All-Natural, Water-Compatible, High-Bioavailability CBD Concentrate Nanoemulsion Manufactured by High-Intensity Ultrasound

Cannabis oils and isolates exhibit poor water solubility, which compromises their bioavailability and results in a delayed onset of therapeutic action after oral or topical administration. When consumed in the form of nanoemulsions, however, they provide exceptionally high bioavailability and therapeutic effect, and are absorbed by the body rapidly and completely.

CBD American Shaman contracted Industrial Sonomechanics (ISM) to develop a formulation and production procedure for a stable, water-compatible, all-natural nanoemulsion of its CBD & Terpene Rich Hemp Oil.

Problems

- CBD American Shaman's cannabis oil emulsion products exhibited short shelf lives due to phase separation.
- These products' therapeutic effects were delayed and weak.

Goals

- To develop an all-natural, stable, water-compatible nanoemulsion formulation for the CBD & Terpene Rich Hemp Oil Concentrate.
- To optimize and scale up the production procedure for this product using ISM's Barbell Horn Ultrasonic Technology [1].

Results

- ISM was able to formulate a kinetically stable, fully water-compatible, CBD & Terpene Rich Hemp Oil Concentrate nanoemulsion using all-natural ingredients.
- The product's bioavailability increased, its onset of therapeutic action shortened, and longer-lasting effects were reported.
- The production procedure was successfully scaled-up: CBD American Shaman is now able to quickly produce large quantities of this product.

We started working with Industrial Sonomechanics after extensively researching the nanoemulsification process and equipment providers that can help us make better and more stable emulsions. We explored many options, but after speaking to ISM, we were confident that their BSP-1200 ultrasonic processor was the way to go and that they were the most knowledgeable in this field. Our emulsions are now stable and no longer separate - we use them in several of our product lines. The positive feedback we constantly receive from our customers regarding our improved water-soluble products is overwhelming - they love the fact that our products have become more fast-absorbing and that the CBD therapeutic effects last longer. We look forward to releasing a new line of CBD products and to using ISM equipment and formulations to make nanoemulsions for the rest of our merchandise.

Vince Sanders
President and CEO, CBD American Shaman

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BACKGROUND AND SUMMARY

CBD American Shaman contracted ISM to develop the formulation for an all-natural, stable, water-compatible nanoemulsion of its CBD & Terpene Rich Hemp Oil Concentrate, as well as to optimize and scale up the manufacturing procedure for this product using ISM ultrasonic equipment.

ABOUT

CBD American Shaman™

Over a decade ago, CBD American Shaman's President and CEO, Vince Sanders, began his research of the medicinal effects of cannabis in an effort to save a close family member from a disease. After many years of studying and experimenting with CBD and its therapeutic effects, he decided to commercialize this research and began selling his first line of CBD-based products.

The business grew very quickly, and today the company offers a variety of items, including skin care formulas, oils, infused beverages, pet care (feline, canine) products as well as white label solutions. The company's large customer base varies from direct consumers to vitamin stores, grocery stores, convenience stores, and medical practitioners. CBD American Shaman is passionate and committed to continuous research and development in the cannabis field for the benefit of its customers, and plans on launching several new products within the next year.

All CBD American Shaman products are made in the United States with hemp coming from Norway. The company uses the same import process as pharmaceutical-grade CBD drug manufacture laboratories.

Company headquarters: Kansas City, MO

Industry: medical cannabis, cosmetic, health and wellness, nutraceutical.

Website: www.americanshamancbd.com

Significance of the Study

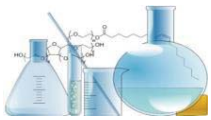
In recent years, concentrated cannabis extracts have become popular because they allow for convenient routes of administration, such as oral or transdermal. There are, however, several important challenges. Concentrates are sticky, viscous and hydrophobic substances, which are difficult to handle and incompatible with water. When consumed orally, their poor water solubility results in low bioavailability (only a small fraction is absorbed into the bloodstream) and a delayed onset of action.

The most promising solution is to formulate cannabis extracts as water-compatible nanoemulsions. This approach has been successfully used by the pharmaceutical industry to deliver a variety of hydrophobic (water-insoluble) medicinal substances to the bloodstream, resulting in a higher and more predictable bioavailability as well as a faster onset of action. Since these formulations are water-compatible, they can be easily mixed into any beverage, which simplifies consumption and makes it possible to create attractive and potent products.

