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# Nanoemulsions: An emerging platform for increasing the efficacy of nutraceuticals in foods

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ABSTRACT

Both whole and processed foods contain numerous bioactive substances that improve human health and performance, including macronutrients, micronutrients, and nutraceuticals. Many of these substances are strongly hydrophobic and chemically labile, which can diminish their beneficial health effects, since only a small fraction of the ingested amount is actually absorbed and utilized by the body. In the gastrointestinal tract, the overall bioavailability of a hydrophobic substance is determined by its bioaccessibility, transformation, and absorption. The design of functional foods with enhanced biological activity depends on identifying the relative importance of these three different processes for specific bioactive substances, and then using this knowledge to optimize the nature of food matrices to boost bioavailability. In this review, we focus on the utilization of oil-in-water nanoemulsions for this purpose because their compositions, structures, and properties can be easily manipulated. Nanoemulsions can be used as *delivery systems* where the hydrophobic bioactive substances are loaded into the oil phase either before or after homogenization. Alternatively, they can be utilized as *excipient systems*. In this case, the bioactive substances are located within an existing food product (such as a fruit or vegetable), which is then consumed with a specially-designed excipient nanoemulsion (such as a sauce, dressing, or cream). Research has shown that for both delivery and excipient systems, the oral bioavailability of hydrophobic bioactives can be enhanced considerably in the presence of a nanoemulsion, provided its properties have been carefully designed. This review article outlines the principles of the design of nanoemulsion-based delivery and excipient systems for boosting the bioavailability of hydrophobic bioactive substances.

## 1. Introduction

A low oral bioavailability has been reported for numerous hydrophobic nutrients, nutraceuticals, and pharmaceuticals when they are ingested orally, which has been attributed to a low bioaccessibility, low absorption, and/or chemical transformation of the bioactive substances within the gastrointestinal tract (GIT) [1,2]. Numerous studies have shown that oil-in-water nanoemulsions, which contain small emulsifier-coated lipid droplets dispersed in water, can greatly enhance the bioavailability of hydrophobic substances [3–5]. The ability of nanoemulsions to boost bioavailability is highly dependent on their compositions and structures, as this impacts the gastrointestinal fate of the co-ingested bioactive substances [6–8]. This review highlights the main factors impacting the bioavailability of hydrophobic bioactive substances (such as nutrients, nutraceuticals, and pharmaceuticals). It then shows how this knowledge can be used to design nanoemulsions that can effectively increase their bioavailability and therefore bioactivity.

## 2. Bioavailability

### 2.1. Definition

Initially, it is helpful to provide a definition of the bioavailability of a hydrophobic bioactive substance that is taken orally. For the purposes of this manuscript, it will be defined as the fraction of the ingested bioactive substance that reaches the site-of-action within the human body in a biologically active form (Fig. 1) [9]:

$$BA = B^* \times A^* \times D^* \times M^* \times E^* \quad (1)$$

A brief overview of the main terms in this equation is given below:

- The *bioavailability* (BA) is taken to be the fraction of the bioactive

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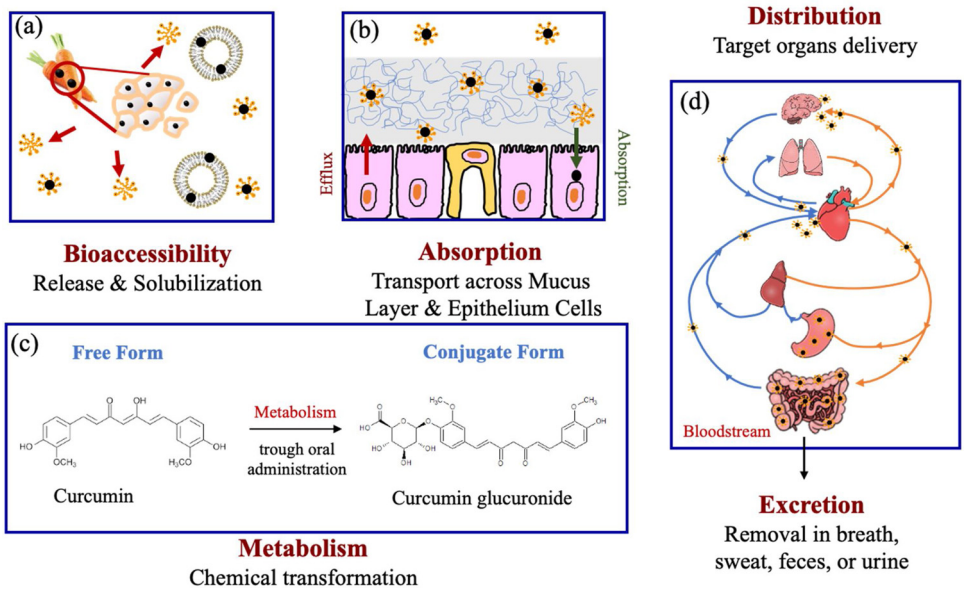


**Fig. 1.** The bioavailability of a hydrophobic bioactive depends on a number of potentially rate-limiting factors: (a) bioaccessibility; (b) absorption; (c) metabolism; and (d) distribution and excretion.

substance that reaches the intended site-of-action;

