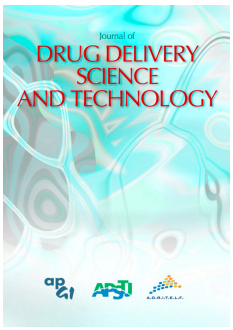
Journal Pre-proof



Cannabis Extract Nanoemulsions Produced by High-intensity Ultrasound: Formulation Development and Scale-up

Shlomo Leibtag, Alexey Peshkovsky

PII: S1773-2247(20)31242-9

DOI: https://doi.org/10.1016/j.jddst.2020.101953

Reference: JDDST 101953

To appear in: *Journal of Drug Delivery Science and Technology*

Received Date: 18 February 2020

Revised Date: 27 May 2020

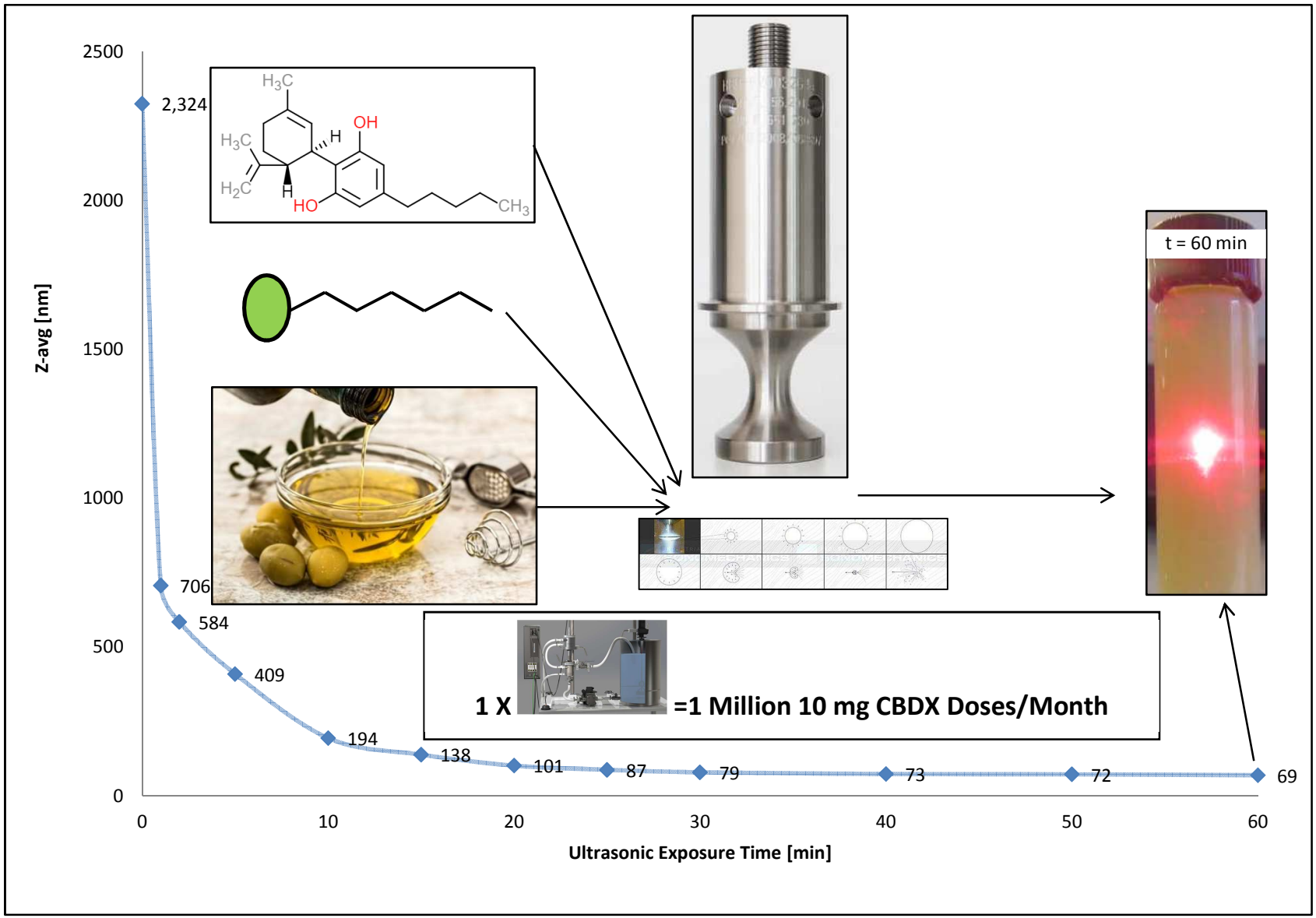
Accepted Date: 20 July 2020

Please cite this article as: S. Leibtag, A. Peshkovsky, Cannabis Extract Nanoemulsions Produced by High-intensity Ultrasound: Formulation Development and Scale-up, *Journal of Drug Delivery Science and Technology*, https://doi.org/10.1016/j.jddst.2020.101953.

CRedIT:

Shlomo Leibtag: Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Visualization.

Alexey Peshkovsky: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project Administration.



Graphical Abstract

Cannabis Extract Nanoemulsions Produced by High-intensity Ultrasound: Formulation Development and Scale-up

Shlomo Leibtag [Industrial Sonomechanics, LLC], 7440 SW 50th Terrace #110, Miami, FL 33155

Alexey Peshkovsky [Industrial Sonomechanics, LLC], 7440 SW 50th Terrace #110, Miami, FL 33155

Corresponding Author:
Shlomo Leibtag[1]

E-mail: shlomo@sonomechanics.com

1. Present Address:
10 North Calvert Street
Unit 903
Baltimore, MD 21202
USA

Abstract

Over the past several decades, it has been demonstrated that cannabinoids offer a wide range of therapeutic benefits. Their oral administration, however, while arguably the most convenient and discrete, has been associated with low bioavailability, delayed onset of action and poor reproducibility resulting from the extracts' strongly lipophilic character. To overcome these obstacles, cannabinoids can be incorporated into oil-in-water nanoemulsions: a process known to enhance the delivery of lipophilic bio-actives by making them behave like water-soluble (hydrophilic) compounds. In this manuscript, formulation development and production scale-up procedures for a cannabis extract (CBDX, 55% cannabidiol)-containing nanoemulsion are described. Nanoemulsion samples were prepared by high-intensity ultrasonic liquid processing, and the formulation was optimized for carrier oil and surfactant(s) contents as well as for the hydrophilic-lipophilic balance (HLB) of the surfactant mixture. Translucent CBDX-containing nanoemulsions with median droplet sizes well below 100 nm were possible to form with synthetic surfactants (Tween 80 / Span 80 mixture), but not with a natural surfactant (Q-naturale®). By utilizing Barbell Horn® Ultrasonic Technology (BHUT), the nano-emulsification process was successfully scaled up, achieving a commercial-level processing rate equivalent to one million nanoemulsified 10 mg CBDX doses made per month with a single bench-scale ultrasonic liquid processor (BSP-1200).

CRedIT:

Shlomo Leibtag: Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Visualization. **Alexey Peshkovsky**: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project Administration.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest:

None

1 Introduction:

The discovery of the CB1 and CB2 endogenous cannabinoid receptors has spurred an exponential growth of studies exploring the endocannabinoid system and its regulatory functions in health and disease [1]. Over the last several decades, it has been demonstrated that medicinal cannabis has many therapeutic benefits [2,3]. The most studied cannabinoids, tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), have shown promising results in the management of chronic pain [4], decreasing spasticity and inflammation in neurodegenerative disorders [5] and limiting vomiting and nausea induced by chemotherapy [6].

It is generally agreed that due to better patient compliance, oral administration of pharmaceuticals is preferred over other delivery routes [7]. The lipophilic nature and consequent low aqueous solubility of cannabinoids [8–11], however, result in their low bioavailability (*F*) and long peak concentrations times when administered orally (<20% [12], >2 hr [13], respectively). This presents a major difficulty in designing and systemically delivering cannabinoid-based formulations for most therapeutic applications.

1.1 Delivery Routes of Cannabinoids

Due to the above-mentioned obstacles involved in oral delivery, alternative administration routes of cannabinoids are predominately used. The oldest and most traditional route is pulmonary delivery via inhalation of the smoke produced by burning the plant matter (smoking). This route is simple (requires just the plant matter and a pipe or rolling paper), avoids first-pass metabolism [7,14] and allows the effects to be felt almost immediately [12]. Smoking, however, is generally not a desired method for medicinal purposes due to the associated carcinogenic combustion by-products, which are harmful to the lungs [15], and because patients (especially the elderly) may not be compliant because of the harshness of smoking. As an alternative to smoking, a different pulmonary route of administration -

vaporization of cannabis plant matter or of extracted cannabis oils (vaping) - has recently became popular [16]. Vaping is sometimes claimed to be a safer alternative to traditional smoking, yet such claims are largely unsubstantiated [17] and, like nicotine-based vaping, it should not be viewed as harmless [18]. In addition, this method also suffers from the unavoidable variability in patient-to-patient inhalation patterns, resulting in unpredictable bioavailability. Specifically, parameters such as the frequency of puffs and patient-specific inhalation and exhalation rates greatly influence the degree of drug exposure [12] and likely contribute to the imprecision in recorded bioavailability of 2% - 50% [12] of inhaled (smoked or vaporized) cannabis.

Other delivery routes of cannabinoids that similarly circumvent first pass metabolism, such as sub-lingual [8,19], intranasal [11,20,21], topical, transdermal [11,22] and rectal [14], have also been explored. A sub-lingual (below the tongue) spray (Sativex®) containing a near one-to-one mix of THC to CBD has been developed and approved in Europe for the treatment of spasticity associated with multiple sclerosis (MS) [5]. While exceeding the bioavailability of orally administered synthetic cannabinoid capsules [19], sub-lingual administration requires the patient to hold the sprayed liquid under the tongue [23], which is unreliable because an involuntary reflex and/or the bitter taste of cannabinoid extracts [24] may cause the patient to swallow (wash-down) the spray and send the active cannabinoid towards the digestive absorption pathway (below). Further, a high concentration of ethanol used as a solubilizing agent in Sativex® may cause harmful irritation [8,24]. Transdermal and intranasal delivery of cannabinoids have been studied in various animal models [11,21], reporting bioavailabilities that are low, variable and highly dependent on the solubilizing agent. Rectal delivery of cannabinoids has demonstrated high bioavailability in dogs (67% [14]) and about 30 times the blood plasma levels compared to oral capsule administration in human subjects [14], but this method is hindered by low patient compliance and the fact that absorption can be interrupted by defecation [25].

