



"The painting is finished  
when it has erased the idea"

# Table of Contents

Nomenclature	4
Preface	5
Introduction	6
Composition	7
Formula	8
Workflow	9
Cannabis	10
Trichomes	11
Constituents	12
Extraction	13
Delivery System	14
Bioavailability	14
Carrier Oil	15
Emulsion	16
Homogenization	17
Oil Droplet Size	18
Instability Pathways	19
GI Tract	20
Summary	21
Glossary	22
References	23 - 24

# Nomenclature

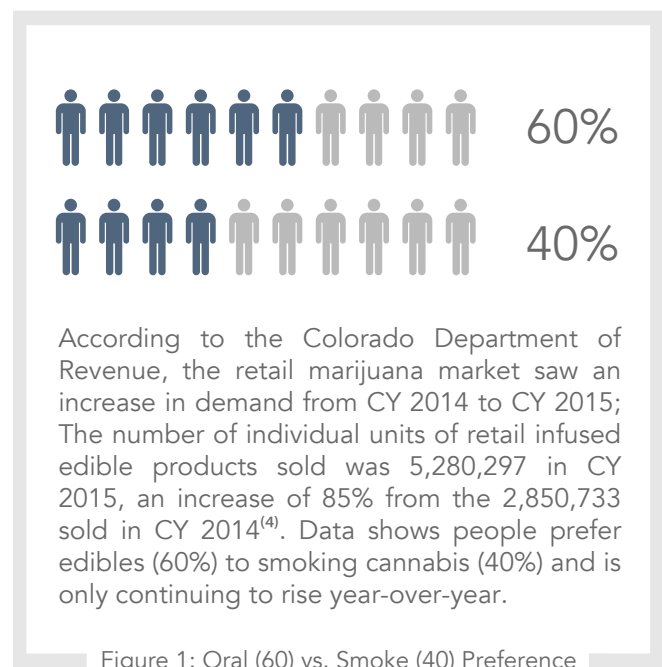
## Abbreviations and Symbols

<b>ADI</b>	Acceptable Daily Intake
<b>BMI</b>	Body Mass Index
<b>GMP</b>	Good Manufacturing Practices
<b>GRAS</b>	Generally Recognized as Safe
<b>HLB</b>	Hydrophilic-Lipophilic Balance
<b>HPLC</b>	High Performance Liquid Chromatography
<b>J</b>	Joule is a derived unit of energy
<b>K</b>	Kelvin is a unit of measure for temperature ( $K - 273.15 = ^\circ C$ )
<b>LN<sub>2</sub></b>	Liquid Nitrogen Dosing
<b>MDS</b>	Mean Droplet Size
<b>MPa</b>	Unit of pressure (1 MPa = 1,000,000 Pa)
<b>nm</b>	Nanometer
<b>o/w</b>	Oil-in-Water
<b>pH</b>	Acidity or Alkalinity of an Aqueous Solution
<b>SC-CO<sub>2</sub></b>	Supercritical Carbon Dioxide Extraction
<b>μm</b>	Micrometer
<b>w/o</b>	Water-in-Oil
<b>w/w</b>	Weight / Weight

# Preface

One of the first delivery systems you think of when someone mentions cannabis is smoking, but this presents many drawbacks. For instance, it is not acceptable for non-smokers, unpleasing aesthetically, and carries the risk of carcinogens due to the formation of compounds during combustion. Furthermore, there is current legislation throughout the United States which prohibits smoking in public as well as local municipalities now issuing odor control fines to combat cannabis smell. Legalization is definitely changing the way you consume cannabis and the best alternative without smoking is oral administration.

Commonly referred to as “edibles”, oral consumption comprises of at least half of the total cannabis sales in legal states like Colorado and Washington (Fig. 1). Unfortunately, current edible products consist of unhealthy sugary snacks like gummy bears, brownies, candy bars, and soda pop. We submit to you a change in philosophy for the cannabis industry if you look at statistics, future trends, and feed back from most millennials. The creation of healthy edible products with consumer friendly labels (e.g., all-natural). Not only will this combat the major obesity and diabetes problem in the U.S., but it will help destroy the stigma of cannabis because it deserves more respect.



We have attempted in this white paper to summarize a vast amount of complicated data in a fashion comprehensible to the general reader based on the ideology of creating health and wellness beverages. Consequently, only a few key references will be examined so that our company is transparent while protecting patent pending and proprietary processes. It is intended to provide the reader a clear view of where scientific research stands in relationship to cannabis beverages and the likely paths which that relationship may take in the future.

*J. Grillo*

# Introduction

The aim of this white paper is to present a brief overview of the growing interest in cannabis and the development of a functional beverage market in the United States now that responsible legalization is here to stay. This herbaceous plant is very complex in its chemistry, due to the vast number of constituents, which can lead remarkably to numerous beverage formulations. The purpose of this paper is to help fill the knowledge gap between the art and science of cannabis beverages when technology becomes their main link. Unfortunately, this paper will not be discussing the polarization of this plant and other various legalities involved, but rather a more productive glimpse into the commercial application of cannabis beverages as this emerging industry evolves into a well respected business amongst our peers.

Le Herbe was established in 2014 with the desire to create premium cannabis beverages because healthy options were not available when the legal industry was created. Our team commissioned renowned food scientists from all over the world to help create "Formula 420", which incorporates natural cannabis oil into an aqueous environment (non-alcoholic) (Fig. 2). The following core concepts of this white paper are derived from diligent research, development, and associated technical challenges that arose like dosing, bioavailability, dispersion, degradation, and stability. It is important to note that our company ethos is to support local farmers and process cannabis products naturally without the use of harmful solvents, pesticides, synthetic, or GMOs. The following information will be in accordance with these views based on organic ingredients and produced in the least amount of steps while reducing the carbon footprint.

## Methods

Health and wellness beverages containing bioactive compounds (e.g., terpenoids, flavonoids & cannabinoids), as opposed to essential nutrients, are increasingly being utilized as functional food and beverage ingredients. The technical challenge of dealing with cannabis is that these bioactive compounds are lipophilic (fat-loving). Bioactives have low solubility in hydrophilic (water loving) environments and so cannot be directly incorporated into an aqueous solution like beverages. Instead, they must be encapsulated within some form of delivery system that contains lipophilic particles that can easily be dispersed within water (Fig. 3). Lucky for Le Herbe, milk, juice and soft drinks have been using these oil-in-water (o/w) emulsions to overcome similar technical hurdles for decades (e.g., clouding, weighting & flavor oils). Cannabis beverage manufacturers will have to decide which system is the most appropriate if considering an optimized workflow (Diagram 1).

