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Enhancing Efficacy, Performance, and Reliability of Cannabis Edibles: Insights from Lipid Bioavailability Studies

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Abstract

The legal sale of cannabis-enriched foods and beverages for medical or recreational purposes is increasing in many states and countries, especially in North America and Europe. These food-based cannabis delivery systems vary considerably in their compositions and structures, ranging from low-viscosity watery beverages to solid fatty chocolates. The rate and extent of release of the bioactive components in cannabis within the human gastrointestinal tract (GIT) affect their health and psychoactive effects. Studies with other types of hydrophobic bioactives, such as nutraceuticals and vitamins, have shown that food composition and structure have a major impact on their bioaccessibility, transformation, and absorption within the GIT, thereby influencing their bioavailability and bioactivity. This review outlines how insights on the bioavailability of other lipophilic bioactives can be used to facilitate the design of more efficacious and consistent cannabis-enriched products intended for oral consumption. In particular, the importance of food-matrix composition (such as fat type and level) and structural organization (such as fat domain dimensions) are discussed.

INTRODUCTION

The legislation governing the medical and recreational use of cannabis is changing rapidly in many states and countries, which has led to growing interest in the development of cannabis edibles, i.e., foods or beverages that contain enough cannabis to have a physiological effect (Peters & Chien 2018). The intake of cannabinoids in the form of edibles rather than smoking may reduce its negative health effects, but further research is still required (Russell et al. 2018). Although cannabis is still illegal at the federal level in the United States, where it is classified as a Schedule 1 substance under the *Controlled Substances Act* of 1970, its sale has been legalized in numerous states, including Alaska, California, Colorado, Illinois, Maine, Massachusetts, and Washington. There is therefore a growing market for edible cannabis products for both medicinal and recreational use. Indeed, it has been reported that the global market for cannabis edibles was approximately $8.4 billion in 2017 and is predicted to increase to approximately $25.7 billion by 2022 (Malochleb 2019). At present, however, there is a poor understanding of how cannabis edibles behave within the human body after ingestion (Martin et al. 2018). This knowledge is important to ensure their safety, improve their consistency, increase their efficacy, and modulate their effects. For instance, it is possible to create fast- or slow-acting cannabis products by altering the composition or structure of the foods they are consumed with. Furthermore, it is important that they are delivered in a form that reliably produces a dose with the intended beneficial effects and without any potentially adverse effects. The purpose of this review is therefore to provide some background about the potential impact of food-matrix effects on the fate of cannabis edibles within the human gastrointestinal tract (GIT). This knowledge is mainly based on the insights that have been gained from studies on the bioavailability of other kinds of hydrophobic bioactive substances, such as nutraceuticals and oil-soluble vitamins. However, recent studies on the impact of food-matrix effects on cannabinoid pharmacokinetics and bioactivity are also covered.

Many different species of cannabis plants contain substantial levels of bioactive substances, which have been reported to exhibit psychoactive effects as well as other potentially beneficial effects, such as antimicrobial, antioxidant, anti-inflammatory, and pain-relief activities (Bonini et al. 2018). The most common are *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* as well as new strains created by cross-breeding these strains to obtain beneficial traits. *Cannabis sativa*, however, is currently the most widely used natural source of psychoactive cannabinoids. These substances are mainly found in the female flowers of the cannabis plant and have a terpenophenolic structure (Bonini et al. 2018). They are believed to play an important role in protecting the plant from water loss by forming a hydrophobic barrier on the surfaces of the leaves. Furthermore, they may prevent attack by insects, fungi, and bacteria because of their pesticide-like activity and invasion by other plant species because of their herbicide-like activity. There are more than 100 different kinds of cannabinoid, but the *trans*-D-9 tetrahydrocannabinol (D9-THC) has the most potent psychoactive effects.

Despite the recent increase in interest in using cannabis for its functional properties, *C. sativa* has been utilized by humankind for tens of thousands of years for this purpose. This plant probably originated within specific regions of central and Southeast Asia and then spread around the globe (Bonini et al. 2018). There is evidence that *C. sativa* has been used for more than 12,000 years for its beneficial properties. Initially, it is believed to have been used mainly for its fibrous attributes to form ropes, twine, nets, and clothes but also for its bioactive properties as an herbal medicine or mind-altering substance. Cannabis was used in ancient China as a treatment for fatigue, rheumatism, and malaria, and in ancient Egypt to relieve pain and enhance mood (Bonini et al. 2018). In Medieval Europe, the cannabis plant was primarily used for manufacturing textiles but also for its medicinal and mind-altering effects. In nineteenth-century Europe, cannabis was

widely used recreationally for its psychoactivity, especially by creative types, but in the twentieth century many Western countries banned its use.

CANNABIS CHEMISTRY

The cannabis plant contains hundreds of different bioactive compounds that can be classified into groups according to their molecular structure, such as cannabinoids, terpenoids, flavonoids, and alkaloids (Bonini et al. 2018). In general, the cannabinoid group has the strongest psychoactivity. There are more than a hundred different kinds of cannabinoids in the cannabis plant, which can be classified as either acidic or neutral depending on whether they have carboxyl groups or not. In the plant, the cannabinoids are usually synthesized in the acid form and may then be converted into the neutral form by specific enzymes that remove the carboxyl groups. Cannabinoids are predominantly hydrophobic molecules found in the wax-like substances excreted by the trichomes (small protrusions on the surfaces of the leaves) of female cannabis plants. There are 10 major subclasses of cannabinoids extracted from cannabis plants, which vary in their molecular structures, physicochemical properties, and biological effects. Some of the most important effects are listed below (Bonini et al. 2018, Hilton 2019):

- Tetrahydrocannabinol (THC): This cannabinoid exhibits potent psychoactive effects as well as various other pharmacological activities, such as pain-relief, appetite-stimulation, brain-health, antioxidant, antinausea, and antispasmodic properties. The *trans*-Δ9 tetrahydrocannabinol (Δ^9-THC) is the most prevalent type of THC found in the cannabis plant, but other isomers are also present (such as Δ^8-THC). In plants, THC often occurs in the carboxylated form, tetrahydrocannabinolic acid (THCA or THC-COOH), which is nonpsychoactive but can be converted to THC by heating or during storage. In the body, THC is metabolized to a hydroxylated form, 11-hydroxy-Δ9 tetrahydrocannabinol (11-OH-Δ^9-THC or THC-OH), which is also psychoactive. Further metabolism, however, leads to a reduction in the bioactivity of the molecule.
- Cannabidiol (CBD): This cannabinoid has a relatively low psychoactive effect but is claimed to have other beneficial pharmacological attributes, including anti-inflammatory effects, mood enhancement, pain relief, and decreased appetite. Interestingly, CBD is reported to have an opposite effect on appetite to THC, which may be important when formulating cannabis edibles.
- Cannabigerol (CBG): This cannabinoid does not have a strong psychoactive effect but is claimed to exhibit other pharmacological properties, such as antimicrobial, antioxidant, anti-inflammatory, and pain-relief effects.
- Cannabichromene (CBC): This cannabinoid also does not have a strong psychoactive effect but is also claimed to have other beneficial pharmacological attributes, including antimicrobial, anti-inflammatory, and pain-relief effects.

