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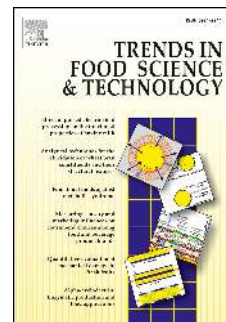
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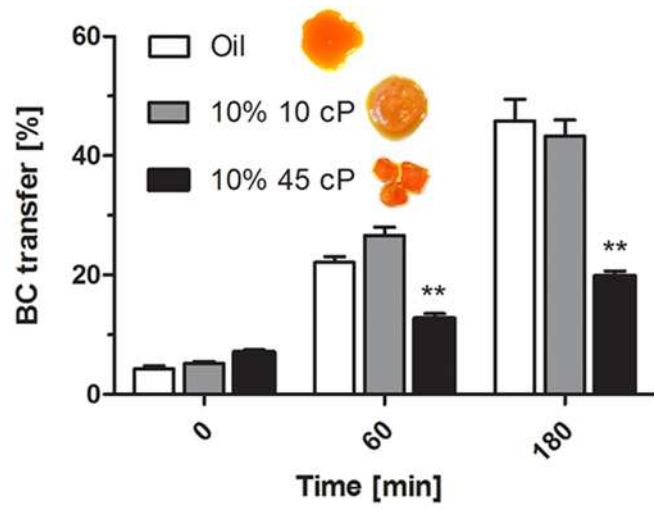
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**Edible oleogels for the oral delivery of lipid soluble molecules: composition and structural design considerations**

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## **Edible oleogels for the oral delivery of lipid soluble molecules: composition and structural design considerations**

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### **Abstract:**

#### *Background:*

Edible oleogels, oils structured by non-triglyceride networks, can be used for the delivery of lipid-soluble molecules due to their composition, functional properties, and structure. Different oleogelators exist, including small molecules that crystallize to form colloidal or fibrillar networks and hydrophobic polymers that self-assemble under specific processing conditions. Several types of edible oleogels have been characterized, but only select systems have been used in oral delivery applications.

#### *Scope and Approach:*

This review covers the potential for use of edible oleogels for lipophilic molecular delivery. Factors affecting lipolysis relevant to oil gelation will be discussed, as well as the relationship between lipolysis and bioaccessibility. The use of lipid-based delivery systems to increase the bioaccessibility of poorly water-soluble molecules is emphasized, and oleogels are introduced as a delivery material. The review then discusses different methods of oleogelation, and addresses properties of oleogels that may be beneficial for delivery.

#### *Key Findings and Conclusions:*

Oleogel structure, mechanical strength, composition, and gelator type are factors that may affect the rate and extent of lipolysis of the material. These in turn affect the delivery of lipid-soluble molecules from the oleogel. Crystalline oleogels used in oral delivery formulations have been shown to offer increased bioaccessibility, prevention against bioactive recrystallization, and targeted or delayed bioactive release. In addition, the ability to manipulate oleogel physicochemical properties with gelator type, formulation, and processing parameters is beneficial for tailoring the material functionality. Ethylcellulose oleogels are unique food-grade polymer oleogels that could be used for delivery, similar to other crystalline oleogel systems.

**Keywords:**

Oleogel, oral delivery, bioaccessibility, ethylcellulose, bioactive, lipophilic

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**Text:**

## **1.0 Introduction**

Edible oil gels (oleogels) have been a subject of interest in recent years due to their application potential in cosmetics, foods, and pharmaceuticals. The gelled oil, by definition, is made of a majority liquid fraction, but exhibits solid or solid-like behaviour. Regarding structure, a gel should also have continuous microstructure and permanent macrostructure on the time scale of a given experiment (Flory, 1953). The gelation of edible oils is related to the gelation of other organic solvents, however it differs in that edible oils are complex mixtures of molecules and are more polar compared to other organic solvents (Pernetti, van Malssen, Flöter, & Bot, 2007). Oils are composed mostly of triglyceride (TAG) molecules—three fatty acids esterified to a glycerol backbone—with minor amounts of monoglycerides (MAGs), diglycerides (DAGs), fatty acids (FAs), and other fat soluble molecules.

Oleogels have shown promise in edible applications as alternatives to conventional fats (Co & Marangoni, 2012; Marangoni & Garti, 2011; Patel & Dewettinck, 2015; Pernetti et al., 2007; Rogers, 2009). Fats are structured by TAG molecules that crystallize, forming a space-filling network of crystals, and are responsible for many of the desirable organoleptic properties of high-fat foods. However, TAGs that are crystalline at room temperature contain high amounts of saturated or *trans* fatty acids. *Trans* fats, while being beneficial for the shelf life and sensory properties of processed foods, have been shown to elicit negative health effects and have recently been stripped of their GRAS (Generally Recognized as Safe) status by the Food and Drug Administration in the United States (Food and Drug Administration, 2015). This follows the actions of other organizations and countries that have recommended or mandated the complete elimination or reduction of *trans* fats in processed foods (Uauy et al., 2009). Although there is an ongoing debate on the impact of saturated fats on risk of cardiovascular disease (Bier, 2015), dietary guidelines worldwide continue to recommend limiting consumption of these fats. For example, the recently released 2015-2020 Dietary Guidelines for Americans, recommends consuming less than 10 % of calories per day from saturated fats, and includes oils as components of a healthy eating pattern (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). Consumers are therefore interested in products with zero

*trans* and low saturated fat content, and manufacturers continue to search for ways to reduce or eliminate these ingredients in their products without compromising quality. Oleogels provide a novel alternative to these fats, being solid-like material made with lipids rich in unsaturated fatty acids.

To make an oleogel, a low concentration of gelator molecule is added to oil. With the appropriate processing (heating, stirring and cooling, for example), the molecules are dispersed in the oil phase and self-assemble to form 3-D networks, structuring the liquid oil. Their assembly is driven by Van der Waals forces, hydrogen bonding, steric interactions, ionic interactions, or covalent bonding (Pernetti et al., 2007). Oleogelators are soluble in the oil such that they can be dispersed but precipitate to form a network during gelation (Suzuki & Hanabusa, 2010). An ideal oleogel for edible application would have modifiable physicochemical properties, in order to match those of a fat being replaced or to achieve other desired functionalities, such as slowed release. Stability of the material over a given period of time is also important. For food or pharmaceutical applications, gelators should have ‘generally recognized as safe’ (GRAS) status or come from natural sources.

Lipid structuring, by the formation of an oleogel or an alternatively structured system, can also have physiological implications. Food structure has a direct relationship with digestibility and nutrient bioaccessibility, as factors such as composition, molecular state, particle size and matrix all affect the fate of ingested materials (McClements, Decker, & Park, 2008; Norton, Gonzalez Espinosa, Watson, Spyropoulos, & Norton, 2015). In lipid systems, this relationship can be exploited to create materials with given levels of lipolysis, modifiable release profiles and increased bioaccessibility of lipid soluble molecules. The mechanism of lipid digestion and the effect of structure on lipolysis is therefore an important aspect to consider when designing oleogel systems. Different lipid-based systems for delivery, mainly emulsion-based, have been reviewed but these discussions have not included oleogels or other alternative structured lipids within their scope (Humberstone & Charman, 1997; Porter, Trevaskis, & Charman, 2007).

The delivery of bioactive molecules is another possible application for oleogels, and has gained attention in recent years in the pharmaceuticals industry. In particular, their lipid medium is well suited for increasing the bioavailability of lipid soluble molecules and their gel matrix could

offer benefits of sustained release and protection of the deliverable molecule. Several applications of edible oleogels have appeared in the literature for drug or nutraceutical delivery and offer interesting insights into the relationship of gel structure and delivery. Gelation has been shown to be successful at preventing precipitation of bioactives and slow lipolysis and release of nutraceuticals from crystalline and fibrillar oleogel networks (Duffy et al., 2009; Iwanaga, Sumizawa, Miyazaki, & Kakemi, 2010; Lupi et al., 2013; Murdan, Andrysek, & Son, 2005). Ethylcellulose oleogels, the only known food-grade polymer oleogel has been proposed as a material with delivery potential (Davidovich-Pinhas, 2015; Zetzl & Marangoni, 2012). Structure-functionality characteristics of the gel have been well researched, but polymer oleogels have never been explored for delivery applications.

This review will begin with an overview of the mechanism of lipolysis and structural factors affecting lipolysis. Previous studies on lipid structuring and their effect on lipid digestion are also discussed. To explore the use of gels for oral delivery, lipid-soluble bioactive molecules will be introduced, with a focus on  $\beta$ -carotene (BC). Challenges involved in the delivery of those lipid soluble molecules will be covered, leading to a discussion on current delivery strategies for these molecules and the use of novel oil-based gels for delivery. Various edible oil-gelling strategies and their delivery-related applications will be reviewed, followed by the properties, structure, functionality, and application potential of EC oleogels. The purpose of this review is to provide a background for a discussion on the digestibility of ethylcellulose oleogels and their potential application as delivery material for fat-soluble bioactive molecules.

## 2.0 Lipid digestion

Lipid digestion is a complex process of emulsification, lipolysis, and micellarisation, and is followed by absorption. It is also a dynamic process, where the gastro-intestinal environment is constantly changing as food enters and is broken down, nutrients are absorbed, and the material travels through. The rate and extent of lipolysis determines lipid bioavailability, lipid profile in the blood over time, and the bioavailability of lipid soluble molecules (Mu & Høy, 2004). The design of functional lipid-based foods and systems requires knowledge of the mechanism of digestion, as well as an understanding of the effects of structure and composition on lipolysis.

The first step of lipid breakdown occurs in the mouth, where food is mechanically processed,



mixed with saliva and formed into a food bolus. This stage is short (5-20 seconds in the mouth) and the changes to the lipid phase that occur here depend on the initial physical properties of the lipid phase as well as the structure of the matrix containing the lipid material (McClements, Decker, Park, & Weiss, 2008). In the bolus, lipids are generally present as droplets, sized under 1  $\mu\text{m}$  to over 1 mm in size, depending on their initial state (McClements, Decker, Park, et al., 2008).