## General Composition

**LN<sub>2</sub>**



**Water**



**Oil(s)**



**Emulsifier(s)**



**Antioxidant(s)**

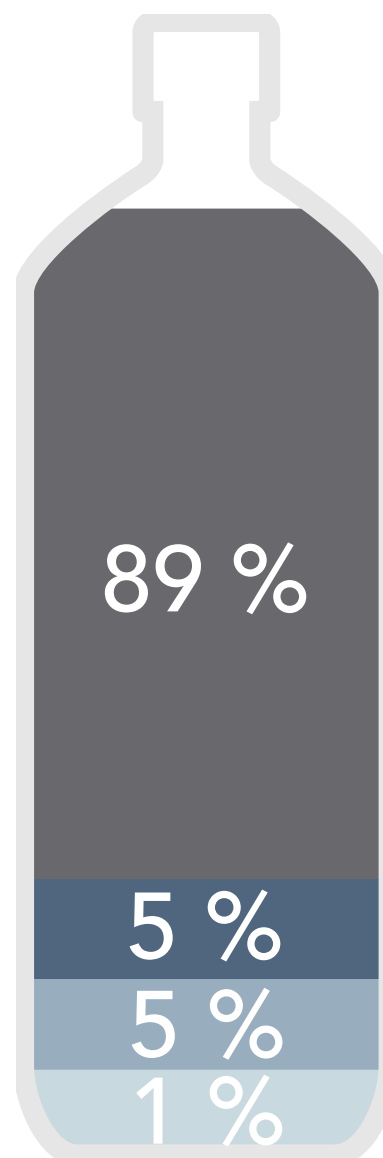
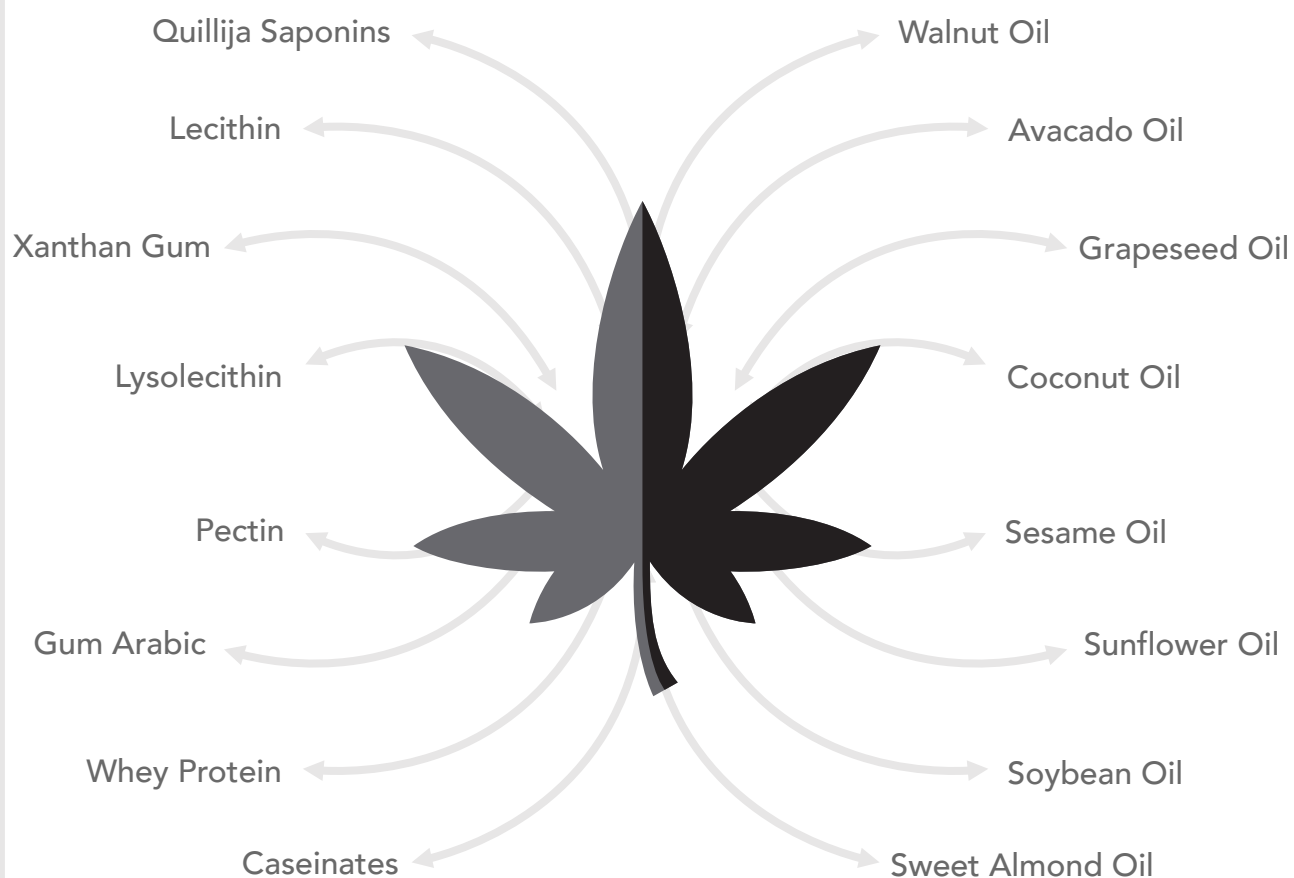


Figure 2: General Composition (w/w)

## General Formula



**Emulsifier**



**Cannabis Oil**



**Carrier Oil**

Figure 3: General Formula (all-natural)



# General Workflow

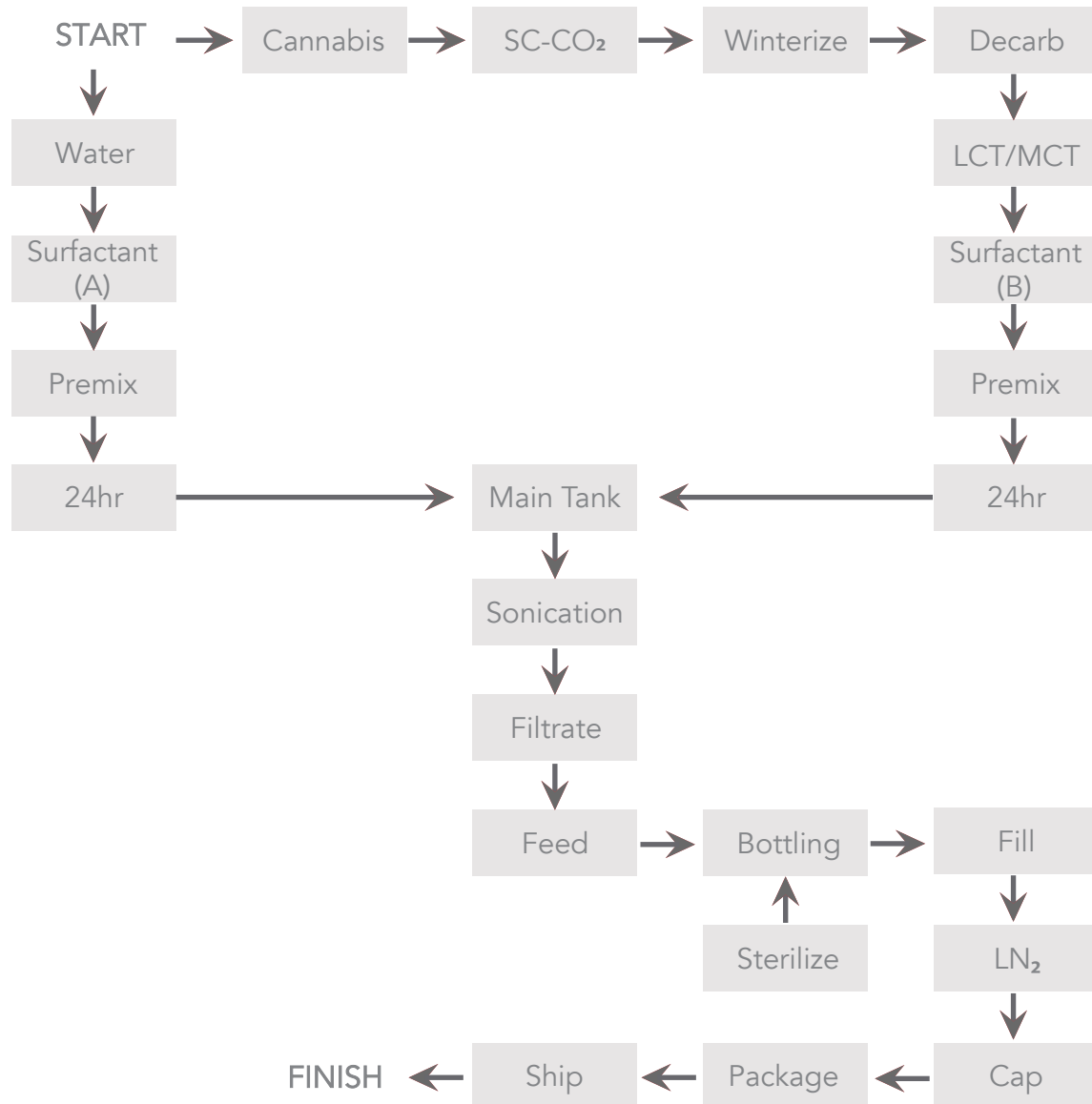
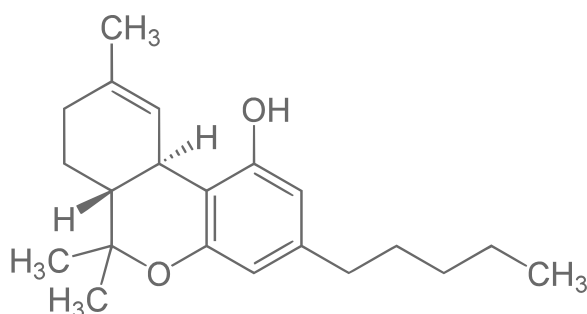


Diagram 1: General Workflow (commercial)

# Cannabis

For thousands of years cannabis has been used in beverage preparations and considered in the halls of antiquity to be "food of the gods"<sup>(1)</sup>. Some of the earliest writings of cannabis associated with drinking were discovered in India (bhang lassi), China (mafeisan), Persia (sabzi), and Russia (assis/esrar). Most of the cannabis beverages historically consist of boiling or grinding cannabis leaves into a powder, combining with milk or alcohol, and mixed with other herbal substances to form a synergistic effect. Indeed, cannabis is a treasured tool in the herbalist and alchemist arsenal, but it has only been in the past 50 years that scientific methods have provided a clear understanding of the numerous health benefits. Today, scientists are learning so much about the positive interactions with this plant and how it relates to major physiological functions discovered in the 1990's called the endocannabinoid system<sup>(2)</sup>.

