The dynamic transformation of micro-and nano particle of lipids in gastrointestinal tract: pros and cons for the potential health effects of food components

Abstract

A significant amount of lipids particles exists in our foods with a wide range of functionality. One important function of many micro- and nanoparticles of lipids is to enhance the oral bioavailability of nutrients and nutraceuticals. This SIB provides a summary on how these lipid particles transform in the gastrointestinal tract and how these particles interact with different food components to render different health effects.

1. Introduction

Lipids are important ingredients of daily diet, and they exist in our foods often in the form of micro- and nanoparticles such as oil droplets found in milk and other dairy products. Moreover, micro- and nanoparticles of lipids are widely used as functional ingredients in the foods for a wide range of purposes such as providing desirable texture and mouthfeel, and delivery of flavor and nutrients. Tremendous efforts have been made to develop lipid particle-based food delivery systems to enhance the oral bioavailability of nutrients and nutraceuticals [1, 2]. These lipid particles within the delivery systems often undergo a dynamic transformation process (i.e., assembly, disassembly and reassembly) in the gastrointestinal tract (GIT) to facilitate the delivery of the target food components (e.g., nutrient/nutraceuticals) to the blood circulation, thus an enhanced bioavailability (Figure 1) [1, 2]. However, the compositions of foods are complex, and they may contain components with potential harmful effects on human health, such as pesticide residues, certain inorganic nanoparticles and micro(nano)plastics. The lipid particle delivery systems may interact with these potentially harmful components, leading to enhanced adverse health effects. Herein, the interaction between lipid particles and different bioactive food components and associated impact on human health is summarized.
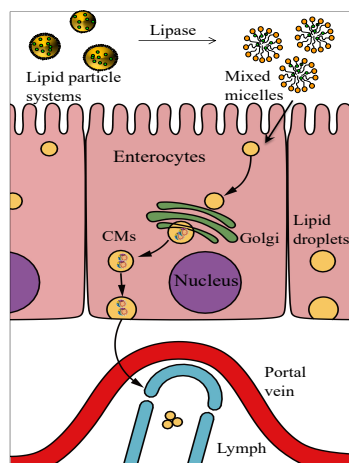
Figure 1. The bioavailability of lipophilic components may be increased by lipid particle systems via a mixed micelles and chylomicrons (CMs) – mediated mechanism in the gastrointestinal tract. The same mechanism could also influence the uptake of detrimental food components.

2. Assembly, disassembly and reassembly of food lipid particles

Lipid particles in foods can be formed naturally, such as milk fat droplets. In contrast, many types of man-made lipid particles can be assembled as lipid particle-based delivery systems for different functionalities in food, such as nanoemulsions, microemulsions, liposomes, and solid lipid nanoparticles. There are various processing techniques to fabricate these man-made lipid particles [1, 2].

As a major class of food ingredients and nutrients, vegetable and animal fats (triglycerides or triacylglycerols, TAGs) are widely used to produce lipid particles. After ingestion, these TAG-based lipid particles are disassembled into free fatty acids (FFAs) and monoacylglycerols (MAGs) by the action of lipase in the lumen of the small intestine. Subsequently, FFAs and MAGs, along with endogenous bile salts and phospholipids, are reassembled to form mixed micelles (a type of biological lipid particles with a complex mixture of colloidal structures) in the small intestine lumen (Figure 1). The type of lipid has significant impact on lipid particle digestion and mixed micelle formation. For example, the medium chain triacylglycerols (MCTs) produce faster digestion rates, higher overall digestibility, smaller mixed micelles than long chain triacylglycerols (LCTs)[3].

