility, availability, activity, acceptability and polarity would be noteworthy concerns to look at, when developing nanoemulsions. Considering all these factors would inadvertently affect the cost of production for much larger commercial applications. Conclusively, nanoemulsions indeed could be utilized in several sectors other than the food industry.

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## Compliance with ethical standards

**Conflict of interest** The author has no conflicts of interest to declare that are relevant to the content of this article.

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## References

- Adjonu R, Doran G, Torley P et al (2014) Whey protein peptides as components of nanoemulsions: A review of emulsifying and biological functionalities. *J Food Eng* 122:15–27. <https://doi.org/10.1016/j.jfoodeng.2013.08.034>
- Ahmed K, Li Y, McClements DJ et al (2012) Nanoemulsion-and emulsion-based delivery systems for curcumin: Encapsulation and release properties. *Food Chem* 132(2):799–807. <https://doi.org/10.1016/j.foodchem.2011.11.039>
- Aithal GC, Nayak UY, Mehta C et al (2018) Localized in situ nanoemulgel drug delivery system of quercetin for periodontitis: development and computational simulations. *Molecules* 23(6):1363. <https://doi.org/10.3390/molecules23061363>
- Akhter S, Jain GK, Ahmad FJ et al (2008) Investigation of nanoemulsion system for transdermal delivery of domperidone: *ex-vivo* and *in vivo* studies. *Curr Nanosci* 4(4):381–390. <https://doi.org/10.2174/157341308786306071>
- An HZ, Safai ER, Eral HB et al (2013) Synthesis of biomimetic oxygen-carrying compartmentalized microparticles using flow lithography. *Lab Chip* 13(24):4765–4774. <https://doi.org/10.1039/C3LC50610J>
- An Y, Yan X, Li B et al (2014) Microencapsulation of capsanthin by self-emulsifying nanoemulsions and stability evaluation. *Eur Food Res Technol* 239(6):1077–1085. <https://doi.org/10.1007/s00217-014-2328-3>

- Anjali CH, Sharma Y, Mukherjee A et al (2012) Neem oil (*Azadirachta indica*) nanoemulsion—a potent larvicidal agent against *Culex quinquefasciatus*. *Pest Manag Sci* 68(2):158–163. <https://doi.org/10.1002/ps.2233>
- Arredondo-Ochoa T, García-Almendárez BE, Escamilla-García M et al (2017) Physicochemical and antimicrobial characterization of beeswax–starch food-grade nanoemulsions incorporating natural antimicrobials. *Int J Mol Sci* 18(12):2712. <https://doi.org/10.3390/ijms18122712>
- Artiga-Artigas M, Guerra-Rosas MI, Morales-Castro J et al (2018) Influence of essential oils and pectin on nanoemulsion formulation: a ternary phase experimental approach. *Food Hydrocoll* 81:209–219. <https://doi.org/10.1016/j.foodhyd.2018.03.001>
- Ashaolu TJ (2020a) Applications of soy protein hydrolysates in the emerging functional foods: a review. *Int J Food Sci Technol* 55(2):421–428. <https://doi.org/10.1111/ijfs.14380>
- Ashaolu TJ (2020b) Soy bioactive peptides and the gut microbiota modulation. *Appl Microbiol Biotechnol* 104:9009–9017. <https://doi.org/10.1007/s00253-020-10799-2>
- Asua JM (2002) Miniemulsion polymerization. *Prog Polym Sci* 27(7):1283–1346. [https://doi.org/10.1016/S0079-6700\(02\)00010-2](https://doi.org/10.1016/S0079-6700(02)00010-2)
- Aziz ZAA, Mohd-Nasir H, Setapar M et al (2019) Role of nanotechnology for design and development of cosmeceutical: application in makeup and skin care. *Front Chem* 7:739. <https://doi.org/10.3389/fchem.2019.00739>
- Azmi NAN, Elgharbawy AA, Motlagh SR et al (2019) Nanoemulsions: factory for food, pharmaceutical and cosmetics. *Processes* 7(9):617. <https://doi.org/10.3390/pr7090617>
- Azuma K, Ippoushi K, Ito H et al (2002) Combination of lipids and emulsifiers enhances the absorption of orally administered quercetin in rats. *J Agric Food Chem* 50(6):1706–1712. <https://doi.org/10.1021/jf0112421>
