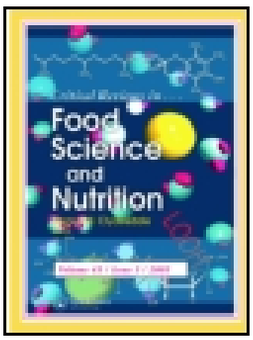

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REVIEW

Emulsion, hydrogel and emulgel systems and novel applications in cannabinoid delivery: a review

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ABSTRACT

Emulsions, hydrogels and emulgels have attracted a high interest as tools for the delivery of poorly soluble hydrophobic nutraceuticals by enhancing their stability and bioavailability. This review provides an overview of these delivery systems, their unique qualities and their interactions with the human gastrointestinal system. The modulation of the various delivery systems to enhance the bioavailability and modify the release profile of bioactive encapsulates is highlighted. The application of the delivery systems in the delivery of cannabinoids is also discussed. With the recent increase of cannabis legalization across North America, there is much interest in developing cannabis edibles which can provide a consistent dose of cannabinoids per portion with a rapid time of onset. Indeed, the long time of onset of psychoactive effects and varied metabolic responses to these products result in a high risk of severe intoxication due to overconsumption. Sophisticated emulsion or hydrogel-based delivery systems are one potential tool to achieve this goal. To date, there is a lack of evidence linking specific classes of delivery systems with their pharmacokinetic profiles in humans. More research is needed to directly compare different classes of delivery systems for the gastrointestinal delivery of cannabinoids.

KEYWORDS

Bioavailability; cannabidiol; cannabinoid; cannabis; delivery system; emulgel; emulsion; hydrogel; pharmacokinetic; tetrahydrocannabinol

Introduction

Delivery systems designed to entrap, suspend, protect and deliver nutraceuticals are of great interest in both the food and pharmaceutical industries. They are excellent tools to be applied whenever a bioactive agent, such as a drug or nutraceutical compound must be delivered in an efficient way to the human organism. Selection of the appropriate delivery system depends on many factors, such as the hydrophobicity or hydrophilicity of the bioactive encapsulate, the route of delivery into the body and the desired release profile of the compound. Delivery systems are particularly advantageous for hydrophobic nutraceuticals and drugs. These compounds suffer from immiscibility with the digestive fluids and low intestinal permeability which can severely limit their oral bioavailability (Yang and Chiang 2019).

The most common delivery systems used for the delivery of hydrophobic bioactive agents are emulsions. Emulsions generally consist of an oil phase suspended in an aqueous phase (or vice versa) stabilized with various surfactants and emulsifiers. Structurally, these thermodynamically unstable systems vary significantly. Some examples of modern emulsion systems include: (1) nano or microemulsions, which feature very small particle sizes, (2) double emulsions, which have a characteristic water in oil in water structure, (3) polymer stabilized or multilayer emulsions which employ proteins or polysaccharides as stabilizers, (4) Pickering emulsions which use larger, solid particles as stabilizers, and (5) solid lipid nanoparticles or nanostructured lipid carriers which feature a solidified oil phase, and many other combination systems.

Emulsion systems for specialized applications have been extensively reviewed in recent years. These reviews have been mainly focused on very specialized emulsion systems such as the review on self-emulsifying drug delivery systems written by Prasad, Vasavi, and Hari (2020). Therein, the reviewers focus on all aspects of these currently researched systems such as the composition, the modes of administration and the varying methods of preparation. Novel emulsifiers extracted from food matrices have also been a popular subjects for reviews such as use of nanocellulose, soy polysaccharides or gums (Das et al. 2020; Kedzior et al. 2020; Nejatian, Abbasi, and Azarikia 2020). Many reviews have also focused on systems designed to deliver specific bioactives such as polyunsaturated fats or carotenoids (Wang et al. 2020; Zare et al. 2020). Emulsion systems are a broad topic with extensive research being carried out in many different facets, and further innovation is possible in each of these directions. This review will pay special attention to the bioavailability considerations of various emulsion systems.

Hydrogels are networks of polymers or biopolymers which can hold water and swell to several times their native size. They can consist of synthetic polymers, but more often in food applications polysaccharides or proteins are selected to make up their structure. Hydrogels are used extensively

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in biomedical applications such as tissue engineering and wound dressings, but they can also be utilized as a component of a delivery system for of bioactive ingredients. Many recent advances in this field involve the use of novel biopolymers for construction of the hydrogel matrix. While gelatin and alginate are some of the most common polymers used for hydrogels, there have been research groups looking into many different proteins and polysaccharide such as chitosan, casein and modified starch or cellulose components (Bacakova et al. 2020; Nascimento et al. 2020; Qu and Luo 2020).

Alone, hydrogels are most often used to deliver hydrophilic bioactive ingredients. However, they can also be used in combination with emulsion systems in order to entrap and deliver hydrophobic compounds. Combining emulsion and hydrogel systems can lead to very specialized structures to achieve increased stability of the delivery system or encapsulated bioactive ingredient, to achieve controlled release of a hydrophobic compound over a period of time, or even to provide burst release of the encapsulate in response to specific physical or physiological triggers. Reviews that involve emulgel systems often focus on the novel functionality that these systems can achieve. For instance, Corstens, Berton-Carabin, de Vries, et al. (2017) reviewed emulgels with the specific function of increasing satiety by delaying lipolysis of entrapped oils through the use of tight gel networks. Emulgels have also been widely applied for topical or ophthalmic delivery of hydrophobic drugs. They are considered ideal for this application due to their rheological properties, the ability to entrap nano sized droplets within the gel matrix with increased stability and the opportunity to co-deliver permeation enhancers in the matrix of the gel (Aithal, Narayan, and Nayak 2020). Overall, emulgels are very varied systems which can be designed for specialized delivery profiles by selecting appropriate polymers and oil phases in their conception.

With the recent increase of cannabis legalization across North America, these delivery systems are starting to be applied for delivering cannabinoids in food, beverage and pharmaceutical settings. There is a surge of research in this field and evidence is slowly being established. Recent focus has primarily been on cementing the health effects of cannabis products. While the negative health consequences of smoking cannabis cigarettes has been established, little else can be said regarding the long term health consequences of consuming cannabis through other means (Russell et al. 2018).

Furthermore, many clinical studies have been published regarding the pharmacokinetics of cannabinoid compounds in the human body. These studies most often compare the pharmacokinetics between different methods of cannabis consumption. A recent analysis by Lim, Sharan, and Woo (2020) compared the pharmacokinetics of cannabis reported in multiple clinical studies when cannabis was taken through an oral capsule, an oral solution or an oromucosal spray. This was one of the few studies that endeavored to create a model for overall cannabis pharmacokinetics for oral versus oromucosal routes of administration. This step is important due to the very variable results that cannabis pharmacokinetic studies achieve due to an individual's metabolism and digestive process. One weakness of this study, however, is that the exact nature of the delivery systems studied for oral or oromucosal delivery were left undefined. On the other hand, McClements (2020) recently published a review which provides a summary of delivery systems which have been used for cannabis applications. This review is very thorough regarding the types of delivery systems which have been employed for cannabinoid delivery. However, it does not provide a link between the applied delivery systems and the biological outcomes of cannabinoids in the form of clinical pharmacokinetic data.

It is well established that the nature of a delivery system used to deliver a bioactive agent can greatly affect its rate of absorption and metabolism. Understanding the pharmacokinetics of individual cannabis containing delivery systems is of utmost importance for developing cannabis products for the market which can produce consistent effects and provide a consistent dose per edible portion. This consistency, in turn, will allow for consumers to better titrate their cannabinoid intakes, which will lead to fewer negative health effects associated with accidental cannabis overconsumption.

This review will begin by providing an overview of recent advances in emulsion, hydrogel and emulgel systems for the delivery of hydrophobic bioactive compounds. It will then review in detail the varied delivery systems that have been used in food and pharmaceutical applications for the delivery of cannabinoid compounds. There will be a special emphasis on comparing the pharmacokinetic data provided for well-defined oral and oromucosal cannabinoid delivery systems.

Emulsions

Oil in water emulsions consist of oil droplets surrounded by a thin layer of emulsifier and suspended in an aqueous continuous phase. This is the most common type of emulsion used in food products due to the low cost of production, the simplicity of the preparation and the ease of scale up (McClements 2016). However, these emulsions are prone to physical instabilities and do not offer any substantial control over the release profiles of the bioactive substances they encapsulate.

There are many factors that contribute to the speed of destabilization of an emulsion. Stoke's law describes several of these factors:

$$v_{Stokes} = -\frac{2gr^2(\rho_2 - \rho_1)}{9\eta_1}$$

Where v is the creaming or sedimentation velocity, g is the acceleration due to gravity, r is the radius of the particles in the dispersed phase, ρ_1 and ρ_2 are the densities of the continuous and dispersed phases, respectively, and η_1 is the shear viscosity of the continuous phase (McClements 2016). Based on this equation, oil droplets of larger size are more prone to physical instabilities such as creaming, flocculation and coalescence. Li et al. (2020) observed this phenomenon

in their study evaluating the droplet size and physical stability of emulsions stabilized with chicken myofibrillar protein modified by ultrasound for 0, 3 or 6 minutes. Droplet size within their emulsions decreased with increasing levels of chicken myofibrillar protein ultrasonication, ranging from 2.08 μm without ultrasonication to 1.62 μm after 3 minutes of ultrasonication and 0.98 μm after 6 minutes of ultrasonication. Paired with this, the emulsion stability index (ESI) increased with the decreasing droplet size. ESI increased 21.51% from baseline with the 3-minute ultrasound treatment and 55.94% from baseline with the 6-minute ultrasound treatment. These findings were supported by many other studies such as Sun et al. (2019) who found increased emulsion stability with decreasing oil droplet size when testing emulsions stabilized with flax seed gum.

Nanoemulsions

Nanoemulsions which have much smaller particle sizes (1 – 500 nm range) offer better stability than conventional emulsions to droplet aggregation, creaming and sedimentation due to stronger Brownian motion forces counteracting destabilizing forces such as gravity (Zhao, Wei, et al. 2020). These emulsions also tend to scatter light more weakly and have a more transparent appearance than conventional emulsions. Most importantly, it has been found that nanoemulsions offer a better bioavailability of encapsulated ingredients due to altered absorption in the gastrointestinal tract (McClements 2016). However, in order to achieve these smaller droplet sizes, nanoemulsions require a greater energy input during their creation than conventional emulsions.

Xu, Mukherjee, and Chang (2018) evaluated the physical stability of nanoemulsions prepared with whole soybean protein isolate as well as the 7S or 11S fractions of soy protein isolate. These researchers reported that as the oil droplet sizes decreased from $>$ 1000 nm to $<$ 200 nm the emulsion stability increased in tandem. Additionally, they found that droplets $<$200 nm were stable to heating up to 60 °C and had no significant difference in their droplet sizes after 45 days of storage at 4 °C. They attributed this to the small droplets being resistant to gravitational separation and the soy proteins creating a robust barrier around the droplets. This increase of stability with emulsions at the nano size as opposed to the micro size has been confirmed in other studies such as Fernández-Ávila, Escriu, and Trujillo (2015) who found that emulsions created through ultra-high pressure homogenization had a smaller droplet size and greater stability than those created through standard homogenization.

Another significant advantage that nanoemulsions offer is their ability to be optically transparent. This is due to the particles being so small that they do not significantly scatter light. This could be of use in creating foods which benefit from a non-cloudy appearance such as a juice or drink. Barzegar et al. (2018) evaluated the optical transparency of nanoemulsions of peppermint oil and Tween 80 created through the spontaneous emulsification method. They found that during 90 day room temperature storage emulsions created with 150-225% surfactant to oil ratio decreased in particle size from 50-88 nm to 4-15 nm and became optically transparent during storage without any creaming effect or other sign of physical instability. Alshahrani (2019) also found that optical transparency of nanoemulsions increased with decreasing particle size. Through the spontaneous emulsification method nanoemulsions of ostrich oil were created. Nanoemulsions with particle sizes of 110.5 nm had a 93.4% light transmittance rate whereas those of 82.2 nm had a 96.6% light transmittance rate, indicating higher transparency.

One of the key reasons that nanoemulsions with small particle sizes are so highly sought after in food and pharmaceutical applications is that decreasing particle size increases intestinal bioavailability of the encapsulated nutraceuticals. Bekerman, Golenser, and Domb (2004) studied the oral bioavailability of cyclosporine administered orally in a nanodispersion with varying particle sizes. Nanodispersions were formed by the self-emulsification method and formulations were tailored with varying levels of surfactant and organic solvent in order to create 6 unique treatments with particle sizes ranging from 400 nm – 25 nm. In vivo trials were then performed on human healthy volunteers (4-6 volunteers for each of the 6 formulations) by orally administering the six formulations and measuring cyclosporine levels in the blood up to 25 hours after administration. The investigators found that Cmax (the maximum concentration of blood cyclosporine) increased proportionally with decreasing particle size, with the highest blood concentration being found for the 25 nm dispersion.

Double emulsions

The most common forms of double emulsions are the water in oil in water (W/O/W) and oil in water in oil (O/W/O). The W/O/W emulsion consists of small water droplets suspended in a larger oil droplet which is then suspended in an aqueous medium. The W/O/W emulsion is most appropriate to use for the protection of water-soluble bioactive compounds. It is also useful in creating highly viscous low fat food products and in tailoring flavor delivery systems (McClements 2016). In practice, these emulsions are not often used in the food industry due to the higher number of functional ingredients required and their high susceptibility to breakdown during storage or when exposed to stressful processing conditions.

As an example of the delivery of hydrophilic bioactive ingredients, Ilyasoglu Buyukkestelli and El (2019) developed a double emulsion system to encapsulate iron. This system served a dual purpose, to protect the food matrix from oxidative rancidity which can be accelerated by the presence of a metal ion, and to increase the in vitro bioaccessibility of the encapsulated iron. The researchers tested three ratios of primary emulsion (W1/O) to continuous phase (W2) in ratios of 40:60, 30:70 and 20:80. The researchers found that iron's bioaccessibility was greatest with the 20:80 emulsion. They attributed this to a higher level of sodium caseinate being present in the W2 phase, which chelates iron during

digestion and helps to prevent inhibition by other compounds.

Other than the simple delivery of water soluble bioactive molecules, double emulsions may be used to deliver a combination of lipophilic and hydrophilic ingredients simultaneously. Dima and Dima (2020) created a W/O/W emulsion to co-encapsulate various calcium salts and vitamin D3. They found that despite both bioactive molecules being delivered to the intestine simultaneously, the bioavailability of vitamin D3 was greater in the control samples than those containing calcium salts in their inner aqueous core. This was attributed to the calcium salts causing free fatty acids to precipitate which had a negative effect on micellization. These studies show that it is often difficult to predict the effect of a double emulsion system on the bioaccessibility of the encapsulated compounds.

Double emulsions are also extremely useful as flavor delivery systems. They may be used to co encapsulate flavors with different lipophilicities, or to modulate the flavor release profile of encapsulated hydrophilic compounds. An example of co encapsulation of synergistic flavor compounds is evident in the work done by HeeJeong et al. (2017), where they created double emulsions with sodium chloride in the external water phase and abalone hydrolysate in the internal water phase. The purpose of this research was to decrease the amount of sodium used in the preparation of cheese without decreasing the intensity of the salty flavor perceived by sensory analysis. This led to their choice of including abalone hydrolysate as a salt enhancer compound. The researchers found that despite the decreased salt content of the cheese, the panelists detected a more intensely salty flavor and had a higher preference for the cheeses containing this double emulsion compared to the full salt control cheese. An example of a double emulsion used to prolong the release profile of sweetness in a gum was developed by Rocha-Selmi et al. (2013) who created an emulsion of aspartame solution and soybean oil which were then entrapped within coacervate microcapsules made from gelatin and gum Arabic. The resultant complex coacervate showed lowered solubility in water, which in turn is known to delay the release profile of encapsulated hydrophilic materials.

