1 **Enhancing nutraceutical bioavailability by controlling the**
2 **composition and structure of gastrointestinal contents: Emulsion-**
3 **based delivery and excipient systems**

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17 **Journal:** *Food Structure*

18 **Submitted:** December 2015/ **Revised:** June 2016

19 **Short Title:** Enhancing nutraceutical bioavailability through controlling food structure

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Abstract

The oral bioavailability of hydrophobic bioactives can be improved using food matrices that breakdown within the gastrointestinal tract to form colloidal structures capable of altering bioaccessibility, absorption, and/or transformation. Emulsions are particularly suitable for this purpose because their compositions, structures, and properties can be controlled, and they are already widely used in foods. The bioavailability of isolated bioactives can be improved by incorporating them within *emulsion-based delivery systems (EDS)*, while the bioavailability of bioactives in whole foods can be improved by ingesting them with *emulsion-based excipient systems (EES)*. This review discusses the design, fabrication, and utilization of EDS and EES.

Keywords: nutraceuticals; vitamins; excipient systems; delivery systems; functional foods; nanoemulsions.

1. Introduction

There are many examples of hydrophobic components originating from food sources that have potential health benefits when ingested regularly as part of an individual's diet, such as oil-soluble vitamins (*e.g.*, A, D, and E) and nutraceuticals (*e.g.*, carotenoids, curcumin, ω -3 fatty acids, conjugated linoleic acids, and coenzyme Q10) (Aluko, 2012; Huang, Yu, & Ru, 2010; Li & McClements, 2010). Nevertheless, the beneficial health effects of many of these dietary bioactive agents may not be realized because they have low or variable bioavailability after ingestion (Fernandez-Garcia et al., 2012; Rein et al., 2013; Zou, Liu, Liu, Xiao, & McClements, 2015). Many different physicochemical and physiological factors contribute to the poor bioavailability of this type of bioactive agent, however, these factors can be grouped into three main categories: bioaccessibility; absorption; and transformation. The most important factors limiting bioavailability have to be elucidated for a particular bioactive agent within a particular food matrix in order to develop an effective approach to improve its bioavailability (McClements & Xiao, 2014).

The bioavailability of hydrophobic bioactives can be enhanced using two major strategies (**Figure 1**). In the first strategy, the bioactives are isolated from their original environment (such as in a plant, animal or microorganism), purified, and then converted into a bioactive ingredient, such as β -carotene, curcumin, resveratrol, or vitamin D, which is then incorporated into a suitable functional food or beverage product (McClements, 2015b). This may be achieved by simply mixing the bioactive ingredient with a food product at some stage during its production, *e.g.* adding vitamin D to milk prior to homogenization. Alternatively, isolated bioactive ingredients are often incorporated into colloidal delivery systems, which are then incorporated into a food matrix. Numerous types of colloidal delivery systems are available to encapsulate hydrophobic bioactive ingredients, including microemulsions, nanoemulsions, emulsions, liposomes, solid lipid nanoparticles, biopolymer particles, and microgels (Huang et al., 2010; Li & McClements, 2010; Marze, 2013; Norton, Espinosa, Watson, Spyropoulos, & Norton, 2015; Ting, Jiang, Ho, & Huang, 2014; Velikov & Pelan, 2008). These colloidal delivery systems can be specifically designed to improve the oral bioavailability of hydrophobic bioactive agents by altering their bioaccessibility, absorption or transformation. In addition, they must be designed so that they are economical, robust, and suitable for introduction into a food product without adversely altering its physical or sensory properties. Isolating bioactives from their original

environment and utilizing them as ingredients is particularly suitable for applications where the bioactives are present within a food processing waste-stream that is usually discarded, such as the byproducts of fruit, vegetable, meat, or fish processing (Kim & Mendis, 2006; Schieber, Stintzing, & Carle, 2001).

Another approach that can be employed to improve the bioavailability profile of hydrophobic bioactives is to leave them in their original environment in nature (such as fruits, vegetables, nuts, cereals, meat, or fish), and then consume these foods with specially-designed *excipient foods* (McClements & Xiao, 2014). These excipient foods typically do not have any biological activity themselves, but they enhance the bioavailability of bioactives in the foods that they are ingested with. Thus, the amount of bioactive agent that is actually absorbed by the systemic circulation is increased, thereby boosting its bioactivity and potential health benefits. The composition and structure of excipient foods are specifically designed to improve the bioaccessibility, absorption, or transformation profiles of bioactive components within the gastrointestinal tract (GIT).

Oil-in-water emulsions are particularly suitable for the development of both delivery systems and excipient systems because their compositions and structures can be easily manipulated, and because they are already widely utilized in the food industry, *e.g.*, in dressings, sauces, soups, beverages, dips, creams, and desserts. The objective of this article is to provide a brief overview of the main factors that limit the oral bioavailability of hydrophobic bioactives, and then to describe how emulsion-based delivery or excipient systems can be designed to overcome these limitations by altering the bioaccessibility, absorption, or transformation of bioactives in the GIT. In particular, the importance of controlling the physicochemical and structural properties of the colloidal phases formed within the GIT after ingestion of a delivery or excipient system is stressed.

2. Factors Limiting the Bioavailability of Hydrophobic Bioactives

There are many different physicochemical and physiological factors that impact the oral bioavailability of hydrophobic bioactives in foods. Recently, a systematic approach has been developed to identify the major factors limiting the bioavailability of specific bioactive agents (McClements, 2015a). The *Nutraceutical Bioavailability Classification Scheme* (NuBACS) divides the major factors limiting the bioavailability of bioactives into three major categories

based on the physiochemical or physiological mechanisms limiting bioavailability (**Figure 2**): Bioaccessibility (B^*); Absorption (A^*); Transformation (T^*). For each of these categories, a bioactive agent is given the symbol “(+)” when this mechanism does not have a major influence on bioavailability and “(-)” when it does have a major impact on bioavailability. Associating sub-categories with each major category provides more detailed insight into the mechanisms responsible for limiting the bioavailability of a specific bioactive agent. For bioaccessibility, the sub-categories are poor liberation from the original food matrix (L), poor solubilization in the gastrointestinal fluids (S), and interactions that promote bioactive insolubility (I). For absorption, the sub-categories are poor transport through the mucus layer (ML), tight junctions (TJ), or bilayer membrane (MP), inhibition of active transporters (AT), or the presence of efflux transporters (ET). For transformation, the sub-categories indicate whether the change in bioactivity is due to chemical (C) or metabolic (M) processes. For instance, the NuBACS characterization of curcumin present within powdered turmeric would be $B^*(-)_{L,S} A^*(+) T^*(-)_{C,M}$, because the overall bioavailability is mainly limited by poor liberation from plant cell tissues, poor solubility in gastrointestinal fluids, and chemical/metabolic transformation in the GIT.

3. Emulsion-based delivery and excipient systems

The composition and structure of emulsion-based delivery systems (EDS) and emulsion-based excipient systems (EES) can be specifically designed to increase the bioavailability of hydrophobic bioactives by altering their bioaccessibility, absorption, and/or transformation profiles in the GIT. In this section, we highlight how EDS and EES with different properties can be fabricated, and then highlight how they can be designed to improve bioavailability.

3.1. Fabrication

The two most commonly used emulsion-based systems are oil-in-water conventional emulsions ($d > 100$ nm) or nanoemulsions ($d < 100$ nm), which are comprised of emulsifier-coated oil droplets dispersed in a water phase (McClements, 2015a) (**Figure 3**). These two types of systems are both thermodynamically unstable colloidal dispersions that consist of emulsifier-coated oil droplets suspended within an aqueous medium. The only difference between them is the size of the droplets, which leads to some differences in their physicochemical properties and physiological behavior. In the remainder of this article, the term “emulsion” is used to refer to both conventional emulsions and nanoemulsions for the sake of convenience. A number of

different methods are available to prepare emulsions for research or commercial applications (McClements, 2015a). These methods can be conveniently divided into two major groups: high-energy (HE) methods and low-energy (LE) methods (Yang, Marshall-Breton, Leser, Sher, & McClements, 2012). HE-methods rely on mechanical devices that generate disruptive forces to mix the oil and water phases together, as well as to convert any large oil droplets into smaller ones (Abbas, Hayat, Karangwa, Bashari, & Zhang, 2013). In the food industry, there are a number of different mechanical devices that are used in the laboratory, pilot plant or factory for this purpose, including high-shear mixers, colloid mills, high-pressure valve homogenizers, microfluidizers, sonicators, membrane homogenizers, and microchannel devices (Einhorn-Stoll, Weiss, & Kunzek, 2002; McClements, 2015a; Perrier-Cornet, Marie, & Gervais, 2005). LE-methods do not require the use of specialized equipment; instead they rely on the spontaneous generation of small oil droplets in certain surfactant-oil-water systems when their composition or environment is changed in a specific way (Forgiarini, Esquena, Gonzalez, & Solans, 2001; Komaiko & McClements, 2015; Sadurní, Solans, Azemar, & García-Celma, 2005; Solans & Solé, 2012). The most widely investigated LE-methods for food applications are spontaneous emulsification, emulsion inversion point, and phase inversion temperature methods (Komaiko & McClements, 2014; Ostertag, Weiss, & McClements, 2012; Rao & McClements, 2010; Saberi, Fang, & McClements, 2013). The major advantages of HE-methods are that they can be applied to a wide range of different oil and emulsifier types, and they can generate small droplets at relatively low emulsifier-to-oil ratios (EOR). For example, emulsions can be produced from proteins, polysaccharides, phospholipids, and surfactants often at EORs of 0.1 or less, using flavor oils, essential oils, medium chain triglycerides, or long chain triglycerides (Pichot, Watson, & Norton, 2013; Qiu, Zhao, Decker, & McClements, 2015; Verrijssen et al., 2014). On the other hand, the main disadvantages of these methods are that specialized mechanical devices (homogenizers) are required that must be purchased and maintained (Komaiko & McClements, 2015). The main advantage of LE-methods is that they are simple and inexpensive to implement since no specialized equipment is required to fabricate them. Conversely, the main limitation is that they are usually only suitable for fabricating emulsions from a narrow range of oils and emulsifiers, and require relatively high emulsifier-to-oil ratios. For example, synthetic surfactants (such as Tweens or Spans) are usually required that must be used at emulsifier-to-oil ratios of 0.5 to 2, and only certain types of oil can be homogenized (Komaiko & McClements,

2014; Yang et al., 2012). The availability of various fabrication methods to prepare emulsions means there is considerable scope for designing EDS and EES with different compositions, structures, and properties. Having said this, not all of the available methods are suitable for the large scale production of emulsions required for commercial applications.