- Bai L, Huan S, Gu J et al (2016) Fabrication of oil-in-water nanoemulsions by dual-channel microfluidization using natural emulsifiers: saponins, phospholipids, proteins, and polysaccharides. *Food Hydrocoll* 61:703–711. <https://doi.org/10.1016/j.foodhyd.2016.06.035>
- Bajpai VK, Kamle M, Shukla S et al (2018) Prospects of using nanotechnology for food preservation, safety, and security. *J Food Drug Anal* 26(4):1201–1214. <https://doi.org/10.1016/j.jfda.2018.06.011>
- Bakshi P, Jiang Y, Nakata T et al (2018) Formulation development and characterization of nanoemulsion-based formulation for topical delivery of heparinoid. *J Pharm Sci* 107(11):2883–2890. <https://doi.org/10.1016/j.xphs.2018.07.015>
- Barradas TN, e Silva KGDH, (2020) Nanoemulsions of essential oils to improve solubility, stability and permeability: a review. *Environ Chem Lett* 1–19. <https://doi.org/10.1007/s10311-020-01142-2>
- Berkowitz AC, Goddard DM (2009) Novel drug delivery systems: future directions. *J Neurosci Nurs* 41(2):115–120. <https://doi.org/10.1097/jnn.0b013e318193458b>
- Bilbao-Sáinz C, Avena-Bustillos RJ, Wood DF et al (2010) Nanoemulsions prepared by a low-energy emulsification method applied to edible films. *J Agric Food Chem* 58(22):11932–11938. <https://doi.org/10.1021/jf102341r>
- Borba CM, Tavares MN, Macedo LP et al (2019) Physical and chemical stability of  $\beta$ -carotene nanoemulsions during storage and thermal process. *Food Res Int* 121:229–237. <https://doi.org/10.1016/j.foodres.2019.03.045>
- Bouchemal K, Briançon S, Perrier E et al (2004) Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimisation. *Int J Pharm* 280(1–2):241–251. <https://doi.org/10.1016/j.ijpharm.2004.05.016>
- Burapapadk K, Kumpugdee-Vollrath M, Chantasant D et al (2010) Fabrication of pectin-based nanoemulsions loaded with itraconazole for pharmaceutical application. *Carb Polym* 82(2):384–393. <https://doi.org/10.1016/j.carbpol.2010.04.071>
- Chang CB, Knobler CM, Gelbart WM et al (2008) Curvature dependence of viral protein structures on encapsidated nanoemulsion droplets. *ACS Nano* 2(2):281–286. <https://doi.org/10.1021/nn700385z>
- Chang Y, McLandsborough L, McClements DJ (2012) Physical properties and antimicrobial efficacy of thyme oil nanoemulsions: influence of ripening inhibitors. *J Agric Food Chem* 60(48):12056–12063. <https://doi.org/10.1021/jf304045a>
- Chowdhury P, Gogoi M, Borchetia S et al (2017) Nanotechnology applications and intellectual property rights in agriculture. *Environ Chem Lett* 15(3):413–419. <https://doi.org/10.1007/s10311-017-0632-4>
- Christiansen KF, Vegarud G, Langsrud T et al (2004) Hydrolyzed whey proteins as emulsifiers and stabilizers in high-pressure processed dressings. *Food Hydrocoll* 18(5):757–767. <https://doi.org/10.1016/j.foodhyd.2003.12.002>
- Cortés-Muñoz M, Chevalier-Lucia D, Dumay E (2009) Characteristics of submicron emulsions prepared by ultra-high pressure homogenisation: effect of chilled or frozen storage. *Food Hydrocoll* 23(3):640–654. <https://doi.org/10.1016/j.foodhyd.2008.07.023>
- Dasgupta N, Ranjan S, Gandhi M (2019a) Nanoemulsion ingredients and components. *Environ Chem Lett* 17(2):917–928. <https://doi.org/10.1007/s10311-018-00849-7>
- Dasgupta N, Ranjan S, Gandhi M (2019b) Nanoemulsions in food: market demand. *Environ Chem Lett* 17(2):1003–1009. <https://doi.org/10.1007/s10311-019-00856-2>
- de Oliveira RJ, Brown P, Correia GB et al (2011) Photoreactive surfactants: a facile and clean route to oxide and metal nanoparticles in reverse micelles. *Langmuir* 27(15):9277–9284. <https://doi.org/10.1021/la202147h>
- Donsì F, Annunziata M, Vincenzi M et al (2012) Design of nanoemulsion-based delivery systems of natural antimicrobials: effect of the emulsifier. *J Biotechnol* 159(4):342–350. <https://doi.org/10.1016/j.jbiotec.2011.07.001>