Why ISM's Barbell Horn Ultrasonic Technology?

High-amplitude ultrasound is a well-established technique for the production of nanoemulsions [2]. The required high ultrasonic amplitudes are relatively easy to produce on a laboratory scale. Due to technological limitations, however, when a conventional ultrasonic processor is scaled up, its maximum ultrasonic amplitude drops well below the level needed for the nano-emulsification. ISM's patented Barbell Horn Ultrasonic Technology [1] overcomes this limitation and makes it possible to continuously produce cannabis extract nanoemulsions on laboratory, bench and industrial scales, guaranteeing reproducible results and exceptional product quality.

MATERIALS & METHODS



Materials and Experimental Steps

CBD & Terpene Rich Hemp Oil Concentrate (55% CBD) was obtained from CBD American Shaman. Olive oil was obtained from a local supermarket. Tween 80 and Span 80 surfactants were purchased from Sigma Aldrich (St. Louis, MO). A Quillaja Saponin (Q-Naturale, HLB = 13.5) sample was generously provided by Ingredion (Bridgewater, NJ). Quillaja Saponin is a natural surfactant obtained from Quillaja Saponaria Molina tree. It is extracted by a natural process and used in a range of beverages, including popular functional and flavoured waters. Particle size distributions in all experiments were measured by laser diffraction.

The formulation optimization phase comprised the following steps:

- **Step 1.** Required HLB Screening and Adjustment.
- **Step 2.** Optimization of Carrier Oil Concentration.
- **Step 3.** Optimizing Quillaja Saponin Concentration.

Ultrasonic Processors and Procedures

The experiments were conducted using two ISM ultrasonic liquid processors:

- LSP-500 laboratory-scale processor configured in the batch mode (Fig. 1a) was utilized for the formulation optimization phase.
- BSP-1200 bench-scale processor configured in the flow-through mode (Fig. 1c) was utilized for the scaled-up production phase.

During the **formulation optimization phase**, each sample volume was 25 mL, and the following processing parameters were implemented: ultrasonic amplitude = 90 μm, average sample temperature = 45 °C, exposure time = 6 min. Processed samples were passed through a 0.45 μm filter.

During the **scaled-up production phase**, the total sample volume was 6 L, and the following processing parameters were implemented: ultrasonic amplitude = 90 μm, average sample temperature = 45 °C, exposure time = 75 min. Processed samples were passed through a 0.45 μm filter.

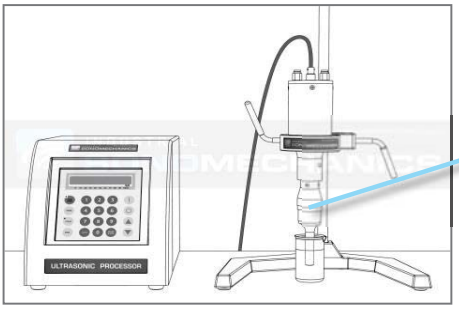


Figure 1a. LSP-500 in the batch mode equipped with a Conventional horn (CH).

Figure 1b. Conventional horn (left) and Half-wave Barbell Horn (right).

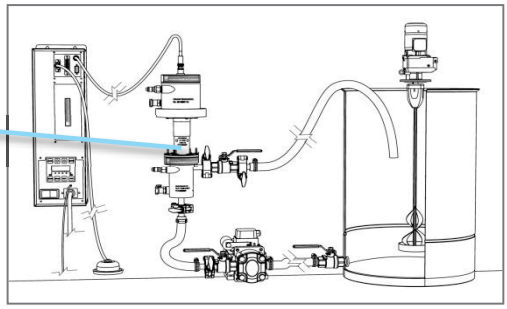


Figure 1c. BSP-1200 in the flow-through mode equipped with a Half-wave Barbell horn (HBH).

RESULTS AND DISCUSSION

Formulation Optimization Phase

Step 1. Required HLB Screening and Adjustment.