Digestive absorption is generally the most convenient and patient-compliant method of drug delivery [7,26,27], yet delivering poorly water-soluble species via the gastrointestinal track (GIT) generally leads to inefficient absorption of the drug. In studies of CBD or THC administered as an oral dose to human subjects, low bioavailability is exhibited (4 - 20%) [12–14,28], and thus a high dose is required for therapeutic effect. Additionally, the onset of action is slow as peak concentrations are not reached for at least 2 hours [13]. When co-administered with dietary lipids, highly lipophilic pharmaceuticals are incorporated into the lipid digestion/absorption pathway [27,29] and to that, post-prandial administration is generally recommended [30]. It has been demonstrated in rats that cannabis formulations containing sesame oil (mostly Long-Chain Triglycerides (LCTs)) can double the bioavailability of active cannabinoids [31] compared to a formulation without LCT oil. This is likely due to LCT's preferentially partitioning to the lacteals, as oppose to the hepatic portal vein, in the form of chylomicrons (with cannabinoids incorporated), stimulating intestinal lymphatic delivery and avoiding cannabinoid loss by first-pass metabolism in the liver [32]. However, even in conjunction with LCTs the bioavailability is rather low (21.5% [31]) and it is likely that other factors, such as slow micellization in the duodenum and the competing elimination from the GIT, ultimately limit the bioavailability of cannabinoids. Thus, to further increase the bioavailability of orally administered lipophilic drugs, such as cannabinoids, delivery vehicles that increase their apparent aqueous solubility are of great interest [33].

1.2 Nanoemulsions

A rapidly developing and promising method for enhancing the aqueous compatibility of ingested lipophilic compounds and ultimately increasing their bioavailability and accelerating their onset of action is to incorporate them into oil-in-water (O/W) nanoemulsions [34–39]. Nanoemulsions are kinetically stable liquid-liquid dispersions of spherical droplets in which the dispersed phase droplet diameter (D) is typically near or below 200 nm [40]. Such small droplets have very high surface area-to-volume ratios which promotes high surface tension (γ) at the water - oil interface. This increased γ

coupled with small D steeply increases the pressure difference between the inside and the outside of the droplet surface, known as the Laplace pressure ($\Delta P = \frac{4\gamma}{D}$) [35,41], and represents an energy barrier that must be overcome to form nanoemulsions. A typical nanoemulsion concentrate for pharmaceutical drug delivery contains an oil phase, consisting of the active lipophilic compound dissolved in a carrier oil, surfactant(s) and water. LCT carrier oils are commonly used in nanoemulsion formulations as they simplify processing by lowering the viscosity of the oil phase [42] and, as mentioned above, can increase the bioavailability of lipophilic drugs [31,32]. Surfactants are amphiphilic species with polar heads and non-polar tails that preferentially adsorb to water/oil interfaces and are essential to nanoemulsion formation because they reduce the surface tension between the two immiscible phases and, therefore, lower the energy barrier that has to be overcome during the nanoemulsion formation. Surfactants are also critical to the long-term stability of nanoemulsions as they sustain small droplets, thereby allowing Brownian motion to overwhelm any gravitational separation routes (creaming, sedimentation) [41,43]. Additionally, the polar head groups at the droplet surface protect the particles from flocculation or coalescence via electrostatic/steric repulsion [42]. Arguably, the most prevalent additional nanoemulsion destabilization mechanism is Ostwald-ripening [43]. This phenomenon is driven by the Laplace pressure at the surface of nanoemulsion droplets, which preferentially forces oil molecules from smaller droplets into the continuous aqueous phase, followed by their uptake into larger droplets. This effectively allows larger droplets to grow at the expense of smaller ones. Wooster et al. [42] demonstrated that Ostwald-ripening is significantly curtailed in nanoemulsions containing LCT oils with poor aqueous solubility, as dissolution of the oil phase into the continuous phase is unfavored.

Aside from a steep increase in the bioavailabity of poorly water-soluble compounds incorporated into O/W nanoemulsions [36,41,44–46], there are two particular characteristics to nanoemulsions that manifest themselves when all of their droplets fall below 100 nm in diameter. Firstly, visible light scatters weakly when passing through such nanoemulsions, resulting in their optical

translucency [35,47] and making it possible to incorporate them into an array of products without causing visual alteration. Secondly, it allows for the nanoemulsions to easily pass through a sterile filter (220 nm pore size), which must be done in order to remove any microbial or particulate contamination, without rejecting any of the dispersed oil droplets.

1.3 Fabrication of Nanoemulsions

Nanoemulsion fabrication methods are divided into low-energy/bottom-up and high-energy/top-down groups. Low-energy approaches generally require much greater amounts of harsh surfactants [43] and, from the commercial point of view, present potentially prohibitive material costs, making them impractical for the production of nanoemulsions beyond laboratory scale [35,48]. High-energy nano-emulsification methods are driven by mechanical devices that promote high-intensity cavitation in pre-mixed formulations and are generally more appropriate for the commercial production of nanoemulsions [43]. Cavitation provides high-shear forces that break up and disperse oil droplets to form stable nanoemulsions.

High-Pressure Homogenization (HPH) is an umbrella term, encompassing nano-emulsification methods that rely on high pressure differences to promote cavitation. A widely used HPH device called Microfluidizer® (Microfluidics™ International Corporation, Warminster, MA) utilizes high pressures to force pre-emulsified formulations into an interaction chamber consisting of microchannels that impinge onto each other to promote cavitation [43]. While this method has gained increasing prevalence since the mid-1990s [49], a significant drawback to utilizing a Microfluidizer® is the high pressure (commonly, >3000 atm) that must be maintained throughout the process, resulting in a high power requirement [43] that imposes significant operating and maintenance costs.

Over the past decade, high-intensity ultrasonic liquid processing has become a well-established high-energy technique for the commercial preparation of food and pharmaceutical-grade

nanoemulsions [35,43,47–51]. This technique involves driving a transducer coupled to a horn (a.k.a. probe, sonotrode, waveguide radiator), vibrating at an ultrasonic frequency (typically 20 kHz) and a peak-to-peak amplitude of 80-100 μm in a liquid mixture of water, oil(s) and surfactant(s) [65]. This intensely vibrating horn promotes acoustic cavitation - the violent formation and asymmetric implosion of vacuum bubbles [52]. Acoustic cavitation causes micro-jets and intense shear forces in the liquid that break up and disperse the oil droplets. The newly-formed oil surface then readily becomes coated with available surfactants [47]. Along with water and oil viscosities [35,42], the carrier oil and surfactant types [42,48] as well as the intensity and duration of cavitation will ultimately dictate the final droplet size in an ultrasonically prepared nanoemulsion [47,53]. The intensity of ultrasound and of the resulting acoustic cavitation is proportional to the displacement amplitude of the ultrasonic horn. The output surface area of the horn in contact with the liquid, at a given amplitude, pressure and liquid type, dictates the ultrasonic power delivered to the liquid load and, therefore, the scale of the ultrasonic process. Although nanoemulsion formulations containing cannabis extracts and polysorbate surfactants processed ultrasonically were first produced nearly 50 years ago [54], the optimization methodologies for these formulations were not developed until recently [47].

Further, the implementation of high-amplitude ultrasonic processes to commercial production of cannabinoid-loaded nanoemulsions was believed to be impractical due to limitations attributed to conventional ultrasonic horn designs (large input diameter, small output diameter) [43]. Conventional horns do not allow their output surface area and maximum achievable amplitude to scale independently of each other. Thus, when larger scales are desired, high amplitudes cannot be maintained, and the resulting cavitation intensity is insufficient for nano-emulsification [47,50,52]. This limitation has been successfully overcome by Barbell Horn® Ultrasonic Technology (BHUT) [47,50,55,56], which allows the output surface of a horn to increase without limiting the maximum amplitude achievable by the horn. The application of BHUT has demonstrated the possibility of producing pharmaceutical-grade

nanoemulsions at an industrial-scale [47,50,55,57] with as much as 60 times higher productivity rates than those possible with laboratory-scale ultrasonic liquid processors [50]. Further, in the preparation of the MF59® vaccine adjuvant nanoemulsion, BHUT demonstrated a productivity rate eight times greater than a Microfluidizer® while having a 12 times lower power requirement [43].

The overall objective of this study was to investigate and demonstrate the feasibility of implementing BHUT for the commercial production of CBD-containing nanoemulsions. Carrier oil and surfactant content as well as the Hydrophilic-Lipophilic Balance (HLB) of the surfactant mixture were optimized on the laboratory-scale to minimize the median droplet size in the nanoemulsions. Subsequently, a scaled-up nano-emulsification study was performed to determine the bench-scale productivity rate for CBD-containing nanoemulsions prepared via BHUT.

2 Materials and Methods:

2.1 Materials

Industrial hemp-derived, CBD extract (CBDX, 55% CBD) was generously gifted by American Shaman (Olathe, KS, USA). Two food-grade synthetic surfactants, Tween 80 (HLB = 15), Span 80 (HLB = 4.3), were purchased from Sigma-Aldrich (St. Louis, MO, USA) and one food-grade natural surfactant, Q-naturale® (14% w/w solution of Quillaja saponin, HLB = 13.5), was provided by Ingredion (Englewood, CO, USA). Refined olive oil and distilled water were purchased from a local super-market.

2.2 Formulation Optimization

A convenient nanoemulsion formulation optimization method was adapted from Peshkovsky et al. [47,57]. Briefly, when two surfactants are incorporated into a nanoemulsion, the HLB of the mixture can be modulated by altering the ratios of the surfactants while maintaining their combined amount at a constant level. The resulting HLB (HLB_{AB}) is described by equation 1:

$$HLB_{AB} = \frac{HLB_A M_A + HLB_B M_B}{M_A + M_B} \quad (1)$$

where HLB_A and HLB_B refer to the independent HLB values of surfactant A and B and M_A and M_B are the corresponding masses of surfactants A and B, respectively. For any oil dispersed in an aqueous phase, we describe its optimal HLB (HLB_{OPT}) as the HLB_{AB} at which the minimum droplet size is achieved. Accordingly, the formulation optimization was performed by preparing a series of nanoemulsions in which the water phase, oil phase and total surfactant content, as well as all processing parameters remained constant while the HLB_{AB} was systematically varied.