- Donsì F, Wang Y, Huang Q (2011) Freeze–thaw stability of lecithin and modified starch-based nanoemulsions. *Food Hydrocoll* 25(5):1327–1336. <https://doi.org/10.1016/j.foodhyd.2010.12.008>
- Eral HB, López-Mejías V, O'Mahony M et al (2014) Biocompatible alginate microgel particles as heteronucleants and encapsulating vehicles for hydrophilic and hydrophobic drugs. *Crystal Growth Des* 14(4):2073–2082. <https://doi.org/10.1021/cg500250e>
- Farshi P, Tabibiazar M, Ghorbani M et al (2019) Whey protein isolate-guar gum stabilized cumin seed oil nanoemulsion. *Food Biosci* 28:49–56. <https://doi.org/10.1016/j.fbio.2019.01.011>
- Feng J, Zhang Q, Liu Q et al (2018) Application of nanoemulsions in formulation of pesticides. In: *Nanoemulsions*. Academic Press, pp 379–413. <https://doi.org/10.1016/B978-0-12-811838-2.00012-6>
- Foegeding EA, Davis JP, Doucet D et al (2002) Advances in modifying and understanding whey protein functionality. *Trends Food Sci Technol* 13(5):151–159. [https://doi.org/10.1016/S0924-2244\(02\)00111-5](https://doi.org/10.1016/S0924-2244(02)00111-5)
- Gaillet S, Rouanet JM (2015) Silver nanoparticles: their potential toxic effects after oral exposure and underlying mechanisms—a review. *Food Chem Toxicol* 77:58–63. <https://doi.org/10.1016/j.fct.2014.12.019>
- Ganta S, Talekar M, Singh A et al (2014) Nanoemulsions in translational research—opportunities and challenges in targeted cancer therapy. *AAPS PharmSciTech* 15(3):694–708. <https://doi.org/10.1208/s12249-014-0088-9>



- Geoghegan F, Wong RWK, Rabie ABM (2010) Inhibitory effect of quercetin on periodontal pathogens *in vitro*. *Phytother Res* 24(6):817–820. <https://doi.org/10.1002/ptr.3014>
- Gharibzadeh SMT, Mohammadnabi S (2017) Effect of novel bioactive edible coatings based on jujube gum and nettle oil-loaded nanoemulsions on the shelf-life of Beluga sturgeon fillets. *Int J Biol Macromol* 95:769–777. <https://doi.org/10.1016/j.ijbiomac.2016.11.119>
- Ghasemi S, Jafari SM, Assadpour E et al (2018) Nanoencapsulation of d-limonene within nanocarriers produced by pectin-whey protein complexes. *Food Hydrocoll* 77:152–162. <https://doi.org/10.1016/j.foodhyd.2017.09.030>
- Ghosh V, Mukherjee A, Chandrasekaran N (2013) Ultrasonic emulsification of food-grade nanoemulsion formulation and evaluation of its bactericidal activity. *Ultrason Sonochem* 20(1):338–344. <https://doi.org/10.1016/j.ultsonch.2012.08.010>
- Golfomitsou I, Mitsou E, Xenakis A et al (2018) Development of food grade O/W nanoemulsions as carriers of vitamin D for the fortification of emulsion based food matrices: a structural and activity study. *J Mol Liq* 268:734–742
- Gordon EM, Cornelio GH, Lorenzo CC et al (2003) First clinical experience using a ‘pathotropic’ injectable retroviral vector (Rexin-G) as intervention for stage IV pancreatic cancer. *Int J Oncol* 24(1):177–185. <https://doi.org/10.3892/ijo.24.1.177>
- Graves S, Meleson K, Wilking J et al (2005) Structure of concentrated nanoemulsions. *J Chem Phys* 122(13):134703. <https://doi.org/10.1063/1.1874952>
- Guglielmini G (2008) Nanostructured novel carrier for topical application. *Clin Dermatol* 26(4):341–346. <https://doi.org/10.1016/j.clindermatol.2008.05.004>
- Gundewadi G, Sarkar DJ, Rudra SG et al (2018) Preparation of basil oil nanoemulsion using *Sapindus mukorossi* pericarp extract: Physico-chemical properties and antifungal activity against food spoilage pathogens. *Indus Crops Prod* 125:95–104. <https://doi.org/10.1016/j.indcrop.2018.08.076>
- Gupta A, Eral HB, Hatton TA et al (2016) Nanoemulsions: formation, properties and applications. *Soft Mat* 12(11):2826–2841. <https://doi.org/10.1039/C5SM02958A>
- Gurpreet K, Singh SK (2018) Review of nanoemulsion formulation and characterization techniques. *Indian J Pharm Sci* 80(5):781–789. <https://doi.org/10.4172/pharmaceutical-sciences.1000422>
