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Historical Perspective

Recent developments in industrial applications of nanoemulsions

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ABSTRACT

Nanotechnology is being utilized in various industries to increase the quality, safety, shelf-life, and functional performance of commercial products. Nanoemulsions are thermodynamically unstable colloidal dispersions that consist of at least two immiscible liquids (typically oil and water), as well as various stabilizers (including emulsifiers, texture modifiers, ripening inhibitors, and weighting agents). They have unique properties that make them particularly suitable for some applications, including their small droplet size, high surface area, good physical stability, rapid digestibility, and high bioavailability. This article reviews recent developments in the formulation, fabrication, functional performance, and gastrointestinal fate of nanoemulsions suitable for use in the pharmaceutical, cosmetic, nutraceutical, and food industries, as well as providing an overview of regulatory and health concerns. Nanoemulsion-based delivery systems can enhance the water-dispersibility, stability, and bioavailability of hydrophobic bioactive compounds. Nevertheless, they must be carefully formulated to obtain the required functional attributes. In particular, the concentration, size, charge, and physical properties of the nano-droplets must be taken into consideration for each specific application. Before launching a nanoscale product onto the market, determination of physicochemical characteristics of nanoparticles and their potential health and environmental risks should be evaluated. In addition, legal, consumer, and economic factors must also be considered when creating these systems.

1. Introduction

The use of nanoemulsions in the pharmaceutical, cosmetic, and food industries has been increasing rapidly over the past decade or so due to their advantages over conventional emulsions for specific applications. Nanoemulsions can be designed to improve the appearance, stability, release properties, and bioavailability of emulsified food products, such as soft drinks, beverages, dressings, sauces, and deserts. Moreover, they can be incorporated into packaging materials to increase the shelf life of food products. As an example, nanoemulsions have been widely used to increase the bioavailability of vitamins and nutraceuticals [1]. They have also been used to increase the water-dispersibility and matrix compatibility of hydrophobic ingredients like oil-soluble antioxidants, antimicrobials, colors, and flavors. In the cosmetics industry, nanoemulsions have been used to increase the skin permeation properties of active ingredients, which is due to the small size of the particles they contain [2].

This review article provides the reader with the fundamental aspects of nanoemulsion formulation and production, as well as insights into their applications within the food, pharmaceutical, and cosmetic industries, with a focus on studies published in the last five years.

2. Constituent of nanoemulsions

2.1. Oil and aqueous phase

Nanoemulsions are composed of at least two phases: a non-polar (usually oil) and a polar (usually water) phase. The water phase may contain soluble or dispersed water-soluble ingredients, such as sugars, salts, proteins, and polysaccharides. The oil phase is often composed of one or more water-insoluble substances, such as triglyceride oils, essential oils, lipid substitutes, waxes, lipid-soluble vitamins, colors, flavors, and preservatives. Different oil types are chosen for different purposes. Oil soluble vitamins (such as vitamins A, D, and E) and

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polyunsaturated oils (such as fish, algal, or flaxseed oils) may be utilized in functional foods and beverages for their potential nutritional benefits [3]. Essential oils may be used in foods, cosmetics, and personal care products due to their natural antimicrobial and antioxidant properties. Each type of oil phase has its own unique challenges. For instance, polyunsaturated oils are prone to lipid oxidation, whereas essential oils are prone to volatilization and Ostwald ripening. Hence, specific strategies have to be developed to create stable nanoemulsions from different types of the oil phase.

A stable nanoemulsion cannot usually be formed by simply homogenizing oil and water phases together. Typically, an emulsifier is required to adsorb to the droplet surfaces and prevent them from aggregating with each other during emulsion formation, storage, and utilization. In addition, it may also be necessary to add other kinds of stabilizers to enhance the shelf life and functional performance of nanoemulsions, such as texture modifiers, weighting agents, and ripening inhibitors. Texture modifiers are substances that are usually added to the continuous phase of nanoemulsions for thickening or gelling purposes, which may help to limit droplet movement and thereby improve stability [4]. Weighting agents are mostly used in O/W nanoemulsions and are added to the oil phase to reduce the density difference between the two phases, thereby decreasing the driving force for gravitational separation. Owing to their higher densities than water, ester gum, brominated vegetable oil, and sucrose acetate isobutyrate are widely used as weighting agents in food systems [5]. Ripening inhibitors are highly hydrophobic substances that are added to the oil phase to retard the net diffusion of oil molecules from small to large droplets. Long chain triglycerides such as corn oil, sunflower oil or palm oil can be used as ripening inhibitors to inhibit Ostwald ripening [6].

2.2. Emulsifiers and other stabilizers

Several kinds of stabilizers can be used to improve the stability of nanoemulsions [7]. Emulsifiers are amphiphilic substances that adsorb to droplet surfaces where they lower the interfacial tension (thereby improving droplet formation) and they form a protective coating (thereby improving droplet stability). Molecular emulsifiers are usually amphiphilic molecules where the non-polar part protrudes into the oil phase and the polar part protrudes into the water phase. Typically, the lower the interfacial tension, the smaller the droplets produced [8]. Several kinds of emulsifiers are available for utilization in food products, including small molecule surfactants, phospholipids, polysaccharides, and proteins, which are discussed in more detail below.

2.2.1. Small molecule surfactants

Small molecule surfactants are relatively low molecular weight (< 2 kDa) amphiphilic molecules that typically have a polar head group and a non-polar tail group. Due to their small size, they can rapidly adsorb to oil-water interfaces during homogenization. Monoglycerides, organic acid esters of monoglycerides, sorbitan esters, and saponins are common examples of small molecule surfactants. DATEM (diacetyl tartaric acid monoglycerides) and CITREM (citric acid esters of monoglycerides) are anionic synthetic surfactants. They have a wide application range from coffee creamers and salad dressings to meat products and beverages [9]. Tweens and Spans are non-ionic surfactants that are widely used in the food, cosmetic, and drug industries because they have been shown to be nontoxic and nonirritating at the levels required [10]. More recently, there has been growing interest in identifying natural alternatives to synthetic surfactants due to increasing consumer demand for clean-label products that are assumed to be better for human health and the environment. Saponins are natural amphiphilic molecules found in various edible plants, including quillaja, soybeans, chickpeas, peas, and tea. They are amphiphilic due to the presence of a hydrophobic aglycone part and a hydrophilic sugar part. Consequently, they can rapidly adsorb to oil droplet surfaces during homogenization, reduce the interfacial tension, and form a protective coating. Consequently, they are particularly suitable for application in the formulation of natural plant-based nanoemulsions.

2.2.2. Phospholipids

Lecithins are phospholipids composed of two fatty acid tails attached to a glycerol backbone and a zwitterionic phosphate group [11]. They are amphiphilic because the phosphate group is hydrophilic and the fatty acid chains are lipophilic. Consequently, they can adsorb to oil-water interfaces and lower the interfacial tension. Lecithins are natural compounds that can be extracted from various sources including, eggs, soybeans, and sunflowers. They are often not effective at forming and stabilizing O/W or W/O emulsions when used alone because they have intermediate HLB numbers and solubilities in both phases. For this reason, lecithins are often chemically or enzymatically hydrolyzed to remove one of the fatty acid tails to produce lysolecithins [9]. Lysolecithins tend to be more suitable for producing O/W nanoemulsions because they are more hydrophilic than lecithins [12].

2.2.3. Proteins

Proteins are amphiphilic substances because they have both polar and nonpolar amino acids exposed on their surfaces. Many edible proteins have been shown to be good emulsifiers in O/W nanoemulsions where they can form a protective coating around the oil droplets that stabilizes them through a combination of steric and electrostatic repulsion [13]. However, emulsions stabilized by proteins are usually sensitive to changes in pH and ionic strength due to the characteristic electrical properties of proteins. In particular, they tend to aggregate near their isoelectric points or at high salt concentrations because of weakening of the electrostatic repulsion. Some common protein-based emulsifiers are milk proteins (*e.g.,* whey, casein, β-lactoglobulin, α-lactalbumin, lactoferrin, and bovine serum albumin), meat and fish proteins (*e.g.,* gelatin and myosin), egg proteins (*e.g.,* egg white, egg yolk, or ovalbumin), and plant proteins (*e.g.,* soy, pea, and rice proteins) [14]. Protein-based emulsifiers are commonly used in emulsified food products like mayonnaise, salad dressings, meringues, confectionary, and baked products. Nowadays, new sources for protein emulsifiers have been searched due to the increased demand for vegan/vegetarians' products and increased cost. As a result, new sources such as pea, soy, chickpea, and lentil are investigated as new plant protein sources [15–17].

