Lipid delivery systems for food applications

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Abbreviations:

ULV – unilamellar vesicles; OLV – oligolamellar vesicles; MLV – multilamellar vesicles; SUV – small unilamellar vesicles; LUV – large unilmellar vesicles; GUV- giant unilamellar vesicles; SLNs – Solid lipid nanoparticles; NLCs – Nanostructured lipid carriers; EPA – eicosapentaecois acid; DHA – Docosahexaenoic acid; TBA – thiobasbituric acid.

Abstract

Bioactive lipids play an important role in human health. These lipophilic substances cannot be synthesized within the human body and must be obtained through dietary ingestion. For this reason, there is an opportunity in the food industry to develop functional foods based on bioactive lipids. However, these compounds have poor stability during the production and storage and have low levels of absorption in the gastrointestinal tract. For these reasons, many strategies have been developed in the last years to enhance their stability and their bioavailability such as nanoencapsulation. This chapter aims to highlight different kinds of nanoscale delivery systems that have been designed to encapsulate bioactive lipids. This includes nanoemulsions, nanoliposomes, solid lipid nanoparticles, and nanostructured lipid carriers.

Keywords: bioactive lipids, nanotechnology, bioavailability, SLNs, NLCs, nanoliposomes, nanoemulsions

Introduction

Bioactive lipids provide certain health benefits to human health when consumed in appropriate amounts. Depending on their mechanism of action, they may boost the immune system, reduce inflammation, improve brain function, bone and eye health, reduce coronary diseases and act as antioxidants (McClements & Öztürk, 2021).

Most of these compounds are not naturally synthesized in the human body, and as such they must be obtained through dietary ingestion. However, many people do not get enough quantities of these bioactive compounds in their regular diets. Moreover, their tendency to degrade during processing and storage, compound poor stability, and absorption characteristics within the human gut are also responsible for their low levels in the general population diet (Mcclements, 2015a; Salminen, Gömmel, Leuenberger, & Weiss, 2016).

Considering these facts, the food industry has been searching for methods of fortifying foods with stable and bioavailable forms of these bioactive nutrients. In this context, nanotechnology has emerged as a powerful alternative for bioactive lipids incorporation into foods, as through their encapsulation they are protected and delivered in bioactive quantities in foods, thereby improving their efficacy (Shin, Kim, & Park, 2015; Yao, McClements, & Xiao, 2015). This chapter aims to highlight the potential of nanoscale delivery systems for improving the stability during storage and bioavailability of bioactive lipids in foods.

Nanoscale lipid delivery systems

Nanoscale delivery systems can be used to improve the stability, and bioavailability of bioactive lipids (Akhavan, Assadpour, Katouzian, & Jafari, 2018; Assadpour & Mahdi Jafari, 2019; Mcclements, 2015a; Shin et al., 2015). For these specific applications, nanotechnology has advantages over conventional encapsulation technologies, due to the smaller particle size and larger surface area of the carrier particles employed. These characteristics entail s good reactivity,

aqueous solubility or efficient absorption (Pateiro et al., 2021). Several lipid-based nanoscale delivery systems have been developed to protect and deliver bioactive lipids, which differ in their compositions, structures, and functionalities (Mcclements, 2015a; McClements & Öztürk, 2021). The functional performance of many of these delivery systems can be tailored to specific applications by changing the size, shape, charge, composition, or aggregation state of the nanoparticles they contain (McClements & Öztürk, 2021). The most used nanoscale lipid delivery systems are highlighted below.

Nanoemulsions

Generally, an emulsion consists of two immiscible liquids, with one of the liquids being dispersed as small spherical droplets in the other (McClements, 2010). Emulsions are typically classified according to the spatial distribution of the oil and water phases relative to each other. A system that consists of oil droplets dispersed in the water phase is called oil-in-water (o/w) emulsion, whereas a system that consists of water droplets dispersed in the oily phase is called water-in-oil (w/o) emulsion (de Souza Simões et al., 2017).

A nanoemulsion can be considered a conventional emulsion that contains very small droplets (between 20 and 100nm). Nanoemulsions consist of oil droplets dispersed within an aqueous continuous phase, with each oil droplet being surrounded by a thin interfacial layer consisting of the emulsifier agent (McClements, 2010).

