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Improving oral bioavailability of nutraceuticals by engineered nanoparticle-based delivery systems

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Many important nutraceuticals have poor oral bioavailability, which greatly lowers their efficacy as health-promoting agents. Engineered nanoparticles (ENs) can be used to fabricate delivery systems that improve oral bioavailability through a number of mechanisms: increasing nutraceutical stability in foods and the gastrointestinal tract (GIT); enhancing nutraceutical solubility in intestinal fluids; facilitating nutraceutical absorption by GIT; and decreasing first-pass metabolism in the gut and liver. This review depicts the mode of actions of different food-grade ENs in improving oral bioavailability of nutraceuticals.

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Introduction

Nutraceuticals are foods and food constituents that provide health benefits beyond basic nutrition. Accumulating evidence has suggested that dietary consumption of nutraceuticals is associated with decreased risks of multiple chronic diseases. However, many nutraceuticals have poor oral bioavailability, which significantly lowers their efficacy as disease-preventing agents [1••,2,3,4••]. An effective way to improve oral bioavailability of nutraceuticals is to utilize nanotechnology to encapsulate nutraceuticals in engineered nanoparticles (ENs)-based delivery systems [1••,5,6].

Engineered nanoparticle-based delivery systems for nutraceuticals

Nanotechnology has become an important means of producing novel materials and structures for a wide range of applications within the food industry. Numerous ENs have been fabricated and tested for their potential use as delivery systems for nutraceuticals with the purpose of enhancing their health benefits through encapsulation, protection and/or controlled release of nutraceuticals [1••,3,4••]. Improving oral bioavailability of nutraceuticals has become a promising strategy to enhancing their efficacy in humans. Recently, considerable advances have been achieved in designing and manufacturing ENs to increase the oral bioavailability of nutraceuticals. Generally, depending on the presence or absence of lipids as the major components of the delivery systems, ENs can be categorized as lipid-based or non-lipid-based (Table 1). Recent reviews have provided comprehensive descriptions of the manufacture and characteristics of different type of ENs suitable for food applications [1••,7–11,12••]. This review elaborates the impact of ENs on oral bioavailability. It is noteworthy that, different from the ENs utilized in the pharmaceutical industry, ENs for food application has to be manufactured with 100% food-grade materials, such as edible lipids, proteins, carbohydrates, and surfactants, which has considerably increased challenges in creating effective delivery systems.

Oral bioavailability of nutraceuticals

The oral bioavailability of a nutraceutical is defined as the fraction of the ingested nutraceutical that actually reaches the systemic (blood) circulation in an active form [13]. Only these nutraceuticals are available to be distributed to the tissues and organs where they can exert their beneficial health effects. For ingested nutraceuticals, there are a few barriers preventing them from reaching the systemic circulation in an active form, for example chemical instability during digestion, poor solubility in GI fluids, slow absorption from the GIT, and first-pass metabolism (Figure 1). The oral bioavailability (F) of a nutraceutical encapsulated in ENs can be estimated by the following equation [1••,12••]:

$$F = F_B \times F_A \times F_M$$

Here, F_B is the fraction of an ingested nutraceutical that survives passage through the upper GIT and that is released from the food matrix/ENs into the GI fluids, thereby becoming bioaccessible for absorption by enterocytes. F_A is the fraction of the bioaccessible nutraceutical that is actually absorbed by the enterocytes and then transported to the portal blood or lymph (and into the systemic circulation). F_M is the fraction of absorbed nutraceutical that is in an active form after first-pass metabolism in the GIT and liver (and any other forms of metabolism). In the following sections, the effects of food-grade EN-based delivery

Table 1

Engineered nanoparticles based delivery systems for improving oral bioavailability of nutraceuticals.