2.2.4. Polysaccharides

Most edible polysaccharides are large hydrophilic molecules with poor surface activity. However, there are some natural and some chemically-modified amphiphilic polysaccharides that can be sued as emulsifiers, such as gum arabic, modified starch, and modified cellulose [18]. Gum arabic is a natural emulsifier that is very good at stabilizing oil droplets from aggregation. It is amphiphilic because it has hydrophobic polypeptide chains and hydrophilic carbohydrate blocks on the same molecule. Gum arabic is widely used as an emulsifier in soft drink applications to form and stabilize cloud and flavor emulsions. It forms relatively low viscosity solutions, which is advantageous for many applications. Unlike protein-based emulsifiers, polysaccharide-based ones typically show better stability at intermediate pH values, high ionic strengths, and high temperatures because they mainly provide stabilization through steric repulsion. The main disadvantage of gum arabic is its relatively high costs because relatively high concentrations are required to form emulsions or nanoemulsions, *e.g.,* a 1:1 ratio of emulsifier-to-oil [19]. Because polysaccharides are relatively large molecules, their adsorption rate is relatively slow, which makes it challenging to make nanoemulsions containing small oil droplets.

Several researchers have carried out experiments to compare the relative effectiveness of different kinds of emulsifiers at forming and stabilizing nanoemulsions. Liu et al. compared the emulsification activities of several emulsifiers, including four small molecule surfactants (CITREM, saturated distilled monoglycerides (SDM), polyglycerol fatty

acid esters (PGFE), and succinylated monoglycerides (SMG)), one phospholipid (lecithin), and one polysaccharide (gum arabic) [20]. SMG, which had the lowest molecular weight, was the most efficient at forming nanoemulsions containing small oil droplets. In another study, the influence of Tween 80, lecithin, whey protein isolate, or gum arabic on the formation and stability of curcumin-loaded nanoemulsions was examined [21]. The small molecule surfactant (Tween 80) gave the smallest droplet sizes, which can be attributed to its ability to rapidly adsorb to the droplet surfaces and reduce the interfacial tension. Liao et al. investigated the solubilizing effects of different types of emulsifiers, including ionic synthetic surfactants, non-ionic synthetic surfactants, and natural surfactants (glycyrrhizic acid) [22]. The glycyrrhizic acid was found to produce nanoemulsions with the smallest droplets, which were also stable to changes in temperature and salt addition. However, the nanoemulsions were unstable under strongly acidic conditions because the glycyrrhizic acid lost its negative charge, which reduced the electrostatic repulsion between the droplets. Researchers have also compared the emulsification properties of tea saponin, quillaja saponin, and Tween 80 [23]. They reported that the tea saponin was the most efficient emulsifier to produce nanoemulsions that were resistant to changes in temperature, pH, and salt addition. Many other recent studies have also been conducted on assessing the performance of different kinds of surfactants at forming and stabilizing nanoemulsions, which are summarized in Table 1.

3. Techniques for preparing nanoemulsions

3.1. High energy techniques

3.1.1. High pressure valve homogenization

High pressure valve homogenization (HPVH) is based on forcing a coarse emulsion through a narrow valve under high pressure. Typically, a coarse emulsion is prepared by blending oil, water, and emulsifier together using a high shear mixer. This emulsion is then fed into inlet of the HPVH device. A pump pulls the emulsion into the homogenizer and then forces it through a narrow valve. Disruptive forces such as cavitation, shear, and turbulence cause the large oil droplets in the coarse emulsion to break up and form smaller droplets [37]. The size of the droplets can be reduced by reducing the gap size of the valve, increasing the number of cycles, and increasing the pressure.

HPVH is one of the most common emulsification methods used to form emulsions and nanoemulsions in the laboratory and factory [38]. Several studies have shown that it can be used to produce nanoemulsions. Goh et al. evaluated the effect of the number of passes through the homogenizer (1, 3, and 5) on the formation and stability of kenaf seed oil nanoemulsions [39]. The mean droplet diameter of the nanoemulsions produced ranged from around 78 to 112 nm depending on the homogenization conditions used. These authors reported that 1 pass was enough to obtain stable nanoemulsions with nanosized droplets, low polydispersity, and high charge. Using additional passes caused a slight further reduction in droplet size, but would be more time consuming and costly. Liu et al. examined the impact of homogenization pressure on the formation of cinnamon oil nanoemulsions using HPVH [40]. They showed that particle size first decreased but then increased with increasing operating pressure. The initial decrease in size with increasing pressure can be attributed to the greater disruptive forces, whereas the later increase in size can be attributed to the loss of emulsifier functionality at the high temperatures generated as a result of operating at high pressures.

3.1.2. Microfluidization

Microfluidization also involves converting a coarse emulsion into a nanoemulsion by forcing it through a series of narrow channels at high pressure that are designed to make the emulsion collide with either itself

Table 1
Current examples of emulsifiers used to formulate nanoemulsions

Type of emulsifier	Emulsifier concentration (%)	Oil phase	Emulsification method	Particle diameter (nm)	Significant results	Citation
Tea saponin	0.15	Silymarin	High pressure homogenization	192 – 360	Tea saponin is a good canditate to stabilize nanoemulsions with poorly soluble drugs and to be used as cryoprotectant in freeze drying.	[24]
Lignin	0.1, 0.5, 1.0	Soybean oil	High pressure homogenization	> 173	Lignin containing nanoemulsions had both physical and oxidative stability.	[25]
Tween 80 / Span 80	10	Alpha-linolenic acid	Emulsion phase inversion	> 129.2	Nanoemulsions were stable for 25 days. Vitamin E addition could even increase the stability even in high temperature environment containing metal ions.	[26]
Tween 80 / Span 80	5, 7.5, 10, 12.5, 15	Clove oil	Spontaneous emulsification	> 97.22	Clove oil nanoemulsions prepared with mixture of Tween 80 and Span 80 showed strong antibasterial effect on *E. coli* and *S. aureus*	[27]
(Wang et al., 2020)	3 - 18	Eucommia ulmoides seed oil	Dynamic high pressure microfluidization	> 179.9	Nanoemulsification improved the stability of *Eucommia ulmoides* seed oil which is highly susceptible to rancidiy in bulk form	[28]
Rice bran protein	10	Soybean oil	High pressure homogenization	200 - 225	Rice bran protein increased the bioavailiabilty and cell permeability of nanoemulsions loaded with quercetin.	[29]
Polyoxypropylene (POP) chains	4.76 – 7.89	η-tetradecane	Phase inversion temperature	20 - 300	POP surfactants were found to be effective as mush as polyoxyethylene chains to produce nanoemulsions with PIT method.	[30]
Tween 80	2.5	Cinnamon oil	Ultrasonication	3.63 – 38.23	(Paudel et al., 2019)	[31]
Tween 80 / Span 80	5	Clove oil	Ultrasonication	36.0 – 145.3	Stable clove oil nanoemulsions can be produced to use as nanopesticide	[32]
Tween 60 / Span 60	10	Dodecane	Ultrasonication	> 64	Excessive use of surfactants decreased the thermal conductivity of nanoemulsion CO_2 absorbents	[33]
Span 80	1	Citronella oil	Hydrodynamic cavitation	60	Hydrodynamic cavitation increased the stability and decreased the energy consumption when compared to conventional ultrasonication	[34]
Soy lecithin / Tween 80	2.5, 5, 7.5, 10	Avocado oil	Ultrasonication	103 - 249	Tween 80 contributed better physical and oxidative stability to the nanoemulsions.	[35]
Tween 80 / Span 80	5	Fish oil	Ultrasonication	82	Nanoemulsions stored at 25 °C showed better oxidative stability than that of 4 °C due to oxygen being less soluble in high temperatures	[36]

or with the walls of the device at high speed [41]. These high-speed collisions lead to the generation of intense turbulence, cavitation, and shear forces, which break the large droplets into smaller ones. The design of the interaction chamber is particularly important for effective microfluidizition. Typically, the channels in the interaction chamber have a Y- or Z-shaped junction.