The bolus travels down the esophagus to the stomach, where a variety of gastric fluids is secreted to break down different food components. The acidic environment of the stomach (pH ~1-3) also helps in this step of digestion (Carey, Small, & Bliss, 1983). Among these fluids is gastric lipase, an enzyme that hydrolyzes TAGs, producing diglycerides (DAGs), monoglycerides (MAGs) and free fatty acids (FFAs) (Carey et al., 1983). Gastric lipase preferentially hydrolyses FFAs esterified to the *sn*-3 carbon on the TAG glycerol backbone, with significantly lower activity on the *sn*-1 FA (Mu & Høy, 2004). The DAGs, MAGs, and FFAs resulting from this process are surface active and can adsorb to the droplet oil-water interface. Because of the acidic environment, most FFAs are protonated and long chain fatty acids remain inside the oil droplets (Carey et al., 1983). The combination of the emulsifying properties of lipid digestion products with the shear forces in the stomach results in the formation of an emulsion of lipid droplets of diameter 1-50  $\mu\text{m}$  (Armand et al., 1994). In healthy humans, 10 to 30 % of TAGs ingested are hydrolysed at this stage (Armand et al., 1994; Carey et al., 1983).

The contents of the stomach are gradually released into the small intestine where the majority of the lipid digestion and absorption takes place. Peristaltic contractions continue in the duodenum, adding to the increase in oil droplet surface area (Carey et al., 1983). The increase in pH from the stomach to the small intestine causes long chain fatty acids to become partly ionized and move to the droplet interface (Linthorst, Bennett Clark, & Holt, 1977). The presence of lipid in the duodenum triggers the gallbladder and pancreas to secrete bile and digestive enzymes, respectively, into the small intestine. Bile is made up of a variety of phospholipids, cholesterol, and electrolyte salts; the phospholipids act as emulsifiers along with the lipid digestion products, reducing the size of lipid droplets and stabilizing the oil-water interface (Carey et al., 1983). Bile salts promote lipolysis by displacing digestion products from the oil-water interface (Bauer, Jakob, & Mosenthin, 2005)

Lipases and co-lipases secreted by the pancreas are active at the oil-water interface. The ability of pancreatic lipase to hydrolyse lipids depends on the presence of a co-lipase, which displaces bile salts from the droplet interface and forms a complex with the lipase, allowing access to the TAG molecules (Borgström, 1975). Pancreatic lipase has specific activity, preferentially hydrolyzing the *sn*-1 and *sn*-3 fatty acids from the glycerol backbone (Mu & Høy, 2004). In the presence of bile salts at a critical concentration, mixed micelles of digestion products are formed with lipophilic centres, surrounded by the bile salts, lipolysis products, and other compounds (Borgström, 1975). Bile salts play an essential role in lipid digestion, as they remove digestion products from the interface of the oil droplet allowing digestion to continue, and also prevent the reformation of TAGs from digestion products at the oil-water interface (Bauer et al., 2005). The formation of micelles is dependent on the concentrations of lipid digestion products, phospholipids, bile salts, and other molecules present in the aqueous phase, along with pH and ionic strength of the environment (Bauer et al., 2005).

From their bile-salt micelles, fatty acids and monoglyceride products are absorbed into the enterocytes, where they are reassembled into triglyceride molecules and subsequently lipoproteins. Some short chain and medium chain fatty acids, which are water soluble, can be absorbed directly by the stomach mucosa or in the small intestine without being incorporated into micelles (Mu & Høy, 2004).

Systems designed to control or limit lipid digestion have further physiological significance. Reduction in food intake and satiety can be caused by lipids or lipid digestion products reaching the ileum, triggering the ileal brake mechanism that signals the body to slow down gastric emptying (Van Citters & Lin, 1999). This mechanism has been proposed as a strategy for combatting obesity, offering appetite control (Maljaars, Peters, Mela, & Masclee, 2008). Slowed intestinal lipolysis by colipase inhibition was also shown to suppress appetite in rats, decreasing their high-fat food intake (Mei, Lindqvist, Krabisch, Rehfeld, & Erlanson-Albertsson, 2006). The complex relationship between food structure, digestion and satiety therefore has implications for the design of food systems to help combat obesity.

### **3.0 Factors affecting lipolysis**

The physicochemical properties of lipids, including chemical structure and the physical state of

the lipid have been shown to influence the rate and extent of lipolysis (McClements, Decker, & Park, 2008). In addition, the structure and composition of the matrix surrounding the lipid can also affect bioaccessibility of the lipid. Several reviews on the influence of structure on lipid digestibility are available (Marze, 2013; McClements, Decker, & Park, 2008; Michalski et al., 2013). Since lipid digestibility affects other physiological processes such as intestinal solubilisation of fat soluble molecules (Ting, Jiang, Ho, & Huang, 2014) and gastric emptying (Maljaars et al., 2008), the relationship between lipid structure and lipolysis is an important consideration in the design of functional food systems. It should be noted that structural factors may also influence lipid absorption and metabolism, contributing to the overall bioavailability of TAGs and of lipid soluble molecules (Michalski et al., 2013).

### 3.1 Triglyceride composition

Research on complex lipid systems has shown that TAG fatty acid composition and positionality can influence the rate and extent of lipid digestion. The rate of enzyme hydrolysis is higher for TAGs with short chain fatty acids and medium chain fatty acids than for long chain fatty acids (Carey et al., 1983). This is a factor to consider when selecting oil type for a lipid-based system. Several studies on lipid-based delivery systems have seen an effect on lipolysis with changes in TAG composition. When comparing *in-vitro* lipolysis of canola oil, corn oil, coconut oil, and medium-chain TAGs (MCT) for delivery of curcumin, MCT showed a significantly higher extent of lipolysis than the other oils and was therefore selected to be the liquid phase in an edible oleogel (Yu, Shi, Liu, & Huang, 2012). Oil-in-water emulsions with similar droplet sizes stabilized with  $\beta$ -lactoglobulin showed higher rates of lipolysis for medium chain TAG oil compared to long chain TAG oil (McClements & Li, 2010). This was explained by the solubility of the digestion products from the different oils: shorter fatty acids are more soluble in the aqueous medium and are readily removed from the surface of the oil droplet, while those with longer hydrocarbon chains accumulate on the surface of the oil droplet and impede lipase access (McClements & Li, 2010).

### 3.2 Lipid physical state

The physical state and polymorphic form of the lipid have also been shown to influence lipolysis. In their work, Bonnaire et al. (2008) found that solid lipid nanoparticles showed a significantly

lower degree of lipolysis than liquid nanoparticles of the same composition after 120 min of *in-vitro* duodenal digestion. Lower lipolysis for solid particles is likely due to difficulty of lipase adsorption to the solid droplet surface and the dense molecular packing of lipid molecules in the  $\beta$ -polymorphic form, restricting lipase access (Bonnaire et al., 2008). Effects of solid fat content on fatty acid absorption, lipid bioavailability and postprandial lipemia have also been seen and are reviewed by Michalski et al (2013).

### 3.3 Lipid droplet surface area

Lipids are present in food systems in many forms, in bulk (margarine or butter), emulsified (mayonnaise, ice cream, milk, or cheese), or contained within a complex matrix (bread, cake). Following ingestion, lipids are processed in the mouth and stomach, resulting in the formation of a crude emulsion of droplets before reaching the duodenum (McClements, Decker, & Park, 2008). A number of *in-vitro* digestion studies have found that decreasing the initial size of oil droplets in an emulsion system results in an increase in rate of lipolysis, due to the increase in surface area available for lipase activity (McClements & Li, 2010). This effect of surface area was also seen in *in-vitro* digestion experiments on bulk oil systems, where samples which were emulsified prior to digestion showed a significantly higher extent of transfer of  $\beta$ -carotene, corresponding to a higher degree of lipolysis (A. J. Wright, Pietrangelo, & MacNaughton, 2008). The effects of initial emulsion droplet size on digestion are often not as straight forward when more complex models or *in-vivo* experiments are employed to simulate digestion. Lipid droplet size can change during passage through the gastrointestinal tract with the presence of digestive fluids, shear forces, and changes in pH, altering the lipolysis profile of different formulations (McClements, Decker, Park, et al., 2008). In one example, soft and hard whey protein emulsion gels were subject to *in-vitro* gastric conditions using a human gastric simulator, a complex model incorporating mechanical contractions, digestive fluids, and emptying (Guo, Ye, Lad, Dalglish, & Singh, 2014). It was found that oil droplets released from the soft gel coalesced after gastric processing, whereas those in the hard gel did not, because they were not fully released from their protein matrix after 300 min of simulated gastric digestion. Unique lipid or mixed systems, such as emulsions, oleogels, or bulk phases, could therefore be designed to have specific particle size after processing to achieve a desired functionality. This could be done, for example, by varying

droplet size and emulsifier type for an emulsion, or matrix hardness and initial capsule size or shape for a gel.

### 3.4 Matrix effects

The composition and structure of the food matrix containing the lipid will also influence lipolysis. This effect could be due to direct interference of matrix components on digestion, or through the physical entrapment of the lipid within a larger structure. When lipid is encased in a structure or surrounded by an interfacial layer, lipase access can be slowed or impeded, and the overall digestion time of the material may be lengthened due to the time needed to breakdown the matrix surrounding the lipid components (McClements, Decker, Park, et al., 2008). This is a commonly employed strategy in the design of novel emulsions for delivery and digestibility control, where oil droplets can be coated with different emulsifiers or aqueous biopolymers, preventing lipase diffusion or otherwise limiting access of the lipase to the oil-water interface (Mun, Decker, & McClements, 2007).

Different molecules in complex food systems, such as dietary fibres, can affect the rate of lipid digestion by directly interfering with mechanisms involved in digestion. Some dietary fibres can bind with bile salts, inhibiting their emulsification action (Kritchevsky & Story, 1974). Other dietary fibres, such as cellulose ethers, are surface active and can competitively adsorb to the oil-water interface of lipid droplets, preventing access for the bile salts and lipase (Torcello-Gómez & Foster, 2014). Surface active molecules interfering with lipolysis could be naturally present in the body, or originate as breakdown products from ingested food (McClements, Decker, & Park, 2008). All components of gels or other delivery systems (emulsifiers, gelling agents, fibres, etc.) and their digestion products should therefore be considered for their effect on digestion.