Before sonication, a coarse emulsion of each sample was prepared by mixing the *oil phase* (pre-mixed refined olive oil, CBDX and the lower-HLB surfactant) and *aqueous phase* (pre-mixed distilled water and the higher-HLB surfactant) (25 g total) in a 40 mL vial on a magnetic stirrer at 500 rpm for 10

minutes. The coarse emulsion was then sonicated for 6 minutes with a 500 W laboratory-scale ultrasonic liquid processor (LSP-500, Industrial Sonomechanics, Miami, FL), using a conventional horn (CH, Tip Diameter = 12.7 mm) vibrating at the frequency of 20 kHz and the ultrasonic amplitude of 90 μm peak-to-peak. During processing, the vial was placed in an ice/water bath to maintain the liquid temperature below 60˚C at all times. Once sonicated, samples were filtered through 1 μm glass fiber filters (Omicron) and then diluted 100-fold before performing particle size analysis by Laser Diffraction (AimSizer 2012, HMKTest, Dandong, China). The median diameter of the nanoemulsion droplets (d_{50}) was the primary size characterization value reported.

2.3 Process Scale-up Demonstration

Using the determined HLB_{OPT} for the CBDX nanoemulsion, a 4.2 Kg nanoemulsion sample was processed using a 1200 W bench-scale ultrasonic liquid processor (BSP-1200, Industrial Sonomechanics, Miami, FL), equipped with a Half-Wave Barbell Horn® (HBH, Tip Diameter = 32 mm) operating in a flow-through reactor chamber (with a cooling jacket used to maintain the nanoemulsion temperature below 60˚C at all times) at the frequency of 20 kHz and the ultrasonic amplitude of 90 μm peak-to-peak (Fig. 1). Samples were drawn at predetermined time points, diluted 100-fold and the intensity-weighted average droplet diameter (Z-avg) for each sample was determined via Dynamic Light Scattering (DLS) (Zetasizer, Malvern Panalytical Inc.).

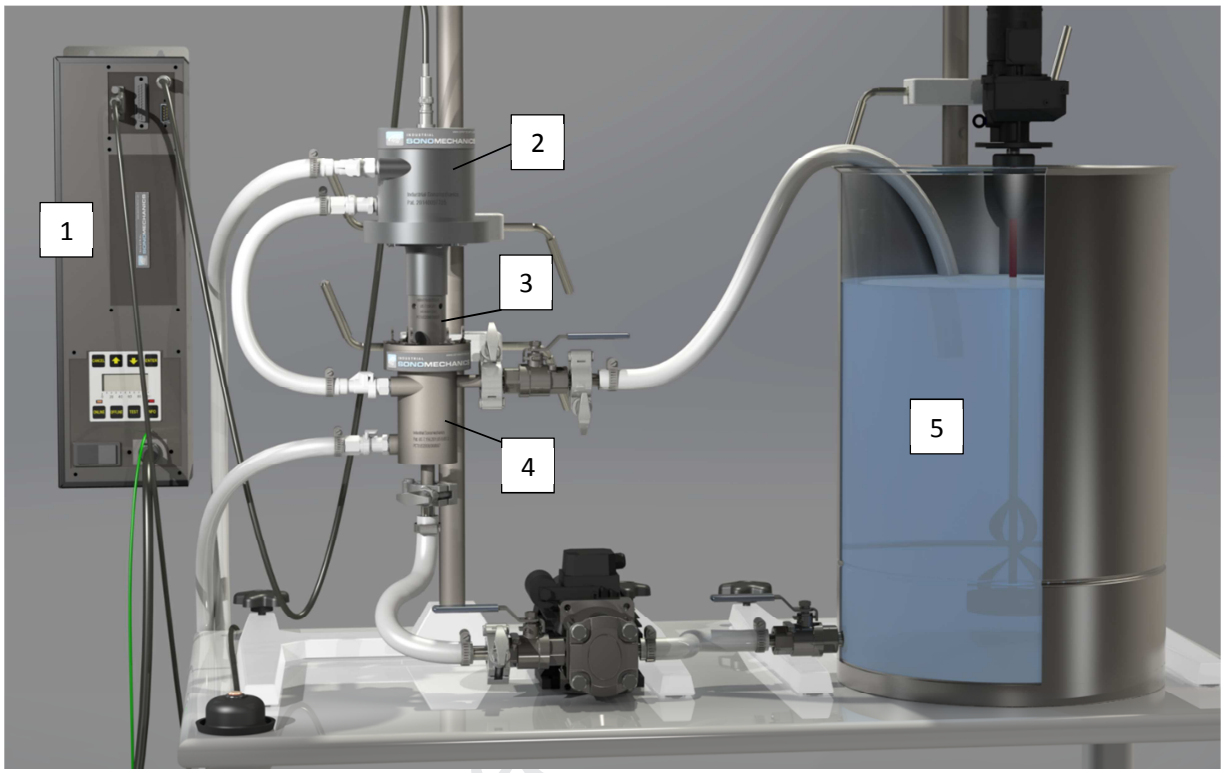


Figure 1. BSP-1200 Ultrasonic Processor in the Flow-Through Mode. The 1,200 W ultrasonic generator (1) excites vibration in the piezoelectric transducer (2). The vibration amplitude is then amplified by the HBH-type Barbell Horn® (3) which comes into contact with the process liquid flowing through the reactor chamber (4) and promotes acoustic cavitation in the liquid. The process liquid recirculates from the stirred tank (5) to the reactor chamber and back. Water cooling to the piezoelectric transducer and process liquid are provided via cooling jackets surrounding the piezoelectric transducer and reactor chamber.

3 Results and Discussion:

3.1 Importance of Carrier Oil

The first step in the optimization of the CBDX-containing nanoemulsion formulation was to understand the importance of including a carrier oil. LCTs are known to assist the absorption of lipophilic bio-actives [30,31,58], but their effect on CBDX-containing nanoemulsion droplet sizes was unclear. Two nanoemulsion samples were prepared; their composition and d_{50} values are displayed in Table 1. Refined olive oil was used as the LCT carrier oil.

It is evident that the presence of a carrier oil in the formulation significantly reduces the d_{50} even though the total oil-phase content was 2.3 times greater. To understand why, one must consider the rheological state of the dispersed droplets. Cannabis extracts are highly viscous at room temperature. Combining such an extract with a carrier oil, however, drastically lowers the resulting oil-phase viscosity, making it much less resistant to shear forces. Indeed, Wooster et al. [42], suggests that for high-shear-promoted droplet size reduction, the optimal ratio of oil phase to aqueous-phase viscosities (η_{oil}/η_{water}) is 0.5 – 5. While our carrier oil-containing nanoemulsion did not reach this optimal range, the drastic decrease in its d_{50} value compared with the formulation without carrier oil can be attributed to the significant reduction of its η_{oil}/η_{water}.

Surfactant (2:1, Tween 80:Span 80)	CBDX (55% CBD)	Refined Olive Oil	Total Oil-Phase	Water	Approx. η_{oil}/η_{water} (@ 25˚C) [59]	d_{50} [nm]
4.5%	5.4%	0	5.4%	90.1%	10,000	590
4.5%	5.4%	7.2%	12.6%	82.9%	50	170

Table 1. Comparison of carrier oil-containing and non-carrier oil-containing nanoemulsion formulations (all in % w/w).

3.2 Carrier Oil Content Optimization Using a Natural Surfactant-Based Formulation

The drastic decrease in the d_{50} value due to the presence of a LCT carrier oil, coupled with LCTs' assistance in the digestion and absorption of lipophilic species, demonstrates the need for its incorporation into cannabis extract-containing nanoemulsions. As the carrier oil concentration increases, however, it is reasonable to expect that the droplet diameter minimization due to the oil-phase viscosity reduction would eventually be outweighed by the overall increase in the total oil-phase loading. To determine the optimal carrier oil content range, an optimization study was performed. Q-naturale was used as the surfactant. Since this product comprises Quillaja saponin (14% solution in water) extracted from Quillaja saponaria tree bark, it yields an all-natural nanoemulsion formulation, containing no synthetic components. A series of nanoemulsion samples were formulated containing constant Quillaja saponin (4.5% w/w) and CBDX (5.4% w/w) amounts, while the carrier oil (refined olive oil) content was increased (0 - 14.4% w/w).

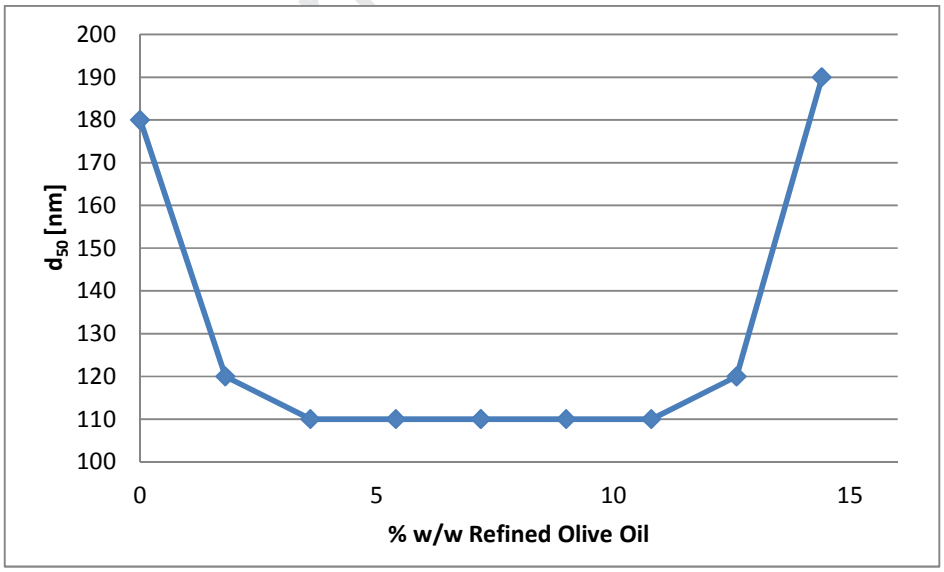


Figure 2. Carrier Oil Content and Droplet Size: Carrier oil content optimization in a CBDX (5.4% w/w) nanoemulsion produced with Q-naturale (Quillaja saponin content = 4.5% w/w).

Fig. 2 demonstrates that even a small amount of carrier oil (3.6% w/w) greatly reduces the d_{50} value. After this reduction, the value temporarily plateaus as the effects of further oil-thinning are counter-balanced by the increasing total oil-phase loading. When the carrier oil content increases beyond 12% w/w, the oil-phase loading-promoted diameter increase takes over. The optimal formulation was taken at the midpoint of the plateau, resulting in the concentration displayed in Table 2.

Quillaja Saponin (from Q-Naturale)	CBDX (55% CBD)	Refined Olive Oil	Total Oil- Phase	Water	d_{50} [nm]
4.5%	5.4%	7.2%	12.6%	82.9%	110

Table 2. Optimized carrier (refined olive) oil content for CBDX-containing nanoemulsion formulation (all in % w/w).