- The *bioaccessibility* (B*) is taken to be the fraction of the bioactive substance present within the gastrointestinal fluids in a physical state capable of being absorbed by the body. For hydrophobic substances, this is usually taken to be the fraction solubilized within the mixed micelles generated inside the small intestine.
- The *absorption* (A*) is taken to be the fraction of the bioaccessible bioactive substance that is capable of moving through the gastrointestinal fluids, crossing the mucus layer, and then being absorbed by the epithelium cells that line the human gut. Absorption may occur through various transcellular and paracellular processes depending on nature of the bioactive component and food matrix. After absorption, the bioactive may enter the bloodstream through either the portal vein or the lymphatic system, with the latter system being more important for strongly hydrophobic substances.
- The *distribution* (D*) is taken to be the fraction of the absorbed bioactive substance that actually reaches the intended site-of-action after the substance has been distributed amongst the various tissues within the human body. As mentioned above, the site-of-action is often taken to be the systemic circulation (bloodstream). In some cases, however, it may also depend on how easily the bioactive substance is transported from the bloodstream to specific target organs (such as the brain, heart, lungs, or colon).
- The *metabolism* (M*) is taken to be the fraction of the bioactive substance at the site-of-action that is in a biologically active form. As the bioactive substance passes through the gastrointestinal tract and the body it may undergo various chemical transformations due to the presence of chemical reagents (gastric acids) or metabolic or digestive enzymes. As a result, its biological activity may change, as the new molecules produced may be more or less bioactive than the parent molecule.
- The *excretion* (E*) is taken to be the fraction of the bioactive substance remaining at the site-of-action in a biologically active form after any excretion processes have occurred. Over time, the bioactive substances will be removed from the human body due to various processes, and will eventually be excreted, for instance in the breath, sweat, feces, or urine.

It should be noted that all of these processes are time-dependent, leading to changes in the pharmacokinetics of the bioactive substance. In order to be effective, it is important that the concentration of the bioactive at the site-of-action is above some critical levels. Conversely, it may be important to ensure that the concentration is not too high, as this can lead to toxic effects for some bioactives [10–13]. For many bioactive substances, the overall oral bioavailability is primarily limited by one or two of these processes. For instance, for highly hydrophobic substances (like carotenoids) it is mainly limited by their very low bioaccessibility, whereas for highly chemical labile substances (like curcumin) it mainly limited by their biochemical transformations [1,14].

### 2.2. Gastrointestinal fate of bioactives with nanoemulsions

It is useful to briefly review the potential gastrointestinal fate of ingested bioactives in the presence of nanoemulsions used as delivery or excipient systems (Fig. 2). For delivery systems, the hydrophobic bioactives are usually encapsulated inside digestible lipid droplets comprised of triacylglycerols (TGs) [15]. After they pass through the mouth and stomach (where their size and interfacial composition may change), the lipid droplets are digested by lipase in the gastric and small intestinal fluids, which releases the bioactive substances and generates free fatty acids (FFAs) and monoacylglycerols (MGs) [16]. These lipid digestion products then mix with bile salts and phospholipids to form mixed micelles that can solubilize and transport the bioactives to the epithelium cells. The bioactives, FFAs, and MGs are then absorbed by the epithelium cells. Inside these cells, the FFAs and MGs are reassembled into TGs that are then packaged into chylomicrons (a form of lipoprotein) with the hydrophobic bioactive substances [17]. The bioactive-loaded chylomicrons then travel through the lymphatic system and into the bloodstream where they can be taken up by certain tissues [18]. For excipient systems, most of the processes are the same, with the exception of the initial processes. In this case, the bioactives are initially in a food product (such as a fruit and vegetable) that is co-ingested with the excipient nanoemulsions. Consequently, the bioactives must first be released from the food product, and then be taken up by undigested lipid droplets (mouth or stomach) or mixed micelles (small intestine).

In later sections, we will highlight some of the main properties of delivery or excipient nanoemulsions that can be manipulated to control these processes.