3.2. Design Parameters

The composition and structure of oil-in-water emulsions can easily be altered to provide EDS and EES with functional properties tailored for particular applications (**Figure 3**) (McClements, 2015a):

Droplet concentration: The concentration of oil droplets in an emulsion can easily be varied by using different oil-to-water ratios during emulsion formation, or by diluting/concentrating an emulsion after preparation. Emulsions with oil contents ranging from <0.1% to > 50% can be created depending on product formulation and fabrication method. The total oil content of an emulsion may influence various parameters related to the bioavailability of hydrophobic bioactives, such as their partitioning between oil and water phases, their solubilization in mixed micelles, and their permeability through cell membranes (McClements, 2015a).

Droplet size distribution: Emulsion droplet size can simply be controlled by manipulating production formulation and homogenization conditions (McClements, 2011). The particle size distribution of an emulsion influences the physicochemical and sensory properties of food products (such as appearance, texture, mouthfeel, and stability), as well as the gastrointestinal fate of bioactives (Mason, Wilking, Meleson, Chang, & Graves, 2006; Salvia-Trujillo, Qian, Martin-Belloso, & McClements, 2013a). For example, the surface area of oil exposed to lipase in the GIT increases as the droplet size decreases, which will lead to faster lipid digestion and release of bioactives (Salvia-Trujillo et al., 2013a). However, it should be noted that it is the size of the lipid droplets that reaches the small intestine, rather than the initial size, which determines their digestion rate.

Droplet composition: The composition of the lipid phase in oil-in-water emulsions can be altered by including different types and amounts of hydrophobic substances, such as triacylglycerol oils, flavor oils, essential oils, mineral oils, waxes, and antioxidants (Ozturk, Argin, Ozilgen, & McClements, 2015; Xu et al., 2013; Zhang, Zhang, Zhang, Decker, & McClements, 2015b). Moreover, the molecular characteristics of the lipids in a particular category can be varied, such as the chain length, unsaturation, and position of the fatty acids in

188 triacylglycerol molecules. Lipid phase composition influences the rate and extent of lipid
189 digestion within the GIT, and therefore the release rate of hydrophobic bioactives(Ozturk et al.,
190 2015; Salvia-Trujillo, Sun, Urn, Park, & McClements, 2015; Yang & McClements, 2013). The
191 release of free fatty acids and monoacylglycerols from digestible lipids also increases the
192 solubilization capacity of the mixed micelle phase in the small intestine. The nature of the lipid
193 digestion products (such as chain length and unsaturation) impacts the solubilization capacity
194 since it determines the dimensions of the hydrophobic domains with the mixed micelle phase.
195 These domains must be large enough to accommodate the hydrophobic bioactives otherwise they
196 may not be fully solubilized within the GIT fluids.

197 *Structural organization:* The structural organization of the oil droplets in an emulsion also
198 influences their GIT fate(Golding, 2013; Golding et al., 2011). Oil lipid droplets may be freely
199 dispersed, they may be clustered together into flocs, or they may be embedded within carrier
200 particles(McClements, 2015b). These carrier particles can be designed to inhibit the release and
201 digestion of oil droplets in certain regions of the GIT, but then promote their release and
202 digestion in other regions(Day et al., 2014; Wooster et al., 2014). If the oil droplets remain as
203 clusters in the small intestine, then the rate of lipid digestion may be decreased because it is more
204 difficult for the lipase to access the oil droplet surfaces.

205 *Interfacial composition:* The oil droplets in an emulsion are normally coated by an
206 interfacial layer whose composition, structure, thickness, reactivity, and charge can be controlled
207 by using different emulsifier types during emulsion formation, or by using post-homogenization
208 methods, such as electrostatic deposition or competitive adsorption(McClements & Rao, 2011).
209 The properties of the interfacial coating determine the stability of the oil droplets in different
210 parts of the GIT (*e.g.*, whether they are stable, flocculated, or coalesced), which altersthe amount
211 of oil exposed to the digestive enzymes(Golding & Wooster, 2010; Golding et al., 2011). The
212 nature of the interfacial coatings also influences the ability of bile salts and digestive enzymes to
213 adsorb to the surfaces of oil droplets(Couedelo et al., 2015).

214 *Aqueous phase composition:* Water-soluble functional ingredients can be incorporated into
215 the water phase of emulsions either before or after they are formed. These functional ingredients
216 include chelating agents, antioxidants, surfactants, minerals, and biopolymers that may be able to
217 alter the bioaccessibility, absorption, or transformation of hydrophobic bioactives in the
218 GIT(McClements & Xiao, 2014). Specific aqueous phase components may therefore be added

to control specific physicochemical phenomenon that might normally decrease bioavailability. For example, antioxidants could be added to inhibit the oxidation of polyunsaturated lipids within the GIT(Martinez, Nieto, Castillo, & Ros, 2014), or permeation enhancers could be added to increase the absorption of bioactives across the epithelium cells(Wang, Valenzano, Mercado, Zurbach, & Mullin, 2013).

3.3. Mechanisms of Action

Emulsion-based delivery or excipient systems can be designed to improve the bioavailability of hydrophobic bioactives through numerous mechanisms (**Figure 2**). Some of the most important mechanisms that impact the bioaccessibility, absorption, or transformation of hydrophobic bioactives are highlighted in this section.

3.3.1. Bioaccessibility

The oral bioaccessibility (B^*) of a hydrophobic bioactive can be taken to be the fraction of the amount initially ingested that is solubilized within the gastrointestinal fluids in a form that can be absorbed by the epithelium cells(Fernandez-Garcia, Carvajal-Lerida, & Perez-Galvez, 2009). EDS or EES may be designed to enhance the bioaccessibility of hydrophobic bioactives through a number of mechanisms.

Liberation: In the case of excipient systems, the bioactives are originally located within another food product (such as a fruit, vegetable, nut, legume, or cereal). In this case, the emulsions may promote the liberation of the bioactive components from their natural environment and into the GIT fluids. The oilphase in EESacts as an organic solvent that candissolve hydrophobic bioactives, thereby favoring their transfer from plant tissues into oil droplets(Liu, Bi, Xiao, & McClements, 2015, 2016; Salvia-Trujillo & McClements, 2016; Zhang et al., 2016a, 2016b). Small oil droplets may promote transfer theycan penetrate into plant tissues and come into close proximity with the bioactives, and because they have a high specific surface area.An EES may also contain additional ingredients that facilitate the breakdown of the plant tissue and thereby promote the liberationof the bioactives, *e.g.*, chelating agents or surfactants. In the case of EDSs, liberation of the bioactives is not usually a problem since they are already encapsulated within small digestible lipid droplets.

Solubilization: Another important factor impacting the bioaccessibility of hydrophobic bioactives is their solubilization inintestinal fluids. By definition, hydrophobic bioactives have a

low water-solubility, and therefore tend to be insoluble in aqueous GIT fluids. However, their bioaccessibility can be increased considerably if they are solubilized within mixed micelles. Mixed micelles are colloidal structures (usually micelles, vesicles, or liquid crystals) that have non-polar domains capable of incorporating hydrophobic molecules (Yao, Xiao, & McClements, 2014). In micelles, the non-polar domains are the hydrophobic cores formed by the surfactant tails, whereas in vesicles they are the hydrophobic layers formed by the surfactant tails in the bilayer structure. In the absence of digestible lipids, simple micelles are formed by bile salts and phospholipids that can solubilize hydrophobic bioactives up to a certain extent. In the presence of digestible lipids, mixed micelles are formed due to the release of free fatty acids (FFAs) and monoacylglycerols (MAGs) resulting from the action of lipases on the lipid phase (Porter & Wasan, 2008; Yao et al., 2014). The dimensions of the hydrophobic domains formed by the mixed micelle phase are critical in determining the solubilization of hydrophobic bioactives: if these domains are not large enough, then the bioactives will not be solubilized.