3.3 HLB_{OPT} Determination Using Tween 80 and Span 80-Based Formulations

In order to further minimize the d_{50} of CBDX-containing nanoemulsions, a series of HLB_{AB} optimizations were performed. Three formulations were optimized: 1) comprising 5.4% of CBDX and no carrier oil (HLB Opt. 1), 2) comprising 12.6% of refined olive oil and no CBDX (HLB Opt. 2) and 3) comprising 7.2% of refined olive oil and 5.4% of CBDX (HLB Opt. 3). All three formulations contained 4.5% of total surfactant (Tween 80 and Span 80). A cubic regression was performed on each of the HLB_{AB} optimizations and their first derivatives were taken to determine HLB_{AB} values at which the droplet size distributions reached their minimum d_{50}.

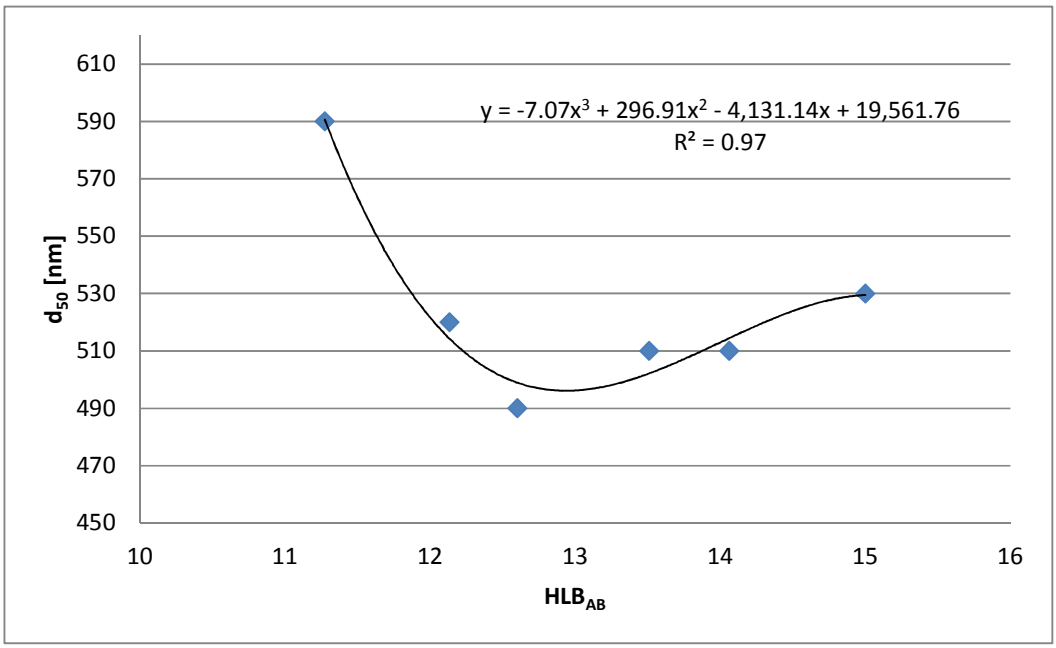


Figure 3. HLB Opt. 1: HLB_{AB} optimization of carrier oil-free, CBDX (5.4% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

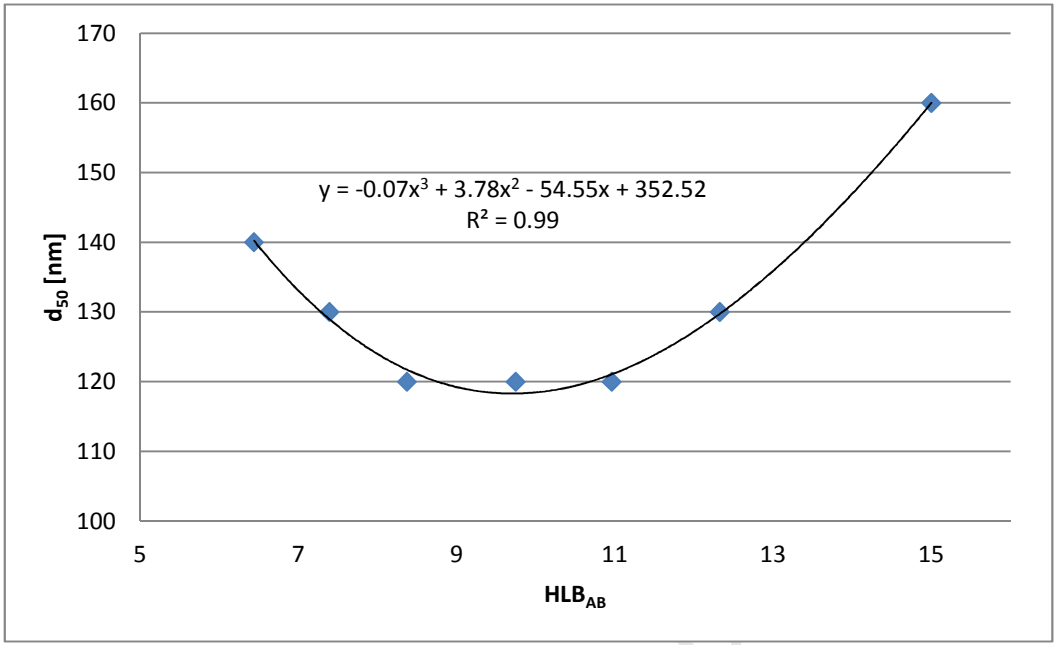


Figure 4. HLB Opt. 2: HLB_{AB} optimization of CBDX-free, refined olive oil (12.6% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

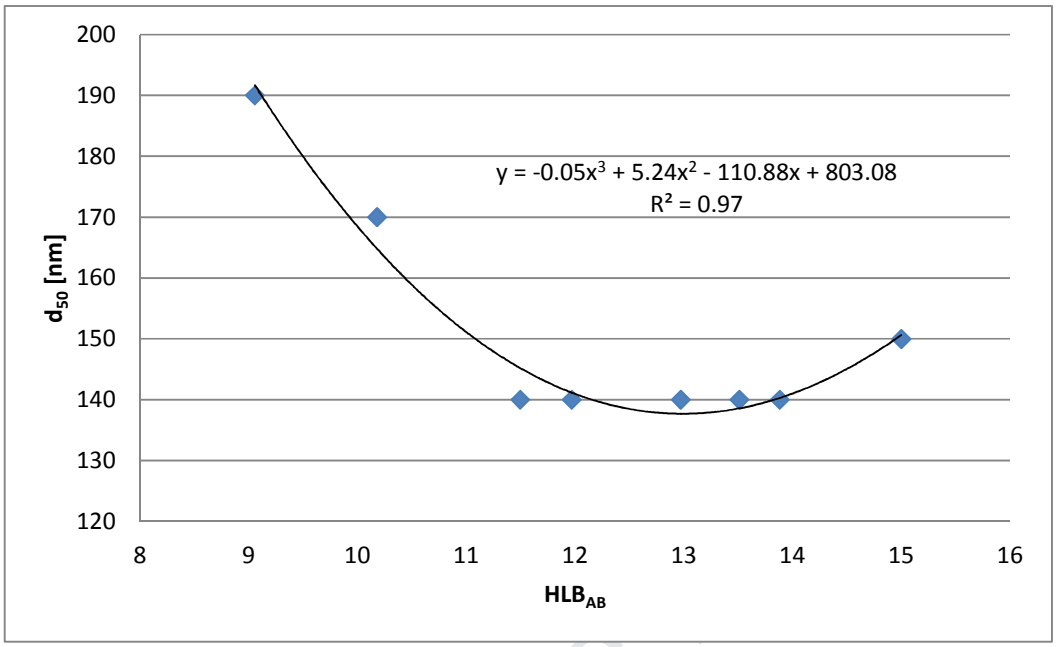


Figure 5. HLB Opt. 3: HLB_{AB} optimization of CBDX (5.4% w/w) and refined olive oil (7.2% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

Opt. No.	HLB_{OPT}	Minimum d_{50} [nm]
HLB Opt. 1	12.9	490
HLB Opt. 2	9.7	120
HLB Opt. 3	13.0	140

Table 3. HLB_{OPT} and corresponding minimum d_{50} values for each HLB_{AB} optimization.

Each optimization demonstrates that the HLB_{AB} plays a significant role in the ultimate size of the droplets in a nanoemulsion formed via high-intensity ultrasonic cavitation and that by fine-tuning the HLB_{AB}, the d_{50} can be significantly minimized. The HLB_{OPT} for carrier oil-free CBDX was 12.9 (Fig. 3), which contrasts the HLB_{OPT} of about 9.5 previously determined for a refined hemp seed extract optimized with Tween 80 and Span 80 [60]. This discrepancy in HLB_{OPT} is likely due to the fundamental difference in chemical composition between the refined hemp oil (>85% unsaturated fatty acids) and CBDX (55% CBD). The HLB_{OPT} for refined olive oil (Fig. 4) was determined to be 9.7, which agrees with the previous finding for the refined hemp seed oil [60] and demonstrates that oils consisting of mostly unsaturated fatty acids have similar HLB_{OPT} values, regardless of their source. For the combination of the refined olive oil and CBDX (Fig. 5), the HLB_{OPT} remained near that of the pure CBDX (HLB_{OPT} = 13). The HLB_{AB}-optimized formulation of the CBDX/refined olive oil-in-water nanoemulsion is presented in Table 4.

Tween 80	Span 80	HLB_{AB}	CBDX (55% CBD)	Refined Olive Oil	Total Oil-Phase	Water	d_{50} [nm]
3.7%	0.8%	13	5.4%	7.2%	12.6%	82.9%	140

Table 4. HLB_{AB}-optimized CBDX formulation with the Tween 80 and Span 80 ratio corresponding to the HLB_{OPT} value (all in % w/w).

3.4 Translucency Approach

Another interesting character of nanoemulsions is their capability to become translucent when their d_{50} falls well below 100 nm [47]. Beyond providing significant enhancements in the digestive adsorption of lipophilic actives [61], an important advantage of translucent nanoemulsions is that they can be incorporated into an array of water-based products without causing any visual alteration. To determine the total concentration of surfactants required for translucency, a series of two HLB_{AB}-optimized formulation samples (Tables 2 and 4) were prepared, in which the total surfactant amount was incrementally increased. Fig. 6 shows the reduction in d_{50} achieved by an increase in the ratio of the total surfactant to total oil-phase concentrations (ϕ).