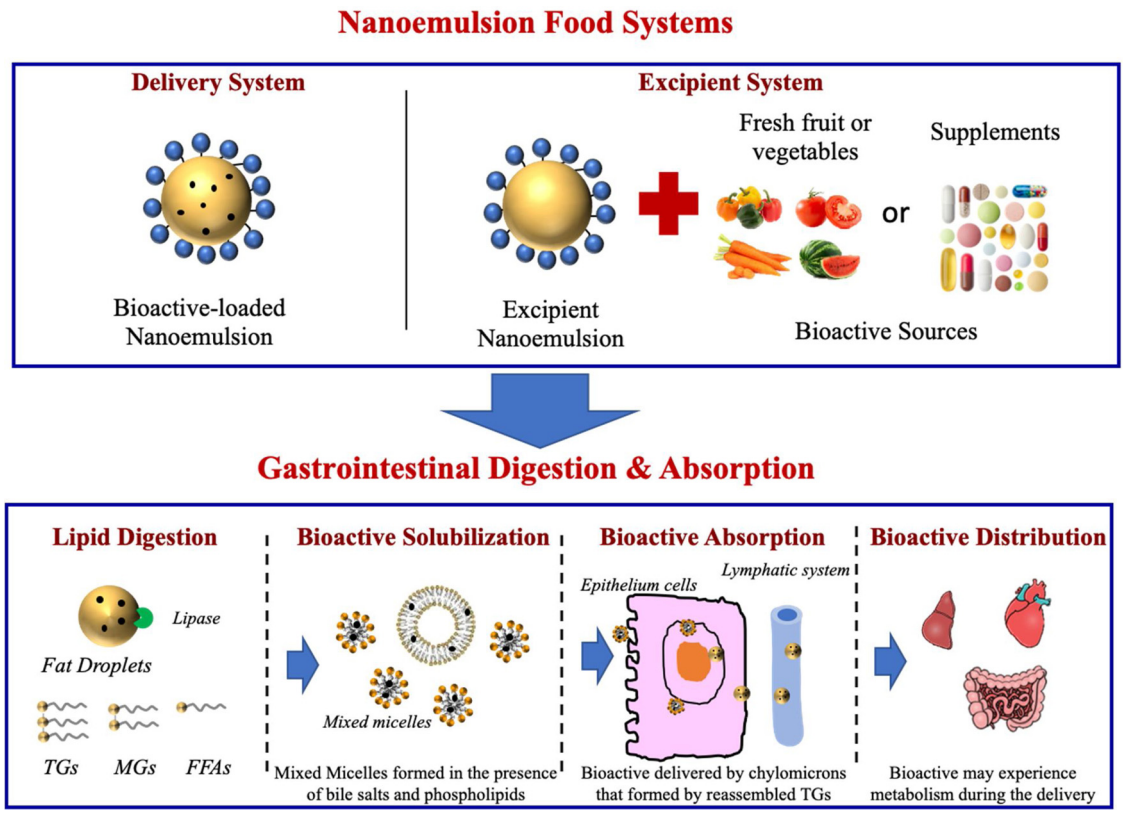


**Fig. 2.** Gastrointestinal fate of hydrophobic bioactive substances in nanoemulsion-based foods: delivery systems and excipient systems.

## 3. Nanoemulsion design to improve bioavailability

The composition and structure of oil-in-water nanoemulsions can be controlled to enhance the bioavailability, and therefore biological activity, of ingested hydrophobic bioactive substances [9,19]. In this section, the major factors that can be manipulated are highlighted (Fig. 3).

In general, oil-in-water nanoemulsions consist of small emulsifier-coated lipid droplets dispersed within an aqueous environment [20]. By definition, the mean diameter of the droplets in nanoemulsions is assumed to be ≤ 200 nm, which is what distinguishes them from conventional emulsions. Like emulsions, nanoemulsions are thermodynamically unstable systems, thereby distinguishing them from microemulsions, which are thermodynamically stable [21]. The basic building blocks of nanoemulsions are oil, water, and emulsifier, but bioactive substances and other additives can also be incorporated into these multiphase systems. The two main categories of factors that can be controlled when formulating nanoemulsions are:

(i) *Droplet characteristics*: The oil phase composition, oil droplet size, and emulsifier type can be varied by selecting different ingredients and processing operations.
(ii) *Additives*: Additives with specific functional attributes, such as permeation enhancers, thickeners, antioxidants, and chelating agents, can be included in the oil, water, or interfacial regions of nanoemulsions. These additives may be added before and/or after homogenization depending on their polarities.

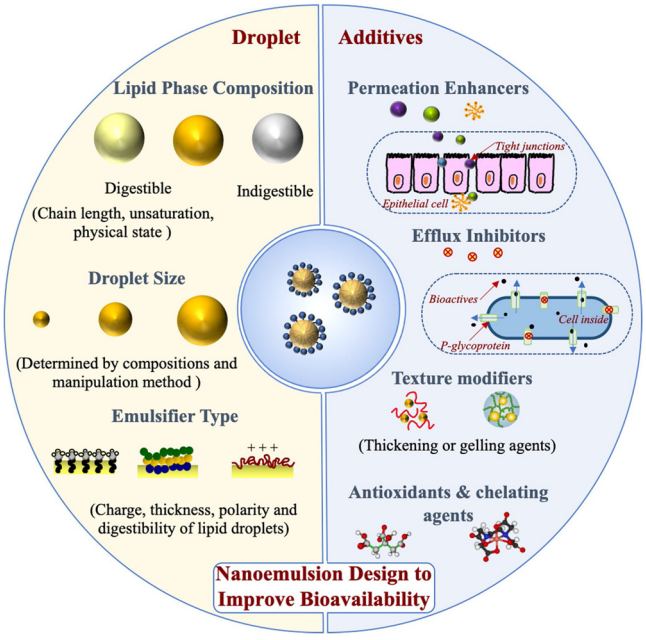


**Fig. 3.** The composition or structure of oil-in-water nanoemulsions can be designed to enhance the bioavailability of bioactives.