Making low fat food products is another common use for double emulsions. While conventional fat replacers often result in undesirable sensory changes in food products, a similar fat reduction can often be achieved through double emulsions. For instance, Tekin, Sahin, and Sumnu (2017) used a W/O/W emulsion to reduce the fat content of an ice cream. After sensory evaluation it was found that the fat content could be reduced by 2.8% without any significant changed to overall acceptability scores from sensory panelists. Another similar study was done by Yildirim, Sumnu, and Sahin (2016) where a reduced fat mayonnaise was created with a W/O/W emulsion. In this study the fat content was successfully reduced by 36.6% while maintaining favorable viscosity and particle size values. Although the fat reduction in this case was much greater, the mayonnaise was not submitted to sensory evaluation and therefore it is impossible to say whether it would have rated as equally acceptable to full fat mayonnaise.

Despite these interesting applications, double emulsions suffer from higher rates of instability than conventional emulsions. This is due to the complex droplet within droplet microstructure of these emulsions. Not only can coalescence occur between separate oil droplets, it can also occur between the inner water droplets. Another issue is the osmotic diffusion from the W_2 to the W_1 phase or vice versa, when the two phases have differing osmotic pressure values (Dima and Dima 2020). Due to the necessarily larger droplet sizes these emulsions are also vulnerable to gravitational separation and creaming instabilities. Ilyasoglu Buyukkestelli and El (2019) confirmed this finding in their work on double emulsion containing iron. The sample with the highest creaming stability was that with the smallest droplet size (8.23 μm). However, all emulsions stored at room temperature for 15 days had a significant creaming index, indicating physical instability and droplet aggregation. This very short shelf life would present an additional challenge for the incorporation of the system into a food item.

Biopolymer stabilized emulsions

Biopolymer stabilized emulsions, also known as multilayer emulsions, consist of oil droplets which can be coated in a thin layer of surfactant and then laminated with one or more layers of charged biopolymer molecules, before suspension in an aqueous medium. The main advantages of this type of emulsion consist of better protection from physical and chemical instabilities and most importantly the ability to finely tune the controlled or targeted release of the encapsulated compound. This can allow the bioactive material to be fully protected against the harsh conditions of the gastrointestinal tract until it reaches the small intestine, or even allow the material to be selectively targeted toward one uptake organ in the body (McClements 2016). The main drawbacks of this technique are that the preparation involves many additional ingredients and processing steps. Also, due to the droplets having an electrostatic charge it is often only possible to create dilute solutions to avoid aggregation.

This type of emulsion system is uniquely suited to the targeted delivery of bioactives due to the many options for surface functionalization of biopolymer molecules. The functional groups present on these polymers can be modified with small molecules, carbohydrates, aptamers, peptides, proteins or antibodies in order to interact with specific receptors in the target tissue. For instance, Ben-David-Naim et al. (2019) studied the enhanced uptake of nanoparticles decorated with an apolipoprotein B100 derived peptide into breast cancer cells. This system was designed to take advantage of the tumor cell's overexpression of receptor sites which results in enhanced uptake of the modified nanoparticles. In this case, although significant uptake of modified nanoparticles into the tumor cells was observed, it was not a significantly different effect from the uptake of non-decorated nanoparticle controls. In a similar trial, Shang et al.

(2019) created poly(N-isopropylacrylamide-co-acrylic acid) nanogel (PNA) stabilized nanocapsules crosslinked with cystamine and functionalized with a cyclic peptide c(Arg-Gly-Asp-d-Phe-Lys) (cRGD) to enhance the uptake of an anticancer drug into tumor cells. Unlike the trial by Ben-David-Naim et al. (2019), this system did successfully result in an enhanced uptake into tumor cells and an enhanced anti-cancer activity. Despite the high potential of targeted delivery of these systems it can be difficult to predict the exact biological outcome due to the complexity of receptor expression on targeted cells.

The controlled release of active ingredients from polymer stabilized emulsion systems can occur in response to physical, chemical or biological stimuli. Many of the most common release triggers involve pH, temperature or ionic strength changes. There can also be delivery systems which are tuned to more specific biological markers, such as differences in reduction potential found in the intracellular versus the extracellular environment. The targeted delivery system designed by Shang et al. (2019) featured Poly(N-isopropylacrylamide-co-acrylic acid) nanoparticles cross linked through disulfide bridges on cystamine residues to maintain stability during circulation and achieve reduction sensitive drug release. When the nanocapsules are taken up into the cell, intracellular glutathione then degrades the disulfide bridge through a reduction reaction and the integrity of the nanocapsules weakens, allowing the release of the active ingredients. This system is an excellent example of a controlled release system which acts at the cellular level.

There are also several different techniques by which polymers may be used to coat and stabilize emulsion droplets. Even when using the same biopolymers, the method of applying them to the outer surface of emulsion droplets may significantly change the stability and release properties of the emulsion. Xu et al. (2019) compared the differences in encapsulated fatty acid release from three emulsion systems made by direct mixing of polymers, layer by layer deposition or heteroaggregation using the same biopolymers in each; whey protein isolate and flaxseed gum. The direct mixing technique consisted of direct addition of the polymers into the aqueous phase of the emulsion prior to homogenization. Layer by layer deposition consisted of a primary emulsion being formed with oil droplets and whey protein suspended in the aqueous phase. After this was completed the flaxseed gum solution was added and the emulsion was homogenized a second time to create a coating of flaxseed gum over the droplets. The heteroaggregation technique consists of two separate emulsion being prepared, one with whey protein and the second with flaxseed gum. After these emulsions were created separately, they were combined to allow the oppositely charged oil droplets to aggregate together. When submitted to the small intestinal phase of in vitro digestion, it was found that the direct mixing and layer by layer emulsion systems both presented a high level of burst release of encapsulated fatty acids in the first 30 minutes of digestion, whereas the heteroaggregated system was much more suited for controlled release applications with a gradual release of fatty acids over 120 minutes.

Coacervates

Coacervates are another unique form of polymer stabilized emulsion. In many typical polymer stabilized emulsion systems, net charge of the droplets is strong and electrostatic interactions are weak, therefore forming soluble complexes. However, if net charge is low and electrostatic interactions are stronger, a coacervate is formed instead (Zhang et al. 2015). It is also possible to form either simple or complex coacervate systems. Simple coacervation usually involves one polymer, often a protein, which is coacervated using the modulation of pH in relation to the protein's isoelectric point (Elhassan et al. 2018). Complex coacervation is a technique which has been extensively used in recent research to encapsulate various compounds, and it usually involves the complexation of two oppositely charged polymers such as a protein and a polysaccharide. The strength of association between the two polymers can be controlled by many factors including the pH, mixed ratio, ionic strength, surface charge density, and total concentration of biopolymers (Mohammadian et al. 2019).

Solid lipid nanoparticle/nanostructured lipid carrier

Solid lipid nanoparticle (SLN) suspensions are similar to conventional emulsions, in that they consist of lipid droplets coated with emulsifier and suspended in an aqueous phase. However, in SLN the lipid phase is completely solidified. This provides advantages over conventional emulsions such as improved stability and enhanced chemical stability of encapsulated bioactives. While this type of emulsion is less vulnerable to coalescence or Ostwald ripening, they do tend to suffer from issues with sedimentation, particle aggregation and flocculation. Also, in some cases the bioactive components may be ejected from the solid core after crystallization has occurred (McClements 2016). This is due to many bioactive components having lesser solubility in solid oil compared to liquid oil. Another special feature of this type of system is the ability to fine tune the release profile of the compound by carefully choosing the melting temperature of the matrix. Choosing a fat with a melting point close to a biological level will allow faster release of the compound during digestion, whereas fats with a higher melting temperature will remain solid during digestion and slow the release. In contrast, there is a newer generation of this technology called nanostructured lipid carriers (NLC), in which the lipid phase is only partially solid. This imparts the additional advantages of reducing drug leakage during storage and improving the entrapment and release properties when compared to SLN (Ali Akhoond et al. 2018).

Roles of emulsifiers

The emulsion's quality and stability are very dependent on the chosen emulsifier. There are a wide variety of molecules found in nature that can act as emulsifiers in food systems. The main criteria to determine whether a compound can act as an appropriate emulsifier are as follows: (1) The molecule

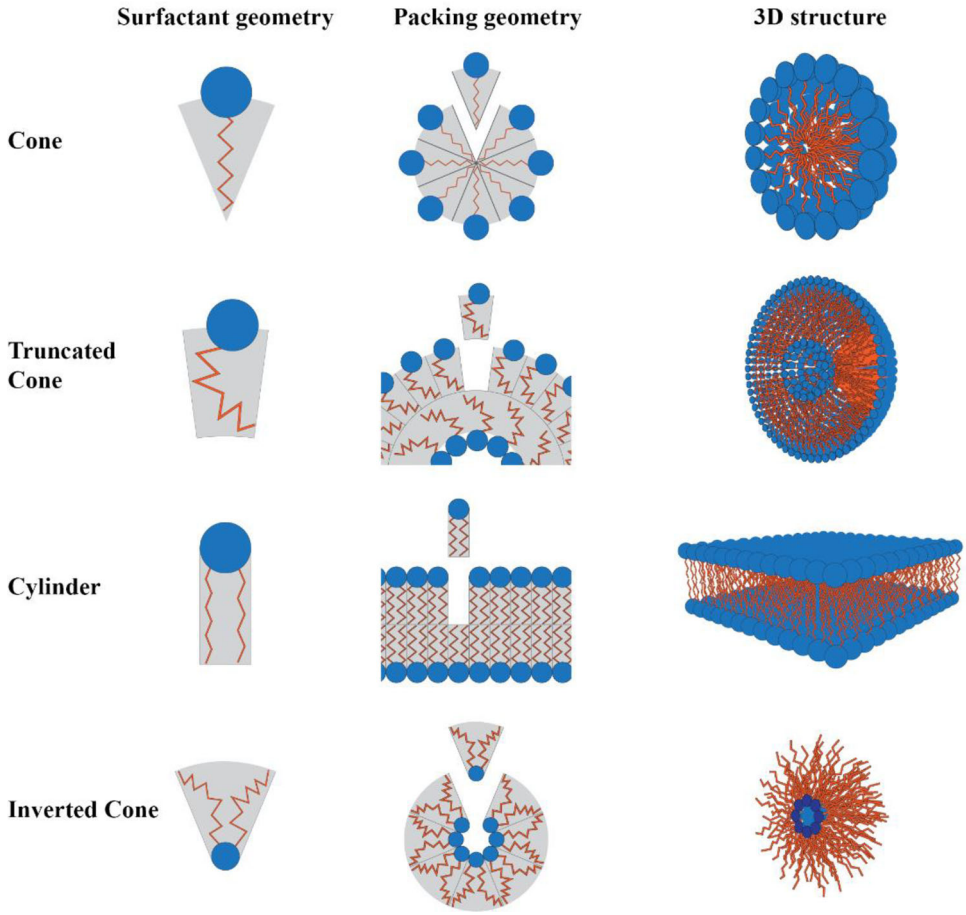

Figure 1. Small molecule surfactant self-association structures.

must be able to quickly adsorb to the surface of a droplet during homogenization, (2) The compound must be able to reduce interfacial surface tension significantly, and (3) The compound must create a barrier around the droplet which is either resistant to rupture, or creates an electrostatic force which is sufficient to prevent droplet aggregation (McClements 2016). In addition to these physical requirements, selected emulsifiers must be food safe, permitted for use by regulatory agencies, and cost effective. Given these criteria, it is evident that research into different emulsifier types is necessary to choose the optimal compound or combination of compounds for each food system.

Emulsifiers may be divided into two broad categories: small molecule surfactants and biopolymer-based food emulsifiers. Small molecule surfactants are typically small, surface active molecules with a hydrophilic head group and a hydrophobic tail group. These two distinct sections allow the compound to act as an emulsifier by traveling to the interfacial area where it will orient itself with the head group in the aqueous phase and the tail group in the oil phase in order to decrease undesirable hydrophobic interactions (McClements 2016). This subsequently decreases the interfacial tension at the oil water interface and allows droplets to be disrupted more easily during a homogenization or sonication process, resulting in smaller droplet sizes. The hydrophilic head group on these surfactants can be anionic, cationic, zwitterionic or nonionic. In the case of surfactants with charged head groups, electrostatic repulsion assists in preventing droplet aggregation, whereas in the case of uncharged head groups short range repulsive forces perform this function.

Part of the advantage presented by small molecule surfactants is their ability to form predictable structures within the continuous phase of an emulsion. When dispersed in an aqueous or oil phase in levels above their critical micelle concentration, these surfactants will form loose structures such as micelles, reverse micelles, nonspherical micelles, vesicles or bilayers. The type of structure that a certain surfactant molecule is likely to form is determined by its molecular geometry (McClements 2016). When these molecules associate with each other, they take a form which will allow for the most efficient packing of molecules possible, which is determined by their curvature. Thus, those with a wider head group than tail group will tend to form a normal micelle or nonspherical micelle, whereas those with a wider tail and more narrow head group will form reverse micelles (Figure 1). This tendency to form association structures is extremely useful for the encapsulation of nutraceutical compounds.

Small molecule surfactants

Small molecule surfactants have a long history of use in commercial food production. They have habitually been

used to stabilize a wide variety of food products, such as baked goods, beverages, seasonings, and dairy products (Oellig, Link, and Schwack 2020). However, due to increasing concerns about cytotoxicity and adverse health effects with long administration, as well as concerns regarding poor biodegradability, consumers and industry are increasingly looking to replace synthetic surfactants with natural ones in food products (Dammak et al. 2020).

Most synthetic surfactants consist of enzymatically produced mono or diacylglycerols as well as mono or diacylglycerols with modified head groups. Native mono and diacylglycerols tend to be more hydrophobic, and therefore are best suited for stabilizing W/O emulsions (Hasenhuettl and Hartel 2019). Other surfactants made form mono and diacylglycerols with modified head groups include organic acid esters such as citric acid esters (CITREM), lactic acid esters (LACTEM), tartaric acid esters (TATEM), acetic acid esters (ACETEM), monoacetyl and diacetyl tartaric acid esters (DATEM) and mixed acetic and tartaric acid esters (MATEM) (Oellig, Link, and Schwack 2020). Depending on the choice of organic acid, these surfactants can be hydrophilic or hydrophobic and can stabilize either W/O or O/W emulsions. Some other examples of modified fatty acid esters include polyol esters of fatty acids such as sucrose fatty acid esters (SFAE) and stearoyl lactate salts.

The emulsification properties for these native and modified mono and diglyceride compounds depend heavily on the nature of the lipid chain(s) which they contain. Fredrick et al. (2013) studied the difference on the foaming properties of cream in the presence of saturated or unsaturated monoglyceride emulsifiers. The two emulsifiers had distinct properties, with saturated monoglycerides creating a more stable emulsion foam whereas unsaturated monoglycerides increased the disruptability of oil droplets within the cream. Similarly, Köhler and Grosch (1999) evaluated the effect of DATEMs hydrocarbon chain features on its ability to enhance bread loaf volume. They concluded that the optimal chain length for increasing loaf volume during baking was 18 carbons and that DATEMs with unsaturated monoglyceride chains or those from diglycerides had the greatest enhancement qualities.