Microfluidization is increasingly being utilized in industry to form nanoemulsions on a large scale, as well as in research laboratories. For instance, Foo et al. used nanocrystalline cellulose as a natural stabilizer to form black cumin seed O/W Pickering nanoemulsions. Coarse emulsions were formed by ultrasonication, which were then further processed using microfluidization to produce nanoemulsions [42]. Hidajat et al. studied the effect of homogenization pressure (500, 1000, or 1500 bar) and the number of passes (1-10) on the droplet size of limonene O/W nanoemulsions [43]. The mean droplet diameter decreased with increasing homogenization pressure and the number of passes. In another study, microfluidization was used to produce andrographolide-loaded nanoemulsions, which were used as an anticancer treatment [44]. These authors found that the mean droplet diameter decreased with increasing pressure up to a point but then decreased when the pressure was increased further. Again, this result suggests that over-processing can cause a reduction in the efficiency of homogenization, which may be because of the loss of emulsifier functionality at high pressures and temperatures.

3.1.3. Ultrasonication

Ultrasonication uses high-intensity high-frequency pressure waves that generate disruptive forces capable of breaking up and intermingling the oil and water phases, as well as converting large droplets into smaller ones. The ultrasonic waves are applied to the sample using a sonotrode that contains a piezoelectric material, which converts electrical energy into mechanical energy [45]. Intense cavitation, turbulent, and shear forces are generated near the tip of the sonotrode, which causes any substances in their vicinity to be broken down. The efficiency of ultrasonication depends on the power, process time, emulsifier type, emulsifier concentration, interfacial tension, and fluid viscosities [46]. A major advantage of this approach for laboratory studies is that nanoemulsions can be produced using low volumes of material. However, there are also some large-scale ultrasonication devices that are used commercially [2,41].

Several studies have focused on the properties of nanoemulsions produced using ultrasonication. Ghazy et al. reported that anise O/W nanoemulsions with mean droplet diameters around 440 nm could be successfully prepared by ultrasonication, which exhibited good antimicrobial activity against various bacteria [47]. Ahmad et al.successfully used ultrasonication to prepare eugenol-loaded nanoemulsions for the treatment of wounds [48]. The effects of ultrasonication time and oil: surfactant ratio on the properties of celery oil nanoemulsions and their anticancer activity has also been investigated [49]. An oil-to-surfactant ratio of 1:3 was found to be optimum for producing nanoemulsions containing small droplets. The mean droplet diameter of the nanoemulsions was found to decrease as the ultrasonication time was increased from 5 to 20 minutes.

3.2. Low energy techniques

Nanoemulsions can also be produced using various kinds of low-energy methods, which are based on the spontaneous formation of small droplets when the composition or environment of a surfactant-oil-water system is changed in a controlled manner [50].

3.2.1. Spontaneous emulsification

Spontaneous emulsification is based on bringing two phases together that are not at equilibrium at a constant temperature [51]. For instance, a mixture of oil and surfactant may be added to a water phase. Emulsification is achieved by diffusion of some of the components from one phase to another after mixing, without having to provide any additional external energy. For instance, pouring an organic phase containing water-miscible components (such as surfactants, cosurfactants, or cosolvents) into an aqueous phase creates chemical instability followed by a rapid diffusion of these components from the oil phase to the water phase. This mechanism has been described as a “diffusion and stranding” mechanism. The rapid movement of components from one phase to another leads to the generation of supersaturated regions that promotes nucleation and droplet growth phenomena [52].

This method has been used to form several kinds of nanoemulsion-based delivery systems. For example, Zhao et al. formulated self nanoemulsified delivery systems containing buckwheat flavonoids [53]. The resulting nanoemulsions were shown to exhibit good antioxidant activity and have a good oral bioavailability. In another study, a self nanoemulsified delivery system containing limonene was produced using this method [54]. The impact of using different kinds of cosurfactants and surfactants on the formation and stability of the nanoemulsions was examined. The authors reported that a combination of Tween 80 as the surfactant and propylene glycol as a cosurfactant gave the smallest droplet size (highest transmittance).

3.2.2. Phase inversion temperature method

This method is mainly based on changes in the solubility and optimum curvature of nonionic surfactants with temperature. In such systems, a transition occurs from W/O emulsion at high temperatures to O/W emulsions at low temperatures. The temperature where the transition occurs is called the phase inversion temperature (PIT) [38]. Below the PIT, a surfactant is predominantly hydrophilic because its head groups are hydrated and therefore it favors the formation of O/W emulsions or nanoemulsions. As the temperature increases, the head groups of the surfactants become progressively dehydrated, and so their water-solubility decreases, which favors the formation of W/O emulsions or nanoemulsions [55]. Chuesiang et al. successfully produced antimicrobial cinnamon oil nanoemulsions using the PIT technique [56]. These nanoemulsions were shown to be effective at extending the shelf life of fish by inhibiting microbial growth.

3.2.3. Phase inversion composition method

The phase inversion composition (PIC) method is somewhat like the PIT method, in that it involves changes in the solubility and optimum curvature of surfactants to form nanoemulsions. However, in this approach, changes in surfactant solubility and optimum curvature are brought about by changing the composition of the system at a constant temperature [57]. For example, a phase inversion from O/W to W/O type emulsion can be achieved by the addition of salt to a colloidal system stabilized by an ionic surfactant. Conversely, a phase inversion from a W/O to O/W emulsion can be made by dilution of this kind of system with water. In both cases, a change in ionic strength is responsible for changes in surfactant properties that favor one type of emulsion or nanoemulsion over another [55].

The PIC method is often more appropriate for industrial scale applications than the PIT method because it is usually easier to change the composition of a system by adding a new component rather than making a sudden change in temperature [58].

The PIC method has been used recently in the emulsification of different vegetable oils, including coconut, sunflower, olive, palm, and jojoba oils [59]. Nanoemulsions could be successfully produced from coconut and sunflower oils, whereas only emulsions could be produced using the other oils. Gledovic et al.used the PIC approach to create nanoemulsions loaded with red raspberry seed oil and fruit extracts, which were shown to have antioxidant properties [60].

3.2.4. Emulsion phase inversion

The emulsion phase inversion (EPI) technique is like the spontaneous emulsification technique because it involves pouring one phase into another phase. However, the EPI method involves titrating an aqueous

phase into an organic phase (oil and surfactant) with continuous stirring. The water droplet concentration in the oil phase increases until a critical point is reached, and then a phase inversion from a W/O to O/W system occurs. The critical point is affected by factors such as viscosity, stirrer speed, and water addition rate. The mechanism of phase inversion in this method is different from the methods discussed earlier. In the EPI method, the phase inversion is usually governed by catastrophic inversion, whereas in the PIT and PIC methods it is governed by transitional inversion [38]. Catastrophic inversion typically occurs when the water-to-oil ratio changes, whereas transitional inversion occurs when surfactant properties (such as solubility or optimum curvature) change due to an alteration in formulation parameters such as temperature, pH, or salinity [61].

The EPI method has recently been used to form nanoemulsions fortified with omega-3 fatty acids, such as DHA and EPA [62]. The surfactant and oil phase composition significantly affected the droplet size produced but stirring speed did not have a major effect. The nanoemulsions produced using this method could be incorporated into apple juice without adversely affecting its appearance. Hien & Dao.analyzed the difference between the EPI and PIT methods at formulating black pepper O/W nanoemulsions [63]. They reported that the EPI nanoemulsion had better stability during long term storage at 30°C but the PIT nanoemulsions were more resistant to high temperatures.

4. Applications of nanoemulsions in foods

Nanoemulsions have found a broad range of applications in the food industry to improve the safety, quality, nutrition, and shelf life of foods [64]. In this section, several applications of nanoemulsions in foods and beverages are highlighted to demonstrate their potential benefits.