### 3.1. Droplet properties

#### 3.1.1. Lipid phase composition

The bioavailability of hydrophobic substances in the presence of nanoemulsions is highly dependent on the characteristics of lipid phase, such as its digestibility, and the structure of any lipid digestion products (mixed micelles) formed [22]. The lipid phases used to formulate nanoemulsions may be either digestible or indigestible depending on the ability of lipase to hydrolyze the molecules. Digestible lipid phases are mainly comprised of triacylglycerol oils isolated from plant, animal, marine or microbial sources (such as canola, corn, olive, safflower, sunflower, dairy, fish, or algae oils), whereas indigestible lipid phases are mainly comprised as non-triacylglycerol oils, such as flavor, essential, or mineral oils (such as lemon, lime, thyme, clove, and paraffin

oils) [23–25].

Indigestible lipid phases cannot be hydrolyzed by lipases in the human GIT and so cannot generate free fatty acids (FFAs) and monoacylglycerols (MGs), which are critical constituents of mixed micelles [24,26]. As a result, nanoemulsions formulated from indigestible oils are not very effective at increasing the bioaccessibility of hydrophobic bioactive substances [24–27]. However, indigestible oils can be mixed with digestible oils, which can enhance bioaccessibility by improving droplet stability (maintaining a small droplet size), while still generating some mixed micelles [26,28]. This phenomenon will be discussed in more detail in the next section.

In contrast, digestible lipid phases are hydrolyzed by lipases in the GIT, thereby generating FFAs and MGs that can form mixed micelles, which can then solubilize and transport the hydrophobic substances to the epithelium cells [29,30]. The rate and extent of lipid digestion within the small intestine influences the release kinetics of the encapsulated bioactives, as well as their solubilization kinetics in the mixed micelles, thereby impacting the bioaccessibility. If the bioactive substance is not fully released from the lipid droplets, or not fully solubilized by the mixed micelles, then it may have a low bioaccessibility. After solubilization, hydrophobic bioactive substances are located within the non-polar domains that make up the interior of the mixed micelles [31–33].

The fatty acid composition of digestible lipid phases (particularly the chain length and unsaturation of the FFAs) has a major impact on the bioaccessibility of hydrophobic substances [22]. This effect has been attributed to the dimensions of the non-polar domains inside the mixed micelles – if a bioactive molecule is too large to fit inside these non-polar domains, then it will not be solubilized. This effect has clearly been shown for carotenoids using both delivery and excipient systems. For instance, the in vitro bioaccessibility of β-carotene encapsulated within nanoemulsions was reported to be relatively small (≈2 %) when medium chain triglycerides were used as the oil phase but relatively large (≈66 %) when corn oil was used [32]. This effect was attributed to the fact that the medium chain triglycerides contained medium-chain free fatty acids (MC-FFAs), whereas the corn oil contained long-chain free fatty acids (LC-FFAs). The in vivo bioavailability of fucoxanthin (another carotenoid) has also been reported to be much higher when delivered in nanoemulsions formulated from LC-FFAs rather than MC-FFAs [34]. in vitro studies have also shown that the bioaccessibility of carotenoids in carrots is appreciably higher when they are co-ingested with a nanoemulsion containing LC-FFAs than one containing MC-FFAs [35].

The degree of unsaturation of the fatty acids in a digestible lipid phase has also been shown to have a major impact on the bioaccessibility of hydrophobic substances. Nanoemulsions formulated from lipids containing high levels of polyunsaturated fatty acids, such as fish oil, lead to a lower bioaccessibility than those containing high levels of monounsaturated fatty acids, such as corn or sunflower oil [35–37]. This phenomenon is because the non-polar domains in mixed micelles assembled from polyunsaturated fatty acids are smaller than those formulated from monounsaturated fatty acids because the former have a highly kinked structure due to the presence of multiple double bonds [23].

The oil phase composition can also influence the transformation and absorption of hydrophobic bioactive substances under GIT conditions. For instance, an oil phase comprising of many polyunsaturated fatty acids may promote the chemical degradation of bioactive substances that are prone to oxidation. Moreover, some fatty acids have been shown to increase the permeability of the epithelium cell walls, which may promote absorption [38].

The composition of the lipid phase influences its physical state (solid or liquid), which can impact lipid digestion and bioactive bioavailability. Typically, the tendency for a lipid phase to be solid under GIT conditions increases as the chain length and saturation of the FFAs increases. in vitro GIT studies, have shown that liquid oil droplets are digested more rapidly than solid fat particles [39], which is probably because it is more difficult for the lipase to access the ester bonds when the TGs are in the solid state. Nanoemulsions containing solid fat particles can be fabricated from high-melting lipids, which may be natural (lard or wax), processed (hydrogenated oils), or created by oleo-gelation [40–42]. It has been reported that lipid digestion is reduced appreciably when oleo-gels are formed in the lipid phase, which then reduces the bioaccessibility of any encapsulated nutraceuticals or pharmaceuticals [43–45].