Conversely, natural surfactants are isolated from biological sources, such as plants fungi and bacteria. They can include phospholipids such as phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol. Blends of phospholipids are commonly known as lecithins and are most often extracted from soybeans, milk, rapeseed and egg (McClements 2016). Saponins are another class of emulsifier which are extracted from plant sources. The most common source of saponins is the bark of the *Quillaja saponaria* tree but alternative sources of saponins can include ginseng, and the *Gynostemma pentaphyllum* tree (Dammak et al. 2020). In addition to these surfactants from plant sources, there have been a multitude of novel biosurfactants produced by fungi, yeasts and bacteria. These biosurfactants are varied in terms of their structures and functions and have been the focus of several other in-depth reviews (Nitschke and Silva 2018; Ohadi et al. 2020; Ribeiro, Guerra, and Sarubbo 2020).

Constant research is being done to isolate and utilize novel surfactants from natural sources. One such compound is cardanol, which is extracted from cashew nut shell liquid, an agricultural waste material which is available in great quantities in developing countries. Cardanol is a monohydroxyl phenol that has a long unsaturated alkyl side chain at the meta-position (Di Bello et al. 2017). Its hydrophilic phenol group acts as the head of the surfactant whereas the alkyl side chain acts as the hydrophobic tail group. An additional advantage of this compound is that the phenol head group provides it with antioxidant qualities which enhance its ability to protect whatever active compound it encapsulates. It was for this reason that Di Bello et al. (2017) chose cardanol in conjunction with cholesterol to encapsulate CBD which has been shown to undergo oxidative degradation when exposed to light or oxygen (Lindholst 2010). This compound is a prime example of a novel surfactant which has desirable qualities and whose cost of use is not prohibitive.

Protein emulsifiers

Proteins acts as emulsifiers by forming thin and electrically charged interfacial layers around oil droplets. Due to this characteristic, the main force preventing droplet aggregation is electrostatic repulsion. This makes protein stabilized emulsions particularly prone to destabilizing with changes in pH or ionic strength. Employing a protein as an emulsifier at a pH close to its isoelectric point will result in the oil droplet lacking a net surface charge and being more prone to aggregation and separation. Some globular proteins are also sensitive to temperature changes. Heating these proteins causes them to unfold and expose their hydrophobic inner regions, creating attraction between protein molecules and leading to flocculation of oil droplets (McClements 2016).

Protein emulsifiers for foods can be extracted from multiple sources animal sources for protein emulsifiers can include dairy, meat and egg. Animal based protein emulsifiers are some of the most ubiquitous in the development of emulsion systems. Whey protein isolate is widely used for the stabilization of simple emulsions, double emulsions, nanoemulsions and Pickering emulsions. Some of the features that make it a popular choice for emulsion systems include its nutritional quality, its action at ambient temperatures its amphiphilic nature and its biocompatibility (Liu et al. 2020; Weinbreck, Minor, and De Kruif 2004). The most common protein emulsifier extracted from meat sources is gelatin. This protein acts as an emulsifier both by adsorbing to the oil water interface and by increasing the viscosity of the solution. At high temperatures gelatin has a flexible random coil structure, which undergoes a helix to coil transition when cooled (McClements 2016). This transition is what gives the protein its excellent gelling ability. Egg contains distinct surface active proteins in both its white and yolk components. While egg white components excel at stabilizing foams, egg yolk components are more appropriate for the stabilization of emulsions. Emulsifying proteins can also be extracted from plant sources such as legumes and

cereals. Of these, soy protein is the most researched. There are multiple protein fractions that may be isolated from soy and their ability to act as effective emulsifiers depends heavily on the purification and isolation conditions used (Xu, Mukherjee, and Chang 2018).

Although these proteins are the most commonly used and widely available choices, there is constant research being conducted to isolate novel protein emulsifiers from various sources. Pea and rice proteins are finding more applications in the food industry due to their low allergenicity and excellent nutritional value. Zhao, Shen, et al. (2020) compared the technofunctional properties of novel pea and rice proteins to more common wheat and soy proteins in terms of solubility, water absorption and emulsifying ability. While they found pea protein's emulsifying qualities to be very good, and close to the qualities possessed by soy protein, rice protein's technofunctional properties were deemed of lesser quality. Similarly, Hu et al. (2018) extracted yam soluble protein from Chinese yam and evaluated the technofunctional properties including emulsifying properties. They found that yam soluble protein presented promising emulsifying properties at pH levels away from its isoelectric point of 3.5. This protein would therefore be acceptable for use in non-acidic food products. Seeds have also been the focus of research for novel protein emulsifiers. Tirgar et al. (2017) evaluated the effect of different extraction methods on the technofunctional properties of flaxseed protein compared to commercially available pea protein. The emulsifying capacity, emulsifying activity index and emulsifying stability index varied with extraction method but were all found to be superior to that of commercial pea protein. The best emulsification characteristics were found in the alkali extracted flaxseed protein as opposed to the enzymatically extracted fractions.

Polysaccharide emulsifiers

Polysaccharides polymers are also widely used as emulsifiers. Polysaccharides tend to be stable at a wider range of environmental conditions then proteins, but they generally require a much higher concentration to be effective. Many different polysaccharides are available to use as emulsifiers in food.

Gum Arabic is often used in the beverage industry, and the surface-active component consists of branched hydrophilic arabinogalactan blocks attached to a hydrophobic polypeptide backbone. This polymer forms a thick interfacial coating which prevents droplet aggregation mainly through stearic repulsion with some small amount of electrostatic repulsion (McClements 2016). This emulsifier is stable to changes in pH, temperature and ionic strength. This emulsifier requires a 1:1 ratio of emulsifier to oil phase and is particularly useful for beverage emulsions due to its low viscosity when compared with other gums (Williams and Phillips 2009).

Starches modified by adding hydrophobic components along their backbone, such as an octenyl succinate derivative of waxy maize, are also emulsifiers used in the beverage industry. Similarly to gum Arabic, these starches prevent droplet aggregation by stearic hindrance, are stable at a wide range of environmental conditions and require a large ratio of 1:1 starch to oil phase in order to stabilize emulsions effectively (McClements 2016). Modified celluloses such as methyl cellulose, hydroxypropyl cellulose and methyl hydroxypropyl cellulose may also be used as emulsifiers.

While these are some of the standard polysaccharide-based emulsifiers used in food processing, there are novel polysaccharide emulsifiers which are also being investigated. Pectins form various plant sources have been investigated for emulsification properties. Neckebroeck et al. (2020) investigated the emulsification properties of three different carrot pectin fractions produced form acid extracted carrot pectin. Pectin fractions rich in homogalacturonan and pectin fractions rich in rhamnogalacturonan were compared to whole, unfractionated carrot pectin. The authors found that whole pectin performed better at decreasing interfacial tension and at creating stable emulsions than either of the fractionated pectins. This was attributed to the whole pectin creating a more viscous emulsion which could combat gravitation separation phenomena, and a possible beneficial effect of having both linear and branched domains present for enhanced emulsification properties.

Various novel emulsifiers have also been extracted from sugar beets. Namely, sugar beet fiber and sugar beet pectin. Maravic et al. (2019) examined the individual and combined emulsification properties of sugar beet fiber, sugar beet pectin and octenyl succinic anhydride modified malodextin. The authors found that the combination of either sugar beet or sugar fiber with the OSA modified maltodextrin resulted in enhanced emulsifying properties, such as increased stability or small droplet sizes and high droplet uniformity. This was not true for systems which combined sugar beet pectin and sugar beet fiber, likely due to the polysaccharides competing for adsorption to the droplet interface.

Amidated pectin has also been investigated as a novel emulsifier. Amidated pectin can be produced from the de-esterification of high methoxyl pectin in the presence of ammonium ions. Jiang et al. (2020) created gliadin nanoparticles coated with amidated pectin for the stabilization of Pickering emulsions. Pickering emulsions stabilized with these particles expressed better emulsion stability than gliadin nanoparticles constructed from gliadin and other pectins. This was attributed to amidated pectin's enhanced gelling ability at acidic conditions when compared to other pectins.

As can be surmised from these studies, part of the mechanism that allows polysaccharide polymers to act as effective emulsifiers is the physical entanglement of oil droplets and water. This entanglement phenomenon is highly related to the viscosity modifications that a polysaccharide will bring to an aqueous solution (Chen et al. 2019). In their study, Chen et al. investigated the microstructure of several modified insoluble soy fibers (ISF) and the resultant change in the ISF's ability to hold water or oil, to modulate viscosity and to act as an emulsifier. Of the four treatments applied to ISF (alkaline treatment (AT), ultrasonic alkaline treatment

(UAT), steam-cooking alkaline treatment (SAT) and ultrasonic steam-cooking alkaline treatment (USAT)), the AT sample was found to be the most effective emulsifier based on it creating the emulsion with the smallest droplet sizes and the longest shelf stable time. This was related to the changes in the sample's rheological properties. The AT sample had rheology parameters which classified it as a firm elastic structure, which allowed the oil droplets to move about freely during the homogenization process and yet immobilized them sufficiently to prevent phase separation upon standing. Contrarily, some of the other samples such as USAT had even higher viscosity than the AT sample, but this was detrimental to the emulsifying ability. The USAT sample's rheology showed gel-like behavior which inhibited the oil droplet's movement during the homogenization step and resulted in larger droplet sizes. In accordance with Stokes' law discussed previously, emulsions with smaller droplet sizes and higher viscosity are more stable over time, which is what lead to the most optimal results with the AT sample (Chen et al. 2019).

Emulsifier synergy

It should be noted that each type of emulsifier (small molecule surfactant, protein or polysaccharide) has its own advantages and disadvantages. For example, small molecule surfactants tend to quickly adsorb to the droplet's surface but they can be more easily displaced due to their small size (Moran-Valero, Ruiz-Henestrosa, and Pilosof 2017). Proteins tend to form thin, viscoelastic emulsion interfaces and can be used in small concentrations, but are easily disrupted by changes in pH, temperature or ionic strength. Polysaccharides are resistant to many environmental conditions but they require larger concentrations to be effective and often have an impact on the viscosity of the aqueous solution (McClements 2016). It is therefore often advantageous to combine different classes of emulsifiers in order to take advantage of the synergies between them.

Small molecule surfactants may synergize with polymers in a variety of ways. Firstly, small molecule surfactants may bind to protein or polysaccharide chains though electrostatic or hydrophobic interactions. This may lead to conformational changes in the polymer molecules which affects their stability and interactions. This in turn affects the large scale properties of the solution such as appearance, rheology and phase behavior (McClements 2016). These emulsifier-polymer interactions are also utilized in many food products. For instance, monoglycerides and stearoyl lactylates may be added to breads to improve softness and delay staling. This occurs due to the surfactants forming inclusion complexes with the starch chains by inserting their hydrophobic tails into the helical coils formed by the linear regions of the amylose or amylopectin chains. Surfactants may also interact with proteins either directly, by binding with them, or indirectly, by competing with them or displacing them from an interface. This second use is particularly useful in foods where oil droplet coalescence is desirable such as in ice cream or whipped cream.

Small molecule surfactants are also capable of synergizing with each other in a variety of ways. Moran-Valero, Ruiz-Henestrosa, and Pilosof (2017) found that combining both lecithin and glycerol monostearate in a 10% O/W solution had the effect of creating small oil droplet sizes similar to those achieved with lecithin alone, but with much greater resistance to coalescence and flocculation phenomena. They hypothesized that the decreased flocculation and coalescence phenomena was due to the lecithin interrupting the crystalline monoglycerides network that may form when the emulsion is allowed to stand for extended periods of time. The presence of glycerol monostearate may also assist in anchoring the lecithin into the oil phase due to its higher hydrophobic affinity and ability to form both hydrophobic interactions and hydrogen bonds with the lecithin component.

Proteins and polysaccharides may also have synergistic interactions as emulsifiers. Due to their complimentary characteristics, with proteins being effective in low concentrations and having an ability to form small emulsion droplets but fragile to certain environmental stresses and polysaccharides having the opposite profile, the combination of these two polymers may have better effects than either of the two in isolation. Protein-polysaccharide complexes may be created by either physical or covalent bonding which may be initiated either before or after the homogenization process (McClements 2016). Protein-polysaccharide complexes have shown significant improvements to an emulsion's stability to pH changes, high salt concentrations, thermal variations, freeze thaw cycling and dehydration.

In one study, Angkuratipakorn et al. (2017) explored the synergistic action of a polygalacturonase oligoester nonionic surfactant coupled with cellulose nanocrystals extracted from rice bran and gum Arabic on the droplet size and stability of O/W emulsions. It was found that combining surfactant with cellulose nanocrystal and gum Arabic had the most desirable effects by increasing the emulsion's stability and droplet uniformity. This study shows that there was a synergistic effect present between the polygalacturonase oligoester surfactant and the cellulose nanocrystals, but not with the gum Arabic component.

The work of Zhang et al. (2021) may be cited as an example of synergism between polysaccharide and protein emulsifiers. These authors studied the synergistic effects between soy protein emulsifiers and steviol glycosides on interfacial activities at an oil/water interface. They found that emulsions co-stabilized with steviol glycosides and soy protein displayed smaller particle sizes and higher stability than those stabilized with soy protein alone. They attributed this to the soy protein creating hydrophilic microenvironments for the steviol glycoside monomers to reside in at the interface. Synergism is also possible between small molecule surfactants such as glycolipids which possess different lengths of hydrocarbon chains. Sekhar et al. (2020) synthesized glycolipids with varying lengths of hydrophobic tails. While investigating the surface-active properties of these emulsifiers, they found that a combination of the short chain glycolipids and long chain glycolipids resulted in

foaming, wetting and emulsification properties than either emulsifier acting alone (Table 1).

Hydrogels

Hydrogels are a type of controlled release delivery system that may be used in food, industrial and biomedical applications. They consist of biopolymers, such as starch or protein chains, with semi-solid morphology that can swell to several times their original size and contain a considerable amount of water (Wang et al. 2012). Hydrogels are useful for a variety of reasons, mainly because they can provide a protective environment for bioactive compounds which can mimic biological conditions and therefore protect the structure or activity of the encapsulated compound. Also, by modulating the composition of the hydrogel, it can be tailored to react to certain stimuli such as pH or temperature, which allows the release conditions of the encapsulated compound to be well controlled (Karp et al. 2019; Zhang et al. 2015).

Many materials may be used to create hydrogels, but for food use 'Generally Regarded as Safe' (GRAS) protein and polysaccharide biopolymers are most often used. The reason that proteins and polysaccharides are popular substrates for hydrogel formation is due to the high variability in their structures and the many functional groups they contain, which makes them excellent candidates for modification or cross-linking as well as having many different physicochemical properties to choose from (Wang et al. 2012).

Polysaccharide based hydrogels

Polysaccharides may be anionic, cationic or neutral. There are an abundance of anionic polysaccharides, including alginic acid, hyaluronic acid, gellan gum, pectin, xanthan and carrageenan, among others. They may contain hydroxyl, carboxyl and sulfate groups, which lead to highly hydrophilic polymers that may absorb large quantities of water. They are also extremely useful for the creation of hydrogels, as they create a strong network with a simple addition of counter ions such as Ca^{2+} (Wang et al. 2012). For example, Karp et al. (2019) created alginate beads containing the antibiotic florfenicol by dripping alginate-florfenicol solution into a $CaCl_2$ solution. This alginate matrix retained the active ingredient at pH 1.2 (equivalent to stomach conditions), whereas at pH 7.4 (intestinal conditions) a faster release was observed related to the alginate matrix relaxing. Another anionic polysaccharide which is commonly used for construction of hydrogels is hyaluronic acid. Hyaluronic acid is a popular choice in hydrogels used for biomedical applications due to its biocompatibility. In fact hyaluronic acid is distributed in many tissues throughout the body. Zhang et al. (2019) constructed an in situ gelling system of cross-linked sodium alginate and hyaluronic acid. This system gelled rapidly under physiological conditions and succeeded in providing a sustained release of a model drug compound. Furthermore, the rheological properties and degradation rate could be tuned by modification of the precursor solutions.