All the cannabinoids are strongly hydrophobic molecules, with low water solubilities and high melting points (**Table 1**). Various other kinds of cannabinoids may be generated by chemical or biochemical processes within the plant or after the plant has been harvested. These processes may be accelerated by light, oxygen, heat, or acidic conditions as well as by other factors. The bioavailability and bioactivity of these other cannabinoids are different from those mentioned above. In addition to the cannabinoids, the cannabis plant also contains other substances, such as terpenoids like limonene, myrcene, and pinene. These molecules are volatile nonpolar molecules that contribute to the characteristic odor and taste of many cannabis products. Furthermore, many of them have strong antioxidant, antimicrobial, and anti-inflammatory activities as well as the ability to modulate the bioactivity of the cannabinoids (Huestis 2007). Consequently, the chemical

Table 1 Selected molecular and physicochemical properties of some important natural cannabinoids[a,b]

Cannabinoid	Formula	MW (Da)	Melting point (°C)	Boiling point (°C)	Density (kg/m^3)	LogP	Water solubility (mg/L)
THC	$C_{21}H_{30}O_2$	314.5	160	390	1,000	7.68	0.043
THC-OH	$C_{21}H_{30}O_3$	330.5	190	437	1,100	6.58	2.8
THC-COOH	$C_{22}H_{30}O_4$	358.5	208	437	1,100	8.41	0.0071
CBD	$C_{21}H_{30}O_2$	314.5	173	428	1,000	7.03	0.0055
CBC	$C_{21}H_{30}O_2$	314.5	153	429	1,000	8.56	0.0058
CBG	$C_{21}H_{32}O_2$	316.5	172	470	1,000	7.47	0.0038

[a]Water solubility reported at 25°C.
[b]The data are predicted using the ACD/Labs Percepta Platform–PhysChem Module (**http://www.chemspider.com/**) and the EPA (**https://comptox.epa.gov/**). It should be noted that there are often significant differences between predicted and experimental values.
Abbreviations: CBC, cannabichromene; CBD, cannabidiol; CHG, cannabigerol; MW, molecular weight; THC, Δ9-tetrahydrocannabinol; THC-COOH, tetrahydrocannabinolic acid; THC-OH, 11-hydroxy-Δ9-THC.

stability and biological activity of cannabinoids may depend on the nature of the non-cannabinoid substances extracted with them. For this reason, the chemical composition of cannabis extracts must be carefully controlled and monitored to ensure that a consistent product with a well-defined biological activity is obtained. Furthermore, systematic research is still required to understand how the different constituents of cannabis may act in concert (e.g., additively, synergistically, or antagonistically) to produce different biological effects (Worth 2019).

Cannabis oils are usually extracted from plant materials using nonpolar organic solvents such as ethanol, supercritical carbon dioxide, and, sometimes, triglyceride oils (Marangoni & Marangoni 2019). The extracts can then be further fractionated using distillation methods to obtain more consistent and well-defined cannabinoid preparations. In particular, fractionation can be used to provide preparations that have desirable flavor profiles (aroma and taste) as well as the required biological activities.

EDIBLE CANNABINOIDS: COMMON FOOD AND DRINK FORMATS

There is increasing interest in the consumption of edible forms of cannabis, with more than a billion dollars in sales being reported in the United States and Canada in 2017 (Malochleb 2019). Cannabinoids may be delivered in various food and beverage formats, including baked goods such as cookies, brownies, or cakes; candies such as chocolates, caramels, lozenges, and gummies; and beverages such as soft drinks, teas, and alcoholic drinks (Malochleb 2019). Each of these products has a different composition and structure, which influence the bioavailability and bioactivity of the encapsulated cannabinoids. In general, it is important to use a source of cannabinoids of known and reproducible composition to get a consistent flavor profile and biological effects from batch to batch (Martin et al. 2018). This requires good growing, cultivation, and processing practices to be implemented to produce a reliable source. As discussed in a section below, the pharmacokinetics of cannabinoids can be controlled by carefully manipulating the design of the food matrix or by utilizing colloidal delivery systems that can be incorporated into foods. It should be noted, however, that few companies currently appear to be specifically designing the composition and structure of their products to control their pharmacokinetic profiles.

Beverages

Beverages, e.g., tea, coffee, fruit juices, carbonated drinks, beers, wines, and hard liquor, are a popular form of cannabis edibles (Malochleb 2019). These are mainly aqueous-based products that

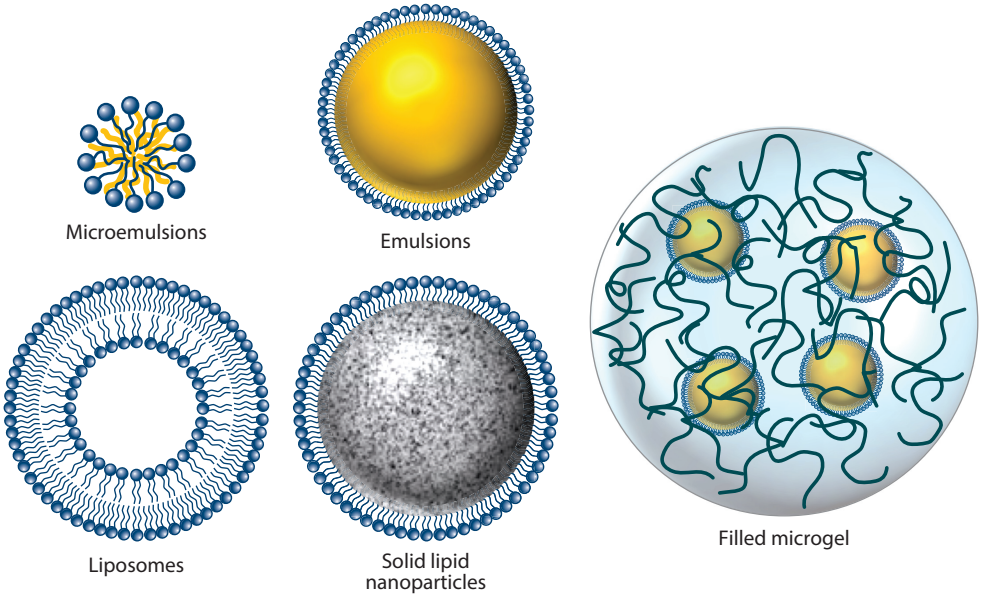

Figure 1

Schematic representation of some common types of colloidal delivery systems that could be used to encapsulate and deliver cannabinoids (*not drawn to scale*). Typically, the particles may range from a few nanometers (microemulsions) to a few thousand micrometers (filled microgels).

have relatively low concentrations of cannabinoids, typically 5–10 mg per serving. Some cannabinoids are chemically modified, either naturally inside the plant or purposely after extraction, to make them more water soluble. For instance, a hydrophilic moiety, such as a carbohydrate group, may be attached to the hydrophobic cannabinoid to increase its water solubility (Akhtar et al. 2015). This kind of cannabinoid can then be directly dispersed into an aqueous-based beverage or other food. More commonly, the highly hydrophobic cannabinoids that predominate in most cannabis plants have to be trapped inside some form of colloidal particle before they can be dispersed into water (Chen & Rogers 2019). These colloidal particles typically have a nonpolar core in which the cannabinoids are dissolved and a polar shell that contacts the surrounding water. Some examples of this kind of colloidal delivery system are highlighted in **Figure 1** and include microemulsions, nanoemulsions, emulsions, biopolymer nanoparticles, and filled hydrogel beads. Methods for creating these different delivery systems are discussed in a section below, as are their potential advantages and disadvantages. In some cases, the beverages are converted into a powdered form, usually by spray drying, which can then be dispersed in water by the consumer. In other cases, a consumer may add cannabinoids to their own beverages using a tincture, which consists of cannabis oil dissolved in alcohol. The release and absorption of the cannabinoids within the body after imbibing a cannabis-infused beverage depend on the composition, dimensions, and surface characteristics of the colloidal particles. In principle, one would expect beverages to be one of the food-matrix formats that lead to the most rapid absorption of cannabinoids by the human body.

Baked Goods

Another popular category of cannabis edibles is baked goods, such as brownies, cookies, cakes, and snack bars (Malochleb 2019). These products are typically formed by mixing sugar, flour, and fat, and possibly salt, eggs, proteins, and flavors together, and then heating in an oven to cook and

solidify them. The fat source is usually butter, margarine, or shortening. Because cannabinoids are highly hydrophobic molecules, they tend to dissolve within the fat phase of these products. Because they have a relatively high boiling point (>390°C; **Table 1**), there should be little loss due to volatilization during the baking process because the temperatures used are typically around 170–210°C (McGee 2004). Furthermore, any THC-COOH (psycho-inactive form) present in the cannabis oils used to make these products may be converted into THC (the psychoactive form) during baking. Baked goods have complex compositions and structures that may be broken down at different rates inside the human body and therefore one might expect them to have a relatively slow and delayed release of cannabinoids, but this could vary considerably from product to product, as well as from person to person depending on their mastication habits.