4.1. Preservatives

Food spoilage due to microbial contamination or chemical degradation reactions is a major challenge in the food industry, leading to considerable economic losses, increased waste, environmental contamination, and food safety concerns. There are many highly effective synthetic preservatives that can be used to inhibit microbial growth or undesirable chemical reactions [65]. However, consumers are increasingly looking for more environmentally friendly and sustainable products, which has led the industry to search for natural preservatives [66]. However, it is often difficult to incorporate these natural substances into foods because of their poor water-dispersibility, chemical instability, or efficacy. For this reason, they are often converted into nanoemulsions before use to overcome these challenges.

Essential oils have been shown to be effective antimicrobials and antioxidants that are safe for use in food products [67]. Common essential oils like those from thyme, sage, oregano, lemon, and orange contain a diverse range of bioactive components, including thymol, carvacrol, α-pinene, β-pinene, eugenol, and D-limonene [66,68–70]. However, the incorporation of these essential oils into foods and beverages is often challenging because of their low water-solubility, poor chemical stability, high volatility, and strong flavors. These challenges can sometimes be overcome by encapsulating these bioactive compounds into nanoemulsions [71–73]. Nanoemulsion-based delivery systems must be compatible with the food matrix that are incorporated into and must not adversely affect the organoleptic properties of the end product. It has been reported that essential oil nanoemulsions can control microbial growth, preserve the quality, and extend the shelf life of food products [74,75]. These antimicrobial nanoemulsions are effective against both Gram-positive and Gram negative bacteria, which is attributed to their ability to disrupt the structure and disturb the function of the cell walls of microorganisms. In addition, they have been shown to inhibit biofilm formation by interrupting intercellular signaling [76]. Studies have also shown that plant-based nanoemulsions can be applied to fruit, vegetable, meat, fish, and dairy products as antimicrobial agents to improve their quality and extent their shelf life (Table 2).

4.2. Colorants

Pigments and dyes are widely used as additives in the food industry to improve the visual appeal of food and beverage products. Food colorants can be obtained from synthetic or natural sources. Synthetic azo compounds are common artificial colorants used in the industry because of their high water-solubility and good chemical stability [99]. Although these compounds are generally recognized as safe (GRAS), there are some concerns about their safety as food additives [100–102]. Consequently, there is strong interest in the utilization of natural colorants in food products, which may be obtained from plants, microorganisms, animals, or insects. Some of these colorants are believed to have better toxicity profiles than synthetic dyes and may also act as nutraceuticals that can promote health [103–105]. Natural food colorants can be classified into different groups according to their molecular characteristics: carotenoids, betalains, chlorophylls, flavonoids (including anthocyanins), and miscellaneous colorants [106,107]. There are, however, limitations to incorporating many kinds of natural colorants into food products due to their low water-solubilities and poor chemical stabilities. For this reason, nanoemulsions have been investigated as a means of increasing the water-dispersibility and chemical stability of several (mainly hydrophobic) natural colorants.

Carotenoids are one of the most widely used natural pigments in foods. They can be isolated from various kinds of fruits, vegetables, and microorganisms and usually provide a strong orange, yellow, or red color [102]. In addition, nature-identical carotenoids can be chemically synthesized or produced using fermentation methods. However, the incorporation of carotenoids into foods is often challenging because they are extremely hydrophobic molecules that are highly susceptible to chemical degradation when exposed to heat, light, or oxygen [108]. These problems can be at least partly overcome by incorporating hydrophobic natural colorants into nanoemulsion-based delivery systems [109]. Encapsulation of the colorants in these systems increases their water-dispersibility and chemical stability [110], as well as their bioavailability [70].

Chaijan et al. investigated the potential of using β-carotene-loaded nanoemulsions as a natural colorant in sausages [108]. There results showed that these carotenoids also improved product quality by acting as natural antioxidants, thus serving dual purpose ingredients. Barman et al. developed a β-carotene-based nanoemulsion from orange (*Citrus reticulate*) peel waste to facilitate their application as a natural colorant in fruit juice [111]. Encapsulation was shown to enhance the color of the fruit juice, increase the bioaccessibility of the β-carotene, and increase the retinol activity equivalent (RAE) of the final product.

4.3. Flavoring agents

Flavoring agents are used to improve the taste and aroma of food products to make them more desirable and palatable. A broad range of different molecules is present in foods that can elicit flavor responses by interacting with sensors in the tongue or nose [112]. However, it is often challenging to incorporate these flavors compounds into food matrices because they are hydrophobic, chemically unstable, or volatile. Encapsulation of flavor molecules within nanoemulsions can often be used to improve their dispersibility, stability, and sensory response [70]. For instance, researchers reported that the release of flavors (orange oil) from foods could be controlled by encapsulating them in nanoemulsions, which were then trapped inside biopolymer microgels [113]. The rate of flavor release was reduced when the nanoemulsions were incorporated into the microgels.

Table 2
Application of antimicrobial plant-based nanoemulsions to fruit, vegetable, meat, fish, and dairy products.

Nanoemulsion with antimicrobial properties	Food products	Significant Findings	References
Carvacrol based nanoemulsion	Sausages inoculated with *E.coli* ATCC 26	▪ Application of nanoemulsion reduced *E. coli* ATCC 26 growth by decimal ▪ The greatest inactivation of bacterial inhibition was found to be more than 2 log cycles after a 5-minute infusion.	[77]
Oregano oil nanoemulsion	Chicken pate	▪ Significantly inhibit Escherichia coli and Staphylococcus aureus ▪ Prolong the shelf-life	[78]
Geraniol and linalool nanoemulsion	Meat	▪ Inhibit the growth of E. coli K12, Listeria innocua, and Pseudomonas lundensis	[79]
Chitosan/cinnamon oil nanoemulsion	Beef patties	▪ Significant decrease in *S. aureus*, *Enterobacteriaceae*, yeast, and mold	[80]
Curcumin-loaded nanoemulsion including pectin-coated oil	Refrigerated chicken fillets	▪ Inhibit the growth of psychrophilic bacteria, yeast, and mold	[81]
Trachyspermum ammi EO nanoemulsion	Hamburgers contaminated with *Aspergillus niger*	▪ Nanoemulsion exhibited an antifungal effect on the growth of the *Aspergillus niger* ▪ Showed Antioxidant activity with reduced TBA index	[82]
Zataria Boiss (ZEO) and Bunium persicum Boiss (BEO) essential oil nanoemulsion including chitosan	Refrigerating Turkey meat	▪ 1% ZEO nanoemulsions exhibited strong inhibitory effects on total viable bacteria, total psychrophilic bacteria, *Pseudomonas spp.*, *Enterobacteriaceae*, lactic acid bacteria, *Salmonella enteritidis*, and *Listeria monocytogenes*. ▪ Shelf life increased from 6 days in the untreated meat to 15-18 days in the nanoemulsion-treated meat	[83]
Nano-emulsified mustard (*Brassica juncea*) EO in combination with gelatin/ hydroxypropyl-β-cyclodextrin	Turkey breast at 4±1 °C	▪ Significantly reduced yeast, moulds, total mesophilic and psychrotrophic bacteria in turkey breast ▪ Resulted in 10-15 days prolonged of shelf-life	[84]
Nanoemulsion incorporated with star anise Essential oil, polylysine and nisin	Yao meat	▪ Nanoemulsion with 1.5% soy protein isolate showed better antimicrobial activity on microorganisms in Yao meat. ▪ The shelf life was extended from 8 days to 16 days due to the inhibition of bacterial growth during storage. ▪ The sensory analysis results suggested a good retention of color, odor and overall acceptance of samples by the application of nanoemulsion.	[85]
Thyme essential oil nanoemulsion	Associated with fish and fish products	▪ Exhibit antimicrobial activity on pathogen bacteria including *Salmonella Paratyphi* A, *S. aureus*, *Klebsiella pneumoniae*, and *Enterococcus faecalis* ▪ Spoilage bacteria including Pseudomonas luteola, Photobacterium damselae, Vibrio vulnificus, E. faecalis, Serratia liquefaciens, and Proteus mirabilis	[86]
Sage essential oil nanoemulsion	Associated with fish and products	▪ The nanoemulsion was effective on S. aureus, S. paratyphi A and P. mirabilis with inhibition zone diameter of 12.63, 12.00 and 12.25 mm. ▪ *P. luteola, S. liquefaciens, P. luteola* and S. paratyphi A had excessive sensitivity as lower concentration of sage essential oil nanoemulsion were needed with values in range 6.25 mg/ml to 12.50 mg/ml MIC.	[87]
Grapefruit, lemon, orange and mandarin essential based nanoemulsion	Rainbow trout fillets	▪ Mandarin and grapefruit EO based nanoemulsion extended shelf life of fish 6 days ▪ Orange and lemon EO based nanoemulsion prolonged of shelf life of fish 4 days	[88]
Chitosan coating nanoemulsion including *Bunium persicum* and *Zataria multiflora* EO	Vacuum-packed fish contaminated with *E. coli* O157:H7	▪ Nanoemulsion of chitosan with 1% of *Bunium persicum* EO was the most inhibitory impact on the growth of *E. coli* O157:H7	[89]
Nanoemulsion including rosemary, laurel, thyme, sage essential oil	Rainbow trout	▪ Shelf life was ectended 3 days with treatment of nanoemulsion ▪ Reduced the load of bacteria	[69]
Sunflower essential oil nanoemulsion	Refrigerated storage of Sea bream and sea bass fillets	▪ Exhibit lower microbial load and longer shelf life	[68]
Sunflower essential oil nanoemulsion	Fish steaks	▪ Significant reduction in heterotrophic and lactic acid bacteria ▪ Prolonged in shelf life	[90]
Nigella sativa oil based nanoemulsion at various levels (0% control, 3%, 5% and 10%).	Ice-cream	▪ Enhanced physical properties of ice-cream and acceptability of consumer	[91]
Pectin/oregano oil based nanoemulsion coatings	Cheese	▪ Showed strong antimicrobial effect on *Candida albicans*, *E. coli* and *Staphylococcus aureus* ▪ Prolong the shelf life of cheese	[92]
Nanoemulsion based edible coatings containing various concentrations of oregano essential oil (1.5, 2 and 2.5 %)	Low fat cheese	▪ Nanoemulsion coatings with ≥2.0 % oregano EO caused 1.4 log reduction of *Staphylococcus aureus* load inoculated on cheese after 15 days. ▪ Nanoemulsion coatings with 2.5 % oregano EO suppressed growth of psychrophilic bacteria and molds and yeasts during 6 or 24 days of storage, respectively	[93]
Citral nanoemulsion	Cut pineapple	▪ Resulted in 2.57 log cfu/g decreases of the *Salmonella enterica* Typhimurium growth	[94]
Cinnamon oil based nanoemulsion (0.1%, 0.25%, 0.5%)	Honeydew and cantaloupe melons inoculated with *L. monocytogenes* and *Salmonella* spp.	▪ 0.5 % nanoemulsion showed more than 7.7 and 5.5 log growth inhibition of *L. monocytogenes* and *Salmonella* spp., respectively	[31]
		▪ More effective on bacteria	[95]