- Head KA, Jurenka JS (2003) Inflammatory bowel disease part 1: ulcerative colitis—pathophysiology and conventional and alternative treatment options. *Altern Med Rev* 8(3):247–283
- Helgeson ME, Moran SE, An HZ et al (2012) Mesoporous organohydrogels from thermogelling photocrosslinkable nanoemulsions. *Nat Mater* 11(4):344–352. <https://doi.org/10.1038/nmat3248>
- Hoeller S, Sperger A, Valenta C (2009) Lecithin based nanoemulsions: a comparative study of the influence of non-ionic surfactants and the cationic phytosphingosine on physicochemical behaviour and skin permeation. *Int J Pharm* 370(1–2):181–186. <https://doi.org/10.1016/j.ijpharm.2008.11.014>
- Jafari SM, He Y, Bhandari B (2007a) Optimization of nano-emulsions production by microfluidization. *Eur Food Res Technol* 225(5–6):733–741. <https://doi.org/10.1007/s00217-006-0476-9>
- Jafari SM, He Y, Bhandari B (2007b) Production of sub-micron emulsions by ultrasound and microfluidization techniques. *J Food Eng* 82(4):478–488. <https://doi.org/10.1016/j.foodeng.2007.03.007>
- Jaiswal M, Dudhe R, Sharma PK (2015) Nanoemulsion: an advanced mode of drug delivery system. *3 Biotech* 5(2):123–127. <https://doi.org/10.1007/s13205-014-0214-0>
- Kaci M, Belhaffef A, Meziane S et al (2018) Nanoemulsions and topical creams for the safe and effective delivery of lipophilic antioxidant coenzyme Q10. *Colloids Surf B Biointerf* 167:165–175. <https://doi.org/10.1016/j.colsurfb.2018.04.010>
- Kaul S, Gulati N, Verma D et al (2018) Role of nanotechnology in cosmeceuticals: a review of recent advances. *J Pharm* 34:20204. <https://doi.org/10.1155/2018/3420204>
- Kentish S, Wooster TJ, Ashokkumar M et al (2008) The use of ultrasonics for nanoemulsion preparation. *Innov Food Sci Emerg Technol* 9(2):170–175. <https://doi.org/10.1016/j.ifset.2007.07.005>
- Kim CK, Cho YJ, Gao ZG (2001) Preparation and evaluation of biphenyl dimethyl dicarboxylate microemulsions for oral delivery. *J Control Rel* 70(1–2):149–155. [https://doi.org/10.1016/s0168-3659\(00\)00343-6](https://doi.org/10.1016/s0168-3659(00)00343-6)
- Kumar DL, Sarkar P (2018) Encapsulation of bioactive compounds using nanoemulsions. *Environ Chem Lett* 16(1):59–70. <https://doi.org/10.1007/s10311-017-0663-x>
- Kumar M, Bishnoi RS, Shukla AK et al (2019) Techniques for formulation of nanoemulsion drug delivery system: a review. *Prev Nutr Food Sci* 24(3):225. <https://doi.org/10.3746/pnf.2019.24.3.225>
- Landfester K (2006) Synthesis of colloidal particles in miniemulsions. *Annu Rev Mater Res* 36:231–279. <https://doi.org/10.1146/annurev.matsci.36.032905.091025>
- Lawrence MJ, Rees GD (2000) Microemulsion-based media as novel drug delivery systems. *Adv Drug Del Rev* 45(1):89–121. [https://doi.org/10.1016/S0169-409X\(00\)00103-4](https://doi.org/10.1016/S0169-409X(00)00103-4)
- Lee SJ, McClements DJ (2010) Fabrication of protein-stabilized nanoemulsions using a combined homogenization and amphiphilic solvent dissolution/evaporation approach. *Food Hydrocoll* 24(6–7):560–569. <https://doi.org/10.1016/j.foodhyd.2010.02.002>
- Liang R, Xu S, Shoemaker CF et al (2012) Physical and antimicrobial properties of peppermint oil nanoemulsions. *J Agric Food Chem* 60(30):7548–7555. <https://doi.org/10.1021/jf301129k>
- Loira I, Morata A, Escott C et al (2020) Applications of nanotechnology in the winemaking process. *Eur Food Res Technol* 1–9. <https://doi.org/10.1007/s00217-020-03519-7>
- Lovelyn C, Attama AA (2011) Current state of nanoemulsions in drug delivery. *J Biomater Nanobiotechnol* 2(05):626. <https://doi.org/10.4236/jbnb.2011.225075>
- Lu WC, Huang DW, Wang CC et al (2018) Preparation, characterization, and antimicrobial activity of nanoemulsions incorporating citral essential oil. *J Food Drug Anal* 26(1):82–89. <https://doi.org/10.1016/j.jfda.2016.12.018>
