Comprehensive REVIEWS in Food Science and Food Safety

Enhancing Nutraceutical Performance Using Excipient Foods: Designing Food Structures and Compositions to Increase Bioavailability

David Julian McClements, Liqiang Zou, Ruojie Zhang, Laura Salvia-Trujillo, Taha Kumosani, and Hang Xiao

Abstract: The oral bioavailability of many bioactives (pharmaceuticals, dietary supplements, nutrients, and nutraceuticals) is limited because of physicochemical and physiological events that occur within the gastrointestinal tract (GIT) after their ingestion. These events include: (i) restricted liberation from drugs, supplements, or foods; (ii) extensive metabolism or chemical transformation during passage through the GIT; (iii) low solubility in intestinal fluids; (iv) low permeation through the intestinal cell monolayer; and (v) efflux from epithelium cells. Bioactive bioavailability can often be improved by designing the composition and structure of food matrices to control their liberation, transformation, solubilization, transport, absorption, and efflux in the GIT. This article reviews the potential impact of food composition and structure on the oral bioavailability of bioactives, and then shows how this knowledge can be used to design *excipient foods* that can improve the bioavailability profile of bioactives. The bioactive may be incorporated within an excipient food or co-ingested with an excipient food. The suitability of oil-in-water emulsions as excipient foods is highlighted. The utilization of excipient foods may provide a new strategy for improving the efficacy of nutraceuticals, supplements, and pharmaceuticals.

Keywords: bioactives, delivery systems, drugs, excipient foods, food effects, functional foods, medical foods, nutraceuticals, pharmaceuticals

Introduction

Commercial products containing bioactive agents intended for oral ingestion are important in the food, supplement, and pharmaceutical industries. These bioactive agents may be nutraceuticals, vitamins, or drugs. A number of these bioactive agents have low or variable oral bioavailability (that is, the fraction of an ingested bioactive that actually reaches the site of action in an active form), which may limit their effectiveness and lead to variations in their efficacy (Fleisher and others 1999; Porter and others 2007; Tang and others 2007; Patel and others 2011; Fernandez-Garcia and others 2012; Rein and others 2013). It is therefore advantageous to develop effective strategies to improve the bioavailability profile of these types of bioactives. The identification of suitable strategies depends on understanding the physicochemical and physiological mechanisms that occur within the human gastrointestinal tract (GIT) that may alter the bioavailability of a bioactive after ingestion. Briefly, these mechanisms include liberation of the bioactive agent from the ingested drug, supplement, or food matrix (Moelants and others 2012b); solubilization within gastrointestinal juices (Porter and others 2007; Pouton and others 2008); transport across epithelial cells (Fleisher and others 1999; Martinez and others 2002); and/or, biochemical or chemical transformation within the GIT (Hurst and others 2007; D'Ambrosio and others 2011; Fernandez-Garcia and others 2012). Numerous studies in the pharmaceutical, nutrition, and food sciences have shown that the oral bioavailability of many bioactive agents is influenced by the nature of any foods co-ingested with them (Charman and others 1997; Brown and others 2004; Porter and others 2007; Pouton and others 2008; Fernandez-Garcia and others 2012; Nagao and others 2013; Rein and others 2013; Varum and others 2013; Yeap and others 2013). The type of ingredients present within the food matrix, as well as their interactions and structural organization, impact the bioavailability of co-ingested bioactive agents (Salvia-Trujillo and others 2013a). The fact that food composition and structure influences the oral bioavailability of bioactive agents can be utilized to specifically design food matrices that improve the efficacy of nutraceuticals, pharmaceuticals, and supplements (McClements and others 2014). A summary of studies on the influence of food matrix on nutraceutical bioavailability is given in Table 1.

In this review article, we describe a recently developed approach for controlling the bioavailability profile of bioactives based on

MS 20151111 Submitted 1/7/2015, Accepted 18/8/2015. *Authors McClements and Xiao are with Biopolymers and Colloids Laboratory, Dept. of Food Science, Univ. of Massachusetts Amherst, Amherst, Mass. 01003, U.S.A. Authors McClements and Kumosani are with Biochemistry Dept., Faculty of Science, Production of Bioproducts for Industrial Applications Research Group and Experimental Biochemistry Unit, King Fahd Medical Research Center, King Abdulaziz Univ., Jeddah, Saudi Arabia. Authors Zou, Zhang, and Salvia-Trujillo are with State Key Laboratory of Food Science and Technology, Nanchang Univ., Nanchang, No. 235 Nanjing East Road, Nanchang 330047, Jiangxi, China. Direct inquiries to author Hajeb (E-mail:*mcclements@foodsci.umass.edu*)*

doi: 10.1111/1541-4337.12170

Table 1–Overview of representative studies showing the potential influence of excipient foods on nutraceutical bioavailability. An excipient food is a food that increases the bioavailability of bioactive agents that are co-ingested with it.

Excipient food component	Nutraceutical in co-ingested food source	Potential excipient food effects	References
Lipids			
Olive oil	β-Carotene and α-Carotene in carrots	Adding olive oil to carrot during cooking increased carotene liberation and solubilization.	(Hornero-Méndez and others 2007)
Olive oil	Phenolics in tomatoes	Adding olive oil to tomato sauce increased liberation and solubilization of phenolics.	(Martínez-Huélamo and others 2015)
Cocoa fat	Phenolics in cocoa	Fat content of cocoa samples enhanced release of phenolic compounds (procyanidins) during duodenal digestion.	(Ortega and others 2009)
Salad oil	Carotenoids in vegetables and salad	Adding oil to salad or vegetables increased liberation and solubilization of carotenoids.	(Huo and others 2007); (Nagao and others 2013)
Phospholipids	β-Carotene in emulsions	Addition of phosphatidylcholines to emulsions increased carotenoid bioaccessibility.	(Verrijssen and others 2015)
Carbohydrates			
Sugars	EGCG in solution	Adding sugars to aqueous solutions protected EGCG against degradation.	(Shpigelman and others 2013)
Starch	β-Carotene in emulsions	Incorporating lipid droplets in starch-based hydrogels increased lipid digestion and carotenoid bioaccessibility	(Mun and others 2015a); (Mun and others 2015b)
Pectin	β-Carotene in emulsions	Adding pectin to emulsions altered lipid digestion and carotenoid bioaccessibility depending on pectin type	(Xu and others 2014), (Verrijssen and others 2014)
Indigestible polysaccharides	Ferulic acid	Binding of ferulic acid to indigestible polysaccharides restricted its release in the small intestine, resulting in low bioavailability.	(Mateo Anson and others 2009)
Sucrose	Favan-3-ols in chocolate	The presence of sucrose in chocolate increases the bioavailability of flavan-3-ol compounds.	(Neilson and others 2009)
Proteins			
Soy protein	Zinc and iron in grain	20% soy protein isolate produced contrasting effects on zinc and iron bioaccessibility from cereals, rice and sorghum.	(Hemalatha and others 2009)
Milk protein	Flavan-3-ols in green tea	Milk protein, most notably sodium-caseinate, significantly decreased bioaccessibility of flavan-3-ols.	(Moser and others 2014)
Protein-rich defatted soybean	Anthocyanins in blueberry juice	Soybean flour increased bioavailability of anthocyanins from blueberry juice.	(Ribnicky and others 2014)
Soy protein	Minerals	Protein decreased mineral bioaccessibility.	(Galán and others 2014)
Milk protein	Polyphenols in jujube juice	Milk proteins extended the time needed to reach a maximal plasma polyphenol concentration in human subjects	(Zhang and others 2013)
Whey protein	Chlorogenic acid or catechin in fruit juice-milk beverage	Whey protein had neutral, antagonistic or synergetic effects on the antioxidant activity of fruit juice-milk beverage.	(He and others 2015)
Complex food matrix	Polyphenols in chokeberry juice	Adding a multicomponent food matrix to chokeberry juice decreased its total phenolic content and antioxidant activity.	(Stanisavljević and others 2015)
Minerals			
Milk minerals	Flavan-3-ols in green tea	The presence of milk minerals significantly increased flavan-3-ol bioaccessibility.	(Moser and others 2014)
Iron and calcium	Zinc in grains	Iron and calcium reduced the bioaccessibility of zinc from food grains.	(Hemalatha and others 2009)
Food additives			
EDTA	Iron in corn-masa tortillas	Adding EDTA improved iron bioavailability in corn-masa tortillas.	(Walter and others 2003)
Ethanol	Quercetin, resveratrol and anthocyanins	Ethanol enhanced cellular absorption of polyphenols and the transport of anthocyanins involving GLUT2.	(Chan and others 2000); (Faria and others 2009)
Xylitol/citric acid and xylitol/vitamin C	Catechins in green tea	The present of xylitol/citric acid and xylitol/vitamin C increased the intestinal uptake of total catechins.	(Shim and others 2012)

food matrix design (McClements and others 2014). The authors are all food scientists whose research involves understanding the role of food composition and structure on the gastrointestinal fate of nutrients and nutraceuticals. Consequently, many of the examples used to demonstrate the principles of excipient foods involve the utilization of nutraceutical-rich foods as examples (Table 1). Nevertheless, many of the same principles can be directly applied to pharmaceuticals and dietary supplements.

Pharmaceuticals and Nutraceuticals

Recently, there has been a growing overlap in the aims and methods of pharmaceutical and food scientists (Patel and others 2011; McClements 2013). Pharmaceutical scientists work on identifying, characterizing, and delivering bioactive agents (pharmaceuticals) in drug preparations designed to prevent or treat specific diseases. Similarly, food scientists are becoming increasingly interested in identifying, characterizing, and delivering bioactive agents (nutraceuticals) in foods designed to prevent or treat diseases. These "nutraceuticals" are claimed to have health benefits over and above their traditional role in human nutrition, including the ability to inhibit inflammation, cancer, diabetes, hypertension, obesity, heart disease, and brain disorders. Nevertheless, there are some important differences between pharmaceuticals and nutraceuticals. Pharmaceuticals are usually given with instructions that specify the dose, frequency, and method of ingestion. Conversely, nutraceuticals are typically consumed as part of a

regular human diet, and are usually present within foods at low and variable levels. For this reason, it is difficult to control the type and amount of nutraceuticals consumed by individuals, and when they are ingested. Another major problem with nutraceuticals is actually establishing their efficacy in human populations. Unlike drugs, it is often difficult to carry out reliable human trials to establish the effectiveness of specific nutraceuticals consumed as part of a complex human diet. Despite these problems, the interest in nutraceutical-rich foods from both consumers and food manufacturers has grown appreciably in recent years, and there are now many examples of functional foods and beverages available commercially.

Defining Excipient Foods

Foods are already being specifically designed to improve human health and wellness by treating or preventing certain types of disease. For example, research is being carried out in the medical field to develop *medical foods* (Weaver and others 2010; Shah 2011; Morgan 2013), whereas research is being carried out in the food industry to develop *functional foods* (Crowe and others 2013). In this section, we begin by defining medical and functional foods, and then introduce the concept of *excipient foods* and show how these products differ from medical and functional foods.

Medical foods

A *medical food* has been defined by the U.S. Food and Drug Administration (FDA) as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical foods are therefore intended to meet specific nutritional requirements that are associated with a particular disease or health condition. Typically, medical foods are prescribed by physicians to patients who have health conditions that lead to impaired ingestion, digestion, absorption, or metabolism of traditional foods. A medical food may by orally ingested by a patient or it may be administered using an enteral feeding tube. Medical foods have been developed to combat a number of diet-related diseases, such as phenylketonuria (Camp and others 2012), coeliac disease (Zannini and others 2013) and lactose intolerance (Matthews and others 2005). These foods are formulated to contain all the nutrients required to maintain human health and wellbeing, but without components that promote disease. For example, phenylketonuria is an inherited disease that leads to a dangerous buildup of phenylalanine in the body due to a lack of a specific enzyme (Camp and others 2012). In this case, medical foods are formulated to contain all the nutrients needed to ensure human health (proteins, carbohydrates, lipids, minerals, vitamins, and so on), but no phenylalanine. Medical foods have also been developed to treat individuals that have compromised pancreatic enzyme function, which means that their digestive tracts are not able to properly digest triacylglycerols (www.alcresta.com). In this case, enzyme-based technologies have been developed to create medical foods where the triacylglycerols are digested prior to feeding. Alternatively, a medical food might be formulated to contain a specific nutrient that the body cannot normally produce itself due to some disease condition.

Functional foods

Currently, there is no definition of *functional foods* by the FDA in the United States, but products that are claimed to be functional foods are still regulated by this agency under the Federal Food, Drug, and Cosmetic Act (Crowe and others 2013). *Functional foods* contain one or more nutraceutical agents dispersed within a natural or processed food product, such as fruit, vegetable, grain, seed, nut, beverage, yogurt, spread, and so on. Many types of processed functional foods are already commercially available: milk fortified with vitamin D; orange juice enriched with calcium; yogurt containing probiotics; spreads fortified with phytosterols; and, breakfast cereals containing ω-3 fatty acids, vitamins, and minerals (Bigliardi and others 2013). Natural foods, such as carrots, tomatoes, kale or cantaloupes, containing appreciable amounts of carotenoids or other nutraceuticals may also be classified as functional foods (Lemmens and others 2014). The types and amounts of functional foods consumed per day are not typically regulated and are determined by an individual's preferences. In a functional food, the bioactive agents may simply be present within a food matrix that acts as a carrier that delivers the bioactives to the body. In this case, the food matrix is not specifically designed to improve the bioavailability of the bioactive agents.

Excipient foods

An *excipient food* is specifically designed to boost the bioavailability of bioactive components that are co-ingested with it (McClements and others 2014) (Figure 1). It may have no bioactivity itself, but it increases the bioactivity of the bioactive components consumed with it by increasing their bioavailability. These bioactive components may be dispersed within the excipient food (integrated-excipient foods) or they may be present within another product (drug, supplement, or food) that is co-ingested with the excipient food (nonintegrated-excipient foods). Nonintegrated excipient foods (such as beverages, desserts, dressings, sauces, or yogurt) could be designed to be consumed with pharmaceutical doses (such as capsules, tablets, or syrups), dietary supplements (such as powders, capsules, or pills), or nutraceutical-rich foods (such as fruits, vegetables, nuts, seeds, and grains). Integrated excipient foods could be designed to be consumed as standalone functional foods, such as beverages, desserts, dressings, sauces, or yogurt fortified with nutraceuticals such as carotenoids, polyphenols, or ω-3 fatty acids. The specific composition and structure of an excipient food depends on the nature of the bioactive agents that it is designed to deliver, and also the factors that normally limit their bioavailability. Classification schemes have been developed to specify the major factors limiting the bioavailability of both drugs and nutraceuticals (see later), which may be used as a guide when designing excipient foods. The types and amounts of excipient foods consumed per day are not currently regulated, and depend on the dietary habits of individuals. In the future, it may therefore be necessary to regulate excipient foods since they do have the ability to alter the bioactivity of co-ingested components. An integrated excipient food can itself be considered to be a functional food as it contains one or more nutraceutical agents within it. In general, however, not all functional foods that contain nutraceuticals may have food matrices that are specifically designed to increase their bioavailability.

It is also useful to introduce the concept of an *excipient ingredient,* which is a food-grade ingredient that has the ability to increase the bioavailability of certain bioactive agents. For example, an excipient lipid may increase the bioavailability of hydrophobic nutraceuticals by increasing their bioaccessibility within the GIT, whereas an excipient antioxidant may increase the bioavailability of nutraceuticals susceptible to oxidation by inhibiting their chemical degradation within the GIT.

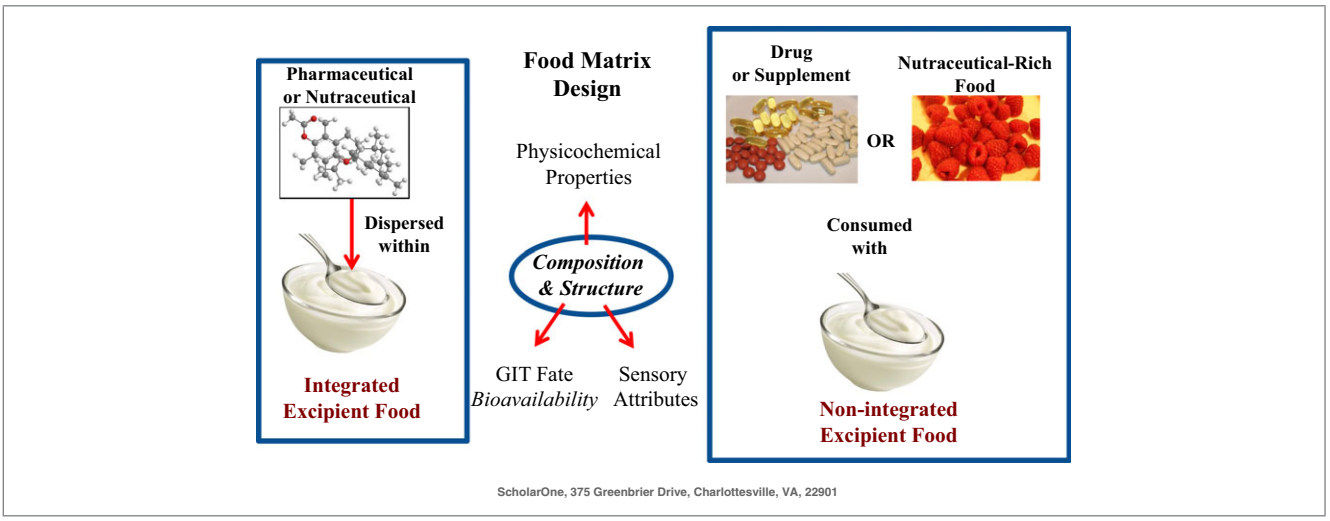

Figure 1–Schematic diagram of the difference between integrated and nonintegrated excipient foods. For integrated excipient foods the bioactive component (pharmaceutical or nutraceutical) is dispersed within the excipient food matrix, but for nonintegrated excipient foods the bioactive component is in another product that is co-ingested with the excipient food.

In the remainder of this review article we focus on excipient foods, and not on medical or functional foods. Nevertheless, much of the material covered will also be relevant to understanding the functional performance of these foods.

Numerous types of food or beverage products could be utilized to enhance the bioavailability and efficacy of bioactive agents through food matrix effects, including soft drinks, fruit juices, dairy beverages, yogurts, dressings, sauces, soups, spreads, candies, and baked goods. As well as being able to increase the bioavailability of the bioactive agents, these foods should also be designed so that they are affordable, convenient, desirable, and can be easily incorporated into a daily diet.

Excipient Foods: Potential Benefits and Limitations

A number of factors have to be considered when creating successful excipient food products (McClements and others 2014). First, the composition and structure of the food matrix must be carefully designed to increase the bioavailability of one or more bioactive agents. Knowledge of the influence of specific food components and structures on the gastrointestinal fate of bioactive agents is therefore required to design excipient foods. Second, the excipient food must have physicochemical and sensory properties that consumers or patients find desirable so as to ensure high compliance (willingness to regularly consume), for example, the product should have a suitable appearance, texture, flavor, and mouthfeel (McClements and others 2009c). Third, food or beverage products should be selected that can easily be incorporated into a routine daily diet, for example, a yogurt that is consumed every breakfast time, or a beverage that is consumed every evening. Fourth, the excipient food itself should not have any adverse health effects if consumed regularly, for example, it should not be too high in fat, cholesterol, sugar, or salt. Fifth, the excipient food should be in a form that is convenient for consumers to purchase, store, and utilize, for example, it should have a reasonably long shelf life and not take up too much storage space.

Some potential food and beverage products that may be used as excipient foods are fortified waters, fruit juices, teas, coffees, creamers, smoothies, milks, creams, yogurts, spreads, desserts, candies, and crackers. The nature of the pharmaceutical or nutraceutical agent that needs to have its bioavailability increased is likely to determine the most suitable type of food matrix to use. For example, a food matrix containing long-chain triglycerides is usually needed to increase the bioavailability of lipophilic nutraceuticals or pharmaceuticals. On the other hand, a food matrix containing high levels of antioxidants may be required to stop the chemical degradation of nutraceuticals or pharmaceuticals that are prone to chemical degradation due to oxidation reactions.