Confectionary

Cannabinoids are commonly delivered in the form of confectionary, such as chocolates, gummies, and lozenges, which have different compositions and structures. Chocolate contains cocoa butter, cocoa liquor, sugar, lecithin, vanilla, and possibly milk powder and flavorings (Beal 2019). In this case, the cannabinoids are mainly located within the fatty domains of the chocolate, such as within the cocoa butter. This fat may increase cannabinoid bioavailability by creating mixed micelles and chylomicrons within the GIT (see below). Gummies are soft chewy gels traditionally produced from gelatin but also from nonanimal gelling agents, such as pectin, agar, and carrageenan (McGee 2004). Gummies may also contain sugar, glucose syrup, starch, organic acids, colors, and flavors to create the required taste, texture, and appearance. Interestingly, gummies do not naturally contain a source of fat, which makes it more difficult to incorporate hydrophobic cannabinoids within them. In this case, cannabinoids may be incorporated into oil droplets or other colloidal particles first.

A problem with delivering cannabinoids using candies is that they are attractive to young children (Murti & Baumann 2017). Indeed, there have been reports in the United States of children becoming sick through eating cannabinoid-enriched candies (Vo et al. 2018). It is therefore important to take special precautions to ensure children are not exposed to these products.

PHARMACOKINETICS, BIOAVAILABILITY, AND BIOACTIVITY OF CANNABINOIDS

An understanding of how food matrices impact the bioavailability and bioactivity of cannabinoids depends on knowledge of the physicochemical and physiological events occurring when they move from the ingested food to the site of action inside the human body (McClements et al. 2015a). The potency of orally ingested cannabinoids depends on many factors, which have to be carefully considered when designing effective food-based delivery vehicles. Some of the most important factors impacting cannabinoid bioactivity are reviewed here, using findings from both cannabinoids and other hydrophobic bioactives. An understanding of the factors impacting the levels of different cannabinoids reaching systemic circulation is critical for designing cannabis edibles with consistent biological effects but is rarely considered in the current generation of commercial products.

Initial Dose

The potency of a cannabinoid depends on the initial concentration (dose) within the food or beverage. Usually, the higher the dose, the greater the potency, although saturation may occur, i.e., once all the cannabinoid receptors in the body are occupied any additional cannabinoids have little effect. The type and level of cannabinoids in a cannabis plant or extract depend on many

factors, including plant breed, maturity, and growing conditions and isolation, purification, and processing conditions.

The level of cannabinoids that can be incorporated into a cannabis edible depends on the nature of the food matrix, especially the fat content. It is much easier to incorporate high levels of hydrophobic cannabinoids into fatty foods, such as baked goods or chocolate, than into predominantly watery foods, such as soft drinks, tea, or alcoholic beverages. Furthermore, the amount that can be included is also influenced by the impact of the cannabinoids on the quality attributes of the food, such as their appearance, texture, and flavor profile.

In-Product Stability

Once incorporated into a food, cannabinoids may undergo chemical changes during production, transport, storage, and utilization, which alter their bioactivity, including their psychoactivity (Martin et al. 2018, Turner et al. 1973). These changes may increase or decrease the potency of the cannabinoids, or they may lead to the formation of harmful degradation products. Dehydration, heating, and UV light all promote decarboxylation of THC-COOH (inactive form), leading to the formation of THC (psychoactive form) (Taschwer & Schmid 2015). Freshly harvested cannabis plants contain different levels of THC-COOH and therefore processing can substantially alter their potency. The conversion of THC-COOH to THC occurs relatively slowly at 50°C but much more rapidly at 100°C and 150°C, with almost complete conversion occurring within an hour or so at the higher temperatures (Taschwer & Schmid 2015).

When cannabis extracts are incorporated into tinctures (alcohol solutions), THC-COOH can be converted into THC during long-term storage, with the conversion rate increasing with storage temperature (Peschel 2016). The long-term stability of THC and THC-COOH in resin slabs and organic solvents has been monitored under freezer, refrigerator, and ambient conditions (Lindholst 2010, Trofin et al. 2012b). THC-COOH was slowly converted to THC during storage, whereas THC and CBD levels decreased due to degradation. The conversion rates increased in the presence of light or at higher storage temperatures. The cannabinoids were almost tenfold more stable in the resin than in the organic solvent. Similar trends were reported when cannabinoids were stored in an oil under comparable storage conditions (Trofin et al. 2012a). These studies show that cannabinoids undergo chemical changes during storage that alter their bioactivity. Knowledge and control of these transformations are therefore critical to ensure an edible product is efficacious and has consistent and predictable effects. Typically, the chemical transformations of cannabinoids are monitored using chromatographic methods, such as gas or liquid chromatography, often coupled with mass spectrometry (Citti et al. 2018, Leghissa et al. 2018).

Bioaccessibility

Before any bioactive agent can be taken in by the human body, it must be in a form that can be absorbed by the layer of epithelium cells lining the GIT (Feeney et al. 2016, Wang et al. 2013). For hydrophobic bioactives, such as cannabinoids, the substances must first be released from the nonpolar domains within foods or beverages and then incorporated into the nonpolar interiors of mixed micelles, which then transport them to the epithelium cells (**Figure 2**). The mixed micelles are formed from endogenous surfactants in the body (bile salts and phospholipids) as well as exogenous surfactants from the food (free fatty acids and monoglycerides). If the oil phase in a food is digestible, which is the case for edible triglycerides (such as butter and coconut, corn, olive, palm, safflower, or sunflower oils), then it is hydrolyzed by lipases in the GIT, promoting the release of the cannabinoids. Conversely, if the oil phase is indigestible, like a mineral, flavor, or essential oil, then the cannabinoids may have to diffuse out, which is typically a much longer and less efficient process.

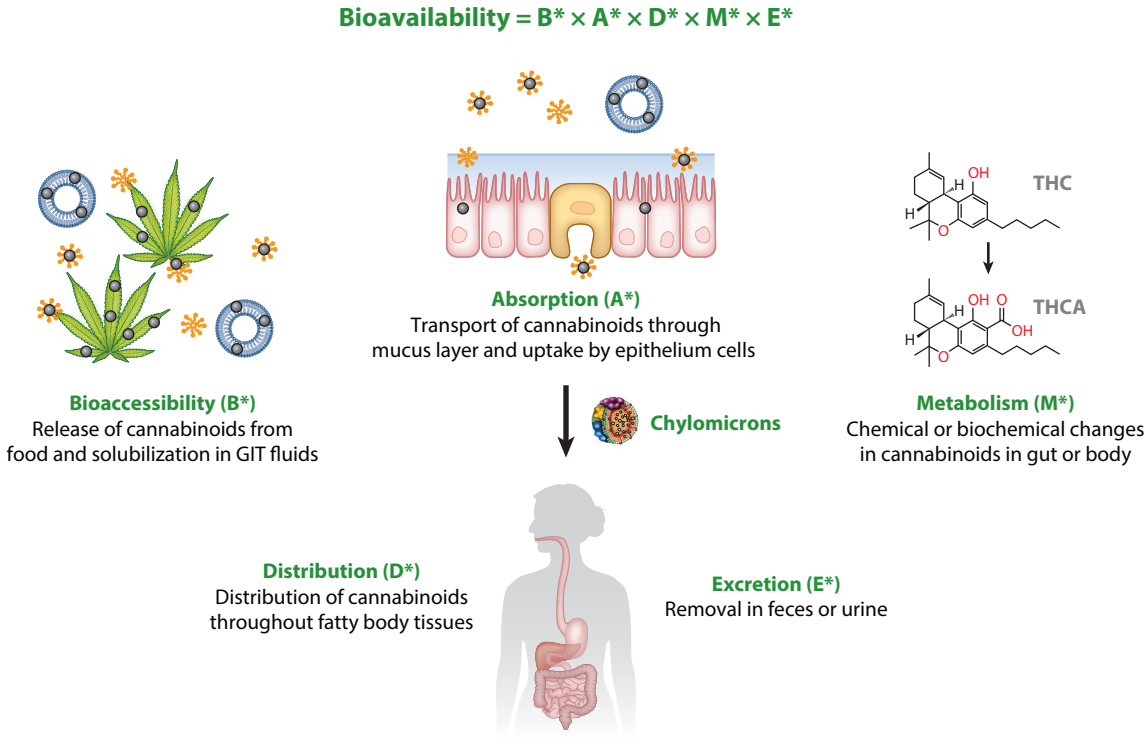

Figure 2

The overall bioavailability of cannabinoids depends on many factors, including their bioaccessibility, absorption, distribution, metabolism, and excretion. These factors are influenced by food format. Abbreviation: GIT, gastrointestinal tract.