By comparison, there are very few cationic polysaccharides. Namely, there are chitin and chitosan which are both amino polysaccharides. Chitin has a structure similar to cellulose, with certain hydroxyl groups being replaced with acetamido groups on its backbone. Due to the presence of both hydroxyl and acetyl amido groups on the moiety, there is a high rate of intra molecular hydrogen bonding, resulting in high crystallinity and low solubility (Wang et al. 2012). On the other hand, chitosan is a partially deacetylated derivative of chitin, containing many amino groups. The advantage of creating this deacetylated derivative of chitin is that it is soluble in organic acid solutions, making it more accessible for chemical reactions.

Generally, the deacetylation of chitin is carried out under highly alkaline conditions and at high temperature. However, there are novel green methods of chitin deacetylation being developed. Rujiravanit et al. (2020) developed a method to deacetylate chitin using electrical discharge plasma. These authors found that using electrical discharge plasma with or without the addition of NaOH, the percentage deacetylation achieved was higher than for conventional heat treatment under the same solvent conditions. Another advantage of this technique is that the percentage of deacetylation can be controlled by modulating the temperature of the reaction and the ratio of methanol to water. This is valuable due the fact that chitosan's physicochemical properties depend on the level of deacetylation it has undergone (Rujiravanit et al. 2020) .

Chitosan has been utilized for the construction of hydrogel beads which are used to suspend hydrophilic nutraceuticals such as polyphenols. Trifković et al. (2014) designed chitosan hydrogel beads using an emulsion cross-linking technique with glutaraldehyde. These were then freeze dried prior to loading. Loading of the system was achieved by rehydrating the desiccated beads in an aqueous solution of thyme polyphenols. Satisfactory levels of encapsulation efficiency were achieved, and during gastrointestinal release studies a sustained release profile was observed.

Similarly, Yuan, Jacquier, and O'Riordan (2018) synthesized chitosan beads through ionic gelation with phosphoric acid. The beads were loaded with a variety of different payloads (bovine serum albumin, whey protein isolate, insulin and casein hydrolysate) by incorporation of the substrates into the gelling solution. The release profile for each encapsulate varied significantly and were dependent on both the molecular wight and the structure of the entrapped molecules. The authors found that the majority of intact proteins were retained within the bead's matrix in the presence of simulated gastric fluid but released their payloads when immersed in simulated intestinal fluid and the release profile was related to the molecular weight of the protein.

The advantage of having both positively and negatively charged polymers available is that they may be combined by electrostatic self-assembly to create more complex structures. Such structures are sensitive to pH changes, and they may be designed to loosen their structure and release their ingredients only under certain conditions such as intestinal fluid. Hu et al. (2019) created just such a polyelectrolyte complex

Table 1. Types of emulsions & their encapsulated ingredients.

Authors	Type of emulsion	Bioactive encapsulate	Aqueous phase	Organic phase	Emulsifiers	Blending method	Particle size
Simple emulsion (O/W)							
Li et al. (2020)	O/W simple emulsion	None	Distilled water	Soybean oil	Chicken myofibrillar protein	Homogenization	2082.67 to 983.67 nm
Sun et al. (2019)	O/W simple emulsion	None	Distilled water	Olive oil	Flaxseed gum	High speed blender	25 – 82 μm
Chen, McClements, et al. (2018)	O/W simple emulsion	None	Distilled water	Soybean oil	Ovalbumin – tannic acid complexes	High speed homogenization and high-pressure homogenization	1 – 10 μm
Chen et al. (2019)	O/W simple emulsion	None	Distilled water	Corn oil	Treated insoluble soybean fibers	High speed homogenization and high-pressure homogenization	0.3 – 200 μm
Moran-Valero, Ruiz-Henestrosa, and Pilosof (2017)	O/W simple emulsion	ω-3 fatty acids	Distilled water	Chia oil	Lecigran 1000 P and glycerol monostearate	Homogenization and ultrasonication	0.244 – 1.363 μm
Nanoemulsion (O/W)							
Xu, Mukherjee, and Chang (2018)	O/W nanoemulsion	None	Phosphate buffer	Peanut oil	Soybean protein isolate	Ultrahigh pressure homogenization	>1000 nm to <200 nm
Fernández-Ávila, Escriu, and Trujillo (2015)	O/W nanoemulsion	None	Distilled water	Soybean oil	Soy protein isolate	Ultrahigh pressure homogenization or conventional homogenization	0.51 to 0.23 μm
Barzegar et al. (2018)	O/W nanoemulsion	Peppermint oil	Distilled water	Peppermint oil	Tween 80	Spontaneous emulsification (magnetic stirring)	132 to 30 nm
Alshahrani (2019)	O/W nanoemulsion	Ostrich oil	Distilled water	Isopropyl myristate	Tween 80	Spontaneous emulsification	82.2 to 110.5 nm
Di Bello et al. (2017)	Nanovesicles	Cannabidiol	Borate buffer	None	Cardanol, cholesterol	Mechanical stirring and sonication	276.9 nm
Guan, Chen, and Zhong (2019)	Nanoencapsulation	Caffeic acid phenethyl ester, thymol	Aqueous propylene glycol	None	Sucrose fatty acid ester	Temperature cycle method with stirring	155.0 to 26.4 nm
Multiple emulsion (W/O/W or O/W/O)							
Ilyasoglu Buyukkestelli and El (2019)	$W_1/O/W_2$ Double emulsion	Ferric chloride (hydrophilic)	Phosphate buffer	Olive oil	PGPR sodium caseinate	Homogenizer	0.99 to 9.86 μm
Dima and Dima (2020)	$W_1/O/W_2$ Double emulsion	Calcium & vitamin D3	Distilled water with gum Arabic, sodium alginate or chitosan	Linseed oil	Span 80, lecithin	Sonication, homogenization	15.82 – 11.32 μm
Rocha-Selmi et al. (2013)	$W_1/O/W_2$ Double emulsion coacervate	Aspartame	Distilled water with gelatin and gum Arabic	Sunflower oil	Soybean lecithin	Homogenizer	102.38 – 84.22 μm
Yildirim, Sumnu, and Sahin (2016)	$W_1/O/W_2$ double emulsion	Sodium chloride	Distilled water with sodium caseinate, xanthan gum, or lecithin-whey protein concentrate	Sunflower oil	PGPR	High speed homogenizer, food processor	249.68 – 7.22 μm
Multilayer emulsions							
Ben-David-Naim et al. (2019)	Polymeric based nanoparticles	siRNA against osteopontin	tris-EDTA buffer solution and		Poly(D,L-lactic-co-glycolic acid) and PGLA-	Sonication	207.3 – 233.9 nm

(*continued*)

Table 1. Continued.

Authors	Type of emulsion	Bioactive encapsulate	Aqueous phase	Organic phase	Emulsifiers	Blending method	Particle size
			poly(vinyl alcohol) solution	Ethyl acetate (subsequently evaporated)	polyethylene glycol-ApoB-P and polyethyleneimine		
Shang et al. (2019)	Pickering emulsion	Doxorubicin hydrochloride	Water	Chloroform (subsequently evaporated)	Poly(N-isopropylacrylamide -co-acrylic acid) nanogel particles	Homogenization, ultrasonication	150 – 250 nm
Xu et al. (2019)	Polymer stabilized emulsion	Free fatty acids	Phosphate buffer	MCT oil	Whey protein isolate and flaxseed gum	Homogenization, microfluidization	5646.7 – 252.3 nm
Coacervates							
Wang, Adhikari, and Barrow (2014)	O/W Multicore complex coacervation	Tuna Oil and antioxidant extract Duralox Blend AN 110 XT	Gelatin dispersion	Tuna oil	SHMP solution (Sodium hexametaphosphate)	Homogenizer	50–80 μm
Yang et al. (2014)	O/W Complex coacervation	Vanilla oil	Chitosan and Arabic Gum& distilled water	Vanilla oil	Span 83	Stirring	5.2 to 10.3 μm
Solid Lipid Nanoparticles							
Ali Akhoond et al. (2018)	O/W Solid lipid nanoparticles	Lycopene	Distilled water	Glycerol monostearate and glycerol distearate	Tween 80, lecithin	High shear homogenization ultrasonication	74.93 – 183.4 nm
Nanostructured lipid carriers							
Ali Akhoond et al. (2018)	O/W nanostructured lipid carriers	Lycopene	Distilled water	Glycerol monostearate, glycerol distearate and MCT oil	Tween 80, lecithin	High shear homogenization ultrasonication	74.93 – 183.4 nm
Pickering emulsion							
Angkuratipakorn et al. (2017)	O/W Pickering emulsion	None	Distilled water	Rice bran oil	Rice bran cellulose nanocrystals, PG1.5SFR0.05and gum Arabic	Homogenization and sonication	4.45 – 18.03 μm
Cirri, Mura, and Mora (2007)	O/W Self-micro emulsifying drug delivery system	Xibornol (hydrophilic)	Transcutol	Labrafil M1944 (Oleoyl macrogol-6 glycerides), Labrafil M2125 (Linoleoyl macrogol-6 glycerides) and Labrafac CC (Medium chain triglycerides)	Labrasol (Caprylocaproyl macrogol-8 glycerides) and Labrafac PG (Propylene Glycol caprylate/caprate). Transcutol (Diethylene glycol monoethyl ether)	Vigorous stirring	N/D
Xu et al. (2002)	W/O microemulsion	Insulin (hydrophilic)	phosphate-buffered saline	Propanediol	Soybean lecithin and Borneol	Stirring	N/D
Polavarapu et al. (2011)	O/W micro encapsulation	Fish oil & olive oil	dried glucose sirup & distilled water	Fish oil & olive oil	Sugar beet pectin	Shear mixer + high pressure 2-stage homogenizer	0.41 to 0.43 μm
Koo et al. (2014)	O/W microencapsulation	Peppermint oil	Alginate, pectin & distilled water	Peppermint oil	Tween-80, xanthan gum and glycerol	Coaxial electrospray encapsulation	1.58 to 3.24 μm
Edris and Bergnståhl (2001)	$O_1/W/O_2$ Double emulsion	Orange oil	Water	Vegetable oil	Sodium caseinate (hydrophilic emulsifier) and PGPR (lipophilic emulsifier)	High speed colloid mill, microfluidizer	6.4 μm
Carrillo-Navas et al. (2012)	$W_1/O/W_2$ Double emulsion	Chia essential oil	Aqueous solutions of ternary	Chia essential oil	Panodan SDK (water-soluble surfactant)	Homogenizer	8-40 μm

			biopolymers blends		and Gindsted PGPR 90 (oil-soluble surfactant)		
Tekin Pulatsü, Sahin, and Sumnu (2018)	W1/O/W2 Double emulsion	Sunflower oil	Guar gum and gum tragacanth in water	Sunflower oil	PGPR, lecithin	High-speed homogenizer, food processor	25 to 85 μm
Andrade (2016)	$W_1/O/W_2$ Double emulsion	Vitamin D3 or Phytosterols	Sodium caseinate in water	Soybean oil	PGPR and sodium caseinate	Homogenizer, microfluidizer	5 to 40 μm
de Cindio, Grasso, and Cacace (1991)	$W_1/O/W_2$ Double emulsion	None	Water	Liquid paraffin	Span 80 Tween 80	Mixer with paddle or propeller attachments	10 to 20 μm

from salecan and N,N,N,-trimethyl chitosan for the controlled release of green tea polyphenols. This hydrogel was effective at retaining the active ingredient when immersed in simulated gastric fluid for 2 h, while releasing it after being immersed in simulated intestinal fluid for the next 8 h. The authors surmised that this effect was due to the low pH of the gastric fluid strengthened the hydrogen bonds between the carboxyl groups and created a denser hydrogel network under these conditions, whereas under the higher pH of the simulated intestinal fluid the water uptake of the gel was greater, which created a looser network for the active ingredient to diffuse through freely.

Protein based hydrogels

Some of the most commonly used proteins for hydrogel formation are gelatin, whey protein, and soy protein, which are all abundantly available and have excellent gelling properties (Wang et al. 2012). Gelatin is by far the most widely used protein for generation of hydrogels. This is due to its unique gelation properties. Gelatin is derived from the hydrolytic degradation of collagen, and it retains one of its fundamental structures, the tropocollagen rod, which is a triple helical structure. Gelatin is also easily soluble in warm water but forms thermoreversible transparent gels when cooled. When present in a warm, sol state, gelatin has a random coil structure. Upon cooling this random coil structure undergoes a coil to helix transition whereby it partially regains the collagen triple helix structure. This triple helix provides a more rigid structure and the sol solution becomes a gel (Van Den Bulcke et al. 2000). Gelatin also has several advantages for its use as a hydrogel matrix. It is biocompatible and has GRAS status, and due to the large number of functional side groups it may easily be modified or cross linked to adjust its physicochemical properties for use as a biomaterial.

Proteins such as gelatin can also be extracted from novel sources for use in hydrogels. Chen, Mao, et al. (2020) used fish gelatin from tilapia skin to prepare a hydrogel. The toughness of this gelatin hydrogel was further enhanced by soaking the matrix in a $(NH_4)_2SO_4$ solution which increased the strength of hydrophobic and electrostatic interactions within the gel. Fish waste has also been investigated a potential source of novel proteins for hydrogel construction. Martins, Costa, and Prentice (2018) used protein isolates form Whitemouth croaker processing waste to construct a hydrogel matrix. The authors found that this protein, when acid modified with or without ethanol treatment could form a hydrogel matrix with super absorbent properties.

A novel protein from a plant source used for the construction of hydrogel beads by Piornos et al. (2017) is lupin protein. In this work, lupin protein was included in the matrix of alginate hydrogel beads to enhance the encapsulation efficiency of oil into the beads. By optimizing the ratios of the ingredients used in the system the authors were able to achieve a 98.3% encapsulation efficiency for linseed oil within the beads. Incorporation on lupin protein in the hydrogel matrix enhanced the encapsulation efficiency due to its emulsifying properties.

Release mechanisms for bioactive encapsulates

The next factor which affects the diffusion of a solute from a hydrogel is its affinity for the hydrogel matrix, as well as its shape and size. If a solute is of a similar or larger size than the hydrogel's pore it will not diffuse freely from the matrix. Similarly, if that solute has hydrogen bonding, or electrostatic interactions with the polymer matrix it will retard its diffusion from that matrix (Branco et al. 2010). This is of special importance regarding protein molecules, whose surface charge can change depending on the pH of the environment. Through careful selection of the hydrogel's matrix diffusion of a protein can be limited to a specific pH range where the protein carries a favorable charge. Having a matrix with attractive reactions to the solute will slow release whereas having a matrix with repulsive interactions will hasten it.

Branco et al. (2010) developed a self-assembling hydrogel matrix made from small peptides with a pore size of $22-23$ nm and a net positive charge. They tested the release profiles of various model proteins with differing sizes and isoelectric points to evaluate the influence of protein size and charge on the release profile. These authors found that at pH 7.4 the small, positively charged protein lysozyme diffused rapidly and completely (nearly 100% release) from the gel's matrix. Larger positively charged proteins such as lactoferrin also released rapidly with 85% of the protein released within 10 days. Larger, neutral proteins such as human IgG were more heavily retained in the gel's matrix (up to 40%), while small and large negatively charged proteins such as lactalbumin and BSA were retained up to 90% within the gel's matrix. These results clearly demonstrate the interaction of both size and charge on the individual protein's release profiles from the charged gel matrix.

Simple release mechanisms

The hydrophobicity of the matrix also plays a role in the diffusion mechanics of an active ingredient. Chen and Subirade (2009) developed microspheres of combined soy protein and zein for the controlled release of riboflavin. Zein was chosen as an addition to the hydrophilic soy protein due to its hydrophobicity, being rich in leucine, proline, alanine and phenylalanine. The authors found that active ingredient diffusion was much slower with a hydrophobic matrix, zein, compared with a hydrophilic matrix, soy protein. This was due to the aqueous solvent having a difficult time penetrating to the center of the hydrophobic particles to allow for active ingredient diffusion.