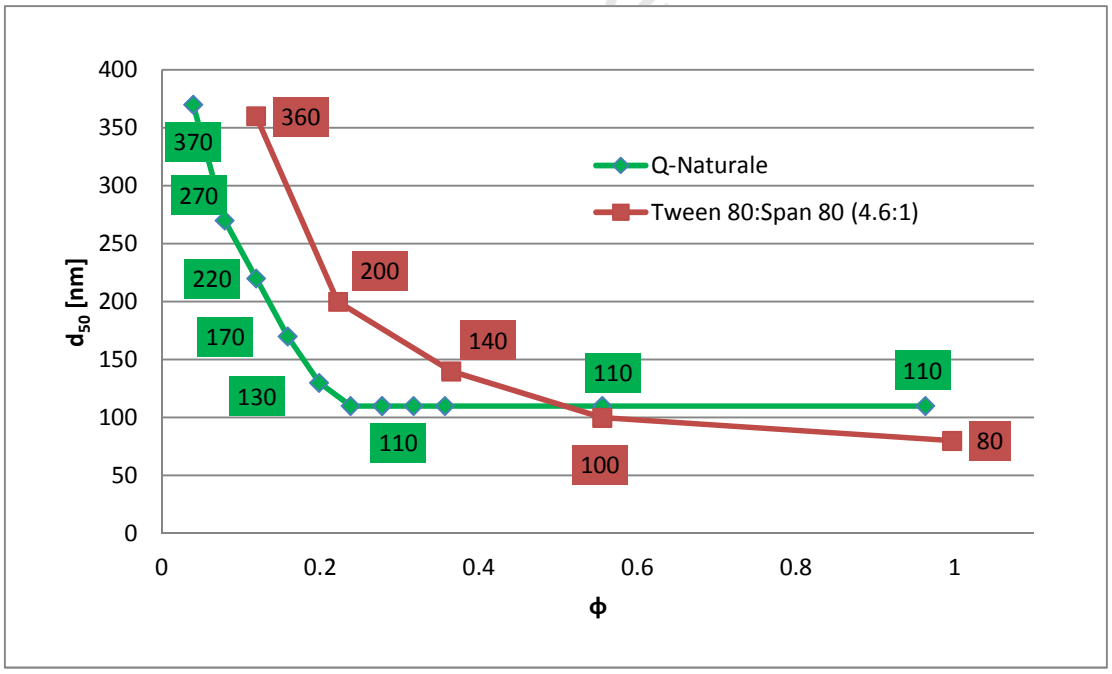


Figure 6. Translucency Approach: The droplet size dependence on surfactant to oil ratio (Φ) of the natural and HLB_{AB}-optimized synthetic surfactant formulations. Refined olive oil (7.2% w/w) and CBDX (5.4% w/w) were used in both formulations.

As demonstrated in Fig. 6, Q-naturale outperforms the HLB_{AB}-optimized Tween 80/Span 80 combination at low values of ϕ, despite the similarity in the respective HLB values of the two surfactant systems (HLB = 13.5 for Q-naturale and 13 for the HLB_{AB}-optimized Tween 80/Span 80). As the total surfactant

concentration increases, the d_{50} of the Q-naturale nanoemulsions plateaus at ϕ=0.2, d_{50} = 110 nm, failing to reach values corresponding to translucency. On the other hand, the d_{50} of the Tween 80/Span 80-based nanoemulsions continues to decrease with increasing ϕ. Otzurk et al. [38] observed this effect with nanoemulsions containing Q-naturale and claimed that the plateauing was due to a shear force limitation occurring above certain surfactant concentrations. By that reasoning, however, the Tween 80/Span 80-based formulation would have shown a similar limiting effect, since both formulations were prepared under identical ultrasonic processing conditions (ultrasonic amplitude and exposure time). Therefore, it is unlikely that the plateauing we observed was due to shear force limitations, but rather that it had to do with the character and packing capabilities of the surfactants. At low surfactant concentrations, Q-naturale is more efficient at forming smaller droplets than Tween 80 and Span 80. As Q-naturale concentration is increased, however, the minimum d_{50} is achieved when bulky hydrophilic groups of Quillaja saponin crowd so closely that steric repulsion between the neighboring groups prevents any further droplet size reduction. Tween 80 (the primary surfactant in the synthetic surfactant-based formulation), on the other hand, has linear hydrophilic groups that can pack more tightly, and therefore, can sustain smaller droplets by allowing more surfactant molecules to adsorb to their surface. The compositions of natural and synthetic surfactant-based formulations that produced the smallest droplets are presented in Table 5.

Surfactant Type	Quillaja Saponin (from Q-Naturale)	Tween 80	Span 80	CBDX (55% CBD)	Refined Olive Oil	Total Oil-Phase	Water	d_{50} [nm]
Synthetic	0	10.4%	2.2%	5.4%	7.2%	12.6%	74.8%	80
Natural	12.1%	0	0	5.4%	7.2%	12.6%	75.3%	110

Table 5. Optimized CBDX nanoemulsion formulations (all in % w/w).

3.5 Process Scale-up Demonstration

Cannabinoid-based nanoemulsions formed via high-intensity ultrasonic cavitation have been developed here and in earlier works [54], but no scale-up demonstration of this process has yet been made. To that, the process scale was increased to 4.2 kg of nanoemulsion by transferring it to a BSP-1200 configured in the flow-through mode (Fig. 1). HLB_{AB}, ratio of refined olive oil-to-CBDX and ϕ for the optimized synthetic surfactant-based translucent nanoemulsion formulation (Table 5, first line) were utilized, but the concentrations of surfactants (Tween 80 and Span 80) and oils (CBDX and refined olive oil) were reduced to achieve the CBDX content of 1% w/w. This was done to allow a single dose of 10 mg of CBDX to be conveniently dispensed via a single gram (or milliliter) of the nanoemulsion. An ultrasonic exposure time effect study (Fig. 7) for this formulation (1% w/w CBDX, 1.3% w/w refined olive oil, 1.9% w/w Tween 80, 0.4% w/w Span 80) was performed by collecting samples at predetermined time points during the process and analyzing them by DLS. Photographs of selected samples with a red light beam illuminating them from behind were also taken (superimposed in Fig. 7).

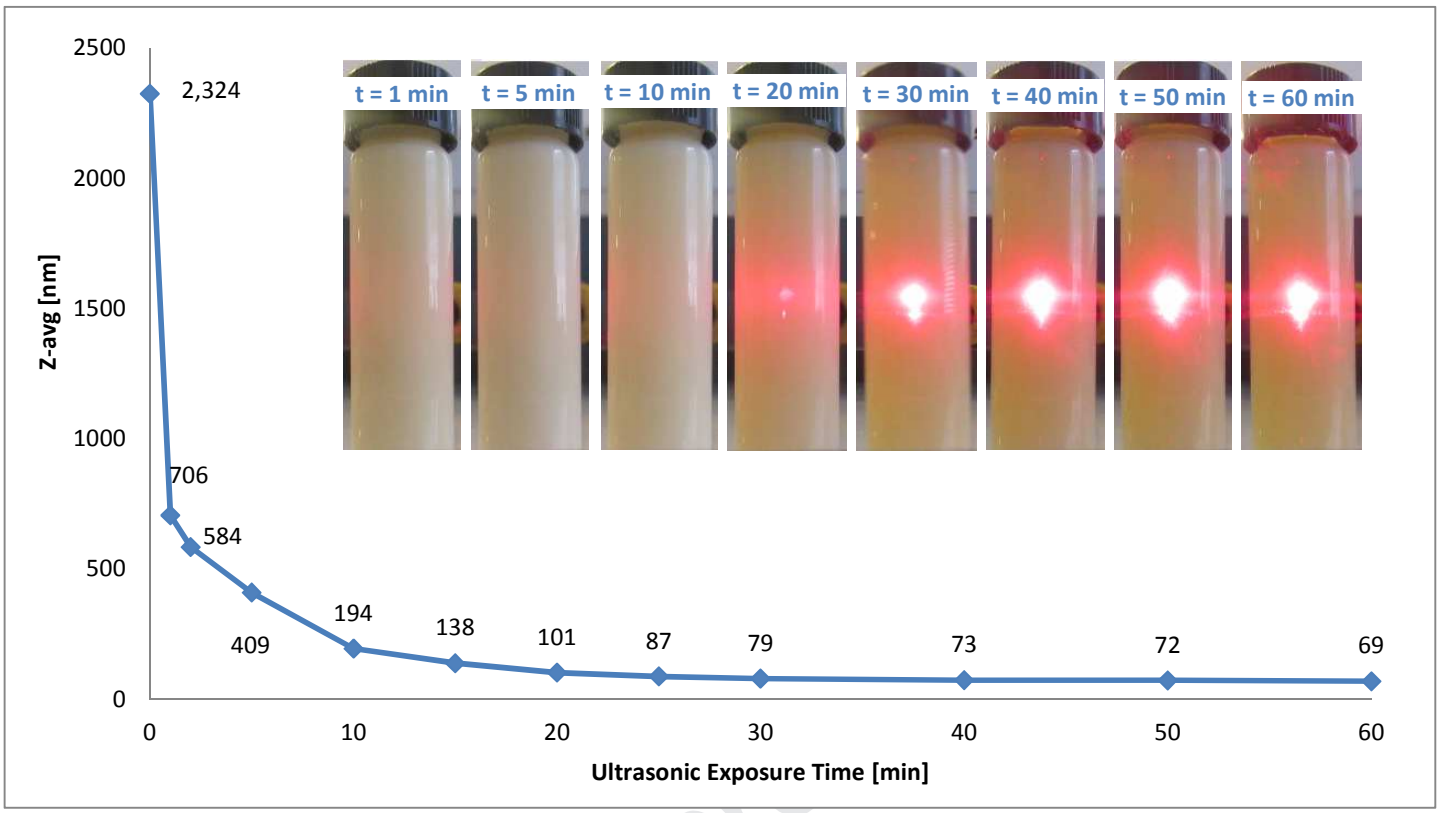


Figure 7. Scaled-up Ultrasonic Nano-emulsification: Droplet size (Z-avg) dependence on ultrasonic exposure time is shown for 4.2 Kg of nanoemulsion (1.0% w/w CBDX, 1.3% w/w refined olive oil, 1.9% w/w Tween 80, 0.4% w/w Span 80). Z-avg values were determined via DLS and photographs were taken with a red laser (650 nm) positioned one foot behind sample vials.