(*continued on next page*)

Table 2 (*continued*)

Nanoemulsion with antimicrobial properties	Food products	Significant Findings	References
Rosemary, oregano and cinnamon essential oil encapsulated in nanoemulsion	fresh celery inoculated with *E. coli* and *L. monocytogenes*	▪ The inhibition of *E.coli* and *L. monocytogenes* occurred with below 60 min with 5-log reduction	
Thymol nanaoemulsion	Refrigerated tomatoes	▪ Inhibit the growth of *Botrytis cinerea*	[96]
Edible coating including lemon oil nanoemulsion	Freshly cut Fuji apples	▪ Improved the safety and quality ▪ Inhibit microbial growth	[74]
Oregano essential oil nanoemulsion	Fresh lettuce	▪ Decreased growth of *S. Typhimurium*, ▪ and *E. coli* O157:H7	[97]
Chitosan-based edible coatings incorporating mandarin oil nanoemulsion	Green beans	▪ Exhibit antimicrobial effect on *Listeria innocua*	[98]

4.4. Vitamins and nutraceuticals

Vitamins are micronutrients that are essential for normal human function – without a sufficient quantity of them in the diet, specific disease states will occur [114]. Nutraceuticals are food ingredients that are not essential for normal human function, but they are claimed to enhance human health by improving performance or by inhibiting or treating chronic diseases [115]. Like the other active ingredients discussed earlier, the incorporation of many vitamins and nutraceuticals into foods and beverages is often challenging because of their poor water-solubility, chemical stability, and bioavailability. These challenges can often be overcome by encapsulating them within well-designed nanoemulsion-based delivery systems [116,117]. Encapsulation of hydrophobic bioactive agents within nano-scale oil droplets improves their water dispersibility and can enhance their chemical stability. Moreover, the small size of the oil droplets means they have a high specific surface area, leading to rapid and complete digestion under gastrointestinal conditions. In addition, the digestion of the lipid phase results in the generation of free fatty acids and monoacylglycerols that can contribute to the formation of mixed micelles. As a result, more bioactive agents are released from the droplets and incorporated into the mixed micelles, where they can be transported to the epithelium cells for absorption [118,119]. As a result, the bioavailability of vitamins and nutraceuticals can be increased appreciably. Nevertheless, the properties of the nanoemulsions have to be carefully controlled to ensure they have the required physicochemical, functional, and gastrointestinal attributes, including their oil phase composition, physical state, emulsifier type, and particle size [119]. Nanoemulsion-based delivery systems have already been used to successfully encapsulate and improve the performance of a broad spectrum of oil-soluble vitamins and nutraceuticals, including carotenoids, flavonoids, polyphenols, vitamins A, D, and omega-3 fatty acids (Table 3).

4.5. Biodegradable coating and packaging films

Packaging materials play an important role in maintaining food safety and quality during storage, as well as extending the shelf-life of foods [137–139]. Typically, plastics are used as packaging materials in foods due to their low cost, flexibility, heat-sealing abilities, high mechanical strength, and good barrier properties [140,141]. However, increasing environmental concerns about the pollution and poor sustainability of plastic packaging materials have led to growing interest in the development of biodegradable coatings and films [142–144].

Nanoemulsions are particularly useful for incorporating hydrophobic bioactive agents into biodegradable packaging materials assembled from natural products, such as proteins, polysaccharides, and lipids [140,145]. For instance, they can be used to introduce non-polar preservatives (such as antioxidants and antimicrobials) into the packaging

Table 3
Ingredients, fabrication methods, and applications of nanoemulsions used to encapsulate and deliver nutraceuticals in functional foods.

Nutraceuticals	Ingredients	Methods	Applications	Reference
Vitamin D	Vegetable oils (sesame oil or olive oil or grape seed oil), Tween 80	High-shear homogenization and ultrasound method	Dairy products	[120]
Vitamin D_3	Soy protein isolate	High-pressure homogenization	Food industry	[121]
Vitamin D	Pea protein	pH-shifting and ultrasonication treatment	non-fat cow milk, canned orange juice, orange juice powder, banana milk, and infant formula	[122]
Vitamin E	Mustard oil and surfactant Tween-80.	Low energy method	Fruit juice	[123]
Vitamin E	Orange oil, whey protein isolate and gum arabic	High pressure homogenization	Beverage industry	[124]
Vitamin E	Quillaja saponin and lecithin	High pressure homogenization	Food industry	[125]
Coenzyme Q10	Soybean oil, whey protein isolate, lecithin and octenyl succinic anhydride-modified starch	a microfluidizer	High protein beverage	[126]
Beta-carotene	Orange peel extract	Ultrasonic homogenization	Juice and also natural colorant in food products	[127]
Astaxanthin	Flaxseed, olive and corn oil	High-pressure homogenization	Functional foods	[128]
Lutein	Medium-chain triglycerides, non-ionic surfactant	Low-energy emulsification	Functional foods	[129]
Resveratrol	Medium-chain triglycerides, bovine casein or caprine casein	High-pressure homogenization	Food industry	[130]
Thymol	Thymol, Tween 80	Ultrasound Sonication	an antimicrobial agent in the meat products (sausage)	[131]
Carvacrol	Carvacrol oil, Tween 80 and Span 80	Sonication	Food formulation as an antimicrobial agent	[132]
Probiotic organism (*Enterococcus faceium*)	Gum Arabica, whey protein concentrate, Inulin (prebiotic), and coconut oil	Sonication	Food products	[133]
Probiotic organism Lactobacillus delbrueckii subsp. bulgaricus	Soy protein isolate, gum Arabica, tween 80 and sunflower oil	High energy method.	Food products	[134]
omega-3 PUFA	flaxseed vegetable oil, Tween 80 and Span 80	Low-energy emulsification	Yogurt	[135]
omega-3 PUFA	sesame protein isolate, Tween 80 and Span 80	High pressure emulsification	Functional foods	[136]

materials, thereby prolonging the shelf life of fresh fruit, vegetable, cheese, meat, and seafood products (Fig. 1). Consequently, they can be used to create active packaging materials with novel functionalities. Nanoemulsions can be incorporated into coatings applied directly to the surfaces of foods, or they can be incorporated into separate films that are used to package foods [146].