The swelling properties of a hydrogel also have a significant impact on the release profiles of the encapsulated compounds. When a solvent penetrates into a hydrogel's matrix the retained bioactive molecules travel into the external environment due to a difference in chemical potential (Wang et al. 2012). As the water travels inwards, it creates a concentration gradient which draws out the hydrogel's solutes. The swelling rate of the hydrogel, in turn, is controlled by the matrix's structure, degree of crosslinking and hydrophobicity or hydrophilicity profile. If a hydrogel contains

ionizable side chains, it may also be subject to osmotic swelling.

While creating hydrogel microspheres of varying hydrophobicity, Chen and Subirade (2009) also explored the three dimensional structure of their soy protein/zein beads and the effect that those structures had on hydrogel swelling. While blending soy protein and zein, the researcher noted that zein had a more crystalline structure then soy protein, but that it was miscible with the amorphous regions of the soy protein structure. When swelling was examined, the solvent penetrated rapidly into the soy protein spheres hydrophobic, amorphous structure. The pure zein microspheres, on the other hand exhibited many crystalline regions within their structure and had much reduced swelling capacity. When the two polymers were blended the swelling properties increased proportionally to the level of soy protein included in the matrix. The swelling of a hydrogel matrix also affects the diffusion constant of an encapsulated solute as it penetrates toward the center.

Near the periphery of the hydrogel the diffusion constants are higher and in an equilibrium state whereas near the center the coefficients are increasing as a function of time in a sigmoidal fashion (Abbasi, Eslamian, and Rousseau 2008). This is due to the pores on the outside of the gel having reached their maximum diameter, which favors the transfer kinetics of solutes out of the gel by making the solutes relatively smaller to the pore sizes compared to the unswollen pores within the core of the hydrogel. Solutes which are small in comparison with the matrix pore size will have higher diffusion coefficients (Abbasi, Eslamian, and Rousseau 2008).

Swelling is also determined by the isoelectric point of the protein matrix that makes up the hydrogel. Near the isoelectric point, repulsive forces between polymer strands are minimized, which creates a more compact matrix and less solvent penetration, whereas far from the isoelectric point polymer strand will repel one another which also increases the diameter of the mesh (Chen and Subirade 2009).

Degradation of a hydrogel occurs when the matrix dissolves due to the presence of acids, salts, mechanical erosion, or enzymatic lysis (Abbasi, Eslamian, and Rousseau 2008). Enzymatic degradation is particularly attractive because it allows for the targeted delivery of encapsulated compounds within specific regions of the gastrointestinal tract. Enzymatic digestion of hydrogels is complicated by several factors, such as the conformation of the hydrogel polymers, the degree of cross linking of the matrix and the enzyme's ability to penetrate into the hydrogel's core (Wang et al. 2012). Volić et al. (2018) examined the digestive degradation of hydrogel beads made form alginate and soy protein. They found that the beads had only marginal shrinking in simulated gastric fluid with pepsin. A portion of the shrinking was due to the alginate losing its negative charge in the low pH environment, which caused the polymer chains to retract inwards, while some of the shrinking was also due to pepsin hydrolysis. When the beads were transferred to simulated intestinal fluid, they first began to swell, and then experienced rapid degradation. Swelling was due to the exchange of Ca^{2+} ions with Na^{+} ions present in the solution. The electrostatic attraction between alienate COO^{-} and the positive ions therefore decreased as the charge density of the ions decreased. This loosening of the network allowed the soy protein component to diffuse outwards and be digested by the pancreatin enzymes. The enzymes were also able to penetrate inside the beads at this point to accelerate lysis of the hydrogel.

Stimulus responsive and controlled release mechanisms

Other than these basic mechanisms, there have been hydrogels developed to release their contents under triggered conditions. There are three main categories of stimuli that may be used to initiate hydrogel degradation: physical stimuli such as temperature, light, ultrasound, and electric or magnetic fields; chemical stimuli such as pH, ionic strength; and biological stimuli such as a change in glucose levels (Wang et al. 2012). Many of the hydrogels previously described were sensitive to chemical stimuli found in the human gastrointestinal tract such as pH or ionic strength. Temperature sensitive hydrogels may be tuned to release their contents under physiologic conditions (35-37 °C), or through the application of an external heat source.

Zhang et al. (2015) developed a hydrogel made by the electrostatic complexation of gelatin and caseinate to encapsulate casein coated lipid droplets. This system was designed to protect and suspend fat soluble flavor compounds within the hydrogel matrix during storage and subsequently release them in the mouth at a controlled rate when a physiological temperature is reached. In this system, the degradation of the hydrogel is attributed to the gelatin component of the matrix undergoing a helix-to-coil transition at 35 °C.

As a contrast to this system, Liu et al. (2010) created hydrogels which explosively degrade when exposed to an external heat source. This hydrogel is created from cross-linked poly(Nisopropylacrylamide), a thermosensitive polymer with a drastic phase transition property. When this polymer reaches its lower critical solution temperature, it transitions from hydrophilic to hydrophobic and shrinks dramatically. This polymer was used as a capsule to contain a water in oil emulsion with dispersed nanoparticles of bioactive compounds. When the temperature was increased from 20 °C to 50 °C, phase transition occurred, the capsule shrank and suddenly increased the internal liquid pressure of the capsule. Upon reaching a critical pressure, the outside of the capsule ruptured, forcibly squirting its contents into the local environment. While the aforementioned 50 °C rupture temperature is well outside the physiological range, the utility of this system is that it could be triggered with a site-specific thermotherapy such as infrared or microwave irradiation. By applying the heat stimulus only to the desired organ or tumor site, a very targeted and rapid delivery of bioactive compounds can be achieved.

The light triggered delivery of bioactive compounds can be achieved by a similar mechanism. Many hydrogel systems are now using imbedded gold nanoshells or nanorods particles to induce a light triggered thermogenic effect. Jiang et

al. (2019) created a nanogel within hydrogel system from thermosensitive poly(N-isopropylacrylamide) with embedded gold nanorods. This system has the advantage of being able to carefully control the rate and amount of released active ingredient from the gel through adjustment of the number of embedded nanorods and by the intensity of applied near infrared light. The researchers stimulated the hydrogel with an 808 nm laser at 1150 mW cm − 2 for 7 min to trigger release of the embedded compounds. During this time the samples went from 25 °C to 65 °C. This rise in temperature is due to the gold nanorods absorbing the light due to their longitudinal resonance and converting that light energy into heat energy (Jiang et al. 2019). A very similar response can be seen from hydrogels embedded with magnetic nanoparticles in order to create a thermogenic reaction when exposed to alternating magnetic fields. Unlike light or heat stimuli these magnetic fields have the additional advantage of being able to penetrate more deeply into tissues (Jalili et al. 2017).

The release of encapsulated materials in response to ultrasound follows a different mechanism then for the hydrogels sensitive to light or heat. Kwok et al. (2001) developed a coating for a hydrogel that would stop the ambient leakage of bioactive compounds from the hydrogel matrix and allow pulsatile diffusion only when the matrix was exposed to ultrasound. This coating was made from ordered, crystalline methylene chains which were immobilized onto the hydrogel's surface. In response to the ultrasound stimulus the chains would vibrate and lose their crystalline structure, allowing the active component to diffuse form the matrix. Upon cessation of the stimulus the methylene chains re-orient themselves into their crystalline conformation due to van der Waal forces and the diffusion of the active component stops. Like the magnetic field stimulus, this type of delivery is advantageous since ultrasound can penetrate deeply into tissues and is known to be safe for use.

Glucose sensitive hydrogels have also been developed for measuring glucose blood levels in a noninvasive way, or even providing a means to release an insulin bolus in a glucose dependent manner. Kim, Yoon, and Kim (2019) developed a hydrogel with immobilized glucose oxidase with a matrix made from cross linked poly(vinyl alcohol) and β-cyclodextrin for noninvasive glucose detection. The hydrogel was connected to an electrical sensor. When the hydrogel was applied to skin with an increasing level of glucose, the reduction peak is shifted and the current is decreased, providing a method of quantifying the amount of glucose present.

While these stimuli responsive hydrogels are extremely interesting for targeted delivery of bioactive substances, most are still being used solely in the pharmaceutical or biomedical fields (Wang et al. 2012). This is due to the use of specialized, responsive polymers that do not have GRAS status. Many of the more basic hydrogel systems, however, are fully compatible for use in foods due to their matrices being made up of polymers derived from food sources. Hydrogels are particularly useful for delivery systems that require prolonged, controlled release rates of the encapsulated substances. While there is potential for these systems to be used for rapid or burst release this research area requires more investigation (Table 2).

Combined hydrogel emulsion systems

When an emulsion is entrapped within the matrix of a hydrogel, this can be called an emulsion gel, an emulsion hydrogel, an emulgel or an emulsion filled gel. These types of systems offer several advantages, such as enhancing the stability of the entrapped emulsion, offering additional protection of the entrapped bioactive compounds against harsh digestive conditions and allowing for a fine-tuned control over the release conditions of the emulsion (Lu, Mao, et al. 2019; Verma et al. 2018). These types of gels are extremely useful for entrapping hydrophobic bioactive compounds in an aqueous environment and they find application in many different products (Figure 2).

Emulgels can be easily incorporated into the matrix of foods and offer several unique utilities, such as improving the textural characteristics of low-fat foods, improving the shelf life of meat products and delivery of hydrophobic bioactive ingredients, or co delivery of both hydrophilic and hydrophobic ingredients. Of the nutraceuticals delivered in this way, some of the more commonly researched ones are fat soluble vitamins, carotenoids, unsaturated fatty acids, phenolic compounds, flavor compounds and probiotics.

Fat soluble vitamins can be encapsulated alone, or co-encapsulated with other vitamins and minerals into the matrix of a gel. For instance, Chen, Mao, et al. (2020) created a system for the encapsulation of vitamin E within an acid gelled whey protein isolate (WPI) matrix. WPI is often used as both an emulsifier and a gelling agent in emulgels due to the ability of protein emulsifiers to recruit the O/W interface in the gelling process and create a stronger gel network. In this work, the researchers investigated synergistic action between different classes of emulsifiers in strengthening the gel network. Synergism was found between the polysaccharide emulsifiers (Octenyl succinic anhydride modified starch and gum Arabic) and WPI, but not between the small molecule surfactant emulsifiers (glycerol monostearate and tween 20) and WPI for the enhancement of gel strength and preservation of Vitamin E's activity. Gels with greater strength have also been shown to be more appropriate for controlled release applications. This gel system would therefore be highly relevant for the sustained release of highly active vitamin E from its matrix.

Another example of such a system was devised by Bao et al. (2020), who co-encapsulated both vitamins A and E into the matrix of a cold-set gel consisting of WPI. Vitamin A was dissolved in ethanol and then dispersed within the aqueous phase of the gel whereas vitamin E was dissolved in sunflower oil which was then made into the oil phase of the emulgel. Whereas vitamin E is fully soluble in sunflower oil, vitamin A is not, and by combining it with the aqueous phase containing the protein stabilizer the compound was encouraged to travel to the interfacial protein membrane where it had increased solubility. This demonstrates the

Table 2. Types of hydrogel systems, their polymer makeup and release conditions.

Author	Polymer	Cross linking	Bioactive encapsulate	Release conditions	Special features
Karp et al. (2019)	Alginate and Eudragit RS®	Ionic gelation	Florfenicol	pH responsive	Slow, controlled release
Hamedi et al. (2020)	Bacterial cellulose and schizophyllan	Amine grafting and glutaraldehyde cross linking	None	None specified	Antibiotic activity
Hu et al. (2019)	Salecan and N,N,N-trimethyl chitosan	Electrostatic self-assembly	Green tea polyphenols	pH responsive	Targeted intestinal delivery
Van Den Bulcke et al. (2000)	Gelatin methacrylamide	Radical polymerization via photoinitiation with LWUV light	None	Temperature responsive	Gel properties can be modulated with degree of cross linking
Liu et al. (2018)	Propylene glycol alginate and zein	Electrostatic self-assembly	Curcumin	None specified	Sustained release
Volić et al. (2018)	Alginate and soy protein isolate	Ionic gelation	Thyme essential oil	pH responsive	Targeted intestinal delivery
Danyuo et al. (2019)	Frompoly-n-isopropylacrylamide (P(NIPA)	Copolymerization and chemical cross linking with N,N′-Methylenebis-acrylamide	Prodigiosin	Temperature responsive	Implantable gel for thermo triggered release
Chen and Subirade (2009)	Soy protein isolate and zein	Gelation with glacial acetic acid	Riboflavin	None specified	Adjustable release kinetics with differing polymer ratios
Abbasi, Eslamian, and Rousseau (2008)	Gelatin and malodextrin	Genipin crosslinking	Caffeine	None specified	None specified
Zhang et al. (2015)	Gelatin and caseinate	Electrostatic complexation	Corn oil	Temperature responsive	Release of lipophilic active agents into the mouth
Liu et al. (2010)	Poly(Nisopropylacrylamide)	Polymerization with UV irradiation with 2,2-dimethoxy-2-phenylacetophenone photoinitiator	FluoSpherepolystyrene beads	Temperature responsive	High velocity burst release of encapsulates
Jiang et al. (2019)	Gold nanorod (AuNR)-embedded poly(N-isopropylacrylamide)	Copolymerization and chemical cross linking with N,N′-Methylenebis-acrylamide	Doxorubicin and curcumin	Near-infrared light-triggered	On-demand and localized therapeutic delivery via application of near-infrared light
Jalili et al. (2017)	Gelatin methacrylate embedded with poly(N-isopropylacrylamide-co-acrylamide and magnetic nanoparticle nanogels	Free radical polymerization and UV irradiation	Doxorubicin	Temperature and magnetic field dependent	Injectable hydrogels loaded with stimuli responsive nanogels for on-demand and localized delivery of therapeutics
Kwok et al. (2001)	2-Hydroxyethyl methacrylate monomer coated with ordered methylene chains	Radical polymerization	Ciprofloxacin	Ultrasound-responsive	On-demand release of encapsulates with minimal non-triggered leakage
Kim, Yoon, and Kim (2019)	Poly(vinyl alcohol)/b-cyclodextrin hydrogel with immobilized glucose oxidase	Chemical cross-linking with citric acid	None	Glucose-responsive	Patch sensor for noninvasive glucose monitoring

importance of the relative solubilities of different lipophilic ingredients included in the matrix of an emulgel. Tuning the oil phase and interfacial conditions to the specific ingredients which are being encapsulated enhances overall loading capacity of the system and can allow for the co-encapsulation of multiple bioactive agents within the same system.