Matrix effects are also relevant in the design of oleogels to control digestibility or release, where the presence of a structuring network could slow the release of oil from the system and hence delay the exposure of the oil to the lipase. In these formulated systems, the nature of the structuring matrix (i.e. the type of bonds present, the strength of the network) could affect the rate of matrix breakdown, erosion, and/or digestion (McClements, Decker, Park, et al., 2008).

In a recent experiment, the effect of hardness on the *in-vitro* digestion of whey protein emulsion gels was investigated using a human gastric simulator model (Guo et al., 2014). Soft and hard

whey protein gels with different microstructural properties were prepared by heat-treating protein-stabilized soybean oil-in-water emulsions in the presence of NaCl. These gels were then prepared to simulate oral processing and introduced into the gastric model to examine the breakdown of the gel bolus. It was found that the soft gels disintegrated faster under the effects of proteolysis and mechanical digestion after 300 min, releasing the lipid droplets. In comparison, the harder gels were merely broken into smaller particles and no oil droplets were released, although the proteins were still hydrolyzed at a similar rate. These differences were attributed to the differences in gel structure between the two samples, where oil droplets were more tightly bound to the protein matrix in the harder gel and the protein structures were different (Guo et al., 2014). The study of this gelled emulsion system illustrates the importance of matrix structure and composition on the digestion and release of lipids.

#### 3.4.1 Non-TAG structured lipids and effects on digestion

Oleogels are an example of a material where the complexity of the matrix could affect access of the lipase to the lipid. However, few *in-vitro* and *in-vivo* experiments have been conducted on the effects of matrix composition on oleogel digestibility. The digestibility of oleogels has often only been examined from a delivery perspective (see 6.0 Strategies to gel oil and delivery applications of oleogels) but can also be looked at through a nutritional lens.

Using human trials, Marangoni et al. (2007) found that consumption of oil contained in a monoglyceride-structured emulsion resulted in lower blood serum triglyceride loading and lower serum insulin levels for the same glucose levels compared to consumption of liquid oil (Figure 1 and 2). A link between microstructuring of oil phase and modulation of physiological response was suggested. However, further *in-vivo* studies on the same MAG-structured oil system by Rush et al. (2008) found that postprandial glycemic, TAG and FFA levels were suppressed after consumption of the structured emulsion compared to the unstructured ingredients only when the emulsion remained intact. No significant differences were seen in these levels after consumption of pasta with melted emulsion compared to unstructured oil equivalent. Similarly, Wright et al. (2014) found that when the MAG-structured emulsion was baked in a cookie or cake formulation, no effects of structured emulsion versus liquid equivalent on postprandial levels were observed. The findings from these studies suggest that the MAG-stabilized emulsion

structure must be intact for the system to have an effect on postprandial TAG and insulin levels.

**\*\*Insert Figure 1 and Figure 2\*\***

In their application of MAG-structured oil and Span 20 gels for the delivery of curcuminoids, Yu et al. (2012) found that there was no significant difference in extent of lipolysis between gelled and liquid samples, after *in-vitro* digestion simulating fed or fasted state. It was suggested this could be due to the partial melting of the gel structure at 37 °C and the mechanical processing of the gel in the *in-vitro* assay. This further supports the notion that integrity of the gel structure is necessary to see an influence on lipid digestibility.

Similarly, Hughes et al. (2011) studied human physiological response after consumption of another structured oil product, a 12-hydroxystearic acid (12-HSA) oleogel made with canola oil. Their results were compared with the response after consumption of liquid oil, butter, and margarine. In contrast to Marangoni et al. (2007), they found no significant difference in postprandial serum TAG or FFA levels in test subjects after consumption of the gelled canola oil compared to the unstructured canola oil. The gels used in this experiment (2% w/w 12-HSA composition) were weak and shear sensitive, which may be why no effect of structure on physiological response was seen. This supports the idea that the type of oil structuring method employed (including its ingredients, physicochemical properties, micro and macrostructure) plays a role in the physiological behaviour of the material.

Because lipid digestibility is linked with the solubilisation and uptake of lipid-soluble molecules, the structural and compositional design of oleogels also plays a key role in the application of the gels as delivery material for bioactive lipophilic components.

#### **4.0 Challenges in the delivery of lipid soluble bioactive molecules**

Many fat soluble molecules naturally present in food systems are associated with positive health benefits, including long chain poly-unsaturated fatty acids, carotenoids, antioxidants, and phytosterols (McClements, Decker, Park, & Weiss, 2009). Consumption of these bioactives, or 'nutraceuticals', is associated with physiological benefits such as cancer prevention; protection against heart disease, cardiovascular disease, and macular degeneration; and promotion of mental health (Rao & Rao, 2007; Ruxton, Reed, Simpson, & Millington, 2007).

Effective delivery of lipid soluble compounds can be challenging, therefore specifically designed delivery systems are used to enhance their bioavailability by overcoming limitations in matrix compatibility, solubility, or chemical stability. This is also a subject of importance in the pharmaceutical industry, where lipid soluble drugs can benefit from the strategies proposed for the effective delivery of naturally occurring bioactive molecules (Dahan & Hoffman, 2008). Due to its highly lipophilic character and extensive characterization,  $\beta$ -carotene (BC) is an ideal molecule to serve as a model lipophilic molecule and has been used in previous research characterizing novel delivery materials (Liang, Huang, Ma, Shoemaker, & Zhong, 2013; Nik, Corredig, & Wright, 2011). It is important to keep in mind, however, that different lipophilic molecules could show different digestibility behaviour and levels of bioavailability from the same system due to their diverse chemical and physical compositions (Nik et al., 2011).

Some challenges exist in the effective delivery of lipophilic bioactive molecules. The bioaccessibility of a molecule is defined as the fraction which is released and available to be absorbed in the intestine (Rein et al., 2013). Bioaccessibility is specifically an obstacle for fat-soluble molecules, which are insoluble in the aqueous environment of the digestive tract. For these molecules, solubilisation into mixed micelles in the aqueous phase is necessary to be absorbed into epithelium cells in the small intestine and be active in the body. For example, when BC is consumed, only the micellarised portion of the carotenoid can be absorbed into the enterocytes to be incorporated into chylomicrons and transported to the liver to be distributed to different tissues (Rao & Rao, 2007). Although absorption and transport of hydrophobic molecules also affect their bioavailability, bioaccessibility is still a limiting factor for the activity of many lipid soluble bioactives from natural food matrices.

#### 4.1 Food matrix effects

Similar to its effect on lipid digestibility, the food matrix can affect and limit the bioaccessibility of lipid soluble molecules. When bioactive molecules are complexed with other molecules or trapped within food structures, their bioavailability is lowered. This effect has been seen in *in-vitro* and *in-vivo* experiments, where heat treatment increases the bioaccessibility of carotenoids from vegetables by weakening the protein-carotenoid complexes and softening the cell walls (Hedrén, Diaz, & Svanberg, 2002; Rao & Rao, 2007). Ferulic acid, a compound naturally found



in whole grain wheat has low bioaccessibility, due to its binding to polysaccharides. However, when bread made with flour and added free ferulic acid was consumed, the bioaccessibility of the molecule increased to above 60 % (Mateo Anson et al., 2011). The introduction of purified bioactives into especially designed delivery systems is one way to increase the level of bioactive molecules in the diet (McClements, Decker, & Park, 2008; Oehlke et al., 2014).

#### 4.2 Solubility in digestate

Because micellar solubilisation is a necessary step for the absorption of non-water soluble molecules, factors that affect the production and volume of micelles also affect bioavailability. For example, the rate and extent of lipid hydrolysis affect the transfer of  $\beta$ -carotene and other lipophilic molecules to the aqueous phase from the hydrophobic phase (Nik, Corredig, & Wright, 2010; Nik et al., 2011).

Lipid soluble compounds have increased bioavailability when consumed with digestible lipids because lipolysis increases the micellar volume available for solubilisation while at the same time decreases the volume of bulk lipid phase (Furr & Clark, 1997; Nik et al., 2011). Using an *in-vitro* digestion model, Hedrén et al. (2002) showed an increase in bioaccessibility of  $\beta$ -carotene in cooked carrot samples from 27% to 39% when they were consumed with cooking oil. It was also found that consumption of yellow peppers with a long-chain triglyceride emulsion increased BC micellarisation to over 70 % from under 30 % for a sample containing no oil (Liu, Bi, Xiao, & McClements, 2015). In humans, consumption of salad with avocado or avocado oil has been shown to increase carotenoid absorption (Unlu, Bohn, Clinton, & Schwartz, 2005). The presence of lipid in the small intestine also stimulates the secretion of digestive liquids from the pancreas, promoting emulsification of lipids and lipid digestion products, and facilitating hydrolysis (Porter et al., 2007).

Although there is a general effect of lipids on transfer, the TAG chemical composition is also an influencing factor. Long-chain TAGs (LCT) facilitate higher solubilisation of carotenoids *in-vitro* than both medium-chain TAGs (MCT) and indigestible oils (Huo, Ferruzzi, Schwartz, & Failla, 2007; Liu et al., 2015). Liu et al. (2015) found that the bioavailability of carotenoids under simulated gastrointestinal conditions increased to above 70 % in the presence of LCT compared to ~ 45 % and under 30 % in the presence of MCT and indigestible oil, respectively.

This effect was due to the digestion products from LCTs forming micelles with hydrophobic cores large enough to solubilize the carotenoids. In *in-vitro* experiments, the quantity of TAG necessary for optimum transfer of carotenoids was shown to be 0.5-1 % of the meal, however conflicting reports appear in literature on the overall effect of lipid quantity on the transfer of bioactive molecules (Huo et al., 2007).

The manipulation of bioavailability with the addition of lipid as discussed above can also be seen in the design and evaluation of drug delivery materials (Humberstone & Charman, 1997; Porter et al., 2007). As is the case with delivery of nutraceuticals, there is no consensus on the quantity of lipid necessary to enhance drug transfer and absorption in oral lipid-based formulations (Porter et al., 2007).