Many studies have shown that nanoemulsions containing essential oils or other phytochemicals can be used as natural preservatives in food packaging materials [147]. However, some preservatives alter the optical, mechanical, barrier, or sensory properties of these packaging materials, which must be accounted for when designing and producing these novel materials [143,148,149].

Huang et al. reported that nanoemulsion-loaded edible coatings and films significantly prolonged the shelf life of chicken meat during storage at 4 °C, which was shown by a decrease in total viable bacterial, yeast count, mold count, pH changes, and TBARS values [109]. Xiong et al. investigated the effects of nanoemulsion-loaded pectin edible coatings on fresh pork loin stored in high oxygen modified atmosphere packaging [150]. They showed that these coatings significantly increased the shelf life of the meat product by inhibiting microbial growth, delaying oxidation, and reducing undesirable color and texture changes. Khan et al. reported that gelatin films containing curcumin nanoemulsions exhibited antimicrobial effects against *Salmonella typhimurium* and *Escherichia coli,* which extended the shelf life of fresh broiler chickens from 10 to 16 days compared to the control [151]. Simiarly, Shokri et al. reported that chitosan films containing an essential oil nanoemulsion increased the shelf life of Rainbow trout fillets during 16 days storage at 4 °C by decreasing microbial growth and oxidation [152].

Essential oil nanoemulsions were shown to exhibit antifungal activity in Minas Padrao cheese by inhibiting the growth of *Cladosporium sp., Fusarium sp.,* and *Penicillium sp* [153]. They also reported that the *Penicillium sp.* exhibited higher resistance against antifungal nanoemulsions than other fungi. Amiri et al. showed that corn starch films containing essential oil nanoemulsions extended the shelf life of ground beef patties stored at 4 °C for 20 days, which was again attributed to their antimicrobial and antioxidant properties [154]. Interestingly, incorporation of the essential oil nanoemulsions lowered the tensile strength and increased the elongation at break of the films, which may be undesirable for practical applications. Sodium caseinate coatings containing ginger oil nanoemulsions were shown to decrease the total aerobic psychrophilic bacteria on refrigerated chicken breast fillets, thereby improving their quality attributes during storage [135].

Severino et al. reported that the shelf life of fresh green beans was extended by more than 11 days during cold storage when they were coated with a carvacrol nanoemulsion-modified chitosan solution [77]. In another study, the shelf life of fresh-cut fuji apples was improved by applying lemongrass oil nanoemulsion-based coatings [74]. Similar results were reported when grape berries were treated with lemongrass oil nanoemulsion-based coatings [155]. Chu et al. reported that edible coatings and films containing essential oil nanoemulsions decreased the weight loss, firmness, total soluble solids, titratable acidity, and microbial load of strawberries [156].

5. Applications of nanoemulsions in pharmaceuticals

Delivery systems are widely used in the pharmaceutical industry to encapsulate, protect, and release drugs in a bioavailability and bioactive form [157]. Nanoemulsions have been investigated as potential drug delivery systems for many years [158]. The small size and large surface area of lipid droplets lead to rapid digestion of the oil phase and release of the drug, which can then be solubilized in mixed micelles capable of penetrating through the mucus layer to the epithelium cells [159]. The nanoemulsion-based delivery systems used in pharmaceutical applications typically contain droplets with diameters in the range of about 20 to 500 nm [107,160]. Typically, hydrophobic drugs are encapsulated within the oil droplets in O/W nanoemulsions [161–163]. Some of the major advantages of using nanoemulsions are that the composition,

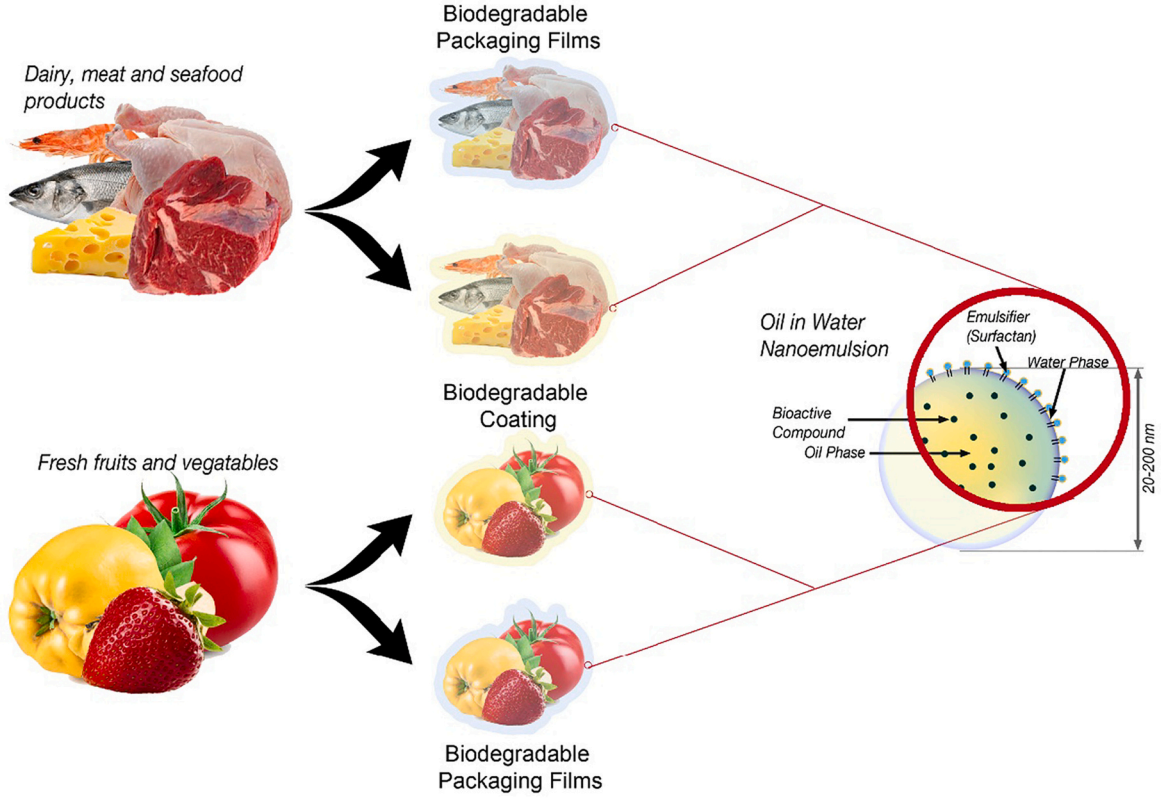

Fig 1. The antioxidant and antimicrobial properties of embedded nanoemulsions, edible films and coatings used in the food industries

structure, and properties of the oil droplets can easily be manipulated, and they can be produced on a large scale using existing technologies, such as HPVHs and microfluidizers [164]. In more advanced systems, the surfaces of the oil droplets in nanoemulsions can be decorated with functional groups, such as monoclonal antibodies, targeting moieties, hydrophilic polymers and/or diagnostic markers [164]. Some reports have indicated that nanoemulsions can increase the drug retention time at the target site, thereby resulting in fewer adverse side effects and reducing toxicity (Aboumanei et al., 2021), or lowering the dose required [165].