- Macedo JP, Fernandes LL, Formiga FR et al (2006) Micro-emultocrit technique: a valuable tool for determination of critical HLB value of emulsions. *AAPS PharmSciTech* 7(1):146–152. <https://doi.org/10.1208/pt070121>
- Mahato R (2017) Nanoemulsion as targeted drug delivery system for cancer therapeutics. *J Pharm Sci pharmacol* 3(2):83–97. <https://doi.org/10.1166/jpsp.2017.1082>
- Mahmood Z, Jahangir M, Liaquat M et al (2017) Potential of nanoemulsions as phytochemical delivery system for food preservation. *Pak J Pharm Sci* 30(6):2259–2263
- Majeed H, Liu F, Hategekimana J et al (2016) Bactericidal action mechanism of negatively charged food grade clove oil nanoemulsions. *Food Chem* 197:75–83. <https://doi.org/10.1016/j.foodchem.2015.10.015>
- Mansour HM, Rhee YS, Wu X (2009) Nanomedicine in pulmonary delivery. *Int J Nanomed* 4:299
- Mao L, Xu D, Yang J et al (2009) Effects of small and large molecule emulsifiers on the characteristics of  $\beta$ -carotene nanoemulsions prepared by high pressure homogenization. *Food Technol Biotechnol* 47(3):336–342
- Mao L, Yang J, Xu D et al (2010) Effects of homogenization models and emulsifiers on the physicochemical properties of  $\beta$ -carotene nanoemulsions. *J Dispers Sci Technol* 31(7):986–993. <https://doi.org/10.1080/01932690903224482>

- Maurya VK, Aggarwal M (2019) A phase inversion based nanoemulsion fabrication process to encapsulate vitamin D3 for food applications. *J Steroid Biochem Mol Biol* 190:88–98. <https://doi.org/10.1016/j.jsbmb.2019.03.021>
- McClements DJ, Jafari SM (2018) General aspects of nanoemulsions and their formulation. In: *Nanoemulsions*. Academic Press, pp 3–20. <https://doi.org/10.1016/B978-0-12-811838-2.00001-1>
- McClements DJ, Bai L, Chung C (2017) Recent advances in the utilization of natural emulsifiers to form and stabilize emulsions. *Ann Rev Food Sci Technol* 8:205–236. <https://doi.org/10.1146/annurev-food-030216-030154>
- Mishra RK, Soni GC, Mishra RP (2014) A review article on nanoemulsion. *World J Pharm Pharm Sci* 3(9):258–274. <https://doi.org/10.7897/2230-8407.0913>
- Mohammadi A, Jafari SM, Esfanjani AF et al (2016) Application of nano-encapsulated olive leaf extract in controlling the oxidative stability of soybean oil. *Food Chem* 190:513–519. <https://doi.org/10.1016/j.foodchem.2015.05.115>
- Nedovic V, Kalusevic A, Manojlovic V et al (2011) An overview of encapsulation technologies for food applications. *Proc Food Sci* 1:1806–1815. <https://doi.org/10.1016/j.profoo.2011.09.265>
- Nikiforidis CV, Karkani OA, Kiosseoglou V (2011) Exploitation of maize germ for the preparation of a stable oil-body nanoemulsion using a combined aqueous extraction–ultrafiltration method. *Food Hydrocoll* 25(5):1122–1127. <https://doi.org/10.1016/j.foodhyd.2010.10.009>
- Nirmal NP, Mereddy R, Li L et al (2018) Formulation, characterisation and antibacterial activity of lemon myrtle and anise myrtle essential oil in water nanoemulsion. *Food Chem* 254:1–7. <https://doi.org/10.1016/j.foodchem.2018.01.173>
- Noori S, Zeynali F, Almasi H (2018) Antimicrobial and antioxidant efficiency of nanoemulsion-based edible coating containing ginger (*Zingiber officinale*) essential oil and its effect on safety and quality attributes of chicken breast fillets. *Food Control* 84:312–320. <https://doi.org/10.1016/j.foodcont.2017.08.015>
- O'Sullivan JJ, Drapala KP, Kelly AL et al (2018) The use of inline high-shear rotor-stator mixing for preparation of high-solids milk protein-stabilised oil-in-water emulsions with different protein: fat ratios. *J Food Eng* 222:218–225. <https://doi.org/10.1016/j.jfoodeng.2017.10.015>
- Park SJ, Hong SJ, Garcia CV et al (2019) Stability evaluation of turmeric extract nanoemulsion powder after application in milk as a food model. *J Food Eng* 259:12–20. <https://doi.org/10.1016/j.jfoodeng.2019.04.011>