Numerous studies have shown that the bioaccessibility of hydrophobic bioactives is increased when they are coingested with triglycerides (McClements 2018). The hydrolysis of triglycerides is initiated within the stomach by gastric lipase but predominantly occurs in the small intestine due to pancreatic lipase (Koziolek et al. 2018). Triglycerides consist of a glycerol backbone with three fatty acids attached via ester bonds. The position, length, and degree of unsaturation of the fatty acid chains attached to the glycerol backbone vary considerably among different foods, which has a pronounced influence on the bioaccessibility of coingested hydrophobic bioactives (McClements 2018). The length of the fatty acid chains influences the dimensions of the hydrophobic domains within the mixed micelles, which in turn influence the nature of the hydrophobic bioactives that can be incorporated. If the bioactive has molecular dimensions that are too large to fit inside the mixed micelles, then the bioaccessibility is relatively low. Typically, the solubilization capacity of mixed micelles increases as the chain length of the fatty acids increases and the degree of unsaturation decreases (McClements 2018). This latter effect is because highly unsaturated fatty acid chains, such as those in ω-3 oils, are highly bent, thereby reducing their length.

The impact of carrier oil type on bioaccessibility has clearly been shown for highly hydrophobic bioactives, like carotenoids (Chacón-Ordóñez et al. 2018, Kopec & Failla 2018). Carotenoids have a low bioaccessibility in mixed micelles generated by digestion of medium-chain triglycerides (MCTs), such as those found in coconut oil, because the hydrophobic domains are too small to accommodate them (Qian et al. 2012, Salvia-Trujillo et al. 2013). Conversely, carotenoids have a relatively high bioaccessibility in mixed micelles generated from long-chain triglycerides (LCTs).

To the author's knowledge, similar experiments have not been carried out using cannabinoids. Cannabinoids have different molecular structures than do carotenoids—in particular, they are shorter molecules that may be able to fit into smaller hydrophobic domains inside mixed micelles, but this needs to be tested. This phenomenon may be important because it could mean that the bioactivity of cannabinoids is impacted by the nature of the oil used to dissolve them. On the basis of previous studies with hydrophobic bioactives, it is anticipated that the bioaccessibility would be higher for digestible than nondigestible oils and would be higher for LCT oils (such as sunflower oil) than for MCT oils (such as coconut oil). It is therefore important to carry out systematic studies on the impact of oil type and level on the bioaccessibility and bioavailability of different cannabinoids using a combination of in vitro and in vivo methods.

Absorption

Once hydrophobic bioactives have been solubilized inside mixed micelles they travel through the GIT fluids and the mucus layer coating the epithelium cells (McClements et al. 2015a). When they reach the surfaces of the epithelium cells, there is a local decrease in pH, which causes the carboxyl groups on the fatty acids to become more protonated ($-COO^- \rightarrow -COOH$) (Yeap et al. 2013). As a result, the fatty acids become more nonpolar, causing the mixed micelles to break down and their fatty acids to become integrated into the cell walls where they can be absorbed. Presumably, the encapsulated hydrophobic bioactives are transferred into the epithelium cells at the same time. In addition, there may be specific fatty acid transporters on the apical side of the epithelium cells that bind the fatty acids and convey them through the cell walls (Wang et al. 2013).

After being transported into the epithelium cells, the lipid digestion products and hydrophobic bioactives are carried to the endoplasmic reticulum, where the fatty acids and monoglycerides are re-esterified into triglycerides (Dash et al. 2015, Mansbach & Siddiqi 2016). The bioactives and triglycerides are then packaged into natural lipid nanoparticles (chylomicrons) that are coated with a layer of phospholipids and proteins. The chylomicrons are released into the lymphatic system, which transports them to systemic circulation, thereby avoiding first-pass metabolism (Managuli et al. 2018; Zgair et al. 2016, 2017). Unlike LCT oils, MCT oils are primarily absorbed directly into the systemic circulation via the portal vein (rather than the lymphatic system) because of their relatively high water solubility. As a result, there may be fewer lipids available to form chylomicrons to solubilize the cannabinoids. Incorporating cannabinoids into edibles that have sufficiently high levels of digestible LCTs may therefore be advantageous for increasing their potency.

Transformation

Cannabinoids may be chemically transformed (usually degraded) as they travel through the GIT. For instance, they may undergo chemical modifications in the highly acidic environment of the human stomach (Garrett & Tsau 1974, Harvey 1999). THC stored under acidic conditions degrades fairly rapidly (half-life of 15 min at pH 1 and 37°C) into hydroxycannabidiol. In addition, cannabinoids may be metabolized by enzymes in the GIT (Cherniakov et al. 2017, Joyce et al. 2016). The chemical transformation of cannabinoids inside the human gut may affect their bioaccessibility, absorption, and bioactivity. Hence, further research is needed to better understand the impact of cannabinoid and food-matrix type on their chemical transformation within the GIT. This knowledge is important to ensure that the right quantity and form of cannabinoids reaches the intended site of action.

Distribution, Metabolism, and Excretion

After being absorbed into the bloodstream, the cannabinoids are rapidly distributed throughout the tissues of the human body (Huestis 1999). In the bloodstream, it has been estimated that

approximately 60% of the cannabinoids are associated with lipoproteins, 28% with albumin proteins, and 9% with blood cells (Harvey 1999), but these values are likely to depend on the delivery vehicle. As with other hydrophobic bioactives, the lipoproteins first become attached to the vascular endothelium (i.e., the surfaces of the cells lining the blood vessels) and then the triglycerides within them are hydrolyzed by lipoprotein lipase (Olivecrona 2016), which releases the free fatty acids, monoglycerides, and cannabinoids. The cannabinoids are then absorbed by the fatty tissues where they may remain stored for several weeks and be slowly released over time (Johnson et al. 2016). Cannabinoids may also rapidly distribute throughout the lipid bilayers of the cell walls in many tissues within the human body because of their highly lipophilic character (Huestis 1999).

Cannabinoids that enter the human body are rapidly converted into various metabolites due to the presence of metabolic enzymes mainly located in the liver (Joyce et al. 2016). The cannabinoids are susceptible to biochemical transformation through both Phase I and Phase II metabolism. THC and CBD may undergo metabolism in the liver due to the presence of metabolic enzymes, such as cytochrome P450 enzymes (Molnar & Fu 2016). THC is first converted into a hydroxylated form (THC-OH), which is also psychoactive, but then into a carboxylic acid form (THC-COOH), which is not psychoactive, as well as into various other metabolites. CBD undergoes a similar fate when it is metabolized in the body. The parent molecules and metabolites may then be excreted in the feces or urine. About one-third of ingested cannabinoids have been reported to be excreted in the urine while the other two-thirds are excreted in the feces (Joyce et al. 2016). The biochemical transformations of cannabinoids in the human body depend on the delivery route used (e.g., oral, inhalation, or transdermal), which impacts their bioavailability and bioactivity. More research is needed to understand how the composition and structure of cannabis edibles impact the distribution, metabolism, and excretion of cannabinoids.

Pharmacokinetic Profile

The overall pharmacokinetic profile of cannabinoids is governed by the various factors mentioned above. Early research showed that there was a rapid absorption period, followed by a rapid distribution period, and then a much slower elimination period (Huestis 1999). The elimination period is slow because the cannabinoids accumulate within fatty tissues from which they are only slowly released over time. As a result, cannabinoids may remain in the body for several days or weeks depending on the amount consumed and the person involved.

A schematic representation of a typical pharmacokinetic profile showing changes in blood levels of cannabinoids over time after ingestion is shown in **Figure 3**. The concentration of cannabinoids increases to a maximum value (C_{MAX}) after a certain time (T_{MAX}) and then slowly falls back to the baseline level. The area under the curve (AUC) provides information about the total amount of cannabinoids to which the body was exposed. The C_{MAX} value is typically much lower, whereas the T_{MAX} value is much longer for edibles (a few hours) than for inhalation (<10 minutes) (**Figure 4**). Furthermore, the cannabinoid blood levels take longer to return to baseline (6–20 hours) for edibles than for inhalation (3–6 hours). In addition, there may be an increase in the level of the various metabolites present, as some molecules break down and others are formed (**Figure 5**). The type and level of these metabolites depend on the delivery format. For instance, edibles may undergo more metabolism in the gut and liver than do inhaled forms (Harvey 1999).