Bioactive lipids are normally entrapped inside oil droplets, either before or after the formation of the nanoemulsion. This type of nanoemulsion can be produced using cooking oil, water, and emulsifier with low or high energy approaches. Low energy approaches rely on the spontaneous formation of small oil droplets when the system composition or environmental conditions change in a specific way (Liu, Huang, Chen, Lin, & Wang, 2019). On the other hand, high energy approaches use mechanical devices to break down the oil and water phases thus forming tiny oil droplets that are coated with emulsifiers (Aswathanarayan & Vittal, 2019; Liu et al., 2019).

Various food-grade emulsifiers can be used to create edible nanoemulsions, including synthetic surfactants, biosurfactants, phospholipids, proteins, and polysaccharides (A. Salem & M. Ezzat, 2019; Banasaz, Morozova, Ferrentino, & Scampicchio, 2020). Normally, emulsifier coated oil droplets are prevented from coalescing with each other, generating strong electrostatic and/or steric repulsive forces between them. Additionally, the small droplet size in nanoemulsions offers strong resistance to gravitational separation (Aswathanarayan & Vittal, 2019). However, they are susceptible to droplet growth through Ostwald ripening, when the oil phase used has appreciable solubility in water (Sharma, Cheng, Bhattacharya, & Chakkaravarthi, 2019). In this case, they must be carefully designed to reduce this form of instability, for example by addition of insoluble surfactants in the dispersed phase, using high-pressure homogenization, or using high viscosity oils, such as soybean (Sharma et al., 2019).

This delivery system has many advantages (table 1) such as being easy to prepare, good stability to gravitational separation, flocculation, and coalescence. Furthermore, nanoemulsions are useful when optical clarity is required in a product; and when the rapid release of functional compounds is needed. When considering the disadvantages of this delivery system, the limited number of food-grade emulsifiers available, and the large compound concentrations required are the main drawbacks associated with this methodology.

Nanoliposomes

Liposomes are tiny, spherical amphiphilic lipid vesicles bearing an aqueous internal cavity (Akhavan et al., 2018). Considering the processing condition and the chemical structure, liposomes have one or more concentric bilayers (Emami, Azadmard-Damirchi, Peighambardoust, Valizadeh, & Hesari, 2016). Usually, these nanostructures are characterized according to the total number of lamellae, size, and phospholipid charge (Emami et al., 2016; Patil & Jadhav, 2014). According to lamellarity, liposomes can be categorized as unilamellar vesicles (ULV), oligolamellar vesicles (OLV), and multilamellar vesicles (MLV). Concerning the size, the vesicle

129 can be classified as small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), and giant
130 unilamellar vesicles (GUV). Regarding the phospholipid charge they can be anionic, cationic, or
131 neutral (Emami et al., 2016; Patil & Jadhav, 2014).

132 The formulation of liposomes includes the interaction between the aqueous moiety and
133 amphiphilic lipids. The polar head of phospholipids is oriented in the location of the aqueous
134 phase of the internal and external media, and the hydrophobic tails are associated with the bilayer
135 (Akhavan et al., 2018). The presence of both lipid and aqueous moieties enables the entrapment
136 and delivery of water-soluble, lipid-soluble, and amphiphilic compounds (Emami et al., 2016).
137 Liposomes offer some interesting features: 1) controlled delivery system, 2) eco-friendly and non-
138 toxic properties, 3) enhanced solubility rate of fat-based amphiphilic bioactive, 4) enhanced
139 bioavailability of nutrients (Akhavan et al., 2018). The term nanoliposomes are exclusively linked
140 with the structure size, which starts at 10 nm. Nanoliposomes have the same physical,
141 compositional and thermodynamic characteristics as liposomes, however, their bioavailability is
142 much higher than the conventional liposomes (Akhavan et al., 2018).

143

144 *Solid Lipid Nanoparticles - SLNs*

145 Nanoparticles gained special attention in the last years in drug delivery research due to their
146 physicochemical properties, ultra-small size, and their ability to cross various biological barriers
147 (Dhiman, Awasthi, Sharma, Kharkwal, & Kulkarni, 2021). SLNs contain lipid droplets that are
148 crystalized and have an organized crystalline structure with the bioactive compounds
149 accommodated within the lipid matrix (Katouzian, Faridi Esfanjani, Jafari, & Akhavan, 2017).
150 These nanoparticles were introduced in the early 1990s when these nanostructures were
151 manufactured by replacing the liquid state lipid (oil) with the solid one in the emulsion and thus
152 the lipids are solid at ambient temperature as well as the body temperature (Katouzian et al.,
153 2017). SLNs can be characterized by their small size (50-100nm) and lack of toxicity (Silva et
154 al., 2018).