Mixed micelles are dissembled to FFAs and MAGs before being absorbed into the enterocytes. Absorbed FFAs and MAGs are then reassembled into TAGs by specific Enzymes. TAG droplets interact with other lipids and proteins, such as apo-lipoprotein B48 to form another type of biological lipid particle, chylomicrons inside of enterocytes (Figure 1). Chylomicrons are lipoprotein particles consisting of a hydrophobic core containing TAGs, cholesterol, and other lipophilic components, and a hydrophilic shell consisting of phospholipids and proteins[4]. The morphologies, dimensions and amounts of chylomicrons formed in the enterocytes might depend on the nature of the FFAs. For instance, monounsaturated FFAs (oleic acids) tend to form larger size and amount of chylomicrons, compared to polyunsaturated FFAs (linoleic or linolenic acid) with the same chain length[5].

The abovementioned dynamic fate of lipid particles in the GIT has a profound impact on the bioavailability and biofunction of many dietary components [1, 2]. However, as mounting

research has provided current understanding on the interaction between lipid particles and some food components such as lipophilic nutraceuticals, much more research is needed to elucidate the role of lipid particles in newly emerged food research topics such as the potential adverse effects of foodborne inorganic particles and micro(nano)plastics.

3. Lipid particles improve the bioavailability of nutrients and nutraceuticals

Bioavailability of food components, such as nutrients and nutraceuticals, is defined as the fraction of the ingested food components that actually reach the systemic (blood) circulation in active forms [1, 2]. Only these food components are available to be distributed to the tissues and organs where they can exert their beneficial health effects. For ingested food components, there are a few barriers preventing them from reaching the systemic circulation in active forms, e.g. chemical instability during digestion, poor solubility in GI fluids, slow absorption from the GIT, and first-pass metabolism.

Many nutrients and nutraceuticals in food are lipophilic, such as vitamin D, vitamin E, carotenoids, flavonoids, and curcuminoids, among others [6-11]. Their bioavailability can be improved through incorporation into naturally formed and man-made lipid particle systems. Lipid particles have been developed to protect nutrients and nutraceuticals from degradation and improve their stability in the GIT. During disassembly and reassembly of these lipid particles, the formation of mixed micelles and chylomicrons has been considered as critical processes that enhance the bioavailability of lipophilic nutrients and nutraceuticals.

3.1. *Mixed micelles increase bioaccessibility*

In the small intestinal lumen, lipophilic bioactive food components need to be solubilized in the intestinal fluid before they can be absorbed by the enterocytes. The soluble fraction of these components is considered bioaccessible. Mixed micelles are excellent vehicles to solubilize a wide range of lipophilic food components in the intestinal lumen due to their superior lipophilicity and surfactant-like properties (Figure 1) [1, 2].

The composition of mixed micelles, such as the type of FFAs, plays an important role in improving bioaccessibility of lipophilic food components. For molecules like vitamin D, vitamin E, and carotenoids, mixed micelles made from long chain TAGs produce greater bioaccessibility than those made from medium chain TAGs[7, 12, 13]. In contrast, mixed micelles made from median chain TAGs yield greater bioaccessibility for curcumin than that from long chain TAGs [14]. The degree of saturation of the mixed micelle FFAs also affects the bioaccessibility. For example, the bioaccessibility of carotenoids can be enhanced more by mixed micelles derived from monounsaturated TAGs (such as corn oil) than that from polyunsaturated TAGs (such as fish oil) [15]. These findings suggest that the effects of different mixed micelles on bioaccessibility are specific to different nutrients and nutraceuticals; therefore, lipid particle systems should be specifically designed for particular nutrients and nutraceuticals in order to effectively improve their bioaccessibility. The size of lipid particles can also influence bioaccessibility. Nanoemulsions with smaller particles (r ≈ 100 nm) have been reported to yield a higher bioaccessibility of β-carotene than those with larger particles (r ≈1000 nm) [16]. A potential explanation for this phenomenon is that smaller lipid particles generate mixed micelles more rapidly than larger particles during lipid digestion, which can increase the rate of transfer of lipophilic molecules from the particles to the mixed micelles. More research is needed to establish a detailed

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relationship between the properties of mixed micelles and bioaccessibility of different classes of food components (for example nutrients/nutraceuticals with different degrees of lipophilicity or different molecular shapes and sizes).