The drugs in nanoemulsions can be delivered by various routes, including oral, topical, transdermal, and parenteral [166]. Nanoemulsions have been used for parenteral administration of nutrients (such as carbohydrates, fats, vitamins, and minerals) to patients who cannot eat [167]. For oral administration, nanoemulsions may increase the bioavailability and efficacy of drugs due to their rapid digestion and release properties. For this reason, they have been explored for their potential application as drug delivery systems for diuretics, hormones, steroids, and antibiotics [168]. Moreover, several drugs have been encapsulated in O/W nanoemulsions for topical treatment of eye diseases such as dry eye syndrome and glaucoma [163]. The bioavailability of the drug was increased after encapsulation in the nanoemulsion and patient compliance was improved due to the ease of application to the eye [169]. Fardous et al. developed an organogel-based nanoemulsions to deliver hydrophobic drugs [170]. These nanoemulsion gels had a high drug loading efficiency (~97%) and a small droplet diameter (206 nm). Paclitaxel-loaded nanoemulsion gels exhibited a significant decrease in the growth of melanoma cells *in vitro* and *in vivo*, without exhibiting cytotoxic effects.

Numerous studies have shown that O/W nanoemulsions can improve the antimicrobial activity of essential oils against various microorganisms like fungi and bacteria [171–173]. Encapsulation of essential oils in nano-sized droplets can disrupt the cell membranes of microorganisms, as well as interfere with key biochemical pathways, thereby leading to microbial inactivation [6]. For instance, nanoemulsions loaded with cayenne pepper have been shown to exhibit strong antimicrobial activity against several disease-causing bacteria, including *Staphylococcus aureus, Salmonella enterica serova Triphimurim, Escherichia coli,* and *Vibrio parahaemolyticus* [174]. Fopase et al. synthesized a nanoemulsion-based drug delivery system containing eucalyptus oil and surfactin and then investigated its antibacterial and anticancer properties [175]. These nanoemulsions contained small spherical droplets (175 nm) and were shown to exhibit broad-spectrum antibacterial activity with an IC90 value comparable to a well-established antibacterial agent (kanamycin). A doxorubicin-loaded nanoemulsion was shown to be highly effective against cancer cells. Hosny et al. investigated the potential of using statin-loaded coconut oil nanoemulsions as a hypolipidemic drug for the treatment of burns [172]. They showed a significant synergistic effect of coconut oil and simvastatin in promoting wound closure, as well as anti-inflammatory and antimicrobial effects, thereby highlighting the potential of this formulation for the treatment of burn wounds.

Recently, nanoemulsions have been used to create drug delivery systems to treat autoimmune, cancer, and chronic diseases [164]. Many anticancer drugs are strongly hydrophobic molecules with poor water-solubility, so they cannot easily target the cancerous site [176]. In some cases, hydrophobic drugs can be encapsulated in nanoemulsions containing droplets with specific ligands attached to their surfaces, so that they can target specific tissues, cells, or organs [177]. Gupta et al. synthesized paclitaxel (Taxol) loaded chitosan-based nanoparticles for applications in cancer treatment and used them in the treatment of different cancer types [178]. They concluded that the nanoparticle-loaded drug exhibited better activity compared to pure paclitaxel, with a sustained release profile, higher cell uptake, and reduced hemolytic toxicity. Nanoemulsions have also been used in vaccine development, where they are typically utilized to encapsulate antigens [179].

6. Applications of nanoemulsions in cosmetics

Nanoemulsions have also been explored for their potential applications within the cosmetic industry. This is mainly because they can introduce novel or improved functional attributes, such as higher stability, better textural properties, greater skin penetration, and higher efficacy [180,181].

Ascorbic acid is a component of healthy skin found in both the dermis and epidermis. Ascorbic acid has therefore been widely employed in the cosmetic industry as an anti-pigmentary, anti-wrinkle, and antioxidant agent [182]. However, its level in the skin decreases due to photo-aging and chronological aging [183]. It is a chemically unstable compound that tends to degrade rapidly when exposed to air, and it also has a relatively low penetration efficiency across the skin [184]. Zaid Alkilani et al. developed a nanocarrier to deliver ascorbic acid dermally [185]. Ascorbic acid-loaded patches were prepared by including 80 mg/mL ascorbic acid in an O/W nanoemulsion that was then mixed with a solution of gel-forming polymers (hydroxypropyl methylcellulose and sodium carboxymethyl cellulose) and a plasticizer (PEG400). The patches were then formed from the resulting nanoemulsion suspension using a solvent casting technique. These formulations had good physicochemical properties, remained stable for 2 months, and gave a high skin penetrability of the ascorbic acid.

Researchers have developed topical cosmetic formulations to treat cellulite that contain active ingredients such as caffeine, retinol, camphor, and L-carnitine [186]. Caffeine is normally used in anti-cellulite and anti-aging products [187]. Caffeine is applied in topical formulations owing to its lipolytic activity. Freire et al. prepared a nanoemulsion containing caffeine (1% w/v) using different surfactants (*oleth*-20 and *oleth*-3) *via* the phase inversion temperature method [188]. The researchers found that the caffeine-loaded nanoemulsions had good sensorial and stability properties but did not improve the skin permeation of caffeine, which was attributed to the fact that it was a hydrophilic substance.

Quercetin is a natural flavonoid with strong antioxidant activity. Consequently, it has been explored for its potential applications in cosmetic and pharmaceutical products. Dario et al. developed a nanoemulsion containing quercetin with nonionic and cationic surfactants and showed good biocompatibility with the skin and low eye irritancy [189]. The authors suggested quercetin nanoemulsions may be suitable for skin and eye care applications due to their antioxidant properties.

Kojic acid is a substance that can be used to cause depigmentation of the skin [190]. Kojic acid esters, specifically kojic monooleate, can be utilized as skin-whitening agents to reduce hyperpigmentation by inhibiting tyrosinase. Tyrosinase is responsible for the production of melanin and high levels of melanin lead to skin disorders like hyperpigmentation. Indeed, a nanoemulsion containing kojic monooleate has recently been shown to exhibit a strong depigmenting effect [191], which suggests it may be used as a cosmetic agent to prevent hyperpigmentation.

Nanoemulsions loaded with plant-based bioactive agents have also been reported to be effective as anti-wrinkle, moisturizing, anti-acne, and whitening products [192,193]. Consumers often consider bioactive phytochemicals to be better for the environment and for skin health than synthetic ones [194]. Quercetin-loaded nanoemulsions applied topically were reported to have anti-herpes and antiviral activity [195,196]. Catechin-loaded nanoemulsions were reported to exhibit anti-melanogenesis, antioxidant, anti-inflammatory, and anti-aging effects [197]. Gallic acid-loaded nanoemulsions have been reported to exhibit antioxidant, anti-tyrosinase, and anti-bacterial effects [198,199]. Catechin- and kaempferol-loaded nanoemulsions have been reported to exhibit strong antioxidant activity [200,201]. Curcumin-loaded nanoemulsions have exhibited antiviral and wound healing activities [202,203]. Resveratrol-loaded nanoemulsions have been reported to exhibit antioxidant activity against UV radiation [204,205]. Lycopene-loaded nanoemulsions have been reported to exhibit good

anti-inflammatory and antioxidant activities [206].

Garcia-Bilbao et al. developed nanoemulsions enriched with retinyl palmitate and the Dead Sea water to treat skin diseases such as photoaging, psoriasis, atopic dermatitis [207]. Farahin et al. used nanoemulsions to encapsulate a microalgae (*Tetraselmis tetrathele*) extract for cosmeceutical purposes [208]. Nanoemulsions containing vegetable oils as an oil phase have been widely used as delivery systems for hydrophobic agents in cosmetics [209].