Interactions: The bioaccessibility of certain types of hydrophobic bioactives may be limited because their interactions with other constituents in the GIT lead to the formation of insoluble precipitates. For instance, the long chain FFAs released after the digestion of certain sources of lipids may interact with calcium ions in the small intestine and form insoluble salts that are not easily absorbed (Li, Hu, & McClements, 2011). Incorporating ingredients in EDS or EES that inhibit the formation of precipitates may modulate these types of unfavorable interactions. For example, the addition of chelating agents (such as EDTA) may inhibit the formation of insoluble calcium salts with long chain FFAs (Devraj et al., 2013). Nevertheless, it is important to consider other potential roles that any ingredient added to an emulsion may have. If the amount of chelating agents added is too high, then this may actually inhibit lipid digestion by preventing the long chain FFAs being removed from the lipid droplet surfaces.

3.3.2. Absorption

After the hydrophobic bioactives have been solubilized in the gastrointestinal fluids they need to be transported through the mucus layer to the apical surfaces of the epithelium cells that line the GIT (Porter, Trevaskis, & Charman, 2007). Once they reach the epithelium cells the hydrophobic bioactives must be absorbed, which may take place through various mechanisms, such as passive diffusion through the phospholipid bilayers, transfer by active transporters embedded in the bilayers, or diffusion through tight junctions separating cells. The absorption

(A*) can therefore be defined as the fraction of hydrophobic bioactive that is present in a bioaccessible form in the GIT that is actually transported across the layer of epithelium cells by one or more of these mechanisms, and then reaches the systemic circulation. Emulsions can be designed to enhance the absorption of hydrophobic bioactives through a number of processes.

Mucus layer: Designing emulsions that breakdown in the GIT to form mucus-penetrating mixed micelles may promote the transport of hydrophobic bioactives through the mucus layer (Cone, 2009; Lafitte, Thuresson, & Soderman, 2007). These mixed micelles should be small enough to penetrate through the pores (≈ 400 nm) in the mucus, and they should not be strongly attracted to the biopolymer molecules in the gel network(Ensign, Cone, & Hanes, 2012).

Epithelium Cell membranes: After the mixed micelles come near the surface of the epithelial cells they may release hydrophobic bioactives due to the change in local environment (such as pH), and then absorbed by the cells (Fasinu, Pillay, Ndesendo, du Toit, & Choonara, 2011) (**Figure 2**). Many hydrophobic bioactives are absorbed by passive diffusion because they have a relatively high solubility in the non-polar domains of the phospholipid bilayer that makes up the scaffolding of the epithelium cell membranes. Nevertheless, some hydrophobic bioactives may also be absorbed due to the presence of active transporters embedded in the phospholipid bilayers. EDS or EES may be designed to contain ingredients that increase the permeability of the cell membrane by altering active or passive transport mechanisms(Bohdanowicz & Grinstein, 2013). A number of food-grade components have the capability of altering cell membrane permeability, including piperine(Dudhatra et al., 2012), sucrose monoesters (Yamamoto, Katsumi, Kusamori, & Sakane, 2014), and rhamnolipids (Jiang, Long, & Meng, 2013).

Tight Junctions: Very small(less than a few nanometers) water-dispersible molecules or nanoparticles may be transported into the body by travelling through the narrow channels (“tight junctions”) between epithelial cells(Groschwitz & Hogan, 2009). However, some components in foods can increase the dimensions of tight junctions, and thus enhance uptake by this mechanism(Maher, Brayden, Feighery, & McClean, 2008), e.g., Tween 80 (Buyukozturk, Benneyan, & Carrier, 2010; Gupta, Hwang, Doshi, & Mitragotri, 2013); chitosan (Chen et al., 2013; Pillay et al., 2012), zinc (Wang et al., 2013), and EDTA (Lemmer & Hamman, 2013). This may occur through a variety of mechanisms, including modifying protein expression and modulating signaling pathways (Kosinska & Andlauer, 2013).

Efflux Mechanisms: The uptake of some hydrophobic bioactives is limited because of the

presence of efflux transporters in the cell membranes that pump them back into the intestinal lumen (Constantinides & Wasan, 2007; Fasinu et al., 2011). Efflux transporters may reduce the uptake of bioactives by decreasing the total amount absorbed, as well as by increasing the extent of metabolism that occurs as the bioactive moves into and out of the epithelium cells. Some food components inhibit efflux transporters, thereby promoting the uptake of bioactives, *e.g.*, quercetin, resveratrol, and piperine (Challa, Babu, Challa, Johnson, & Maheswari, 2013; Choi, Choi, & Kang, 2009; Jin & Han, 2010; Kang, Cho, Shim, Kim, & Lee, 2009).

3.1.3. Transformation

The overall oral bioavailability of many hydrophobic bioactives is limited because they are prone to chemical or biochemical transformation within the GIT fluids. For instance, curcumin degrades rapidly when exposed to alkaline conditions and certain metabolic enzymes (Heger, van Golen, Broekgaarden, & Michel, 2014), whereas polyunsaturated lipids may undergo degradation due to oxidation reactions (Kenmogne-Domguia, Moisan, Viau, Genot, & Meynier, 2014; Sy, Dangles, Borel, & Caris-Veyrat, 2013). Emulsions may be designed to control the various factors that impact the transformation of bioactive agents.

Control of Molecular Environment: The degradation rate, extent, and pathway of a bioactive molecule often depends on its local molecular environment (McClements & Decker, 2000; Yucel, Elias, & Coupland, 2013). A bioactive molecule may be present in an oil phase, an aqueous phase, or at an oil-water interface, and may have different chemical and biochemical stabilities in these different locations. For example, certain types of chemical reactions involving hydrophobic bioactives occur faster when the molecules are in a water phase than in an oil phase, *e.g.*, acid-catalyzed citral degradation (Choi, Decker, Henson, Popplewell, & McClements, 2009) or base-catalyzed curcumin degradation (Zou et al., 2015). In these cases, it may be important to ensure that the bioactive agents remain within a lipid phase as long as possible throughout the GIT, which may be achieved by altering the oil droplet concentration, size, or composition. Recent studies have shown that the rate of curcumin degradation under simulated GIT conditions occurred more rapidly when the droplet size in an emulsion was decreased (**Figure 4**). This effect may be attributed to the fact that there was a greater fraction of curcumin molecules near the surfaces of the oil droplets as their size decreased, and therefore in closer proximity to the water phase (Zou et al., 2015).

Addition of Inhibitors: Many types of chemical or biochemical degradation reactions can be

inhibited by adding specific molecules (inhibitors) that interact with reactants, intermediates, or products (Dudhatra et al., 2012). A common example is the antioxidants often incorporated into foods to inhibit lipid oxidation (Tarvainen, Phuphusit, Suomela, Kuksis, & Kallio, 2012). Other examples include food constituents that inhibit the activity of enzymes in the GIT, and thereby alter their digestion or metabolism (Dudhatra et al., 2012; Shimizu, 2010). Adding appropriate inhibitors may therefore enhance the fraction of a bioactive component present in a biologically active form within the GIT. The selection of one or more inhibitors for a particular application relies on a good understanding of the mechanisms responsible for degradation of the bioactives involved.

4. Applications of Emulsion-based Systems

In this section, the application of EDS and EES to enhance the bioavailability of hydrophobic bioactives is highlighted. For the sake of convenience, we mainly use examples of research from our own laboratory, but other relevant work is also discussed where applicable. Examples of how emulsion-based systems can be used to alter bioaccessibility, absorption and transformation are discussed in separate sections.

4.1. Bioaccessibility

The most commonly used approach of increasing the overall bioavailability of hydrophobic bioactives using emulsion-based systems has been to enhance their dispersion/solubility in aqueous GIT fluids. The lipid droplets in emulsions act as a non-polar phase that can incorporate hydrophobic bioactives in a form that can easily be dispersed in water (Degrou, George, Renard, & Page, 2013; Zou, Liu, Liu, Xiao, & McClements, 2015a). The hydrophobic bioactives are added to the oil phase prior to homogenization in the case of delivery systems, but may be transferred into the oil phase after mixing with a food in the case of excipient systems. Oil droplets can then carry the hydrophobic bioactives through the GIT until they reach a location where they are digested and release the bioactives. If the oil droplets are fabricated from digestible lipids (such as triacylglycerols), then they will generate free fatty acids (FFAs) and monoacylglycerols (MAGs) when they are digested by lipase (**Figure 5**). The FFAs and MAGs released from the oil droplets interact with phospholipids, bile salts, and cholesterol released by the body to form mixed micelles (Devraj et al., 2013). As mentioned earlier, the mixed micelle phase is a compositionally and structurally complex colloidal dispersion that contains micelles,

vesicles, and liquid crystals(Yao et al., 2014). These colloidal particles have non-polar domains capable of solubilizing hydrophobic bioactives, and certain types of them (micelles) are small enough to transport the bioactives through the mucus layer to the epithelium cells where they are absorbed. The ability of emulsions to increase the bioaccessibility of hydrophobic bioactives depends on the concentration, size, composition, aggregation state, and interfacial properties of the oil droplets.

