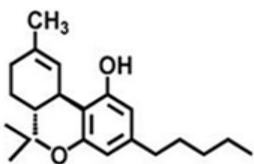


## Application Note

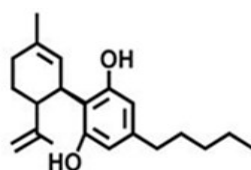
### Use of Microfluidizer™ technology for Cannabis Products

28 States in the United States and Washington DC have legalized medical marijuana, among those 8 States plus Washington DC have legalized marijuana for recreational use. In 2016 the revenue was ~ 6.7 billion. An increase of 30% in the next 4 years is forecasted. Possible up to 50% of products being legally sold are for oral consumption. Commonly referred to as “Edibles”, oral products have a lot of advantages over smoking. There are >700 strains of Cannabis, growers constantly come up with new strains, some of them take off and become recognizable, others disappear. Growers usually target certain characteristics when they combine 2 strains. There are about 111 cannabinoids. The two main ingredients are Tetrahydrocannabinol (THC) and Cannabidiol (CBD). THC produces the euphoric effect with some therapeutic benefits, CBD offers a wide range of proven medical benefits such as anti-inflammatory, anti-oxidant, anti-anxiety, etc.

However, there’s a major challenge when formulating cannabis oil into consumable products. Cannabis oil has poor water solubility and low bioavailability. Bioavailability through smoking can vary between 2-56%. Direct oral administration of raw or un-encapsulated cannabis oil, e.g., eating a cookie, provides even lower bioavailability of only 6-20%. On top of this, the onset of the effect can be delayed as much as 60 minutes and it takes hours after digestion to reach peak effect.



Δ<sup>9</sup>-tetrahydrocannabinol  
(THC)



Cannabidiol  
(CBD)

### Why Microfluidizer™ Technology

The low bioavailability of cannabis oil can be overcome by formulating the products into nano-emulsions or encapsulations. It has been demonstrated that previously mentioned bioavailability can be increased by multiple folds to 50-75% through nano-formulations. For edibles, the time required to respond to a recreational edible is also reduced even at lower dosages. For CBD based creams and lotions, nanoemulsion formulations typically achieve same therapeutic effects at much lower dosage as a result of increased bioavailability. The adverse effect is also reduced with reduced dosage.

When making a nanoemulsion, droplet size distribution, or polydispersity (PDI), is another important consideration in addition to the droplet size since it can greatly affect the stability of the nanoemulsion. High polydispersity indicates existence of large droplets, which can destabilize the emulsion through phenomenon such as Ostwald ripening. Therefore, narrow size distribution is desired and often means longer product shelf life.

Last but not least, when the droplet size drops below 100nm, nanoemulsions often become translucent or even transparent in appearance. This can be particularly beneficial in clear beverage applications.

Microfluidizer technology is the only technology that can create nano-sized emulsions or encapsulations meet all above requirements. Unlike all other types of technologies, whether they be mixers or homogenizers, Microfluidizer processors provide highest uniform shear rates on the market by utilizing fixed geometry interaction chambers and extremely high constant processing pressures. Microfluidizer technology also guarantees scale up so that product processing and results are consistent from development to manufacturing. In addition, Microfluidizer processors have a proven track of record with meeting all FDA requirements for food and pharmaceutical productions.

For cannabis producers, extractors, and processors who need to improve their products, whether recreational (THC) or therapeutic (CBD), the Microfluidizer high-shear processors provide a scalable solution with the highest efficiency which will differentiate the products by improving shelf life, stability, and effectiveness with significantly less amount of expensive cannabis oil.