Potential benefits

There are a number of potential benefits of developing excipient foods to increase the oral bioavailability of pharmaceuticals and nutraceuticals.

Pharmaceuticals: The oral bioavailability of many lipophilic drugs is known to be relatively low and highly variable, which may reduce their efficacy and cause undesirable side effects (Porter and others 2007; Williams and others 2013). Drug manufacturers often recommend that this type of drug be consumed with foods. However, there may be large variations in food effects on drug bioavailability depending on the precise composition and structure of the food consumed. Consuming this type of drug with a fixed quantity of an excipient food with a well-defined composition and structure may therefore reduce the variations in bioavailability that would otherwise occur. Another potential advantage of consuming drugs within an integrated excipient food is related to patient compliance. A patient may be reluctant to regularly take large amounts of conventional drug delivery forms (such as capsules, pills, or syrups), but be more inclined to regularly consume medical foods that look and taste desirable.

Nutraceuticals: In principle, the regular consumption of a nutraceutical-rich diet may have beneficial effects on human health and well-being, including enhancing performance and preventing diseases, such as cancer, diabetes, heart disease, and hypertension (Bigliardi and others 2013; Rein and others 2013). However, the oral bioavailability of many nutraceuticals is normally low and variable due to their solubility, permeability, or stability characteristics within the gastrointestinal tract (McClements and others 2015). Consequently, their potential health benefits are not being fully realized (Fernandez-Garcia and others 2012). The development of food matrices specifically designed to enhance the bioavailability of nutraceuticals may be able to overcome these problems.

Potential Limitations

There are numerous legal, technical, and commercial challenges to the development of successful excipient foods.

Pharmaceuticals: A patient may have to take numerous kinds of drugs each day, often at different times of the day, with each drug having different factors that limit its oral bioavailability. In principle, it is possible to incorporate a number of drugs into a single integrated-excipient food, but this may be inconvenient and costly to prepare and would have to be tailored to the specific needs of each patient. Alternatively, a separate integrated-excipient food could be created for each type of drug that had to be taken, but this would require a patient to eat a number of different drug-containing excipient foods. This problem could be overcome by packaging the drugs into small food portions, such as candy pieces, crackers, or snack bars. Another approach would be to design nonintegrated excipient foods with compositions and structures that are able to increase the bioavailability of a wide range of different drugs. Thus, it may be possible to cover a wide range of drugs using a single excipient food, or just a small number of excipient foods. An additional problem is that patients have different food preferences and so a range of excipient foods may have to be produced to satisfy these different tastes: fruit drinks, beverages, yogurts, spreads, candies, and desserts.

Nutraceuticals: There are also a number of potential limitations of developing excipient foods for nutraceutical applications. First, an excipient food may also increase the bioavailability of any components in foods that may be deleterious to human health (Rietjens and others 2015). For example, the bioavailability of any harmful lipophilic components within a food could be increased by ingestion with an excipient food designed to improve the bioavailability of hydrophobic nutraceuticals. Alternatively, an excipient food that inhibits metabolizing enzymes or efflux mechanisms associated with epithelial cells may promote the absorption of harmful substances (Shimizu 2010). Second, even for beneficial bioactive components there is often an optimum range of nutraceutical concentrations in the systemic circulation where the health benefits are observed. If the levels are lower than this range, then the bioactive component may be ineffective, but if the levels are higher than this range, then the bioactive component may actually have adverse effects. For example, high levels of absorbed oil-soluble vitamins may cause a problem to human health. The types and amounts of nutraceuticals and excipient foods consumed each day are not regulated, and therefore it is difficult to control the total amount of bioactive agents consumed as part of a diet. Third, foods contain a wide range of different types of nutraceuticals with different molecular and physicochemical properties. Consequently, it may be necessary to design a range of different excipient foods suitable for increasing the bioavailability of different types of nutraceuticals. Fourth, consumers have their own unique food preferences and so it would be necessary to develop a range of excipient products: soft drinks, fruit juices, dairy beverages, yogurts, candies, desserts, spreads, and baked goods. Fifth, there may be natural variations in the type and amount of bioactive components present within fruits and vegetables, for example, depending on breed, growing conditions, and storage conditions. Consequently, it may be necessary to design excipient foods to take into account the natural variation in bioactive components that may occur. Finally, it will be important to educate consumers about the potential risks and benefits associated with excipient foods so they can make informed decisions about the type and amounts of excipient foods to consume, and to determine the most appropriate excipient food to consume with particular nutraceutical-rich foods.

Gastrointestinal Factors Limiting Bioavailability

Information about the major factors that normally limit the oral bioavailability of bioactive agents is essential for the successful design of effective excipient foods. In this section, we focus on the factors that may limit bioavailability that are associated with the gastrointestinal tract (GIT), and not on those that occur after absorption of the bioactive agent into the systemic circulation, since these are the factors that can be most easily controlled through food matrix design. The major gastrointestinal factors influencing the overall oral bioavailability (BA) of a bioactive component can be summarized by the following equation, as also shown schematically in Figure 2 (Arnott and others 2012; McClements 2013):

$$BA = B^* A^* T^*. \quad (1)$$

Here, $B^\star$, $A^\star$ and $T^\star$ are the fractions of the bioactive agent that are bioaccessible, absorbed, and in a biologically active state after any transformations in the GIT, respectively. Each of these values depends on the nature of the bioactive agent, as well as that of the food matrix. It should be noted that transformations that alter nutraceutical bioavailability may occur within a food product during manufacture, transport and storage (for example due to mechanical processes, pH variations, or temperature changes), or within the gastrointestinal tract. This factor is important to consider when designing excipient foods.

Bioaccessibility

The bioaccessibility of a bioactive agent depends on the fraction that is in a form within the GIT that can be absorbed by the human body (Figure 2). Typically, a bioactive agent must be soluble within the gastrointestinal fluids, although certain types of particulate matter can be absorbed by the epithelium cells. For hydrophilic bioactives, the bioaccessibility is simply the fraction of the amount ingested that is dissolved within the gastrointestinal fluids, whereas for hydrophobic bioactives it is typically taken to be the fraction that is incorporated within the mixed micelles formed in the small intestine. The bioaccessibility of a bioactive agent may be limited by a number of factors depending on its nature and that of the food matrix:

Liberation. The bioaccessibility of a bioactive agent may be limited by its ability to be released from its original environment (Figure 2). For example, a drug may be trapped within the solid matrix of a tablet or capsule, or a nutraceutical may be trapped within the cellular structure of a fruit or vegetable (Figure 3). Studies have shown that highly lipophilic nutraceuticals (carotenoids) remain trapped within the cellular structure of raw vegetables and are not fully liberated in the GIT after ingestion (Failla and others 2007; Panozzo and others 2013). For this type of bioactive agent it is important to ensure that it is fully released from the surrounding matrix within the GIT. For nutraceuticals, this can be done by changing food processing conditions (such as cooking or homogenization), by altering eating habits (such as the duration or intensity of mastication), or by altering excipient food properties (such as their composition and structure). For pharmaceuticals, it may be possible to alter the conditions within the GIT to facilitate the breakdown of the matrix surrounding the drug: by controlling pH, ionic strength, enzyme activity, food composition, gastric motility, or gastric transit time. This could be achieved by incorporating excipient ingredients within an excipient food that can modulate these processes (see Excipient Food Ingredient section).

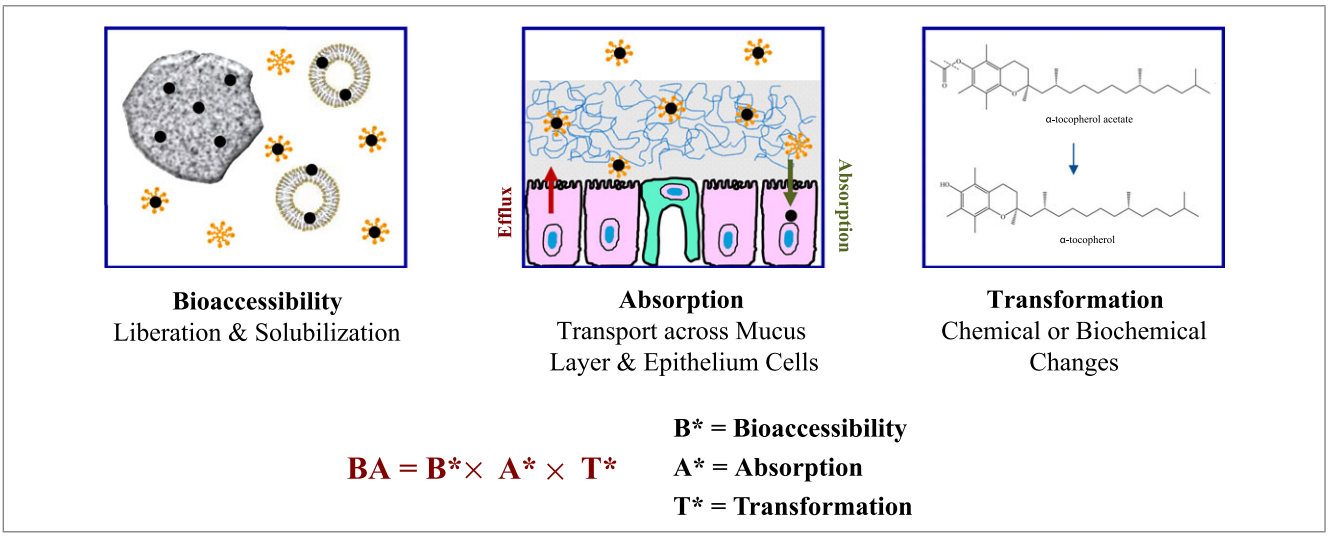

Figure 2–The overall oral bioavailability of bioactives is governed by three main factors: bioaccessibility; absorption; and transformation. The various processes occurring within the figures are described in the text.

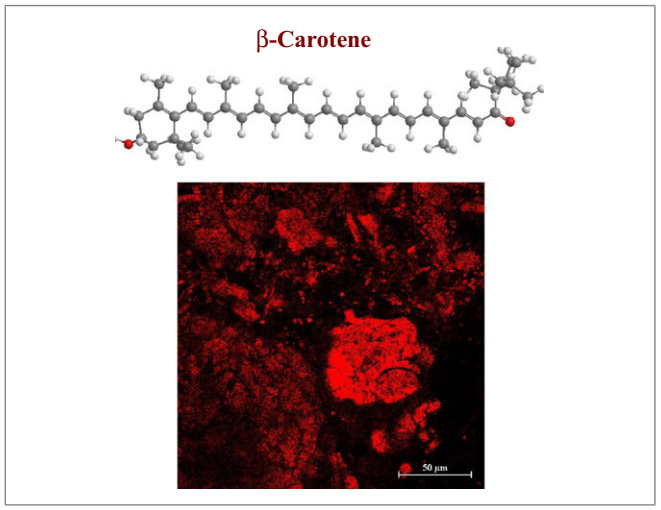

Figure 3–Auto-fluorescence of carotenoids inside the chromoplasts of homogenized tomato pulp. Images kindly supplied by Laura Trujillo-Salvia (Univ. of Massachusetts).

Solubility. The bioaccessibility of a bioactive agent may be limited by its solubility in the aqueous gastrointestinal fluids (Figure 2). Hydrophilic bioactives readily dissolve in aqueous solutions up to their solubility limit, and therefore it is important to establish their equilibrium solubilities and how these are affected by changing gastrointestinal conditions (such as pH, ionic strength, and interactions with gastrointestinal or food components). By definition, hydrophobic bioactives have a low solubility in aqueous solutions, and therefore they need to be incorporated into the hydrophobic regions of mixed micelles (micelles and vesicles) within the small intestine before they can be readily absorbed by epithelium cells (Porter and others 2008). Crystalline bioactives may have to dissolve in the gastrointestinal fluids before they can be absorbed (Williams and others 2013), although sufficiently small crystals may be directly absorbed by epithelium cells (Gao and others 2013). The bioavailability of solubility-limited bioactives may be improved by utilizing excipient food compositions or structures that enhance their solubility in gastrointestinal fluids (McClements and others 2014). For example, triglyceride-rich excipient foods break down in the small intestine to form mixed micelles that increase the solubilization capacity for lipophilic bioactives.

Interactions. The bioavailability of certain types of bioactive agents are limited due to their interactions with other constituents present in the gastrointestinal tract (Figure 2). These constituents may come from the human body itself (phospholipids, bile salts, minerals, mucus, or enzymes), or they may arise from the co-ingested food (proteins, dietary fibers, minerals, or surfactants). A bioactive agent may form an insoluble complex with one of these constituents that decreases its bioaccessibility. For example, negatively charged long-chain saturated fatty acids interact with positively charged calcium ions in the gastrointestinal fluids and form calcium soaps that have low bioaccessibility (Wydro and others 2007). There are many other types of molecular interactions that may occur within the complex environment of the gastrointestinal fluids that may alter the bioaccessibility of certain bioactive agents. Chelating agents may bind to mineral ions and alter their normal function in the digestion and absorption process. Electrically charged biopolymers, such as proteins or polysaccharides, may bind to other charged species in the gastrointestinal tract (such as phospholipids, bile salts, mineral ions, or enzymes) through electrostatic interactions (Wydro and others 2007). Some of these interactions will decrease the bioaccessibility of bioactive agents, whereas others will increase it. Knowledge of the nature of the interactions occurring within the GIT can therefore be utilized to select ingredients in excipient foods that will promote the bioaccessibility of specific bioactives.

Absorption

Even after a bioactive agent is liberated from an ingested drug or food and solubilized within the gastrointestinal fluids, it must still be absorbed by the epithelium cells before it becomes bioavailable. The bioactive agent must travel across the mucus layer, through the epithelium cells, and into the systemic circulation. A number of factors may limit the absorption of bioactive agents through this process.

Mucus layer transport. The epithelium cells that line the internal walls of the gastrointestinal tract are covered by a layer of

mucus (Figure 2). This mucus layer protects the underlying cells from damage, contains metabolic enzymes that can transform nutrients and other compounds, and acts as a semi-permeable membrane that selectively allows certain components through (Scaldaferri and others 2012). The transport of bioactive agents to the epithelium cells may be restricted if they are too large to pass through the pores (≈ 400 nm) in the gel-like mucus layer (Cone 2009). The transport of bioactive agents may also be limited if they are attracted to the mucus molecules that make up the gel network, for example, through electrostatic, hydrogen bonding, or hydrophobic interactions. The absorption of some electrically charged or nonpolar molecules may therefore be limited due to their interactions with the gel network that makes up the mucus layer. An excipient food may be designed so that it breaks down into small particles (mixed micelles) in the gastrointestinal fluids that can transport the bioactive molecules through the mucus layer.

Passive membrane transport. An important factor that limits the passive absorption of many bioactive agents is their ability to travel through the phospholipid bilayer that makes up the scaffold of the epithelium cell membrane (Figure 4). The interior of the phospholipid bilayer is hydrophobic, and so only lipophilic bioactive molecules can easily penetrate into and through it, whereas hydrophilic ones cannot. Certain types of food components have the ability to alter the permeability of the phospholipid bilayer, such as some surfactants and biopolymers (see section on "Excipient Food Ingredients"). It may therefore be possible to increase the bioavailability of certain bioactive agents by including food components in an excipient food that increase cell membrane permeability.

Active membrane transport. Certain types of bioactive agents cannot easily be transported through the phospholipid bilayer because they are too hydrophilic or too large. However, they may still be absorbed by the epithelium cells due to the presence of *active transporters* (Figure 4). Typically, an active transporter consists of one or more proteins embedded within the phospholipid bilayers (Fasinu and others 2011; Dahan and others 2012). Active transporters require an energy source to function (such as ATP). Many different types of active transporters have been identified that are capable of transporting different kinds of bioactive agents across cell membranes, such as certain free fatty acids, vitamins, drugs, and nutraceuticals (Tso and others 2004; Lo and others 2009; Dudhatra and others 2012). The fraction of bioactive molecules absorbed by active transport mechanisms may be relatively high when the bioactives are present at low concentrations in the GIT, but may decrease appreciably if the transporters become saturated or if other substances compete for the active sites.

Tight junction transport. Many small hydrophilic bioactive molecules cannot easily travel through the phospholipid bilayer, but they can still be absorbed by passing through the tight junctions that separates adjoining epithelium cells (Figure 4) (Kosinska and others 2013). At normal physiological conditions, the channels in the tight junctions are relatively narrow (radius < 0.7 nm) and so only allow small molecules to pass through them, such as, amino acids and sugars (Seki and others 2008; Tsutsumi and others 2008). However, tight junction dimensions may increase in the presence of some substances that may be found in foods, such as certain surfactants, biopolymers, minerals, and chelating agents (Shimizu 2010; Rosenthal and others 2012; Lerner and others 2015). As a result, larger molecules or even small particles may pass through them and be absorbed. It may therefore be possible to enhance the bioavailability of certain types of bioactive agents by including ingredients in an excipient food that increase the tight junction dimensions. Having said this, there may be some health risks associated with doing this, since a recent review indicated that substances in foods that increase the intestinal tight junction permeability may promote autoimmune diseases (Lerner and others 2015)

Efflux mechanisms. After absorption by epithelium cells, some bioactives are transported back into the lumen of the GIT by efflux transporters embedded in the phospholipid bilayers (Figure 4) (Misaka and others 2013). These efflux transporters therefore limit the uptake of certain types of bioactive agents into the systemic circulation (Actis-Goretta and others 2013). The bioavailability may be decreased for 2 reasons: (i) the bioactive is expelled from the epithelium cells; (ii) the extent of metabolism is increased as the bioactive agent is repeatedly absorbed and effluxed by the epithelium cells.

Transformation

The bioavailability and bioactivity of many bioactive agents depend on their molecular structure, which may be altered by chemical or biochemical transformations occurring within the GIT.

Chemical transformation. The biological activity of many types of bioactive molecules are altered within the GIT because they undergo chemical transformations, such as oxidation, reduction, or hydrolysis. Polyunsaturated lipids (such as ω-3 fatty acids or carotenoids) may be oxidized (Carail and others 2013; Kenmogne-Domguia and others 2014), carotenoids may undergo isomerization (cis-trans) (Ferruzzi and others 2006), curcumin may undergo degradation under neutral and alkaline conditions (Salem and others 2014), while proteins and peptides may be hydrolyzed by the highly acidic environment of the stomach (Moreno 2007; Wickham and others 2009).