3.2   *Mixed micelles and chylomicrons facilitate trans-enterocyte lymphatic transport*

The presence of mixed micelles in the intestinal lumen can greatly enhance trans-enterocyte lymphatic transport of lipophilic nutrients and nutraceuticals, a critical step of GI absorption [17]. This enhancement in absorption is associated with production of chylomicron in the enterocytes stimulated by the mixed micelles (Figure 1) [1, 2]. Mixed micelles can "carry" lipophilic nutrients and nutraceuticals across cell membrane and enter enterocytes. Inside the enterocytes, components of mixed micelles are reassembled to form chylomicrons that is highly lipophilic. Lipophilic nutrients and nutraceuticals tend to incorporate into chylomicrons due to their lipophilicity. These nutrients and nutraceuticals are then transported together with chylomicrons across enterocytes to enter lymphatic circulation. Eventually, lymph fluid carries the nutrients and nutraceuticals and pools them into the blood stream. The degree of unsaturation of fatty acids in mixed micelles is an important factor influencing the absorption of nutrients and nutraceuticals. For example, mixed micelles formed with oleic acid ($C_{18:1}$), linoleic acid ($C_{18:2}$), or linolenic acid ($C_{18:3}$) have different effects on trans-enterocyte transport of 5-demethylnobiletin, a citrus flavonoid [18]. Mixed micelles formed with oleic acid lead to the formation of higher amounts of chylomicrons in the enterocytes, thus result in much higher trans-enterocyte transport of 5-demethylnobiletin, than mixed micelles formed with linoleic acid or linolenic acid.

First-pass metabolism (also known as first-pass elimination) is a process during which a nutraceutical is metabolized by a wide array of enzymes present mainly in the enterocytes and liver cells. The result of first-pass metabolism is that only a fraction of the ingested nutraceutical reaches the systemic circulation unchanged, which leads to a decreased oral bioavailability. Lipid particle systems can be designed to help nutraceuticals bypass first-pass metabolism and thus increase their bioavailability [1, 2]. Lipid particle systems, such as nano-emulsions, have been used to bypass liver metabolism by promoting intestinal lymphatic transport of lipophilic nutraceuticals [1]. As mentioned above, lipid particle systems can promote chylomicron-mediated transport of nutraceuticals from enterocytes to the lymphatic circulation (Figure 1). Subsequently, lymph carries chylomicron-associated nutraceuticals to the systemic circulation via the subclavian vein without passing through the liver, thus avoiding first-pass metabolism in the liver [19]. Chylomicrons can also protect nutraceuticals from first-pass metabolism in enterocytes. This is because that nutraceutical associated with the chylomicrons have less chance to interact with metabolizing enzymes within the enterocytes in comparison to nutraceuticals freely present in the cytoplasm of enterocytes [18, 20]. The FFA type of lipid particle systems plays an important role in the first-pass metabolism of nutraceuticals in the enterocytes. For example, olive oil-based nano-emulsion resulted in a minimal metabolism of pterostilbene in enterocytes, whereas flaxseed oil-based nano-emulsion led to extensive metabolism of pterostilbene [20]. More mechanistic investigations are needed to establish the relationship between the characteristics of lipid particle systems and their effects on first-pass metabolism of specific nutraceuticals.

4. Potential adverse effects of lipid particles

Harmful materials such as pesticide, inorganic nanoparticles, and micro(nano)plastics can make their way into our food supplies by various means. lipid particles in food can interact with these harmful food components and lead to adverse health effects.

