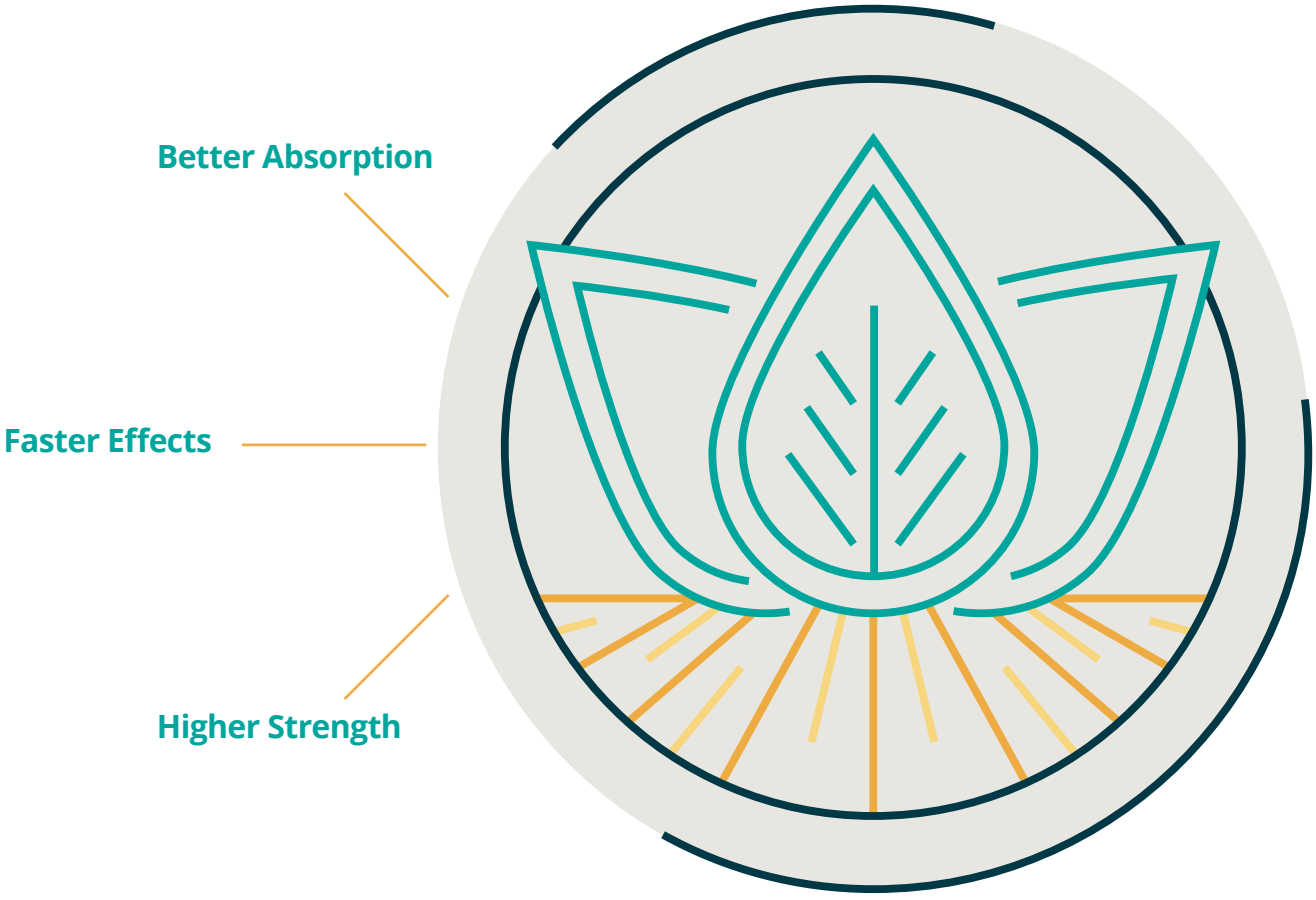
REALIZE

2020 White Paper

Making More Effective Cannabis Infused Products with Improved Bioavailability



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Potency Equivalents of Cannabinoids for Different Delivery Systems*

Cannabis Extract
No Delivery System

4x more potent
Lipid Delivery System

100x more potent
Emulsion Delivery System
Realize™

Figure 1: Oral dosing equivalents of different types of cannabidiol (CBD). Comparing the relative bioavailability of CBD with CBD in an emulsion delivery system and a lipid delivery system. *Data adapted from the study: Pharmacokinetics of CBD Taken Orally.

What is bioavailability?