Biochemical transformation. Many bioactive agents are metabolized by specific enzyme systems (Phase I and Phase II) within the gastrointestinal tract, including resveratrol (Planas and others 2012), quercetin (Petri and others 2003), and epicatechin (Actis-Goretta and others 2013). Typically, metabolism increases the polarity of lipophilic bioactives by attaching hydrophilic moieties to the parent molecule, which promotes re-absorption by the kidney and excretion through the urine. Commonly, Phase I metabolism reactions include hydrolysis, reduction, and oxidation. Many classes of enzymes are involved in these metabolic reactions, including reductases, esterases, CYP450 enzymes, and dehydrogenases. For example, genistein and nobiletin are susceptible to oxidation by CYP 450 enzymes (Koga and others 2011). Phase I metabolites are often substrates for Phase II enzymes, thereby causing further changes in their molecular structures, physicochemical properties, and biological activities. Phase II metabolism usually involves conjugation reactions between the parent bioactive molecules or their Phase I metabolites and endogenous molecules. Some of the major kinds of enzymes involved in Phase II metabolism are glutathione-S-transferases, glucuronyltransferases, sulfo-transferases, methyl-transferases, epoxide hydrolase, and acetyl-transferases (Velderrain-Rodriguez and others 2014). Phase II metabolism *in vivo* contributes to low bioavailability of many bioactives. For example, the metabolism of curcumin in the GIT leads to a variety of metabolites with different biological properties (Dempe and others 2013; Metzler and others 2013). Depending on the relative bioavailability and bioactivity of the parent compound and its metabolites, metabolism may be either detrimental or beneficial to the overall performance of bioactive

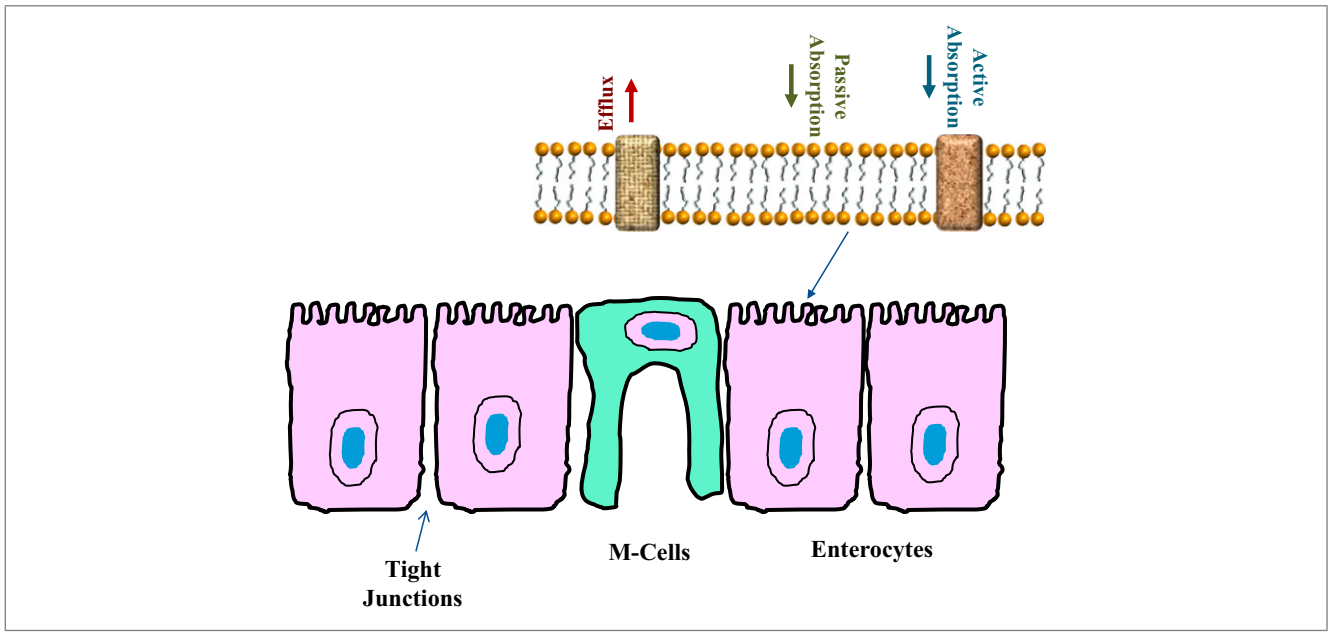

Figure 4–The absorption of bioactive agents may be limited due to their transport across the epithelium cell through passive, active or efflux mechanisms.

agents. In some cases, metabolism reduces the bioavailability and bioactivity of pharmaceuticals and nutraceuticals, but in other cases it may actually increase them. Consequently, it may be possible to alter the bioavailability profile of bioactive components by using food matrices that alter chemical or biochemical transformations.

Bioactive agents not absorbed in the small intestine reach the large intestine where they may be further transformed due to fermentation by the microflora in the colon (Bosscher and others 2009; Monagas and others 2010). Colonic fermentation can cause appreciable alterations in the bioavailability and bioactivity of bioactive agents. For example, anthocyanins are typically not easily absorbed in the small intestine because they are highly hydrophilic molecules, but they may be converted into suitable forms for absorption by colonic bacteria (Stevenson and others 2009; Hribar and others 2014).

Characterizing Factors Limiting Bioavailability

The oral bioavailability of bioactive agents may be improved by controlling the composition or structure of excipient foods to control the bioaccessibility, absorption, and transformation of bioactive agents. The type of excipient food that is most appropriate will depend on the nature of the bioactive agent. In this section, we briefly review classification schemes for pharmaceuticals and nutraceuticals that may be useful for identifying the most appropriate excipient food to increase their bioavailability.

Pharmaceuticals: biopharmaceutical classification scheme

The *biopharmaceutical classification scheme* (BCS) groups the major factors limiting the bioavailability of pharmaceuticals into 4 major categories depending on their solubility and permeability characteristics:

Class I: *High Solubility: High Permeability:* This class includes pharmaceuticals that have high solubility in gastrointestinal fluids and high permeability across epithelium cell membranes. The oral bioavailability of this class of pharmaceuticals is therefore not limited by their solubility or permeability characteristics.

Class II: *Low Solubility: High Permeability:* This class includes pharmaceuticals with low solubility in gastrointestinal fluids, but high permeability across epithelium cell membranes. Many highly hydrophobic drugs fall into this category because they have very low water-solubility, but can easily be transported across phospholipid bilayers. The bioavailability of this kind of pharmaceutical can be enhanced using approaches that increase their solubility in gastrointestinal fluids, such as chemical modification (pro-drugs) or lipid-based delivery systems (Porter and others 2008; Williams and others 2013).

Class III: *High Solubility: Low Permeability:* This class includes pharmaceuticals with high solubility in gastrointestinal fluids, but low permeability across epithelium cell membranes. Many highly hydrophilic drugs fall into this category because they have high water-solubility, but are not easily transported across epithelium cell membranes. The bioavailability of this kind of drug may be increased by chemical modification (pro-drugs) or by co-administration with substances that increase cell membrane permeability (Lennernas and others 2007; Saaber and others 2014).

Class IV: *Low Solubility: Low Permeability:* This class includes compounds that have low solubility in gastrointestinal fluids and low permeability across epithelium cell walls (Williams and others 2013). This type of drug typically has low oral bioavailability because it is limited by both poor solubility and poor permeability characteristics.

The bioaccessibility of some drugs may also be limited by some of the other factors discussed in Section 5, such as poor liberation, adverse interactions, chemical transformation, metabolism, or efflux.

Nutraceuticals: nutraceutical bioavailability classification scheme

A new classification scheme has recently been proposed to characterize the major factors limiting the bioavailability of nutraceuticals: the Nutraceutical Bioavailability Classification Scheme or

Table 2–Tabular representation of the main factors limiting the bioavailability of bioactives.

Bioaccessibility	Absorption	Transformation
Liberation: the bioactive must be released from the drug, supplement of food matrix	*Mucus layer:* the bioactive must be transported across the mucus layer that coats epithelium cells	*Chemical transformation*: some bioactives undergo chemical degradation within the GIT
Solubilization: the bioactive must be solubilized within GIT fluids	*Tight junctions:* some bioactives may pass through tight junctions separating epithelium cells	*Biochemical transformation*: some bioactives are digested or metabolized by enzymes in the GIT
Interactions: the bioactive may interact with other food components	*Membrane permeation:* some bioactives may be transported through the phospholipid bilayer *Active Transport:* some bioactives are transported by active transport proteins *Efflux:* some bioactives are removed from epithelium cells by efflux proteins	

NuBACS (McClements and others 2015). A nutraceutical is classified by a $B^{\star}A^{\star}T^{\star}$ designation according to the major factors limiting its bioavailability: Bioaccessibility (B*); Absorption (A*); Transformation (T*) (Figure 2). Each major category is designated "(+)" if it is nonlimiting and "(-)" if it is limiting. Further information is provided by using subscripts to specify the precise physicochemical mechanisms responsible for low bioavailability, such as poor liberation (L), low solubility (S), tight junction transport (TJ), metabolism (M) and so on (Table 2). For example, a lipophilic nutraceutical (such as curcumin) whose overall bioavailability is limited by low bioaccessibility due to low solubility and chemical/biochemical transformation in intestinal fluids would be classified as $B^{\star}(-)_{S}\ A^{\star}(+)\ T^{\star}(-)_{M,C}$. Quantitative values could be given to each of the individual factors that limit the overall bioavailability if appropriate analytical protocols and instrumentation are available.

An advantage of these classification schemes is that many pharmaceuticals and nutraceuticals can be grouped together into broad categories where a common strategy can be used to improve their bioavailability characteristics. For example, lipid-based delivery systems (such as oily solutions or emulsions) that form mixed micelles after lipid digestion may be used to increase the oral bioavailability of many Class II lipophilic pharmaceuticals and many $B^{\star}(-)_{S}$ class lipophilic nutraceuticals.

Impact of Food Matrix On Bioavailability

Knowledge of the impact of food composition and structure on the oral bioavailability of bioactive agents can be used to specifically design excipient foods to improve their oral bioavailability characteristics. This section highlights some key mechanisms by which food matrix properties can potentially affect the oral bioavailability of bioactive agents. It is assumed that the food matrix consists of typical food-grade components, such as proteins, carbohydrates, lipids, minerals and water.

Bioaccessibility

Potential mechanisms of action.

Release from food or drug matrices. Drugs are usually delivered using some kind of pharmaceutical preparation, such as a syrup, powder, tablet or capsule. Similarly, nutraceuticals are usually contained within fluid, semi-solid, or solid food matrices. In some cases, the bioactive agent is rapidly released from the surrounding matrix after ingestion, but in other cases its release is inhibited because the matrix does not readily disintegrate within the GIT (Figure 3). A variety of mechanical, chemical, and biochemical processes are involved in matrix disintegration (van Aken 2010; Lentle and others 2011; Koziolek and others 2013b). A pharmaceutical preparation (such as a tablet or capsule) is typically swallowed directly without breaking down in the mouth. A liquid food (such as a beverage) may only spend a short period in the mouth prior to swallowing. Conversely, many semi-solid and solid foods undergo extensive oral processing within the mouth to generate fragments that are small enough to swallow, including fruits, vegetables, nuts, meat, fish, and baked products. Foods that spend more time in the mouth are susceptible to breakdown by mechanical forces, dissolution, and enzyme activity within the oral cavity. After being swallowed, pharmaceutical or food matrices may be further disrupted in the stomach and small intestine due to a combination of mechanical forces, physicochemical processes, chemical reactions, and enzyme activities. The stomach and small intestine subject foods to churning, grinding, and peristalsis motions that aid in the disruption of matrices (Kong and others 2008; Lentle and others 2010; Koziolek and others 2013b). Pharmaceutical or food matrices containing water-soluble constituents (such as salts, solutes, or polymers) may be disrupted due to simple dissolution within aqueous GIT fluids. Matrices containing constituents held together by electrostatic attraction (such as ionic polymers or surfactants) may be dissociated due to changes in the pH or ionic strength of the GIT fluids (Lentle and others 2011; Matalanis and others 2012). Matrices containing lipophilic constituents held together by hydrophobic attraction (such as surfactants, phospholipids, polymers, or lipids) may be disrupted by biological surfactants secreted by the GIT (bile salts and phospholipids). Matrices consisting of digestible food components (lipids, starches, and proteins) may be broken down by digestive enzymes secreted by the GIT (lipases, amylases, and proteases).

An improved understanding of the factors that affect these breakdown mechanisms for specific pharmaceutical preparations or nutraceutical-rich foods can be used to design excipient foods that promote them. The composition and structure of an excipient food may be specifically designed to stimulate the release of gut hormones that promote the secretion of digestive acids, enzymes, or bile salts (Covasa 2010; Boyer 2013). Increased levels of these digestive components may enhance the breakdown of certain pharmaceutical or food matrices and, therefore, increase the amount of bioactive agent released in the GIT. An excipient food may also be designed so that it changes the length of time that the bioactive agents spend within the GIT. This can be achieved by controlling the rate at which the excipient food is digested within different regions of the GIT, by introducing food components that alter the rheological properties of the GIT fluids (such as dietary fibers), or by including food components that delay gastric emptying or alter intestinal motility (such as certain phytochemicals, dietary fibers, and lipids) (Koziolek and others 2013a). Excipient food compositions or structures that increase the GIT transit time may alter the bioaccessibility of pharmaceuticals or nutraceuticals by giving them longer time to be released and absorbed. On the other hand, an increased transit time may lead to more extensive

chemical degradation or metabolism, which may be either desirable or undesirable in terms of bioavailability and bioactivity.

The inclusion of lipids in an excipient food may promote the liberation of nonpolar bioactives from their original pharmaceutical or food matrices by acting as a hydrophobic reservoir. For example, researchers have shown that the addition of olive oil to carotenoid-rich carrots during cooking increases the amount of carotenoids liberated from the food thereby increasing their bioavailability (Hornero-Méndez and others 2007). Recent experiments in our laboratory, have shown that the amount of soluble curcumin released from the solid state increased when powdered curcumin was heated in the presence of an excipient emulsion prior to introduction in a simulated GIT (Zou and others 2015a). The bioavailability of other types of bioactive components may also be enhanced by including specific components in food matrices. For example, the bioavailability of iron from tortillas has been shown to be improved by the addition of disodium EDTA (a food-grade chelating agent), which forms a water-soluble bioavailable complex with iron (NaFeEDTA) (Walter and others 2003).

The inclusion of certain acids, alkalis, minerals, or chelating agents within an excipient food may enhance the release of bioactive agents in pharmaceutical or food matrices by modulating the molecular interactions normally holding the matrix components together. For example, the chelating agent EDTA may bind calcium ions within the GIT and thereby break down calcium alginate or pectate structures. An excipient food may contain constituents that can control the pH of the GIT fluids after food ingestion, such as acids, alkalis, or buffers (Kalantzi and others 2006). For instance, an excipient food containing high protein levels may lead to a lower acidity (higher pH) in the stomach due to the buffering capacity of the protein molecules (Park 1991). An alteration in the pH-time profile of the gastric fluids may change the rate at which certain pharmaceutical or food matrices are broken down and so alter the release of drugs or nutraceuticals. It may also alter the chemical degradation of bioactive agents that are unstable under certain pH conditions, which could also impact bioavailability (see later). Based on this type of knowledge, the composition and structure of excipient foods can be designed to promote the breakdown of pharmaceutical or food structures and thereby facilitate the release of bioactive agents.

Solubilization within intestinal fluids. Once a drug or nutraceutical has been released from a pharmaceutical or food matrix it should be solubilized in the intestinal fluids so it can be transferred to the epithelial cells where it is absorbed. For hydrophilic bioactives, this step should not be limiting because they are normally readily soluble in aqueous solutions (unless they form insoluble complexes – see later). For hydrophobic bioactives, this may be limited because of their inherently low solubility in aqueous solutions. The bioavailability of hydrophobic bioactives may be enhanced considerably when they are consumed with pharmaceutical delivery systems or foods that have high levels of digestible lipids (Charman and others 1997; Porter and others 2007; Williams and others 2013). This effect can be attributed to numerous physicochemical and physiological effects that promote increased solubilization of the hydrophobic bioactives within the intestinal fluids (Varum and others 2013). First, the consumption of relatively high levels of lipids promotes the release of digestive enzymes and bile salts within the gastrointestinal fluids, which increases their solubilization capacity. Second, ingestion of high lipid levels can reduce gastric motility and slow down transit through the GIT, thereby increasing the time available for bioactives to be released, solubilized, and absorbed. Third, ingestion of digestible lipids (such as triacylglycerols) leads to the generation of free fatty acids (FFA) and monoacylglycerols (MAG) in the GIT fluids. These lipid digestion products are incorporated into mixed micelles, thereby increasing the solubilization capacity of the intestinal fluids. The nature of the lipids consumed has a major impact on the solubilization capacity of the mixed micelles formed within the GIT. For example, free fatty acids and monoacylglycerols with different chain lengths and degrees of unsaturation form hydrophobic domains within micelles and vesicles that have different molecular dimensions, and which therefore have different abilities to incorporate hydrophobic bioactives. Fourth, ingestion of surface active substances (such as phospholipids or surfactants) may also enhance the solubilization capacity of the intestinal fluids since they can also be incorporated into mixed micelles (Rozner and others 2010; Rupp and others 2010; Cirin and others 2012; Verrijssen and others 2015). Thus, it may be possible to formulate excipient foods that will increase the solubility of certain bioactive components in the gastrointestinal fluids. For example, an excipient food containing a high level of digestible triacylglycerols could be utilized to enhance the bioaccessibility of highly lipophilic bioactives.

Alteration of interactions. The bioaccessibility of certain pharmaceuticals and nutraceuticals may be either enhanced or limited due to their interactions with other components in the gastrointestinal tract. These components may be secreted by the human body (such as mucin or calcium ions), or they may arise from ingested foods (such as proteins, dietary fibers, minerals, or chelating agents). For example, anionic long-chain FFAs generated by lipid digestion form insoluble complexes with cationic calcium ions in the GIT fluids that have limited bioaccessibility (Devraj and others 2013). Food-grade cationic biopolymers, such as chitosan, can bind anionic bile salts and free fatty acids, and so reduce the amount of any solubilized bioactives available for absorption (Thongngam and others 2005; Helgason and others 2008). It may therefore be possible to include ingredients within excipient foods that can control these interactions so as to enhance the solubility of some bioactives or to prevent the precipitation of others.

Absorption. The composition and structure of an excipient food may alter the absorption of bioactives through a number of mechanisms, and thereby alter their overall bioavailability.

Increase in mucus layer transport. Bioactive components solubilized within the GIT fluids must travel across the mucus layer before they can be adsorbed by the epithelium cells (Cone 2009). The ability of the bioactives to move through the mucus layer depends on the size of the particles they are contained within, and any attractive interactions with molecules within the mucus gel network. It may therefore be possible to increase the bioavailability of certain drugs or nutraceuticals by ensuring that colloidal structures are formed within the intestinal fluids that are able to transport them across the mucus layer. These colloidal particles should be small enough to pass through the pores of the mucus layer (< 400 nm), and should not interact strongly with the gel network. For hydrophilic bioactives, it may be possible to form small molecular complexes with constituents from the excipient food matrix that have these characteristics. For hydrophobic bioactives, this might be achieved using an excipient food matrix that forms small mixed micelles that can easily penetrate through the mucus layer.

Increase in cell membrane permeability. Once a bioactive component has travelled through the mucus layer and reached the apical side of the epithelial cells it may be absorbed due to various passive or active transport mechanisms (Fasinu and others 2011; Dahan and others 2012) (Figure 4). The absorption mechanism(s)

involved depend on the nature of the bioactive molecules, the properties of any colloidal particles or molecular complexes associated with them, the type of epithelium cells (enterocytes or M-cells) involved, and the GIT location where absorption occurs (des Rieux and others 2006; Doherty and others 2009; Ensign and others 2012; Bohdanowicz and others 2013).

Tight junction transport: Small hydrophilic molecules may travel through narrow channels between epithelial cells known as tight junctions (Figure 4). Usually, bioactive molecules must be smaller than a few nanometers to pass through these channels. Nevertheless, certain food components can increase the dimensions of these channels and so enhance absorption through the tight junctions (Maher and others 2008): surfactants such as Tween 80 (Buyukozturk and others 2010; Gupta and others 2013); biopolymers such as chitosan (Pillay and others 2012; Chen and others 2013), mineral ions such as zinc (Wang and others 2013), and chelating agents such as EDTA (Lemmer and others 2013). Incorporation of these components into excipient foods may therefore lead to enhanced absorption of certain types of bioactive molecules.

Passive or Active Membrane Transport – Bioactive agents may also be absorbed by epithelial cells due to passive or active transport mechanisms (Figure 4). Hydrophobic bioactive molecules are often transported across cell membranes by a passive mechanism because of their high solubility in the phospholipid bilayer. When they reach the other side of the cell membrane, they are assembled into vesicle-like structures that move them into the interior of the epithelium cells where they are stored, processed, or transported. Certain kinds of bioactive molecules are transported across the cell membranes by specific or nonspecific protein-transporter systems, which consist of one or more proteins embedded in the phospholipid bilayer (Bohdanowicz and others 2013). There are a number of food molecules that are able to increase the absorption of bioactive components by altering passive or active transport mechanisms, such as piperine (Dudhatra and others 2012), sucrose monoesters (Yamamoto and others 2014), and rhamnolipids (Jiang and others 2013). Incorporation of these types of molecules into excipient foods may therefore be utilized to alter the bioavailability profile of certain drugs and nutraceuticals.