SLNs are constituted by two components, the matrix lipids, and the surface stabilizers. Other compounds such as co-surfactants, preservatives, cryoprotectants, and charge modifiers can be added (Dhiman et al., 2021). The preferred lipid matrix for the production of SLNs are monoacid triglycerides (such as tristearin, tripalmitin, and trilaurin), fatty acids (particularly stearic acid), steroids, and waxes. The stabilizers used include phospholipids, soybean or egg lecithin, poloxamers, and polysorbates (20, 60, and 80) (Dhiman et al., 2021; Silva et al., 2018). SLNs bioactive compounds carriers appear to be an attractive solution due to their large number of advantages (Table 1): 1) high entrapment efficiency, 2) eco-friendly (organic solvents are not used in their production), 3) low-cost and easy scale-up, 4) capacity to encapsulate hydrophilic and hydrophobic compounds, 5) ability to protect the core bioactive compounds against external conditions improving their stability, 6) provide a controlled release profile, 7) passible of being used in liquid or solid food products, 8) non-toxic, with excellent biocompatibility (Fathi, Mozafari, & Mohebbi, 2012; Gonçalves, Martins, Duarte, Vicente, & Pinheiro, 2018; Katouzian et al., 2017; Vega-Vásquez, Mosier, & Irudayaraj, 2020).

Despite the several advantages, the delivery of bioactive compounds through SLNs have few limitations such as low loading capacity; the dispersions have high water content; unexpected transitions in fat crystalline structures leading to the expulsion of core materials during storage and possible gelation during the storage (Fathi et al., 2012; Katouzian et al., 2017; Mishra et al., 2018; Vega-Vásquez et al., 2020).

Nanostructured Lipid Carriers - NLCs

Nanostructured lipid carriers appear to overcome the limitations of SLNs and are considered the second generation of SLNs (Gonçalves et al., 2018; Nobari Azar, Pezeshki, Ghanbarzadeh, Hamishehkar, & Mohammadi, 2020). NLCs are produced from solid and liquid lipid mixtures. This mixing results in a melting point depression and consequently in a non-ideal crystalline structure (Mishra et al., 2018; Nobari Azar et al., 2020). The formation of this disorder solid

matrices prevents the bioactive compound expulsion by avoiding the crystallization of lipids. Moreover, this structure enhances the NLCs loading capacity since those different spatial lipids promote the distance between glycerides fatty chains and general unstructured crystal (Mishra et al., 2018).

NLCs can be divided into three different types: imperfect type, multiple type, and amorphous type. Imperfect type NLCs are prepared by mixing solid lipids with small amounts of oils (liquid lipids) and thus demonstrate high drug loading. For multiple type NLCs, the amount of liquid lipids is higher than solid lipids. Therefore, yields high drug solubility as compared to solid lipids. Amorphous type NLCs are prepared with additional specific lipids to avoid crystallization of solid lipid upon cooling (Katouzian et al., 2017; Mishra et al., 2018).

As previously mentioned NLCs minimize the problems associated with the SLNs, moreover, NLCs have some distinct advantages (table 1): better physical stability, controlled particle size, controlled and extended bioactive compounds release, low production cost, the biodegradability of the lipid used, and a high content of delivery compounds entrapped (Nobari Azar et al., 2020).

Applications of nanoscale delivery systems in the food industry

In the last years, one of the major trends in the food industry has been the development of functional foods in order to improve human health and wellbeing (Mcclements, 2015b). An important point in this process is the stability and the bioavailability of the bioactive compounds added to the foodstuffs, as production processes that generally lead to a loss of bioactive compounds mainly due to oxidative reactions. For this reason, nano-scale delivery systems have been used to improve bioavailability and protect them during production and storage. Vitamins, omega-3 fatty acids, and phenolic compounds are among the main bioactive molecules nowadays used in functional foods' development and commonly encapsulated using lipid delivery systems.