#### 3.1.2. Droplet size

The size of the lipid droplets in nanoemulsions is also important in determining their ability to enhance the bioavailability of ingested hydrophobic substances. Generally, the smaller the droplets, the faster the rate of lipid digestion, and the higher the bioaccessibility of the bioactives [33,46–48]. The droplet size of nanoemulsions can be controlled by varying their composition (i.e., the type and concentration of oil, aqueous phase, and emulsifier) or by manipulating the processing method (i.e., homogenizer type and operating conditions) [20,49]. Factors such as emulsifier type, emulsifier-to-oil ratio, relative viscosity of the dispersed and continuous phases, and ionic strength, have all been shown to impact the droplet size in nanoemulsions [50–52]. Typically, increasing the ratio of emulsifier-to-oil, decreasing the ratio of oil-to-aqueous phase, decreasing the oil-to-aqueous phase viscosity ratio, and/or reducing the oil-water interfacial tension promote the formation of small droplets. Emulsifiers that adsorb to the droplet surfaces rapidly, decrease the interfacial tension appreciably, and create a protective coating tend to generate small droplets during homogenization [53,54]. The nature of the homogenization method used also impacts the droplet size. For nanoemulsions generated using high-energy methods, such as microfluidization, high-pressure homogenization, and sonication, the droplet size decreases with increasing energy input [55,56]. However, one must be careful not to over-process, since this can promote droplet flocculation or coalescence. These phenomenon may occur if the temperature of the nanoemulsion gets too high during homogenization, as some emulsifiers lose their functional performance at high temperatures [57,58]. For nanoemulsions fabricated by low-energy approaches, such as spontaneous emulsification or phase inversion temperature methods, the droplet size depends on the nature of the surfactant, oil, and water phases used, as well as the preparation conditions, such as stirring speeds, titration rates, and cooling rates [26,28,59,60]. Nanoemulsions containing relatively polar oils (such as essential and flavor oils) are prone to droplet growth through a phenomenon known as Ostwald ripening, which can be inhibited by mixing them with water-insoluble substances (“ripening inhibitors”) prior to homogenization [61,62].

#### 3.1.3. Emulsifier type

The surface characteristics of the lipid droplets in oil-in-water nanoemulsions impact their stability, functionality, and gastrointestinal fate. These characteristics can be modulated by using different kinds of emulsifiers to coat the lipid droplets, including surfactants, phospholipids, proteins, polysaccharides, or their combinations [53]. The nature of the emulsifier used can impact the bioavailability of encapsulated hydrophobic substances through a variety of mechanisms: (1) binding to key gastrointestinal components, such as lipases, proteases, bile salts, or calcium [63–66]; (2) altering the aggregation state of the lipid droplets in the small intestine, thereby altering the surface area of lipids exposed to the lipase [67,68]; (3) altering the rheology of the gastrointestinal fluids [19]; (4) binding to the hydrophobic substances themselves [6,69,70]; (5) increasing the solubilization capacity of the mixed micelles by being incorporated into them [71]; (6) increasing the permeability of the epithelium cells by interacting with the phospholipid bilayers, cell membrane transporters, or tight junctions [72,73], (7) acting as antioxidants that reduce the chemical degradation of the hydrophobic substances [74–76]. Consequently, the bioavailability of

bioactives can be enhanced by selecting an appropriate emulsifier or combination of emulsifiers to coat the lipid droplets [77,78].

### 3.2. Additives

A variety of other functional ingredients can be incorporated into nanoemulsions used as delivery or excipient systems to enhance the bioavailability of hydrophobic substances.

#### 3.2.1. Permeation enhancers

Some additives can increase the permeability of the epithelium cells coating the GIT walls, thereby increasing the amount of bioactive substances absorbed. They may do this by various mechanisms, including increasing the fluidity of the phospholipid bilayers, opening up the tight junctions, or increasing the flux through protein transporters [79], thereby increasing the ability of the bioactive substances to be taken in [80]. Penetration enhancers are widely used in pharmaceutical formulations to increase the ability of bioactive substances to cross biological barriers such as the skin, blood-brain barrier, mucus layer, and epithelium cells [79]. For oral applications, a variety of food-grade ingredients can be used as penetration enhancers in nanoemulsion to enhance the penetration of hydrophobic substances, including flavor oils (such as limonene) [81] or fatty acids (such as oleic acid) [82].

#### 3.2.2. Efflux inhibitors

After a bioactive substance has been absorbed by the epithelial cells, it may be transported back into the gastrointestinal lumen as a result of the action of efflux transporters [83]. These efflux transporters are specific proteins (such as P-glycoprotein) embedded in the phospholipid membranes of the cells that can transfer certain substances from inside to outside the epithelium cells [84]. The presence of efflux transporters limits the amount of some bioactive substances that can be absorbed by the human body, thereby reducing their bioactivities [85]. Certain components in foods inhibit these efflux transporters, thereby increasing the amount of bioactive substances that are absorbed. Piperine from black pepper is probably the most widely known example of an efflux inhibitor in foods, but there are various other food components that can exhibit similar effects, including curcumin and resveratrol [84].

#### 3.2.3. Texture modifiers

Thickening or gelling agents can be used as additives in nanoemulsions to modify the textural properties, alter the mouthfeel, and or enhance the physical stability [86,87]. Thickening agents are usually hydrophilic biopolymers (especially polysaccharides) that have highly extended structures when dispersed in aqueous solutions [88]. As a result, they alter the fluid flow during shearing, thereby increasing energy dissipation (friction), leading to an increase in solution viscosity [87]. In contrast, gelling agents are usually hydrophilic biopolymers (polysaccharides or proteins) that form cross-links with each other, thereby leading to the creation of a 3D-network that fills the volume of the container, leading to the establishment of a hydrogel. In addition to their ability to modify the rheology and mouthfeel of food products, texture modifiers can also modify the behavior of nanoemulsions within the human gut. For instance, they may slow down mixing and mass transport processes within the gastrointestinal fluids, which reduces the ability of key GIT constituents (such as digestive enzymes or bile salts) to interact with the lipid droplets, thereby inhibiting their digestion. As a result, the bioactive substances may not be released from the lipid droplets, or the formation of mixed micelles may be suppressed, leading to a reduction in their bioaccessibility [89].