One of the main advantages over historical preparations is the fact that we can now create better formulations. Take for instance the green plant material that was used in ancient times called chlorophyll. This should never be used in 21st century cannabis formulations because chlorophyll initiates lipid oxidation. This green pigment will give your beverage a foul taste, unpleasant aroma, and cause unnecessary problems with forming a stable emulsion. The green plant matter from questionable growers may contain heavy metals, fertilizer residue, pesticides, and molds that could have serious adverse risk in terms of health and product liability claims. Furthermore, the green plant matter has no bioactive utility apart from being a vehicle to carry chemical compounds to the trichomes (Fig. 5), which is the main component of cannabis oil that you want in your formulation (Fig. 2, 3). Trichomes are where the most important constituents are located (Table 1) and reside all over the male and female plants, but particularly concentrated in the area of the female flowers. Even though health and wellness beverages are gaining popularity, consumers won't buy beverages if they don't taste good. Cost and taste will remain a major challenge for cannabis beverages, but can be overcome by organic sun grown cannabis and proper beverage recipes like "Formula 420".



- Formula: C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>
- Molar Mass: 314.47 g/mole
- pK: 10.6
- logP (water pH7/octanol): 3.78
- Solubility in water 23 °C: 2.8 mg/L
- Solubility in 0.15 M NaCl: 0.77 mg/L
- Melting Point: < 298 K (N/A)
- Glass Transition: 9.3 °C

Tetrahydrocannabinol in excess of its solubility instantaneously forms a stable emulsion or micellar dispersion<sup>(3)</sup>

Figure 4: Δ<sup>9</sup>-THC Physicochemical Properties

# Trichomes

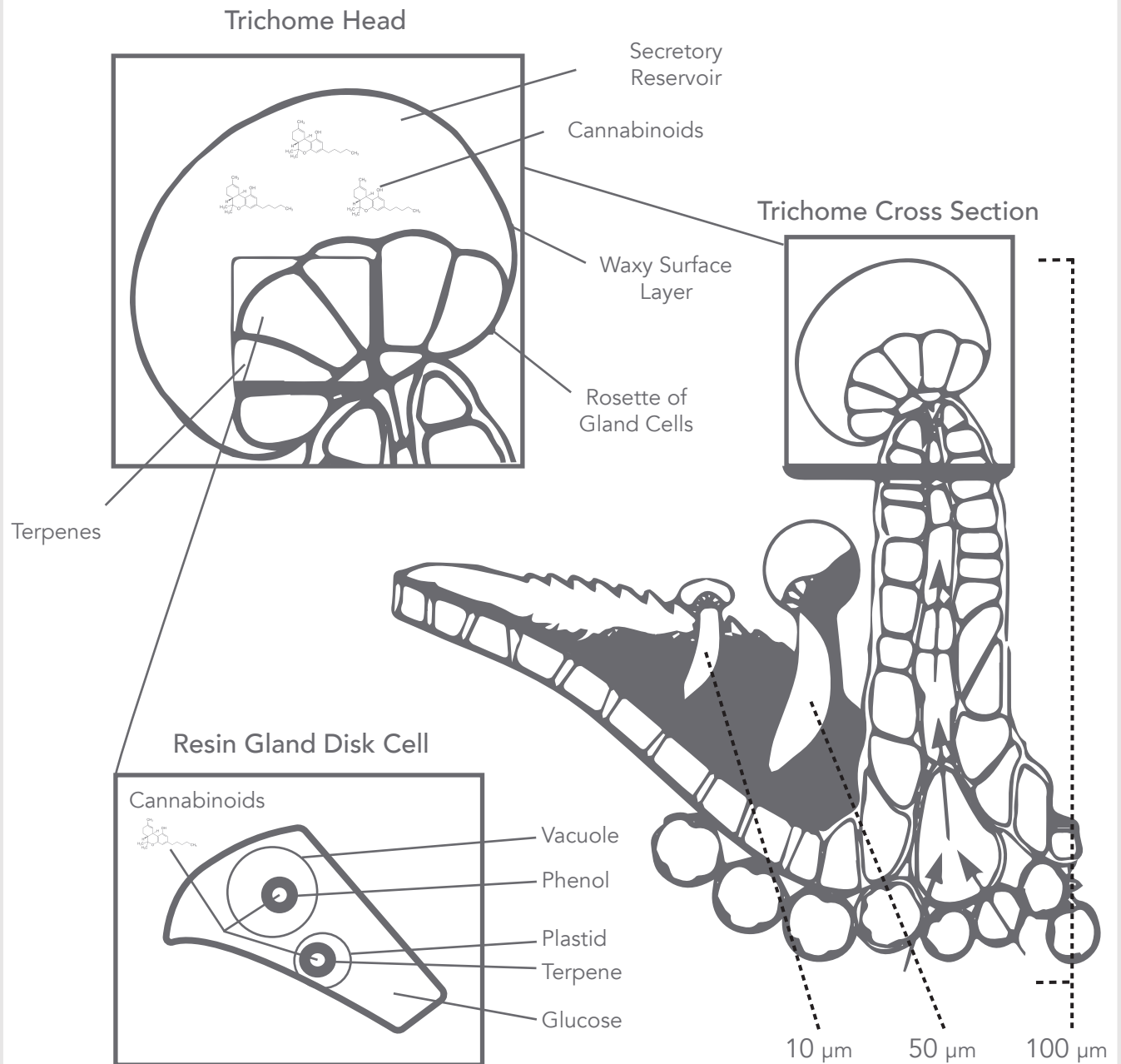


Figure 5: Cannabis Trichomes (Pate et al.)

# Constituents

Cannabinoids	104
CBG type	17
CBC type	8
CBD type	8
$\Delta^9$ THC type	18
$\Delta^8$ THC type	2
CBL type	3
CBE type	5
CBN type	10
CBND type	2
CBT type	9
Misc. type	22
Nitrogenous compounds	27
Amino Acids	18
Proteins, enzymes, & glycoproteins	11
Sugars & related compounds	34
Hydrocarbons	50
Simple alcohols	7
Simple aldehydes	12
Simple ketones	13
Simple acids	20
Fatty acids	23
Simple esters & lactones	13
Steroids	11
Terpenes	120
Non-cannabinoid phenols	25
Flavonoids	23
Vitamins	1
Pigments	2
Elements	9

\*chemical class

Table 1: Total Constituents 545 <sup>(5)</sup>

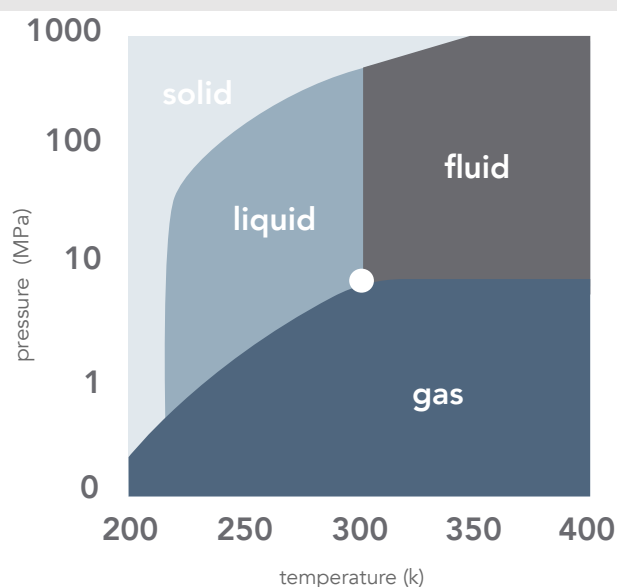
# Extraction

In order to meet the requirements of food quality for cannabis beverages, you need to safely extract trichomes from the green plant material. Among the technologies available to preserve cannabis constituents, Supercritical CO<sub>2</sub> (SC-CO<sub>2</sub>) extraction and fractionation can be applied as a preferred method to extract and isolate compounds from plant material<sup>(6)</sup>. Carbon dioxide (CO<sub>2</sub>) is non-flammable, relatively inert, abundant and inexpensive when used in the extraction process. Furthermore, the use of CO<sub>2</sub> is acceptable in the food industry and Generally Recognized As Safe (GRAS)<sup>(7)</sup>. Additionally, the waste plant material can be easily recycled, contrary to plant material soaked in solvents, in the case of classical extraction. From an ecological point of view, the alternative process is also more sustainable as it consumes less energy and generates less waste. Since waxes are co-extracted with constituents when using SC-CO<sub>2</sub>, a further purification step is needed to obtain an extract pure enough to be used in the beverage formulations. This can be easily achieved by adding a winterization step (i.e., freezing the extract to precipitate the waxes and a simple filtration isolates the cannabinoids from the waxes). The purity of the final extract after winterization is around 85 % at optimal conditions (Fig. 6). Customized applications of SC-CO<sub>2</sub> can be achieved so that constituents with different molecular weights can be separated into groups during extraction<sup>(8)</sup>. This can be helpful if you want to use psychotropic (THC) or non-psychotropic (CBD) cannabinoids in beverage formulations.