Bioavailability is the proportion and rate a drug or active ingredient enters the bloodstream. Once in the bloodstream it can access the site of action and illicit a physiological response.

Why is bioavailability important for cannabis infused products?

Bioavailability directly influences the effects of cannabis infused products impacting their time of onset, intensity and duration. Designing products with bioavailability in mind aids in creating optimal dosages while minimizing any unwanted side effects.

Infused products have low bioavailability

Cannabis edibles and oral dosage forms suffer from low bioavailability of cannabinoids. Cannabinoids are the active ingredients found in the plant and its extracts. When taken orally only 4%-12% of the total cannabinoids consumed reach the bloodstream [1]. In comparison, smoking cannabis can reach a bioavailability above 50% within minutes of inhalation [2-5]. Furthermore, the poor bioavailability of cannabinoids results in delayed onset; effects are typically felt between 60 to 120 minutes before [6].

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How does low bioavailability impact the consumer?

Waste money:

Only a fraction of the cannabinoids in edibles or oral dosages reach the blood stream; over 88% of the active ingredients are wasted. Hence a consumer that pays $60 for 1000 mg of cannabidiol (CBD) is only receiving the benefits from the 40 to 120 mg of the CBD that is actually absorbed. Similarly, a consumer that buys a marijuana edible for $20 that has 100 mg of Δ 9-tetrahydrocannabinol (THC) only receives the benefit from the 4 to 12 mg that are absorbed.

Higher dosages:

In some cases, the low bioavailability requires the consumer to ingest large doses before effects are felt. High dosages of cannabinoids can cause digestive issues such as diarrhea, nausea, abdominal pain, or vomiting. In particular diarrhea is a common side effect when CBD oil is consumed in large quantities [7]. Increasing bioavailability reduces the required dosage and can mitigate certain side effects.

Delayed effects:

The delayed effects can cause consumers to prematurely consume additional doses, resulting in intense and unpleasant experiences.

What causes the low oral bioavailability of cannabinoids?

Cannabinoids are lipophilic (fat soluble) and have low aqueous solubility [8, 9]. Lipophilic drugs with low solubility, such as cannabinoids often have low oral bioavailability [10]. A deeper look at the body's digestive system reveals that there is an unstirred water layer (UWL) that lines the gastrointestinal tract (GIT). The UWL acts as a barrier to the absorption of lipophilic materials such as cannabinoids. Thus prior to reaching the absorptive surfaces of the GIT a cannabinoid must become water dispersible allowing it to permeate the UWL. Naturally this process of cannabinoid solubilization is inefficient leading to low oral bioavailability.

How can cannabis oral bioavailability be increased?

It is possible to increase the oral bioavailability of cannabinoids by using drug delivery systems that promote solubilization. Lipid delivery systems and oil-in-water (O/W) emulsion delivery systems are known to increase the bioavailability of lipophilic drugs through solubilization [10-12]. A pharmacokinetic study titled: Pharmacokinetics of CBD Taken Orally (PK Oral CBD) was conducted to evaluate the impact of these delivery systems on the bioavailability of a model cannabinoid: CBD. In the PK Oral CBD study, three formulas were compared: CBD with no delivery system, CBD in a lipid delivery system and CBD in Realize™ emulsion delivery system. The results of the PK Oral CBD study are presented in Figure 2.