Gastrointestinal targeting of emulgels

The combination of an oil in water emulsion entrapped within the matrix of a hydrogel also offers unique opportunities to release the emulsion and bioactive encapsulates only when it reaches a certain area of the gastrointestinal tract for therapeutic effects. For instance, the delivery of flavor compounds is most appropriate within the oral cavity, whereas nutrients benefit from protection through the gastric area of the GI tract and release for absorption in the lumen of the small intestine. Zhang et al. (2015) created an emulsion filled hydrogel specifically for the delivery of flavor compounds into the mouth by complexation of caseinate and gelatin in the presence of caseinate coated lipid droplets. By using gelatin, which undergoes a gel to sol transition at physiological temperature, the matrix of the hydrogel beads dissociates when introduced to the mouth and releases the emulsion immediately, allowing for flavor dispersion. When targeting the stomach for release of bioactive encapsulates, floating hydrogel matrices are often used for their gastroretentive features. Bera et al. (2017) created such a system for the gastric release of Flurbiprofen to improve its biopharmaceutic effect. All the tested formulations succeeded in controlled release of the entrapped Flurbiprofen over the course of 7 h, without any initial burst release. In addition,

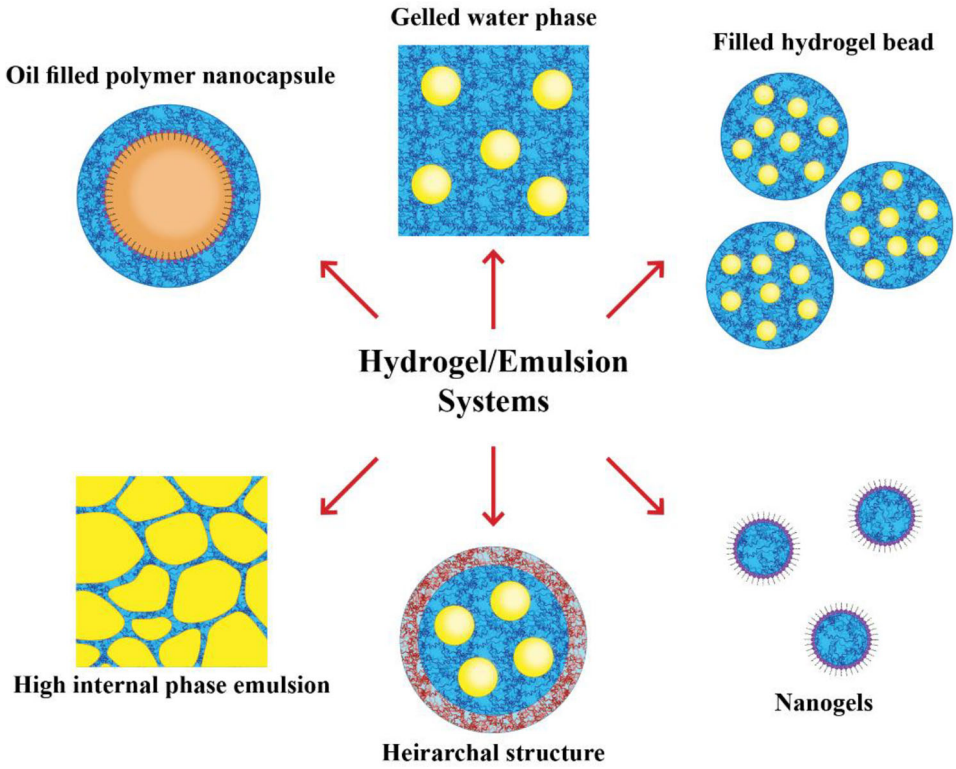

Figure 2. Types of hydrogel-emulsion systems.

modification of the polymer composition resulted in differing levels of buoyancy or mucoadhesion of the emulgel. Lesser amounts of LM-pectin and increasing CS increased the porosity of the gel and increased buoyancy, whereas increasing amounts of LM-pectin enhanced the mucoadhesive properties of the gel. These two features will allow for enhanced delivery of the entrapped drug to the lumen of the stomach.

Finally, many emulgel systems are designed for targeted release of the active ingredients into the lumen of the small intestine. This type of release pattern is often desirable for fragile nutraceuticals which need to be protected from the highly acidic conditions of the stomach. Subsequent release of the protected compounds into the small intestine ensures high levels of bioactivity and transfer into circulation. The alginate bead system developed by Corstens, Berton-Carabin, Elichiry-Ortiz, et al. (2017) is an excellent example of a system for the intestinal delivery of fatty acids. The researchers homogenized safflower oil with an aqueous solution of sodium alginate, and the emulsion was extruded into a $CaCl_2$ solution to induce hardening of the beads. The resulting beads showed controlled release of their entrapped fatty acids when submitted to simulated intestinal fluid, but not simulated gastric fluid. Furthermore, release of the entrapped oil sped up with increasing size of mesh pores and smaller bead size, while the release of the entrapped oil slowed down with smaller pore size and increased bead size.

While this type of system is well suited to releasing bioactive encapsulates progressively into the upper and lower segments of the small intestine, there have also been systems designed specifically for release of hydrophobic bioactives exclusively into the lower intestine. Wooster et al. (2019) tackled this challenge in designing a delayed release, rather than slowed release, hierarchically structured hydrogel for the condensed delivery of fatty acids to the lower small intestine. The system consisted of an emulsion of sunflower oil entrapped within a gelatin core, which was further surrounded by a shell material of β-lactoglobulin and xanthan gum. Digestion in simulated gastric fluid showed no significant degradation of the shell material or release of the core ingredients. On the other hand, digestion in simulated intestinal fluid showed slow degradation of the shell material for the first two hours of digestion, followed by a rapid burst release of core material at the two-hour mark. Selection of gelatin as the core material allowed this rapid burst release profile because once the shell was ruptured in digestion, the core had already reached a liquid state and was therefore highly miscible with intestinal fluids. Additionally, the delay period before burst release was achieved could be modulated by increasing or decreasing the shell thickness or changing the ratio of shell biopolymers.

Controlled delivery of emulgels

Another advantage of entrapping an emulsion within the matrix of a hydrogel is the ability to tune the release of the emulsion to a specific set of environmental triggers. In the previous section concerning hydrogels, systems were described which responded to physical, chemical and biological triggers such as ultrasound, magnetic fields, temperature, ionic strength, pH and glucose levels. Engineering both parts of these combined systems to fill specific roles can lead to enhanced biological effects within the body and fine-

tuned control over the delivery parameters for encapsulated bioactive compounds.

The added advantage of entrapping an emulsion within a hydrogel is to have each component of the system respond to a different trigger or serve a different purpose. For instance, a hydrogel could be tuned to release its contents under a specific condition (like ultrasound, or sustained release) and then the emulsion itself could be decorated with ligands which target the encapsulates toward a specific tissue or receptor.

Another special application of these combined systems is the carefully controlled modulation of drug release into the body. Nanoparticle systems such as solid lipid nanoparticles, liposomes, nanoemulsions, polymeric nanospheres and many more have been shown to be excellent vehicles for drug delivery due to their enhanced ability to be taken up by cells. However, these types of systems suffer from very rapid clearance from blood circulation by the reticuloendothelial system and therefore offer many challenges to the sustained release of their encapsulated bioactive compounds (Dorraj and Moghimi 2015). Dorraj and Moghimi (2015) worked on overcoming this issue by embedding a solid lipid nanoparticle system into an injectable thermoresponsive hydrogel matrix. This system was designed to be injected into a target site as a liquid which will then undergo body heat induced transition into an erodible gel embedded with the SLN. The selected hydrogel polymer (Poloxamer 407) erodes when exposed to an aqueous environment such as that found in the intracellular space. Over the course of 20 hours the system eroded at a constant rate of 0.14 mg/hour, resulting in sustained release on the entrapped SLN dispersion to a target tissue without the risk of premature clearance.

Use of an emulsion within a hydrogel matrix can also be applied in order to prevent premature diffusion of aqueous bioactives out of a hydrogel matrix in a non-triggered manner. Lu, Dong, et al. (2019) created an acoustically responsive hydrogel scaffold made from fibrin, containing a double emulsion (W_1/PFC/W_2) with growth factor entrapped within the innermost W_1 compartment. Under resting conditions, the fibrin matrix keeps the payload in place and the perfluorocarbon organic phase prevents the growth factor from diffusing out of the hydrogel matrix. On the other hand, when exposed to localized ultrasound, the PFC layer is vaporized, which allows for spatially and temporally controlled release of growth factor for precise therapeutic effects. Another example of a very similar system was developed by Martin-Saavedra et al. (2017). These researchers developed thermosensitive liposomes entrapped within a fibrin hydrogel matrix embedded with gold nanorods. In response to locally applied near infrared light, the gold nanorods create heat, which in turn interacts with specialized phospholipids in the liposome's bilayer and creates an aqueous pore to allow the diffusion of encapsulated bioactives.

Bioavailability, bioaccessibility and bioactivity of emulgels

As discussed previously, emulsion systems can offer enhanced absorption of bioactive compounds in the gastrointestinal tract through their small particle sizes. On the other hand, hydrogels are excellent for maintaining the bioactivity of encapsulated compounds as they pass through harsh gastric conditions to then be released within the lumen of the small intestine. It is therefore of no great surprise that combining hydrogel and emulsion systems can have enhancing effects on the bioavailability and bioaccessibility of encapsulated compounds. Bioavailability and bioaccessibility are two methods of measuring how much of a compound is ready to be taken up and utilized by the body.

Bioaccessibility is normally measured by in vitro tests such as simulated digestion and is comprised of the fraction of bioactive compound which is released from the food matrix and is accessible for absorption in the small intestine (Carbonell-Capella et al. 2014). Practically, it is measured by separating the micelle phase of the in vitro digesta by centrifugation and evaluating the quantity of bioactive compound found therein. Bioavailability, on the other hand, measures how much of a nutrient or compound reaches systemic circulation in a living organism and is used in metabolism (Carbonell-Capella et al. 2014). Experimentally, this is determined by blood plasma concentrations of the bioactive compound in a living organism and a measure of area under the curve in pharmacokinetic studies.

With the effects of the encapsulated emulsion on a system's bioaccessibility generally resulting in fast intestinal absorption, and the effects of the hydrogel matrix also affecting the system's bioaccessibility by delaying the release of the emulsion into the intestine for digestion, combined systems can have varying effects on the timing and general bioaccessibility of the encapsulated compounds. Some of the factors that determine the overall bioaccessibility include the size of the mesh in the hydrogel matrix, the relative solubility of the encapsulated compound, and the size of suspended oil droplets. Chen, McClements, et al. (2018) compared different markers of digestion and bioaccessibility for a system consisting of a corn oil emulsion containing quercetin, entrapped within a gel matrix made form sodium caseinate and gellan gum. They found that the non-gelled emulsions exhibited higher quercetin bioavailability and faster rates of digestion than their gelled counterparts. This was attributed to the dense network limiting access of digestive lipases and proteases to their substrates in the gels. This system was concluded to be unfavorable for increasing the bioavailability of quercetin, but appropriate for applications where delayed digestion is sought.

Conversely, Park, Mun, and Kim (2018) compared the bioaccessibility features of an emulsion containing β-carotene and the same emulsion entrapped within the matrix of a hydrogel based on rice starch and xanthan gum. They found that the lipid digestion rate for emulgels containing high amounts of xanthan gum was higher than for the fluid emulsion. This was attributed to the starch and xanthan gum matrix keeping smaller oil droplets in suspension throughout the simulated digestion which created a higher droplet surface area for intestinal lipases to act upon. However, the bioaccessibility measures for β-carotene were highest for the starch only emulgel and dropped with

Table 3. Types of emulgels & their applications.

Authors	Matrix polymers	Oil phase	Homogenization method	Gelling method	Encapsulated bioactives	Targeted delivery
Emulgels for delivery of bioactives						
Bao et al. (2020)	Whey protein isolate	Sunflower oil	Homogenizer, High pressure homogenizer	Cold-set gelation	Resveratrol and α-tocopherol	Gastrointestinal system – stomach & small intestine
Chen, Mao, et al. (2020)	Whey protein isolate	Sunflower oil	Homogenizer, High pressure homogenizer	Acid induced gelation	Vitamin E	N/D
Zhang et al. (2015)	Caseinate and gelatin	Corn oil	High pressure homogenizer	Electrostatic complexation	None	Mouth
Bera et al. (2017)	Kondogogu gum-Zn^{+2}-low methoxyl pectinate with calcium silicate	Olive oil, sunflower oil and light liquid paraffin	Homogenizer	Ionotropic gelation	Flurbiprofen and zinc	Stomach
Corstens, Berton-Carabin, Elichiry-Ortiz, et al. (2017)	Alginate	Safflower oil	Homogenizer	Ionic gelation	None	Small intestine
Wooster et al. (2019)	Gelatin (core), β-lactoglobulin and xanthan gum (shell)	Sunflower oil, brominated vegetable oil	Homogenizer, High pressure homogenizer	Heat induced gelation	None	Lower small intestine
Dorraj and Moghimi (2015)	Poloxamer 407	Stearic acid	Spontaneous emulsification	Thermoreversible gelation	None	Target injected tissue
Lu, Dong, et al. (2019)	Fibrin	Perfluorocarbons	Sonication, microfluidization	Enzymatic cross linking	Dextran	Target implanted tissue
Martin-Saavedra et al. (2017)	Fibrin	Lysolipid-incorporated thermosensitive liposomes	N/A	Enzymatic cross linking	Doxorubicin	Target implanted tissue
Park, Mun, and Kim (2018)	Rice starch and xanthan gum	Soybean oil	Homogenization, microfluidization	Heat induced gelation	β-carotene	Gastrointestinal system
Chen, McClements, et al. (2018)	Gellan gum	Corn oil	Microfluidization	Acid induced gelation	Quercetin	Gastrointestinal system
Jain, Winuprasith, and Suphantharika (2020)	Dual modified rice starch	Soybean oil	Homogenization, high pressure homogenization	DN/	Lycopene	N/D
Liu et al. (2019)	Whey protein isolate	Camellia oil	Homogenization	Acid induced gelation	β-carotene	Small intestine

increasing levels of xanthan gum in the system despite the higher rates of lipolysis. This result suggested an interaction between xanthan gum and β-carotene during digestion which would decrease the β-carotene's bioaccessibility. These studies demonstrate the complex nature of the interactions between different components of the hydrogel matrix, the size of the emulsion droplets present and the encapsulated compound.

Another factor which affects the overall bioavailability and bioaccessibility of an encapsulated compound is the compound's remaining bioactivity when it reaches the site of absorption. Many food antioxidant compounds are chemically sensitive to pH, temperature, oxygen and light and can therefore lose desirable biological activity when exposed to the conditions of the gastrointestinal tract (Cornacchia and Roos 2011). Liu et al. (2019) showed that bioactivity of β-carotene can be preserved to a greater extent when the carotenoid is encapsulated in a gelled emulsion system compared to a non-gelled emulsion system. The researchers prepared high internal phase emulsions containing β-carotene dissolved in camellia oil with heat denatured whey protein isolate (WPI) as an emulsifier. Select samples had a further addition of glucono-δ-lactone to induce cold-set gelation of the WPI. Samples were submitted to in vitro digestion, and then a portion of the digesta was collected to evaluate the chemical stability of the β-carotene portion. The results showed that the samples containing higher levels of WPI and the samples that were gelled by the addition of glucono-δ-lactone had a higher remaining bioactivity level than the non-gelled samples. This activity preservation was due to the entrapment of the β-carotene into a dense gel network, which increases the path length for pro-oxidants or hydrogen ions to reach the compounds. Another observation from this study was that gelled and non-gelled systems containing higher levels of WPI also had higher levels of β-carotene bioactivity after digestion. This effect was due to the WPI itself increasing the antioxidant capacity of the system. Upon digestion, WPI is known to release antioxidant

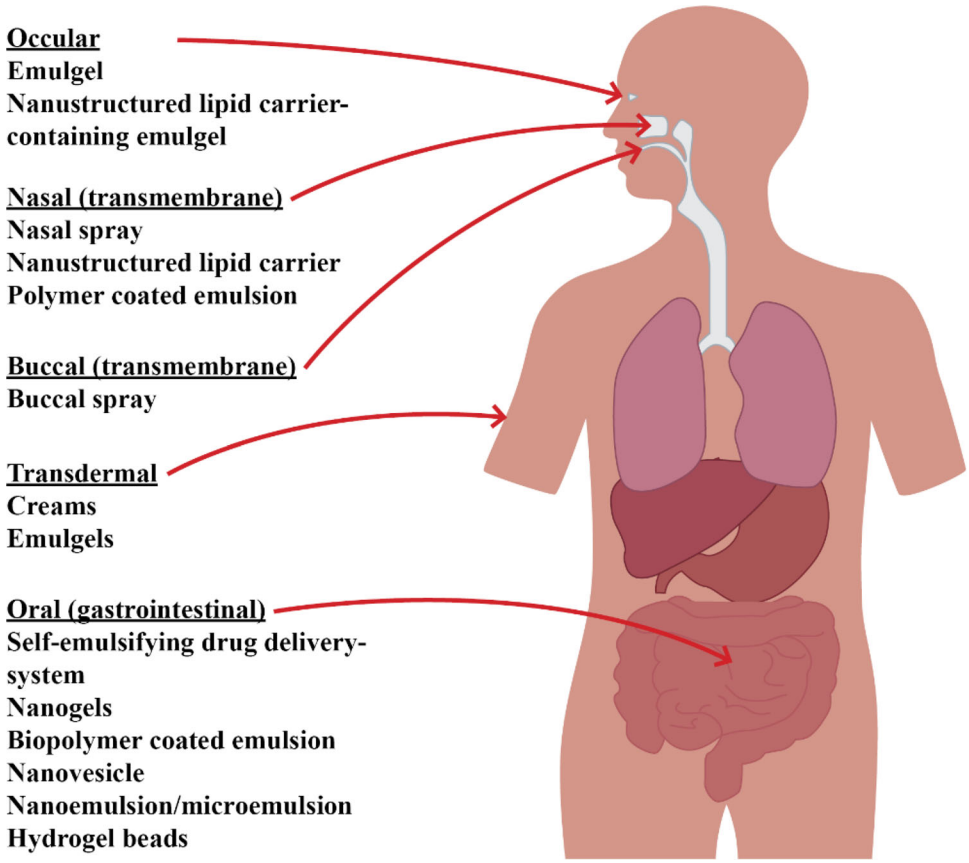

Figure 3. Cannabinoid delivery systems and their routes of administration.

peptides during digestion which had a further protective effect on the encapsulated β-carotene (Table 3).