- The solubilities of two different non-psychoactive cannabinoids (CBG and CBD), in SC-CO<sub>2</sub> have been determined at 315, 326, and 334 K and in the pressure range from 11.3 to 20.6 MPa. They can be extracted in higher amounts with SC-CO<sub>2</sub> than with classical hexane extraction<sup>(9)</sup>.

- The solubility of  $\Delta^9$ -THC in SC-CO<sub>2</sub> has been determined at 315, 327, 334 and 345 K and in the pressure range from 13.2 to 25.1 MPa. The SC-CO<sub>2</sub> yield of  $\Delta^9$ -THC is at maximum 98 %, which is comparable to classical hexane extraction<sup>(10)</sup>.

- Cannabinol (CBN) is a decomposition product of the  $\Delta^9$ -THC. The solubility of CBN in SC-CO<sub>2</sub> was determined at 314, 327, and 334 K and in the pressure range from 13.0 to 20.2 MPa<sup>(11)</sup>.



CO<sub>2</sub> is a supercritical fluid at temperatures higher than 304.2 (K) and pressures higher than 7.38 (MPa). Under these conditions the distinction between the gas / liquid phase is nonexistent, and CO<sub>2</sub> can only be described as a fluid<sup>(8)</sup>.

Figure 6: SC-CO<sub>2</sub> as a Fluid

# Delivery System

Now that we have successfully identified components of the cannabis plant that we want to use (Fig. 5) and how to safely extract the bioactive compounds (Fig. 6) it's time to create our cannabis beverage. However, there are a number of technical challenges associated with directly incorporating cannabis oil into beverages due to its volatility, poor solubility, and low bioaccessibility. Bioactive cannabis constituents (Table 1) are highly unstable to oxidation and may therefore be lost during processing, storage, or transit. Recent technological advances that make use of lipids, proteins and polysaccharides are contributing to meet this challenge<sup>(33)</sup> and have opened the door to new delivery systems.

Oral cannabis delivery systems are classified into two main groups, liquid and solid. For the purpose of this white paper we will be discussing a liquid delivery system. In order to understand the delivery system concept you will need to grasp bioavailability. But first, we will need to transform the  $\Delta^9$ -THC-acid naturally present in the cannabis plant into the psychoactive  $\Delta^9$ -THC form via decarboxylation so that the cannabinoids are activated. The highest yield of  $\Delta^9$ -THC was obtained at 110 °C and 110 min<sup>(18)</sup>.

## Bioavailability

Bioavailability following the smoking route varies from 2 - 56%, due in part to intra and inter-subject variability in smoking dynamics, which contributes to uncertainty in dose delivery<sup>(19 22)</sup>. The number, duration, and spacing of puffs, hold time, and inhalation volume, or smoking topography, greatly influences the degree of drug exposure<sup>(23 25)</sup>. Oral bioavailability is even worse with an estimation between 10 - 20%<sup>( 26)</sup> and a more accurate assessment of 6% estimated after a 20mg THC dose in a cookie<sup>(27)</sup>. In laymen's terms, you are paying \$5 for a cookie with 20 mg of THC, using only 6%, and throwing the rest in the garbage. It is important to note that edibles produce a different pharmacokinetic profile than smoking or vaping<sup>(28 29)</sup>. Onset of the effect is delayed to approximately 30 to 60 minutes, peak blood levels of THC occur approximately three hours later, and the effects can last over six hours<sup>(30)</sup>.

Low oral THC bioavailability may be due to poor absorption, degradation by stomach acid, and/or bio-transformation to metabolites during first passage through the liver<sup>(31)</sup>. A suitable delivery system like nanoemulsions<sup>(12)</sup> can solve this problem and multiply the previously mentioned bioavailability by at least 4-5 fold. For instance, "Formula 420" has bioavailability between 50 - 75% and varies accordingly to BMI<sup>(31)</sup>. Consumers would have to buy approximately 8.33 cookies (20 mg THC per) for \$41.65 in order to get the effects of just 1 cannabis beverage, Le Herbe, at MSRP \$6.99 (20 mg THC 12oz).

# Carrier Oil

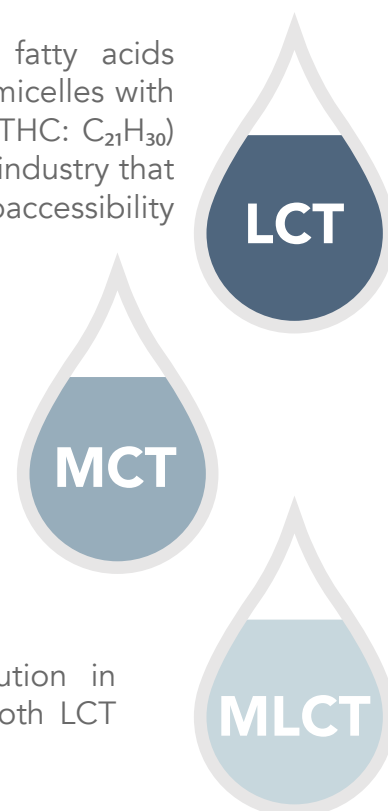
To prepare a stable oil-in-water (o/w) nanoemulsion it is necessary to encapsulate the lipophilic bioactive compounds (Table 1) into a carrier oil. The carrier oil should be food grade, not adversely affect product quality (such as appearance, taste, texture, or stability), protect from chemical degradation during storage, and increase bioavailability after ingestion<sup>(13)</sup>. Carrier oils are very important to help stabilize the emulsion from Ostwald ripening, which is the major destabilization mechanism in nanoemulsions (Fig. 10). This problem arises due to the increased solubility of dispersed phase into the aqueous phase and can be tackled by introducing the dispersed phase with strong hydrophobic properties<sup>(14)</sup>.

The composition of the carrier oil has a substantial impact on the physicochemical stability of nanoemulsions when simulated in the gastrointestinal tract (GI Tract)<sup>(15)</sup> (Diagram 2). The rate and extent of lipid digestion is higher for MCT emulsions than for LCT emulsions, which is attributed to differences in the water dispersibility of the medium and long chain fatty acids formed during lipolysis. On the other hand, the total bioaccessibility of bioactives after digestion was higher for LCT emulsions than for MCT emulsions, which was attributed to the greater solubilization capacity of mixed micelles formed from long chain fatty acids due to their ability to better accommodate lipophilic molecules<sup>(34)</sup>.

Long-chain triglycerides (LCT) contains relatively long-chain fatty acids (between 12 - 20 carbon atoms), which are able to form mixed micelles with a hydrophobic core large enough to accommodate bioactives (THC:  $C_{21}H_{30}$ ) with relatively long molecules<sup>(37)</sup>. Research in the pharmaceutical industry that has shown that many highly lipophilic drugs have a higher bioaccessibility when administered with LCT than with MCT<sup>(35, 36)</sup>.

On the other hand, medium-chain triglycerides (MCT) contain appreciably shorter-chain fatty acids (between 12 - 20 carbon atoms), and so mixed micelles formed from its digestion products have hydrophobic cores that are too small to easily accommodate some bioactives<sup>(15)</sup> like cannabis (Fig. 4). MCT is from the hydrolysis of coconut oil and fractionation process. MCT are esterified with glycerol and 100 times more soluble in water than are LCT<sup>(16)</sup>.

Medium-long-chain triglycerides (MLCT) is a possible resolution in choosing between carrier oils. It is manufactured containing both LCT and MCT<sup>(17)</sup>.



# Emulsion

Many natural foods consist either partly or wholly as emulsions, or have been in an emulsified state sometime during their production, including milk, cream, beverages, infant formula, soups, cake batters, salad dressings, mayonnaise, cream liqueurs, sauces, deserts, dips, salad cream, ice cream, coffee whitener, spreads, butter, and margarine<sup>(41)</sup>. Beverage emulsions are o/w emulsions that are prepared in a concentrated form and then diluted several hundred times in sugar/acid solution prior to consumption in order to produce the finished beverage, either carbonated or non-carbonated<sup>(40)</sup>. Selection of an emulsifier is a key factor determining the shelf-life and physicochemical properties of the emulsion. Emulsions stabilized by surfactants (Fig. 7) or other types of stabilizing agents, including phospholipids, amphiphilic proteins, or polysaccharides<sup>(38)</sup>, namely stabilized emulsions, have been developed to provide controlled release, improved entrapment efficiency, and protection from degradation<sup>(39)</sup>. It is important to point out that cannabinoids degrade rapidly upon storage if not protected. For instance, in storage at 40 °C, pure THC (%) degrades in 1 month ( $74.3 \pm 5.7$ ) and in 2 months (99.8). This can be solved by adding antioxidants like ascorbic acid to minimize degradation to 1 month ( $3.0 \pm 0.5$ ) and 2 months ( $5.8 \pm 1.3$ )<sup>(57)</sup>. Furthermore, adding nitrogen atmospheres<sup>(58)</sup>, like "Formula 420", can even achieve astounding results like stability for 1 year and degradation below 5%.