Oil Concentration: *In vitro* and *in vivo* studies have shown that the bioaccessibility of hydrophobic bioactives can be improved when they are ingested with sufficiently high amounts of certain types of digestible lipids. As an example, data from the author's laboratory on the influence of lipid content of EES on the bioaccessibility of carotenoids from carrots is shown in **Figure 6**. Carotenoid bioaccessibility increased as the oil concentration of co-ingested oil-in-water emulsions was increased from 0 to 8%. These emulsions were fabricated from long chain triglycerides (corn oil) that are able to generate a mixed micelle phase with non-polar domains large enough to accommodate carotenoid molecules. The amount of mixed micelles formed after lipid digestion increases as the amount of digestible oil droplets increases, thereby leading to greater carotenoid solubilization. Numerous other studies have also reported an increase in the bioaccessibility of hydrophobic bioactives with increasing oil droplet concentration in emulsions. The bioaccessibility of carotenoids naturally present in salad vegetables was reported to increase as the amount of co-ingested oil droplets increased (Huo, Ferruzzi, Belury, Schwartz, & Failla, 2007a; Huo, Ferruzzi, Schwartz, & Failla, 2007b; Moelants et al., 2012; Svelander, Lopez-Sanchez, Pudney, Schumm, & Alminger, 2011). Studies using a simulated GIT have shown that the bioaccessibility of carotenoids and curcumin is increased in the presence of digestible oil droplets (Ahmed, Li, McClements, & Xiao, 2012; Liu et al., 2015, 2016; Salvia-Trujillo & McClements, 2016; Salvia-Trujillo, Qian, Martin-Belloso, & McClements, 2013b; Zhang et al., 2016b). Animal feeding studies have reported that the bioavailability of carotenoids and Coenzyme Q10 increased in the presence of fat in emulsion-based delivery systems, which was mainly attributed to their ability to increase bioaccessibility (Cho et al., 2014b; Salvia-Trujillo et al., 2015; Sato et al., 2011). The bioaccessibility of genistein solubilized in the fat phase of model custards was reported to increase in the presence of fat (Sanz & Luyten, 2007). The bioaccessibility of cocoa polyphenols from cocoa liquor increased with fat content, which

was attributed to the formation of mixed micelles that could solubilize the hydrophobic bioactives (Ortega, Reguant, Romero, Macià, & Motilva, 2009).

Oil Type: The nature of the oil phase used to fabricate emulsions also has a major effect on the bioaccessibility of some hydrophobic bioactives because it impacts the dimensions of the non-polar domains formed within the mixed micelle phase (Porter et al., 2007; Porter & Wasan, 2008). The bioaccessibility of hydrophobic bioactives has been reported to be much lower when the co-ingested oil droplets contain indigestible lipids (such as a mineral, essential, or flavor oils) than when they contain digestible lipids (such as triglyceride oils) (Cho et al., 2014a; Ozturk et al., 2015; Qian et al., 2012; Rao, Decker, Xiao, & McClements, 2013; Salvia-Trujillo et al., 2013b). At least two physicochemical processes may contribute to this phenomenon. First, the hydrophobic bioactives may not be fully liberated from oil droplets containing indigestible lipids. Instead, they remain trapped inside the hydrophobic droplet interiors and pass through the small intestine without being absorbed. Second, there will be no FFAs and MAGs generated from oil droplets comprised of indigestible lipids, and therefore they cannot enhance the solubilization capacity of the mixed micelle phase.

As mentioned previously, bioaccessibility also depends on the molecular dimensions of the hydrophobic bioactives compared to the non-polar domains in the mixed micelle phase (**Figure 5**). The dimensions of these non-polar domains would be expected to increase with increasing chain length of the hydrocarbon tails of phospholipids, fatty acids, and monoacylglycerols (Israelachvili, 2011). In addition, they would be expected to decrease with increasing unsaturation of the hydrocarbon tails because double bonds cause the tails to become more kinked. The non-polar domains in the mixed micelle phase must be sufficiently large to incorporate the hydrophobic bioactives, otherwise there will be a thermodynamic penalty associated with the unfavorable contact between protruding non-polar bioactives and the surrounding aqueous phase. A number of studies have demonstrated that this phenomenon is particularly important for carotenoids because they are relatively long hydrophobic molecules (Colle, Van Buggenhout, Lemmens, Van Loey, & Hendrickx, 2012; Huo et al., 2007b; Nik et al., 2011; Qian et al., 2012; Salvia-Trujillo et al., 2013b). For example, the bioaccessibility of β -carotene has been reported to be much greater when the oil droplets in both EDS and EES are comprised of long chain triglycerides (LCT) rather than medium chain

triglycerides (MCT)(**Figure 7**). The composition of the oil droplets has also been shown to have a major impact on the bioaccessibility of vitamin D (Ozturk et al., 2015), vitamin E (Yang, Decker, Xiao, & McClements, 2015; Yang & McClements, 2013), Coenzyme Q10 (Cho et al., 2014a), and curcumin (Ahmed et al., 2012). The bioaccessibility of carotenoids from salad vegetables has also been reported to depend on oil type (Huo et al., 2007a; Huo et al., 2007b). The impact of oil phase composition on bioaccessibility depends on bioactive type (**Figure 8**), because this will influence their molecular dimensions and surface chemistry, which will impact their ability to be incorporated into the hydrophobic domains present in the mixed micelle phase.

Droplet Size: The dimensions of the oil droplets in emulsion-based systems may also impact the bioaccessibility of hydrophobic bioactives. Smaller oil droplets are usually digested at a faster rate than larger ones because they have a greater surface area exposed to the lipase molecules (Golding & Wooster, 2010; Li & McClements, 2010). Consequently, the bioactives may be released more rapidly, and the mixed micelle phase may be formed more quickly. Since the majority of lipid digestion and bioactive absorption occurs within the small intestine, it is important to note that it is the dimensions of the oil droplets in this region of the GIT (rather than their initial dimensions) that determines the bioaccessibility. If oil droplets become flocculated or coalesced as they pass through the mouth, stomach, and small intestine, then the rate and extent of lipid digestion and bioactive release may be reduced compared to free droplets (Golding et al., 2011).

The impact of oil droplet dimensions is demonstrated in recent work in our laboratory on the impact of EES on the bioaccessibility of carotenoids from carrots (**Figure 9a**). The bioaccessibility was considerably greater for smaller oil droplets ($d < 500$ nm) than for larger ones ($d > 10,000$ nm), which can be attributed to faster and more extensive digestion of the smaller droplets (**Figure 9b**). As a result, the mixed micelle phase was capable of rapidly solubilizing any carotenoids released from the oil droplets into the intestinal fluids. Numerous other studies using emulsion-based delivery systems have reported that the bioaccessibility of hydrophobic bioactives increases as droplet dimensions decrease for the same reason (Cho et al., 2014a; Liu, Hou, Lei, Chang, & Gao, 2012; Salvia-Trujillo et al., 2013a). Similar results have been reported for emulsion-based excipient systems, *e.g.*, the bioaccessibility of carotenoids from carrots increased with decreasing lipid droplet size (Zhang et al., 2016a).

Interfacial Properties: The nature of the oil droplet interface may also influence bioactive

bioaccessibility through a number of mechanisms. First, the interfacial layer impacts the aggregation state of the oil droplets as they pass through the various stages of the GIT, which influences the lipid surface area exposed to the lipase in the intestinal fluids(Golding et al., 2011). Thus, if the droplets are highly flocculated or coalesced when they reach the small intestine, there will be a decrease in the rate of lipid digestion and bioactive release. Second, the ability of bile salts and lipase to adsorb to the oil droplet surfaces and promote lipid digestion depends on the nature of the interfacial coating. Some emulsifiers are much more effective at inhibiting lipase digestion than others(Li & McClements, 2011; Speranza et al., 2013; Zhang, Zhang, Zhang, Decker, & McClements, 2015a). Thus, by selecting different emulsifiers to modulate interfacial properties, it may be possible to alter lipid digestion and bioactive bioaccessibility(Zou, Liu, Liu, Xiao, & McClements, 2015).Alternatively, it may be possible to modulate these parameters by trapping the oil droplets in larger structures, such as particles fabricated from proteins or polysaccharides (**Figure 2**). In this case, the larger structures surrounding the lipid droplets may have to become porous or disintegrate before the lipid droplets can be digested(McClements, 2010).

4.2.Absorption

Manipulating emulsion properties can also be utilized to modulate the absorption of hydrophobic bioactives by epithelium cells. Various food-grade ingredients have the ability to increase absorption by altering transport mechanisms, tight junctions, or efflux mechanisms, *e.g.*,certain biopolymers, fatty acids, chelating agents, minerals, phytochemicals, and surfactants (Aungst, 2012; Jin & Han, 2010; Whitehead & Mitragotri, 2008).

Studies using a simulated GIT have shown that oil type has a major impact on the structure of the mixed micelles generated, as well as on the structure of the oil bodies and chylomicrons formed within epithelium cells (**Figure 10**)(Yao et al., 2013; Yao et al., 2014). One would expect that the transport of hydrophobic bioactives through the mucus layer would depend on the structure of the mixed micelles, and so may be influenced by oil type. The nature of the oil phase may also influence absorption by altering cell membrane permeability. In a recent, cell culture study it was shown that olive oil led to a greater absorption of a highly hydrophobic bioactive (pterostilbene)than flaxseed oil (Sun et al., 2015). Olive oil is rich inmonounsaturated fatty acids (such as oleic and linoleic acids), which are known to beeffective epithelium cellpermeability enhancers(Whitehead, Karr, & Mitragotri, 2008).Oleic acid is also known to be an effective

efflux inhibitor (Aspenstrom-Fagerlund, Tallkvist, Ilback, & Glynn, 2012), which may promote absorption and decrease metabolism of bioactive agents. The selection of an appropriate oil phase may therefore be an effective way to enhance the absorption of some bioactive agents.

There has been much less work on designing emulsions to alter the absorption of hydrophobic bioactives than to alter their bioaccessibility. Consequently, this will be an important area for research in the future.