Regarding vitamins, they are successfully encapsulated using nanoemulsions, nanoliposomes, or NLCs. Golfomitsou et al. (2013) developed a food-grade O/W nanoemulsion as a carrier for vitamin D (Golfomitsou, Mitsou, Xenakis, & Papadimitriou, 2018). In this work, the

nanoemulsions were produced based on different combinations of oily phase (soybean oil, cocoa butter, or lecithin) and polysorbate 20 in the aqueous phase (Golfomitsou et al., 2018). The prepared carriers were used to fortify milk with a recommended daily intake of vitamin D for adults (600 IU) (Golfomitsou et al., 2018). With the same proposal, Pezeshki et al. (2014) produced NLCs for food fortification with vitamin A. The developed NLCs had high encapsulation efficiency (84-98%) and good stability at 25 ºC (Pezeshki, Ghanbarzadeh, Mohammadi, Fathollahi, & Hamishehkar, 2014). Nanoliposomes were used as potential carriers for vitamin C with an encapsulation efficiency of ca. 65% (Yang et al., 2013).

Oils, particularly omega-3 rich oils, are abundantly used in the food industry due to their potential health benefits. However, they have several problems related with poor oxidative stability. For this reason, encapsulation is the main strategy used by industries to solve this problem when bioactive lipids are used as ingredients for new functional foods. Pomegranate oil has enhanced stability when incorporated in nanoemulsions produced with alpha-tocopherol (Sharif et al., 2017). The same omega-3 rich oil was used in the development of a functional lipid nanocarrier in a combination of beeswax and propolis waxes (Soleimanian, Goli, Varshosaz, & Maestrelli, 2018; Soleimanian, Goli, Varshosaz, & Sahafi, 2018). Conventional emulsions and nanoemulsions were used to improve the gastrointestinal absorption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in rats (Dey, Ghosh, Ghosh, Koley, & Dhar, 2012). The results demonstrated that the nanoemulsion form significantly enhanced the lipid absorption in the small intestine (Dey et al., 2012). Cinnamon essential oil chitosan coated NLCs were used to fortify milk. The results showed an increase in the milk oxidative stability during the storage when compared with the control samples, the thiobarbituric acid (TBA) and peroxide values were significantly lower than the ones registered for the controls (Bashiri, Ghanbarzadeh, Ayaseh, Dehghannya, & Ehsani, 2020).

Finally, phenolics are another important group of compounds in the food industry because of their antioxidant potential and thus have risen has prime targets for encapsulation in order to improve their bioavailability. SLNs are the preferred nanocarrier for these compounds. Neves et al. (2013)

developed SLNs using cetyl palmitate and polysorbate 60 for delivery of resveratrol with enhanced oral bioavailability (Neves, Lúcio, Martins, Lima, & Reis, 2013). With the same goal, Pandita et al. 2014 produced resveratrol loaded SLNs with stearic acid and poloxamer 188. This formulation improved significantly the oral bioavailability of resveratrol when compared with a drug suspension with the same compound (Pandita, Kumar, Poonia, & Lather, 2014). Quercetin was also encapsulated with the same objective with SLNs being produced using soya lecithin and organic solvents. The produced particles enhanced the intestinal absorption of this antioxidant compound (Li et al., 2009). Additionally, an *in vivo* study showed that the encapsulation of curcumin in SLNs enhanced its bioavailability. In fact, the amount of curcumin present in serum was 39 times superior to the levels obtained in control samples (curcumin dispersed in tween 80) (Kakkar et al., 2010).

Biological fate and safety of lipid delivery systems

Lipid digestion is a complex combination of biochemical and physicochemical processes that take place in the gastrointestinal tract. The presence of naturally occurring salts in the oral cavity imposes considerable changes in the stability of lipid-based nanostructures due to the changes in the ionic strength of the matrix. Moreover, mucin, present in saliva, has a propensity to cause aggregation of nanodroplets through depletion flocculation or bridging phenomena (Akhavan et al., 2018). As oil droplets reach the stomach, their aggregation status changes due to the extremely low pH along with shear conditions. Thus, a small amount of hydrolysis occurs as a result of gastric lipase, but it should be noted that the main digestion is carried out by pancreatic lipase in the small intestine. The role of bile salts available in intestinal juice is to allow the enzyme binding process, displacing the primary emulsifying elements from the oil-water interface (McClements, 2018). During the lipolysis phase, free fatty acids and monoacylglycerols are formed and aggregate on the oil surface, which subsequently interrupts the lipolysis reaction due to displacement of the lipase enzyme through the increased surface activity of free fatty acid and monoacylglycerols. Furthermore, calcium ions can form insoluble soaps from free fatty acids and