Le Herbe has extensive knowledge on the selection of the most suitable types of natural emulsifiers, sources of raw materials (e.g., water, oil, emulsifiers, thickening agents, minerals, acids, bases, vitamins, flavors, colorants) and offers consulting services to cannabis manufacturers on the most appropriate processing, storage, transport, and usage conditions (e.g., ultrasonication, nitrogen dosing, packaging, sterilization). We not only license our current cannabis beverages like cold brew coffee, green tea, kombucha, coconut water and roots tonic, but have a technical team that can help manufacturers with the development of their emulsion system like o/w or w/o and other complex emulsions like o/w/o or w/o/w.

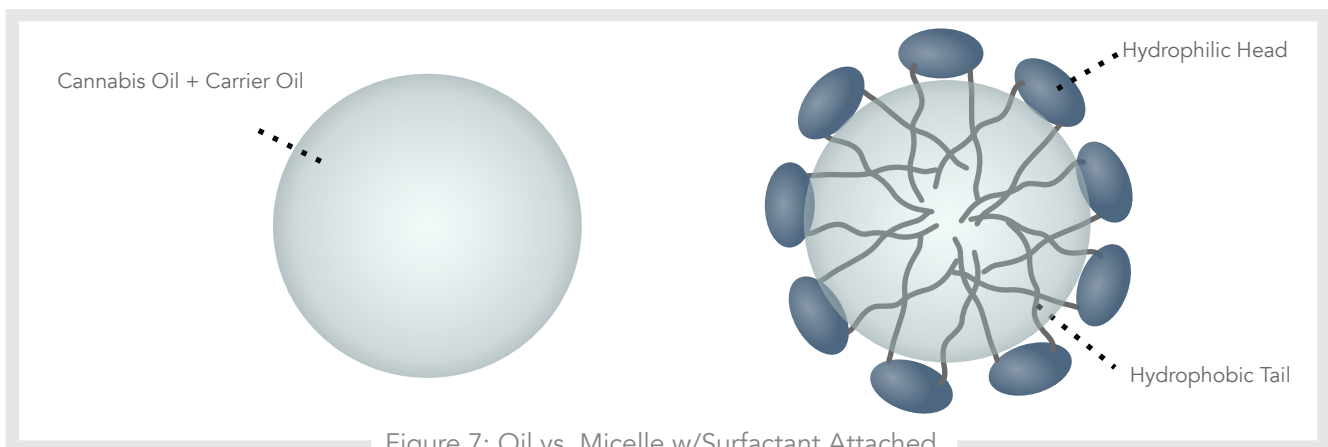


Figure 7: Oil vs. Micelle w/Surfactant Attached



# Homogenization

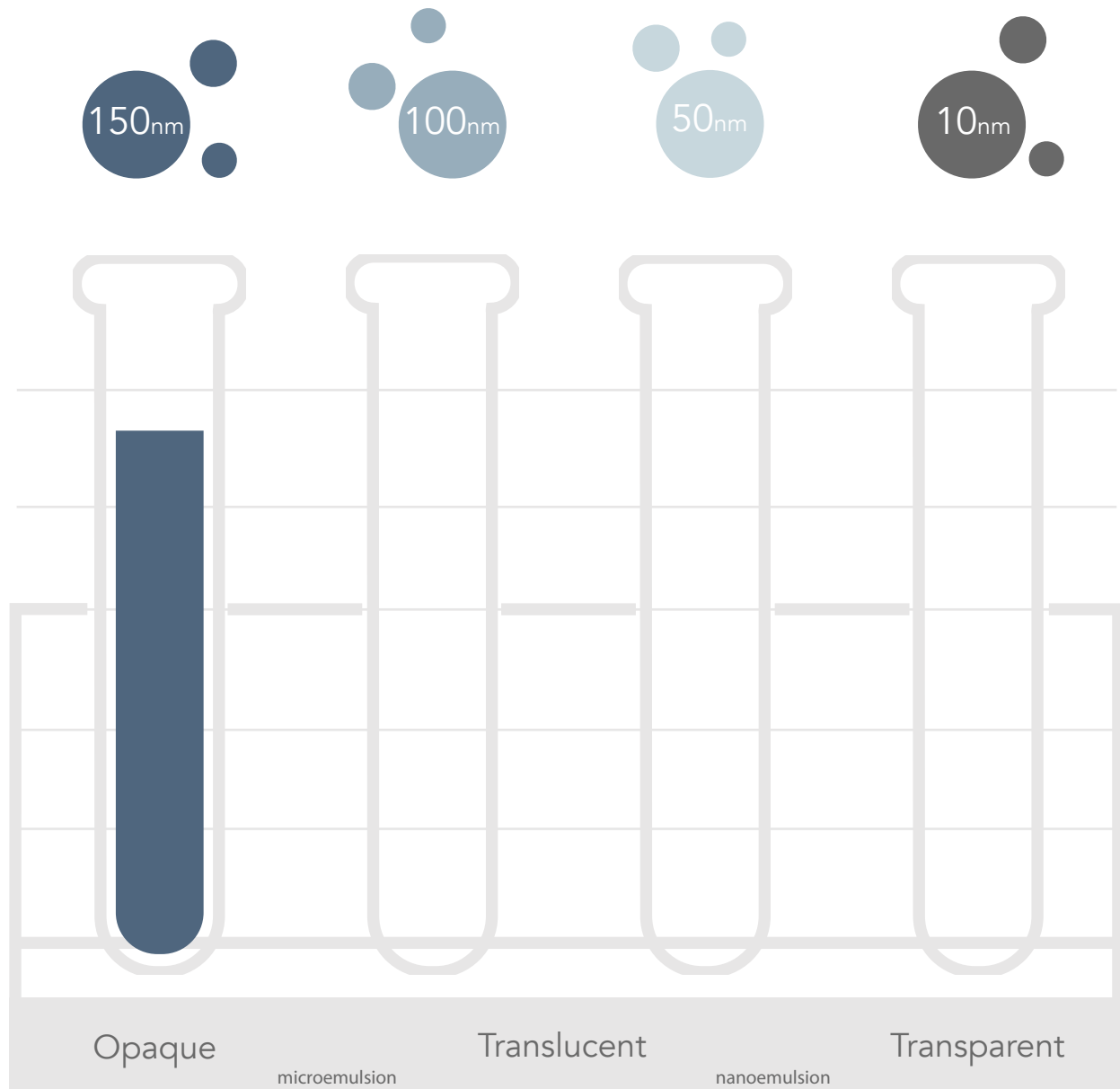
Emulsions can be prepared several ways using top down or bottom up approaches depending on the underlying principle. For the purpose of this white paper we will be discussing mechanical processes (top down) that employ shear force to break large emulsion droplets into smaller ones (Fig. 9). High-pressure homogenization (HPH, including microfluidization) and high-amplitude ultrasonic processing are currently the leading two methods used to produce nanoemulsions of superior quality<sup>(53)</sup>. In recent years, ultrasound-assisted emulsification process has gained popularity among food processors for the production of nanoemulsions, mainly due to its energy-efficiency, low production cost, ease of system manipulation and better control over formulation variables<sup>(54, 55)</sup>. Ultrasonic emulsification involves the production of high intensity (low frequency) acoustic waves (Fig. 8) followed by the disruption of droplets under the influence of cavitation effects in the liquid medium<sup>(56)</sup>.

To assess if any damage to bioactives compounds using ultrasonic emulsification occurs, analysis by HPLC was conducted. This showed that there was minimal production of free fatty acids, monoglycerides or diglycerides upon sonication<sup>(51)</sup>. This is consistent with the results of Pandit and Joshi<sup>(50)</sup> who found that energy in-put levels of around 1000 J/mL were required for the hydrolysis of fatty oils by cavitation. Next to hydrolysis and solvolysis reactions, oxidation is the main cause for instability<sup>(37)</sup>.