#### 4.3 Solubility in delivery medium

Low solubility of hydrophobic bioactives in hydrophilic systems also provides a barrier for bioavailability, as it reduces the initial quantity of bioactive that can be delivered in a given system. Some bioactives, such as BC, are crystalline in their natural food matrices and in their extracted and purified form. When crystalline, there is an energy barrier to dissolution in the digestive emulsion, and the molecule is difficult to incorporate into a delivery system (McClements et al., 2009). Curcumin, a lipophilic bioactive, showed very low bioaccessibility *in-vitro* when present in an aqueous suspension and precipitated out of a MCT solution after one month of storage due to low solubility (Yu et al., 2012). The issue of solubility is especially challenging because many delivery materials for drugs or nutraceuticals are aqueous-based.

#### 4.4 Chemical degradation

Bioactives and lipid-soluble drugs for delivery can be sensitive to chemical degradation, such as oxidation or hydrolysis (McClements & Li, 2010). Protection from these effects is necessary for bioactive molecules to retain their biological activity. Some matrices allow more bioactive degradation to take place than others do and must be considered in an effort to maximize bioavailability. For example, BC is highly sensitive to oxidation, and can decompose into a variety of products. BC concentration in sodium caseinate-stabilized emulsions decreased to 60-85 % of original content after 30 days of storage at room temperature under no-light conditions

and emulsions with smaller droplet size were more susceptible to oxidation (Yi, Li, Zhong, & Yokoyama, 2014). BC degradation was also more advanced after encapsulation in a solid lipid nanoparticle compared to a liquid nanoparticle (Helgason et al., 2009).

Bioactives may also be sensitive to degradation in biological environments and they must be protected before they reach their site of absorption. For example, curcumin is susceptible to hydrolysis in alkaline environments and showed elevated bioactivity *in-vitro* when encapsulated in modified  $\epsilon$ -polylysine micelles (Yu, Li, Shi, & Huang, 2011).

## **5.0 Current delivery strategies for lipophilic bioactives**

To overcome the challenges of delivery of lipid soluble molecules, various structured systems have been designed. These have been reviewed extensively in other publications (Marze, 2013; McClements et al., 2009; Ting et al., 2014). These systems can be classified as lipid-based, surfactant-based, or biopolymer-based, where all three address the effective delivery of hydrophobic molecules using differing strategies.

### *5.1 Lipid-based delivery systems*

Lipid-based systems with delivery applications appearing in literature are most often emulsion-based, including conventional oil-in-water emulsions, nano-emulsions, multiple emulsions, solid lipid nanoparticle emulsions, gelled oil-in-water emulsions, and self-emulsifying systems. A newer approach is the use of lipid-based gels for delivery, which will be discussed in depth in the following section.

As mentioned above, the presence of lipids increases the bioavailability of lipid soluble molecules in a number of ways. Lipids also provide a favourable environment for the solubilisation of hydrophobic compounds and could contain other hydrophilic antioxidants, protecting the deliverable molecule against degradation (Liu et al., 2015). The presence of lipid in the system and its chemical composition will also affect absorption and transport of lipid soluble molecules in the body (Porter et al., 2007). Lipid-based systems can be altered by manipulating the TAG composition or processing conditions, to modulate release, provide protection, or change other physicochemical characteristics of the system.

Some challenges encountered with lipid-based systems are the stability of the systems against recrystallization or coalescence and the need for food-grade status ingredients. Given the structural diversity of gels and the increase in number of food-grade gelling strategies available for liquid oil, oleogels are another lipid-based medium worth exploring for delivery applications (Wang, Gravelle, Blake, & Marangoni, 2016).

#### *5.1.1 Gels for delivery*

Organogels (gels made with non-aqueous solvents) have been used for delivery purposes in non-oral applications, including transdermal, rectal, and parenteral delivery of drugs (Sagiri et al., 2014). Several reviews exist on their potential for pharmaceutical and drug delivery applications (Murdan, 2005; Sagiri et al., 2014; Vintiloiu & Leroux, 2008). Organogels for oral delivery are less common, with only a few examples appearing in literature (Iwanaga et al., 2010; Lupi et al., 2013; Murdan et al., 2005). The use of oil as the solvent for organogels with delivery applications is also rare, but would provide benefits of biocompatibility and generally recognized as safe (GRAS) ingredients for the development of novel food-grade materials.

Lipid-based gels offer the same advantages as other lipid delivery systems in terms of solubility and increased bioavailability due to the presence of oil in the system. In addition, gels can provide increased stability for bioactive compounds, preventing recrystallization or precipitation, which can occur in liquid or solid lipid systems. Oleogelation has been shown to prevent recrystallization of curcuminoids in oil systems (Yu et al., 2012). Although solid lipid systems, such as solid lipid nanoparticles, can protect bioactive compounds from oxidation or degradation, they are prone to polymorphic rearrangements and changes in crystallinity, which affect the solubility and stability of the bioactive compound within (Müller, Mäder, & Gohla, 2000). Recently, BC solubilized in three different bulk lipids (tristearin, tripalmitin, and saturated monoglyceride) was shown to degrade at different rates as a result of changes in crystal structure over time (Calligaris, Valoppi, Barba, Anese, & Nicoli, 2014). Oleogels, especially polymer-based gels, could offer an alternative solid-like matrix to these solid lipid systems, with increased stability.

In addition to their use in bulk form, oleogels could be used as the dispersed phase in emulsion systems. In this application, gelation of the oil phase could prevent precipitation of a lipophilic

bioactive contained in the oil. This effect was observed in a quercetin delivery system, where a sugar-ester gel was shown to prevent bioactive recrystallization in a MCT-in-water emulsion compared to the equivalent un-gelled system (Xuechen, 2014). Highly lipophilic oleogelators with gelation temperatures under 100 °C, such as waxes, would be ideal for emulsion applications due to their insolubility in water and their manufacturing considerations. In addition, oleogels that are stable to molecular rearrangement, such as polymer oleogels, could provide an advantage over solid TAGs in emulsion systems, due to TAG recrystallization during storage. When recrystallization occurs, molecules encapsulated in the lipid phase can be forced to the surface of the particles, accelerating oxidation and decreasing the bioactivity of the material (Helgason et al., 2009). Polymer oleogelation could slow the mobility of the bioactive in the lipid phase, due to the gel matrix, and avoid the polymorphic transformations that often occur in TAG systems. Oleogelators that are water soluble, such as phytosterols, would not be suitable for stable oleogel-in-water systems, as they are likely to have different structure and stability in the presence of water (Duffy et al., 2009).

Hydrogels are aqueous systems structured by 3-D polymer matrices and have been used extensively in drug delivery applications. They are biocompatible, and can offer slowed or targeted release due to their polymer networks. Hydrogels can also be manipulated to respond to changes in pH or temperature, resulting in increased permeability and allowing molecules to be released (Qiu & Park, 2012). Polymer oleogels, one sub-group of oleogels, are an interesting alternative to hydrogels, as they share the same complex matrix but have a hydrophobic medium (Davidovich-Pinhas, 2015).

The ability to manipulate gel matrices for release control is another unique advantage of oleogels. Controlled release is an especially important quality in drug delivery, where gradual release allows for a steady plasma concentration of the bioactive. This prevents the spikes and drops in levels that are characteristic of immediate release materials and allows for a therapeutic level of bioactive to be present in the body over a longer period of time (Turner, Federici, Hite, & Fassihi, 2004). Gel network structure and mechanical strength can be manipulated in different ways, resulting in changes to gel functionality, such as molecular release. Manipulation of the gel can be achieved through external factors, such as application of heating, cooling and shear, or internal factors such as the addition of small molecules, increase in gelator concentration,

combination of gelators, or change in oil composition. Oleogels are also thermo-reversible, formed by non-covalent bonds, meaning they could be engineered to respond to an external stimulus (a change in temperature or pH, for example) to allow release (Hughes, Rush, & Marangoni, 2011).

## **6.0 Strategies to gel oil and delivery applications of oleogels**

Oleogels can be classified by the size of their oil-gelling molecules, being low molecular weight or high molecular weight molecules. Low molecular weight gelators (LMOGs) can be further subdivided by the method with which they structure oil, through the formation of a 3-D network of crystalline particles or a space-filling fibrillar network. High molecular weight oleogelators, primarily polymers, structure organic solvents by the formation of physical or chemical interactions between strands, resulting in a supramolecular network. Many reviews exist on the topic of oleogelation and organogelation, providing in depth analyses of gel structure, gelation mechanism, and factors affecting gel formation (Bot, Veldhuizen, den Adel, & Roijers, 2009; Co & Marangoni, 2012; Davidovich-Pinhas, Barbut, & Marangoni, 2016; Patel & Dewettinck, 2015; Suzuki & Hanabusa, 2010).

The following section will discuss applications of oleogels for the delivery of lipid soluble molecules or control of lipid digestibility appearing in literature. Details of the physicochemical properties of the gel systems will be discussed, as well as the structure, matrix composition, and impact on release or digestion where applicable. Monoglycerides (MAGs), fatty acids, waxes, sorbitan monostearate (SMS), ceramides,  $\beta$ -phytosterol and  $\gamma$ -oryzanol, sugar esters, 12-hydroxystearic acid (12-HSA), and ricinelaic acid will be covered as examples of LMOG systems. The polymer section will focus on ethylcellulose, the only known food grade polymer gelator used to gel oil directly. Table 1 summarizes all examples found in literature of edible oleogels with oral delivery applications.

\*\* Insert Table 1 here\*\*

### *6.1 Crystalline particles*

Similar to TAGs, different crystalline particles can be used to structure liquid oil by forming colloidal networks that trap the liquid portion of the material. Examples of crystalline particle

gelators include MAGs, DAGs, fatty acids, and fatty alcohols (Co & Marangoni, 2012). Many plant-based waxes can also gel oil at low concentrations (Blake, Co, & Marangoni, 2014). The same processing parameters that affect crystal growth in TAG systems also affect these alternative crystalline systems, including cooling rate and presence of shear above and below crystallization temperature.