CBD Tested in the PK Oral CBD Study

CBD
No Delivery System

CBD
Lipid Delivery System

CBD
Realize™ Emulsion Delivery System

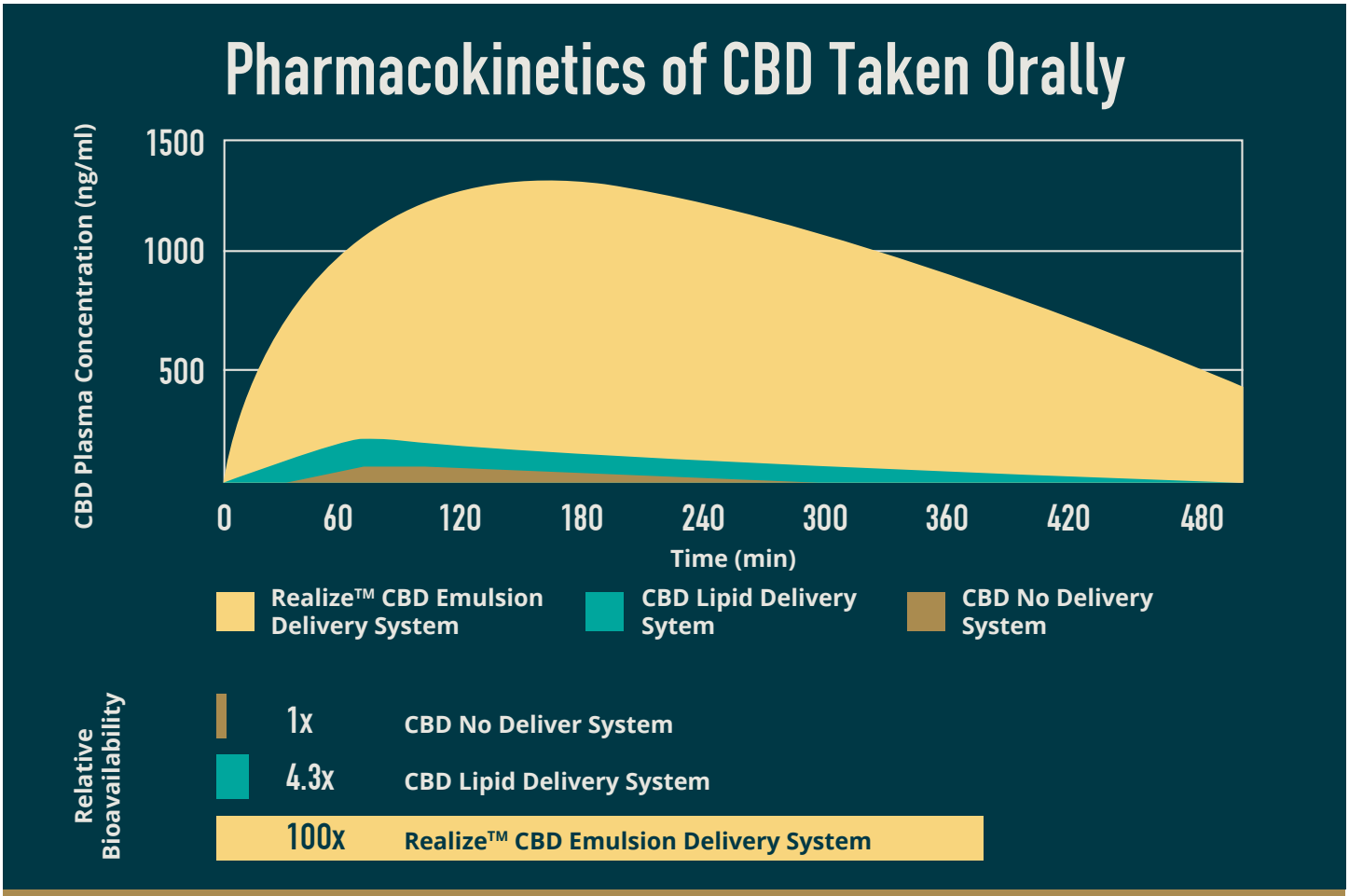

Figure 2: Pharmacokinetics of CBD Taken Orally and the relative bioavailability of CBD compared to CBD in an emulsion delivery system and CBD in a lipid delivery system. See Appendix A.1 for the details of the study and Appendix A.2 for the calculation of relative bioavailability.

What happens when CBD is ingested without a delivery system?

When ingested, CBD has an extremely low bioavailability compared to the lipid delivery system and emulsion delivery systems as shown in Figure 2. This finding indicates that CBD is not being solubilized and effectively absorbed when consumed without a delivery system. Figure 3a illustrates how CBD in its raw form is unable to penetrate the UWL inhibiting absorption.

How do lipid carriers improve bioavailability?

Triglycerides are a great starting point for cannabis formulations because they don't pose any safety concerns and dissolve cannabinoids at high concentrations [13,14]. When digested, triglycerides and cannabinoids are combined with bile and pancreatic juices to form mixed micelles [10,15]. Mixed micelles solubilize cannabinoids allowing them to penetrate the UWL and absorb in the GIT. Figure 3b illustrates the formation of mixed micelles containing triglycerides and cannabinoids that are able to penetrate the UWL and absorb in the GIT.

It is important to note that non-digestible lipid carriers do not form mixed micelles and have been known to reduce the bioavailability of lipophilic compounds [13].

In the PK Oral CBD study, olive oil was chosen as the triglyceride lipid carrier for CBD. The lipid delivery system increased the oral bioavailability of CBD 4.3x compared to CBD with no delivery system.

How do emulsions improve bioavailability?

O/W emulsions are dispersions of oil droplets in an aqueous solution that are stabilized against separation by emulsifiers creating micelles or liposomes. Micelles are small particles that have a hydrophobic (water repelling) core surrounded by a hydrophilic (water compatible) shell. Liposomes are vesicles having an aqueous core surrounded by a lipid bi-layer with a hydrophobic interior and a hydrophilic exterior.