As seen by the plateauing of Z-avg droplet diameters in Fig. 7, the nano-emulsification process was completed in approximately 40 to 60 minutes, corresponding to a processing rate in the range of 6.3 to 4.2 Kg of nanoemulsion per hour. This processing rate is in reasonable agreement with previously determined values for ultrasonic nano-emulsification of soybean oil with Tween 80 and Span 80 using a BSP-1200 [47]. At this processing rate and nanoemulsion composition, about 5,000 units of 10 mg CBDX doses can, therefore, be produced per hour, corresponding to the monthly productivity of nearly one million 10 mg doses of nanoemulsified cannabis extract made with a single BSP-1200 (8-10 hour day, 20 work days per month).

In Fig. 7, the superimposed images of a red light beam shining from behind each sample correlate well with the DLS results in terms of the ability of the light to penetrate through the samples. Initially (t = 0 min until t = 20 min), the beam does not pass through at all because the droplets are much

larger than 100 nm and the light is scattered by them (nanoemulsion appears *milky white*). As the droplets are brought to below 100 nm in diameter (t = 20 min until t = 40 min), the beam passing through the sample becomes brighter as light scattering is mitigated and the nanoemulsion begins to exhibit an increasing degree of translucency. From t = 40 min until t = 60 min, the nanoemulsion droplet diameter plateaus, and the brightness of the beam passing though the sample (demonstrating the sample's translucency) does not increase significantly. This "translucency test" provides a simple qualitative method of determining the end of the nano-emulsification process, which could be utilized as a quality assurance tool or an alternative to expensive particle size analysis in cases where precise droplet size information is not essential.

4 Conclusion

It has been demonstrated that cannabis extract-containing nanoemulsions can be produced via high-intensity ultrasonic processing, and that the nanoemulsion formulation must be optimized for its carrier oil and surfactants' total content and ratio. Further, it was shown that the optimal combination of Tween 80 and Span 80 (HLB_{AB} = 13) was capable of yielding translucent nanoemulsions, while Quillaja saponin from Q-naturale was not. Upon scale-up of the optimized translucent nanoemulsion, the processing rate of approximately 5 kg of nanoemulsion per hour was achieved with a BSP-1200. This processing rate corresponds to one million 10 mg cannabis extract doses per month, made with a single processor. It is, therefore, feasible that ultrasonic processing will soon dominate in the commercial production of water-based cannabis products for the pharmaceutical, food-and-beverage and nutraceutical industries.

5 References

[1] P.Á.L. PACHER, S. BÁTKAI, G. KUNOS, The Endocannabinoid System as an Emerging Target of Pharmacotherapy, Pharmacol. Rev. 58 (2006) 389–462. doi:10.1124/pr.58.3.2.

[2] L. Leung, Cannabis and Its Derivatives: Review of Medical Use, J. Am. Board Fam. Med. 24 (2011) 452–462. doi:10.3122/jabfm.2011.04.100280.

[3] M. Ben Amar, Cannabinoids in medicine: A review of their therapeutic potential, J. Ethnopharmacol. 105 (2006) 1–25. doi:https://doi.org/10.1016/j.jep.2006.02.001.

[4] E.B. Russo, Cannabinoids in the management of difficult to treat pain, Ther. Clin. Risk Manag. 4 (2008) 245–259. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2503660/.

[5] M. Russo, R.S. Calabro, A. Naro, E. Sessa, C. Rifici, G. D'Aleo, A. Leo, R. De Luca, A. Quartarone, P. Bramanti, Sativex in the Management of Multiple Sclerosis-Related Spasticity: Role of the Corticospinal Modulation, Neural Plast. 2015 (2015). doi:10.1155/2015/656582.

[6] M. Duran, E. Pérez, S. Abanades, X. Vidal, C. Saura, M. Majem, E. Arriola, M. Rabanal, A. Pastor, M. Farré, N. Rams, J.R. Laporte, D. Capellà, Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting, Br. J. Clin. Pharmacol. 70 (2010) 656–663. doi:10.1111/j.1365-2125.2010.03743.x.

[7] Y.N. Gavhane, A.V. Yadav, Loss of orally administered drugs in GI tract, Saudi Pharm. J. 20 (2012) 331–344. doi:10.1016/j.jsps.2012.03.005.

[8] D. Hernán Pérez de la Ossa, A. Ligresti, M.E. Gil-Alegre, M.R. Aberturas, J. Molpeceres, V. Di Marzo, A.I. Torres Suárez, Poly-ε-caprolactone microspheres as a drug delivery system for cannabinoid administration: Development, characterization and in vitro evaluation of their antitumoral efficacy, J. Control. Release. 161 (2012) 927–932. doi:https://doi.org/10.1016/j.jconrel.2012.05.003.

[9] I. Cherniakov, D. Izgelov, D. Barasch, E. Davidson, A.J. Domb, A. Hoffman, Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids: Pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration, J. Control. Release. 266 (2017) 1–7. doi:10.1016/j.jconrel.2017.09.011.

[10] I. Ujváry, L. Hanuš, Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy, Cannabis Cannabinoid Res. 1 (2016) 90–101. doi:10.1089/can.2015.0012.

[11] K.S. Paudel, D.C. Hammell, R.U. Agu, S. Valiveti, A.L. Stinchcomb, Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers, Drug Dev. Ind. Pharm. 36 (2010) 1088–1097. doi:10.3109/03639041003657295.

[12] M.A. Huestis, Human Cannabinoid Pharmacokinetics, Chem. Biodivers. 4 (2007) 1770–1804. doi:10.1002/cbdv.200790152.

[13] M.E. Wall, B.M. Sadler, D. Brine, H. Taylor, M. Perez-Reyes, Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women., Clin. Pharmacol. Ther. 34 (1983) 352–363.

[14] R.D. Mattes, L.M. Shaw, J. Edling-Owens, K. Engelman, M.A. Elsohly, Bypassing the first-pass

effect for the therapeutic use of cannabinoids, Pharmacol. Biochem. Behav. 44 (1993) 745–747. doi:10.1016/0091-3057(93)90194-X.

[15] S. Aldington, M. Harwood, B. Cox, M. Weatherall, L. Beckert, A. Hansell, A. Pritchard, G. Robinson, R. Beasley, CANNABIS USE AND RISK OF LUNG CANCER: A CASE-CONTROL STUDY, Eur. Respir. J. 31 (2008) 280–286. doi:10.1183/09031936.00065707.

[16] C. Lanz, J. Mattsson, U. Soydaner, R. Brenneisen, Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis, PLoS One. 11 (2016). doi:10.1371/journal.pone.0147286.

[17] A.J. Budney, J.D. Sargent, D.C. Lee, Vaping cannabis (marijuana): parallel concerns to e-cigs?, Addiction. 110 (2015) 1699–1704. doi:10.1111/add.13036.

[18] C. Pisinger, M. Døssing, A systematic review of health effects of electronic cigarettes, Prev. Med. (Baltim). 69 (2014) 248–260. doi:https://doi.org/10.1016/j.ypmed.2014.10.009.

[19] E.L. Karschner, W.D. Darwin, R.S. Goodwin, S. Wright, M.A. Huestis, Plasma Cannabinoid Pharmacokinetics following Controlled Oral Δ(9)-Tetrahydrocannabinol and Oromucosal Cannabis Extract Administration, Clin. Chem. 57 (2011) 66–75. doi:10.1373/clinchem.2010.152439.

[20] S. Valiveti, R.U. Agu, D.C. Hammell, K.S. Paudel, D. Caroline Earles, D.P. Wermeling, A.L. Stinchcomb, Intranasal absorption of Δ9-tetrahydrocannabinol and WIN55,212-2 mesylate in rats, Eur. J. Pharm. Biopharm. 65 (2007) 247–252. doi:https://doi.org/10.1016/j.ejpb.2006.08.009.

[21] A.M. Al-Ghananeem, A.H. Malkawi, P.A. Crooks, Bioavailability of Δ 9-tetrahydrocannabinol following intranasal administration of a mucoadhesive gel spray delivery system in conscious rabbits, Drug Dev. Ind. Pharm. 37 (2011) 329–334. doi:10.3109/03639045.2010.513009.

[22] A.L. Stinchcomb, B.N. Nalluri, TRANSDERMAL DELIVERY OF CANNABINOIDS, 2012.

[23] T. Goswami, B.R. Jasti, X. Li, Sublingual Drug Delivery, Crit. Rev. Ther. Drug Carr. Syst. 25 (2008) 449–484. doi:10.1615/CritRevTherDrugCarrierSyst.v25.i5.20.

[24] C. Scully, Cannabis; adverse effects from an oromucosal spray, Bdj. 203 (2007) E12. http://dx.doi.org/10.1038/bdj.2007.749.

[25] A.G. de Boer, F. Moolenaar, L.G. de Leede, D.D. Breimer, Rectal drug administration: clinical pharmacokinetic considerations., Clin. Pharmacokinet. 7 (1982) 285–311.

[26] I. Pereira De Sousa, A. Bernkop-Schnürch, Pre-systemic metabolism of orally administered drugs and strategies to overcome it, J. Control. Release. 192 (2014) 301–309. doi:10.1016/j.jconrel.2014.08.004.

[27] H. Ahn, J.H. Park, Liposomal delivery systems for intestinal lymphatic drug transport, Biomater. Res. 20 (2016) 16–21. doi:10.1186/s40824-016-0083-1.

[28] L.E. Klumpers, T.L. Beumer, J.G.C. van Hasselt, A. Lipplaa, L.B. Karger, H.D. Kleinloog, J.I. Freijer, M.L. de Kam, J.M.A. van Gerven, Novel Δ9-tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamic effects, Br. J. Clin. Pharmacol. 74

(2012) 42–53. doi:10.1111/j.1365-2125.2012.04164.x.

[29] L.H.V. Reddy, R.S.R. Murthy, Lymphatic transport of orally administered drugs, Indian J. Exp. Biol. 40 (2002) 1097–1109.

[30] A. Melander, A. McLean, Influence of food intake on presystemic clearance of drugs., Clin. Pharmacokinet. 8 (1983) 286–296.

[31] A. Zgair, J.C.M. Wong, J.B. Lee, J. Mistry, O. Sivak, K.M. Wasan, I.M. Hennig, D.A. Barrett, C.S. Constantinescu, P.M. Fischer, P. Gershkovich, Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines, Am. J. Transl. Res. 8 (2016) 3448–3459. doi:10.1007/s11095-013-1127-z.

[32] A. Zgair, J.B. Lee, J.C.M. Wong, D.A. Taha, J. Aram, D. Di Virgilio, J.W. McArthur, Y.K. Cheng, I.M. Hennig, D.A. Barrett, P.M. Fischer, C.S. Constantinescu, P. Gershkovich, Oral administration of cannabis with lipids leads to high levels of cannabinoids in the intestinal lymphatic system and prominent immunomodulation, Sci. Rep. 7 (2017) 1–12. doi:10.1038/s41598-017-15026-z.