In summary, taking cannabinoids in the form of edibles (oral) rather than by smoking or vaping (inhalation) leads to a very different pharmacokinetic profile and bioavailability. Indeed, it has been reported that between 18% and 50% of cannabinoids is bioavailable by smoking, whereas only 6–20% is bioavailable after oral ingestion (Huestis 1999). This is, however, likely to be highly dependent on the nature of the food or beverage consumed. At present, there is not a

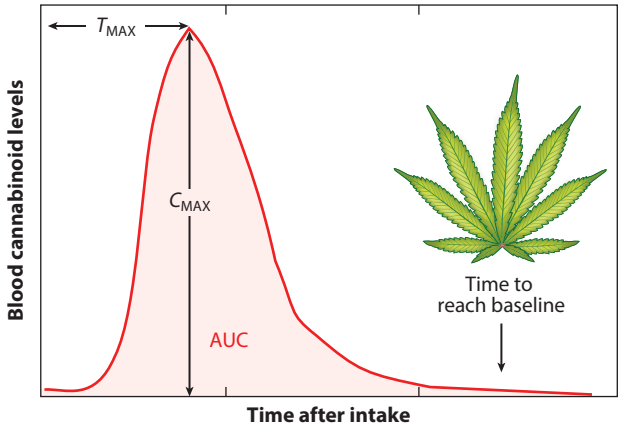

Figure 3

The pharmacokinetics of cannabinoids can be characterized by the change in the concentration in bodily fluids, particularly the blood. Abbreviations: AUC, area under the curve; C_{MAX}, maximum concentration achieved; T_{MAX}, time to reach the maximum.

clear understanding of the role of the food or beverage matrix, such as its composition, structure, and physical state, on the pharmacokinetic profile.

FACTORS AFFECTING THE ORAL BIOAVAILABILITY OF CANNABINOIDS

The effective dose of a cannabinoid someone receives can be described by the following equation:

$$\mathrm{ED} = \mathrm{Dose} \times \mathrm{BA}^{*}. \qquad 1.$$

Here, Dose is the concentration of cannabinoids in the product and BA* is the fraction in a bioavailable form. In general, the bioavailability can be described by the following

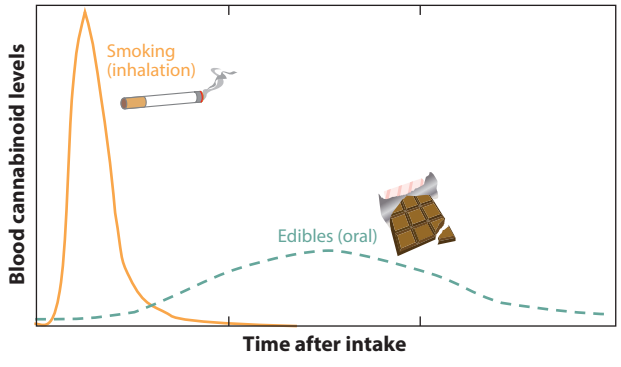

Figure 4

The pharmacokinetics of cannabinoids is very different when consumed as edibles than when inhaled. This schematic representation shows that the blood cannabinoid levels rapidly increase for smoking, then fall back quickly. Conversely, the cannabinoid levels increase more slowly and to a lesser extent for edibles. This is likely to depend on the nature of the food matrix. The time required to reach the maximum level ranges from several minutes for smoking to several hours for edibles.

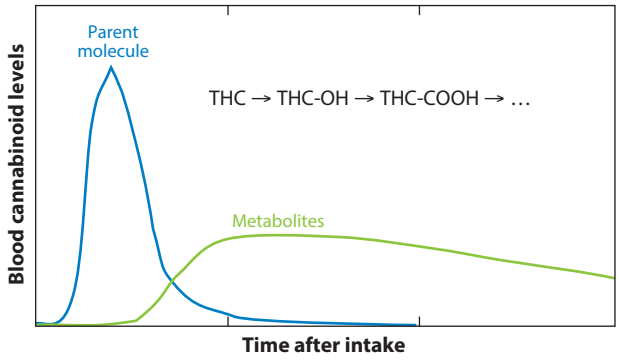

Figure 5

Cannabinoids are metabolized in the human gut and body leading to the generation of different kinds of metabolites with different biological effects. Consequently, it is important to determine the pharmacokinetics of both the parent molecule and any metabolites generated. For edibles, the timescales involved may vary from several hours to days.

expression (**Figure 2**):

$$BA = B^* \times A^* \times D^* \times M^* \times E^*. \quad 2.$$

Here, B^* is the bioaccessibility of the cannabinoids, which is the fraction released from the food matrix and solubilized within the gastrointestinal fluids in a format appropriate for absorption. For hydrophobic bioactives, this is usually assumed to be the fraction solubilized by the mixed micelles in the small intestine (Davidov-Pardo & McClements 2015, Porter et al. 2007). A^* is the absorption of the cannabinoids, which is the fraction of bioaccessible cannabinoids taken up by the epithelium cells (Lundquist & Artursson 2016, Niu et al. 2016). D^* accounts for the distribution of the cannabinoids throughout the human body after absorption, which affects their concentration at the site-of-action. There may be different sites-of-action depending on the desired biological outcome, such as psychoactive or anti-inflammatory effects. M^* represents the metabolic state of the cannabinoids, which is the fraction in a specific molecular form at the site-of-action (e.g., THC or CBD). Cannabinoids are chemically or enzymatically transformed within the human gut and body after ingestion, which alters their molecular state. Finally, E^* is the excretion of the cannabinoids, which depends on how quickly they are excreted from the human body through the urine or feces.

TESTING CANNABIS PHARMACOKINETICS AND BIOACTIVITY

The pharmacokinetics and bioactivity of edible cannabis are tested using both in vitro and in vivo methods. These methods are similar to those used to test other hydrophobic bioactives and thus only a brief description is given here.

In Vitro Activity

Insights into the potential biological activity of specific cannabinoids can be obtained using relatively simple in vitro tests, such as antimicrobial, antioxidant, free-radical scavenging, or enzyme-inhibition assays (Zengin et al. 2018). These assays are useful for rapidly screening different formulations because they can be carried out relatively quickly and cheaply. It is important,

however, not to extrapolate the results from these simple assays to real human situations because they do not account for the complexity of the human body.

Gastrointestinal Fate

The potential gastrointestinal fate of cannabinoids can be studied using digestion models that simulate the mouth, stomach, small intestine, and colon (Minekus et al. 2014). These models consist of a series of stages that mimic the incubation times, temperatures, solution conditions (pH, ionic composition, enzyme activity, and biological surfactants), and mechanical forces of the human GIT. The sample is passed through each stage of the model GIT, and changes in the composition and structure of the formulation are measured, including the bioaccessibility and metabolism of the cannabinoids.

Cell-Culture Studies

Cell-culture models, such as Caco-2 cells, are widely used to provide insights into the absorption and metabolism of hydrophobic bioactives under more realistic conditions (Duran-Lobato et al. 2016, Gleeson 2017). These techniques consist of a layer of living cells that mimic the features of the epithelium cells lining the GIT, e.g., the bilayer membrane, protein transporters, tight junctions, and enzymes. More sophisticated models may also include goblet cells that produce a mucus layer and M-cells that take up particles (Schimpel et al. 2014).

Animal Studies

Animal studies are useful for determining the pharmacokinetic profiles of cannabinoids, i.e., measuring changes in blood and tissue levels of parent molecules and their metabolites (Grotenhermen 2003). Hence, the distribution of cannabinoids throughout the tissues in the animals' bodies can be established. They can also be used to determine the impact of cannabinoids on the behavior of animals, which provides valuable insights into their effects on performance and health (Zanda & Fattore 2018). Animal studies are useful for establishing optimum cannabinoid levels for efficacy as well as to determine toxicity and lethality doses before human studies are carried out.