Inhibition of efflux mechanisms. The uptake of certain bioactive agents is reduced because of the presence of efflux transporters embedded in the phospholipid bilayers that pump them out of the epithelial cells (Constantinides and others 2007; Fasinu and others 2011; Planas and others 2012). For instance, P-glycoprotein (P-gp) and multidrug resistant protein (MRP) are able to pump a variety of bioactive agents out of epithelial cells (Constantinides and others 2007; Fasinu and others 2011). Efflux reduces bioavailability by reducing the amount of bioactive absorbed and by increasing the amount that is metabolized. Some food components are capable of blocking efflux transporters, and so of increasing the uptake of bioactive agents, for example, certain surfactants, chelating agents, biopolymers, and phytochemicals (Jia and others 2008; Jin and others 2010; Fasinu and others 2011; Rein and others 2013). Quercetin, resveratrol, and piperine are all common food constituents that have been shown to act as efflux inhibitors for pharmaceutical agents (Choi and others 2009; Kang and others 2009; Jin and others 2010; Chi and others 2012; Challa and others 2013). Efflux inhibitors may operate through three main mechanisms: they block binding sites on efflux protein surfaces; they interfere with the energy production mechanism required for efflux; they change cell membrane structure thereby altering the conformation and activity of efflux proteins (Fasinu and others 2011).

Transformation. Certain food constituents increase bioavailability by interfering with chemical or biochemical transformations of bioactive agents in the GIT (Dudhatra and others 2012). These constituents may operate through numerous mechanisms. Some food constituents are potent antioxidants that inhibit the oxidation of bioactive agents, such as carotenoids and polyunsaturated fatty acids (Tarvainen and others 2012). These include both natural and synthetic constituents that may retard oxidation reactions through free radical scavenging, singlet oxygen quenching, or chelation, for example, carotenoids, tocopherols, flavonoids, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA) (Decker and others 2011). Certain food constituents inhibit metabolic or digestive enzymes, and therefore alter the rate and extent of metabolism or digestion of bioactive components in the GIT (Shimizu 2010; Dudhatra and others 2012). For example, piperine retards the metabolism of drugs and nutraceuticals, such as ibuprofen, curcumin, resveratrol, carotenoids, vitamins, and amino acids (Dudhatra and others 2012). The ability of many of these constituents to inhibit transformations within the GIT is due to their interactions with metabolic enzymes such as cytochrome P450, glucose dehydrogenase, and others (Dudhatra and others 2012). Sugars have been shown to protect polyphenols (EGCG) from chemical degradation in aqueous solutions, which has been attributed to their ability to reduce oxygen solubility, scavenge reactive oxygen species, and chelate transition metal ions (Shpigelman and others 2013).

Other effects. In this section, some additional effects that food constituents may have on the bioavailability of drugs and nutraceuticals is highlighted. The composition and structure of certain food matrices may change GIT motility, such as, gastric emptying or the motility of the stomach and small intestine (Dudhatra and others 2012; Koziolek and others 2013b; Varum and others 2013). For example, the digestion products of ingested lipids (free fatty acids) may interact with receptors lining the GIT and induce hormonal changes that alter gastric emptying or motility (Little and others 2007). In addition, certain types of food hydrocolloids have also been shown to influence gastric emptying and motility (Gidley 2013). The ingestion of a bioactive agent with a food often changes the period it spends in the stomach, because the body needs sufficient time to fully digest and absorb the nutrients from the food (Varum and others 2013). The length of time a bioactive component or food matrix spends in the stomach may be increased due to the presence of phytochemicals that slow down gastric emptying, such as piperine (Bajad and others 2001). The longer a food remains in the stomach, the greater is the time available for breakdown of any matrix structures that normally inhibit the release of the bioactive agents into the intestinal fluids (for example, cell walls in plant tissues or solid drug forms). An increase in gastric emptying time may also increase the amount of chemical or biochemical transformation of a bioactive substance or surrounding matrix within the stomach. In certain circumstances, this process increases the bioavailability of bioactive agents, such as when the transformed form has a higher bioavailability or bioactivity than the original form. Conversely, in other circumstances, this process may actually decrease bioavailability, as in the case when the transformed form has a lower bioavailability or bioactivity than the original form.

Excipient food ingredients

In the United States, excipient foods designed to enhance the bioavailability of drugs and nutraceuticals should be fabricated from generally recognized as safe (GRAS) ingredients approved by the FDA, or by an equivalent organization in other countries. In this section, the potential impact of some of the most important food components that might be used to formulate excipient foods on the oral bioavailability of bioactives is presented. Excipient foods may contain one or more different types of excipient ingredient to enhance the bioavailability of one or more different drugs or nutraceuticals.

Lipids. The most common form of lipids in foods is triacylglycerols, which vary in the type and position of fatty acid molecules on the glycerol backbone (Akoh and others 2008; Belitz and others 2009). The physical, chemical, and nutritional properties of triacylglycerols depend on the chain length and unsaturation of the fatty acids. Thus, there is considerable scope for altering the lipid profile of excipient foods so as to increase the bioavailability of bioactive agents. Numerous studies have shown that bioavailability of hydrophobic drugs (Porter and others 2007; Pouton and others 2008) and nutraceuticals (Tyssandier and others 2001; Failla and others 2007; Failla and others 2008) can be increased by ingesting them along with digestible lipids. The extent of the increase depends on the type, amount, and structural organization of the lipids consumed (Failla and others 2007; Huo and others 2007b; Goltz and others 2012). In general, the ability of lipids to increase bioavailability may be caused by numerous mechanisms, including increasing bioaccessibility, enhancing absorption, and altering transformation.

Studies have shown that the bioaccessibility of carotenoids from tomatoes (Martínez-Huélamo and others 2015) and carrots (Hedren and others 2002) increases when they are consumed with digestible lipids, which may be because a greater fraction of carotenoids are liberated from the plant tissue and because there are more mixed micelles available to solubilize them. Similarly, the bioaccessibility of procyanidins from cocoa has also been shown to increase when they are ingested with digestible lipids (Ortega and others 2009). The bioaccessibility of highly hydrophobic bioactive agents (such as carotenoids or lipophilic drugs) is often greater when they are ingested with long chain triglycerides (LCT) than when they are ingested with short or medium chain triglycerides (SCT or MCT), which has been attributed to differences in the solubilization capacity of the mixed micelle phase formed by lipid digestion products (Porter and others 2007; Qian and others 2012). No definite conclusions can be drawn about the importance of the degree of fatty acid unsaturation on bioaccessibility, since some studies have shown no significant effect, whereas others have reported that bioaccessibility is lower when the bioactive component is ingested along with lipids containing polyunsaturated rather than monounsaturated fatty acids. *In vitro* studies have shown that hydrophobic bioactives dispersed within nondigestible lipids (such as flavor or mineral oils) have relatively low bioaccessibility because some of the bioactives remain trapped within the nondigested lipid droplets and because fewer mixed micelles are formed to solubilize them (Qian and others 2012; Rao and others 2013).

The bioaccessibility of bioactives encapsulated within emulsified lipids also depends on the size, physical state, and interfacial characteristics of the fat droplets (McClements and others 2010; Troncoso and others 2012). The bioaccessibility has been found to increase with decreasing fat droplet size, to be higher for liquid oils than for solid fats, and to be greater for emulsifiers that form droplets that are stable to flocculation and that allow digestive enzymes to interact with their substrates. This information may be important for designing excipient emulsions to improve oral bioavailability profiles.

The bioavailability of drugs or nutraceuticals may also be altered through other physicochemical processes. Some hydrophobic bioactive agents are highly susceptible to chemical degradation or metabolism when they come into contact with aqueous phase components, such as acids, bases, or enzymes. For example, curcumin, is highly susceptible to hydrolysis under neutral and alkaline conditions (Heger and others 2014). Curcumin may therefore be more stable to chemical degradation when it is trapped within the interior of large fat droplets that are digested slowly, than when in small droplets that are rapidly digested. This is because more of the curcumin is protected from degradation when it is present within the hydrophobic interior of the fat droplets away from the gastrointestinal fluids.

The route that hydrophobic bioactive molecules are transported into the systemic circulation may also depend on the nature of the lipids they are ingested with. When hydrophobic bioactives are ingested with lipids containing long-chain fatty acids (such as LCTs) they are packed into chylomicrons in the epithelial cells and then transported to the systemic circulation *via* the lymphatic route (thereby avoiding first-pass metabolism in the liver) (Porter and others 2008; Pouton and others 2008). Conversely, when hydrophobic bioactives are ingested with lipids containing short- or medium-chain fatty acids (such as SCT or MCT) they are transported to the systemic circulation *via* the portal vein (thereby passing through the liver and undergoing first-pass metabolism) (Borel and others 1998; Yanez and others 2011). Thus, bioactive agents assembled into different structures within the epithelial cells may have different metabolic fates, which will alter their bioavailability profiles.

Carbohydrates. Foods contain a diversity of carbohydrates that can be classified according to their biological origin, molecular structure, physicochemical properties, or nutritional roles (Cui 2005). Carbohydrates may be small molecules such as sugars (such as glucose, fructose, and sucrose) or large biopolymers (such as alginate, carrageenan, cellulose, pectin, or starch). They may also be categorized as either digestible or indigestible according to the ability to be hydrolyzed by digestive enzymes in the upper gastrointestinal tract, such as by amylase (Biliaderis and others 2007; BeMiller and others 2008). The most common digestible food polysaccharide is starch (which is actually a mixture of linear amylose and branched amylopectin), while there are numerous kinds of indigestible polysaccharides, such as agar, alginate, carrageenan, cellulose, guar gum, hemicellulose, locust bean gum, pectin, and xanthan gum. Indigestible polysaccharides are part of a group of polymeric materials found in foods known as dietary fibers (Cui 2005; Biliaderis and others 2007). In general, carbohydrates vary in type, number, sequence, and bonding of the monomers they contain, which leads to differences in molecular weights, electrical characteristics, hydrophobicity, branching, flexibility, and conformation.

Carbohydrates may alter the bioavailability of bioactive agents through numerous physicochemical mechanisms. Polysaccharides may thicken or gel gastrointestinal fluids, thereby altering mixing and diffusion processes associated with digestion, release, and absorption, for example the movement of bile salts and enzymes to lipid droplet surfaces, and transfer of mixed micelles to epithelium cells (Pasquier and others 1996; Espinal-Ruiz and others 2014). As a result there also may be changes in gastric motility or emptying

times that could impact bioavailability of bioactive components, for example free fatty acids released due to lipid digestion (Little and others 2007) or dietary fibers (Gidley 2013). Polysaccharides may also alter the flocculation state of lipid droplets within different regions of the GIT, thereby modulating the ability of lipase to interact with the lipid phase (Espinal-Ruiz and others 2014; Zhang and others 2015). As a result, the rates of lipid digestion and bioactive release and solubilization may be altered. A recent study showed that lipid droplets incorporated in starch-based hydrogels had faster lipid digestion and higher β-carotene bioaccessibility than free lipid droplets, which was attributed to the ability of the starch to prevent the lipid droplets from aggregating in the mouth and stomach and thereby increasing the accessibility of the lipase to the lipid phase (Mun and others 2015a). Additionally, the presence of starch may have prevented the proteins from precipitating mixed micelles containing β-carotene in the GIT fluids (Mun and others 2015b).

Polysaccharides may also form impermeable coatings around certain food components (such as lipid droplets) thereby inhibiting their digestion and the subsequent liberation of bioactive agents (McClements and others 2010; Tokle and others 2012). Ionic polysaccharides may bind oppositely charged molecular species, thereby altering their normal function in the digestion process (Espina-Ruiz and others 2014). For instance, cationic polysaccharides (such as chitosan) may bind anionic bile salts, free fatty acids, or phospholipids, whereas anionic polysaccharides (such as alginate) may bind cationic calcium ions (Fave and others 2004; Armand 2008; McClements and others 2009a; Tzoumaki and others 2013). Cationic polysaccharides (chitosan) may also inhibit lipase activity by interacting directly with the enzyme, thereby decreasing the lipid digestion rate (Tsujita and others 2007). Chitosan may also increase the permeability of cell membranes to certain bioactive agents by increasing the dimensions of the tight junctions between epithelium cells (Pillay and others 2012; Chen and others 2013). Dietary fibers are not digested in the upper gastrointestinal tract, and will, therefore, reach the colon largely intact. However, they are digested by enzymes released by colonic microflora, which can alter the metabolism, activity, and absorption characteristics of any bioactive agents in the colon (Fava and others 2006).

Proteins. Proteins are another type of food biopolymer that may vary considerably in biological origin, molecular structure, physicochemical properties, and nutritional effects (Damodaran 2008; Phillips and others 2011). The presence of proteins in food matrices may also alter the oral bioavailability of bioactive agents through various mechanisms. Many proteins and peptides are good antioxidants and can thus inhibit the degradation of bioactives that are susceptible to oxidation in the GIT, such as omega-3 fatty acids and carotenoids (Delgado and others 2011). Proteins have functional groups that are capable of binding certain bioactive components through electrostatic, hydrophobic, or hydrogen bonding (Bordenave and others 2014). These binding interactions may alter the release, solubility, transformation, and absorption of bioactive agents. For example, the binding of anthocyanins to proteins allows them to travel further along the GIT before being absorbed (Ribnicky and others 2014). The digestion of proteins and peptides within the GIT generates hormonal responses that regulate the intake and processing of foods (Depoortere 2014). This may change the intensity or duration of the mechanical forces that a pharmaceutical or food matrix experiences within the GIT, and thereby alter the rate or extent of bioactive release.

Molecular species within the gastrointestinal fluids (such as mixed micelles, phospholipids, and enzymes) may interact with proteins or peptides in the GIT, thereby altering matrix disruption and bioactive release and transport (Singh and others 2009; Maldonado-Valderrama and others 2011; Singh and others 2011; Yu and others 2011). For example, a milk protein (lactoferrin) has been shown to reduce the bioavailability of a highly hydrophobic nutraceutical (β-carotene) (Tokle and others 2013). This effect was attributed to the formation of an insoluble electrostatic complex involving the cationic protein and anionic digestive components (bile salts or free fatty acids). Certain peptides formed during protein digestion may reduce tight junction permeability, thereby decreasing the uptake of bioactives normally absorbed by this mechanism (Shimizu 2010).

Surfactants. Surfactants are amphiphilic molecules that consist of a polar head group attached to a nonpolar tail group. The functional properties of surfactants depend on the characteristics of both the head and tail groups. The head groups may be anionic, nonionic, cationic, or zwitterionic, while the tail groups may vary in the number, size, position, and saturation of the hydrocarbon chains or aromatic rings. Food-grade surfactants may be synthetic or natural molecules, such as small-molecule surfactants and phospholipids (Kralova and others 2009). Alternatively, surface-active species may be generated within the GIT due to digestion of certain food components, for example free fatty acids and monoacylglycerols are produced by digestion of triacylglycerols (McClements and others 2009b). The presence of sufficiently high concentrations of surfactants in the GIT may alter the bioavailability of bioactives through numerous mechanisms. Surfactants may interact with digestive enzymes, such as amylase, lipase, or protease, which may alter their ability to break down pharmaceutical or food matrices (Delorme and others 2011). Surfactants may be incorporated into mixed micelles within the small intestine and enhance their solubilization capacity for lipophilic bioactive agents (Vinarov and others 2012). Surfactants may adsorb to the surfaces of fat droplets thereby inhibiting the adsorption of lipase, which would slow down the rate of lipid digestion (Li and others 2011b; Troncoso and others 2012). Surfactants may be incorporated into the phospholipid bilayers of epithelium cell membranes thereby altering their permeability to bioactive agents (Fernandez-Garcia and others 2008). Surfactants may increase the dimensions of the tight junctions separating epithelium cells, thereby enhancing the permeability of certain bioactives (Aspenstrom-Fagerlund and others 2007; Buyukozturk and others 2010; Shimizu 2010). Consequently, it may be possible to modulate the bioavailability of certain bioactive agents by including suitable types and levels of surfactants in excipient foods, or by adding food components that break down into biologically active surfactants in the GIT. These surfactants would have to have the appropriate biological effect, without adversely affecting the taste or quality of the excipient food.

Minerals. Foods contain numerous types of mineral ions that contribute to their desirable physicochemical properties, stability, and sensory attributes, for example, sodium, potassium, calcium, selenium, and magnesium (McClements and others 2009c). Mineral ions can alter the bioavailability of bioactive agents through numerous mechanisms. Calcium ions can alter lipid digestion in the small intestine due to their ability to form insoluble soaps with long chain fatty acids (LCFAs) (Hu and others 2010; Devraj and others 2013). At low calcium levels, triacylglycerol digestion is inhibited due to the accumulation of LCFAs at the fat droplet surfaces, since the lipid digestion products inhibit the ability of

lipase to access the remaining nondigested lipids (Fave and others 2004; Devraj and others 2013). At sufficiently high levels, calcium ions form insoluble soaps with the LCFAs through electrostatic complexation, which removes them from the fat droplet surfaces and allows the lipase to interact with the remaining lipids (Patton and others 1979; Patton and others 1985; Devraj and others 2013). Calcium increases the rate and extent of triacylglycerol digestion due to this process (Armand and others 1992; Zangenberg and others 2001b; a; Hwang and others 2009). On the other hand, the formation of insoluble calcium-LCFA complexes reduces the solubilization capacity of the mixed micelles, which may decrease the bioavailability of any lipophilic bioactives (Scholz-Ahrens and others 2006; Karupaiah and others 2007; Lorenzen and others 2007; Devraj and others 2013). Calcium may also influence the enzymatic activity of pancreatic lipase due to its ability to act as a co-factor (Whayne and others 1971a, b; Kimura and others 1982; Mukherjee 2003).

Mineral ions may also have a number of other effects in the GIT that may change the bioavailability of bioactive agents. The presence of high levels of salts increases the ionic strength of the gastrointestinal fluids, which may weaken any electrostatic attraction holding together charged molecules in pharmaceutical or food matrices. Mineral ions (especially multivalent ones) promote bridging flocculation of oppositely charged fat droplets (Lesmes and others 2010), which reduces the surface area of fat exposed to lipase. Droplet flocculation has been shown to slow down lipid digestion and to reduce the bioaccessibility of hydrophobic bioactives (Espinal-Ruiz and others 2014). Some mineral ions cross-link oppositely charged biopolymers within the GIT to form gels (for example, cationic calcium ions promote gelation of anionic pectin or alginate molecules), thereby impacting the ability of digestive enzymes to access matrix components (Li and others 2011b; Spyropoulos and others 2011; Zhang and others 2014a). Certain types of mineral ions (such as zinc) increase the permeability of the epithelium cell membranes and thereby enhance absorption of some bioactives (Wang and others 2013). Consequently, it is possible to incorporate specific types and concentration of mineral ions within excipient foods so as to modulate the digestion of food or drug matrices, and thereby control the release of bioactive agents.

Chelating agents. Multivalent metal ions (such as calcium) play an important role in a number of key gastrointestinal functions. Consequently, the presence of metal ion chelating agents in excipient foods may alter their function. For instance, EDTA has been shown to inhibit efflux transporters in epithelium cell membranes, which may enhance the bioavailability of bioactives that are susceptible to cell expulsion by this route (Fasinu and others 2011). Metal ion chelating agents may also interfere with the normal role that calcium ions play in lipid digestion, for example, complexation of LCFAs at fat droplet surfaces (Hu and others 2010). As a consequence the rate and extent of lipid digestion may be altered, which would affect the bioaccessibility of any lipophilic bioactive components. Chelating agents may also modulate the ability of multivalent ions to promote droplet flocculation or biopolymer gelation within the GIT, which could affect bioavailability. The incorporation of chelating agents into excipient foods may therefore be used to regulate gastrointestinal processes that rely on multivalent ions, thereby controlling the bioavailability characteristics of certain bioactives.

Phytochemicals. Phytochemicals isolated from plants may also be used to increase the bioavailability of some bioactives. For instance, certain polyphenols interact with absorption and efflux transporters in epithelium cell membranes (quercetin, curcumin, piperine, and some catechins), which impacts the uptake of bioactive agents in the cells (Ranheim and others 1994; Zhou and others 2004; Lohner and others 2007; Martel and others 2010). Certain phytochemicals inhibit chemical (lipid oxidation) or biochemical (digestion or metabolism) transformations within the GIT (Shimizu 2010; Dudhatra and others 2012). For example, piperine has been shown to increase the bioavailability of curcumin by inhibiting metabolic enzymes in the GIT (Dudhatra and others 2012), whereas quercetin has antioxidant properties that may inhibit chemical degradation of polyunsaturated components in the GIT (Lesser and others 2006).