4.3. Transformation

Emulsions may also be designed to alter the chemical or biochemical transformation of hydrophobic bioactives in the GIT. For many bioactives, it is desirable to inhibit the transformation of the parent molecule because it is the most bioavailable or bioactive form. However, for other bioactives it may actually be beneficial to promote the transformation of the parent molecule to a particular metabolite because it is more bioavailable or bioactive.

The transformation of hydrophobic bioactives in the GIT may be controlled through a number of approaches. First, it is possible to add active ingredients that inhibit or promote certain types of chemical or biochemical reactions. The oxidative degradation of astaxanthin has been inhibited by adding chelating agents (EDTA) or antioxidants (α -tocopherol) to emulsions (Tamjidi, Shahedi, Varshosaz, & Nasirpour, 2014). The oxidative degradation of lutein solubilized in oil droplets has been inhibited by adding certain kinds of food-grade emulsifiers, *e.g.*, proteins and lecithins (Frede et al., 2014). Piperine has been shown to inhibit curcumin degradation due to its ability to interfere with the activity of certain metabolic enzymes, such as β -glucuronidase (Gulseren, Guri, & Corredig, 2014). Certain types of food-grade emulsifiers can inhibit the degradation of curcumin under simulated GIT conditions, which was attributed to their ability to act as antioxidants (Zou et al., 2015). The addition of these ingredients to emulsions may therefore be used to ensure that a higher fraction of the bioactive is in a more bioavailable or biologically active form.

Second, it is often possible to control the molecular environment of hydrophobic bioactives within the GIT. As mentioned earlier, many bioactives are more stable to chemical or biochemical transformation when they are present within an organic phase (oil) than an aqueous phase (water), and therefore they can be protected by being contained within the interior of oil droplets or mixed micelles (Section 3.1.3).

Third, the transformation of hydrophobic bioactives in the GIT may also depend on the

pathway through which they are transported to the systemic circulation, *i.e.*, portal vein *versus* lymphatic system (Porter & Wasan, 2008; Pouton & Porter, 2008). Predominantly hydrophilic compounds are usually transported into the systemic circulation via the portal vein. As a result, they have to pass through the liver where they undergo extensive modification due to first-pass metabolism. On the other hand, predominantly hydrophobic compounds are packaged into lipoproteins (such as chylomicrons) in the epithelium cells and then transported into the systemic circulation *via* the lymphatic system. In this case, the bioactives do not undergo first-pass metabolism, which may improve their biological activity by reducing their biochemical modification. The absorption pathway of a hydrophobic bioactive may therefore depend on the nature of the digestible lipids ingested with it, since this will impact the nature of the chylomicrons formed (Yao et al., 2014).

Thus, it should be possible to control the transformation of hydrophobic bioactives within the GIT by controlling the composition and structure of emulsions. Consequently, a pathway could be promoted that leads to the highest concentration of the most bioavailable and bioactive metabolites in the GIT. Again, there has been little research in this area previously, and this would be an interesting topic for research in the future.

5. Conclusions

This review article has highlighted the potential for emulsion-based delivery systems (EDS) and excipient systems (EES) to improve the bioavailability of hydrophobic bioactives by controlling the structure and composition of the gastrointestinal contents. Emulsions may be designed to improve the bioaccessibility, absorption, and transformation profiles of hydrophobic bioactives. For example, the bioaccessibility can be improved by forming a mixed micelle phase that contains non-polar domains that are sufficiently numerous and large to accommodate all of the hydrophobic bioactives released. This can be achieved by utilizing EDS or EES that contain sufficiently high quantities of digestible long-chain triglycerides. The absorption can be improved by utilizing emulsions that are capable of forming mixed micelles that easily penetrate through the mucus layer, by incorporating permeation enhancers in the emulsions, or by including efflux inhibitors. The chemical or biochemical transformation of labile bioactives can be manipulated by controlling their molecular environment (oil, water, or interfacial regions) in the GIT, or by adding food components that modulate degradation reactions, such as antioxidants

or chelating agents. The design of emulsions to improve the bioavailability profiles of bioactives is a rapidly growing area, and is likely to continue to advance in the near future. Ultimately, the knowledge gained from these studies should lead to the rational design of functional food and beverage products with improved health promoting attributes.

6. Acknowledgements

This material was partly based upon work supported by the Cooperative State Research, Extension, Education Service, USDA, Massachusetts Agricultural Experiment Station and USDA, NRI Grants (2011-03539, 2013-03795, 2011-67021, and 2014-67021). We also thank the National Aero and Space Administration (NASA) for partial funding of this research (NNX14AP32G), as well as the National Natural Science Foundation of China (NSFC31428017), and the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah (330-130-1435-DSR, 299-130-1435-DSR, 87-130-35-HiCi).

- Abbas, S., Hayat, K., Karangwa, E., Bashari, M., & Zhang, X. (2013). An overview of ultrasound-assisted food-grade nanoemulsions. *Food Engineering Reviews*, 5(3), 139-157.
- Ahmed, K., Li, Y., McClements, D. J., & Xiao, H. (2012). Nanoemulsion- and emulsion-based delivery systems for curcumin: Encapsulation and release properties. *Food Chemistry*, 132(2), 799-807.
- Aluko, R. E. (2012). *Functional Foods and Nutraceuticals*. New York, NY: Springer.
- Aspenstrom-Fagerlund, B., Tallkvist, J., Ilback, N. G., & Glynn, A. W. (2012). Oleic acid decreases BCRP mediated efflux of mitoxantrone in Caco-2 cell monolayers. *Food and Chemical Toxicology*, 50(10), 3635-3645.
- Aungst, B. J. (2012). Absorption Enhancers: Applications and Advances. *Aaps Journal*, 14(1), 10-18.
- Bohdanowicz, M., & Grinstein, S. (2013). Role of phospholipids in endocytosis, phagocytosis, and macropinocytosis. [Review]. *Physiological Reviews*, 93(1), 69-106.
- Buyukozturk, F., Benneyan, J. C., & Carrier, R. L. (2010). Impact of emulsion-based drug delivery systems on intestinal permeability and drug release kinetics. *Journal of Controlled Release*, 142(1), 22-30.
- Challa, V. R., Babu, P. R., Challa, S. R., Johnson, B., & Maheswari, C. (2013). Pharmacokinetic interaction study between quercetin and valsartan in rats and in vitro models. [Article]. *Drug Development and Industrial Pharmacy*, 39(6), 865-872.
- Chen, M. C., Mi, F. L., Liao, Z. X., Hsiao, C. W., Sonaje, K., Chung, M. F., Hsu, L. W., & Sung, H. W. (2013). Recent advances in chitosan-based nanoparticles for oral delivery of macromolecules. *Advanced Drug Delivery Reviews*, 65(6), 865-879.
- Cho, H. T., Salvia-Trujillo, L., Kim, J., Park, Y., Xiao, H., & McClements, D. (2014a). Droplet size and composition of nutraceutical nanoemulsions influences bioavailability of long chain fatty acids and Coenzyme Q10. *Food Chemistry*, 156, 117-122.
- Cho, H. T., Salvia-Trujillo, L., Kim, J., Park, Y., Xiao, H., & McClements, D. J. (2014b). Droplet