	Delivery systems	Functional food components	Ingredients	Function sites	References
Non-lipid-based ENs	Biopolymeric nanogels, antisolvent precipitation	Lipophilic compound (omega-3 fatty acids, CLA, oil soluble vitamins, etc.)	Miscible solvents, biopolymers, surfactants	F_B	[14]
	Biopolymeric nanoparticles	Omega-3/omega-6 polyunsaturated fatty acids	Water, dextrin	F_B & F_A	[15]
	Biopolymeric nanoparticles	Curcumin	Water, β-cyclodextrin, modified starch, surfactant	F_B	[16]
	Organogel based nanoemulsion	Curcumin	Water, organogel, surfactant	F_B & F_A	[17]
	Nanocomplex	Omega-3 fatty acids	Water, β-lactoglobulin, protein	F_B	[18]
	Protein-based micelles	Vitamin D	Water, surfactant (casein)	F_B & F_A	[19]
	Micelles	Curcumin	Water, surfactant	F_B & F_A	[20]
	Nanoformulation	Co Q10	Water, surfactant, glycerol	F_B & F_A	[21]
Lipid-based ENs	Nanoemulsion	Lipophilic compound (vitamin E, β-carotene)	Water, oil, surfactant	F_B & F_A & F_M	[22–26]
	Nanoemulsion	Co Q10	Water, oil, surfactant	F_B & F_A & F_M	[27,28]
	Liposome	Polyphenols (curcumin, resveratrol)	Water, phospholipids, cholesterol	F_B	[29]
	Nanoliposome	EGCG	Water, phospholipids, cholesterol	F_B	[30]
	Nanoemulsion	Curcumin	Water, MCT, surfactant	F_B & F_A	[31]
	Solid lipid nanoparticles	Lipophilic compound (carotenoids, omega-3 fatty acids, phytosterols)	Oil, surfactant	F_A & F_M	[1••,32]
	Microemulsion	Curcumin	Water, surfactants, oil	F_B	[33]
	Micelles	Lycopene	Oil, water, lecithin, surfactant	F_B & F_A	[34]

systems on bioaccessibility, absorption, and first-pass metabolism of encapsulated nutraceuticals are discussed.

Engineered nanoparticles enhance bioaccessibility of nutraceuticals

A nutraceutical is exposed to substantial changes in the composition, structure, and flow behavior of its environment during its passage through the upper GIT, that is mouth, stomach, and small intestine. These conditions may cause changes in the physical state, location, and chemistry of the nutraceutical, therefore decreasing its bioaccessibility. ENs have been developed to protect nutraceuticals from adverse GI conditions. For example, (−)-epigallocatechin gallate (EGCG), a green tea polyphenol, is unstable under the pH conditions found in small intestinal fluids. Encapsulation of EGCG in nanoliposomes fabricated from phospholipids, cholesterol, and Tween 80 decreased its degradation in simulated intestinal fluids around 10-fold [30]. Nutraceuticals can also be encapsulated in solid lipid nanoparticles and biopolymer-based nanoparticles that can be designed to protect nutraceuticals from premature degradation and improve their stability in the GIT [15,35].

To be bioaccessible to enterocyte absorption, a nutraceutical needs to be solubilized within the GIT. Highly lipophilic nutraceuticals, such as carotenoids and curcuminoids have low bioaccessibility due to their poor solubility in aqueous GI fluids. Lipid-based ENs, such as nanoemulsions and solid lipid nanoparticles, have frequently been used to enhance the bioaccessibility of lipophilic nutraceuticals. The nature of the carrier oil used to solubilize lipophilic nutraceuticals within lipid-based ENs has been shown to influence their loading capacity and bioaccessibility [23,36]. After ingestion, the compositions, structures and physiochemical properties of nutraceutical-loaded ENs may be changed appreciably due to their exposure to different GIT conditions, for example their size, charge, physical state, and aggregation state [1••]. The presence of digestible components (protein, lipid and surfactant) also plays an important role in determining the biological fate of lipid-based ENs in the GIT, which in turn has a great impact on the bioaccessibility of nutraceuticals [1••].

In the GIT, digestible carrier oils (mainly triglycerides) in ENs are hydrolyzed by lipases to produce free fatty acids and monoacylglycerols. These lipid digestion products interact with bile salts and phospholipids in the lumen of the small intestine to form 'mixed micelles' with complex structures (Figure 2a) [1••]. Nutraceuticals encapsulated within ENs are transferred to the mixed micelles during