- Peng LC, Liu CH, Kwan CC et al (2010) Optimization of water-in-oil nanoemulsions by mixed surfactants. *Colloids Surf A: Physicochem Eng Asp* 370(1–3):136–142. <https://doi.org/10.1016/j.colsurfa.2010.08.060>
- Pengon S, Chinatangkul N, Limmatvapirat C et al (2018) The effect of surfactant on the physical properties of coconut oil nanoemulsions. *Asian J Pharm Sci* 13(5):409–414. <https://doi.org/10.1016/j.ajps.2018.02.005>
- Pongsumpun P, Iwamoto S, Siripatrawan U (2020) Response surface methodology for optimization of cinnamon essential oil nanoemulsion with improved stability and antifungal activity. *Ultrasonics Sonochem* 60:104604. <https://doi.org/10.1016/j.ultsonch.2019.05.021>
- Prakash A, Vadivel V, Rubini D et al (2019) Antibacterial and anti-biofilm activities of linalool nanoemulsions against *Salmonella typhimurium*. *Food Biosci* 28:57–65. <https://doi.org/10.1016/j.fbio.2019.01.018>
- Primo FL, Michieletto L, Rodrigues MA et al (2007) Magnetic nanoemulsions as drug delivery system for Foscan®: skin permeation and retention in vitro assays for topical application in photodynamic therapy (PDT) of skin cancer. *J Mag Mag Mat* 311(1):354–357. <https://doi.org/10.1016/j.jmmm.2006.10.1183>
- Qian C, McClements DJ (2011) Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: factors affecting particle size. *Food Hydrocoll* 25(5):1000–1008. <https://doi.org/10.1016/j.foodhyd.2010.09.017>
- Qian C, Decker EA, Xiao H et al (2012) Nanoemulsion delivery systems: influence of carrier oil on  $\beta$ -carotene bioaccessibility. *Food Chem* 135(3):1440–1447. <https://doi.org/10.1016/j.foodchem.2012.06.047>
- Qiao W, Wang B, Wang Y et al (2010) Cancer therapy based on nanomaterials and nanocarrier systems. *J Nanomaterials*. <https://doi.org/10.1155/2010/796303>
- Quintão FJ, Tavares RS, Vieira-Filho SA et al (2013) Hydroalcoholic extracts of *Vellozia squamata*: study of its nanoemulsions for pharmaceutical or cosmetic applications. *Rev Bras Farmacogn* 23(1):101–107. <https://doi.org/10.1590/S0102-695X201300500001>
- Rai VK, Mishra N, Yadav KS et al (2018) Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: formulation development, stability issues, basic considerations and applications. *J Control Rel* 270:203–225. <https://doi.org/10.1016/j.jconrel.2017.11.049>
- Rao J, McClements DJ (2011) Food-grade microemulsions, nanoemulsions and emulsions: fabrication from sucrose monopalmitate & lemon oil. *Food hydrocoll* 25(6):1413–1423. <https://doi.org/10.1016/j.foodhyd.2011.02.004>
- Rebolledo S, Sanz MT, Benito JM et al (2015) Formulation and characterisation of wheat bran oil-in-water nanoemulsions. *Food Chem* 167:16–23. <https://doi.org/10.1016/j.foodchem.2014.06.097>
- Reed SG, Bertholet S, Coler RN et al (2009) New horizons in adjuvants for vaccine development. *Trends Immunol* 30(1):23–32. <https://doi.org/10.1016/j.it.2008.09.006>
- Relkin P, Jung JM, Ollivon M (2009) Factors affecting vitamin degradation in oil-in-water nano-emulsions. *J Therm Anal Cal* 98(1):13. <https://doi.org/10.1007/s10973-009-0340-9>
- Relkin P, Shukat R, Bourgaux C et al (2011) Nanostructures and polymorphisms in protein stabilised lipid nanoparticles, as food bioactive carriers: contribution of particle size and adsorbed materials. *Proc Food Sci* 1:246–250. <https://doi.org/10.1016/j.profoo.2011.09.039>
- Relkin P, Yung JM, Kalnin D et al (2008) Structural behaviour of lipid droplets in protein-stabilized nano-emulsions and stability of  $\alpha$ -tocopherol. *Food Biophys* 3(2):163–168. <https://doi.org/10.1007/s11483-008-9064-9>
- Research and Market (2018) Global nanotechnology market outlook 2024. Report ID: 4991720. <https://www.researchandmarkets.com/reports/4536705/global-nanotechnology-market-outlook-2018-2024>. Web assessed on 22nd December 2020.