- size and composition of nutraceutical nanoemulsions influences bioavailability of long chain fatty acids and Coenzyme Q10. *Food Chemistry*, 156, 117-122.
- Choi, J. S., Choi, B. C., & Kang, K. W. (2009). Effect of resveratrol on the pharmacokinetics of oral and intravenous nicardipine in rats: possible role of P-glycoprotein inhibition by resveratrol. [Article]. *Pharmazie*, 64(1), 49-52.
- Choi, S. J., Decker, E. A., Henson, L., Popplewell, L. M., & McClements, D. J. (2009). Stability of Citral in Oil-in-Water Emulsions Prepared with Medium-Chain Triacylglycerols and Triacetin. *Journal of Agricultural and Food Chemistry*, 57(23), 11349-11353.
- Colle, I. J. P., Van Buggenhout, S., Lemmens, L., Van Loey, A. M., & Hendrickx, M. E. (2012). The type and quantity of lipids present during digestion influence the in vitro bioaccessibility of lycopene from raw tomato pulp. *Food Research International*, 45(1), 250-255.
- Cone, R. A. (2009). Barrier properties of mucus. *Advanced Drug Delivery Reviews*, 61(2), 75-85.
- Constantinides, P. P., & Wasan, K. M. (2007). Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein (P-gp) substrate drugs: In vitro/in vivo case studies. [Review]. *Journal of Pharmaceutical Sciences*, 96(2), 235-248.
- Couedelo, L., Amara, S., Lecomte, M., Meugnier, E., Monteil, J., Fonseca, L., Pineau, G., Cansell, M., Carriere, F., Michalski, M. C., & Vaysse, C. (2015). Impact of various emulsifiers on ALA bioavailability and chylomicron synthesis through changes in gastrointestinal lipolysis. *Food & Function*, 6(5), 1726-1735.
- Day, L., Golding, M., Xu, M., Keogh, J., Clifton, P., & Wooster, T. J. (2014). Tailoring the digestion of structured emulsions using mixed monoglyceride-caseinate interfaces. *Food Hydrocolloids*, 36, 151-161.
- Degrou, A., George, S., Renard, C., & Page, D. (2013). Physicochemical parameters that influence carotenoids bioaccessibility from a tomato juice. *Food Chemistry*, 136(2), 435-441.
- Devraj, R., Williams, H. D., Warren, D. B., Mullertz, A., Porter, C. J. H., & Pouton, C. W. (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. *International Journal of Pharmaceutics*, 441(1-2), 323-333.
- Dudhatra, G. B., Mody, S. K., Awale, M. M., Patel, H. B., Modi, C. M., Kumar, A., Kamani, D. R., & Chauhan, B. N. (2012). A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers. *Scientific World Journal*.
- Einhorn-Stoll, U., Weiss, M., & Kunzek, H. (2002). Influence of the emulsion components and preparation method on the laboratory-scale preparation of o/w emulsions containing different types of dispersed phases and/or emulsifiers. *Food/Nahrung*, 46(4), 294-301.
- Ensign, L. M., Cone, R., & Hanes, J. (2012). Oral drug delivery with polymeric nanoparticles: The gastrointestinal mucus barriers. [Review]. *Advanced Drug Delivery Reviews*, 64(6), 557-570.
- Fasinu, P., Pillay, V., Ndesendo, V. M. K., du Toit, L. C., & Choonara, Y. E. (2011). Diverse approaches for the enhancement of oral drug bioavailability. [Review]. *Biopharmaceutics & Drug Disposition*, 32(4), 185-209.
- 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. [Review]. *Food Research International*, 46(2), 438-450.
- Fernandez-Garcia, E., Carvajal-Lerida, I., & Perez-Galvez, A. (2009). In vitro bioaccessibility assessment as a prediction tool of nutritional efficiency. *Nutrition Research*, 29(11), 751-760.
- Forgiarini, A., Esquena, J., Gonzalez, C., & Solans, C. (2001). Formation of nano-emulsions by low-energy emulsification methods at constant temperature. *Langmuir*, 17(7), 2076-2083.
- Frede, K., Henze, A., Khalil, M., Baldermann, S., Schweigert, F. J., & Rawel, H. (2014). Stability and cellular uptake of lutein-loaded emulsions. *Journal of Functional Foods*, 8, 118-127.
- Golding, M. (2013). The Colloidal State and its Relationship to Lipid Digestion. *Formulation Engineering of Foods*, 196-232.
- Golding, M., & Wooster, T. J. (2010). The influence of emulsion structure and stability on lipid digestion. *Current Opinion in Colloid & Interface Science*, 15(1-2), 90-101.
- Golding, M., Wooster, T. J., Day, L., Xu, M., Lundin, L., Keogh, J., & Clifton, P. (2011). Impact of gastric structuring on the lipolysis of emulsified lipids. *Soft Matter*, 7(7), 3513-3523.
- Groschwitz, K. R., & Hogan, S. P. (2009). Intestinal barrier function: Molecular regulation and disease pathogenesis. *Journal of Allergy and Clinical Immunology*, 124(1), 3-20.
- Gulseren, I., Guri, A., & Corredig, M. (2014). Effect of interfacial composition on uptake of curcumin-piperine mixtures in oil in water emulsions by Caco-2 cells. *Food & Function*, 5(6), 1218-1223.
- Gupta, V., Hwang, B. H., Doshi, N., & Mitragotri, S. (2013). A permeation enhancer for increasing transport of therapeutic macromolecules across the intestine. *Journal of Controlled Release*, 172(2), 541-549.
- Heger, M., van Golen, R. F., Broekgaarden, M., & Michel, M. C. (2014). The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancer. *Pharmacological reviews*, 66(1), 222-307.
- Huang, Q., Yu, H., & Ru, Q. (2010). Bioavailability and delivery of nutraceuticals using nanotechnology. *Journal of Food Science*, 75(1), R50-R57.
- Huo, T., Ferruzzi, M. G., Belury, M. A., Schwartz, S. J., & Failla, M. L. (2007a). Impact of amount and triglyceride (TG) structure on micellarization of dietary carotenoids during simulated digestion. *Faseb Journal*, 21(5), A730-A731.
- Huo, T., Ferruzzi, M. G., Schwartz, S. J., & Failla, M. L. (2007b). Impact of fatty acyl composition and quantity of triglycerides on bioaccessibility of dietary carotenoids. *Journal of Agricultural and Food Chemistry*, 55(22), 8950-8957.
- Israelachvili, J. N. (2011). *Intermolecular and Surface Forces (third edition)*. London, UK: Academic Press.
- Jiang, L. F., Long, X. W., & Meng, Q. (2013). Rhamnolipids enhance epithelial permeability in Caco-2 monolayers. [Article]. *International Journal of Pharmaceutics*, 446(1-2), 130-135.
- Jin, M. J., & Han, H. K. (2010). Effect of Piperine, a Major Component of Black Pepper, on the Intestinal Absorption of Fexofenadine and Its Implication on Food-Drug Interaction. [Article]. *Journal of Food Science*, 75(3), H93-H96.
- Kang, M. J., Cho, J. Y., Shim, B. H., Kim, D. K., & Lee, J. (2009). Bioavailability enhancing activities of natural compounds from medicinal plants. [Review]. *Journal of Medicinal Plants Research*, 3(13), 1204-1211.
- Kenmogne-Domguia, H. B., 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 Chemistry*, 152, 146-154.
- Kim, S.-K., & Mendis, E. (2006). Bioactive compounds from marine processing byproducts—a review. *Food Research International*, 39(4), 383-393.
- Komaiko, J., & McClements, D. J. (2014). Optimization of isothermal low-energy nanoemulsion formation: Hydrocarbon oil, non-ionic surfactant, and water systems. *Journal of colloid and interface science*, 425, 59-66.
- Komaiko, J., & McClements, D. J. (2015). Low-energy formation of edible nanoemulsions by spontaneous emulsification: Factors influencing particle size. *Journal of Food Engineering*, 146, 122-128.
- Kosinska, A., & Andlauer, W. (2013). Modulation of tight junction integrity by food components. *Food Research International*, 54(1), 951-960.
- Lafitte, G., Thuresson, K., & Soderman, O. (2007). Diffusion of nutrients molecules and model drug carriers through mucin layer investigated by magnetic resonance imaging with chemical shift resolution. *Journal of Pharmaceutical Sciences*, 96(2), 258-263.
- Lemmer, H. J. R., & Hamman, J. H. (2013). Paracellular drug absorption enhancement through tight junction modulation. *Expert Opinion on Drug Delivery*, 10(1), 103-114.
- Li, Y., Hu, M., & McClements, D. J. (2011). Factors affecting lipase digestibility of emulsified lipids using an in vitro digestion model: proposal for a standardised pH-stat method. *Food Chemistry*, 126(2), 498-505.
- Li, Y., & McClements, D. J. (2010). New mathematical model for interpreting pH-stat digestion profiles: Impact of lipid droplet characteristics on in vitro digestibility. *Journal of Agricultural and Food Chemistry*, 58(13), 8085-8092.
- Li, Y., & McClements, D. J. (2011). Inhibition of lipase-catalyzed hydrolysis of emulsified triglyceride oils by low-molecular weight surfactants under simulated gastrointestinal conditions. *European Journal of Pharmaceutics and Biopharmaceutics*, 79(2), 423-431.
- Liu, X., Bi, J., Xiao, H., & McClements, D. J. (2015). Increasing Carotenoid Bioaccessibility from Yellow Peppers Using Excipient Emulsions: Impact of Lipid Type and Thermal Processing. *Journal of Agricultural and Food Chemistry*, 63(38), 8534-8543.
- Liu, X., Bi, J., Xiao, H., & McClements, D. J. (2016). Enhancement of Nutraceutical Bioavailability using Excipient Nanoemulsions: Role of Lipid Digestion Products on Bioaccessibility of Carotenoids and Phenolics from Mangoes. *Journal of Food Science*, 81(3), N754-N761.
- Liu, Y. W., Hou, Z. Q., Lei, F., Chang, Y. Y., & Gao, Y. X. (2012). Investigation into the bioaccessibility and microstructure changes of beta-carotene emulsions during in vitro digestion. *Innovative Food Science & Emerging Technologies*, 15, 86-95.
- Maher, S., Brayden, D. J., Feighery, L., & McClean, S. (2008). Cracking the junction: Update on the progress of gastrointestinal absorption enhancement in the delivery of poorly absorbed drugs. [Review]. *Critical Reviews in Therapeutic Drug Carrier Systems*, 25(2), 117-168.
- Martinez, J., Nieto, G., Castillo, J., & Ros, G. (2014). Influence of in vitro gastrointestinal digestion and/or grape seed extract addition on antioxidant capacity of meat emulsions. *Lwt-Food Science and Technology*, 59(2), 834-840.
- Marze, S. (2013). Bioaccessibility of Nutrients and Micronutrients from Dispersed Food Systems: Impact of the Multiscale Bulk and Interfacial Structures. *Critical Reviews in Food Science and Nutrition*, 53(1), 76-108.