Human Studies

Human studies are the most informative for determining the pharmacokinetics and biological effects of cannabinoids (Grotenhermen 2003, Huestis 2007, Millar et al. 2018). Measurement of the levels of cannabinoids and their metabolites in the bloodstream over time can be used to establish pharmacokinetic profiles, whereas biomarker measurements, behavioral tests, and questionnaires can be used to establish their bioactivity and efficacy. Furthermore, analysis of the concentrations of cannabinoids and their metabolites in the urine and feces can be used to determine their metabolism and excretion. Randomized double-blind placebo control studies are required to establish the efficacy and safety of cannabinoids. However, these studies are time-consuming and expensive and may be difficult to carry out in many countries because of legal constraints.

BIOLOGICAL EFFECTS OF CANNABINOIDS

Cannabinoids have been claimed to exhibit a broad range of biological activities, which may be either beneficial or detrimental to human health. Cannabinoids have been proposed as therapeutic agents to treat a variety of diseases (Maurya & Velmurugan 2018), including cancer

(Sledzinski et al. 2018, Turgeman & Bar-Sela 2019, Velasco et al. 2016), metabolic syndrome (Waterreus et al. 2016), heart disease (Alfulaij et al. 2018, Durst & Lotan 2011), diabetes (Gruden et al. 2016, Horvath et al. 2012, Sidney 2016), obesity (Rossi et al. 2018), and mental health (Newton-Howes 2018, Walsh et al. 2017). Conversely, they have also been claimed to have adverse effects on physical health, including promoting heart disease (Pacher et al. 2018) and chronic bronchitis (Schwartz 2018) and undermining mental health (Martin et al. 2018, Richardson 2010, Walsh et al. 2017) The beneficial and adverse effects of cannabinoids are related to the dose, type, and delivery format of cannabis that is consumed. In most cases, however, systematic clinical trials have not yet been carried out to establish these effects, and thus it is difficult to disentangle cause-and-effect relationships. One of the main factors contributing to this problem is that many national governments have strict regulations that constrain academic research activities in this area (Abrams 2018). This may change as regulations governing the use of cannabinoids are relaxed. Furthermore, many studies have been carried out using edible cannabinoid formulations whose dose and chemical composition are not clearly defined. In addition, the impact of food-matrix effects on bioavailability and bioactivity are often not accounted for when edibles or other orally ingested formulations are studied. As a result, it is often not easy to compare results from one study to another.

In 2017, the National Academy of Sciences (NAS) carried out a systematic review of the potential health effects of cannabis and cannabinoids (Natl. Acad. Sci. 2017). The NAS found evidence for multiple therapeutic effects of cannabinoids in treating certain health conditions. Cannabinoids appeared to be effective at treating nausea and vomiting in adults undergoing chemotherapy, reducing pain symptoms in adults with chronic pain issues, and reducing spasticity symptoms in adults with multiple sclerosis. The study found no clear evidence that the use of cannabis promoted heart attack, stroke, diabetes, or cancer. The use of cannabis was, however, found to increase the risk of injury and death, such as being in a vehicular accident. There was also some evidence that cannabis could impair both short- and long-term learning, memory, and attention functions, thereby influencing academic achievement and employment prospects. Regular cannabis use was also linked to a variety of mental health issues, such as schizophrenia, bipolar disorders, and suicidal thoughts. One of the main conclusions of this review was that there was a lack of high-quality systematic studies on the health effects of cannabinoids using well-designed randomized clinical trials. Funding for these kinds of studies should, therefore, be a priority in the future.

An important issue to consider when designing cannabis edibles is the potential for synergistic or antagonistic effects between different types of cannabinoids as well as with non-cannabinoid components, such as drugs, nutraceuticals, and food ingredients. Studies have shown that cannabinoids can interact with enzymes or transporters that play an important role in the action of certain drugs, which can either increase or decrease their efficacy (Lucas et al. 2018, Martin et al. 2018). Systematic studies are required to examine these potentially synergistic or antagonistic effects so that reliable formulations that do not have adverse health effects can be developed. Furthermore, there are variations in the response of different people to the same formulation, depending on their genetics, metabolism, microbiome, lifestyle, and body composition (Martin et al. 2018). Again, few rigorous studies have been carried out to understand this phenomenon, which means that it is difficult to develop edible products with predictable effects for broad populations. Another area in which there is still a poor understanding of the gastrointestinal fate and biological effects of cannabis edibles is the fraction of different cannabinoids that reach the colon as well as their impact on the gut microbiota and human health. A recent review highlighted that there was a link between the endocannabinoid system, the gut microbiome, and human health (Cani et al. 2016). Consequently, more systematic studies need to be carried out on the impact of cannabis consumption on the gut microbiome and its implications for health. For all these reasons, the advice given to people starting to use cannabis edibles is start low and go slow.

METHODS OF CONTROLLING CANNABINOID PHARMACOKINETICS

The dose, cannabinoid composition, route of entry, and delivery vehicle format all influence the pharmacokinetics of cannabinoids. Consequently, these parameters can be manipulated to develop cannabis edibles with enhanced efficacy and reliability.

Food-Matrix Design

Studies with other types of hydrophobic bioactives have shown that food-matrix effects can have a large impact on their pharmacokinetics and bioavailability (McClements et al. 2015a,b). There have, however, been far fewer systematic studies of food-matrix effects on the pharmacokinetics of cannabinoids in humans. In one of the few studies in this area, the pharmacokinetic profile of cannabinoids was measured after humans were fed cannabis-loaded brownies with different doses: 10, 25, and 50 mg THC (Vandrey et al. 2017). The maximum blood levels (C_{MAX}) attained were relatively low for all three doses (1–3.5 ng/mL), especially when compared to those achieved after smoking cannabis (15–192 ng/mL). In addition, the time to reach the peak in blood levels (T_{MAX}) was much longer for the brownies (2–3 hours) than for inhalation (<10 minutes). Furthermore, the cannabinoid levels in the blood took much longer to return to baseline for brownies (6–20 hours) than for smoking (3–6 hours). These findings are summarized schematically in **Figure 4**. A recent meta-analysis of human studies on the pharmacokinetics of CBD using various delivery routes, e.g., intravenous and oral administration as well as smoking and nasal sprays, also reported that edible forms of cannabis led to slower and less pronounced blood levels (Millar et al. 2018). However, these researchers also pointed out that there is currently a lack of good studies in this area.

In an animal feeding study with rats, researchers showed that ingesting cannabinoids (THC and CBD) with lipids substantially increased their bioavailability (2.5- and 3.5-fold, respectively) (Zgair et al. 2016). This effect was attributed to the impact of the ingested lipids on the intestinal bioaccessibility and lymphatic transport of the hydrophobic cannabinoids (Zgair et al. 2016, 2017). The consumption of food has also been shown to increase the bioavailability of THC and CBD administered through a nose spray (Stott et al. 2013).

One study with infants found that cannabinoids could be transferred from a mother to an infant through her breast milk (Perezreyes & Wall 1982). Indeed, for heavy cannabis users, there was almost an eightfold higher level of cannabinoids in the mother's milk than in her blood serum. Presumably, the highly hydrophobic cannabinoids were located within the nonpolar interior of the milk-fat globules. Studies with other hydrophobic bioactives have shown that their bioavailability is higher when encapsulated in small digestible fat droplets (McClements 2018). Consequently, one would expect the infant could adsorb high levels of the cannabinoids in the milk, which may lead to adverse health effects in the child.

Excipient Foods

Excipient foods have been introduced as a means of increasing the bioavailability of hydrophobic bioactives in foods, drugs, and supplements (McClements & Xiao 2014, McClements et al. 2015b). An excipient food would not contain any cannabinoids itself but would be specifically designed to increase the bioavailability of cannabinoids ingested at the same time. For instance, the excipient food may contain lipid droplets that rapidly break down and form mixed micelles that solubilize the cannabinoids and carry them to the epithelium cells where they are absorbed. Furthermore, the lipids may stimulate the production of chylomicrons in the epithelium cells, which facilitate transport of the cannabinoids into the systemic circulation. In addition, ingredients can be

included in excipient foods that modulate the metabolism and absorption of cannabinoids. Previous studies suggest that emulsions are particularly suitable for use as excipient foods because many different ingredients can be incorporated to increase the bioavailability (McClements et al. 2015b). For example, an excipient food could be a specially formulated fluid shot or candy that would be taken before consuming the cannabis edible to modulate its pharmacokinetic profile and biological effects.