- Ribeiro RCDA, Barreto SMAG, Ostrosky EA et al (2015) Production and characterization of cosmetic nanoemulsions containing *Opuntia ficus-indica* (L.) Mill extract as moisturizing agent. *Molecules* 20(2):2492–2509. <https://doi.org/10.3390/molecules20022492>
- Riquelme N, Zúñiga RN, Arancibia C (2019) Physical stability of nanoemulsions with emulsifier mixtures: replacement of tween 80 with quillaja saponin. *LWT* 111:760–766. <https://doi.org/10.1016/j.lwt.2019.05.067>
- Roca-Saavedra P, Mendez-Vilabrille V, Miranda JM et al (2018) Food additives, contaminants and other minor components: effects on human gut microbiota—a review. *J Physiol Biochem* 74(1):69–83. <https://doi.org/10.1007/s13105-017-0564-2>
- Saini A, Panwar D, Panesar PS et al (2020) Encapsulation of functional ingredients in lipidic nanocarriers and antimicrobial applications: a review. *Environ Chem Lett* 1–28. <https://doi.org/10.1007/s10311-020-01109-3>
- Salim N, García-Celma MJ, Escibano E et al (2018) Formation of nanoemulsion containing ibuprofen by PIC method for topical delivery.



- Mat Today: Proc 5:172–179. <https://doi.org/10.1016/j.matpr.2018.08.062>
- Sareen S, Mathew G, Joseph L (2012) Improvement in solubility of poor water-soluble drugs by solid dispersion. *Int J Pharm Invest* 2(1):12. <https://doi.org/10.4103/2230-973X.96921>
- Sari TP, Mann B, Kumar R et al (2015) Preparation and characterization of nanoemulsion encapsulating curcumin. *Food Hydrocoll* 43:540–546. <https://doi.org/10.1016/j.foodhyd.2014.07.011>
- Sarkar A, Goh KK, Singh RP et al (2009) Behaviour of an oil-in-water emulsion stabilized by  $\beta$ -lactoglobulin in an *in vitro* gastric model. *Food Hydrocoll* 23(6):1563–1569. <https://doi.org/10.1016/j.foodhyd.2008.10.014>
- Seibert JB, Bautista-Silva JP, Amparo TR et al (2019) Development of propolis nanoemulsion with antioxidant and antimicrobial activity for use as a potential natural preservative. *Food Chem* 287:61–67. <https://doi.org/10.1016/j.foodchem.2019.02.078>
- Shah B, Ikeda S, Davidson PM et al (2012) Nanodispersing thymol in whey protein isolate-maltodextrin conjugate capsules produced using the emulsion—evaporation technique. *J Food Eng* 113(1):79–86. <https://doi.org/10.1016/j.jfoodeng.2012.05.019>
- Shah P, Bhalodia D, Shelat P (2010) Nanoemulsion: a pharmaceutical review. *Syst Rev Pharm*. <https://doi.org/10.4103/0975-8453.59509>
- Shah R, Kolanos R, DiNovi MJ et al (2017) Dietary exposures for the safety assessment of seven emulsifiers commonly added to foods in the United States and implications for safety. *Food Add Cont Part A* 34(6):905–917. <https://doi.org/10.1080/19440049.2017.1311420>
- Shaker DS, Ishak RA, Ghoneim A et al (2019) Nanoemulsion: a review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs. *Sci Pharm* 87(3):17. <https://doi.org/10.3390/scipharm87030017>
- Singh KK, Vingkar SK (2008) Formulation, antimalarial activity and bio-distribution of oral lipid nanoemulsion of primaquine. *Int J Pharm* 347(1–2):136–143. <https://doi.org/10.1016/j.ijpharm.2007.06.035>
- Smolkova B, El Yamani N, Collins AR et al (2015) Nanoparticles in food. Epigenetic changes induced by nanomaterials and possible impact on health. *Food Chem Toxicol* 77:64–73. <https://doi.org/10.1016/j.fct.2014.12.015>
- Sonneville-Aubrun O, Simonnet JT, L'aloret F (2004) Nanoemulsions: a new vehicle for skincare products. *Adv Colloid Interface Sci* 108:145–149. <https://doi.org/10.1016/j.cis.2003.10.026>
- Tan CP, Nakajima M (2005)  $\beta$ -Carotene nanodispersions: preparation, characterization and stability evaluation. *Food Chem* 92(4):661–671. <https://doi.org/10.1016/j.foodchem.2004.08.044>