[33] A. Fahr, X. Liu, Drug delivery strategies for poorly water-soluble drugs, Expert Opin. Drug Deliv. 4 (2007) 403–416. doi:10.1517/17425247.4.4.403.

[34] S. Ganta, M. Talekar, A. Singh, T.P. Coleman, M.M. Amiji, Nanoemulsions in Translational Research—Opportunities and Challenges in Targeted Cancer Therapy, AAPS PharmSciTech. 15 (2014) 694–708. doi:10.1208/s12249-014-0088-9.

[35] D.J. McClements, Edible nanoemulsions: fabrication, properties, and functional performance, Soft Matter. 7 (2011) 2297–2316. doi:10.1039/C0SM00549E.

[36] H. Yu, Q. Huang, Improving the oral bioavailability of curcumin using novel organogel-based nanoemulsions, J. Agric. Food Chem. 60 (2012) 5373–5379. doi:10.1021/jf300609p.

[37] B. Ozturk, S. Argin, M. Ozilgen, D.J. McClements, Nanoemulsion delivery systems for oil-soluble vitamins: Influence of carrier oil type on lipid digestion and vitamin D<inf>3</inf> bioaccessibility, Food Chem. 187 (2015) 499–506. doi:10.1016/j.foodchem.2015.04.065.

[38] B. Ozturk, S. Argin, M. Ozilgen, D.J. McClements, Formation and stabilization of nanoemulsion-based vitamin e delivery systems using natural surfactants: Quillaja saponin and lecithin, J. Food Eng. 142 (2014) 57–63. doi:10.1016/j.jfoodeng.2014.06.015.

[39] L. Zhao, Y. Wei, Y. Huang, B. He, Y. Zhou, J. Fu, Nanoemulsion improves the oral bioavailability of baicalin in rats: In vitro and in vivo evaluation, Int. J. Nanomedicine. 8 (2013) 3769–3779. doi:10.2147/IJN.S51578.

[40] C. Qian, E.A. Decker, H. Xiao, D.J. McClements, Nanoemulsion delivery systems: Influence of carrier oil on β-carotene bioaccessibility, Food Chem. 135 (2012) 1440–1447. doi:https://doi.org/10.1016/j.foodchem.2012.06.047.

[41] D.J. McClements, Nanoemulsions versus microemulsions: terminology, differences, and similarities, Soft Matter. 8 (2012) 1719–1729. doi:10.1039/C2SM06903B.

[42] T.J. Wooster, M. Golding, P. Sanguansri, Impact of Oil Type on Nanoemulsion Formation and

Ostwald Ripening Stability, Langmuir. 24 (2008) 12758–12765. doi:10.1021/la801685v.

[43] Y. Singh, J.G. Meher, K. Raval, F.A. Khan, M. Chaurasia, N.K. Jain, M.K. Chourasia, Nanoemulsion: Concepts, development and applications in drug delivery, J. Control. Release. 252 (2017) 28–49. doi:10.1016/j.jconrel.2017.03.008.

[44] T.V.A. Ha, S. Kim, Y. Choi, H.S. Kwak, S.J. Lee, J. Wen, I. Oey, S. Ko, Antioxidant activity and bioaccessibility of size-different nanoemulsions for lycopene-enriched tomato extract, Food Chem. 178 (2015) 115–121. doi:10.1016/j.foodchem.2015.01.048.

[45] L. Salvia-Trujillo, O. Martín-Belloso, D. McClements, Excipient Nanoemulsions for Improving Oral Bioavailability of Bioactives, Nanomaterials. 6 (2016) 17. doi:10.3390/nano6010017.

[46] Y. Ma, H.G. Li, S.X. Guan, Enhancement of the oral bioavailability of breviscapine by nanoemulsions drug delivery system, Drug Dev. Ind. Pharm. 41 (2015) 177–182. doi:10.3109/03639045.2014.947510.

[47] A.S. Peshkovsky, S.L. Peshkovsky, S. Bystryak, Scalable high-power ultrasonic technology for the production of translucent nanoemulsions, Chem. Eng. Process. Process Intensif. 69 (2013) 77–82. doi:10.1016/j.cep.2013.02.010.

[48] A. Gupta, H.B. Eral, T.A. Hatton, P.S. Doyle, Nanoemulsions: formation, properties and applications, Soft Matter. 12 (2016) 2826–2841. doi:10.1039/C5SM02958A.

[49] S. Kentish, T.J. Wooster, M. Ashokkumar, S. Balachandran, R. Mawson, L. Simons, The use of ultrasonics for nanoemulsion preparation, Innov. Food Sci. Emerg. Technol. 9 (2008) 170–175. doi:10.1016/j.ifset.2007.07.005.

[50] A.S. Peshkovsky, S. Bystryak, Continuous-flow production of a pharmaceutical nanoemulsion by high-amplitude ultrasound: Process scale-up, Chem. Eng. Process. Process Intensif. 82 (2014) 132–136. doi:10.1016/j.cep.2014.05.007.

[51] T.S.H. Leong, T.J. Wooster, S.E. Kentish, M. Ashokkumar, Minimising oil droplet size using ultrasonic emulsification, Ultrason. Sonochem. 16 (2009) 721–727. doi:10.1016/j.ultsonch.2009.02.008.

[52] A.S. Peshkovsky, S.L. Peshkovsky, Acoustic Cavitation Theory and Equipment Design Principes for Industrial Application of High-Intensity Ultrasound, Nova Science Publishers, 2010.

[53] S.M. Jafari, Y. He, B. Bhandari, Production of sub-micron emulsions by ultrasound and microfluidization techniques, J. Food Eng. 82 (2007) 478–488. doi:10.1016/j.jfoodeng.2007.03.007.

[54] H. Rosenkrantz, G.R. Thompson, M.C. Braude, Oral and parenteral formulations of marijuana constituents, J. Pharm. Sci. 61 (1972) 1106–1112. doi:10.1002/jps.2600610715.

[55] A.S. Peshkovsky, From Research to Production: Overcoming Scale-Up Limitations of Ultrasonic Processing, in: D. Bermúdez-Aguirre (Ed.), Ultrasound Advanaces Food Process. Preserv., 2017: pp. 409–423.

[56] S.L. Peshkovsky, M.L. Friedman, W.A. Hawkins, Ultrasonic Rod Waveguide Radiator,

US20060090956A1, 2006. https://patents.google.com/patent/US20060090956.

[57] A. Peshkovsky, MAKING STABLE EMULSIONS A Guide to Formulation and Processing Conditions Optimization, (2015).

[58] C. Qian, E.A. Decker, H. Xiao, D.J. McClements, Nanoemulsion delivery systems: Influence of carrier oil on β-carotene bioaccessibility, Food Chem. 135 (2012) 1440–1447. doi:10.1016/j.foodchem.2012.06.047.

[59] S.N. Sahasrabudhe, V. Rodriguez-Martinez, M. O'Meara, B.E. Farkas, Density, viscosity, and surface tension of five vegetable oils at elevated temperatures: Measurement and modeling, Int. J. Food Prop. 20 (2017) 1965–1981. doi:10.1080/10942912.2017.1360905.

[60] V. Mikulcova, V. Kasparkova, P. Humpolicek, L. Bunkova, Formulation, Characterization and Properties of Hemp Seed Oil and Its Emulsions., Molecules. 22 (2017). doi:10.3390/molecules22050700.

[61] T. Bekerman, J. Golenser, A. Domb, Cyclosporin nanoparticulate lipospheres for oral administration., J. Pharm. Sci. 93 (2004) 1264–1270. doi:10.1002/jps.20057.

Figure Captions

Figure 1. BSP-1200 Ultrasonic Processor in the Flow-Through Mode: The 1,200 W ultrasonic generator (1) excites vibration in the piezoelectric transducer (2). The vibration amplitude is then amplified by the HBH-type Barbell Horn® (3) which comes into contact with the process liquid flowing through the reactor chamber (4) and promotes acoustic cavitation in the liquid. The process liquid recirculates from the stirred tank (5) to the reactor chamber and back. Water cooling to the piezoelectric transducer and process liquid are provided via cooling jackets surrounding the piezoelectric transducer and reactor chamber.

Figure 2. Carrier Oil Content and Droplet Size: Carrier Oil content optimization in a CBDX (5.4% w/w) nanoemulsion produced with Q-naturale (Quillaja saponin content = 4.5% w/w).

Figure 3. HLB Opt. 1: HLB_{AB} optimization of carrier oil-free, CBDX (5.4% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

Figure 4. HLB Opt. 2: HLB_{AB} optimization of CBDX-free, refined olive oil (12.6% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

Figure 5. HLB Opt. 3: HLB_{AB} optimization of CBDX (5.4% w/w) and refined olive oil (7.2% w/w) nanoemulsion using Tween 80 and Span 80 (4.5% w/w total).

Figure 6. Translucency Approach: The droplet size dependence on surfactant to oil ratio (Φ) of the natural and HLB_{AB}-optimized synthetic surfactant formulations. Refined olive oil (7.2% w/w) and CBDX (5.4% w/w) were used in both formulations.

Figure 7. Scaled-up Ultrasonic Nano-emulsification: Droplet size (Z-avg) dependence on ultrasonic exposure time is shown for 4.2 Kg of nanoemulsion (1.0% w/w CBDX, 1.3% w/w refined olive oil, 1.9% w/w Tween 80, 0.4% w/w Span 80). Z-avg values were determined via DLS and photographs were taken with a red laser (650 nm) positioned one foot behind sample vials.