Delivery Systems

A wide variety of particle-based platforms have been developed to encapsulate and deliver hydrophobic bioactives (McClements 2014, Vincekovic et al. 2017), such as nonpolar drugs, vitamins, and nutraceuticals (**Figure 1**). Many of these platforms are also suitable for the encapsulation and delivery of hydrophobic cannabinoids. Typically, these platforms involve trapping the cannabinoids into some kind of colloidal particle, which is then incorporated into a food or beverage. Edible colloidal particles may vary in dimensions from a few nanometers to a few millimeters depending on how they were prepared. In general, colloidal delivery systems differ in terms of the ingredients and manufacturing equipment needed to produce them, the costs involved, their robustness in different food matrices, and their impact on food-matrix properties, such as appearance, texture, and flavor. Furthermore, they vary in terms of their potential impact on the bioavailability and pharmacokinetic profiles of the cannabinoids after ingestion. For instance, they may be designed to give either burst or prolonged release. Some of the advantages and disadvantages of the various delivery systems covered are highlighted in **Table 2**. In this section, the structure, formation, and properties of some of the colloidal delivery systems—microemulsions, emulsions, liposomes, and microgels—that are most likely to be suitable for cannabinoids are provided.

Microemulsions. Microemulsions typically contain the smallest particles of all colloidal delivery systems commonly used: $D = 5–50$ nm (Huang et al. 2010, Narang et al. 2007). Microemulsions form spontaneously when surfactants, and sometimes other components such as cosurfactants, cosolvents, or oils, are mixed with water. The main driving force for their spontaneous formation is the hydrophobic effect (Lazzari et al. 2010, Murgia et al. 2013). Microemulsions are thermodynamically favorable so their structure should not change during storage unless there is an alteration to environmental conditions such as temperature or composition. Structurally, the particles in microemulsions have a hydrophobic core and a hydrophilic shell (**Figure 1**). The core is formed from the nonpolar tails of the surfactants, whereas the shell is formed by their polar head groups. Nonpolar bioactives, such as cannabinoids, can be solubilized within the hydrophobic cores, provided they are not too large (Yao et al. 2014).

There are many potential advantages and disadvantages of using microemulsions as delivery systems of cannabinoids. Typically, no specialized equipment is required to create them. Once the production conditions, such as composition and temperature, have been optimized then the ingredients can simply be mixed and the microemulsion will form spontaneously. The small particles in microemulsions only scatter light weakly and so they appear optically clear, which is an advantage for some food and beverage applications. They also have a long shelf-life because they are thermodynamically stable. However, microemulsions are typically formulated using high levels of synthetic surfactants, which is undesirable because of cost, taste, toxicity, and clean-labeling concerns. This problem can sometimes be overcome by using natural surfactants, such as caseins or saponins, to formulate microemulsions (Haham et al. 2012, Menendez-Aguirre et al. 2014, Mitra & Dungan 2001). Another problem is that microemulsions often have a fairly low loading capacity due to the small size of their hydrophobic cores.

Table 2 Characteristics of major types of colloidal delivery systems that may be suitable for the encapsulation and controlled release of cannabinoids in edibles[a]

Delivery system	Properties	Advantages	Disadvantages
Microemulsions	Self-assembled surfactant-based particles with a hydrophobic core and hydrophilic shell. $D = 5$–50 nm	Thermodynamically stable; easy to fabricate; good stability; optically clear; rapid release	High synthetic surfactant levels; low loading capacity; taste and toxicity issues
Emulsions	Lipid-based particles consisting of a liquid hydrophobic core coated with an emulsifier shell. $D = 100$ nm to 100 μm	Fairly easy to fabricate; can be produced on a large scale; range from optically clear to opaque; high loading; all-natural possible	Thermodynamically unstable; susceptible to droplet aggregation and creaming
Solid lipid nanoparticles	Lipid-based particles consisting of a solid hydrophobic core coated with an emulsifier shell. $D = 100$ nm to 100 μm	Provide extra protection to chemically labile molecules; can retard release; high loading; all-natural possible	Thermodynamically unstable; susceptible to particle aggregation and sedimentation; bioactive may be expelled when particle formed
Liposomes	Phospholipid-based particles with a hydrophilic watery core, surrounded by hydrophobic shell, with a hydrophilic surface. $D = 50$ nm to 50 μm	Can load hydrophilic and lipophilic molecules in one system; all-natural possible	Poor stability in many commercial products; high phospholipid costs
Microgels	Biopolymer-based particles consisting of a porous network of polymer molecules; lipid droplets can be trapped inside. $D = 50$ nm to $2{,}000$ μm	Can control release in the gastrointestinal tract; can protect chemically labile molecules; all-natural possible	Large particles may affect stability and sensory attributes; sometimes difficult to produce on a large scale

[a]The particle diameters (D) given are typical ranges found in foods and beverages.

Studies have shown that cannabinoids, such as THC, can be successfully encapsulated within microemulsions (Lazzari et al. 2010, Murgia et al. 2013). The authors reported that the cannabinoids were incorporated within the hydrophobic core of the microemulsions. These THC-delivery systems were effective at reducing pain in a mice model when administered by gavage to the animals' stomachs. Furthermore, they gave faster pain relief than conventional formulations due to their rapid absorption. The ingredients used to formulate these microemulsions were not food-grade; however, there is no reason why similar delivery vehicles could not be constructed using food ingredients.

Emulsions. Emulsions are thermodynamically unstable colloidal dispersions formulated from two immiscible fluids, typically oil and water (Liu et al. 2015). Oil-in-water (O/W) emulsions, which consist of small oil droplets dispersed in water (**Figure 1**), are the most versatile for incorporating hydrophobic cannabinoids into the majority of foods and beverages. This type of colloidal dispersion can be categorized in terms of the mean particle diameter as either a nanoemulsion ($D <$ 100 nm) or conventional emulsion (100 nm $< D <$ 100 μm) (McClements 2012). Both types can be converted into a powdered form by spray drying, which enables them to be incorporated into dried products.

The creation of a successful emulsion-based product requires careful selection of ingredients and production methods. Emulsions can be produced using oil, water, and an emulsifier, but other

ingredients may also be included to modulate their quality attributes, including thickeners, gelling agents, weighting agents, ripening inhibitors, chelating agents, antioxidants, preservatives, colors, and flavors (Liu et al. 2015).

Various processing methods are available for emulsion production, which can be divided into high- or low-energy methods (McClements & Rao 2011). High-energy methods employ specially designed homogenizers that subject the oil and water phases to intense disruptive forces to break them up and create small droplets, including high-shear mixers, colloid mills, high-pressure valve homogenizers, microfluidizers, and sonicators (Liu et al. 2015). A hydrophilic emulsifier is usually added to the water phase prior to homogenization at a level high enough to cover all the droplets created. Careful selection of the emulsifier is critical for the formation of emulsions with the required performance (McClements & Gumus 2016). Emulsions can also be produced using low-energy methods, which utilize the fact that tiny oil droplets can be spontaneously formed from certain types of surfactant, oil, and water phases when the system composition or temperature is altered in a specific fashion (Komaiko & McClements 2016). Two of the most widely employed low-energy methods for this purpose are the spontaneous emulsification (SE) and phase inversion temperature (PIT) approaches. For low-energy methods, it is important to establish the system composition that will lead to the formation of an emulsion with small droplets that are stable over time.

Each homogenization approach has its benefits and limitations. High-energy methods require specially designed mechanical homogenizers, which are often costly to procure and run. Conversely, they are suitable for large-scale commercial production and are capable of producing emulsions from a broad range of food ingredients, including natural emulsifiers. Low-energy methods require simple mixing devices and so they are inexpensive and easy to implement. Conversely, only a narrow range of surfactants and oils can be used to prepare emulsions by this method. In the food industry, high-energy methods are much more common than low-energy ones.