- Teo SY, Yew MY, Lee SY et al (2017) *In vitro* evaluation of novel phenytoin-loaded alkyd nanoemulsions designed for application in topical wound healing. *J Pharm Sci* 106(1):377–384. <https://doi.org/10.1016/j.xphs.2016.06.028>
- Tiwari S, Tan YM, Amiji M (2006) Preparation and *in vitro* characterization of multifunctional nanoemulsions for simultaneous MR imaging and targeted drug delivery. *J Biomed Nanotechnol* 2(3–4):217–224. <https://doi.org/10.1166/jbn.2006.038>
- van der Ven C, Gruppen H, de Bont DB et al (2001) Emulsion properties of casein and whey protein hydrolysates and the relation with other hydrolysate characteristics. *J Agric Food Chem* 49(10):5005–5012. <https://doi.org/10.1021/jf010144c>
- Vo TD, Lynch BS, Roberts A (2019) Dietary exposures to common emulsifiers and their impact on the gut microbiota: is there a cause for concern? *Compr Rev Food Sci Food Saf* 18(1):31–47. <https://doi.org/10.1111/1541-4337.12410>
- Walia N, Dasgupta N, Ranjan S et al (2019) Methods for nanoemulsion and nanoencapsulation of food bioactives. *Environ Chem Lett* 17(4):1471–1483. <https://doi.org/10.1007/s10311-019-00886-w>
- Wani TA, Masoodi FA, Jafari SM et al (2018) Safety of nanoemulsions and their regulatory status. In: *Nanoemulsions*. Academic Press, pp 613–628. <https://www.sciencedirect.com/science/book/9780128118382>. Accessed 2 Dec 2020
- Wu SH, Hung Y, Mou CY (2013) Compartmentalized hollow silica nanospheres templated from nanoemulsions. *Chem Mater* 25(3):352–364. <https://doi.org/10.1016/B978-0-12-811838-2.00019-9>
- Wulff-Pérez M, Torcello-Gómez A, Gálvez-Ruiz MJ et al (2009) Stability of emulsions for parenteral feeding: Preparation and characterization of o/w nanoemulsions with natural oils and Pluronic f68 as surfactant. *Food Hydrocoll* 23(4):1096–1102. <https://doi.org/10.1016/j.foodhyd.2008.09.017>
- Yen CC, Chen YC, Wu MT et al (2018) Nanoemulsion as a strategy for improving the oral bioavailability and anti-inflammatory activity of andrographolide. *Int J Nanomed* 13:669. <https://doi.org/10.2147/IJN.S154824>
- Yu L, Li C, Xu J et al (2012) Highly stable concentrated nanoemulsions by the phase inversion composition method at elevated temperature. *Langmuir* 28(41):14547–14552. <https://doi.org/10.1021/la302995a>
- Yuan Y, Gao Y, Zhao J et al (2008) Characterization and stability evaluation of  $\beta$ -carotene nanoemulsions prepared by high pressure homogenization under various emulsifying conditions. *Food Res Int* 41(1):61–68. <https://doi.org/10.1016/j.foodres.2007.09.006>
- Yukuyama MN, Ghisleni DDM, Pinto TDJA et al (2016) Nanoemulsion: process selection and application in cosmetics—a review. *Int J Cosmet Sci* 38(1):13–24. <https://doi.org/10.1111/ics.12260>
- Zhang L, Zhang F, Fan Z et al (2019) DHA and EPA nanoemulsions prepared by the low-energy emulsification method: process factors influencing droplet size and physicochemical stability. *Food Res Int* 121:359–366. <https://doi.org/10.1016/j.foodres.2019.03.059>
- Zhao C, Ashaolu TJ (2020) Bioactivity and safety of whey peptides. *LWT* 109935. <https://doi.org/10.1016/j.lwt.2020.109935>
- Zhao L, Seth A, Wibowo N et al (2014) Nanoparticle vaccines. *Vaccine* 32(3):327–337. <https://doi.org/10.1016/j.vaccine.2013.11.069>
- Ziani K, Chang Y, McLandsborough L et al (2011) Influence of surfactant charge on antimicrobial efficacy of surfactant-stabilized thyme oil nanoemulsions. *J Agric Food Chem* 59(11):6247–6255. <https://doi.org/10.1021/jf200450m>

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