Alcohols. Studies in the pharmaceutical area have shown that alcohols (such as ethanol) may appreciably increase the bioavailability of lipophilic drugs (Fagerberg and others 2015). Thus, ingestion of drug preparations with alcoholic beverages can have an adverse impact on their pharmokinetic profiles due to "dose dumping". In principle, it is possible to utilize these effects to modulate the bioaccessibility of nutraceuticals in certain types of foods by co-ingesting them with alcohol-containing excipient beverages or foods. Having said this, this approach is unlikely to be an appropriate method of delivering health-promoting bioactive agents due to the health concerns associated with overconsumption of alcohol.

Excipient Emulsions

In principle, a wide range of different types of products could be used as a basis for forming excipient foods, including soft drinks, dairy beverages, yogurts, creams, desserts, spreads, dressings, baked goods, snack bars, candies, and so on. Each type of product would have to be carefully formulated to increase the bioavailability of one or more bioactive agent, as well as to have desirable physicochemical and sensory properties, such as shelf-life, appearance, texture, flavor, and convenience. In this section, we focus on one category of product that may be particularly suitable for widespread application as an excipient food: oil-in-water emulsions. This type of excipient emulsion can easily be formulated using food-grade ingredients and processing operations, and have applications in a broad range of food products such as beverages, yogurts, dressings, spreads, sauces, dips, and desserts. Emulsions can be used as both integrated and nonintegrated excipient foods, that is the bioactive agent can be incorporated into them, or they can be ingested with pharmaceutical preparations or nutraceutical-rich foods. Examples of some applications of excipient emulsions to improve bioavailability of nutraceuticals are shown in Table 3.

Composition and structure

Oil-in-water emulsions consist of small oil droplets dispersed within a water phase, with each oil droplet being coated by a thin layer of emulsifier (Figure 5) (Dickinson 1992; Friberg and others 2004; McClements 2015). The number, size, composition, and physical state of the oil droplets can be controlled, as well as the nature of the emulsifier used to coat them. Numerous constituents can be incorporated within the oil phase to control its properties, including digestible oils (triacylglycerols), indigestible oils (flavor, essential, and mineral oils), colors, antioxidants, phytochemicals, vitamins, nutraceuticals, and drugs. Various components may also be incorporated into the water phase to control its properties, including water, acids, bases, salts, carbohydrates, proteins, surfactants, chelating agents, and phytochemicals. The properties of the oil droplets can also be controlled using different types of emulsifier to coat them, such as small molecule surfactants, phospholipids, proteins, polysaccharides, and fine particles (Figure 5). The types

Table 3–Overview of representative studies showing the influence of excipient emulsions on nutraceuticals bioaccessibility

Emulsion	Nutraceuticals	Observations	Reference
Corn oil emulsions	Curcumin in powdered form	The solubility and bioaccessibility of curcumin was significantly improved by incubating and co-ingesting with excipient emulsion.	(Zou and others 2015a)
Corn oil emulsions	Curcumin in powdered form	Emulsifier type and droplet size exhibited a significant effect on the solubility and bioaccessibility of curcumin.	(Zou and others 2015b)
Corn oil emulsions	Curcumin in powdered form	The bioaccessibility of curcumin depended on oil type and concentration.	(Ahmed and others 2012)
Olive oil emulsions	Carotenoids in carrot and tomato suspensions	Adding olive emulsions to carrot and tomato suspensions increased carotenoid uptake in the mixed micelle phase.	(Moelants and others 2012)
Peanut oil emulsions	Carotenoids in tomato juice	Lycopene bioaccessibility was dependent on emulsification and emulsifier type	(Degrou and others 2013)
Various emulsions	Carotenoids in vegetables and salads	Addition of oil to salads and vegetables increased lycopene bioaccessibility depending on fatty acid type	(Huo and others 2007); (Nagao and others 2013)

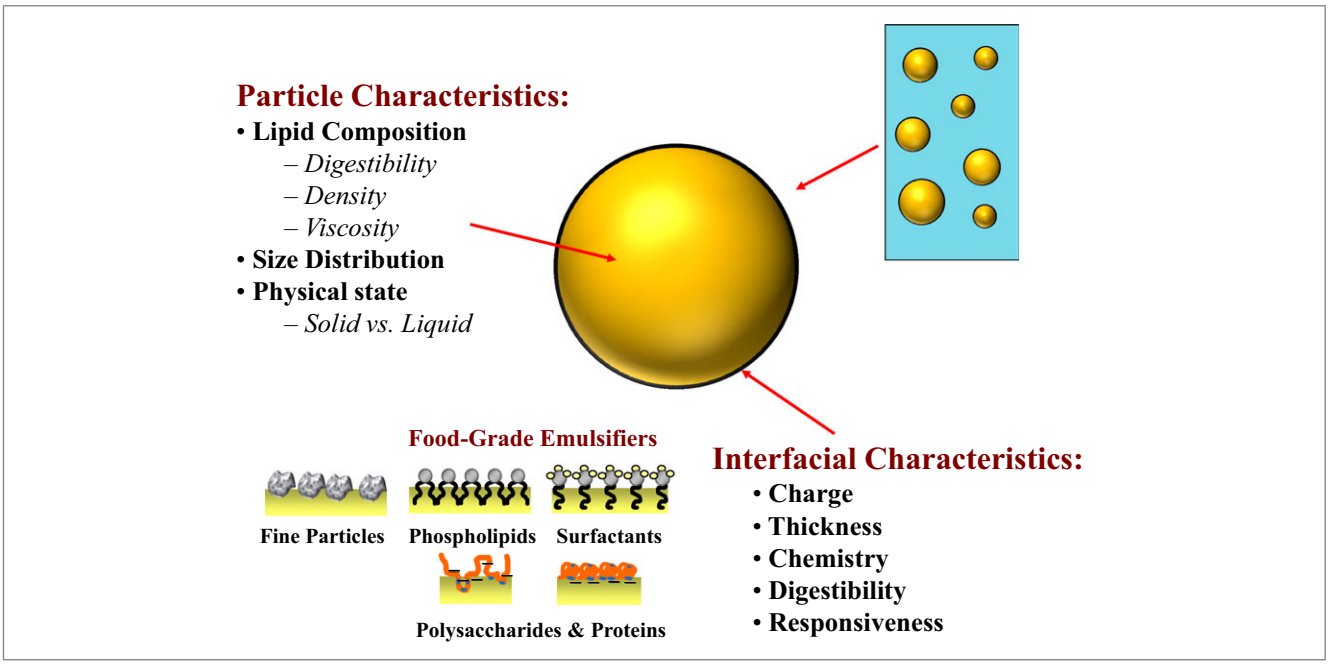

Figure 5–The properties of excipient emulsions can be controlled by altering droplet concentration, composition, size, and physical state, as well as interfacial properties. A variety of emulsifiers are available that vary in their efficacy at forming and stabilizing emulsions, as well as their influence on GIT fate.

of ingredients used to fabricate emulsions influences their formation, stability, physicochemical properties, sensory attributes, and gastrointestinal fate. Consequently, there is considerable scope to design excipient emulsions with different properties by varying the types and concentrations of ingredients used to formulate them.

Emulsions with different particle size distributions are produced by varying the processing methods and ingredients used to fabricate them (McClements 2011; McClements and others 2011). Emulsions are often classified into two broad categories based on their particle size: nanoemulsions ($r < 100$ nm) and conventional emulsions ($r > 100$ nm) (McClements and others 2011). A number of studies have shown that nanoemulsions are more effective at increasing the bioaccessibility of lipophilic bioactive agents than emulsions (see later). The thickness of the interfacial layer can be varied using different types of emulsifiers to stabilize the emulsions. Interfacial layer thickness typically decreases in the following order for different classes of emulsifier: fine particles > polysaccharides > proteins > phospholipids ≈ surfactants (Dickinson 1992). The thickness of the interfacial layer can also be increased by depositing polymers or particles onto the surfaces of the droplets after emulsion formation, for example, by electrostatic deposition. The electrical characteristics of the interfacial layer can be manipulated by choosing emulsifiers with different charges: cationic, neutral, anionic, or zwitterionic. Studies have shown that the gastrointestinal fate of emulsions depends on the size, morphology and charge of the particles they contain, as well as the nature of the emulsifier used to coat the lipid droplets (McClements and others 2010). Consequently, there is considerable scope for manipulating these characteristics to produce excipient emulsions suitable for boosting the bioavailability of certain bioactive agents.

Formation

Emulsions and nanoemulsions can be formed using a range of different fabrication methods, which are typically classified as either high- or low-energy methods (McClements 2015).

High-energy methods. These methods utilize specially-designed mechanical machines known as homogenizers to generate powerful disruptive forces that break up fat droplets and intermingle the oil and water phases. Oil-in-water emulsions are typically fabricated by homogenizing the oil and water phases together in the presence of a water-soluble emulsifier. Numerous homogenizers have been developed to fabricate emulsions, such

as high shear mixers, high pressure homogenizers, microfluidizers, colloid mills, sonicators, and membrane homogenizers (Walstra 1993; 2003; McClements 2015). The selection of a particular homogenizer type and establishment of its optimum operating conditions depend on a number of factors, such as the properties of the materials being homogenized, the desired through put, and the required final emulsion properties. Microfluidizers are often the most effective mechanical homogenizers for producing fine emulsions, and droplet size can typically be reduced by increasing homogenizer pressure, increasing the number of passes, decreasing interfacial tension, and optimizing the oil-water viscosity ratio (Qian and others 2011).

Low-energy methods. These homogenization methods rely on spontaneous formation of oil droplets in certain surfactant-oil-water mixtures when either their composition or environment is changed in a certain way (Anton and others 2009; McClements and others 2011; Solans and others 2012). A variety of low-energy methods have been developed to fabricate emulsions or nanoemulsions:

- Spontaneous emulsification: These methods simply rely on the titration of an oil phase (containing a mixture of oil and hydrophilic surfactant) into a water phase with continuous stirring (Saberi and others 2013). Fine oil droplets are spontaneously produced at the oil-water interface as the hydrophilic surfactant moves from the oil to the water phase.
- Emulsion inversion point methods: These methods rely on the titration of water into an oil phase (containing a mixture of oil and water-soluble surfactant) with continuous stirring. In other words, they are the opposite of spontaneous emulsification methods. The surfactant-oil-water mixtures undergo a series of structural changes as increasing amounts of water are added to the system: W/O → O/W/O → O/W emulsion.
- Phase inversion temperature methods: These methods rely on heating a surfactant-oil-water system slightly above its phase inversion temperature (PIT) and then rapidly cooling with continuous stirring (Anton and others 2009). Fine oil droplets are formed at the oil-water interface due to the low interfacial tension and the movement of surfactant molecules from the oil to water phases during cooling (Anton and others 2009).

Excipient emulsions can be fabricated by either high- or low-energy methods using food-grade ingredients, although there are advantages and limitations for each method. High-energy methods require sophisticated equipment (homogenizers) and have higher operating costs, however, there is much more flexibility in the type of ingredients that can be used to form them. Low-energy methods are very simple to use and do not require any sophisticated equipment, but they are currently only suitable for homogenizing certain types of oils and synthetic surfactants. In addition, the amount of surfactant required to form an emulsion is typically much higher for low-energy methods than for high-energy ones. In some cases, it is possible to fabricate emulsions from all-natural ingredients, which is advantageous for many types of food and beverage products.

The ability to produce emulsions using a variety of different homogenization methods means there is considerable flexibility in creating excipient emulsions with different compositions and structures.

Physicochemical properties

Encapsulation properties. Oil-in-water emulsions are suitable for encapsulating a broad range of bioactive components and excipient ingredients because they have a nonpolar region (the oil droplets), a polar region (the surrounding aqueous phase), and an amphiphilic region (the interfacial layer) (McClements and others 2010). Hydrophobic bioactives and any excipient ingredients are usually dissolved within the oil phase before homogenization, while hydrophilic ones can be added to the water phase either before or after homogenization. For crystalline bioactives or excipient ingredients, it is usually necessary to ensure that they are fully dissolved in the system before emulsion formation, for example, by ensuring they are present below the saturation concentration or by melting them (McClements 2012). For chemically unstable bioactives or excipient ingredients, it is often necessary to control emulsion formation conditions to avoid factors that accelerate their degradation, such as elevated temperatures, oxygen, light, or transition metals (McClements and others 2000; Waraho and others 2011). The chemical stability of any encapsulated ingredients may be improved by altering the structural organization of the emulsion, such as by manipulating interfacial properties or by controlling the location of different reactive species (Coupland and others 1996; McClements and others 2000).

Rheology. Oil-in-water emulsions can be fabricated with a range of different rheological characteristics by controlling their compositions and structures, for example, low viscosity fluids, viscous fluids, semi-solids, and solids (McClements 2015). Thus, they can be prepared with a texture that is most suitable for the particular type of food product that is going to be used as the excipient food (Genovese and others 2007). Typically, the viscosity of oil-in-water emulsions can be increased by increasing the oil droplet concentration, adding thickening agents, or promoting droplet flocculation. In addition, emulsions can either be utilized in a wet form or they can be converted into powders to facilitate their transport, reduce storage costs, and improve their utilization (Soottitantawat and others 2003; Desai and others 2005; Klinkesorn and others 2005; Vega and others 2006).

Optical properties. The appearance of oil-in-water emulsions may vary appreciably depending on their composition and structure (McClements 2015). The turbidity or opacity of emulsions is mainly determined by the scattering of light by the oil droplets. The opacity typically increases with increasing droplet concentration and refractive index contrast, and has a maximum value when the droplet dimensions are approximately equal to the wavelength of light. The color of emulsions is mainly determined by the presence of chromophores that absorb light at selective wavelengths, but is also affected by light scattering by emulsion droplets. The color intensity typically increases as the concentration of dye increases, and as the droplet concentration decreases.

Stability. An excipient emulsion must be designed to remain stable within a product prior to ingestion, but to break down in a particular way in the gastrointestinal tract after ingestion. The stability of emulsions is determined by many different factors, including the physicochemical properties of the oil and water phases, the properties of the oil-water interface, and the nature of the emulsifier at the interface (McClements 2015). Emulsions are thermodynamically stable systems that may break down through a number of different physicochemical mechanisms, including creaming, flocculation, coalescence, Ostwald ripening, and oiling-off (Figure 6). In addition, they may be chemically unstable if some of the components undergo chemical degradation during storage, such as oxidation of polyunsaturated lipids (McClements and others 2000; Waraho and others 2011). Finally, they may become biochemically unstable within the gastrointestinal tract due to the digestion of key components (such as the oil phase or emulsifier)

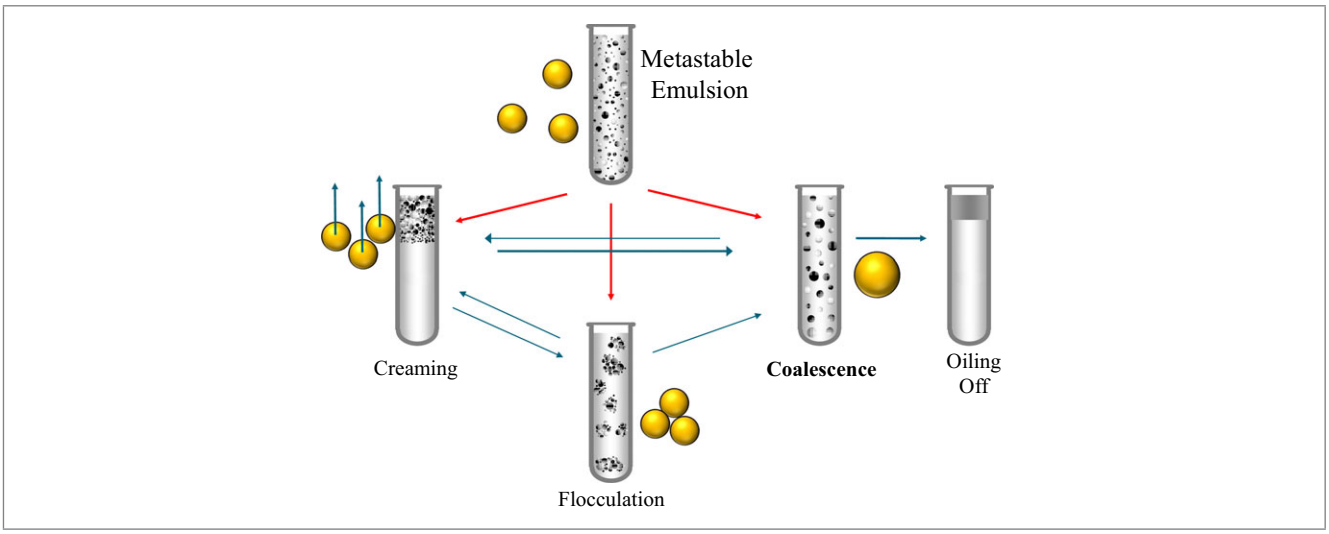

Figure 6–Excipient emulsions may become physically unstable through a variety of physicochemical mechanisms, including gravitational separation (creaming), flocculation, coalescence, and oiling off.

by digestive enzymes. Each of these destabilization mechanisms must be carefully controlled to produce an excipient emulsion that has the required physical properties, sensory attributes, shelf-life, and gastrointestinal function.

There are limitations to using conventional emulsions as delivery systems for nutraceuticals or pharmaceuticals for certain applications, which means that more sophisticated systems are needed (McClements and others 2010). Conventional emulsions are often prone to physical instability when exposed to environmental stresses, such as heating, chilling, freezing, drying, pH extremes, and high mineral concentrations. In addition, one often has limited control over the ability to protect and control the release of functional components, because the small size of the droplets ($\sim \mu$m) and the interfacial layers ($\sim$ nm) means that the time-scales for molecular diffusion of substances out of emulsion droplets is extremely short (McClements 2005). Finally, there are a limited number of emulsifiers that can be used to form the interfacial layers that surround the oil droplets, which limits one's ability to create delivery systems exhibiting a wide range of protection and release characteristics. Consequently, there are continuing attempts to identify novel emulsifiers or for developing new approaches to utilizing existing emulsifiers more effectively to facilitate emulsion formation and improve emulsion stability (Benichou and others 2002; Dickinson 2003; Drusch and others 2006; Drusch 2007; Dickinson 2011).

Ability to increase bioavailability

The ability of oil-in-water emulsions to act as both integrated and nonintegrated excipient foods has been demonstrated in a number of studies using pharmaceuticals and nutraceuticals (Tables 2 and 3).

Integrated excipient emulsions. Numerous studies have shown that hydrophobic bioactives can be encapsulated within oil-in-water emulsions or nanoemulsions, including omega-3 fatty acids (Jiménez-Martín and others 2015), curcumin (Sari and others 2015), lycopene (Tyssandier and others 2001; Ribeiro and others 2006), astaxanthin (Ribeiro and others 2005; Ribeiro and others 2006), lutein (Losso and others 2005; Santipanichwong and others 2007), β-carotene (Santipanichwong and others 2007), plant sterols (Sharma 2005), conjugated linoleic acids (Jimenez and others 2004), and lipid-soluble vitamins (Ziani and others 2012; Saberi and others 2013; Yang and others 2013).

A number of *in vitro* and *in vivo* studies have shown that the bioavailability of encapsulated lipophilic components may be increased when they are incorporated into emulsion-based delivery systems, with the extent of the effect depending on particle size, concentration, composition, and interfacial characteristics (Pinheiro and others 2013; Rao and others 2013; Salvia-Trujillo and others 2013a; Speranza and others 2013). For example, studies have shown that oil type plays an important role in determining the bioavailability of carotenoids (Qian and others 2012; Salvia-Trujillo and others 2013b). Typically, long-chain triglycerides (LCT) give a higher bioaccessibility than short- or medium-chain triglycerides (SCT or MCT) because they form a mixed micelle phase with a high solubilization capacity for these highly hydrophobic bioactives. The long fatty acid chains form hydrophobic regions within the mixed micelle phase that are large enough to accommodate large hydrophobic molecules (Figure 7). An example of this effect is shown in some recent experiments in our laboratory (Figure 8), which show the influence of carrier oil composition on the bioaccessibility of encapsulated carotenoids measured using an *in vitro* GIT model: bioaccessibility increases as the ratio of long-to-medium chain triglycerides increases (Salvia-Trujillo and others 2013b). Emulsions prepared from digestible oils have been reported to give a higher bioaccessibility than those prepared from indigestible oils for a similar reason (Qian and others 2012). These types of integrated excipient emulsions may therefore be suitable for increasing the bioavailability of hydrophobic bioactives, such as BCS Class II pharmaceuticals or NuBACS Class B(-)$_S$ nutraceuticals. To date most of the previous studies using emulsions have focused on increasing the bioavailability of lipophilic bioactive components by enhancing their bioaccessibility within the GIT fluids by increasing the solubilization capacity of the mixed micelle phase. There is certainly a need for further studies on the impact of emulsion-based delivery systems on other mechanisms, such as absorption (passive and active) and transformation (chemical and biochemical).