### *6.1.1 Monoglycerides*

Monoglyceride (MAG) molecules are composed of a single fatty acid attached to a glycerol backbone. In virgin olive oil, MAG crystals are needle-like, while in corn oil, MAG crystals have been described as spherulites (Kesselman & Shimoni, 2007). Like other crystalline systems, anhydrous MAG gels are sensitive to processing parameters. Increasing the concentration of MAG in the gel results in a higher gelation temperature and a harder gel network (Ojijo, Neeman, Eger, & Shimoni, 2004). Shearing can produce gels with weaker or stronger networks than those cooled statically, depending on the shear rate applied and the temperature of application (Ojijo et al., 2004). The complex phase behaviour of monoglyceride-oil mixtures has been characterized for specific systems, revealing changes in molecular packing arrangements of the amphiphilic molecules at different temperatures and volume fractions (Chen & Terentjev, 2011). Monopalmitin and monostearin can be used to gel olive oil, creating a spreadable food product that can be a substitute for hydrogenated and partially hydrogenated vegetable oils (Ojijo et al., 2004).

Yu et al. (2012) studied a monoglyceride oleogel for oral delivery of curcuminoids in a medium-chain TAG (MCT) medium. They experimented with different types of MAGs as gelators and found that although 10 % of monolaurin, monomyristin, monopalmitin, or monostearin, were able to gel MCT, 20 % MAG was necessary to gel the MCT, Span 20, curcuminoid mixture used in the formulation. In addition, only the monostearin was able to form a gel at this concentration. These authors suggested that the presence of Span 20 and curcuminoid in the formulation interfered with the MAG crystalline structure. This brings up an important point in the use of gels for delivery: because of the delicate balance necessary to achieve gelation, gel formation may be inhibited or otherwise affected by the presence of other components in the oil phase (Gravelle, Davidovich-Pinhas, Zetzl, Barbut, & Marangoni, 2016; Murdan, 2005). It was found

that the MAG gel was successful at inhibiting the precipitation of curcuminoids from the oil, leading to better long-term stability. Interestingly, no effect of oil structuring on *in-vitro* lipolysis was seen, possibly due to the partial melting of the gel at 37 °C (Yu et al., 2012).

The relationship between MAG gel structure and release is not fully understood. Realdon and Ragazzi (2001) examined samples of olive oil gelled with glycerol monostearate for application as a topical ointment. Samples were either statically cooled, sheared while cooled, or sheared after gelation, resulting in three samples with distinctly different crystal network morphologies. It was found that although *in-vitro* drug release was different between the three samples, *in-vivo* absorbance tests showed no significant difference between the three samples. Similarly, there was no significant difference in *in-vivo* absorbance between samples with 15 %, 20 % and 25 % gelator concentration, although significant differences in rheological characteristics between the gels were seen.

MAGs are also capable of stabilizing oil droplets in high concentration oil-in-water emulsions (Marangoni et al., 2007). The emulsions have been shown to have different effects on postprandial serum triglyceride, free fatty acid, and insulin levels in humans compared to liquid oil, depending on the structure of the emulsion (see 3.0 Factors affecting lipolysis) (Marangoni et al., 2007; Rush, Jantzi, Dupak, Idziak, & Marangoni, 2008; A. Wright et al., 2014).

#### 6.1.2 Fatty acids and fatty alcohols

Long-chain fatty acids (FAs) can form networks of crystalline platelets at low concentrations in oil, resulting in a gel (Gandolfo, Bot, & Flöter, 2004). Their gelling ability increases with increasing chain length and FAs of 18 carbons or longer can gel oil at 2 % concentration. Similarly, the melting points of these oleogels increase with FA chain length (Daniel & Rajasekharan, 2003). Fatty acids are more efficient gelator molecules than TAGs and therefore need to be added at much lower concentrations to create gels with comparable mechanical properties to fats (Co & Marangoni, 2012).

Mixtures of fatty acids and fatty alcohols have also been used together to form mixed gels; the ratio of stearic acid to stearic alcohol in a formulation gives another way to manipulate gel physical characteristics such as melting point, melting profile, and hardness (Gandolfo et al., 2004; Schaik, van Malssen, Morgado-Alves, Kalnin, & van der Linden, 2007).



Lupi et al. (2013) investigated the use of policosanol, a mixture of fatty acids, to gel olive oil; the policosanol gels were subsequently characterized and tested for their use as controlled delivery systems for oral administration of ferulic acid. They found that a minimum of 3% policosanol was needed in order to provide enough structure to the gels, to crystallize fast enough to immobilize the ferulic acid, and to yield a gel with a melting point above 37 °C. The gel showed slowed release profiles compared to liquid olive oil under *in-vitro* gastric and duodenal conditions, showing the potential of the gel to be used for delayed release formulations. As an added advantage, policosanol has been shown to have nutraceutical properties, including reducing blood lipid levels and cholesterol levels (Varady, Wang, & Jones, 2003).

### 6.1.3 Waxes

Plant waxes such as candelilla wax, sunflower wax, rice bran wax, and carnauba wax can be used to gel oil at concentrations as low as 0.5 % depending on the wax variety (Blake et al., 2014; Toro-Vazquez et al., 2007). Of the waxes, candelilla wax, carnauba wax, and rice bran wax are all US FDA-approved food additives (Blake et al., 2014). Waxes are made up of complex mixtures of alkanes, long chain esters, phytosterols, fatty acids, fatty alcohols, and other hydrocarbons, their compositions varying widely depending on their source. Their high efficiency of gelation has been credited to the morphology of the crystals, which was recently revealed to be platelet-like for candelilla wax, sunflower wax and carnauba wax (Blake & Marangoni, 2015a; Hwang, Kim, Evans, Koga, & Lee, 2015). The shape and size of the crystals affect many of the physicochemical parameters of the bulk system, including its oil binding capacity, hardness, and shear sensitivity (Blake & Marangoni, 2015b, 2015c). These factors would therefore equally influence the use of wax gels as delivery systems.

Although waxes have been proposed for use as structuring agents in fat-based spreads and margarines, no studies have looked at the application of wax oleogels as oral delivery systems. Wax-gelled triglycerides have, however, been used for transdermal drug delivery applications. 10 % beeswax-fish oil oleogels have been shown to delay the release of a lipophilic drug, betamethasone dipropionate, when applied topically in *in-vivo* experiments (Huri, Ng, & Zulfakar, 2013).

#### 6.1.4 Sorbitan monostearate

Sorbitan monostearate (SMS) is a food-grade emulsifier, also called Span 60. It promotes the formation of water in oil emulsions in mixed systems and forms rod-shaped tubes upon crystallization in pure oil (Rogers, 2009). SMS gels are opaque and thermo-reversible, with a minimum gelation concentration in TAG of 10 % (Murdan, Gregoriadis, & Florence, 1999). Recently, it was also shown that SMS at concentrations of 25 % and above can modify the crystal habit of a solid fat blend to induce heat resistance in the system (Peyronel & Marangoni, 2014). The added SMS crystallizes independently of the TAG in the blend, but the two species are held together by strong forces. This unique matrix changes the thermal behaviour of the system.

SMS-TAG gels have been used in transdermal drug release formulations. A fish oil-based topical lotion for pharmaceutical delivery was made with 10 %, 15 % and 20 % SMS but did not show sufficient long-term stability to be used as a commercial product (Huri et al., 2013). SMS has also been applied as a gelator for sorbitan monooleate solvent in an oral delivery application for the drug ciclosporin. An emulsion of SMS gel in water was created, allowing high solubility of ciclosporin in the gel and showing comparable delivery levels to a commercial formulation in *in-vivo* testing in dogs (Murdan et al., 2005). For delivery applications, it should be considered that the microstructure and gelation temperature of SMS gels can be altered by the presence of the solubilized molecule (Murdan, 2005).

Sorbitan monopalmitate (SMP), having the same molecular structure as SMS but with a palmitic acid tail, has also been used as a gelator for castor oil in a controlled drug delivery application (Singh, Pal, Pradhan, & Pramanik, 2013). It was found that a castor oil gel with 47% water and 13 % SMP produced a faster release profile *in-vitro* than the castor oil-SMP formulation with no water due to the amorphous structure of the water-containing gel.

#### 6.1.5 Ceramides

Ceramides are a type of sphingolipid, molecules made of a fatty acid attached to the amino group of a sphingosine molecule. They are food grade, and can be enzymatically synthesized from sphingomyelins extracted from milk and eggs, using phospholipase C to hydrolyze the phosphocholine group from the ceramide structure (Zhang, Hellgren, & Xu, 2006). They can

form lipid gels in oil at 2 % concentration and show an increase in minimum gelation concentration with increasing fatty acid length, unlike many other crystalline gelator molecules (Rogers, Wright, & Marangoni, 2009). Chemically homogeneous ceramides, with one type of fatty acid moiety, have been shown to form long, thin, fibrillar crystal networks in oil, while heterogeneous ceramides form spherulites, resembling the structure of crystalline TAGs in oil (Rogers, Wright, & Marangoni, 2011).

Along with their gelation capabilities, ceramides also have interesting bioactive properties. They have been shown to induce antiproliferative activity and increased apoptosis in cancer cells (Ogretmen & Hannun, 2004). In addition, ceramides are digested and absorbed in the small intestine and therefore could still offer protection to encapsulated nutraceuticals passing through the stomach (Rogers et al., 2011). Despite these effects, there are no reports of the use of ceramide-based oleogels for oral delivery of nutraceuticals or pharmaceuticals. Ceramides also have beneficial properties for cosmetic applications, where they are used in formulations to improve skin hydration and moisture-retention properties and have been shown to be an effective treatment for dermatitis (Zhang et al., 2006). Ceramide-based oleogels could therefore be an interesting material for a variety of drug and nutraceutical delivery applications.