#### 3.2.4. Antioxidants

A number of important hydrophobic bioactive substances, including ω-3 fatty acids and carotenoids, are highly prone to oxidation, which may reduce their bioactivity. The oxidation of these substances typically involves a complex series of free-radical reactions, that includes initiation, propagation and termination stages [90]. The precise nature of the oxidation reaction within a nanoemulsion depends on the molecular characteristics of the various reactive species (reactants, products, prooxidants, and antioxidants), as well as their physicochemical environment [90,91]. Many components in the aqueous phase of nanoemulsions can promote oxidation, including transition metals, enzymes, and photosensitizers. One of the most effective means of retarding oxidation reactions in nanoemulsions is to incorporate antioxidants [92]. Based on their mechanism of action, antioxidants can be classified as chelating agents, free radical scavengers, oxygen scavengers, and reactive species quenchers. Chelating agents, such as EDTA or citrate, can sequester and deactivate prooxidant transition metals, such as iron or copper ions, thereby inhibiting oxidation (see next section). Oxygen scavengers eliminate part of the oxygen in the system thereby retarding the initiation stage of oxidation. Free radical scavengers deactivate free radicals, thereby inhibiting both the initiation and propagation stages of oxidation. The effectiveness of antioxidants depends on their molecular structure, solution conditions, and their physicochemical environment. In many cases, interfacial antioxidants are the most effective at retarding oxidation in nanoemulsions because they are located in the region where chemical reactions occur between water-soluble prooxidants and oil-soluble lipid substrates [93]. In other cases, it may be an advantage to use oil-soluble antioxidants that are located in the interior of the lipid droplets to inhibit oxidation of hydrophobic substances inside the oil phase [93].

#### 3.2.5. Chelating agents

The presence of multivalent metal ions in the aqueous phase of nanoemulsions may adversely impact their physical or chemical quality through a number of mechanisms. For instance, they may form insoluble complexes with other charged ingredients, they may promote the aggregation of charged lipid droplets, or they may promote lipid or protein oxidation reactions [56,94]. For this reason, chelating agents that sequester the metal ions are often added to nanoemulsions to eliminate these undesirable quality defects. Various kinds of cheating agents can be used in commercial products including some amino acids, organic acids, aminocarboxylates, hydroxycarboxylates, and polyphosphates [95]. Most of these cheating agents are synthetic substances and are therefore not regarded as “label friendly” by consumers. Although some natural chelating agents (e.g., citric acid) are also available, they tend to be less effective and may have adverse quality attributes, such as off-flavors, poor solubility, or the requirement for an acid environment to be effective. Some food-grade proteins and polysaccharides have also been shown to be effective at chelating transition metals and inhibiting lipid oxidation in nanoemulsions [91].

In some cases, chelating agents may actually act as prooxidants because of their ability to increase the solubility of transition metals or alter their redox potential [96]. Therefore, it is important to select a chelating agent that is effective under the specific solution conditions in the product, such as pH, ionic composition, and temperature, but that it also does not adversely affect the quality and functional properties of food products.

### 3.3. Effective dose

Another factor that is important to consider when designing a nanoemulsion for this purpose is the dose of the bioactive substance required, and whether this can be achieved using the intended formulation. There is typically an optimum dose required to achieve the desired biological effect. If the dose is too low, then the bioactive will not produce the required effects. Alternatively, if it is too high, then it may produce adverse effects, such as toxicity [97]. The maximum concentration ($C_{max}$) of a hydrophobic bioactive substance that can be incorporated into a nanoemulsion is mainly governed by its oil solubility ($C_{oil}$), and the total oil phase content in the final formulation ($\varphi_{oil}$):

amount = $C_{oil} \times \varphi_{oil}$. Here, $\varphi_{oil}$ is the disperse phase volume fraction, which typically varies from about 0.001 (0.1 %) to about 0.4 (40 %) in oil-in-water nanoemulsions used as delivery systems. Hydrophobic substances vary considerably in their solubility in oils depending on their molecular characteristics (particularly their polarity and molar mass) and the polarity of the surrounding oil phase.

It should be noted that the required dose of a bioactive substance may be reduced considerably when it is ingested with a nanoemulsion, compared to a conventional formulation, because its bioavailability may be greatly increased [98,99].

## 4. Applications of nanoemulsions to enhance bioavailability

In this section, a brief overview of the application of nanoemulsions to increase the bioavailability of hydrophobic substances is given.

### 4.1. Delivery systems

A wide variety of different hydrophobic bioactive substances have been encapsulated within nanoemulsion-based delivery systems so as to enhance their bioavailability, including nutrients, vitamins, and nutraceuticals. In this section, we highlight a number of representative examples to demonstrate their potential efficacy for this application.