Figure 8: Ultrasonication (Top Down Approach)

## Oil Droplet Size



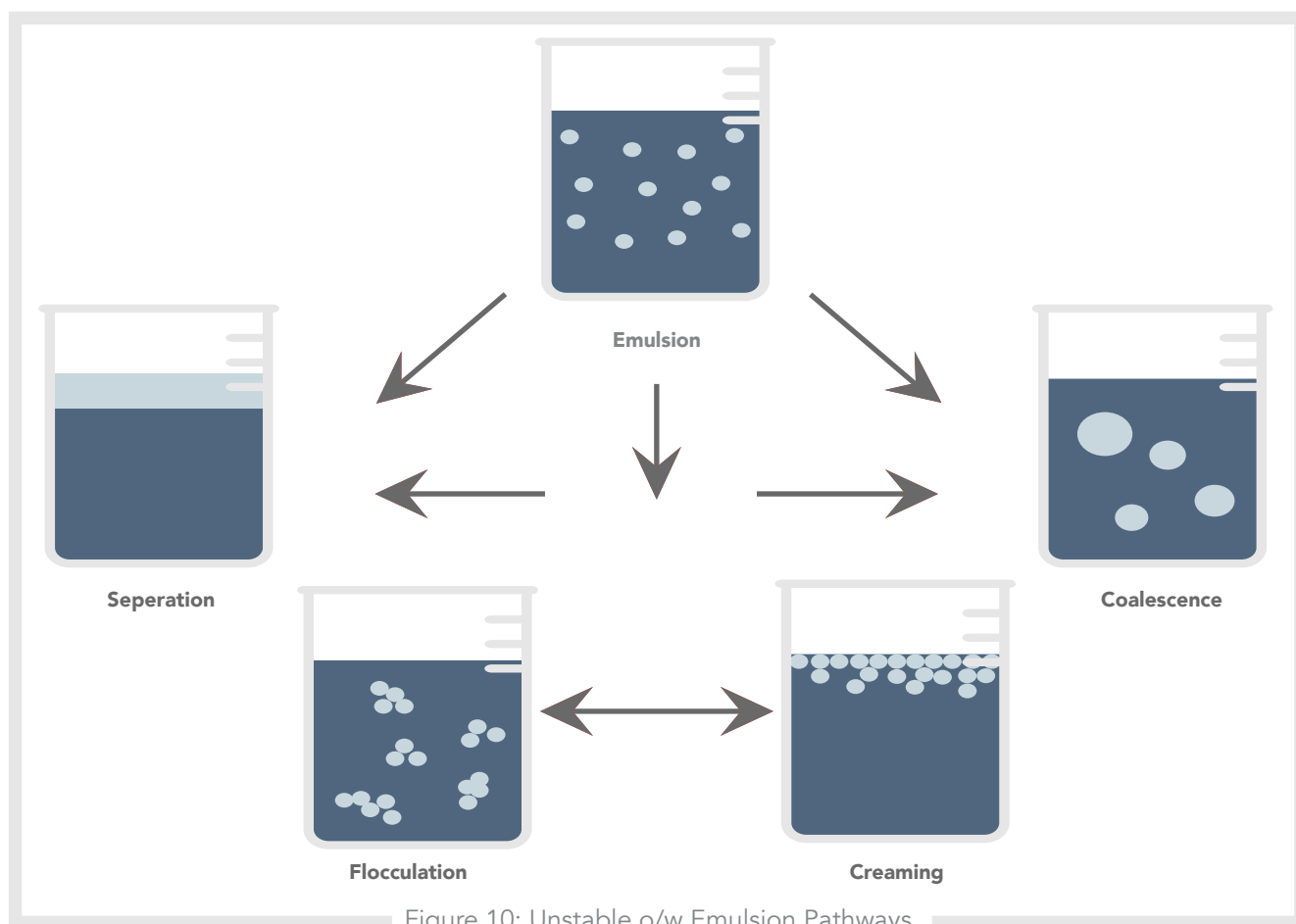
The efficient production of nanoemulsions, with oil droplet sizes of less than 100 nm would facilitate the inclusion of oil soluble bioactive compounds into a range of water based foods. Small droplet sizes lead to transparent emulsions so that product appearance is not altered by the addition of an oil phase<sup>(51)</sup>. If the emulsion droplet size is below the detection limit of the human eye (around 50 nm) then the emulsion can appear translucent and so the visual quality of the product is unaffected<sup>(52)</sup>.

Figure 9: MDS Comparison

# Instability Pathways

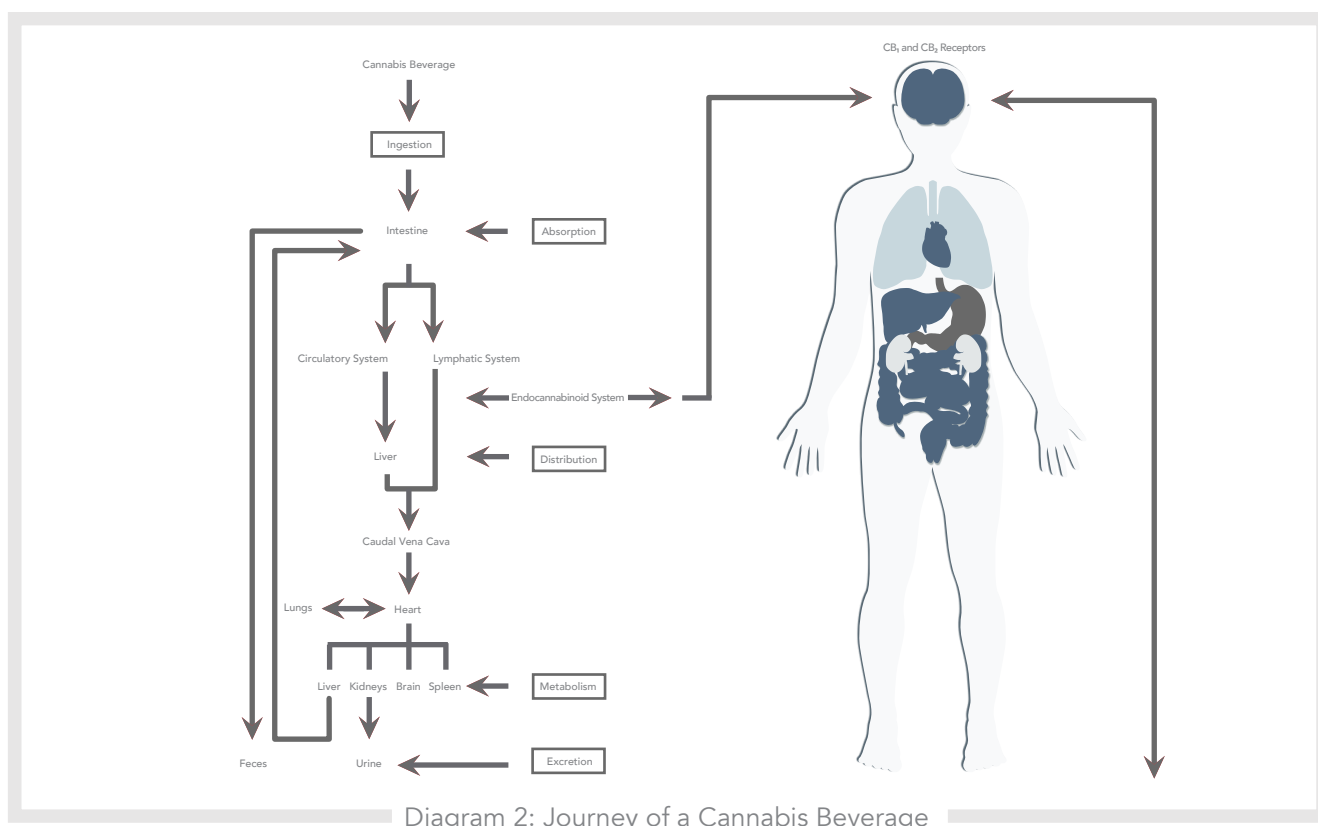
Once the droplets in an o/w cannabis beverage emulsion have been formed during homogenization (Fig. 8), it is important to keep them stable throughout the expected lifetime of the product<sup>(42, 43)</sup>. Emulsions may become unstable through numerous physicochemical processes, which are often highly dependent on the nature of the emulsifier used to stabilize the system<sup>(44)</sup> (Fig. 10).

The rate of these changes can be measured by determining the size and distribution of the oil droplets in emulsion<sup>(46)</sup> (Fig. 9). Stoke's law states that the velocity at which a droplet moves is proportional to the square of the droplet size radius. A decrease in its average globule diameter by a factor of two may decrease the coalescence rate by a factor of 10 - 100<sup>(45)</sup>. The ability of beverage manufacturers to formulate emulsion-based products with desirable and reproducible appearances depends on the knowledge of the relationship between their optical properties, composition and microstructure<sup>(41, 47, 48, 49)</sup>.