## 6.2 Fibrillar networks

### 6.2.1 $\beta$ -Phytosterol and $\gamma$ -oryzanol

$\beta$ -phytosterol and  $\gamma$ -oryzanol self-assemble in oil to form fibrillar networks (Bot & Agterof, 2006). They are part of a larger group of phytosterol ester and phytosterol oleogelators and have been found to gel oil efficiently at a 1:1 molar ratio. To form a network, they co-assemble, forming helical ribbon tubules with diameter of  $\sim 10$ nm, which do not vary widely in size when oil type, ratio of phytosterol to oryzanol, or gelator concentration are varied (Rogers et al., 2014). The oleogels formed are transparent, due to the nanoscale dimensions of the fibers. Oleogels with 5 to 10 % concentration of  $\beta$ -phytosterol and  $\gamma$ -oryzanol are the consistency of solid fat (Bot et al., 2009). A benefit of these gels for use as delivery systems, aside from the edible nature of the phytosterols, are the positive health benefits of the gelators themselves: phytosterols have recognized cholesterol-reducing properties (Katan et al., 2003). A patented formulation for a  $\beta$ -phytosterol and  $\gamma$ -oryzanol structured vegetable oil fat replacement exists (Ritter, van de Sande,

& Muller, 2005). Although the nutritional benefits and the food grade status of the gelator molecules make it a promising system for edible and delivery applications, these gels may be challenging to incorporate into any system containing water. The presence of water can interfere with the gelator's ability to assemble into tubules or cause recrystallization of the network (Bot et al., 2009; Duffy et al., 2009).

Gelled emulsions, such as  $\beta$ -phytosterol and  $\gamma$ -oryzanol-gelled olive oil in water can be created to alter lipolysis profile compared to conventional oil in water emulsions (Duffy et al., 2009). However, in the case of this gelled system, the structure of the emulsion was seen to change over time due to the solubility of the gelator in the water medium, modifying the lipolysis profile of the emulsion.

#### 6.2.2 Sugar esters

Sugar esters, made from the esterification of a sugar and a fatty acid, are capable of gelling edible oils at low concentrations through the formation of crystalline fibrillar networks. Their amphiphilic nature gives them the ability to self-assemble via hydrogen bonding and van der Waals forces to form the high aspect ratio structures (Silverman & John, 2015). Raspberry ketone glucoside fatty acid esters were recently shown to be able to gel MCT oil at concentrations  $< 0.25\%$  (Silverman & John, 2015). Gels with low gelator concentration (0.25 to 2%) showed good long-term stability at room temperature compared to gels with higher ester concentrations.

Recently, a sucrose stearate and MCT gel in a nano-emulsion was studied for its application as a gel delivery system for quercetin (Xuechen, 2014). In contrast to the previous study, a significantly higher concentration of sugar ester was used (20 %) to gel the MCT droplets. The gel was able to prevent the recrystallization of quercetin from the oil medium, increasing the amount of solubilized bioactive in the organogel-in-water emulsion. No comparison of lipolysis profile between the gelled and un-gelled emulsion was conducted.

#### 6.2.3 12-Hydroxystearic acid (12-HSA)

12-hydroxystearic acid (12-HSA) is an extremely efficient gelator, forming long fibrils with high aspect ratio resulting in strong, thermo-reversible gels at gelator concentrations as low as 0.5 %

(Rogers, Wright, & Marangoni, 2008). Although it is not a food grade additive, it is derived from castor oil, a natural compound and has been studied extensively as a model oleogel system. The structure, assembly mechanism, and physicochemical properties of the gel have previously been described (Rogers & Marangoni, 2008; Rogers et al., 2008).

One interesting feature of these gels from a delivery property perspective is the extensive work that has been done on the relationship between gel processing conditions, 12-HSA network structure, and gel functionality. Rogers et al. (2008) showed that both the network crystallinity and the oil binding capacity of these gels could be modified using post-crystallization temperature treatment. 2 % 12-HSA canola oil gels placed at 5 °C were shown to have higher degrees of network branching, higher oil binding capacities, and uniform pore sizes compared to gels set at 30 °C, which showed higher degrees of crystallinity, higher rates of syneresis, and less branched structures. Subsequently, Co and Marangoni (2013) showed that the microstructure of 12-HSA gels could be altered with the use of oscillatory shear during crystallization at different cooling rates. Gel formation under a cooling rate of 30 °C/min resulted in a spherulitic microstructure, while a cooling rate of 1 °C/min yielded a fibrillar network. At a low cooling rate, oscillatory shear resulted in fiber thickening, which could be controlled by the magnitude of strain applied. At a high cooling rate, the application of shear resulted in an increase in the number of spherulites present. These microstructural changes did affect the mechanical properties of the gel; it was found that the presence of shear decreased the mechanical strength and oil binding capacity of the gels. The shear sensitivity of 12-HSA gels does provide a challenge for the use of these gels for edible applications, as shear could result in changes to crystal structure, oil leakage, and loss of any functionality associated with the structured oil (Co & Marangoni, 2013).

To investigate the use of 12-HSA canola oil gels for improved delivery and bioavailability of  $\beta$ -carotene (BC), Hughes et al. (2011) compared the quantity of micellarised BC during simulated digestion of 12-HSA gels and liquid canola oil containing BC. They found that the maximum amount of BC released from the oil was between 0 and 30 min of simulated duodenal digestion, while the maximum BC release from the gel was between 30 and 75 min. They concluded that the structure of the 12-HSA gel provided protection to the lipophilic molecule and had an effect on the rate of release of BC from the material.

Similarly, in their study on 12-HSA soybean oil gels, Iwanaga et al. (2010) found that gels exhibited significantly slower release rates of ibuprofen compared with unstructured soybean oil in simulated intestinal fluid. They further showed that release rates slowed with increasing 12-HSA concentration (2 to 10 %). This was attributed not to the diffusivity of ibuprofen through the matrix, but to the erosion of the gelled substance in the presence of duodenal digestive fluids. The *in-vitro* studies were complemented with *in-vivo* studies in rats, where 10 % 12-HSA soybean oil gels showed lower gastric absorption, lower maximum plasma concentration, prolonged release, and higher bioavailability of ibuprofen compared to both water and soybean oil. This is a significant finding, as it demonstrates *in-vitro* and *in-vivo* the ability to modulate release rates through gelator concentration and the benefits of using 12-HSA as a gelator.

#### 6.2.4 Ricinelaidic acid

Ricinelaidic acid is the *trans*- isomer of ricinoleic acid and gels oil in a similar manner to 12-HSA: dimers of the molecule stack to form crystalline fibers, resulting in a larger fibrillar network structure. These fibres increase in thickness with increasing gelator concentration. A gel can be made at ambient temperatures with 2.5 % ricinelaidic acid in canola oil, whereas 4 % is needed to gel unrefined sesame oil, with its high content of polar molecules (A. J. Wright & Marangoni, 2006). Like 12-HSA gels, ricinelaidic acid oleogels have manipulable structure and elasticity, and could potentially offer similar benefits for nutraceutical or drug delivery. However, during storage, ricinelaidic acid gels can exhibit changes in crystallinity, microstructural features, and mechanical properties, which could provide some challenges for their long term stability and use in delivery applications (A. J. Wright & Marangoni, 2007).

#### 6.3 Polymers

Polymers are a promising class of molecules for edible oil structuring, as there are many food grade polymers available. However, few of these naturally occurring polymers can be used to gel oil directly, because of their hydrophilic nature. From a delivery material perspective, polymer oleogels could provide an interesting complement to hydrogels (aqueous polymer-gelled systems) for lipid-soluble molecules, as hydrogels are frequently used in delivery applications for hydrophilic molecules (Davidovich-Pinhas, 2015).

Single-step or direct polymer gelation is achieved by the formation of a supramolecular network through physical or chemical crosslinking between the polymer strands (Suzuki & Hanabusa, 2010). The strength of the network is dependent on the molecular weight of the polymers, as well as the crosslink density (Gravelle, Barbut, Quinton, & Marangoni, 2014). It has recently been demonstrated that oil can be structured by polymers indirectly, through the formation of porous structures for oil sorption, for example, or by drying an oil-in-water emulsion structure by an amphiphilic polymer (Patel & Dewettinck, 2015). To form these gels, various high-energy processing steps must be taken in order to disperse hydrophilic or amphiphilic polymers in hydrophobic medium. In foam templating for example, highly porous structures are created by drying solutions of polymer in water and subsequently shearing the dried polymer into oil systems (Patel, Schatteman, Lesaffer, & Dewettinck, 2013). As they are made with hydrophilic polymers, these gels exhibit weak thixotropy and could be sensitive to the presence of water (Patel & Dewettinck, 2015). This would be challenging for a delivery application where functionality is obtained from the network structure.

Ethylcellulose is the only food-grade polymer gelator currently known to gel oil directly. The structure and properties of the EC and EC oleogels have recently been reviewed (Davidovich-Pinhas et al., 2016). The gel has shown promise in food applications, including as saturated fat substitute in finely ground meat products, where a valuable property of EC as a gelator is the ability to modulate gel hardness and other physicochemical properties to match those of the replacement fat. In addition, the use of EC oleogels for nutraceutical or drug delivery has been proposed (Davidovich-Pinhas, 2015; Zetzl & Marangoni, 2012). Figure 3 shows a schematic diagram of  $\beta$ -carotene encapsulation in an EC oleogel based on gel structure imaging and BC release studies (unpublished results from the authors' laboratory group).

\*\*Insert Figure 3 here\*\*

### *6.3.1 Ethylcellulose oleogels*

EC oleogels made with vegetable oils have a range of interesting applications in both cosmetics and food industries (Aiache, Gauthier, & Aiache, 1992; Davidovich-Pinhas et al., 2016; Zetzl, Marangoni, & Barbut, 2012). In food, their primary application has been as a solid fat replacement in high fat food products such as finely chopped meat products and cream fillings.

As interest into their properties as solid fat replacements has increased, studies have explored various aspects of the material, including the mechanism of EC oil gelation (Davidovich-Pinhas, Barbut, & Marangoni, 2015; Davidovich-Pinhas, Gravelle, Barbut, & Marangoni, 2015); effect of polymer concentration, molecular weight and oil type on gel strength (Gravelle et al., 2014; Zetzl et al., 2012); gel manufacturing considerations (Gravelle, Barbut, & Marangoni, 2013; Zetzl et al., 2012); effect of solvent polarity on gel properties (Gravelle, Davidovich-Pinhas, Zetzl, et al., 2016); and direct applications in food products (Zetzl et al., 2012). This section will provide a brief overview of EC oleogel properties, with a focus on strategies to manipulate gel physicochemical properties and structure. This information could lead to strategic design of EC oleogels for control of lipid bioavailability or lipophilic nutraceutical release.