Numerous in vitro studies have shown that nanoemulsions can be used to encapsulate carotenoids and increase their bioaccessibility, including β-carotene [100,101], lycopene [102,103], lutein [104], astaxanthin [103], fucoxanthin [34], and zeaxanthin [105]. Nanoemulsion-based delivery systems have also been used to increase the bioaccessibility of a wide range of other hydrophobic bioactive substances, including Coenzyme Q10 [106], vitamin D [24], vitamin E [107–109], pterostilbene [110], resveratrol [111,112], and curcumin [113–115]. In a recent study, it was shown that all-natural curcumin-loaded nanoemulsions had similar or better bioaccessibility as commercial curcumin supplements that were formulated using synthetic ingredients [116]. Typically, the extent of bioaccessibility enhancement depends on the composition and structure of the nanoemulsion used (Fig. 4). As discussed earlier, the bioaccessibility typically increases with increasing oil content, decreasing droplet size, and is higher for digestible lipids that enhance the solubilization capacity of the mixed micelle phase.

It is often assumed that reducing the droplet size of nanoemulsions will increase the bioavailability, but this may not always be the case. Studies have shown that curcumin degrades more rapidly in emulsions containing small lipid droplets [114], which can be attributed to the

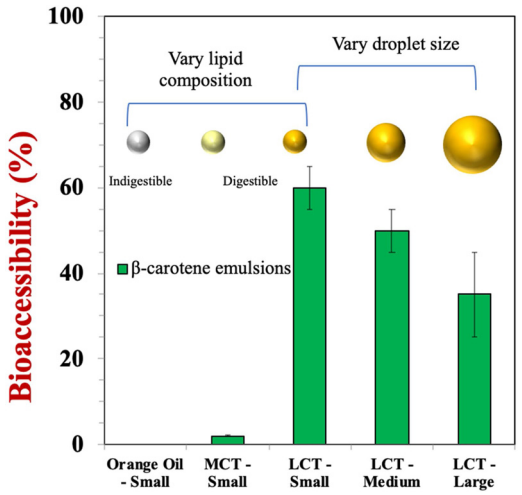


**Fig. 4.** The bioaccessibility of β-carotene in nanoemulsion-based delivery systems depends on lipid phase composition [101] and droplet size [46].

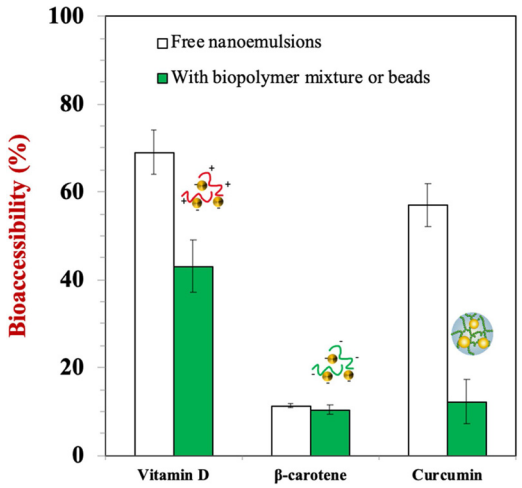


**Fig. 5.** The bioaccessibility of nutraceuticals in nanoemulsion-based delivery systems are often reduced when they are ingested with biopolymers: Vitamin D with chitosan [141]; β-carotene with alginate [119]; and, curcumin in alginate beads [120].

faster exchange of the curcumin molecules between the droplets and surrounding water. Curcumin is more unstable in water than it is in oil [117]. Consequently, it is important to optimize the droplet size to ensure good physical and chemical stability, while also achieving good bioaccessibility, so as to enhance the overall bioavailability.

Biopolymers, such as polysaccharides and proteins, are often incorporated into nanoemulsions as functional ingredients to modify their texture, mouthfeel, or stability. However, it is important to be aware of their potential impact on the bioavailability of any bioactive substances contained within or co-ingested with the nanoemulsions. The type and properties of the biopolymers, especially their molecular weight, charge, interactions, and structural organization can significantly impact the bioaccessibility, metabolism, and absorption of bioactives (Fig. 5). It has been reported that chitosan can significantly decrease the bioaccessibility of hydrophobic bioactives, such as vitamin D and β-carotene, which was attributed to the complexation of the negatively-charged mixed micelles by the positively-charged chitosan molecules [118,119]. Conversely, anionic or neutral biopolymers, such as xanthan, alginate, and β-glucan, did not have a major impact on bioaccessibility [89,119]. However, the bioaccessibility may decrease if the bioactive-loaded lipid droplets are trapped inside crosslinked biopolymers (such as microgels or hydrogel beads), because the biopolymer network inhibits the ability of the digestive enzymes to release the lipid phase [120,121]. It should also be noted that the surface properties of the lipid droplets in nanoemulsions, especially their charge, also has an important impact on the bioaccessibility of bioactives in the presence of biopolymers [89].

Over the past few years, there have been an increasing number of in vivo studies, usually animal or human feeding studies, that have also shown that nanoemulsions can increase the oral bioavailability of hydrophobic bioactive substances. For instance, nanoemulsions have been used to increase the bioavailability of hydrophobic drugs [122–125], nutraceuticals [34,126,127], and vitamins [109,128,129]. These studies highlight the potential application of nanoemulsions in functional foods, supplements, or pharmaceuticals for this purpose.