4.1. _Pesticide residues_

The use of pesticides in agricultural practices inevitably leaves pesticide residues in food products. For example, 60% of green tea samples contain certain levels of pesticides[21]. A large portion of Tunisian grapes contain pesticide residues, among them, 94% exceed the European maximum residue limits[22]. Moreover, pesticide residues can remain very stable during long-term food storage[23]. Many pesticides are lipophilic, and therefore, they may behave similar to lipophilic nutraceuticals in terms of their bioavailability in the GIT. In other words, the lipid particle systems that can enhance bioavailability of lipophilic nutraceuticals may also increase the bioavailability of these pesticides, which in turn may lead to higher toxicity to humans. A high lipid content in the diet has been demonstrated to exacerbate the toxicity of lipophilic pesticides[24]. The presence of food emulsions with tomatoes in the simulated GIT model elevated the bioaccessibility of the pesticide residue on the tomatoes[25]. More research is needed to establish better understanding of the impact of lipid particles systems in food on the bioavailability and potential adverse effects of pesticide residues in foods.

4.2. _Inorganic nanoparticles_

Inorganic nanoparticles have been found in large number of consumer products due to both intentional and unintentional addition. For example, titanium dioxide (TiO_2) nanoparticles are added to over 900 food products as a part of a whitening additive (E171), and they also exist in almost all sunscreen lotions[26]. Silica nanoparticles (SiO_2) are widely used as anticaking agents in powdery food and medicine[27]. Gold nanoparticles are used as food coloring agent and in dental fillings[28]. The size of these inorganic nanoparticles is closely related with their absorption, accumulation and toxicity[29]. Lipids in the food may alter the fate and biological functions of foodborne inorganic nanoparticles in the GIT. For example, liposome can increase intracellular uptake of metal oxide (TiO_2 & SiO_2) nanoparticles by forming lipid interface [30]. Fatty acids increase cytotoxicity of zinc oxide nanoparticles to enterocytes[31]. Moreover, animal studies have shown the combination of TiO_2 nanoparticles and a high fat content in the diet produces enhanced adverse health effects, including gut microbiota dysbiosis, colonic inflammation, as well as hepatic and colonic proteome alterations in mice[32]. Nevertheless, the interaction between lipid particles and inorganic nanoparticles in the GIT and its implication in human health remains poorly understood.

4.3. _Micro(nano)plastics_

In the past decade, evidence has grown that plastic particles and fibers with sizes in the nanometer to micrometer range are accumulating in terrestrial, freshwater, and marine environments[33]. These micro(nano)plastics have also entered the human food chain through tap and bottled water, marine products (e.g., fish, crab, and bivalves) and other food products (e.g., honey, beer, and salt)[34]. Many studies have focused on the presence of micro(nano)plastics and their toxicological effects in aquatic organisms. It has been found that

micro(nano)plastics can be absorbed and accumulate in the organs of aquatic organisms to induce considerable toxicity. However, the influence of foodborne micro(nano)plastics on human health is poorly understood[35]. Due to the lipophilic property of micro(nano)plastics, they could actively interact with dietary lipids and lipid particles. These interactions may lead to altered bioavailability and/or bioactivity of micro(nano)plastics, possibly resulting in increased adverse health effects to humans.

5. Conclusions and future perspectives:

After ingestion, lipid particles in food undergo a dynamic process in GIT to form several different lipid-based particles such as mixed micelles and chylomicrons. This process is critical for the biofunctions of a wide range of lipophilic nutrients and nutraceuticals as it may enhance their bioavailability by (1) improving their bioaccessibility in the intestinal lumen; (2) promoting their trans-enterocyte lymphatic absorption; and (3) protecting them from first-pass metabolism in the intestine and liver. In the meantime, this process may also lead to adverse health effect due to its interaction with harmful food components such as pesticides residues, biopersistent inorganic nanoparticles, and micro(nano)plastics. Future research is needed to better understand the molecular mechanism by which dietary lipid particles interact with other food components in human body and associated health impact.

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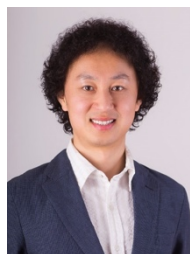
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