#### 6.3.1.1 Ethylcellulose

Commercially available ethylcellulose is a semi-crystalline polymer derivative of cellulose with a 2.5 degree of ethoxy substitution (Davidovich-Pinhas, Barbut, & Marangoni, 2014). This degree of substitution results in the ability of the polymer to be dispersed in liquid oil at high temperatures. It is also soluble in a variety of organic solvents and is favoured in industrial applications for its extensibility, flexibility, and film-forming properties (Dow, 2005). It is FDA approved as a food additive for applications in vitamin binding and filling, coating, and fixative flavouring applications under regulation 21 CFR 172.868 and is currently under review as a general food additive. EC is currently used in oral formulations in the pharmaceutical industry as a matrix filler or as a tablet coating, making use of EC matrix porosity and drug loading capacity to provide benefits of controlled release (Mäki et al., 2006).

#### 6.3.1.2 Mechanism of gelation

EC undergoes a glass transition at ~130 °C, varying with the molecular weight of the polymer (Davidovich-Pinhas et al., 2014). Above this temperature, some crystalline regions of the polymer become amorphous, exposing the ethoxy groups, and allowing the polymer to become soluble in oil (Davidovich-Pinhas, Barbut, et al., 2015). As the solution cools below 100 °C, a network forms due to the formation of hydrogen bonds between EC strands, trapping the oil within the network, resulting in a gel (Davidovich-Pinhas, Gravelle, et al., 2015). The minimum gelation concentration is 4-6 % depending on the molecular weight of the ethylcellulose used,



and the processing parameters employed (Zetzl et al., 2012). It has also been reported that these gels do not form any secondary structures (Davidovich-Pinhas, Barbut, et al., 2015).

#### 6.3.1.3 Gel properties

The properties of the EC gels can be manipulated using different methods to achieve desired functionalities. Oil type, polymer concentration and molecular weight, and addition of small molecules such as surfactants or polar molecules are some ways in which gel formulations and functionality can be manipulated (Gravelle, Davidovich-Pinhas, Zetzl, et al., 2016; Zetzl et al., 2012). These oleogels are also sensitive to external processing parameters: heating, cooling, shear during gelation, and setting temperature can all affect the final gel (Davidovich-Pinhas, Gravelle, et al., 2015; Gravelle et al., 2013; Wang et al., 2016).

##### 6.3.1.3.1 Oil type and polymer concentration

The type of oil used in an EC oleogel can have a strong influence on the mechanical properties of the resulting gel. Zetzl et al. (2012) showed that 10 % 45 cP EC gels made from canola oil or soybean oil varied in hardness from 26 N to 80 N as measured by back extrusion. This difference was later attributed to the presence of polar compounds, oxidative by-products, and free fatty acids in the different oil types, affecting the overall polarity of the oils and influencing the strength of the gel network (Gravelle, Davidovich-Pinhas, Zetzl, et al., 2016). When EC concentration is increased, gel strength increases in a power law fashion (Gravelle et al., 2014; Zetzl et al., 2012). The relationship between EC concentration and gel strength for different oils can be modeled, creating a useful tool for choosing a specific gel formulation for a given application (Gravelle et al., 2014).

##### 6.3.1.3.2 Manufacturing considerations

Heating to above the glass transition temperature of EC is a step in oleogel manufacturing which can introduce some variability in physical characteristics and have considerations for further oleogel applications. Exposure to heat can lead to oxidation of the oil, and products created in the process change the polarity of the oil, affecting the hardness of the gel (Gravelle, Barbut, & Marangoni, 2012). In edible or oral delivery applications, this challenge can be overcome by the addition of small amount of antioxidants, such as butylated hydroxytoluene (BHT) or rosemary

oleoresin, which minimize the formation of primary and secondary oxidation products. The antioxidant chosen could also protect lipid-soluble bioactives in the gel from oxidation.

#### 6.3.1.3.3 Cooling rate and gelation temperature

Because of the physical interactions between strands in the EC gel network, increasing the gel-setting temperature results in a stronger gel. Davidovich-Pinhas et al. (2015) found that allowing the same liquid molten gel formulation to set at temperatures equal to or above 80 °C resulted in an increase in gel strength. This was attributed to the high thermal energy of the system causing a prolonged extended state of the polymer during formation of the hydrogen-bonded network, leading to more entanglement and more inter-polymer junction zones. Interestingly, the polymer network also showed the ability to rearrange after gelation, resulting in a change in gel strength, when the set gel was exposed to high or low temperatures (-20 °C or 80 °C). Formulations set at 80 °C and 100 °C showed good shelf-life stability over a 90 day period under 25 °C storage.

#### 6.3.1.3.4 Solvent quality

Solvent quality is one way to describe and predict solvent-gelator interactions and is often employed as a strategy in the search for new food-grade oleogelating molecules (Gao, Wu, & Rogers, 2012). Using Hansen Solubility Parameter (HSP) theory, solvent quality can be quantified and subsequently adjusted, such that the gelator has optimum solubility in the oil (Hansen, 2007). For EC oleogels, high solubility of the polymer in the oil phase would result in a more open polymer conformation, and an increase in exposed hydroxyl groups available for network formation. However, polymer-solvent interactions must not be so favoured that polymer-polymer interactions do not occur, as no network would result in this case (Gravelle, Davidovich-Pinhas, Zetzl, et al., 2016). In a recent study by Gravelle, Davidovich-Pinhas, Zetzl et al. (2016) on solvent quality considerations for EC oleogels, the HSP of the oil phase was modified by the addition of mineral oil and castor oil to soybean oil, resulting in gels with different mechanical properties. The addition of oleic acid and oleyl alcohol at concentrations of 0.25 % also influenced gel physicochemical properties due to their surface activity, by preferentially interacting with the EC, and improving the overall solubility of the polymer in the oil phase.

Elasticity and oil loss are examples of other gel properties which can be altered by modification of oil polarity (Wang et al., 2016). In addition, different low molecular weight organogelling molecules can be paired with EC (ex. small crystalline particles) to impart unique properties to the gel. In their recent work, Gravelle, Davidovich-Pinhas, Barbut et al. (2016) showed that when a gel was made with EC and a mixture of stearic acid and stearic alcohol (SOSA), the presence of the polymer had an effect on the organization and size of the SOSA crystals. In addition, the SOSA molecules had a plasticizing effect on the EC. As a result, the gel made from the combination of these two gelation strategies showed improved functional properties compared to gels made with either pure system.

Edible oil EC gels tend to be shear-sensitive, due to irreversible destruction of the polymer network. Thixotropic oleogels—gels that recover their viscosity after thinning under fixed shear—can be obtained with the addition of a surfactant, resulting in a gel with a functionality similar to petrolatum (Stortz & Marangoni, 2014). At 45% glycerol monooleate and 55% oil composition, the solvent is optimized for EC solubility by HSP theory and a thixotropic, paste-like gel is obtained. Physicochemical properties such as thixotropy are important when considering applications for these gels, as shearing is likely to be involved in any further processing of a product containing the oleogel. In addition, when using gels for applications dependent on matrix structure, such as for delivery, the integrity of the gel structure affects performance (Rush et al., 2008; Yu et al., 2012).

The changes in gel physicochemical properties with formulation or processing conditions discussed above are often accompanied by changes in gel structure. Knowledge of the structure of these gels is essential in the understanding of the functionality of the gels in applied systems, such as for delivery.

#### *6.3.1.4 Gel structure*

The basic structure of EC oleogels has been described as “coral-like”, when imaged after partial solvent removal of oil with cryo-scanning electron microscopy (cryo-SEM) (Zetzl et al., 2014). Some oil removal was necessary to expose the EC network, revealing strands of polymer supporting pockets of liquid oil. However, excess washing of the gel with solvent caused some damage and collapse of the structure, indicating that the oil inside the polymer network helps to

maintain the structural integrity of the material (Sagiri et al., 2014). Oil pockets in EC oleogels were approximately 3-4.5  $\mu\text{m}$  in diameter and the hardness of the network was hypothesized to be due to the size of the oil pockets as well as the strength of the walls (Zetzl et al., 2014).

Changes in network structure with gel composition and processing conditions are also of interest, as they influence the physical properties of the gel and gel applications. EC molecular weight and concentration effects on the gel structure have been elucidated; in their work, Zetzl et al. found that increases in EC concentration from 10 to 14 % 45 cP EC resulted in a decrease in average pore size from  $\sim 4.5 \mu\text{m}$  to  $3 \mu\text{m}$ . On the contrary, when comparing 45 cP EC gels with 100 cP EC gels, there was no significant difference in pore sizes (Zetzl et al., 2014). It was hypothesized that the observed difference in gel strength with increase in polymer molecular weight was likely due to the strength of the polymer walls: longer polymer strands could form more junction zones, becoming more entangled, leading to a more rigid network.

Oil type has also been shown to affect EC oleogel structure, where gels made with canola oil had on average larger pore sizes than gels made with soybean oil and flaxseed oil (Zetzl et al., 2014). Other studies have shown that the presence of minor components and polar molecules in oils affect the mechanical properties of their EC gels (Gravelle et al., 2012; 2016). Therefore, an effect of those minor components on gel structure and pore size would not be surprising. This is currently being investigated, examining gels made with refined and virgin olive oils.

#### 6.3.1.5 Gel applications

As the relationships between EC oleogel composition, functionality and structure become better understood, the development of new applications of gels in food products is also facilitated. Functionality-matching can be achieved easily and through a variety of strategies, opening up possibilities in the fields of cosmetics, pharmaceuticals and food. However, one area that remains to be fully explained is how oil structuring in an EC oleogel changes its physiological properties, and how this might influence its functionality in a food product or as a drug delivery material. This is currently the subject of investigation, looking at the *in-vitro* digestibility and  $\beta$ -carotene release of different EC oleogels (Figure 4) (unpublished results from the authors' laboratory group).