Tween 80 and Span 80 surfactants were chosen for the Required HLB screening procedure [2], during which the HLB value was modulated by changing these surfactants' relative concentrations in the mixture. At the lower olive oil concentration of 3.6 %, the Required HLB value of the oil phase (hemp oil concentrate + olive oil) was 12 (red line), which did not match the HLB = 13.5 value of Quillaja Saponin. Using a higher amount of olive oil (7.2 %) flattened the HLB line in the higher-value segment (blue line), making it possible to implement Quillaja Saponin for the nano-emulsification process.

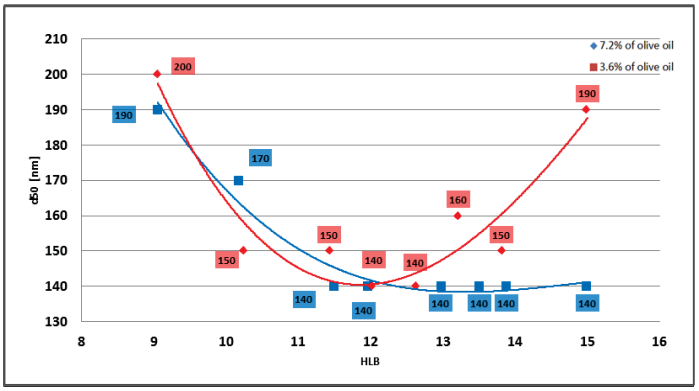


Figure 2. Screening for the Required HLB value of the hemp oil concentrate in olive oil. The following concentrations were constant: total surfactant (Tween 80 + Span 80) = 4.5 %, hemp oil concentrate = 5.4 %. Olive oil concentrations were 3.6 % (red line) and 7.2 % (blue line).

Step 2. Optimization of Carrier Oil Concentration.

An "inverse" experiment confirming that increasing the carrier oil concentration to 7.2 % allows the HLB = 13.5 value of Quillaja Saponin to correctly match the Required HLB of the oil phase was carried out, in which the hemp oil and total surfactant concentrations were maintained at constant values, while the olive oil concentration was varied from 0 to 14 %. The experiment confirmed that olive oil concentrations around 7 % corresponded to the minimum median droplet size (d50 = 110 nm) in the resulting nanoemulsions.

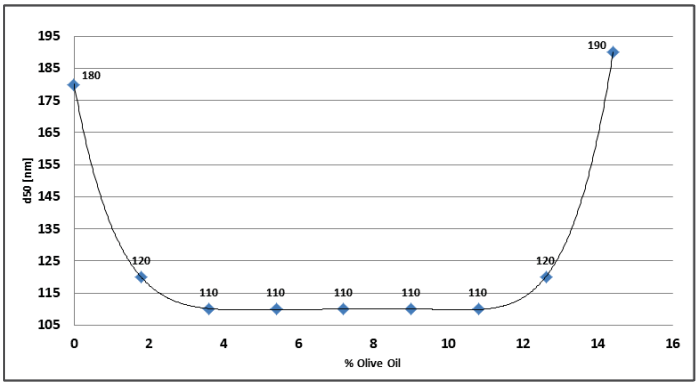


Figure 3. The effect of olive oil concentration on the median droplet size (d50). The following concentrations were constant: Quillaja Saponin from Q-Naturale = 4.5 % (based on 14 % Saponin content in Q-Naturale, HLB = 13.5), hemp oil concentrate = 5.4%.

RESULTS AND DISCUSSION

Step 3. Optimizing Quillaja Saponin Concentration.

The lowest concentration of Quillaja Saponin leading to the minimum median droplet size (d50 = 110 nm) in the resulting nanoemulsion was determined in the final step of this formulation optimization procedure. The minimum d50 value was achieved with 3 % of Quillaja Saponin (Q-Naturale concentration was 21.4%, based on its 14% Quillaja Saponin content). Further increase in the surfactant content did not result in any reduction in the d50 value, and was, therefore, unnecessary.

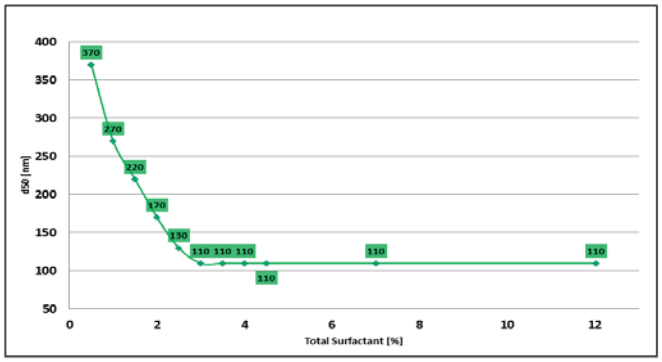


Figure 4. The effect of Quillaja Saponin concentration on the median droplet size (d50). The following concentrations were constant: hemp oil concentrate = 5.4 %, olive oil = 7.2 %.