The emulsion used in the PK Oral CBD study was a proprietary micelle nanoencapsulation technology developed by the team at Realize™. A representation of the micelle structure is shown in Figure 3c for the emulsion delivery system. Micelles containing CBD are able to directly penetrate the UWL and absorb in the GIT. Figure 3c illustrates the micelle penetration of the UWL and absorption into the GIT for the emulsion delivery system.

In the PK Oral CBD study, an emulsion delivery system was used to increase the oral bioavailability of CBD. This delivery system increased the bioavailability of CBD 100x compared to CBD without a delivery system and 25x compared to CBD in a lipid delivery system.

Reducing onset time

An interesting finding from the PK Oral CBD study is that the emulsion delivery system achieved a higher plasma concentration of CBD (342 ng/ml) in 15 minutes compared to the maximum plasma concentrations achieved for CBD without a delivery system (26 ng/ml at 60 minutes) as well as CBD in a lipid delivery system (134 ng/ml at 60 minutes). Neither CBD without a delivery system nor CBD in the lipid delivery system observed any CBD in the bloodstream 15 minutes after ingestion. This finding is a strong indication that the emulsion delivery system can reduce onset times by delivering higher concentrations of cannabinoids to the bloodstream in 1/4th of the time.

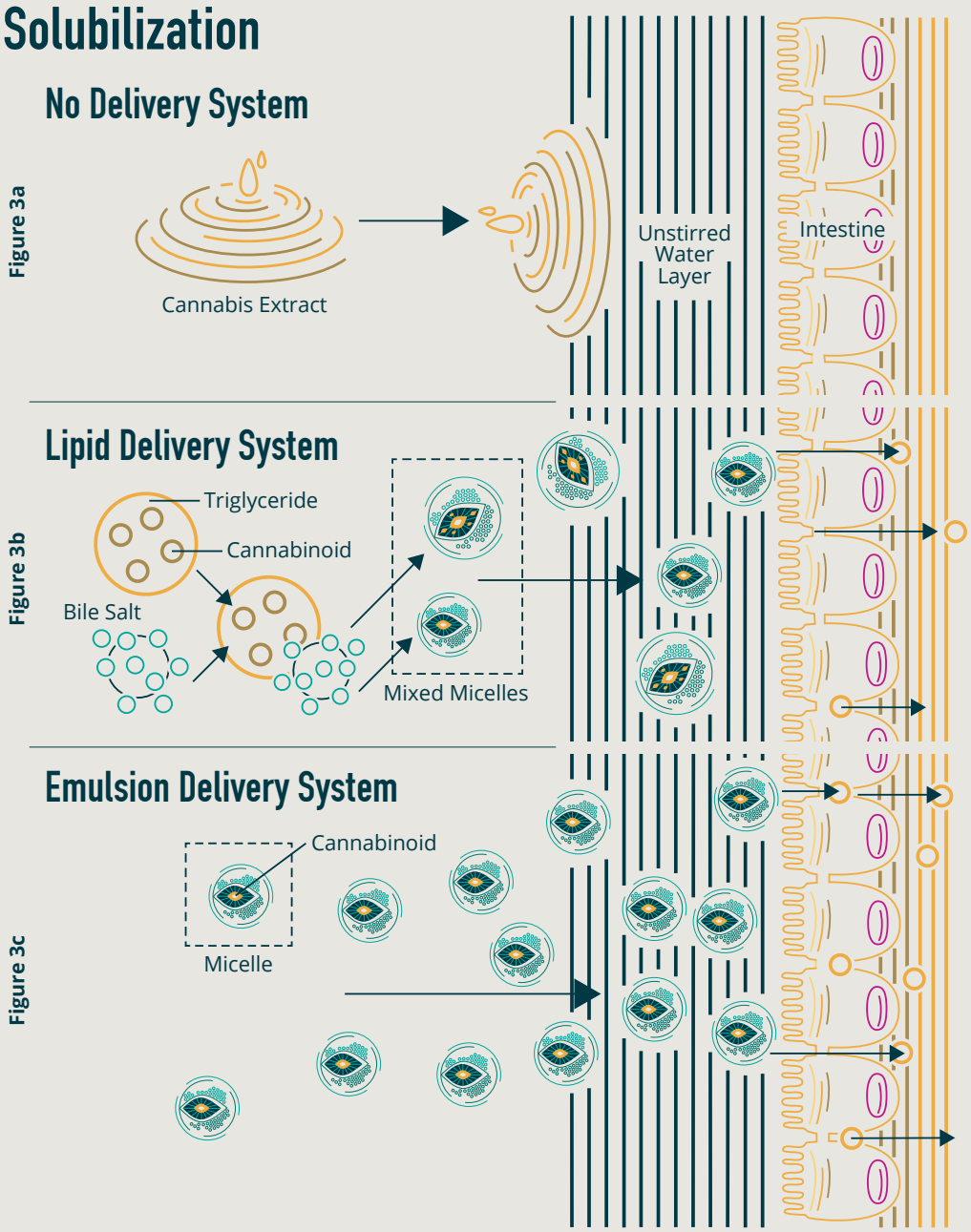

Figure 3: Solubilization and absorption of cannabinoids using different delivery systems.

Figure 3a: Cannabis extract without a delivery system failing to be solubilized.

Figure 3b: Cannabinoids in a lipid delivery system being solubilized into mixed micelles that are able to penetrate the unstirred water layer and absorb into the intestine.

Figure 3c: Cannabinoids in an emulsion delivery system, solubilized by micelles that are able to penetrate the unstirred water layer and absorb into the intestine.

Considerations when choosing emulsions for infused products

Bioavailability: Emulsions will generally increase the bioavailability of cannabinoids; however, the degree of how well they improve bioavailability will vary for different emulsion systems used.

Ingredient list: Many cannabis emulsions are made using synthetic ingredients that may be prohibitive for products that require a clean label. However, some emulsions such as Realize™ emulsion delivery system can be made from all-natural and organic ingredients.

Flavor profile: Many cannabis emulsions are extremely bitter and use chemicals that impart a soapy taste into the infused product. However, few systems exist that mask bitterness and are virtually tasteless. The Realize™ emulsion delivery system was designed to mask the bitter taste of cannabinoids.

Shelf life: Not all emulsions are stable, and hence, they will degrade overtime. This instability can cause issues for products such as RTD beverages that require a long shelf life and are prone to oil separation. Choosing the right emulsion system that has sufficient stability and product compatibility is essential.