Cannabis

With the recent legalization of cannabis and cannabis edibles in Canada, the demand for these products is at an all-time high. In response to federal health standards and consumer demands, there is a high interest in exploring alternate modes of consumption that provide a predictable dose of psychoactive cannabinoid ingredients per portion in order to create consistent and predictable effects in consumers. Some of these can include: edible extracts of cannabis, infused into a food, beverage or comestible oil delivered through the oral (gastrointestinal) route; buccal or nasal cannabis sprays delivered through the transmembrane or oromucosal route; and creams or gels infused with cannabis delivered through the transdermal route. Advanced delivery systems such as the ones described in this review will undoubtedly play a role in the dispersion and stabilization of cannabinoids within various food matrices such as cannabis edibles or beverages. Furthermore, the specialized structures of these delivery systems can allow for the sustained, burst, or triggered release of cannabinoids to a specific set of environmental or biological conditions.

Modes of consumption

While smoking cannabis remains the most prevalent form of consumption, non-combustion-based routes of delivery are gaining in popularity due to the potential of decrease in smoking related health risks. In a recent meta-analysis, the health effects of cannabis consumption through different routes of administration were examined (Russell et al. 2018). It was concluded that, while the health effects of smoking cannabis are clearly documented (coughing and wheezing reduced lung function, chronic bronchitis), there is a lack of high-quality evidence regarding health effects of alternative routes of administration. It was concluded that vaporization and inhalation of cannabinoids from cannabis flowers lessens co-ingestion of combustion-related toxins. Consumption of cannabis edibles, on the other hand, eliminates risks posed by heating or combustion of cannabis flowers, but increases the risk of over-consumption due to the delayed onset of the effects and the difficulty in self-regulating the ingested dose. This propensity for overconsumption can lead to serious health outcomes such as overdose, coma and death, especially in minors. As for topical creams and gels or nasal and oral sprays, there is limited data on health outcomes in the general public as they are typically prescribed in a medical setting (Figure 3).

Other than contributing to differing levels of health risks, the route of administration of cannabis products has a significant effect on the speed of cannabinoid absorption. The speed of uptake and the level of exposure to digestive metabolism will ultimately determine its pharmacokinetic profile. Cannabis inhalation is often preferred by consumers for the speed of physiological effect and the high dose of cannabinoids which is rapidly delivered into circulation.

Spindle et al. (2019) studied the pharmacokinetic profile of cannabinoids delivered by cannabis smoking versus vaporization of cannabinoids from cannabis flower. They found that vaporizing 10 mg of cannabis resulted in higher peak levels of THC in the blood (Cmax) when compared with smoking cannabis (7.53 ng/ml and 3.76 ng/ml respectively). There was, however, a slight delay in time taken to reach these maximal plasma concentrations (Tmax) for vaporization versus smoked cannabis (0.18 h and 0.11 h respectively). Studies investigating the pharmacokinetic differences between smoked and vaporized cannabis vary with regards to which method of administration results in a higher Cmax value (Abrams et al. 2007; Newmeyer et al. 2016; Spindle et al. 2019). However, Tmax seems to be consistent between smoking and vaporization between $0-0.17$ hours.

Cannabis edibles such as cannabis infused brownies, cookies, beverages, oils etc. are absorbed through the gastrointestinal route in a similar way to any other foods. This gastrointestinal absorption takes significantly more time than absorption through the lungs. Cannabinoids introduced into circulation this way will be exposed to many more steps of metabolic transformation, which can damage the cannabinoid's bioactivity, deactivate it, or remove it from circulation. Specifically, cannabinoids are vulnerable to first pass liver which involves Phase I oxidation and Phase II glucuronidation reactions. These reactions serve to transform cannabinoids into water soluble derivatives which can be more easily excreted by the body (Izgelov et al. 2020).

Inhalation such as smoking or vaping remains the fastest route for the administration of cannabinoids, with Tmax being reached in under 15 minutes. This is due to the cannabinoids being absorbed through the alveolar capillaries and transferring directly into systemic circulation. On the other hand, cannabis edibles absorbed through the gastrointestinal tract take much longer to reach maximal systemic circulation, with Tmax being in the range of 2.5 hours and Cmax being much lower for edibles than for smoked cannabis (10.2 ng/ml and 51.6 ng/ml respectively) (Newmeyer et al. 2016) . This delay is due to many factors experienced in the gastrointestinal tract such as residence time of the edible material within the stomach, and the digestion and micellization process which must occur in the small intestine before absorption can proceed. However, Newmeyer et al. (2016) found that the total amount of cannabinoid that reaches systemic circulation (area under the curve, AUC) over the course of 54 hours post-consumption is greater for edible products than for smoked cannabis. This result, however, may have been due to the study design that was employed. Subjects were instructed to consume the smoked or vaped cannabis ad libitum, whereas the edible cannabis was given in a fixed dose equivalent to the entire cannabis cigarette offered to smoking or vaping participants. The short time of onset of the inhaled cannabis may have allowed the subjects to better self-regulate their cannabinoid intake whereas those who consumed the edible product may have had a higher overall dose due to consumption of the full portion offered.

Another recent study by Bartner et al. (2018) compared serum levels of CBD in beagles when the cannabinoid was administered through the oral vs the transdermal route. The researchers compared the pharmacokinetics of CBD in oil, microencapsulated oil beads of an unspecified nature or in CBD-infused transdermal cream. While the researchers were expecting that cannabinoid blood concentration would be higher for the transdermal cream than for the orally administered forms of CBD due to the transdermal route bypassing first pass liver metabolism, the opposite was actually true. The transdermal cream took longer to reach maximal plasma concentrations than the oral methods (Tmax 10-12 h vs 2-4 hours respectively) and the Cmax values were greater in both oral forms than for the transdermal cream. This was attributed to the absorption of the cannabinoid through the transdermal route being incomplete due to diffusion barriers such as the thickness of the skin and the accumulation of hydrophobic CBD in the upper layers of the skin.

Through the analysis of current research, it can be seen that the general effectiveness of cannabis delivery tends to favor inhalation routes first, followed by oral and then transmembrane routes. However, many consumers are seeking rapid and effective delivery of cannabinoids through routes that do not expose them to the additional health risks or inconvenience of smoking or vaping cannabis. To this end, many delivery systems have been devised to enhance the oral and transdermal delivery of cannabinoids. Several delivery systems for the buccal and nasal transmembrane administration of cannabinoids have been devised. These delivery systems are often utilized for administration of cannabinoids as an alternative to opioid painkillers for the treatment of breakthrough pain. They are seen as attractive options for increasing cannabinoid bioavailability by bypassing deactivation by first pass metabolism. Some factors that determine the efficacy of such systems include the level of mucoadhesion between the delivery system and the lining of the mouth (which prevents displacement by chewing or salivary flow), and the efficacy of drug transport across the buccal membrane.

Transmembrane administration

Many transmembrane delivery systems have been designed with these challenges in mind. Hommoss, Pyo, and Muller (2017) designed a spray containing THC for nasal administration. Unlike the mouth, the nose does not pose the challenges of salivary flow or chewing which can dislodge administered compounds, and bioactives can transfer relatively quickly across the thin membranes present therein. These researchers created a solid state NLC formulation from cetyl palmitate stabilized with cationic surfactants cetylpyridinium chloride or benzalkonium chloride. Having a positively charged delivery system enhances the mucoadhesion properties of the particles in relation to negatively charged biological membranes. Additionally, the researchers selected the formulation conditions which resulted in the smallest particle sizes (200 nm) to enhance efficiency of transmembrane transport. This resulted in 75% of entrapped

THC being released within 15 minutes during a THC release study on this system. Furthermore, the selection of a solid lipid carrier as opposed to a liquid oil resulted in much better protection of THC's biological activity over an extended product shelf life of six months. Impressively, after a period of 6 month accelerated storage at 40 °C, the formulation maintained 79% of original THC content. This is in opposition to stability tests done on THC extracts in chloroform where the cannabis extract stored at room temperature without light exposure degraded by 50% after only 91 days (Lindholst 2010). The extended shelf life was attributed to the solid state of the NLC keeping THC within the lipid core and away from the surface of the particle where it could be exposed to oxygen or the external water phase.

Recent studies have cast in doubt whether highly lipophilic cannabinoids are, in reality, absorbed through the transmembrane route when administered through an oromucosal spray or other transmembrane formulation. This suspicion came to light when comparing pharmacokinetic data between studies that performed cannabinoid administration through the transmembrane route on fasted versus fed participants. In a meta-analysis of pharmacokinetic clinical studies regarding plasma levels of CBD, Lim, Sharan, and Woo (2020) found that the bioavailability of oromucosally delivered CBD was 6 fold higher in fed vs fasted participants. Furthermore, in a review of multiple studies investigating the pharmacokinetics of Sativex® and similar oral spray formulations Itin, Domb, and Hoffman (2019) observed that the pharmacokinetic profile of oromucosal cannabinoid sprays administered to subjects in a fed state very closely resembled the pharmacokinetic profile of capsule or solution formulations delivered orally to the gastrointestinal tract. Based on these results, it was suggested that upon administration of oral cannabinoid sprays, at least part of the formulation may be being displaced by salivary flow, swallowed and absorbed through the gastrointestinal tract. In the fed state, cannabinoid absorption in the GIT is enhanced by liver bile production, improved mucosal permeability and lymphatic transport which are stimulated by food digestion. However, in the fasted state these enhanced mechanisms are absent, and the majority of the cannabinoid dose passes through the GIT to be excreted in the feces (Itin, Domb, and Hoffman 2019; Lim, Sharan, and Woo 2020).

A recent study by Itin et al. (2020) was designed to specifically investigate the rate of CBD permeation through the buccal mucosa while eliminating the possibility of salivary displacement and swallowing. To achieve this, the researchers implanted pigs with a mucoadhesive shell on the inside of their buccal mucosa which was filled with a CBD containing formulation. This was done in order to create prolonged contact between the membrane and the drug while protecting it from salivary flow. For the in vivo portion of the study, the shell was left in place for 8 hours before removal, but blood samples were taken from 0 h to 12 h to evaluate the kinetics after removal of the loaded shell. The researchers found that plasma levels of CBD increased very slowly when compared to traditional studies involving Sativex® spray administration and did eventually increase to therapeutic levels. However, upon removal of the shell and cessation of contact with the CBD formulation, plasma levels of CBD continued to increase until the 12 h mark. CBD is a highly lipophilic compound and is known to sequester into peripheral tissues upon administration. The further increase of plasma CBD after removal of the mucoadhesive shell was attributed to slow passive diffusion of the CBD sequestered in the cheek tissues out into blood circulation. These results show that true oromucosal delivery of CBD is possible, but the application is better suited to a prolonged delivery application and the formulation must be protected from salivary flow.

Oral administration

Oral cannabinoid formulations are constantly undergoing improvement in order to increase bioavailability, to decrease the time required for onset of effects, and to improve cannabinoid and formulation stability during the product's shelf life. Many different styles of delivery system have been tested to vehiculate cannabinoids, and each presents its own distinct advantages. In a recent meta-analysis regarding cannabinoid pharmacokinetics from oral solutions and oral capsules, there has been extensive variability between different oral treatments due to their vast differences in formulation (Lim, Sharan, and Woo 2020).

Simple emulsions, nanoemulsions and microemulsions

Simple emulsion systems would be viable for the suspension of cannabinoids, but most researchers have opted for nanoemulsion (particle size <500 nm) and microemulsion (particle size <100 nm) systems in their place. These systems can offer enhanced stability, smaller particle sizes and improved bioavailability over emulsions with larger droplet sizes. Mikulcová et al. (2017) created nanoemulsions of hemp seed oil in water, stabilized with various ratios of Tween and Span emulsifiers. These emulsifiers were combined in order to create a scale of HLB values to select the optimal HLB for hemp oil stabilization. High energy vs low energy emulsification methods were also tested for their effectiveness. It was determined that the optimal conditions for creating emulsions with small droplet sizes (150 nm) were the surfactant combination with an HLB of 9 and high energy homogenization. This emulsion system exhibited the lowest initial particle size and the highest stability against creaming. Although these emulsions did not contain any active THC or CBD due to hemp oil being refined from the seeds of the cannabis plant which have low levels of cannabinoids, such an emulsion could be used for food fortification owing to the high levels of omega 6 and omega 3 fatty acids it contains.

Another reported use of a nanoemulsion containing cannabinoids was documented in treating high intra ocular pressure in rabbits. Here, an oily phase consisting of THC, MCT oil, an antioxidant and phospholipid surfactants were blended with an aqueous phase consisting of water, glycerol

and surfactant by high pressure homogenizer. The resulting emulsion had particle sizes with a mean of 100 nm and exhibited good stability. This emulsion succeeded in its application which was ocular administration of THC to a rabbit glaucoma model, where intraocular pressure was successfully reduced.

Microemulsions (particle size <100 nm) containing cannabinoids are often considered desirable for their increased thermodynamic stability when compared to emulsions with larger particle sizes. Indeed, Lazzari et al. (2010) succeeded in creating a thermodynamically stable microemulsion with very small particle sizes (6.7 – 8.0 nm) from only Solutol®HS15 surfactant and THC in water. This formulation was tested for its painkilling effect in animals, and it was found that it significantly reduced pain response. Furthermore, the analgesic effect was noted much faster than with a conventional THC/ethanol formulation. As discussed previously, this is likely due to the very small particle sizes in the microemulsion enhancing THC bioavailability.

Nanostructured lipid carriers

Delivery systems with completely or partially solidified lipid cores – solid lipid nanoparticles and nanostructured lipid carriers, have increased in popularity for the entrapment of CBD and THC. The main advantage of this system is the preservation of the compound's activity over longer periods. The solid nature of the core sequesters the bioactive component away from the oil water interface where oxidation more readily occurs. Additionally, these systems can be more resistant to creaming and particle coalescence than their liquid oil counterparts.