\*\*Insert Figure 4 here\*\*

## 7.0 Conclusion

Many oil-gelation strategies exist today to make organogels with diverse physicochemical properties. These oil-based gels could be used for the control of lipid digestibility and delivery of lipid soluble molecules, given their food-grade composition and manipulable structures. In this review, the mechanism of lipolysis and the structural factors affecting lipolysis were reviewed, specifically as they applied to gelled oil systems. Factors such as gel composition, particle size, oil type, and matrix structure could have an impact on gel digestibility. The need for delivery systems to improve the bioaccessibility of lipid soluble molecules, such as carotenoids, was discussed, as well as the advantages gained from using a lipid-based system. Subsequently, edible oleogels were proposed as a novel delivery material for lipid-soluble molecules. These gels could improve bioaccessibility of lipid soluble molecules by delivering the molecules in soluble form, and could offer added benefits of protection and controlled release capabilities. Strategies to gel liquid oil were then reviewed, with a focus on EC oleogels. The various ways to alter EC oleogel structure and functionality—oil composition, gelator concentration, gel cooling and setting—make it a promising material for delivery.

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**Figure and table captions:**

**Table 1** Current examples found in literature of edible oleogels with oral delivery applications.

**Figure 1** **A)** Cryo-SEM image of oil droplets in a monoglyceride (MAG)-structured oil-in-water emulsion. **B)** Schematic diagram of MAG bilayers structuring an oil droplet. The red lines represent MAG molecules assembled into stacked crystalline bilayers, with water in between. Co-emulsifying molecules, which help to stabilize the MAG structure, are shown in blue.

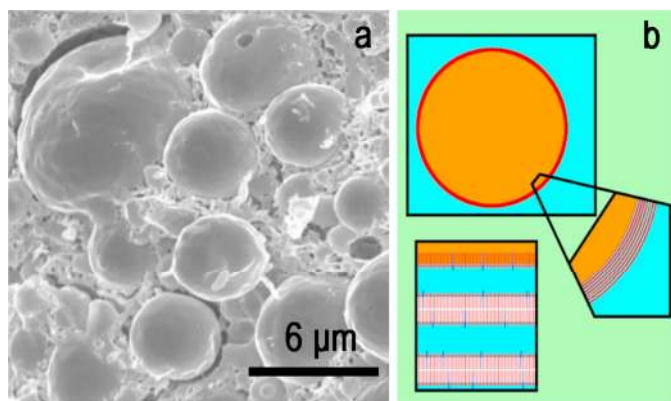
**Figure 2** Average physiological response of five male and four female subjects to acute ingestion of an oil–water mixture or the MAG-structured emulsion. For all panels, the main graph shows the metabolite dynamic in time, while the inset represents the accumulated response (net area under the curve). **(A)** Change in serum triglyceride levels, **(B)** change in plasma free fatty acid levels, **(C)** plasma glucose levels, **(D)** plasma insulin levels. All values represent the averages and standard errors of the subjects' responses. Adapted from Marangoni et al. (2007).

**Figure 3** Network structure of a de-oiled ethylcellulose oleogel, imaged using atomic force microscopy in water in HyperDrive mode. The hydrogen-bonding of ethylcellulose polymer strands that form the coral-like network of the oleogel are represented. The oil is located in the pores of the structure and beta-carotene is solubilized in the oil phase.

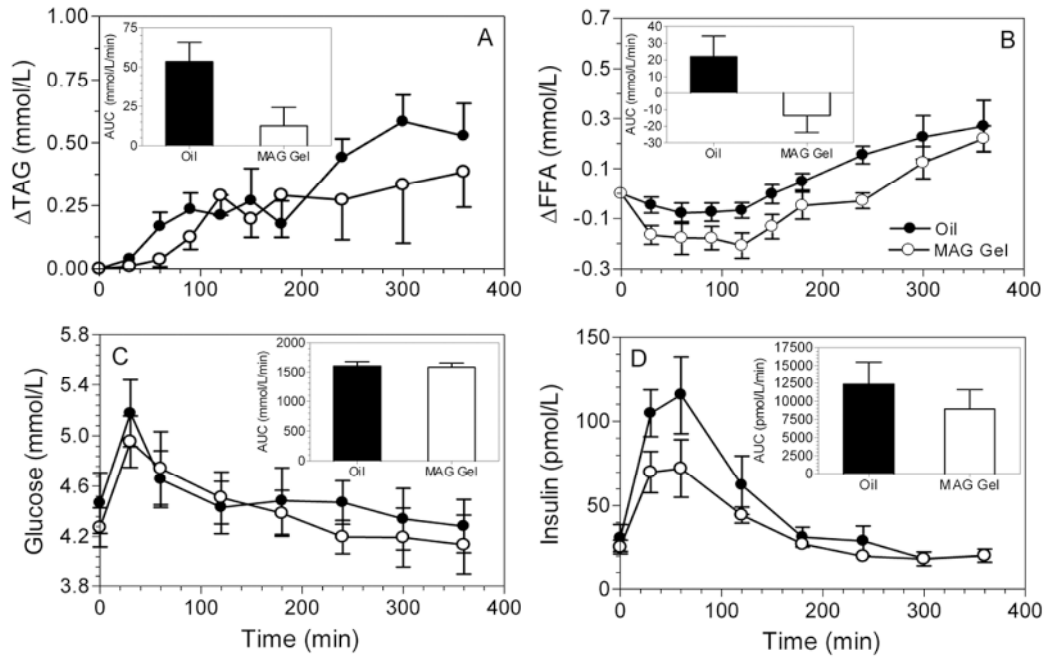
**Figure 4** Beta-carotene transfer from canola oil and 10% w/w 10 cP and 10% w/w 45 cP canola oil ethylcellulose oleogels to the aqueous digestate phase through 180 minutes of *in-vitro* duodenal digestion in a static monocompartmental model. The duodenal digestion followed simulated oral and gastric digestion stages. The 10% 45 cP oleogel was harder than the 10% 10 cP oleogel due to the difference in molecular weight between the polymer blends. Error bars indicate the standard error of the mean for n=3 replicates (unpublished results).

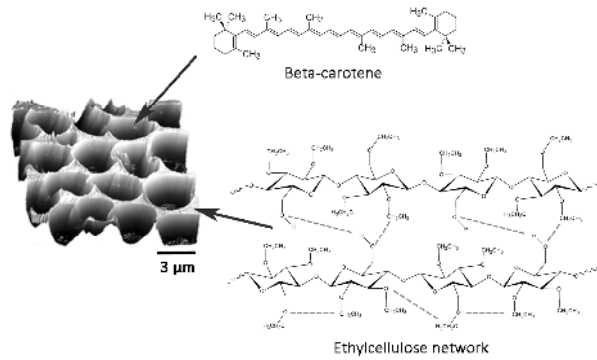
Table 1

Gelator		Gel composition and form	Molecule delivered	Analyses conducted	Reference
Group	Type				
Monoglyceride	Monostearin	MCT-Span 20 solvent; 20% MAG; oleogel	Curcuminoid	<i>In-vitro</i> lipolysis, bioaccessibility	Yu et al. (2012)
Fatty acid	Policosanol (60% octacosanol)	Olive oil; 1-10% policosanol; oleogel spherical particles	Ferulic acid	<i>In-vitro</i> release	Lupi et al. (2013)
Sorbitan ester	Sorbitan monostearate (SMS)	Sorbitan monooleate and polysorbate 20; 18% SMS; gelatin capsules containing oleogel	Ciclosporin	<i>In-vitro</i> bioavailability, <i>in-vivo</i> bioavailability in dogs	Murdan et al. (2005)
	Sorbitan monopalmitate (SMP)	Two systems: castor oil, 25% SMP; and castor oil-water, 13% SMP; oleogel tablets	Metronidazole	<i>In-vitro</i> release, gel disintegration studies	Singh et al. (2013)
Sugar ester	Sucrose stearate	MCT; 20% sugar ester; gel-in-water nanoemulsion	Quercetin	<i>In-vitro</i> bioaccessibility	Xuechen (2014)
Hydroxylated fatty acid	12-hydroxystearic acid	Canola oil; 2% 12-HSA; oleogel	$\beta$ -carotene	<i>In-vitro</i> bioaccessibility	Hughes et al. (2011)
		Soybean oil; 2-10% 12-HSA; oleogel capsules	Ibuprofen	<i>In-vitro</i> release, erosion and diffusion measurements, <i>in-vivo</i> bioavailability in rats	Iwanaga et al. (2010)

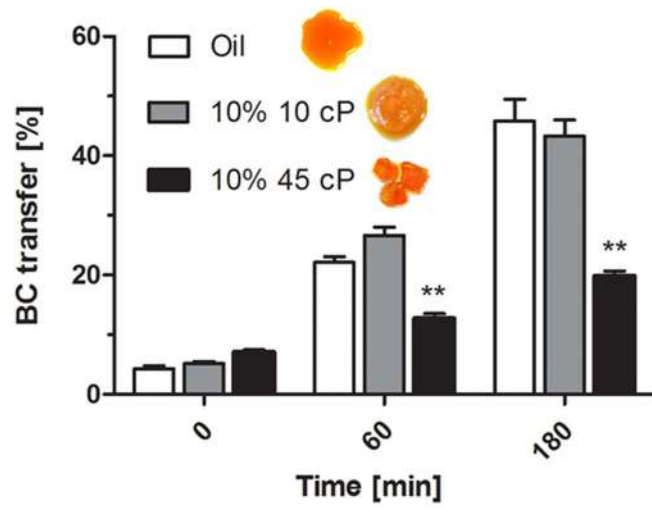


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- Food grade crystalline and polymer oleogelators exist.
- Oleogel mechanical strength can be altered through composition and processing.
- Oleogel matrices can affect the rate of bioactive release.
- Oleogels can provide stability against bioactive recrystallization.
- Ethylcellulose oleogels are polymer-based and could be used for bioactive delivery.