# GI Tract

In order to optimize oral administration of cannabis, to improve bioavailability, you will need to have knowledge of the fate of nanoparticles in the gastrointestinal tract or GI Tract. The ingested cannabis beverage, from Le Herbe, begins a journey when encapsulated (Fig. 7) bioactive compounds (Table 1) enter the mouth and are partially digested through saliva and mastication at a pH between 5 and 7<sup>(39)</sup>. Then the nanoparticles enter the stomach through the esophagus, where they will remain for 30 min to 4 h, depending on whether the stomach is in a fasting or fed state<sup>(39, 59)</sup>. The acidic pH of the stomach (between 1 and 2), along with enzymes, is designed to break down proteins and carbohydrates<sup>(60)</sup>. If the nanoparticle is made out of hydrocolloids and proteins, degradation of the nanoparticles can be significant under the extreme pH of the stomach. Assuming that the particles are able to withstand the acidic pH and remain suspended in the media as an integral nanoparticle, they travel to the small intestine. Nanoparticles enter the intestines through the duodenum, where they are introduced to a pH between 6 and 7.5 and various bile salts from the gall bladder that are designed to emulsify fats. Nanoparticles remain in the small intestines for 3–6 h before traveling to the large intestine or colon<sup>(39, 59)</sup>. It is mainly in the small intestine that the nanoparticles are absorbed to extract bioactive compounds and essential nutrients from “Formula 420”.



# Summary

As this white paper has sought to illustrate, legalization is changing the way people consume cannabis. Moving forward, consumers will likely be using oral administration as the preferred product choice of THC (psychotropic), CBD (non-psychotropic), or one of the other 545 constituents that make up this exquisite plant. The problem is that the majority of current "edible" products consist of unhealthy junk food like cookies and soda pop. This does not mesh well with current efforts to diminish sugar and salt intake as a health hazard. If you look at the millennial population, which is the largest demographic who support responsible cannabis legalization, they are extremely health conscious and want to know what their eating or drinking is fresh and has natural ingredients. Manufacturers will have to decide if they want to add all-natural beverages to their product line or make the switch from candy bars to cannabis beverages before it's too late and your up in smoke.

Le Herbe is poised and ready to take all-natural cannabis beverages to new heights. Our "Formula 420" now surpasses the traditional smoking route in terms of maximizing the absorption of bioactive compounds. For the first time, consumers can now sip premium cannabis beverages (non-alcoholic) inconspicuously and enjoy the same or greater effects than if you were to smoke a joint, take a bowl, or hit a bong. Aesthetics will play a key role in pushing cannabis mainstream and allowing public consumption in the form of a beverage. We believe cannabis beverages can stand toe to toe with alcohol and foresee the availability in every grocery and health food store, bar, restaurant, and coffee shop in the United States.

Is it so hard to imagine that cannabis couldn't be the next great segment of the beverage industry? One plant, Cannabis Sativa L., could be a replacement, alternative, or additive to several mainstream beverage markets like alcohol, probiotic, and coffee just to name a few. Join us along our journey as we blend innovative organic techniques with superb craftsmanship to create cannabis products of exceptional quality and taste.

Cheers!

# Glossary

## Colloidal System

Consist of two immiscible liquids in which one liquid (dispersed phase) is dispersed as a droplet into other liquid (continuous phase) in the presence of surfactant(s).

## Emulsion

Pre-mixture of two immiscible liquids (e.g., oil and water) in the Colloidal System. One of which becomes the so-called continuous phase (i.e. water) and the other the dispersed phase (i.e. oil) that exists in the form of droplets ranging from 10 nm - 100+  $\mu\text{m}$ .

## Homogenization

Breaking down and mixing of components of an emulsion or dispersion through shear forces.

## Lipids

Naturally occurring molecules that include triacylglycerols, fats, waxes, sterols, (e.g., cholesterol), phospholipids (PLs) and many others.

## Micelle

Allows a compound that is normally insoluble (oil) to dissolve in aqueous solutions (oil-in-water micelle).

## Pharmacokinetics

what the body does to a drug

## Pharmacodynamics

what a drug does to the body

## Shear Forces

Necessary for the emulsification process and can be provided by high-pressure homogenization or high-amplitude ultrasonic processing (sonication).

## Surfactant

Substances that lower the surface tension between two liquids or between a liquid and a solid that stabilize the newly generated interface.

# References

- [1] Abel E.L.(1980).  
Marijuana: The First Twelve Thousand Years.  
ISBN 978-1-4899-2189-5
- [2] Pertwee R.G.(2015).  
Endocannabinoids.  
ISBN 978-3-319-20825-1
- [3] Garrett E.R., & Hunt C.A.(1974).  
Physicochemical properties, solubility, and protein binding of delta9-tetrahydrocannabinol.  
J Pharm Sci. 63(7); pp 1056-64.
- [4] Colorado Department of Revenue.(2016).  
Report to Joint Budget Committee.  
MED. pp 1-7.
- [5] ElSohly M.A., & Thomas B.F.(2016).  
The Analytical Chemistry of Cannabis.  
ISBN 9780128046463
- [6] Reverchon E., & De Marco I.(2006).  
Supercritical fluid extraction and fractionation of natural matter.  
J of Supercrit Fluids. 38(2); pp 146-166.
- [7] Food and Drug Administration.(1979).  
Carbon Dioxide.
- [8] Martinez J.L.(2007).  
Supercritical Fluid Extraction of Nutraceuticals and Bioactive Compounds.  
ISBN:9780849370892
- [9] Perrotin-Brunel H., Kroon M.C., van Roosmalen M.J.E., van Spronsen J., Peters C.J., & Witkamp G.J.(2010).  
Solubility of non-psychoactive cannabinoids in supercritical carbon dioxide and comparison with psychoactive cannabinoids.  
J of Supercrit Fluids. 55(2); pp 603-8.
- [10] Perrotin-Brunel H., Perez P.C., van Roosmalen M.J.E., van Spronsen J., Witkamp G.J., & Peters C.J.(2010).  
Solubility of Δ9-tetrahydrocannabinol in supercritical carbon dioxide: Experiments and modeling.  
J of Supercrit Fluids. 52(1); pp 6-10.
- [11] Perrotin-Brunel H., van Roosmalen M.J.E., Kroon M.C., van Spronsen J., Witkamp G.J., & Peters C.J. (2010).  
Solubility of Cannabinol in Supercritical Carbon Dioxide.  
J of Chem & Eng Data. 55(9); pp 3704-7.
- [12] McClements D.J., Decker E.A., Park Y., & Weiss J.(2009).  
Structural design principles for delivery of bioactive components in nutraceuticals and functional foods.  
Crit Rev in Food Sci & Nutri. 49(6); pp 577-606.
- [13] Lesmes U., & McClements D.J.(2009).  
Structure–function relationships to guide rational design and fabrication of particulate food delivery systems.  
Trends in Food Sci & Tech. 20(10); pp 448-457.
- [14] Lee S.J., Choi S.J., Li Y., Decker E.A., & McClements D.J.(2011).  
Protein-stabilized nanoemulsions and emulsions: comparison of physicochemical stability, lipid oxidation, and lipase digestibility.  
J Agri Food Chem. 59; pp 415-427.
- [15] Rao J, Decker E.A., Xiao H., McClements D.J.(2013).  
Nutraceutical nanoemulsions: influence of carrier oil composition (digestible versus indigestible oil) on β-carotene bio-availability.  
J Sci Food Agri. 93(13); pp 3175-83.
- [16] Bach A.C., & Babayan V.K.(1982).  
Am J Clin Nutr. 36(5); pp 950-62.
- [17] Matulka R., Noguchi O., & Nosaka N.(2006).  
Safety evaluation of a medium and long chain triacylglycerol oil produced from medium-chain triacylglycerols and edible vegetable oil.  
Food Chem Tox. 44(9); pp 1530-8.
- [18] Perrotin-Brunel H., Buijs W., van Spronsen J., van Roosmalen M.J.E., Peters C.J., Verpoorte R., & Witkamp G.J.(2011).  
Decarboxylation of Δ9 tetrahydrocannabinol: Kinetics and molecular modeling.  
J of Mol Struct. 987(1-3); pp 67-73.
- [19] Agurell S., & Leander K.(1971).  
Acta Pharm Suecica. 8; pp 391.
- [20] Barnett G., Chiang C.N.(1985).  
Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs.  
St. Louis. p. 75.
- [21] Agurell S., Halldin B.M., Lindgren J.E., Ohlsson A., Widman M., Gillespie H., & Hollister L.(1986).  
Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man.  
Pharmacol Rev. 38(1); pp 21-43.
- [22] Ohlsson A., Lindgren J.E., Wahlen A., Agurell S., Hollister L.E., & Gillespie H.K.(1982).  
Single dose kinetics of deuterium labelled Δ1-tetrahydrocannabinol in heavy and light cannabis users.  
Bio Env Mass Spect. 9(1); pp 6-10.
- [23] Azorlosa J.L., Heishman S.J., Stitzer M.L., & Mahaffey J.M.(1992).  
Marijuana smoking: effect of varying delta 9-tetrahydrocannabinol content and number of puffs.  
J Pharm Exp Ther. 261; pp 114-122.
- [24] Heishman S.J., Stitzer M.L., & Yingling J.E.(1989).  
Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance  
Pharm Bio Behav. 34(1); pp 173-179.
- [25] Perez-Reyes M.(1990).  
Marijuana Smoking: Factors That Influence the Bioavailability of Tetrahydrocannabinol.  
NIDA Res Mono. 99; pp 42-62.
- [26] Wall M.E., Sadler B.M., Brine D., Taylor H. & Perez-Reyes M.(1983).  
Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women.  
Clin Pharmacol & Ther. 34(3); pp 352-63.
- [27] Ohlsson A, Lindgren J.E., Wahlen A., Agurell S., Hollister L.E. & Gillespie H.K.(1980).  
Plasma delta- 9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking.  
Clin Pharmacol & Ther. 28(3); pp 409-16.
- [28] Aggarwal S.K., Kyashna-Tocha M., & Carter G.T.(2007).  
Dosing medical marijuana: rational guidelines on trial in Washington State.  
MedGenMed. 9(3); pp 52.
- [29] Carter G.T., Weydt P., Kyashna-Tocha M., & Abrams D.I.(2004).  
Medicinal cannabis: rational guidelines for dosing.  
IDrugs. 7(5); pp 464-70.
- [30] Lemberger L., Weiss J.L., Watanabe A.M., Galanter I.M., Wyatt R.J., & Cardon P.V.(1972).  
Delta-9-tetrahydrocannabinol: temporal correlation of the psychologic effects and blood levels after various routes of administration.  
N Engl J of Med. 286(13); pp 685-88.
- [31] Goodwin R., Gustafson R.A., Barnes A., Nebro W., Moolchan E.T. & Huestis M.A.(2006).  
Δ9-tetrahydrocannabinol, 11-hydroxy-Δ9-tetrahydrocannabinol and 11-nor-9-carboxy-Δ 9-tetrahydrocannabinol in human plasma after controlled oral administration of cannabinoids.  
Ther Drug Monit. 28(4); pp 545-51.
- [32] Borel T., & Sabliov C.M.(2014).  
Nanodelivery of Bioactive Components for Food Applications: Types of Delivery Systems, Properties, and Their Effect on ADME Profiles and Toxicity of Nanoparticles  
Annual Review of Food Sci & Tech. 5(1); pp 97-213.