7. Gastrointestinal fate of nanoemulsions

It is important to understand the behavior of nanoemulsions inside the human gut after ingestion because this impacts their efficacy and safety [57]. The small size of the oil droplets in nanoemulsions may lead to differences in their gastrointestinal behavior compared to conventional emulsions. The gastrointestinal fate of the oil droplets in O/W nanoemulsions depends on many factors, including their composition, concentration, size, charge, aggregation state, and interfacial properties. These factors impact the rate, extent, and location of nanoemulsion digestion, bioactive release, and bioactive absorption, which can have physiological implications. Some of the key factors are listed here:

- *Droplet size*: Typically, the rate and extent of lipid digestion increases as the droplet size decreases due to the increase in specific surface area. However, the aggregation of oil droplets in the GIT may alter the ability of lipase to adsorb to their surfaces and promote lipid hydrolysis (see later).
- *Droplet composition*: Typically, digestible lipids (like triacylglycerols) will release bioactive agents more readily than indigestible ones (like mineral oils). In principle, digestible lipid droplets will be completely hydrolyzed in the small intestine but indigestible ones could penetrate through the mucus layer and be absorbed, thereby altering the gastrointestinal fate of encapsulated hydrophobic bioactives. The solubilization capacity of the mixed micelles formed after digestion typically increases with increasing chain length of the fatty acid molecules.
- *Interfacial properties*: Typically, the nature of the emulsifier used to coat the lipid droplets will impact the aggregation state of the oil droplets in different regions of the GIT (mouth, stomach, and small intestine). Aggregated droplets are usually digested more slowly than non-aggregated ones, which can affect the bioaccessibility of encapsulated bioactives.
- *Physical state*: Typically, solid fat droplets are digested by lipase more slowly than liquid oil droplets, which again can affect the bioaccessibility of encapsulated bioactives.

The bioavailability of hydrophobic bioactive agents like oil-soluble vitamins and nutraceuticals is usually increased when they are encapsulated within nanoemulsions containing small digestible oil droplets [210]. However, the oil phase must be carefully selected so that the mixed micelles formed after lipid digestion have hydrophobic domains large enough to accommodate any bioactive agents released from the oil droplets. Typically, this means that the fatty acid chains should form hydrophobic domains within the mixed micelles that are larger than the molecular dimensions of the hydrophobic bioactive agents. Nanoemulsions may also be designed to retain and protect bioactive agents in one region of the gastrointestinal tract (GIT), but them release them in another region. This can be achieved by controlling their composition, interfacial properties, or size. Typically, the pharmacokinetics of bioactive agents are different in nanoemulsions than in conventional emulsions. The faster digestion of nanoemulsions often leads to a spike of bioactive agents in the bloodstream.

Encapsulation of nanoemulsion droplets inside microgels can be used to control their gastrointestinal fate, including protecting bioactives from degradation, controlling bioactive release profiles, and transporting bioactives to specific locations of the gastrointestinal tract [211]. Chen et al. showed that encapsulating nanoemulsified omega-3 fatty acids within polysaccharide-protein microgels inhibited their oxidation [212]. Even so, these delivery systems could still release the omega-3 fatty acids under simulated gastrointestinal conditions [213]. Ma et al. encapsulated nanoemulsion droplets within microgel-in-microgel systems using a simple sequential injection−gelation technique [214]. These authors showed that the gastrointestinal fate of the oil droplets could be controlled by altering the composition (alginate or carrageenan) and arrangement (internal or external) of the polysaccharides used to formulate these systems. It was also shown that calcium alginate hydrogels were more resistant to gastrointestinal environments than potassium carrageenan hydrogels, which meant that microgels could be designed to deliver bioactive agents to different regions of the GIT or to control their release rate.

Encapsulating curcumin within nanoemulsions has been shown to increase its bioavailability using a simulated gastrointestinal model [215], which was attributed to the rapid digestion, release, and solubilization kinetics of this system. Zhang et al. evaluated the impact of oil phase composition of nanoemulsions on the bioaccessibility of β-carotene using a simulated gastrointestinal tract [216]. They found that the bioaccessibility of β-carotene was much higher when the oil phase was comprised of long-chain fatty acids than medium-chain ones, which was mainly attributed to the larger hydrophobic domains formed in the mixed micelles for the long-chain fatty acids.

The bioavailability of oil-soluble vitamins can also be improved by encapsulating them within nanoemulsions. For instance, *in vitro* and *in vivo* studies have shown that the bioavailability of vitamin D can be increased by encapsulating it within nanoemulsions [217]. Ozturk et al. studied the effects of carrier oil type on the bioaccessibility of vitamin D_3 encapsulated within O/W nanoemulsions based on quillaja saponin, using a simulated gastrointestinal tract model that included mouth, stomach, and small intestine phases [124]. They reported that nanoemulsions with oil phases containing long chain fatty acids (fish or corn oil) gave the highest vitamin bioaccessibility. Zhou et al. studied the impact of nanocellulose and titanium dioxide (TiO_2) nanoparticles on the gastrointestinal fate of plant-based milk containing vitamin D [218]. The oil droplets in the plant-based milk were strongly flocculated in the stomach but were still fully digested in the small intestine. The addition of titanium dioxide or nanocellulose to the fortified milk did not considerably influence lipid digestion or vitamin bioaccessibility. Nevertheless, the bioaccessibility of vitamin D was relatively low (~20%) in all the plant-based milk samples, which was mainly attributed to aggregation and precipitation of the vitamin-loaded mixed micelles by calcium ions in the small intestine.

Abbasi et al. developed nanoemulsions stabilized by a mixture of whey protein and sodium alginate (WP/SA) for the controlled release of α-linolenic acid (ALA) in the lower locations of the gastrointestinal tract of chickens to enhance the quality of broiler meat [219]. These nanoemulsions displayed high resistance to *in vitro* gastric digestion but a moderately quick release during intestinal digestion. These results suggest that this type of nanoemulsion had the potential to deliver omega-3 fatty acids to the posterior parts of the chicken gastrointestinal tract.

At present, there is still a relatively poor understanding of the gastrointestinal fate of different kinds of nanoemulsions. Clearly, more *in vitro* and *in vivo* research is required to evaluate how specific characteristics of nanoemulsions affect their gastrointestinal fate and potential toxicity.

8. Legislation and health concerns

The increasing application of nanomaterials within different industries has meant that the regulatory framework governing the utilization of these advanced materials in commercial products has had to be developed. The safety aspects of producing nanomaterials are important because employees and employers should be aware of any potential risks. Most nanoemulsions used in the food industry are fabricated from

food-grade substances that are digested within the human gut and should therefore not be a major concern (unlike some inorganic nanoparticles that are not digested and may be absorbed into the body). However, the gastrointestinal fate of indigestible nanoemulsions should be considered, as well as the potential impacts of increasing the bioavailability and changing the pharmacokinetic profile of bioactives.

The use of nanoparticles (d < 100 nm) is regulated within the European Union, but there are no specific regulations in the United States. Although European Union and Switzerland have developed nano-regulations [220], most of the countries do not have specific regulations for the use of nano-derived products. Instead, nanoemulsions are treated like any other novel food product. In general, it is essential to ensure that nanoemulsions are safe to use, and do not have any unintended harmful effects on the human body. Studies are therefore being carried out to understand the possible toxicity of ingested nanoemulsions. Toxic effects may be linked to the nature of the constituents used to formulate nanoemulsions such as synthetic surfactants. Alternatively, the fact that the bioavailability of bioactive agents is higher, and there may be a spike in blood levels after ingestion may cause alterations in their toxicity profile. Further studies should focus on creating the knowledge required to craft good legislation to regulate the utilization and labeling of nanoemulsions in different industries, so as to ensure they are both safe and efficacious.

9. Conclusion

Nanoemulsions have a broad spectrum of applications in different industries because of their unique properties. They can be designed to increase the matrix compatibility, improve stability, extend the shelf-life, control the release, and improve the bioavailability of encapsulated substances (especially hydrophobic ones). Nevertheless, further research is required to establish their ability to be incorporated into real food, cosmetic, and pharmaceutical products without affecting their desirable functional attributes. Moreover, more *in vivo* studies are required to establish the factors that impact the gastrointestinal fate of different kinds of nanoemulsions so that their safety and efficacy can be established. Finally, there is a need for more consumer education about the risks and benefits of nanoemulsions, as well as the need for a strong regulatory framework governing their application in different industries.

Declaration of Competing Interest

The authors confirm that there is no conflict of interest with respect to the work described in this manuscript

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