- Mason, T. G., Wilking, J. N., Meleson, K., Chang, C. B., & Graves, S. M. (2006). Nanoemulsions: formation, structure, and physical properties. *Journal of Physics: Condensed Matter*, 18(41), R635.
- McClements, D. J. (2010). Emulsion design to improve the delivery of functional lipophilic components. In M. P. Doyle & T. R. Klaenhammer (Eds.), *Annual Review of Food Science and Technology, Vol 1* (Vol. 1, pp. 241-269).
- McClements, D. J. (2011). Edible nanoemulsions: fabrication, properties, and functional performance. *Soft Matter*, 7(6), 2297-2316.
- McClements, D. J. (2015a). *Food Emulsions: Principles, Practice, and Techniques* (Third ed.). Boca Raton: CRC Press.
- McClements, D. J. (2015b). *Nanoparticle- and Microparticle-based Delivery Systems: Encapsulations, Protection and Release of Active Compounds*. Boca Raton, FL: CRC Press.
- McClements, D. J., & Decker, E. A. (2000). Lipid oxidation in oil-in-water emulsions: Impact of molecular environment on chemical reactions in heterogeneous food systems. *Journal of Food Science*, 65(8), 1270-1282.
- McClements, D. J., & Rao, J. (2011). Food-Grade Nanoemulsions: Formulation, Fabrication, Properties, Performance, Biological Fate, and Potential Toxicity. *Critical Reviews in Food Science and Nutrition*, 51(4), 285-330.
- McClements, D. J., & Xiao, H. (2014). Excipient foods: designing food matrices that improve the oral bioavailability of pharmaceuticals and nutraceuticals. *Food & Function*, 5(7), 1320-1333.
- Moelants, K. R. N., Lemmens, L., Vandebroeck, M., Van Buggenhout, S., Van Loey, A. M., & Hendrickx, M. E. (2012). Relation between Particle Size and Carotenoid Bioaccessibility in Carrot- and Tomato-Derived Suspensions. [Article]. *Journal of Agricultural and Food Chemistry*, 60(48), 11995-12003.
- Nik, A. M., Corredig, M., & Wright, A. J. (2011). Release of lipophilic molecules during in vitro digestion of soy protein-stabilized emulsions. *Molecular Nutrition & Food Research*, 55, S278-S289.
- Norton, J. E., Espinosa, Y. G., Watson, R. L., Spyropoulos, F., & Norton, I. T. (2015). Functional food microstructures for macronutrient release and delivery. *Food & Function*, 6(3), 663-678.
- 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. *Journal of agricultural and food chemistry*, 57(13), 5743-5749.
- Ostertag, F., Weiss, J., & McClements, D. J. (2012). Low-energy formation of edible nanoemulsions: factors influencing droplet size produced by emulsion phase inversion. *Journal of colloid and interface science*, 388(1), 95-102.
- Ozturk, B., Argin, S., Ozilgen, M., & McClements, D. J. (2015). Nanoemulsion delivery systems for oil-soluble vitamins: Influence of carrier oil type on lipid digestion and vitamin D-3 bioaccessibility. *Food Chemistry*, 187, 499-506.
- Perrier-Cornet, J. M., Marie, P., & Gervais, P. (2005). Comparison of emulsification efficiency of protein-stabilized oil-in-water emulsions using jet, high pressure and colloid mill homogenization. *Journal of Food Engineering*, 66(2), 211-217.
- Pichot, R., Watson, R. L., & Norton, I. T. (2013). Phospholipids at the interface: current trends and challenges. *International journal of molecular sciences*, 14(6), 11767-11794.

- Pillay, V., Hibbins, A. R., Choonara, Y. E., du Toit, L. C., Kumar, P., & Ndesendo, V. M. K. (2012). Orally Administered Therapeutic Peptide Delivery: Enhanced Absorption Through the Small Intestine Using Permeation Enhancers. [Article]. *International Journal of Peptide Research and Therapeutics*, 18(3), 259-280.
- Porter, C. J. H., Trevaskis, N. L., & Charman, W. N. (2007). Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nature Reviews Drug Discovery*, 6(3), 231-248.
- Porter, C. J. H., & Wasan, K. M. (2008). Lipid-based systems for the enhanced delivery of poorly water soluble drugs. *Advanced Drug Delivery Reviews*, 60(6), 615-616.
- Pouton, C. W., & Porter, C. J. (2008). Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Adv Drug Deliv Rev*, 60(6), 625-637.
- Qian, C., Decker, E. A., Xiao, H., & McClements, D. J. (2012). Nanoemulsion delivery systems: Influence of carrier oil on beta-carotene bioaccessibility. [Article]. *Food Chemistry*, 135(3), 1440-1447.
- Qiu, C., Zhao, M., Decker, E. A., & McClements, D. J. (2015). Influence of protein type on oxidation and digestibility of fish oil-in-water emulsions: Gliadin, caseinate, and whey protein. *Food chemistry*, 175, 249-257.
- Rao, J., & McClements, D. J. (2010). Stabilization of phase inversion temperature nanoemulsions by surfactant displacement. *Journal of agricultural and food chemistry*, 58(11), 7059-7066.
- Rao, J. J., Decker, E. A., Xiao, H., & McClements, D. J. (2013). Nutraceutical nanoemulsions: influence of carrier oil composition (digestible versus indigestible oil) on -carotene bioavailability. *Journal of the Science of Food and Agriculture*, 93(13), 3175-3183.
- Rein, M. J., Renouf, M., Cruz-Hernandez, C., Actis-Goretti, L., Thakkar, S. K., & Pinto, M. D. (2013). Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. [Article]. *British Journal of Clinical Pharmacology*, 75(3), 588-602.
- Saberi, A. H., Fang, Y., & McClements, D. J. (2013). Fabrication of vitamin E-enriched nanoemulsions: factors affecting particle size using spontaneous emulsification. *Journal of colloid and interface science*, 391, 95-102.
- Sadurní, N., Solans, C., Azemar, N., & García-Celma, M. J. (2005). Studies on the formation of O/W nano-emulsions, by low-energy emulsification methods, suitable for pharmaceutical applications. *European Journal of Pharmaceutical Sciences*, 26(5), 438-445.
- Salvia-Trujillo, L., & McClements, D. J. (2016). Enhancement of lycopene bioaccessibility from tomato juice using excipient emulsions: Influence of lipid droplet size. *Food Chemistry*, 210, 295-304.
- Salvia-Trujillo, L., Qian, C., Martin-Belloso, O., & McClements, D. J. (2013a). Influence of particle size on lipid digestion and beta-carotene bioaccessibility in emulsions and nanoemulsions. *Food Chemistry*, 141(2), 1472-1480.
- Salvia-Trujillo, L., Qian, C., Martin-Belloso, O., & McClements, D. J. (2013b). Modulating beta-carotene bioaccessibility by controlling oil composition and concentration in edible nanoemulsions. *Food Chemistry*, 139(1-4), 878-884.
- Salvia-Trujillo, L., Sun, Q., Urn, B. H., Park, Y., & McClements, D. J. (2015). In vitro and in vivo study of fucoxanthin bioavailability from nanoemulsion-based delivery systems: Impact of lipid carrier type. *Journal of Functional Foods*, 17, 293-304.
- Sanz, T., & Luyten, H. (2007). In vitro evaluation of genistein bioaccessibility from enriched custards. *Food Hydrocolloids*, 21(2), 203-211.

- Sato, Y., Kobayashi, M., Itagaki, S., Hirano, T., Noda, T., Mizuno, S., Sugawara, M., & Iseki, K. (2011). Pharmacokinetic properties of lutein emulsion after oral administration to rats and effect of food intake on plasma concentration of lutein. *Biopharmaceutics & Drug Disposition*, 32(3), 151-158.
- Schieber, A., Stintzing, F. C., & Carle, R. (2001). By-products of plant food processing as a source of functional compounds—recent developments. *Trends in Food Science & Technology*, 12(11), 401-413.
- Shimizu, M. (2010). Interaction between Food Substances and the Intestinal Epithelium. *Bioscience Biotechnology and Biochemistry*, 74(2), 232-241.
- Solans, C., & Solé, I. (2012). Nano-emulsions: formation by low-energy methods. *Current Opinion in Colloid & Interface Science*, 17(5), 246-254.
- Speranza, A., Corradini, M. G., Hartman, T. G., Ribnicky, D., Oren, A., & Rogers, M. A. (2013). Influence of Emulsifier Structure on Lipid Bioaccessibility in Oil-Water Nanoemulsions. *Journal of Agricultural and Food Chemistry*, 61(26), 6505-6515.
- Sun, Y., Xia, Z. Y., Zheng, J. K., Qiu, P. J., Zhang, L. J., Mc Clements, D. J., & Xiao, H. (2015). Nanoemulsion-based delivery systems for nutraceuticals: Influence of carrier oil type on bioavailability of pterostilbene. *Journal of Functional Foods*, 13, 61-70.
- Svelander, C. A., Lopez-Sanchez, P., Pudney, P. D. A., Schumm, S., & Alminger, M. A. G. (2011). High Pressure Homogenization Increases the In Vitro Bioaccessibility of alpha- and beta-Carotene in Carrot Emulsions But Not of Lycopene in Tomato Emulsions. *Journal of Food Science*, 76(9), H215-H225.
- Sy, C., Dangles, O., Borel, P., & Caris-Veyrat, C. (2013). Iron-induced oxidation of (all-E)-beta-carotene under model gastric conditions: kinetics, products, and mechanism. *Free Radical Biology and Medicine*, 63, 195-206.
- Tamjidi, F., Shahedi, M., Varshosaz, J., & Nasirpour, A. (2014). EDTA and alpha-tocopherol improve the chemical stability of astaxanthin loaded into nanostructured lipid carriers. *European Journal of Lipid Science and Technology*, 116(8), 968-977.
- Tarvainen, M., Phuphusit, A., Suomela, J. P., Kuksis, A., & Kallio, H. (2012). Effects of Antioxidants on Rapeseed Oil Oxidation in an Artificial Digestion Model Analyzed by UHPLC-ESI-MS. [Article]. *Journal of Agricultural and Food Chemistry*, 60(14), 3564-3579.
- Ting, Y., Jiang, Y., Ho, C.-T., & Huang, Q. (2014). Common delivery systems for enhancing in vivo bioavailability and biological efficacy of nutraceuticals. *Journal of Functional Foods*, 7, 112-128.
- Velikov, K. P., & Pelan, E. (2008). Colloidal delivery systems for micronutrients and nutraceuticals. *Soft Matter*, 4(10), 1964-1980.
- Verrijssen, T. A. J., Balduyck, L. G., Christiaens, S., Van Loey, A. M., Van Buggenhout, S., & Hendrickx, M. E. (2014). The effect of pectin concentration and degree of methyl-esterification on the in vitro bioaccessibility of β -carotene-enriched emulsions. *Food Research International*, 57, 71-78.
- Wang, X. X., Valenzano, M. C., Mercado, J. M., Zurbach, E. P., & Mullin, J. M. (2013). Zinc Supplementation Modifies Tight Junctions and Alters Barrier Function of CACO-2 Human Intestinal Epithelial Layers. *Digestive Diseases and Sciences*, 58(1), 77-87.
- Whitehead, K., Karr, N., & Mitragotri, S. (2008). Safe and effective permeation enhancers for oral drug delivery. *Pharmaceutical Research*, 25(8), 1782-1788.
- Whitehead, K., & Mitragotri, S. (2008). Mechanistic analysis of chemical permeation enhancers