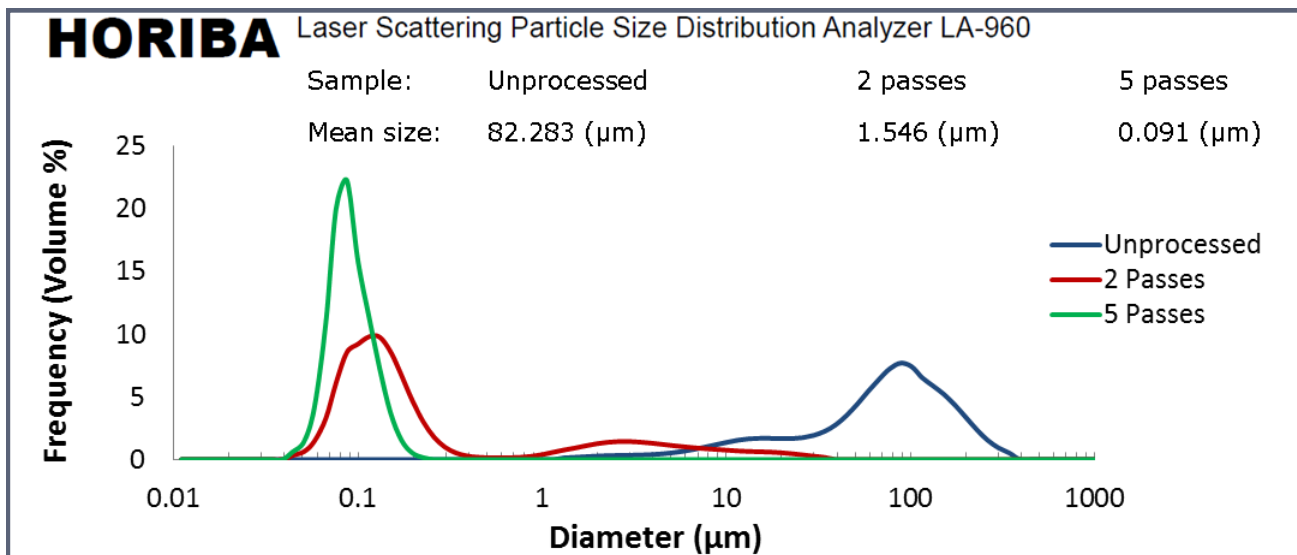
## Formulation and Microfluidization Process – A Case Study

In this study, formulation discovery processes were completed in conjunction with Golden Leaf Holdings and Cascadia Labs. Multiple formulations were prepared prior to processing with a LM20 Microfluidizer which is capable of delivering pressure of up to 30Kpsi.

The aqueous phase and oil phase were prepared separately. The aqueous phase consists of water and surfactant and were mixed with a magnetic stirring plate. The oil phase was formulated with oil at different concentrations. Surfactants can be added to the oil Phase as well and combined with a magnetic stirring plate.

A coarse emulsion, or premix, was then created by combining both phases and mixed with low shear technology such as rotor-stator mixers or similar until a milky solution was obtained. This premix was then passed through the Microfluidizer processor.

The process can be optimized by adjusting process pressure, number of passes, temperature, etc., to yield controllable results as shown below with the particle size analysis data obtained with a laser diffraction instrument. The mean particle size was reduced to less than 100nm after just 5 passes.



### Summary:

- Microfluidizer Processors provides the highest uniform shear which creates among smallest nanoemulsion droplets with narrow distribution.
- Oils such as cannabis oil can be stabilized in water by creating a nanoemulsion which is then possible to be blended in drinks or any type of edible or as an additive to lotions and creams.
- Finer emulsions (smaller droplet size) often increases the bioavailability of a product such as cannabis oil which translates to a more effective product at a smaller dosage.
- Smaller emulsions also mean quicker uptake of the product thus, more rapid effect when consuming edible, which differentiates products made with a Microfluidizer processor.
- Smaller droplets combined with narrow size distribution increase stability, which means extended product shelf life.
- Guaranteed scale up means no issues with product consistency when demand increases.
- Guaranteed compliance with all food and pharmaceutical requirements means no future concerns about FDA compliance using Microfluidizer processors (biopharmaceutical machines are available).

(Special thanks to Chris Harrison from Golden Leaf Holdings, Jeremy Sackett from Cascadia Labs and Horiba for their collaboration)