Cost: Emulsions can be expensive to manufacture and difficult to scale up making them cost prohibitive for certain products.

The Take-Aways

- **The low bioavailability of cannabinoids can be improved by using delivery systems that promote the solubilization of the active ingredients.**
- **In the PK Oral CBD study the lipid delivery system demonstrated a 4.3x increase in bioavailability compared to CBD without a delivery system.**
- **In the PK Oral CBD study, the Realize™ emulsion delivery system demonstrated a 100x increase in bioavailability compared to CBD without a delivery system.**
- **The Realize™ emulsion delivery system used in this study can achieve onset in ¼ of the time and can be used to make faster acting infused products.**

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Dr. Michael Heller is the CEO and Co-founder of Realize. He is the inventor of Realize's proprietary emulsion delivery system. He has his PhD in Chemical Engineering from North Carolina State University and has been researching cannabis drug delivery since 2014.

About Realize

Realize was founded with the purpose of creating innovative cannabis and hemp consumer products that make people feel better: physically, mentally and emotionally. Realize invests heavily into research and development to create the most advanced cannabis formulas and drug delivery systems for their products. All of the company's products are tested extensively for their effectiveness, safety, and authenticity. Learn more about Realize at realizeinside.com, find our products at shoprealize.com, and connect with us on Facebook, Instagram , LinkedIn and YouTube.

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Appendix

A.1 Pharmacokinetics of Oral CBD
The PK Oral CBD study was designed by ESEV RD, experiments were performed by Eurofins Scientific and data was analyzed by ESEV RD.

PK Oral CBD Study Methodology
Three separate CBD delivery systems were tested during the investigation: CBD without a delivery system (Cannabidiol 99.9%); CBD in a lipid delivery system (Cannabidiol infused into olive oil, 25% CBD); and RealizeTM CBD Emulsion Delivery System. Male Sprague Dawley Rats were the model system used to evaluate the plasma pharmacokinetics of CBD (sample population, n=5, per delivery system). A single oral dose of 50 mg CBD/kg were fed to each subject. Blood was collected at the following time points: 15, 30, 60, 90, 120, 240 and 480 minutes. The concentration of CBD in plasma was quantified using HPLC LC/MS/MS. Experimental protocol was adapted from the study: Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), 9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behavior, performed by Dieana et. al. [16].

A.2 Relative bioavailability
Relative bioavailability= (AUC dose A/AUC dose B) x (Dose B/ Dose A)