- [33] Acosta E.(2009). Bioavailability of nanoparticles in nutrient and nutraceutical delivery. *Cur Op in Coll & Inter Sci.* 14(1); pp 3-15.
- [34] Yang Y., & McClements D.J.(2013). Vitamin E bioaccessibility: Influence of carrier oil type on digestion and release of emulsified  $\alpha$ -tocopherol acetate. *Food Chem.* 141(1); pp. 473-81.
- [35] Kossena G.A., Boyd B.J., Porter C.J.H., & Charman, W.N.(2003). Separation and characterization of the colloidal phases produced on digestion of common formulation lipids and assessment of their impact on the apparent solubility of selected poorly water-soluble drugs. *J of Pharm Sci.* 92(3); pp 634-48.
- [36] Nielsen P.B., Müllertz A., Norling T., & Kristensen H.G.(2001). Comparison of the lymphatic transport of a lipophilic drug from vehicles containing  $\alpha$ -tocopherol and/or triglycerides in rats. *J of Pharm & Pharmaco.* 53(11); pp 1439-45.
- [37] Connors, K.A., Amidon, G.L., & Stella, V.J.(1978). Chemical stability of pharmaceuticals.(2nd ed.).
- [38] Guzey D., & McClements D.J.(2006). Formation, stability and properties of multilayer emulsions for application in the food industry. *Adv Coll Inter Sci.* 128(130); pp 227-48.
- [39] McClements D.J., & Li Y.(2010). Structured emulsion-based delivery systems: controlling the digestion and release of lipophilic food components. *Adv Coll & Inter Sci.* 159(2); pp 213-28.
- [40] Tse K., & Reineccius G.A.(1995). Flavor Technology. ACS Symposium Series. 610(13); 172-82.
- [41] McClements D.J.(1999). Food emulsions: principles, practices and techniques.(1st ed.). CRC Press E. pp. 235-66.
- [42] Dickinson E.(2010). Flocculation of protein-stabilized oil-in-water emulsions. *Coll & Surf B Biointer.* 81(1); pp 130-40.
- [43] Fredrick E., Walstra P., & Dewettinck K.(2010). Factors governing partial coalescence in oil-in- water emulsions. *Adv in Coll & Inter Sci.* 153(1-2); pp 30-42.
- [44] McClements D.J., & Gumus C.E.(2016). Natural emulsifiers — biosurfactants, phospholipids, biopolymers, and colloidal particles: Molecular and physicochemical basis of functional performance. *Adv in Coll & Inter Sci.* pp 6.
- [45] Stenius P., Bergenstahl B.A., & Claesson P.M.(1992). Surface Forces and Emulsifiers. NATO ASI Series. pp 269-81.
- [46] Mirhosseini H., Tan C.P., Hamid N.S.A., & Yusof S.(2008). Optimization of the contents of Arabic gum, xanthan gum and orange oil affecting turbidity, average particle size, polydispersity index and density in orange beverage emulsion. *Food Hydrocoll.* 22(7); pp 1212-23.
- [47] Chanamai R., & McClements D.J.(2001). Depletion flocculation of beverage emulsions by gum Arabic and modified starch. *J of Food Sci.* 66(3); pp 457-63.
- [48] Chanamai R., & McClements D.J.(2001). Prediction of emulsion color from droplet characteristics: Dilute monodisperse oil-in-water emulsions. *Food Hydrocoll.* 15(1); pp 83-91.
- [49] Dickinson E.(1994). Colloidal aspects of beverages. *Food Chem.* 51(4); pp 343-47.
- [50] Pandit A.B., & Joshi J.B.(1993). Hydrolysis of fatty oils: effect of cavitation. *Chem Engi Sci.* 48(19); pp. 3440-42.
- [51] Leong T.S.H., Wooster T.J., Kentish S.E., & Ashokkum M.(2009). Minimising oil droplet size using ultrasonic emulsification. *Ultrason Sonochem.* 16(6); pp 721-27.
- [52] Wooster T.J., Golding M., & Sanguansri P.(2008). Impact of oil type on nanoemulsion formation and Ostwald ripening stability. *Langmuir.* 24(22); pp 12758-65.
- [53] Peshkovsky A., & Bystryak S.(2014). Continuous-flow production of a pharmaceutical nanoemulsion by high-amplitude ultrasound: Process scale-up. *Chem Engi & Process Pl.* 82; pp 132-36.
- [54] Mason T.J., Paniwnyk L., Chemat F., & Abert Vian M.(2011). Ultrasonic food processing: Alternatives to Conventional Food Processing. *T Roy Soc of Chem.* pp. 387 414.
- [55] Chemat F., Huma Z.E., & Khan M.K.(2011). Applications of ultrasound in food technology: processing, preservation and extraction. *Ultrason Sonochem.* 18(4); pp 813-35.
- [56] Abbas S., Bashari M., Akhtar W., Li W.W., & Zhang X.(2014). Process optimization of ultrasound-assisted curcumin nanoemulsions stabilized by OSA-modified starch. *Ultrason Sonochem.* 21(4); pp 1265-74.
- [57] Munjal M., ElSohly M.A., & Repka M.A.(2006). Polymeric Systems for Amorphous  $\Delta^9$ -Tetrahydrocannabinol Produced by a Hot-Melt Method. Part II: Effect of Oxidation Mechanisms and Chemical Interactions on Stability. *J Pharma Sci.* 95; pp 2473-85.
- [58] Flora K.P., & Cradock J.C.(1981). Determination of  $\Delta^9$  -Tetrahydrocannabinol in Phrmaceutical Vehicles by HPLC. *J of Chroma.* 206; pp 117-23.
- [59] Kompella U.B., & Lee V.H.L.(2001). Delivery systems for penetration enhancement of peptide and protein drugs: design considerations. *Adv Drug Deliv Rev.* 46(1–3); pp 211-45.
- [60] Ensign L.M., Cone R., & Hanes J.(2012). Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Adv Drug Deliv Rev.* 64(6); pp 557-70.





Reproduction of part or all of the contents of this White Paper in any form is expressly prohibited other than for individual or organization private-use only and may not be recopied and/or shared with a third party. The permission to recopy by an individual or organization does not allow for incorporation of material or any part of it in any work or publication, whether in hard copy, electronic, or any other form. By retaining this document and/or reading this, you agree not to reproduce, print, re-transmit, copy, distribute, publish or sell the content of this White Paper without the prior written consent of Le Herbe, a 420 Ventures Company.