There have been only a few studies on the encapsulation of cannabinoids in emulsions or nanoemulsions. Recently, researchers compared low-energy (spontaneous emulsification) with high-energy (high-shear mixing) methods of producing hemp emulsions (Mikulcova et al. 2017). The authors used different levels and ratios of two nonionic surfactants to form the emulsions, one hydrophilic (Tweens) and one hydrophobic (Spans). The smallest oil droplets (~150 nm) were obtained using the high-energy method when the ratio of surfactants provided a hydrophile–lipophile balance value of approximately 9. A major limitation for the practical application of this approach is that 10% of the synthetic surfactant was required to homogenize 5% of the hemp oil, which would cause challenges in terms of toxicity, cost, and taste. Researchers have also shown that the addition of natural berry polyphenols to hemp emulsions protected the hemp oil from oxidation (Raikos et al. 2015). Although hempseed oil comes from the same plant as cannabinoids (*C. sativa*) it is isolated from a different part of the plant (the seeds) and does not contain psychoactive substances. Instead, it mainly consists of triglyceride oils rich in polyunsaturated fatty acids.

THC has been encapsulated in emulsions containing small oil droplets ($D < 140$ nm), which were shown to be stable to sterilization and long-term storage (nine months) (Muchtar et al. 1992). THC has also been encapsulated within solid lipid nanoparticles (SLNs) prepared by creating an emulsion first and then crystallizing the oil phase (Muchtar et al. 1992). A cannabinoid derivative (CB13) has been encapsulated within lipid nanoparticles designed for oral delivery (Duran-Lobato et al. 2016). These nanoparticles were fabricated using a solvent-emulsion evaporation method from cannabinoids, lipids, lecithin, and surfactants. An animal model has been used to study the bioactivity of a synthetic cannabinoid encapsulated within emulsions (Naveh et al. 2000).

There is clearly a need for more systematic research on the encapsulation and delivery of cannabinoids using food-grade emulsions and nanoemulsions. It should be possible to form all-natural emulsions with good stability and tunable pharmacokinetic profiles. Indeed, multiple companies are already producing cannabis edibles using nanoemulsions to encapsulate the cannabinoids.

Liposomes. Liposomes, also known as vesicles, consist of one or more phospholipid bilayers arranged into an onion skin–type structure (**Figure 1**) (Maherani et al. 2011, Mozafari et al. 2008, Sawant & Torchilin 2010). The formation of liposomes is primarily a result of hydrophobic interactions. Typically, liposomes have dimensions ranging from approximately 50 nm to 50 μm, depending on the composition and preparation method used. Hydrophobic cannabinoids can be trapped inside the nonpolar regions formed by the phospholipid tails in the lipid bilayer (Daeihamed et al. 2017). One limitation of using liposomes is their poor physical stability—they often break down when incorporated into food matrices or when processed (Daeihamed et al. 2017, Silva et al. 2015, Taylor et al. 2005). These problems can sometimes be overcome by incorporating cholesterol into the phospholipid bilayers to increase their rigidity (Takechi-Haraya et al. 2016) or by coating the liposomes with biopolymers (Chun et al. 2013, Laye et al. 2008). Liposomes can be fabricated using a range of methods, varying in cost, time, ease, and equipment needs. Many methods employed within research laboratories are unsuitable for large-scale production of edible food or beverage products, e.g., solvent evaporation methods. Even so, some of the methods used in the laboratory can also be used for large-scale production, e.g., microfluidization.

Liposomes have been widely used to encapsulate, protect, and deliver other types of hydrophobic bioactives intended for oral ingestion, including curcumin (Nguyen et al. 2016), β-carotene (Michelon et al. 2016, Toniazzo et al. 2014), lutein (Zhao et al. 2017), lycopene (Fan et al. 2011), vitamins (Bochicchio et al. 2016), and resveratrol (Caddeo et al. 2013, Hung et al. 2006, Isailovic et al. 2013). Liposome encapsulation can be used to increase both the stability and oral bioavailability of these bioactives (Roy et al. 2016, Takahashi et al. 2009). The author could, however, find very few studies on the utilization of liposomes to encapsulate cannabinoids, although mathematical modeling of their release kinetics suggests they should be suitable (Marangoni & Marangoni 2019). Early studies showed that cannabinoids could be successfully incorporated into lipid bilayers prepared from phospholipids (Hillard et al. 1985, Mavromoustakos et al. 1990), which does suggest that liposomes have potential for cannabinoid delivery.

Biopolymer particles. There is a broad range of colloidal delivery systems that can be fabricated from natural polymers such as proteins and polysaccharides, including protein nanoparticles, coacervates, microgels, and hydrogel beads (McClements 2017a) (**Figure 1**). Hydrophobic bioactives, like cannabinoids, are usually incorporated into a hydrophobic biopolymer matrix (such as zein or gliadin) or solubilized inside fat droplets that are then incorporated into a hydrophilic biopolymer matrix (such as calcium alginate). Biopolymer particles contain cross-linked networks of biopolymer molecules that may have more or less water trapped inside (Joye & McClements 2014; Matalanis et al. 2011; Torres et al. 2016, 2017). The cross-links holding the biopolymer molecules together may be physical forces (such as van der Waals, hydrogen bonding, electrostatic, or hydrophobic) or nonphysical forces (covalent bonds). Biopolymer particles can range in size from less than 100 nm to greater than 1,000 μm depending on the composition and fabrication method used. They can be assembled from a wide range of food-grade proteins and polysaccharides using a diverse range of fabrication techniques, including antisolvent precipitation, injection-gelation, phase separation, and template methods (Matalanis et al. 2011, McClements 2017b). As a result, biopolymer particles with different compositions, structures, and functional properties can be designed for specific applications. Different fabrication techniques have their advantages and

disadvantages depending on their cost, simplicity, potential for scale-up, production capacity, and ability to create particles with well-defined properties.

Many kinds of hydrophobic bioactives have been encapsulated within biopolymer microgels to increase their stability or bioavailability, including carotenoids (Zhang et al. 2016), curcumin (Zhang et al. 2016), resveratrol (Das et al. 2011), and ω-3 oils (Chen et al. 2017). One would therefore expect similar approaches could be used to encapsulate cannabinoids in cannabis edibles. Some studies suggest this approach might work. THC has been successfully encapsulated within biodegradable polymeric microparticles fabricated using an emulsion-solvent evaporation method (de la Ossa et al. 2013). THC encapsulated in powdered beta-cyclodextrin complexes was shown to have a higher bioavailability (16%) than when dissolved in ethanol solutions (1.3%) (Mannila et al. 2006). Encapsulation of CBD in poly-epsilon-caprolactone polymer microspheres (20–50 μm) slowed down their release compared to the nonencapsulated form (de la Ossa et al. 2012). Most of the previous studies have used non-food-grade ingredients, but food-grade biopolymer particles could certainly be developed for cannabis edibles. Encapsulation in biopolymer particles may be particularly suitable for applications in which a prolonged cannabinoid release profile is required.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

The regulations restricting the utilization of medical and recreational cannabinoids are changing rapidly in many countries and states. This has led to a surge of commercial interest in the development of edible forms of cannabis. There is, however, currently little understanding of the impact of food-matrix effects on the pharmacokinetics and bioactivity of cannabinoids. This is problematic because it means it is often difficult to define a dose that is both efficacious and safe for the intended consumer. For medical cannabis products, it is important that the formulation exhibits the desired bioactivity over a particular timescale. For instance, for fast pain relief, it may be necessary to use a formulation that provides rapid release of the cannabinoids, whereas for prolonged pain relief it may be better to have a formulation that provides sustained release. The pharmacokinetic profile may also be important for determining the safety and testing of cannabinoid edibles. For instance, a sustained-release edible may lead to high levels of cannabinoids in the blood over an extended period, which could affect a person's ability to operate a motor vehicle or to safely and effectively carry out mental or manual tasks at work. There is clearly an urgent need for more funding to support research in this area and for a relaxation of the regulations on carrying out this kind of research.

Over the past decade or so, there have been extensive studies on the impact of food-matrix effects on the pharmacokinetics and bioavailability of other highly hydrophobic substances intended for oral ingestion, such as fats, vitamins, and nutraceuticals. The knowledge gained from these studies will be of great use in the development of more consistent and reliable cannabis edibles that have tunable properties, such as burst or sustained release, depending on the application.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. After submitting this article, the author began consulting for a company that aims to produce cannabis-enriched beverages.

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