remove them from the surface of the droplets. Ultimately, lipolysis yields along with lipophilic core materials are solubilized into complex micelles or unilamellar phospholipid vesicles that become ready to be taken up by intestinal cells (Jafari, Katouzian, Rajabi, & Ganje, 2017; McClements, 2018) Likewise, Pyo et al. (2017) stated that lipid nanostructures enter the intestine without dispersion by bile salts due to their extremely small size. Subsequently, colipase or lipase binds to the surface of the lipid nanostructure and induces degradation (Pyo, Müller, & Keck, 2017). As a result, mono and diglycerides are formed that carry surfactant properties. The core material and the lipid structure are solubilized in micelles and these micelles are ready for the absorption process (lymphatic absorption). For the development of this micelle, lipids with higher levels of monoglycerides must be used to prepare the lipid nanoparticles (Pyo et al., 2017).

The impact of lipid-based delivery systems on the human body can be better understood through *in vitro* and *in vivo* studies. The most used are *in vitro* studies. Yu and Huang (2013) evaluated the toxicity of a nanoemulsion using Caco-2 cells. In this work, no cytotoxic effects were reported using nanodroplets with a diameter below 200 nm (Yu & Huang, 2013). Sessa et al. 2014 evaluated the biocompatibility of resveratrol-loaded nanoemulsions in Caco-2 cells and after the permeability using 19 to 21 days old caco-2 monolayers grown in transwell. The results demonstrated that the nanoemulsion did not affect cell metabolism. The nanometric size of these emulsions, with droplets of subcellular dimension, significantly improved the passive transport mechanisms through the cell membrane, an indication of improved bioavailability (Sessa et al., 2014). An animal study with solid lipid nanoparticles loaded with rosmarinic acid for oral use demonstrated that no toxicological effects were found concerning the hematological, renal, and liver function data. Moreover, in the same study, the results show minor changes in the gut microbiota composition and their metabolism (Madureira et al., 2016).

Conclusion

The successful development of nanoscale lipid delivery systems can bring several advantages for the food industry. The nanoformulations are compatible with the food systems due to their high stability in the food matrix. Moreover, they remain stable during the digestion processes, enhancing their bioavailability. The current research suggests that these nanoscale systems are safe in terms of toxicological and genotoxic effects.

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484 Table 1:

Delivery system	Advantages	Disadvantages	References
Nanoemulsion	Good encapsulation capacity. Can be dehydrated to facilitate the handling and storage; fat replacer in food industry	Sensible to pH; susceptible to breakdown and droplets coalescence limited number of food-grade emulsifiers available	(Aswathanarayan & Vittal, 2019; Ganesh & Hettiarachchy, 2016)
SLN	Good chemical protection; controlled release; non-toxic; eco-friendly; low-cost; easy to scale-up; able to encapsulate hydrophobic and hydrophilic compounds	Limited loading capacity due to the crystalline structure, high amount of water, potential expulsion of the bioactive substance during storage	(da Silva Santos, Badan Ribeiro, & Andrade Santana, 2019; Gonçalves et al., 2018; Katouzian et al., 2017; Sagalowicz & Leser, 2010; Vega-Vásquez et al., 2020)
NLC	Higher available space for nutrients, drug release can be modulated; low cytotoxicity levels; low production cost; controlled particle size	Aggregation and particle enlargement	(Akhavan et al., 2018; Das & Chaudhury, 2011; Nobari Azar et al., 2020)
Nanoliposomes	Biodegradable; non-toxic; eco-friendly, enhanced solubility rate of fat-based amphiphilic bioactive	Expensive; requires complex equipment; lower encapsulation efficiency; rapid release of oil entrapped	(Akhavan et al., 2018; Ganesh & Hettiarachchy, 2016; Ghorbanzade, Jafari, Akhavan, & Hadavi, 2017; Sherry, Charcosset, Fessi, & Greige-Gerges, 2013)

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