- for oral drug delivery. *Pharmaceutical Research*, 25(6), 1412-1419.
- Wooster, T. J., Day, L., Xu, M., Golding, M., Oiseth, S., Keogh, J., & Clifton, P. (2014). Impact of different biopolymer networks on the digestion of gastric structured emulsions. *Food Hydrocolloids*, 36, 102-114.
- Xu, D., Wang, X., Jiang, J., Yuan, F., Decker, E. A., & Gao, Y. (2013). Influence of pH, EDTA, α -tocopherol, and WPI oxidation on the degradation of β -carotene in WPI-stabilized oil-in-water emulsions. *LWT-Food Science and Technology*, 54(1), 236-241.
- Yamamoto, A., Katsumi, H., Kusamori, K., & Sakane, T. (2014). Improvement of Intestinal Absorption of Poorly Absorbable Drugs by Various Sugar Esters. [Article]. *Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan*, 134(1), 47-53.
- Yang, Y., Decker, E. A., Xiao, H., & McClements, D. J. (2015). Enhancing vitamin E bioaccessibility: factors impacting solubilization and hydrolysis of alpha-tocopherol acetate encapsulated in emulsion-based delivery systems. *Food & Function*, 6(1), 84-97.
- Yang, Y., Marshall-Breton, C., Leser, M. E., Sher, A. A., & McClements, D. J. (2012). Fabrication of ultrafine edible emulsions: Comparison of high-energy and low-energy homogenization methods. *Food Hydrocolloids*, 29(2), 398-406.
- Yang, Y., & McClements, D. J. (2013). Vitamin E bioaccessibility: Influence of carrier oil type on digestion and release of emulsified alpha-tocopherol acetate. *Food Chemistry*, 141(1), 473-481.
- Yao, M., Chen, J., Zheng, J., Song, M., McClements, D. J., & Xiao, H. (2013). Enhanced lymphatic transport of bioactive lipids: cell culture study of polymethoxyflavone incorporation into chylomicrons. *Food & Function*, 4(11), 1662-1667.
- Yao, M., Xiao, H., & McClements, D. J. (2014). Delivery of Lipophilic Bioactives: Assembly, Disassembly, and Reassembly of Lipid Nanoparticles. In M. P. Doyle & T. R. Klaenhammer (Eds.), *Annual Review of Food Science and Technology*, Vol 5 (Vol. 5, pp. 53-81).
- Yucel, U., Elias, R. J., & Coupland, J. N. (2013). Localization and reactivity of a hydrophobic solute in lecithin and caseinate stabilized solid lipid nanoparticles and nanoemulsions. *Journal of Colloid and Interface Science*, 394, 20-25.
- Zhang, R., Zhang, Z., Zhang, H., Decker, E. A., & McClements, D. J. (2015a). Influence of emulsifier type on gastrointestinal fate of oil-in-water emulsions containing anionic dietary fiber (pectin). *Food Hydrocolloids*, 45, 175-185.
- Zhang, R., Zhang, Z., Zhang, H., Decker, E. A., & McClements, D. J. (2015b). Influence of lipid type on gastrointestinal fate of oil-in-water emulsions: In vitro digestion study. *Food Research International*, 75, 71-78.
- Zhang, R., Zhang, Z., Zou, L., Xiao, H., Zhang, G., Decker, E. A., & McClements, D. J. (2016a). Enhancement of carotenoid bioaccessibility from carrots using excipient emulsions: influence of particle size of digestible lipid droplets. *Food & Function*, 7(1), 93-103.
- Zhang, R., Zhang, Z., Zou, L., Xiao, H., Zhang, G., Decker, E. A., & McClements, D. J. (2016b). Impact of Lipid Content on the Ability of Excipient Emulsions to Increase Carotenoid Bioaccessibility from Natural Sources (Raw and Cooked Carrots). *Food Biophysics*, 11(1), 71-80.
- Zou, L., Liu, W., Liu, C., Xiao, H., & McClements, D. J. (2015). Designing excipient emulsions to increase nutraceutical bioavailability: emulsifier type influences curcumin stability and bioaccessibility by altering gastrointestinal fate. *Food & Function*, 6(8), 2475-2486.
- Zou, L., Liu, W., Liu, C., Xiao, H., & McClements, D. J. (2015a). Utilizing food matrix effects to

915 enhance nutraceutical bioavailability: Increase of curcumin bioaccessibility using
916 excipient emulsions. *Journal of Agricultural and Food Chemistry*, 63(7), 2052-2062.
917 Zou, L., Zheng, B., Liu, W., Liu, C., Xiao, H., & McClements, D. J. (2015). Enhancing
918 nutraceutical bioavailability using excipient emulsions: Influence of lipid droplet size on
919 solubility and Bioaccessibility of Powdered Curcumin. *Journal of Functional Foods*, 15,
920 72-83.
921 Zou, L. Q., Liu, W., Liu, C. M., Xiao, H., & McClements, D. J. (2015). Designing excipient
922 emulsions to increase nutraceutical bioavailability: emulsifier type influences curcumin
923 stability and bioaccessibility by altering gastrointestinal fate. *Food & Function*, 6(8),
924 2475-2486.
925

Emulsion-based Delivery System

Emulsion-based Excipient System

Figure 1: Two emulsion-based approaches can be used to improve the bioavailability of hydrophobic bioactives in foods: (i) *emulsion-based delivery systems* - isolated bioactives are encapsulated within lipid droplets; (ii) *excipient emulsions* – bioactives present within fruits or vegetables are consumed with a specially designed emulsion.

Bioaccessibility
Liberation & Solubilization

Absorption
Transport across Mucus
Layer & Epithelium Cells

Transformation
Chemical or Biochemical Changes

Figure 2: The overall bioaccessibility (BA) of a hydrophobic bioactive may be limited because of its poor bioaccessibility (B*), absorption (A*) or transformation (T*) characteristics: $BA = B^* \square A^* \square T^*$.

Figure 3: The composition or structure of excipient emulsions can be designed to alter the gastrointestinal fate of bioactives from fruits or vegetables consumed with them.

Figure 4: Curcumin may be more protected in large droplets than in small ones because it is better protected from alkaline degradation induced by the surrounding aqueous phase (Zou et al 2015): large ($d_{32} \approx 14 \mu\text{m}$); medium ($d_{32} \approx 0.52 \mu\text{m}$); small ($d_{32} \approx 0.18 \mu\text{m}$).

Figure 5: The ability of the mixed micelle phase to solubilize hydrophobic bioactive components depends on the dimensions of the non-polar domains in the mixed micelle phase.

Figure 6: The bioaccessibility of carotenoids from carrots increases as the concentration of digestible lipids in the excipient emulsions increases (Zhang et al 2015).

Figure 7: The influence of oil type on the bioaccessibility of β -carotene in EDS (Qian et al 2012) and EES (Zhang et al 2015).

Figure 8: The influence of oil type on the bioaccessibility of bioactive compounds: Vitamin D3 (Ozturk et al 2014); Vitamin E (Yang et al 2013); Curcumin (Zou et al 2015); β -carotene (Qian et al 2012).

Medium chain fatty acids are more effective in enhancing the bioaccessibility of bioactive compounds with small molecular mass.

Figure 9a: The bioaccessibility of carotenoids from carrots increases as the size of the digestible lipids in excipient emulsions decreases: $d_{32} = 0.17 \mu\text{m}$ (fine), $0.46 \mu\text{m}$ (medium), and, $10 \mu\text{m}$ (large). (Zhang et al 2015).

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Figure 9b: The rate of lipid digestion increases as the size of the digestible lipids in excipient emulsions decreases: $d_{32} = 0.17 \mu\text{m}$ (fine), $0.46 \mu\text{m}$ (medium), and, $10 \mu\text{m}$ (large). (Zhang et al 2015).

Figure 10: The degree of unsaturation of fatty acids influences the nature of the mixed micelles formed, as well as the nature of the oil bodies and chylomicrons formed by epithelium cells (Data provided by Olivia Yao, 2015).