Encapsulation of drugs within NLC matrices can also lead to very high levels of encapsulation efficiency. Esposito et al. (2016) compared the encapsulation efficiency of rimonabant, a cannabinoid drug in two NLC systems. The first system was prepared through the direct method, with the hot oil phase being added to a hot water phase before mixing, and the second system was prepared by the reverse method, with the hot water phase being added to the hot oil phase before mixing. This simple reversal of the order of addition resulted in an increase of 30% in the encapsulation efficiency of the rimonabant, from 68% in the direct method to 98% in the reverse method. This increase was attributed to fewer losses from the lipid mixture sticking to the glassware during mixing of the phases.

Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems have also been a popular option for the encapsulation of cannabinoids. These systems consist of an emulsion pre-concentrate, which is usually comprised of an active ingredient, a carrier oil, a co-solvent, surfactants and co-surfactants. These components are heated and combined ahead of time into a homogeneous organic phase. This mixture is then incorporated into a delivery vehicle such as a gel capsule. When the capsule is consumed by a subject, it ruptures in the stomach where the gentle churning action causes a spontaneous emulsion to form with the gastric fluids. These systems can often create emulsions with particle sizes in the nm range and their shelf stability is not affected by standard forms of gravitational instability. However, a formulation which lacks stability may have some ingredients precipitate out upon long storage periods. There have been several studies of cannabinoid formulations being incorporated into such delivery systems which resulted in very fast Tmax values and high levels of bioavailability.

One such example of a SEDDS resulting in high cannabinoid bioavailability was recorded by Knaub et al. (2019) who tested the pharmacokinetics of a SEDDS formulation containing CBD against the same dose of CBD (25 mg) diluted in MCT oil on healthy human subjects. Maximum plasma concentration of CBD was 4.4 times higher for the SEDDS then for the MCT oil formulation and Tmax was substantially shorter at 1 h as opposed to 3 h. Cherniakov et al. (2017) had similar results when testing an SEDDS containing both THC and CBD on healthy human volunteers against a similar dose of Sativex oromucosal spray (10 mg). In this case, the SEDDS resulted in a 3-fold increase in Cmax for THC and a 4-fold increase in Cmax for CBD. Tmax was reduced from 2 h to 1 h for THC and 3 h to 1 h for CBD.

Nanovesicle

A nanovesicle is a spherical structure formed by a lipid bilayer whose dimension is within the nm range. Such structures are formed by amphiphilic or surfactant molecules whose geometry favors the formation of a bilayer over that of a micelle or other structure. Vesicles can be used to entrap hydrophobic substances by embedding them between the layers of the structural lipid. Di Bello et al. (2017) created such a system from cardanol and cholesterol on order to encapsulate CBD. This system was selected for this application due to cardanol's antioxidant capabilities and its effect on the chemical stability of the entrapped CBD was evaluated. The resultant vesicle measured 276.9 nm and the researchers determined that the nanovesicular system did in fact increase the chemical stability of entrapped CBD. CBD content and system stability were assessed over the course of 30 days at ambient and refrigerated temperatures. Surprisingly, the vesicular system showed greater preservation of CBD activity at 20 °C after 20 days than at 4 °C. This was ascribed to the vesicular system having reduced stability at 4 °C and showing aggregates and precipitation. Consequently, the system's structure was altered and its ability to protect CBD from the external environment was compromised.

Biopolymer

There have also been many cannabinoid containing systems developed where the entrapped cannabinoid is protected by a polymer shell. These systems have many uses for pharmaceutical applications. They can be designed for both oral and parenteral administration, and the main purposes of the polymer shell include increasing gastrointestinal uptake,

prolonging the release of the entrapped cannabinoid and targeting specific tissues (usually cancerous cells) for payload delivery.

One example of a system designed for prolonged cannabinoid release was devised by Berrocoso et al. (2017). The cannabinoid drug CB13 was entrapped by nanoprecipitation in a matrix of PGLA only, PGLA and PEG, or PGLA which was subsequently decorated with PEG. After oral administration of these formulations to animal test subjects, the pain response was evaluated over time. The formulation with the greatest effect was the one incorporating PGLA and PEG simultaneously. There was a significant prolongation of CB13's analgesic effect, from 9 h with unencapsulated CB13 vs 11 days with the PGLA-PEG formulation.

Gel matrix

There have also been trials carried out on incorporating CBD into pharmaceutical grade gelatin beads (Atsmon et al. 2018). The main advantages of this form of delivery include the ability to tightly control and personalize the dose that an individual patient is receiving (by counting an appropriate number of microbeads). Also, the small individual beads are designed to disperse freely through the gastrointestinal tract to widely release their contents. While this particular matrix did not include any excipients such as surfactants, the CBD entrapped within the gelatin matrix was successfully released once the small intestine was reached by virtue of an acid resistant covering capsule. As the gelatin dissociated the CBD was released to form an emulsion in the intestine with the native digestive fluids and emulsifying agents.

This formulation was tested for its pharmacokinetic profile against Sativex oromucosal spray in 15 healthy volunteers in the fed state, following a standardized meal given before the CBD capsule's administration. Time until maximum plasma CBD concentration were similar in both formulations, talking $3-3.5$ hours to reach peak levels. However, for the same dose of CBD administered, the gelatin capsules showed a bioavailability 134% relative to the Sativex spray.

Fed vs fasted state

With cannabinoids that are administered through food, there are several other important interactions that must be studied to gain a better understanding of the gastrointestinal fates of these compounds. The first is the interaction of the cannabinoid and its delivery system with the matrix of the food which contains it, and the second is the interaction with the gastrointestinal tract in a fed state. Due to these complex interactions, most pharmacokinetic studies are done on fasted individuals to reduce the high inter-subject variability between cannabinoid absorption profiles. Nadulski et al. (2005) studied the pharmacokinetic profile of THC and CBD administered as a tincture with ethanol, either in fasted subjects, no food for 8 h before or 4 h after capsule administration, versus subjects that were fed a standardized meal 1 h after capsule administration. While the pharmacokinetic curves for THC and CBD showed a modest increase in plasma levels in the group that received food after capsule administration, the differences were not statistically significant due to individual variability.

As discussed previously, several studies have also been done concerning differences in absorption for cannabinoid oromucosal sprays in the fasted or fed state. Stott et al. (2013) studied the pharmacokinetic profile of Sativex oromucosal spray on 6 volunteer subjects who either fasted for 10 h pre-dose or were fed a standard high fat breakfast 30 minutes pre-dose. The pharmacokinetic profile demonstrated an enhanced 3-fold increase in Cmax for CBD and THC for the fed group, but Tmax was delayed from 1.5 h in fasted subjects to 4 h in fed subjects. Although in this case these results did reach significant levels, once again the results were marked by very high levels of inter-subject variability.

A few studies have also been conducted for cannabis incorporated into edible food products. Vandrey et al. (2017) evaluated the pharmacokinetic profile of THC after administration of a brownie containing 10, 25 or 50 mg of dried, decarboxylated cannabis flower. After consumption of these products, Tmax ranged from $0.9-2.6$ hours. Cmax values were relatively low when compared to inhaled cannabis ($1.0-3.5$ ng/ml compared to 42-87 ng/ml for smoked cannabis), but despite the very low blood plasma concentrations, subjects experienced significant cognitive and psychomotor alterations. This cannabis was baked directly into the brownie without any extraction or encapsulation steps prior to food preparation, and there were no pharmaceutical-like delivery systems tested in parallel with this mode of consumption, so comparisons between the two modes of delivery are limited.

However, from these examples it is evident that interactions between food consumption and cannabis absorption and metabolism are significant for all dosage forms. Many of these changes are mechanical, such as alteration of the gastric pH and delayed gastric emptying in the fed state, which in turn delays the time of onset for consumed cannabinoids. Also, changes in the physiological state of the intestine in the fed state such as increased mucosal permeability, enhanced lymphatic transport, increased bile flow and increased splanchnic blood flow may enhance the absorption of cannabinoids. Food components may also physically or chemically interact with a delivery system or drug. An example of this is co-administration of lipids with cannabinoids increasing the solubilization and transport into the lymphatic system (Stott et al. 2013).

Oil composition and bioavailability

It is becoming clear that the carrier oil employed to solubilize THC and CBD in a delivery system can also influence gastrointestinal absorption and bioavailability. Co-administration of lipids with cannabinoid compounds (as opposed to lipid free meals) is known to significantly increase the systemic exposure to THC and CBD due the lipid's propensity for being incorporated into chylomicrons for subsequent

Table 4. Summary of pharmacokinetic data for various cannabis delivery systems and routes of administration.

Reference	Cannabinoid	Delivery system	Route of administration	Dose	Tmax (h)	Cmax (ng/ml)	AUC (h*ng/ml)
Zgair et al. 2016	THC	Cannabinoid in ethanol or LCT lipids	IV	4mg/kg	–	–	1624 ± 334
			Oral (lipid free)	12mg/kg	2	65 ± 17	414 ± 130
			Oral (with lipid)	12mg/kg	3	172 ± 34	1020 ± 169
Vandrey et al. 2017	THC	Brownie containing cannabis flower	Oral	10 mg	0.9	1	–
				25 mg	2.6	3.5	–
				50 mg	2.3	3.3	–
Stott et al. 2013	THC	Cannabinoid with propylene glycol, ethanol and peppermint oil	Oromucosal spray (fasted)	10.8 mg THC	1.5	3.98	12.51
	CBD			10 mg CBD	1.39	1.15	5.64
			Oromucosal spray (fed)	10.8 mg THC	4	6.48	34.99
				10 mg CBD	4	3.66	23.13
Spindle et al. 2019	THC	Dried cannabis flower	Smoking	10 mg	0.11	3.76	–
				25 mg	0.13	10.24	–
			Vaporization	10 mg	0.18	7.53	–
				25 mg	0.19	14.36	
Newmeyer et al. 2016	THC	Dried cannabis flower	Smoking	50.6 mg	0.10 – 0.11	44.4 – 51.6	18.0 – 20.4
			Vaporization	50.6 mg	0.10 – 0.11	34.8 – 47.8	9.9 – 11.7
			Oral	50.6 mg	2.3 – 2.5	10.1 – 10.3	37.5 – 43.4
Nadulski et al. 2005	THC	Liquid cannabis extract with ethanol	Oral (fasted)	2.5 mg THC	1.06	3.19	358 (ug*min/L)
	CBD			2.5 mg THC + 1.35 mg CBD	0.93	4.05	450.16 (ug*min/L)
			Oral (fed)	2.5 mg THC + 1.35 mg CBD	1.03	5.29	564 (ug*min/L)
Knaub et al. 2019	CBD	SEDDS CBD in MCT oil	Oral	25 mg	1	13.53	32.63
				25 mg	3	3.05	19.23
Izgelov et al. 2020	CBD	SEDDS	Oral MCT, liquid	15 mg/kg	1	101	579
			Oral LCT, liquid		1.08	137	611
			Oral MCT, solid		5	261	261
			Oral LCT, solid		6	458	458
Cherniakov et al. 2017	THC	SEDDS	Oral	10.8 mg THC	1	5.4	11.6
	CBD			10 mg CBD	1	2.1	6.9
		Cannabinoid with propylene glycol, ethanol and peppermint oil	Transmembrane	10.8 mg THC	2	1.8	8
				10 mg CBD	3	0.5	3.1
Bartner et al. 2018	CBD	CBD oil	Oral	75 mg	–	110.0	25.8
				150 mg	–	67.4	25.2
		Micro-encapsulated CBD (unspecified)	Oral	75 mg	–	62.0	18.2
				150 mg	–	51.3	15.8
		CBD-infused transdermal cream	Transdermal	75 mg	–	11.3	ND
				150 mg	–	27.3	ND
Atsmon et al. 2018	CBD	Gelatin matrix pellets	Oral	100 mg	3.5	47.44	153.04
				10 mg	3	3.22	10.31
		Cannabinoid with propylene glycol, ethanol and peppermint oil	Transmembrane	10 mg	3.5	2.05	7.81

transport in the lymphatic system (Zgair et al. 2016). However, the chain length of a lipid can affect the micellization and uptake mechanisms in the small intestine. Medium chain triglycerides (MCT) have a chain length of 6 to 12 carbons. These lipids are rapidly taken up into the enterocyte and enter systemic circulation through the portal vein, without needing to undergo the micellization process by bile acids in the small intestine. On the other hand, long chain triglycerides (LCT) have chain lengths ranging from 13 to 21 carbons. The increased chain length results in higher levels of hydrophobicity and micellization is necessary for these fats to be packaged into chylomicrons and taken up by the lymphatic system (Izgelov et al. 2020). This alteration in the pathway taken to reach systemic circulation is important for bioactive molecules. Compounds taken up through the portal vein will be processed in the liver and undergo phase I and phase II metabolism for complete or partial deactivation before being released into the bloodstream. This is not the case for compounds treated though the lymphatic system and bioactivity can be better maintained.

It is therefore relevant what lipids are chosen as excipients for cannabinoid containing emulsion systems. Izgelov et al. (2020) tested the effects of different fats and oils used for the synthesis of a self-nano emulsifying drug delivery system on the bioavailability co-encapsulated CBD. Two different systems were tested. The first consisted of a liquid LCT, sesame oil, bring compared to a liquid MCT, MIGLYOL® 812 N, whereas the second consisted of a solid LCT, cocoa butter, compared to a solid MCT, tricaprin. Upon orally administering these formulations to rats, the researchers observed that there was no significant difference in bioavailability for the liquid oil formulations, but that in the solid fat formulations the LCT based system showed a significant 1.7-fold increase in Cmax. The non-significant

result in the first formulation was unexpected. The researchers hypothesized that incorporation of these distinct lipids into a self-emulsifying drug delivery system may alter their state in the gastrointestinal tract. Prepackaging these lipids into micelle format due to the SEDDS may have altered their digestive pathway. This is particularly true for MCT which do not need to be micellized during the digestive process. On the other hand, the significant result for the solid lipid formulations may have been due to a difference in the chain length of the oils involved as cocoa butter has overall longer chain lengths than sesame oil. Overall, the digestion process is complex and multiple factors could have influenced these results (Table 4).

Conclusion

In conclusion, there are a wide variety of emulsion and hydrogel delivery systems being researched for many different applications. Emulsions excel at suspending, protecting and delivering hydrophobic or hydrophilic bioactive compounds. There are many different types of emulsion systems, such as simple emulsions, nanoemulsions, double emulsions, polymer stabilized emulsions, coacervates, and solidified emulsions. Each type of system has its own unique strengths depending on the selected structural characteristics. These strengths can include qualities such as improved stability due to small particle size or a solid lipid core, or enhanced bioavailability of encapsulates.

Hydrogels for food applications are also extremely varied in their makeup. They are often constructed from proteins or polysaccharides and can be held together through covalent linkages or electrostatic forces. Hydrogels have several simple release mechanisms for encapsulated bioactives such as swelling and diffusion, but though careful selection of the polymer composition they can be tuned to release their contents only in response to specific physical, chemical or biological stimuli. This level of control that can be exerted over the release of an encapsulate from a hydrogel is what makes them very valuable components of sophisticated delivery systems such as emulgels or filled hydrogels. These combination emulsion – hydrogel systems are excellent vehicles for the delivery of bioactive compounds, and they can be designed to offer sustained, delayed or targeted release of their encapsulates.

Finally, these systems are beginning to find use in the pharmaceutical and food industry for the delivery of cannabinoid compounds. While clinical trials have been pursued to collect pharmacokinetic data for different modes of cannabis consumption (e.g.: oral, oromucosal, inhaled), very little pharmacokinetic data has been collected to compare the effectiveness of varied oral cannabinoid delivery systems. More research is needed to link advanced delivery systems to their pharmacokinetic outcomes, and to compare the effectiveness of specific delivery systems for delivering cannabinoids through the gastrointestinal route.

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Declaration of interest statement

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