Nonintegrated excipient emulsions. The creation of nonintegrated excipient emulsions that are co-ingested with pharmaceuticals or with nutraceutical-rich foods is a more recent development (McClements and others 2014). Nevertheless, some

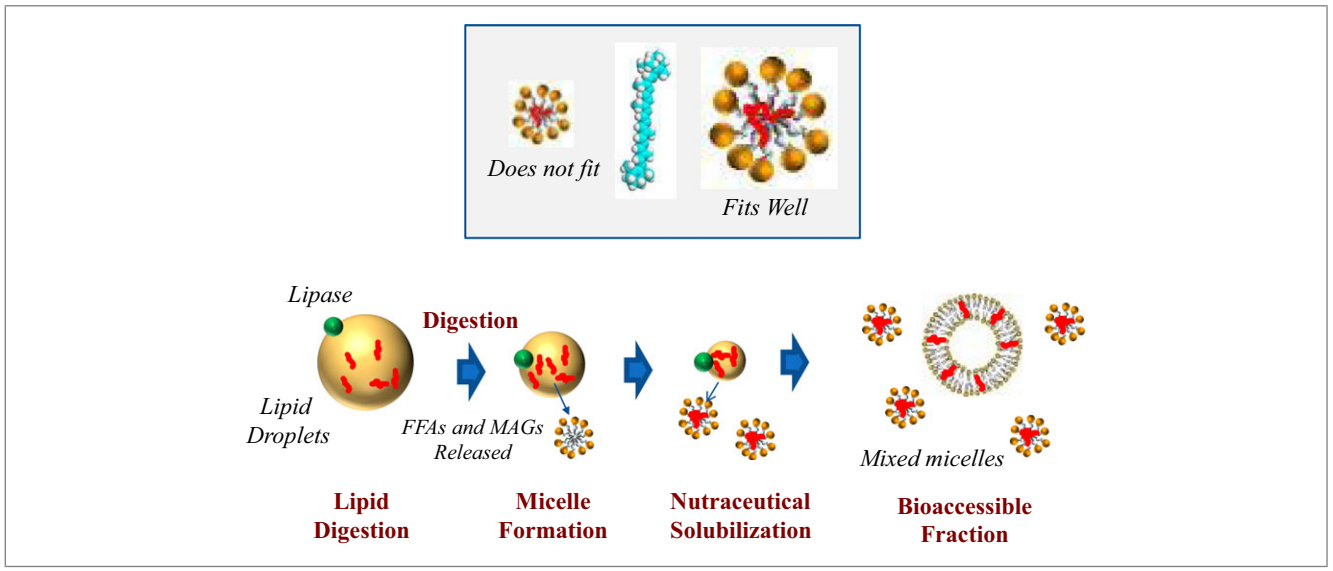

Figure 7–The bioaccessibility of large hydrophobic nutraceuticals (such as carotenoids) may be limited when they are too large to fit into the hydrophobic domains of mixed micelles.

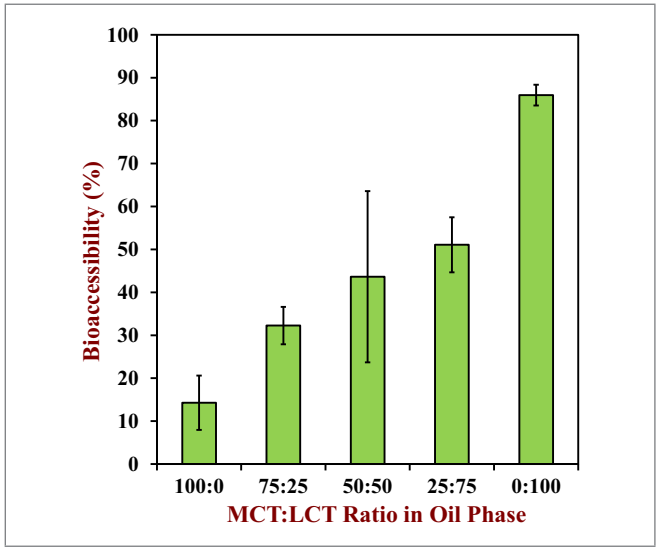

Figure 8–Effect of medium chain triglyceride (MCT) to long chain triglyceride (LCT) ratio on the bioaccessibility (%) of β-carotene incorporated in oil-in-water nanoemulsions containing 1% total oil phase measured using a simulated small intestine model (pH stat). Data from Salvia-Trujillo (2013).

studies have already shown that this type of excipient emulsion may also be able to increase the bioavailability of certain drugs and nutraceuticals.

The *in vitro* bioaccessibility of curcumin has been shown to be significantly improved by co-ingesting powdered curcumin with an excipient emulsion, with the extent of the enhancement depending on droplet size and emulsifier type (Zou and others 2015a; Zou and others 2015b). It was postulated that the presence of the lipid droplets increased curcumin bioaccessibility by increasing the solubilization capacity of the mixed micelle phase formed in the GIT tract after lipid digestion. This study suggested that smaller lipid droplets were more effective at increasing curcumin bioaccessibility due to their faster and more complete digestion, whereas larger lipid droplets were more effective at increasing curcumin stability to chemical transformation because the curcumin was more isolated from the surrounding aqueous phase. Consequently, there may be an optimum particle size required to provide the best overall bioavailability. Additionally, other components within excipient emulsions may also contribute to the overall bioavailability of curcumin. For example, the interaction of curcumin with proteins such as β-lactoglobulin (Sneharani and others 2010), soy protein (Tapal and others 2012) or caseinate (Pan and others 2013) may improve its solubility and chemical stability under GIT conditions. Curcumin bioavailability has also been shown to depend on the type and concentration of oil used to form excipient emulsions, which can again be attributed to differences in solubilization and chemical transformation (Ahmed and others 2012).

The bioavailability of other highly lipophilic bioactive molecules has also been shown to be enhanced when they are co-ingested with excipient emulsions. For example, recent studies in our laboratory have shown that increasing the fat content of excipient emulsions co-ingested with cooked carrots increases the bioaccessibility of the carotenoids from the plant tissue (Figure 9). In addition, further studies in our laboratory using carrots have shown that the bioaccessibility of carotenoids is much higher when the excipient emulsion contains LCT than MCT (data not shown). The bioaccessibility of carotenoids in carrots and tomatoes has also been shown to be increased when they are mixed with olive oil emulsions prior to digestion, which was mainly attributed to enhanced solubilization in mixed micelles (Moelants and others 2012a). Studies suggest that the movement of carotenoids from fruit or vegetable matrices into gastrointestinal fluids is often a limiting step in determining their overall bioavailability (Degrou and others 2013). The presence of small lipid droplets in excipient emulsions may facilitate this transfer process, but this depends on the nature of the emulsifier used and how it interacts with the bioactive molecules (Degrou and others 2013). The properties of the oil phase within an excipient food would also be expected to influence carotenoid bioaccessibility by altering the solubilization capacity of the mixed micelle phase (Lemmens and others 2014). Some studies have reported no significant effect of the degree of unsaturation of the oil phase on carotenoid bioaccessibility (Huo and others 2007a), whereas others have reported that polyunsaturated fatty acids resulted in significantly lower carotenoid

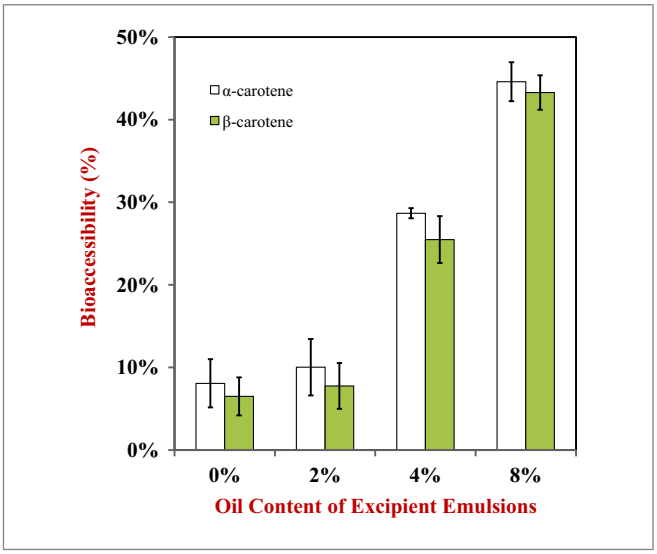

Figure 9–Effect of fat content of excipient emulsions on the bioaccessibility (%) of carotenoids in boiled carrots measured using simulated GIT model.

bioaccessibility than monounsaturated fatty acids (Nagao and others 2013).

It should be noted that milk may be considered to be a natural excipient emulsion, which consists of lipid droplets, proteins, carbohydrates, and minerals dispersed within an aqueous medium. However, milk has been shown to both increase and decrease the bioavailability of bioactive components in foods and therefore it might not be suitable for certain applications. Studies have shown that skimmed milk decreased the total antioxidant capacity of tea infusion more than either whole or semi-skimmed milk, which suggests that the fat droplets may have had a protective role (Ryan and others 2010). Co-ingestion of green tea extract with milk led to a higher intestinal permeability of catechins (Caco-2 model) than green tea extract without milk (Xie and others 2013). The addition of milk to blended fruit juice improved the bioaccessibility of lipophilic nutraceuticals, but reduced the bioaccessibility of hydrophilic ones (Rodríguez-Roque and others 2014). The bioavailability of hydrophilic bioactives (caffeic acid) in blueberries was also reduced when co-ingested with milk (Serafini and others 2009). The bioaccessibility of chlorogenic acids in coffee has been shown to be positively correlated with the fat content of milk, but not with the protein, carbohydrate, or calcium contents (Tagliazucchi and others 2012). It has also been reported that milk significantly lowers the excretion of urinary flavan-3-ol metabolites (Mullen and others 2009). Most studies have attributed the inhibitory effect of milk on the bioavailability or bioactivity of nutraceuticals to the presence of the milk proteins, because phenolic compounds can bind to milk proteins through hydrogen bonds and hydrophobic interactions (Zhang and others 2014a). Overall, these studies highlight the importance of carefully designing excipient emulsions so that they increase the bioavailability of both hydrophilic and hydrophobic bioactives.

Conclusions

Excipient foods are specifically designed to increase the oral bioavailability of bioactive agents such as pharmaceuticals or nutraceuticals. The bioactive agent may be incorporated into the excipient food matrix (integrated), or it may be consumed with a separate excipient food (nonintegrated). Excipient foods may have no inherent bioactivity themselves, but they are fabricated to have compositions and structures that promote the bioactivity of other components consumed with them. The fabrication of successful excipient foods, therefore, depends on understanding the impact of particular food components and structures on the bioavailability of particular bioactives. Numerous strategies can be utilized to increase oral bioavailability depending on the nature of the bioactive agent, such as enhancing the bioaccessibility and absorption of bioactive agents, while controlling their chemical or metabolic transformation within the GIT.

The creation of excipient foods may be beneficial to both the pharmaceutical and food industries. In the pharmaceutical industry, manufacturers could design excipient foods that are meant to be consumed with drug preparations so as to control their bioavailability profiles. In the food industry, manufacturers could create excipient foods that boost the uptake of beneficial nutraceuticals in natural or processed fruits or vegetables. However, more research is required to understand the role of specific excipient food ingredients on the bioavailability of particular bioactive agents, and to understand the influence of ingredient interactions on bioavailability when excipient foods are consumed as part of a complex diet containing many different components. In addition, it will be important to ensure that excipient foods do not have any adverse effects on human health, such as boosting the bioavailability or bioactivity of toxins in the diet.

Acknowledgments

This material was partly based upon work supported by the Cooperative State Research, Extension, Education Service, USDA, Massachusetts Agricultural Experiment Station (Project No. 831) and USDA, NRI Grants (2011-03539, 2013–03795, 2011–67021, and 2014–67021). This project was also partly funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant numbers 330-130-1435-DSR, 299-130-1435-DSR, 87-130-35-HiCi. The authors, therefore, acknowledge with thanks DSR technical and financial support.

References

Actis-Goretta L, Leveques A, Rein M, Teml A, Schafer C, Hofmann U, Li HQ, Schwab M, Eichelbaum M, Williamson G. 2013. Intestinal absorption, metabolism, and excretion of (-)-epicatechin in healthy humans assessed by using an intestinal perfusion technique. Am J Clin Nutr 98:924–33.

Ahmed K, Li Y, McClements DJ, Xiao H. 2012. Nanoemulsion- and emulsion-based delivery systems for curcumin: encapsulation and release properties. Food Chem 132:799–807.

Akoh CC, Min DB. 2008. Food lipids: chemistry, nutrition, and biotechnology. 3rd ed. Boca Raton, Fla.: CRC Press.

Anton N, Vandamme TF. 2009. The universality of low-energy nano-emulsification. Intl J Pharm 377:142–47.

Armand M. 2008. Milk fat digestibility. Sci Des Alim 28:84–98.

Armand M, Borel P, Ythier P, Dutot G, Melin C, Senft M, Lafont H, Lairon D. 1992. Effects of droplet size, triacylglycerol composition, and calcium on the hydrolysis of complex emulsions by pancreatic lipase—an in vitro study. J Nutr Biochem 3:333–41.

Arnott JA, Planey SL. 2012. The influence of lipophilicity in drug discovery and design. Expert Opin Drug Discov 7:863–75.

Aspenstrom-Fagerlund B, Ring L, Aspenstrom P, Tallkvist J, Ilback NG, Glynn AW. 2007. Oleic acid and docosahexaenoic acid cause an increase in the paracellular absorption of hydrophilic compounds in an experimental model of human absorptive enterocytes. Toxicology 237:12–23.

Bajad S, Bedi KL, Singla AK, Johri RK. 2001. Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice. Planta Med 67:176–79.

Belitz HD, Grosch W, Schieberle P. 2009. Food chemistry. 4th ed. Berlin , Germany: Springer.

BeMiller JN, Huber KC. 2008. Carbohydrates. In: Damodaran S., Parkin K. L. and Fennema O. R. editors. Food chemistry. 4th ed. Bocan Raton, Fla.: CRC Press. p 83–154.

Benichou A, Aserin A, Garti N. 2002. Protein-polysaccharide interactions for stabilization of food emulsions. J Disper Sci Technol 23:93–123.

Bigliardi B, Galati F. 2013. Innovation trends in the food industry: the case of functional foods. Trends Food Sci Technol 31:118–29.

Biliaderis CG, Izydorczyk MS. 2007. Functional food carbohydrates. 1st ed. Bocan Raton, Fla.: CRC Press.

Bohdanowicz M, Grinstein S. 2013. Role of phospholipids in endocytosis, phagocytosis, and macropinocytosis. Physiol Rev 93:69–106.

Bordenave N, Hamaker BR, Ferruzzi MG. 2014. Nature and consequences of non-covalent interactions between flavonoids and macronutrients in foods. Food Funct 5:18–34.

Borel P, Tyssandier V, Mekki N, Grolier P, Rochette Y, Alexandre-Gouabau MC, Lairon D, Azais-Braesco V. 1998. Chylomicron beta-carotene and retinyl palmitate responses are dramatically diminished when men ingest beta-carotene with medium-chain rather than long-chain triglycerides. J Nutr 128:1361–67.

Bosscher D, Breynaert A, Pieters L, Hermans N. 2009. Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects. J Physiol Pharmacol 60:5–11.

Boyer JL. 2013. Bile formation and secretion. Comprehen Physiol 3:1035–78.

Brown MJ, Ferruzzi MG, Nguyen ML, Cooper DA, Eldridge AL, Schwartz SJ, White WS. 2004. Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressings as measured with electrochemical detection. Am J Clin Nutr 80:396–403.

Buyukozturk F, Benneyan JC, Carrier RL. 2010. Impact of emulsion-based drug delivery systems on intestinal permeability and drug release kinetics. J Controlld Release 142:22–30.

Camp KM, Lloyd-Puryear MA, Huntington KL. 2012. Nutritional treatment for inborn errors of metabolism: indications, regulations, and availability of medical foods and dietary supplements using phenylketonuria as an example. Mol Genet Metabol 107:3–9.

Carail M, Goupy P, Reynaud E, Dangles O, Caris-Veyrat C. 2013. Oxidative cleavage products of lycopene: production and reactivity in a biomimetic experimental model of oxidative stress. In: Winterhalter P. and Ebeler S. E. editors. Carotenoid cleavage products. Washington: Amer Chemical Soc. p 191–205.

Challa VR, Babu PR, Challa SR, Johnson B, Maheswari C. 2013. Pharmacokinetic interaction study between quercetin and valsartan in rats and in vitro models. Drug Dev Ind Pharm 39:865–72.

Charman WN, Porter CJH, Mithani S, Dressman JB. 1997. Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharmaceut Sci 86:269–82.

Chen MC, Mi FL, Liao ZX, Hsiao CW, Sonaje K, Chung MF, Hsu LW, Sung HW. 2013. Recent advances in chitosan-based nanoparticles for oral delivery of macromolecules. Adv Drug Deliv Rev 65:865–79.

Chi YC, Lin SP, Hou YC. 2012. A new herb-drug interaction of Polygonum cuspidatum, a resveratrol-rich nutraceutical, with carbamazepine in rats. Toxicol Appl Pharmacol 263:315–22.

Choi JS, Choi BC, Kang KW. 2009. Effect of resveratrol on the pharmacokinetics of oral and intravenous nicardipine in rats: possible role of P-glycoprotein inhibition by resveratrol. Pharmazie 64:49–52.

Cirin DM, Posa MM, Krstonosic VS. 2012. Interactions between sodium cholate or sodium deoxycholate and nonionic surfactant (tween 20 or tween 60) in aqueous solution. Ind Eng Chem Res 51:3670–76.

Cone RA. 2009. Barrier properties of mucus. Adv Drug Deliv Rev 61:75–85.

Constantinides PP, Wasan KM. 2007. Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein (P-gp) substrate drugs: in vitro/in vivo case studies. J Pharmaceut Sci 96:235–48.

Coupland JN, McClements DJ. 1996. Lipid oxidation in food emulsions. Trends Food Sci Technol 7:83–91.

Covasa M. 2010. Deficits in gastrointestinal responses controlling food intake and body weight. Am J Physiol-Regul Integr Comp Physiol 299:R1423–R39.

Crowe KM, Francis C. 2013. Position of the academy of nutrition and dietetics: functional foods. J Acad Nutr Dietet 113:1096–103.

Cui SW. 2005. Food carbohydrates: chemistry, physical properties and applications. Boca Raton, Fla.: Taylor and Francis.

D'Ambrosio DN, Clugston RD, Blaner WS. 2011. Vitamin A metabolism: an update. Nutrients 3:63–103.

Dahan A, Miller JM. 2012. The Solubility-permeability interplay and its implications in formulation design and development for poorly soluble drugs. AAPS J 14:244–51.

Damodaran S. 2008. Amino acids, peptides and proteins. In: Damodaran S., Parkin K. L. and Fennema O. R. editors. Food chemistry. 4rth ed. Bocan Raton, Fla.: CRC Press. p 217–330.

Decker EA, Chen B, Panya A, Elias RJ. 2011. Understanding antioxidant mechanisms in preventing oxidation in foods. In: Decker E. A., Elias R. J. and McClements D. J. editors. Oxidation in foods and beverages and antioxidant applications. Vol 1: Understanding mechanisms of oxidation and antioxidant activity. Woodhead Publishing, Cambridge, UK. p 225–48.