Final Formulation:

The optimal formulation for American Shaman's CBD & Terpene Rich Hemp Oil Concentrate nanoemulsion was, therefore, determined to be:

1. Hemp oil concentrate ---------- 5.4% (CBD concentration is 3% or 30 mg/ml).
2. Olive oil ----------7.2%.
3. Quillaja Saponin ---------- 3% (Q-Naturale concentration is 21.4%, based on 14% Saponin content).
4. Water ----------91.6% (18.4% coming from Q-Naturale).

Scaled-up Production Phase

This phase of the case study was carried out with the same ultrasonic processor (BSP-1200, Fig. 5) and at the same set of conditions (total sample volume = 6 L, ultrasonic amplitude = 90 μm, average sample temperature = 45 °C, exposure time = 75 min), as those currently implemented by CBD American Shaman for the production of all their nanoemulsion-based products, including water-soluble hemp oils, body lotions as well as feline and canine products. The combination of formulation and processing parameters developed in the course of this project yields an all-natural, fully water-compatible and kinetically stable nanoemulsion with the median droplet size value of 110 nm. Customers report improved bioavailability and longer-lasting therapeutic effects.

RESULTS AND DISCUSSION

Conclusions

This case study and feedback from customers have shown that all-natural, water-compatible and stable nanoemulsions of cannabis extract oils can be easily manufactured by high-amplitude ultrasonic processing. With the use of ISM's Barbell Horn Ultrasonic Technology [1], the process can be reliably transferred from the laboratory to the commercial scale without reducing the required high ultrasonic amplitudes and treatment intensities, thereby guaranteeing reproducible results and exceptional product quality. Further scale up can be achieved by upgrading to ISM ISP-3000 industrial-scale processor, which can produce approximately 20 L of this type of nanoemulsion per hour.

Figure 5. BSP-1200 Ultrasonic processor configured in the flow-through mode.

> *We are now receiving tons of positive feedback from our customers on the improved absorption and longer-lasting effects of this new formulation! People love the flavor as well as how easily the products can be mixed with beverages. The BSP-1200 processor is very easy to operate, and ISM provided great technical support. The company has a huge advantage over their competitors - they can develop advanced formulations and offer equipment able to run the nano-emulsification process on a large scale, while other ultrasound companies cannot do any of that. The staff is very knowledgeable and responds fast to inquiries. It was a no brainer to go with them.*
>
> ***Vince Sanders***
> *President and CEO, CBD American Shaman*

References

[1] Peshkovsky, S.L., Peshkovsky, A.S., High capacity ultrasonic reactor system. Industrial Sonomechanics, LLC, U.S. Patent No.: 8,651,230 (2014), International Application No.: PCT/US2008/068697 (2008).

[2] Peshkovsky, A.S., Peshkovsky, S.L., and Bystryak, S., Scalable high-power ultrasonic technology for the production of translucent nanoemulsions. Chem. Eng. Process., 2013, 69: p. 77-82.

ABOUT INDUSTRIAL SONOMECHANICS

Industrial Sonomechanics, LLC, (ISM) is a research & development, equipment design and process consulting firm, specializing in high-intensity ultrasonic technology for liquid treatment by acoustic cavitation. Our patented Barbell Horn Ultrasonic Technology (BHUT) enables the generation of extremely high ultrasonic amplitudes and cavitation intensities at any scale, making it possible to directly apply laboratory optimization results in an industrial production environment.

ISM ultrasonic liquid processors (homogenizers, sonicators, mixers) are ideal for the production of nanoemulsions, nanocrystals and liposomes. Other common applications are cell disruption, plant oil extraction, degassing, dispersing, transesterification, desulphurization, and sterilization. Industries utilizing ISM technology include pharmaceutical, medical cannabis, cosmetic, nutraceutical, food & beverage, printer ink, paint, adhesive, pesticide, chemical and alternative fuel.

HAVE QUESTIONS?

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