### 4.2. Excipient systems

Nanoemulsion-based excipient systems have also been investigated for their ability to boost the bioavailability of hydrophobic bioactive substances in a variety of natural food products, as well as in nutraceutical supplements (Fig. 6). Excipient nanoemulsions have been shown to increase the bioaccessibility of carotenoids (α-and β-carotene)

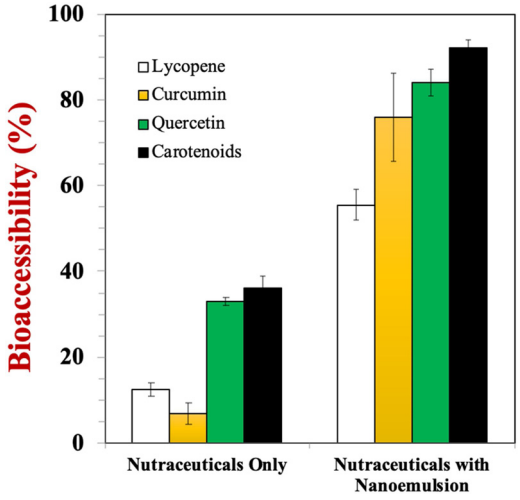


**Fig. 6.** The bioaccessibility of nutraceuticals in fresh produce or powders can be enhanced significantly by consuming them with excipient nanoemulsions: lycopene from tomato [133]; powdered curcumin [115,134]; powdered quercetin [120]; and, carotenoids from mango [136].

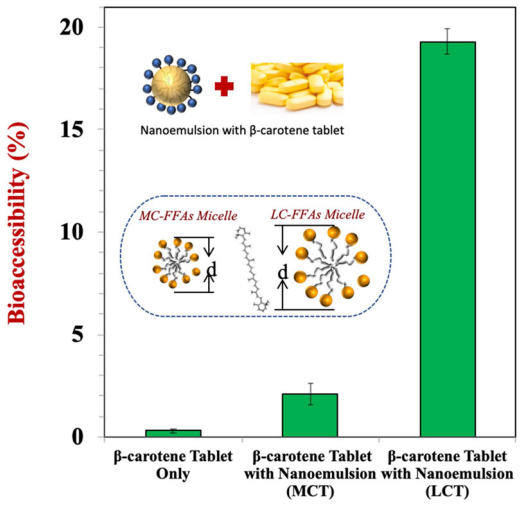


**Fig. 7.** The bioaccessibility of β-carotene in commercial supplements can be improved by co-consuming them with excipient nanoemulsions [140].

in both raw and cooked carrots [35,47,130]. The magnitude of this effect depended on the composition and structure of the nanoemulsions used. For instance, carotenoid bioaccessibility increased with increasing fat content [130] and decreasing droplet size [47], and was higher for oils that formed larger mixed micelles (i.e., long chain length and lower unsaturation of the FFAs) [35]. Excipient nanoemulsions have also been shown to increase the bioaccessibility of lycopene in tomatoes [131–133], curcumin in powdered form [134], quercetin in powdered form [76,135], carotenoids and phenolics in mangoes [136], carotenoids in yellow pepper [137], and carotenoids in spinach [138,139]. As with delivery systems, the ability of the excipient nanoemulsions to increase the bioavailability of the hydrophobic substances increases as the number and solubilization capacity of the mixed micelles formed in the small intestine increases.

The ability of co-ingested nanoemulsions to increase the bioaccessibility of the carotenoids (β-carotene) in commercial supplements has also been shown [140]. The excipient nanoemulsions were able to greatly boost the bioaccessibility of the β-carotene in both capsules and tablets. For instance, the bioaccessibility was increased from around 0.3 % for pure tablets to around 20 % for tablets in the presence of excipient nanoemulsions containing LC-FFAs. As expected, the effects were much less pronounced when nanoemulsions containing MC-FFAs were used, because the mixed micelles formed were not as effective at solubilizing the carotenoids released from the supplements (Fig. 7).

## 5. Conclusions

Nanoemulsions have considerable potential for increasing the bioavailability of hydrophobic substances, such as pharmaceuticals, nutraceuticals, and nutrients. They are considerably flexible for this purpose because their compositions and structures can easily be manipulated by selecting different functional ingredients and processing operations. Nanoemulsions can be used to encapsulate hydrophobic bioactive substances within the lipid droplets, and therefore be used as delivery systems. Alternatively, they can be co-ingested with bioactive-rich foods, supplements, or drugs, and therefore be utilized as excipient systems. In both cases, substantial increases in the bioavailability of hydrophobic bioactives can be achieved if the nanoemulsions are designed properly. Another advantage of nanoemulsions is that they can be used in either a fluid or solid form. Powdered forms are simply created by spray drying or freeze drying a fluid nanoemulsion. These powders can then be used to create tablets or capsules, which may be more suitable for supplement or pharmaceutical applications.

## CRediT authorship contribution statement

**Ruojie Zhang:** Conceptualization, Writing - original draft, Writing - review & editing. **Zipei Zhang:** Writing - original draft, Writing - review & editing. **David Julian McClements:** Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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