Degrou A, Georgé S, Renard CMGC, Page D. 2013. Physicochemical parameters that influence carotenoids bioaccessibility from a tomato juice. Food Chem 136:435–41.

Delgado MCO, Tironi VA, Anon MC. 2011. Antioxidant activity of amaranth protein or their hydrolysates under simulated gastrointestinal digestion. LWT-Food Sci Technol 44:1752–60.

Delorme V, Dhouib R, Canaan S, Fotiadu F, Carriere F, Cavalier JF. 2011. Effects of surfactants on lipase structure, activity, and inhibition. Pharmaceut Res 28:1831–42.

Dempe JS, Scheerle RK, Pfeiffer E, Metzler M. 2013. Metabolism and permeability of curcumin in cultured Caco-2 cells. Mol Nutr Food Res 57:1543–49.

Depoortere I. 2014. Taste receptors of the gut: emerging roles in health and disease. Gut 63:179–90.

des Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V. 2006. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Controll Release 116:1–27.

Desai KGH, Park HJ. 2005. Recent developments in microencapsulation of food ingredients. Drying Technol 23:1361–94.

Devraj R, Williams HD, Warren DB, Mullertz A, Porter CJH, Pouton CW. 2013. In vitro digestion testing of lipid-based delivery systems: calcium ions combine with fatty acids liberated from triglyceride rich lipid solutions to form soaps and reduce the solubilization capacity of colloidal digestion products. Intl J Pharm 441:323–33.

Dickinson E. 1992. Introduction to food colloids. Cambridge, UK: Royal Society of Chemistry.

Dickinson E. 2003. Hydrocolloids at interfaces and the influence on the properties of dispersed systems. Food Hydrocoll 17:25–39.

Dickinson E. 2011. Mixed biopolymers at interfaces: competitive adsorption and multilayer structures. Food Hydrocoll 25:1966–83.

Doherty GJ, McMahon HT. 2009. Mechanisms of endocytosis. Ann Rev Biochem 78:857–902.

Drusch S. 2007. Sugar beet pectin: a novel emulsifying wall component for microencapsulation of lipophilic food ingredients by spray-drying. Food Hydrocoll 21:1223–28.

Drusch S, Schwarz K. 2006. Microencapsulation properties of two different types of n-octenylsuccinate-derivatised starch. Eur Food Res Technol 222:155–64.

Dudhatra GB, Mody SK, Awale MM, Patel HB, Modi CM, Kumar A, Kamani DR, Chauhan BN. 2012. A comprehensive review on pharmacotherapeutics of herbal bioenhancers. Scient World J.

Ensign LM, Cone R, Hanes J. 2012. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Adv Drug Deliv Rev 64:557–70.

Espina-Ruiz M, Parada-Alfonso F, Restrepo-Sanchez L-P, Narvaez-Cuenca C-E, McClements DJ. 2014. Interaction of a dietary fiber (pectin) with gastrointestinal components (bile salts, calcium, and lipase): a calorimetry, electrophoresis, and turbidity study. J Agric Food Chem 62:12620–30.

Espinal-Ruiz M, Parada-Alfonso F, Restrepo-Sanchez L-P, Narvaez-Cuenca C-E, McClements DJ. 2014. Impact of dietary fibers methyl cellulose, chitosan, and pectin on digestion of lipids under simulated gastrointestinal conditions. Food Funct 5:3083–95.

Fagerberg JH, Sjogren E, Bergstrom CAS. 2015. Concomitant intake of alcohol may increase the absorption of poorly soluble drugs. Eur J Pharmaceut Sci 67:12–20.

Failla ML, Chitchumroonchokchai C, Ishida BK. 2008. In vitro micellarization and intestinal cell uptake of cis isomers of lycopene exceed those of all-trans lycopene. J Nutr 138:482–86.

Failla ML, Huo T, Thakkar SK. 2008. Asia pacific journall of clinical nutrition 17:200–3.

Fasinu P, Pillay V, Ndesendo VMK, du Toit LC, Choonara YE. 2011. Diverse approaches for the enhancement of oral drug bioavailability. Biopharmaceut Drug Disposit 32:185–209.

Fava F, Lovegrove JA, Gitau R, Jackson KG, Tuohy KM. 2006. The gut microbiota and lipid metabolism: implications for human health and coronary heart disease. Curr Med Chem 13:3005–21.

Fave G, Coste TC, Armand M. 2004. Physicochemical properties of lipids: new strategies to manage fatty acid bioavailability. Cell Mol Biol 50:815–31.

Fernandez-Garcia E, Carvajal-Lerida I, Jaren-Galan M, Garrido-Fernandez J, Perez-Galvez A, Hornero-Mendez D. 2012. Carotenoids bioavailability from foods: from plant pigments to efficient biological activities. Food Res Intl 46:438–50.

Fernandez-Garcia E, Rincon F, Perez-Galvez A. 2008. Developing an emulsifier system to improve the bioaccessibility of carotenoids. J Agric Food Chem 56:10384–90.

Ferruzzi MG, Lumpkin JL, Schwartz SJ, Failla M. 2006. Digestive stability, micellarization, and uptake of beta-carotene isomers by Caco-2 human intestinal cells. J Agric Food Chem 54:2780–85.

Fleisher D, Li C, Zhou Y, Pao LH, Karim A. 1999. Drug, meal and formulation interactions influencing drug absorption after oral administration—clinical implications. Clin Pharmacok 36:233–54.

Friberg S, Larsson K, Sjoblom J. 2004. Food emulsions. 4th ed. New York, N.Y.: Marcel Dekker.

Gao L, Liu G, Ma J, Wang X, Zhou L, Li X, Wang F. 2013. Application of drug nanocrystal technologies on oral drug delivery of poorly soluble drugs. Pharmaceut Res 30:307–24.

Genovese DB, Lozano JE, Rao MA. 2007. The rheology of colloidal and noncolloidal food dispersions. J Food Sci 72:R11–R20.

Gidley MJ. 2013. Hydrocolloids in the digestive tract and related health implications. Curr Opin Coll Interf Sci 18:371–78.

Goltz SR, Campbell WW, Chitchumroonchokchai C, Failla ML, Ferruzzi MG. 2012. Meal triacylglycerol profile modulates postprandial absorption of carotenoids in humans. Mol Nutr Food Res 56:866–77.

Gupta V, Hwang BH, Doshi N, Mitragotri S. 2013. A permeation enhancer for increasing transport of therapeutic macromolecules across the intestine. J Controll Release 172:541–49.

Hedren E, Diaz V, Svanberg U. 2002. Estimation of carotenoid accessibility from carrots determined by an in vitro digestion method. Eur J Clin Nutr 56:425–30.

Heger M, van Golen RF, Broekgaarden M, Michel MC. 2014. The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancers. Pharmacol Rev 66:222–307.

Helgason T, Weiss J, McClements DJ, Gislason J, Einarsson JM, Thormodsson FR, Kristbergsson K. 2008. Examination of the interaction of chitosan and oil-in-water emulsions under conditions simulating the digestive system using confocal microscopy. J Aqua Food Product Technol 17:216–33.

Hornero-Méndez D, Mínguez-Mosquera MI. 2007. Bioaccessibility of carotenes from carrots: effect of cooking and addition of oil. Innovat Food Sci Emer Technol 8:407–12.

Hribar U, Ulrih NP. 2014. The metabolism of anthocyanins. Curr Drug Metabol 15:3–13.

Hu M, Li Y, Decker EA, McClements DJ. 2010. Role of calcium and calcium-binding agents on the lipase digestibility of emulsified lipids using an in vitro digestion model. Food Hydrocoll 24:719–25.

Huo T, Ferruzzi MG, Schwartz SJ, Failla ML. 2007a. Impact of fatty acyl composition and quantity of triglycerides on bioaccessibility of dietary carotenoids. J Agric Food Chem 55:8950–57.

Huo T, Ferruzzi MG, Schwartz SJ, Failla ML. 2007b. Impact of fatty acyl composition and quantity of triglycerides on bloaccessibility of dietary carotenoids. J Agric Food Chem 55:8950–57.

Hurst S, Loi CM, Brodfuehrer J, El-Kattan A. 2007. Impact of physiological, and biopharmaceutical factors in absorption and metabolism mechanisms on the drug oral bioavailability of rats and humans. Expert Opin Drug Metab Toxicol 3:469–89.

Hwang S, Lee S, Ahn IS, Yung JK. 2009. Highly efficient production of monoglycerides by the continuous removal of fatty acids from lipase-catalyzed oil hydrolysis. Biocatal Biotrans 27:290–95.

Jia JX, Wasan KM. 2008. Effects of monoglycerides on rhodamine 123 accumulation, estradiol 17 beta-D-glucuronide bidirectional transport and MRP2 protein expression within Caco-2 cells. J Pharm Pharm Sci 11:45–62.

Jiang LF, Long XW, Meng Q. 2013. Rhamnolipids enhance epithelial permeability in Caco-2 monolayers. Intl J Pharm 446:130–35.

Jiménez-Martín E, Gharsallaoui A, Pérez-Palacios T, Carrascal JR, Rojas TA. 2015. Suitability of using monolayered and multilayered emulsions for microencapsulation of ω-3 fatty acids by spray drying: effect of storage at different temperatures. Food Bioprocess Technol 8:100–11.

Jimenez M, Garcia HS, Beristain CI. 2004. Spray-drying microencapsulation and oxidative stability of conjugated linoleic acid. Eur Food Res Technol 219:588–92.

Jin MJ, Han HK. 2010. Effect of piperine, a major component of black pepper, on the intestinal absorption of fexofenadine and its implication on food-drug interaction. J Food Sci 75:H93–H96.

Kalantzi L, Goumas K, Kalioras V, Abrahamsson B, Dressman JB, Reppas C. 2006. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. Pharmaceut Res 23:165–76.

Kang MJ, Cho JY, Shim BH, Kim DK, Lee J. 2009. Bioavailability enhancing activities of natural compounds from medicinal plants. J Med Plants Res 3:1204–11.

Karupaiah T, Sundram K. 2007. Effects of stereospecific positioning of fatty acids in triacylglycerol structures in native and randomized fats: a review of their nutritional implications. Nutr Metabol 4:1–17.

Kenmogne-Domguia HB, Moisan S, Viau M, Genot C, Meynier A. 2014. The initial characteristics of marine oil emulsions and the composition of the media inflect lipid oxidation during in vitro gastrointestinal digestion. Food Chem 152:146–54.

Kimura H, Futami Y, Tarui S, Shinomiya T. 1982. Activation of human pancreatic lipase activity by calcium and bile-salts. J Biochem 92:243–51.

Klinkesorn U, Sophanodora P, Chinachoti P, McClements DJ, Decker EA. 2005. Stability of spray-dried tuna oil emulsions encapsulated with two-layered interfacial membranes. J Agric Food Chem 53:8365–71.

Koga N, Ohta C, Kato Y, Haraguchi K, Endo T, Ogawa K, Ohta H, Yano M. 2011. In vitro metabolism of nobiletin, a polymethoxy-flavonoid, by human liver microsomes and cytochrome P450. Xenobiotica 41:927–33.

Kong F, Singh RP. 2008. Disintegration of solid foods in human stomach. J Food Sci 73:R67–R80.

Kosinska A, Andlauer W. 2013. Modulation of tight junction integrity by food components. Food Res Intl 54:951–60.

Koziolek M, Garbacz G, Neumann M, Weitschies W. 2013a. Simulating the postprandial stomach: biorelevant test methods for the estimation of intragastric drug dissolution. Mol Pharmaceut 10:2211–21.

Koziolek M, Garbacz G, Neumann M, Weitschies W. 2013b. Simulating the postprandial stomach: physiological considerations for dissolution and release testing. Mol Pharmaceut 10:1610–22.

Kralova I, Sjoblom J. 2009. Surfactants used in food industry: a review. J Disper Sci Technol 30:1363–83.

Lemmens L, Colle I, Van Buggenhout S, Palmero P, Van Loey A, Hendrickx M. 2014. Carotenoid bioaccessibility in fruit- and vegetable-based food products as affected by product (micro)structural characteristics and the presence of lipids: a review. Trends Food Sci Technol 38:125–35.

Lemmer HJR, Hamman JH. 2013. Paracellular drug absorption enhancement through tight junction modulation. Expert Opin Drug Deliv 10:103–14.

Lennernas H, Abrahamsson B, Persson EM, Knutson L. 2007. Oral drug absorption and the biopharmaceutics classification system. J Drug Deliv Sci Technol 17:237–44.

Lentle RG, Janssen PWM. 2010. Manipulating digestion with foods designed to change the physical characteristics of digesta. Crit Rev Food Sci Nutr 50:130–45.

Lentle RG, Patrick WMJ. 2011. The physical processes of digestion. New York, N.Y.: Springer.

Lerner A, Matthias T. 2015. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. Autoimmun Rev 14:479–89.

Lesmes U, Baudot P, McClements DJ. 2010. Impact of interfacial composition on physical stability and in vitro lipase digestibility of

triacylglycerol oil droplets coated with lactoferrin and/or caseinate. J Agric Food Chem 58:7962–69.

Lesser S, Wolffram S. 2006. Oral bioavailability of the flavonol quercetin—a review. Curr Topn Nutraceut Res 4:239–56.

Li Y, McClements DJ. 2011b. Controlling lipid digestion by encapsulation of protein-stabilized lipid droplets within alginate-chitosan complex coacervates. Food Hydrocoll 25:1025–33.

Li Y, McClements DJ. 2011b. Inhibition of lipase-catalyzed hydrolysis of emulsified triglyceride oils by low-molecular weight surfactants under simulated gastrointestinal conditions. Eur J Pharmaceut Biopharmaceut 79:423–31.

Little TJ, Russo A, Meyer JH, Horowitz M, Smyth DR, Bellon M, Wishart JM, Jones KL, Feinle-Bisset C. 2007. Free fatty acids have more potent effects on gastric emptying, gut hormones, and appetite than triacylglycerides. Gastroenterology 133:1124–31.

Lo CM, Tso P. 2009. Physicochemical basis of the digestion and absorption of triacylglycerol. Woodhead Publ Food Sci Technol Nutr 94–125.

Lohner K, Schnabele K, Daniel H, Oesterle D, Rechkemmer G, Gottlicher M, Wenzel U. 2007. Flavonoids alter P-gp expression in intestinal epithelial cells in vitro and in vivo. Mol Nutr Food Res 51:293–300.

Lorenzen JK, Nielsen S, Holst JJ, Tetens I, Rehfeld JF, Astrup A. 2007. Effect of dairy calcium or supplementary calcium intake on postprandial fat metabolism, appetite, and subsequent energy intake. Am J Clin Nutr 85:678–87.

Losso JN, Khachatryan A, Ogawa M, Godber JS, Shih F. 2005. Random centroid optimization of phosphatidylglycerol stabilized lutein-enriched oil-in-water emulsions at acidic pH. Food Chem 92:737–44.

Maher S, Brayden DJ, Feighery L, McClean S. 2008. Cracking the junction: update on the progress of gastrointestinal absorption enhancement in the delivery of poorly absorbed drugs. Crit Rev Ther Drug Carr Syst 25:117–68.

Maldonado-Valderrama J, Wilde P, Macierzanka A, Mackie A. 2011. The role of bile salts in digestion. Adv Colloid Interface Sci165:36–46.

Martel F, Monteiro R, Calhau C. 2010. Effect of polyphenols on the intestinal and placental transport of some bioactive compounds. Nutr Res Rev 23:47–64.

Martínez-Huélamo M, Tulipani S, Estruch R, Escribano E, Illán M, Corella D, Lamuela-Raventós RM. 2015. The tomato sauce making process affects the bioaccessibility and bioavailability of tomato phenolics: a pharmacokinetic study. Food Chem 173:864–72.

Martinez MN, Amidon GL. 2002. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. J Clin Pharmacol 42:620–43.

Matalanis A, McClements DJ. 2012. Impact of encapsulation within hydrogel microspheres on lipid digestion: an in vitro study. Food Biophys 7:145–54.

Matthews SB, Waud JP, Roberts AG, Campbell AK. 2005. Systemic lactose intolerance: a new perspective on an old problem. Postgrad Med J 81:167–73.

McClements DJ. 2005. Food emulsions: principles, practice, and techniques. 2nd ed. Boca Raton, Fla.: CRC Press.

McClements DJ. 2011. Edible nanoemulsions: fabrication, properties, and functional performance. Soft Matter 7:2297–316.

McClements DJ. 2012. Crystals and crystallization in oil-in-water emulsions: implications for emulsion-based delivery systems. Adv Colloid Interface Sci 174:1–30.

McClements DJ. 2013. Utilizing food effects to overcome challenges in delivery of lipophilic bioactives: structural design of medical and functional foods. Expert Opin Drug Deliv 10:1621–32.

McClements DJ. 2015. Food emulsions: principles, practice, and techniques. 3rd ed. Boca Raton, Fla.: CRC Press.

McClements DJ, Decker EA. 2000. Lipid oxidation in oil-in-water emulsions: impact of molecular environment on chemical reactions in heterogeneous food systems. J Food Sci 65:1270–82.

McClements DJ, Decker EA, Park Y. 2009a. Controlling lipid bioavailability through physicochemical and structural approaches. Crit Rev Food Sci Nutr 49:48–67.

McClements DJ, Decker EA, Park Y. 2009b. Controlling lipid bioavailability through physicochemical and structural approaches. Crit Rev Food Sci Nutr 49:48–67.

McClements DJ, Decker EA, Park Y, Weiss J. 2009c. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. Crit Rev Food Sci Nutr 49:577–606.

McClements DJ, Li F, Xiao H. 2015. The nutraceutical bioavailability classification scheme: classifying nutraceuticals according to factors limiting their oral bioavailability. Ann Rev Food Sci Technol 6. 299–327.

McClements DJ, Li Y. 2010. Structured emulsion-based delivery systems: controlling the digestion and release of lipophilic food components. Adv Colloid Interface Sci 159:213–28.

McClements DJ, Rao J. 2011. Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. Crit Rev Food Sci Nutr 51:285–330.

McClements DJ, Xiao H. 2014. Excipient foods: designing food matrices that improve the oral bioavailability of pharmaceuticals and nutraceuticals. Food Funct 5:1320–33.

Metzler M, Pfeiffer E, Schulz SI, Dempe JS. 2013. Curcumin uptake and metabolism. Biofactors 39:14–20.

Misaka S, Muller F, Fromm MF. 2013. Clinical relevance of drug efflux pumps in the gut. Curr Opin Pharmacol 13:847–52.

Moelants KR, Lemmens L, Vandebroeck M, Van Buggenhout S, Van Loey AM, Hendrickx ME. 2012a. Relation between particle size and carotenoid bioaccessibility in carrot-and tomato-derived suspensions. J Agric Food Chem 60:11995–2003.

Moelants KRN, Lemmens L, Vandebroeck M, Van Buggenhout S, Van Loey AM, Hendrickx ME. 2012b. Relation between particle size and carotenoid bioaccessibility in carrot- and tomato-derived suspensions. J Agric Food Chem 60:11995–2003.

Monagas M, Urpi-Sarda M, Sanchez-Patan F, Llorach R, Garrido I, Gomez-Cordoves C, Andres-Lacueva C, Bartolome B. 2010. Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites. Food Funct 1:233–53.

Moreno FJ. 2007. Gastrointestinal digestion of food allergens: effect on their allergenicity. Biomed Pharmacother 61:50–60.

Morgan SL. 2013. Dietary supplements and medical foods for osteopenia and osteoporosis. J Clin Densitom 16:394–401.

Mukherjee M. 2003. Human digestive and metabolic lipases—a brief review. J Mol Catal B–Enzym 22:369–76.

Mullen W, Borges G, Donovan JL, Edwards CA, Serafini M, Lean ME, Crozier A. 2009. Milk decreases urinary excretion but not plasma pharmacokinetics of cocoa flavan-3-ol metabolites in humans. Am J Clin Nutr 89:1784–91.

Mun S, Kim Y-R, McClements DJ. 2015a. Control of beta-carotene bioaccessibility using starch-based filled hydrogels. Food Chem 173:454–61.

Mun S, Kim Y-R, Shin M, McClements DJ. 2015b. Control of lipid digestion and nutraceutical bioaccessibility using starch-based filled hydrogels: influence of starch and surfactant type. Food Hydrocoll 44:380–89.

Nagao A, Kotake-Nara E, Hase M. 2013. Effects of fats and oils on the bioaccessibility of carotenoids and vitamin e in vegetables. Biosci Biotechnol Biochem 77:1055–60.

Ortega N, Reguant J, Romero M-P, Macià A, Motilva M-J. 2009. Effect of fat content on the digestibility and bioaccessibility of cocoa polyphenol by an in vitro digestion model. J Agric Food Chem 57:5743–49.

Pan K, Zhong Q, Baek SJ. 2013. Enhanced dispersibility and bioactivity of curcumin by encapsulation in casein nanocapsules. J Agric Food Chem 61:6036–43.

Panozzo A, Lemmens L, Van Loey A, Manzocco L, Nicoli MC, Hendrickx M. 2013. Microstructure and bioaccessibility of different carotenoid species as affected by high pressure homogenisation: a case study on differently coloured tomatoes. Food Chem 141:4094–100.

Park YW. 1991. Relative buffering capacity of goat milk, cow milk, soy-based infant formulas, and commercial nonprescription antacid drugs. J Dairy Sci 74:3326–33.

Pasquier B, Armand M, Guillon F, Castelain C, Borel P, Barry JL, Pieroni G, Lairon D. 1996. Viscous soluble dietary fibers alter emulsification and lipolysis of triacylglycerols in duodenal medium in vitro. J Nutr Biochem 7:293–302.

Patel AR, Velikov KP. 2011. Colloidal delivery systems in foods: a general comparison with oral drug delivery. LWT-Food Sci Technol 44:1958–64.

Patton JS, Carey MC. 1979. Watching fat digestion. Science 204:145–48.

Patton JS, Vetter RD, Hamosh M, Borgstrom B, Lindstrom M, Carey MC. 1985. The light-microscopy of triglyceride digestion. Food Microstruct 4:29–41.

Petri N, Tannergren C, Holst B, Mellon FA, Bao YP, Plumb GW, Bacon J, O'Leary KA, Kroon PA, Knutson L, Forsell P, Eriksson T, Lennernas H,

Williamson G. 2003. Absorption/metabolism of sulforaphane and quercetin, and regulation of phase II enzymes, in human jejunum in vivo. Drug Metabol Disposit 31:805–13.

Phillips GO, Williams PA. 2011. Handbook of food proteins. 1st ed. Oxford, U.K.: Woodhead Publishing.

Pillay V, Hibbins AR, Choonara YE, du Toit LC, Kumar P, Ndesendo VMK. 2012. Orally administered therapeutic peptide delivery: enhanced absorption through the small intestine using permeation enhancers. Intl J Peptide Res Therapeut 18:259–80.

Pinheiro AC, Lad M, Silva HD, Coimbra MA, Boland M, Vicente AA. 2013. Unravelling the behaviour of curcumin nanoemulsions during in vitro digestion: effect of the surface charge. Soft Matter 9:3147–54.

Planas JM, Alfaras I, Colom H, Juan ME. 2012. The bioavailability and distribution of trans-resveratrol are constrained by ABC transporters. Arch Biochem Biophys 527:67–73.

Porter CJH, Trevaskis NL, Charman WN. 2007. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov 6:231–48.

Porter CJH, Wasan KM. 2008. Lipid-based systems for the enhanced delivery of poorly water soluble drugs. Adv Drug Deliv Rev 60:615–16.

Pouton CW, Porter CJ. 2008. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Adv Drug Deliv Rev 60:625–37.

Qian C, Decker EA, Xiao H, McClements DJ. 2012. Nanoemulsion delivery systems: influence of carrier oil on beta-carotene bioaccessibility. Food Chem 135:1440–7.

Qian C, McClements DJ. 2011. Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: factors affecting particle size. Food Hydrocoll 25:1000–8.

Ranheim T, Gedde-Dahl A, Rustan AC, Drevon CA. 1994. Effect of chronic incubation of Caco-2 cells with eicosapentaenoic acid (20:5, n-3) and oleic acid (18:1, n-9) on triacylglycerol production. Biochem J 303 (Pt 1):155–61.

Rao JJ, Decker EA, Xiao H, McClements DJ. 2013. Nutraceutical nanoemulsions: influence of carrier oil composition (digestible versus indigestible oil) on—carotene bioavailability. J Sci Food Agric 93:3175–83.

Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, Pinto MD. 2013. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. Br J Clin Pharmacol 75:588–602.

Ribeiro HS, Guerrero JMM, Briviba K, Rechkemmer G, Schuchmann HP, Schubert H. 2006. Cellular uptake of carotenoid-loaded oil-in-water emulsions in colon carcinoma cells in vitro. J Agric Food Chem 54:9366–9.

Ribeiro HS, Rico LG, Badolato GG, Schubert H. 2005. Production of O/W emulsions containing astaxanthin by repeated Premix membrane emulsification. J Food Sci 70:E117–E23.

Ribnicky DM, Roopchand DE, Oren A, Grace M, Poulev A, Lila MA, Havenaar R, Raskin I. 2014. Effects of a high fat meal matrix and protein complexation on the bioaccessibility of blueberry anthocyanins using the TNO gastrointestinal model (TIM-1). Food Chem 142:349–57.

Rietjens I, Tyrakowska B, van den Berg S, Soffers A, Punt A. 2015. Matrix-derived combination effects influencing absorption, distribution, metabolism and excretion (ADME) of food-borne toxic compounds: implications for risk assessment. Toxicol Res 4:23–35.

Rodríguez-Roque MJ, Rojas-Graü MA, Elez-Martínez P, Martín-Belloso O. 2014. In vitro bioaccessibility of health-related compounds as affected by the formulation of fruit juice- and milk-based beverages. Food Res Intl 62:771–8.

Rosenthal R, Heydt MS, Amasheh M, Stein C, Fromm M, Amasheh S. 2012. Analysis of absorption enhancers in epithelial cell models. Barrier Channels Formed Tight Junct Proteins II 1258:86–92.

Rozner S, Shalev DE, Shames AI, Ottaviani MF, Aserin A, Garti N. 2010. Do food microemulsions and dietary mixed micelles interact? Colloids Surf B - Biointerf 77:22–30.

Rupp C, Steckel H, Muller BW. 2010. Solubilization of poorly water-soluble drugs by mixed micelles based on hydrogenated phosphatidylcholine. Intl J Pharm 395:272–80.

Ryan L, Petit S. 2010. Addition of whole, semiskimmed, and skimmed bovine milk reduces the total antioxidant capacity of black tea. Nutr Res 30:14–20.

Saaber D, Wollenhaupt S, Baumann K, Reichl S. 2014. Recent progress in tight junction modulation for improving bioavailability. Expert Opin Drug Discov 9:367–81.

Saberi AH, Fang Y, McClements DJ. 2013. Fabrication of vitamin E-enriched nanoemulsions: factors affecting particle size using spontaneous emulsification. J Colloid Interface Sci 391:95–102.

Salem M, Rohani S, Gillies ER. 2014. Curcumin, a promising anti-cancer therapeutic: a review of its chemical properties, bioactivity and approaches to cancer cell delivery. Rsc Adv 4:10815–29.

Salvia-Trujillo L, Qian C, Martin-Belloso O, McClements DJ. 2013a. Influence of particle size on lipid digestion and beta-carotene bioaccessibility in emulsions and nanoemulsions. Food Chem 141: 1472–80.

Salvia-Trujillo L, Qian C, Martin-Belloso O, McClements DJ. 2013b. Modulating beta-carotene bioaccessibility by controlling oil composition and concentration in edible nanoemulsions. Food Chem 139:878–84.

Santipanichwong R, Suphantharika M. 2007. Carotenoids as colorants in reduced-fat mayonnaise containing spent brewer's yeast beta-glucan as a fat replacer. Food Hydrocoll 21:565–74.

Sari TP, Mann B, Kumar R, Singh RRB, Sharma R, Bhardwaj M, Athira S. 2015. Preparation and characterization of nanoemulsion encapsulating curcumin. Food Hydrocoll 43:540–6.

Scaldaferri F, Pizzoferrato M, Gerardi V, Lopetuso L, Gasbarrini A. 2012. The gut barrier new acquisitions and therapeutic approaches. J Clin Gastroenterol 46:S12–7.

Scholz-Ahrens KE, Schrezenmeir J. 2006. Milk minerals and the metabolic syndrome. Intl Dairy J 16:1399–407.

Seki T, Harada S, Hosoya O, Morimoto K, Juni K. 2008. Evaluation of the establishment of a tight junction in Caco-2 cell monolayers using a pore permeation model involving two different sizes. Biol Pharmaceut Bull 31:163–6.

Serafini M, Testa MF, Villaño D, Pecorari M, van Wieren K, Azzini E, Brambilla A, Maiani G. 2009. Antioxidant activity of blueberry fruit is impaired by association with milk. Free Rad Biol Med 46:769–74.

Shah RC. 2011. Medical foods for alzheimer's disease. Drugs Aging 28:421–8.

Sharma R. 2005. Market trends and opportunities for functional dairy beverages. Aust J Dairy Technol 60:195–8.

Shimizu M. 2010. Interaction between food substances and the intestinal epithelium. Biosci Biotechnol Biochem 74:232–41.

Shpigelman A, Zisapel A, Cohen Y, Livney YD. 2013. Mechanisms of saccharide protection against epigallocatechin-3-gallate deterioration in aqueous solutions. Food Chem 139:1105–12.

Singh H, Sarkar A. 2011. Behaviour of protein-stabilised emulsions under various physiological conditions. Adv Colloid Interface Sci 165:47–57.

Singh H, Ye AQ, Horne D. 2009. Structuring food emulsions in the gastrointestinal tract to modify lipid digestion. Prog Lipid Res 48:92–100.

Sneharani AH, Karakkat JV, Singh SA, Rao AGA. 2010. Interaction of curcumin with beta-lactoglobulin-stability, spectroscopic analysis, and molecular modeling of the complex. J Agric Food Chem 58:11130–9.

Solans C, Sole I. 2012. Nano-emulsions: formation by low-energy methods. Curr Opin Coll Interface Sci 17:246–54.

Soottitantawat A, Yoshii H, Furuta T, Ohkawara M, Linko P. 2003. Microencapsulation by spray drying: influence of emulsion size on the retention of volatile compounds. J Food Sci 68:2256–62.

Speranza A, Corradini MG, Hartman TG, Ribnicky D, Oren A, Rogers MA. 2013. Influence of emulsifier structure on lipid bioaccessibility in oil-water nanoemulsions. J Agric Food Chem 61:6505–15.

Spyropoulos F, Norton AB, Norton IT. 2011. Self-structuring foods based on acid-sensitive mixed biopolymer to impact on satiety. 11th International Congress on Engineering and Food (Icef11) 1:1487–93.

Stevenson DE, Scheepens A, Hurst RD. 2009. Bioavailability and metabolism of dietary flavonoids - much known - much more to discover.

Tagliazucchi D, Helal A, Verzelloni E, Conte A. 2012. The type and concentration of milk increase the in vitro bioaccessibility of coffee chlorogenic acids. J Agric Food Chem 60:11056–64.

Tang J, Sun J. 2007. Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Curr Drug Ther 2: 85–93.

Tapal A, Tiku PK. 2012. Complexation of curcumin with soy protein isolate and its implications on solubility and stability of curcumin. Food Chem 130:960–5.

Tarvainen M, Phuphusit A, Suomela JP, Kuksis A, Kallio H. 2012. Effects of antioxidants on rapeseed oil oxidation in an artificial digestion model analyzed by UHPLC-ESI-MS. J Agric Food Chem 60:3564–79.

Thongngam M, McClements DJ. 2005. Isothermal titration calorimetry study of the interactions between chitosan and a bile salt (sodium taurocholate). Food Hydrocoll 19:813–9.

Tokle T, Lesmes U, Decker EA, McClements DJ. 2012. Impact of dietary fiber coatings on behavior of protein-stabilized lipid droplets under simulated gastrointestinal conditions. Food Funct 3:58–66.

Tokle T, Mao Y, McClements DJ. 2013. Potential biological fate of emulsion-based delivery systems: lipid particles nanolaminated with lactoferrin and beta-lactoglobulin coatings. Pharmaceut Res 30:3200–13.

Troncoso E, Miguel Aguilera J, McClements DJ. 2012. Fabrication, characterization and lipase digestibility of food-grade nanoemulsions. Food Hydrocoll 27:355–63.

Tso P, Nauli A, Lo CM. 2004. Enterocyte fatty acid uptake and intestinal fatty acid-binding protein. Biochem Soc Trans 32:75–8.

Tsujita T, Takaichi H, Takaku T, Sawai T, Yoshida N, Hiraki J. 2007. Inhibition of lipase activities by basic polysaccharide. J Lipid Res 48:358–65.

Tsutsumi K, Li SK, Hymas RV, Teng CL, Tillman LG, Hardee GE, Higuchi WI, Ho NFH. 2008. Systematic studies on the paracellular permeation of model permeants and Oligonucleotides in the rat small intestine with chenodeoxycholate as enhancer. J Pharmaceut Sci 97:350–67.

Tyssandier V, Lyan B, Borel P. 2001. Main factors governing the transfer of carotenoids from emulsion lipid droplets to micelles. Biochim Biophys Acta - Mol Cell Biol Lipids 1533:285–92.

Tzoumaki MV, Moschakis T, Scholten E, Biliaderis CG. 2013. In vitro lipid digestion of chitin nanocrystal stabilized o/w emulsions. Food Funct 4:121–9.

van Aken GA. 2010. Relating food emulsion structure and composition to the way it is processed in the gastrointestinal tract and physiological responses: what are the opportunities? Food Biophys 5:258–83.

Varum FJO, Hatton GB, Basit AW. 2013. Food, physiology and drug delivery. Intl J Pharm 457:446–60.

Vega C, Roos YH. 2006. Invited review: spray-dried dairy and dairy-like emulsions compositional considerations. J Dairy Sci 89:383–401.

Velderrain-Rodriguez GR, Palafox-Carlos H, Wall-Medrano A, Ayala-Zavala JF, Chen CYO, Robles-Sanchez M, Astiazaran-Garcia H, Alvarez-Parrilla E, Gonzalez-Aguilar GA. 2014. Phenolic compounds: their journey after intake. Food Funct 5:189–97.

Verrijssen TAJ, Smeets KHG, Christiaens S, Palmers S, Van Loey AM, Hendrickx ME. 2015. Relation between in vitro lipid digestion and beta-carotene bioaccessibility in beta-carotene-enriched emulsions with different concentrations of L-alpha-phosphatidylcholine. Food Res Intl 67:60–6.

Vinarov Z, Tcholakova S, Damyanova B, Atanasov Y, Denkov ND, Stoyanov SD, Pelan E, Lips A. 2012. Effects of emulsifier charge and concentration on pancreatic lipolysis: 2. Interplay of emulsifiers and biles. Langmuir 28:12140–50.

Walstra P. 1993. Principles of emulsion formation. Chem Eng Sci 48:333.

Walstra P. 2003. Physical chemistry of foods. New York, N.Y.: Marcel Decker.

Walter T, Pizarro F, Olivares M. 2003. Iron bioavailability in corn-masa tortillas is improved by the addition of disodium EDTA. J Nutr 133:3158–61.

Wang XX, Valenzano MC, Mercado JM, Zurbach EP, Mullin JM. 2013. Zinc supplementation modifies tight junctions and alters barrier function of Caco-2 human intestinal epithelial layers. Digest Dis Sci 58:77–87.

Waraho T, McClements DJ, Decker EA. 2011. Mechanisms of lipid oxidation in food dispersions. Trends Food Sci Technol 22:3–13.

Weaver MA, Johnson A, Singh RH, Wilcox WR, Lloyd-Puryear MA, Watson MS. 2010. Medical foods: inborn errors of metabolism and the reimbursement dilemma. Genet Med 12:364–9.

Whayne TF, Felts JM. 1971a. Activation of lipoprotein lipase—an evaluation of calcium as a cofactor. J Am Oil Chem Soc 48:A101–6.

Whayne TF, Felts JM. 1971b. Activation of lipoprotein lipase—evaluation of calcium, magnesium, and ammonium as cofactors. CircRes 28:649–55.

Wickham M, Faulks R, Mills C. 2009. In vitro digestion methods for assessing the effect of food structure on allergen breakdown. Mol Nutr Food Res 53:952–58.

Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJH. 2013. Strategies to address low drug solubility in discovery and development. Pharmacol Rev 65:315–499.

Wydro P, Krajewska B, Hac-Wydro K. 2007. Chitosan as a lipid binder: a langmuir monolayer study of chitosan–lipid interactions. Biomacromolecules 8:2611–17.

Xie Y, Kosińska A, Xu H, Andlauer W. 2013. Milk enhances intestinal absorption of green tea catechins in in vitro digestion/Caco-2 cells model. Food Res Int 53:793–800.

Yamamoto A, Katsumi H, Kusamori K, Sakane T. 2014. Improvement of intestinal absorption of poorly absorbable drugs by various sugar esters. Yakugaku Zasshi - J Pharm Soc Jpn 134:47–53.

Yanez JA, Wang SWJ, Knemeyer IW, Wirth MA, Alton KB. 2011. Intestinal lymphatic transport for drug delivery. Adv Drug Deliv Rev 63:923–42.

Yang Y, McClements DJ. 2013. Encapsulation of vitamin E in edible emulsions fabricated using a natural surfactant. Food Hydrocoll 30:712–20.

Yeap YY, Trevaskis NL, Quach T, Tso P, Charman WN, Porter CJH. 2013. Intestinal bile secretion promotes drug absorption from lipid colloidal phases via induction of supersaturation. Mol Pharmaceut 10:1874–89.

Yu HL, Huang QR. 2011. Investigation of the absorption mechanism of solubilized curcumin using caco-2 cell monolayers. J Agric Food Chem 59:9120–6.

Zangenberg NH, Mullertz A, Kristensen HG, Hovgaard L. 2001a. A dynamic in vitro lipolysis model I. Controlling the rate of lipolysis by continuous addition of calcium. Eur J Pharmaceut Sci 14:115–22.

Zangenberg NH, Mullertz A, Kristensen HG, Hovgaard L. 2001b. A dynamic in vitro lipolysis model II: evaluation of the model. Eur J Pharmaceut Sci 14:237–44.

Zannini E, Kingston W, Arendt EK, Waters DM. 2013. Technological challenges and strategies for developing low-protein/protein-free cereal foods for specific dietary management. Food Res Intl 54:935–50.

Zhang H, Yu D, Sun J, Liu X, Jiang L, Guo H, Ren F. 2014a. Interaction of plant phenols with food macronutrients: characterisation and nutritional–physiological consequences. Nutr Res Rev 27:1–15.

Zhang R, Zhang Z, Zhang H, Decker EA, McClements DJ. 2015. Influence of emulsifier type on gastrointestinal fate of oil-in-water emulsions containing anionic dietary fiber (pectin). Food Hydrocoll 45:175–85.

Zhang S, Vardhanabhuti B. 2014b. Intragastric gelation of whey protein-pectin alters the digestibility of whey protein during in vitro pepsin digestion. Food Funct 5:102–10.

Zhou SF, Lim LY, Chowbay B. 2004. Herbal modulation of P-glycoprotein. Drug Metab Rev 36:57–104.

Ziani K, Fang Y, McClements DJ. 2012. Encapsulation of functional lipophilic components in surfactant-based colloidal delivery systems: vitamin E, vitamin D, and lemon oil. Food Chem 134:1106–12.

Zou L, Liu W, Liu C, Xiao H, McClements DJ. 2015a. Utilizing food matrix effects to enhance nutraceutical bioavailability: increase of curcumin bioaccessibility using excipient emulsions. J Agric Food Chem 63:2052–62

Zou L, Zheng B, Liu W, Liu C, Xiao H, McClements DJ. 2015b. Enhancing nutraceutical bioavailability using excipient emulsions: influence of lipid droplet size on solubility and bioaccessibility of powdered curcumin. J Funct Foods 15:72–83.