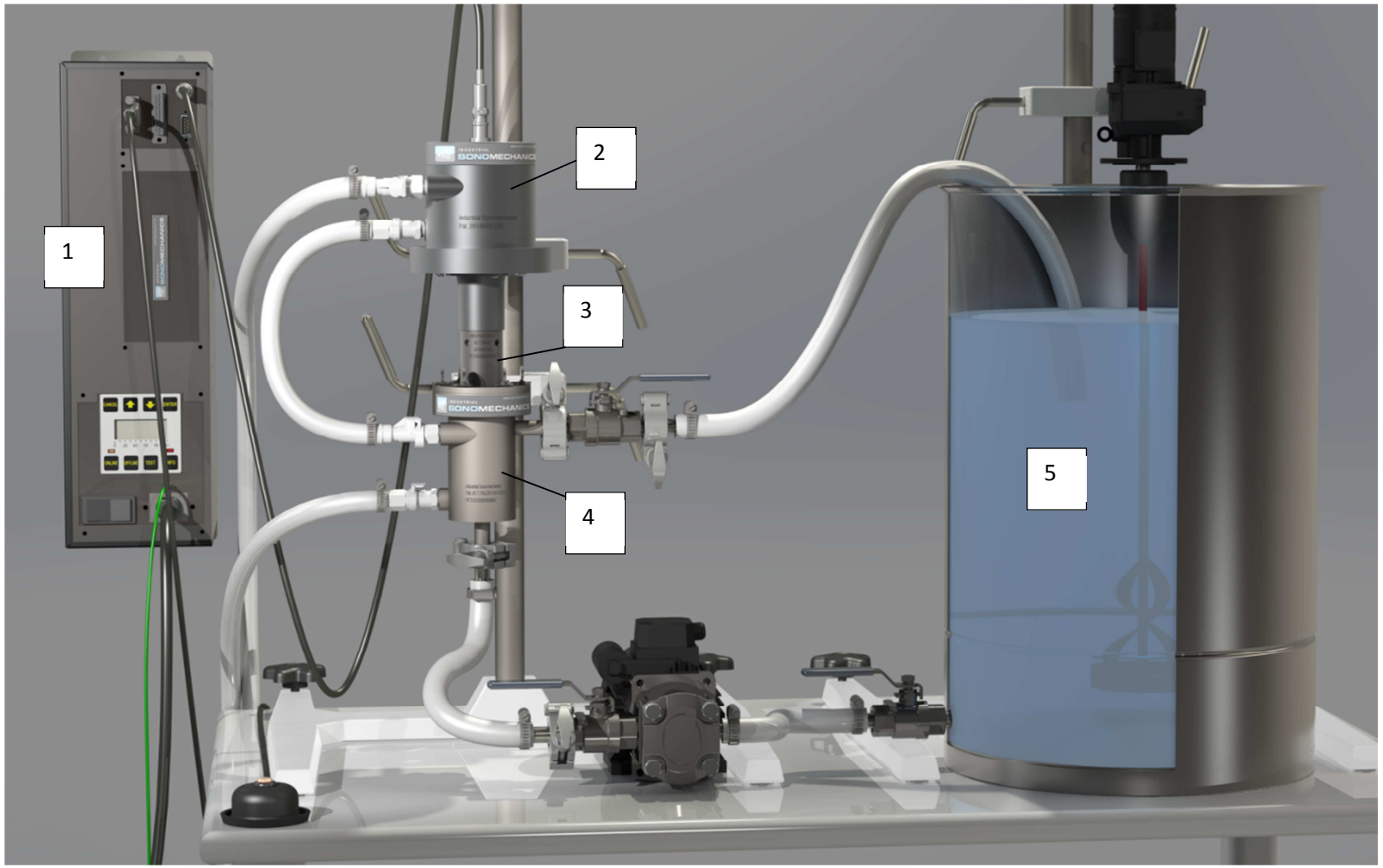


Figure 1. BSP-1200 Ultrasonic Processor in the Flow-Through Mode.

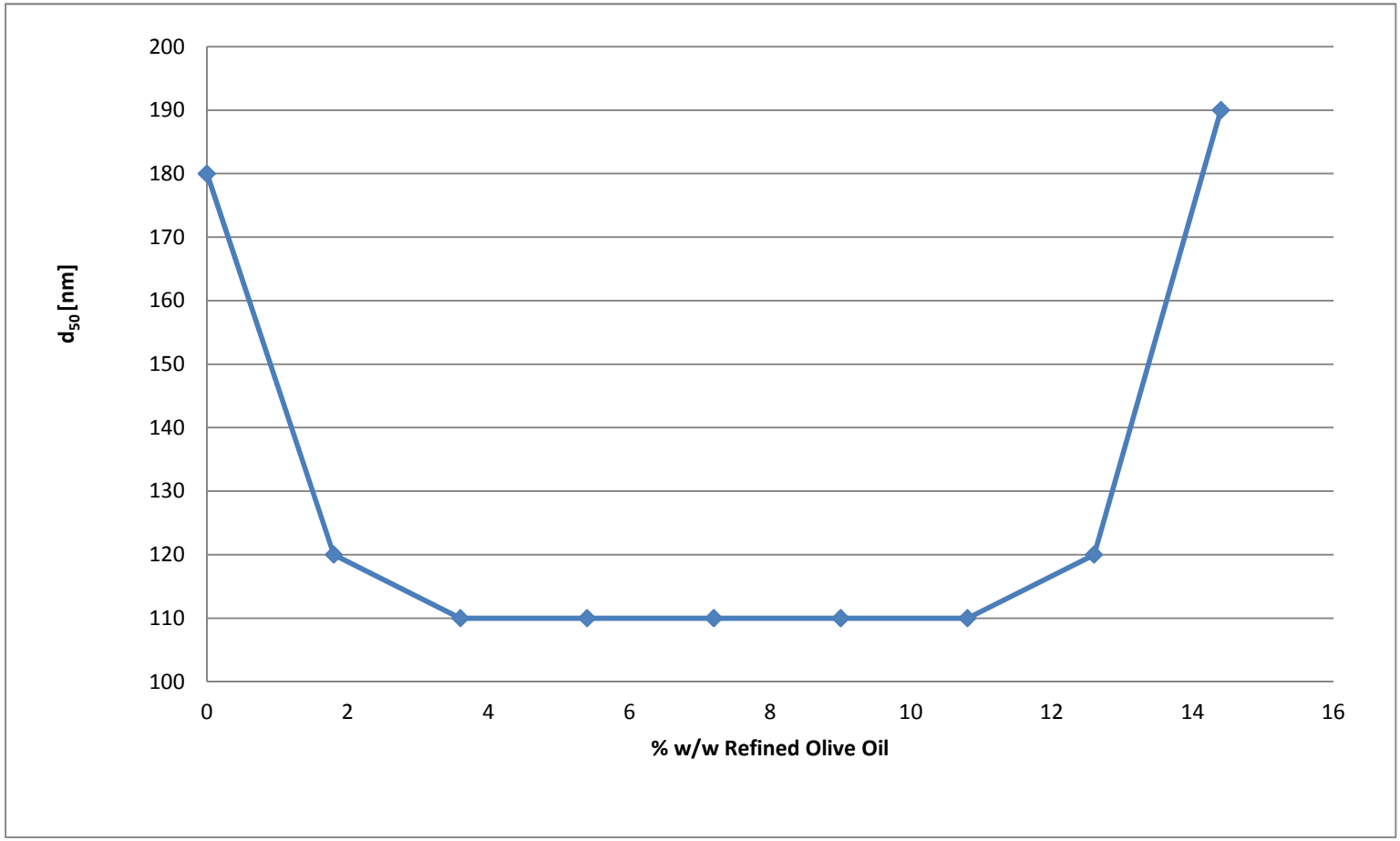


Figure 2. Carrier Oil Content and Droplet Size

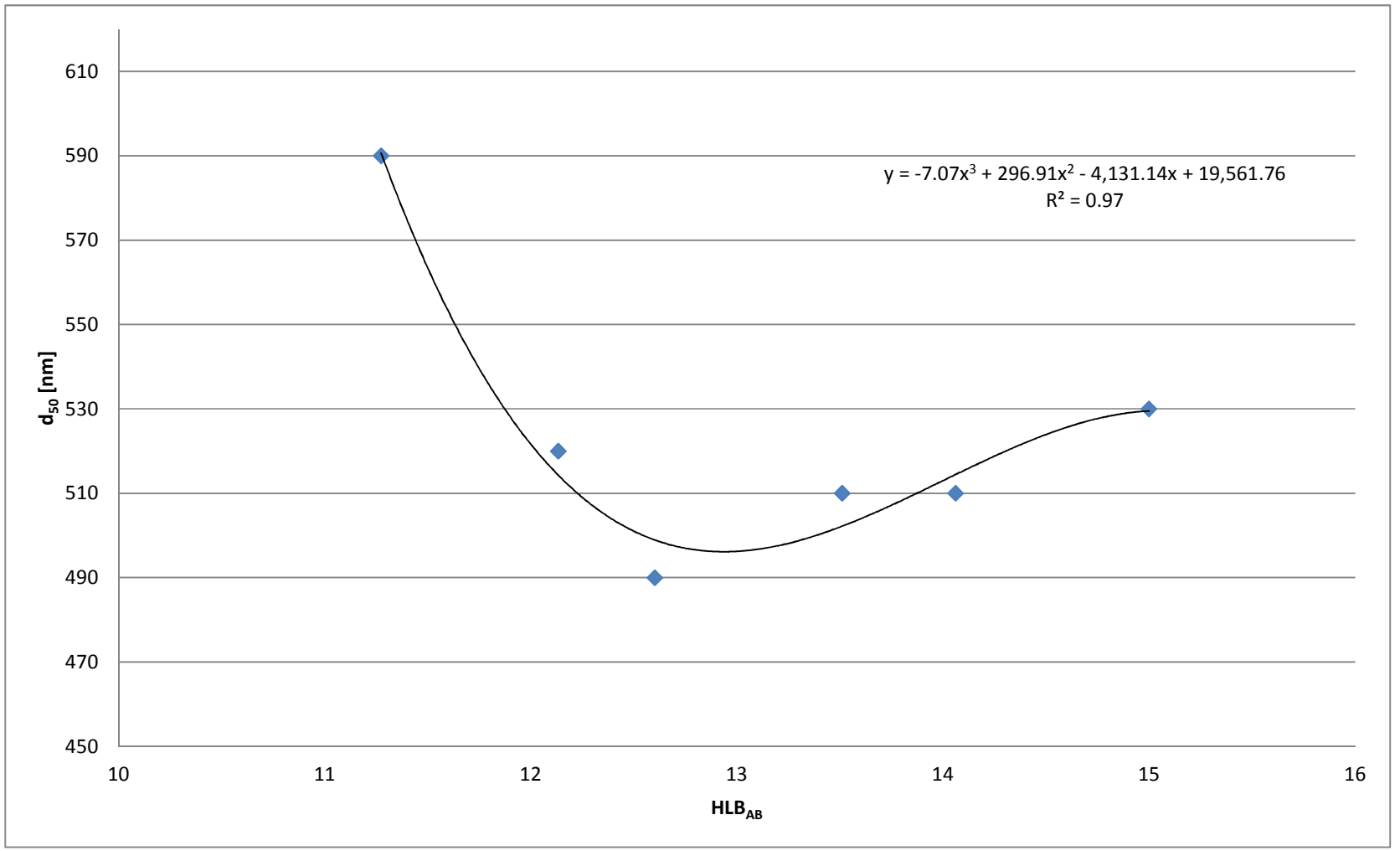


Figure 3. HLB Opt. 1

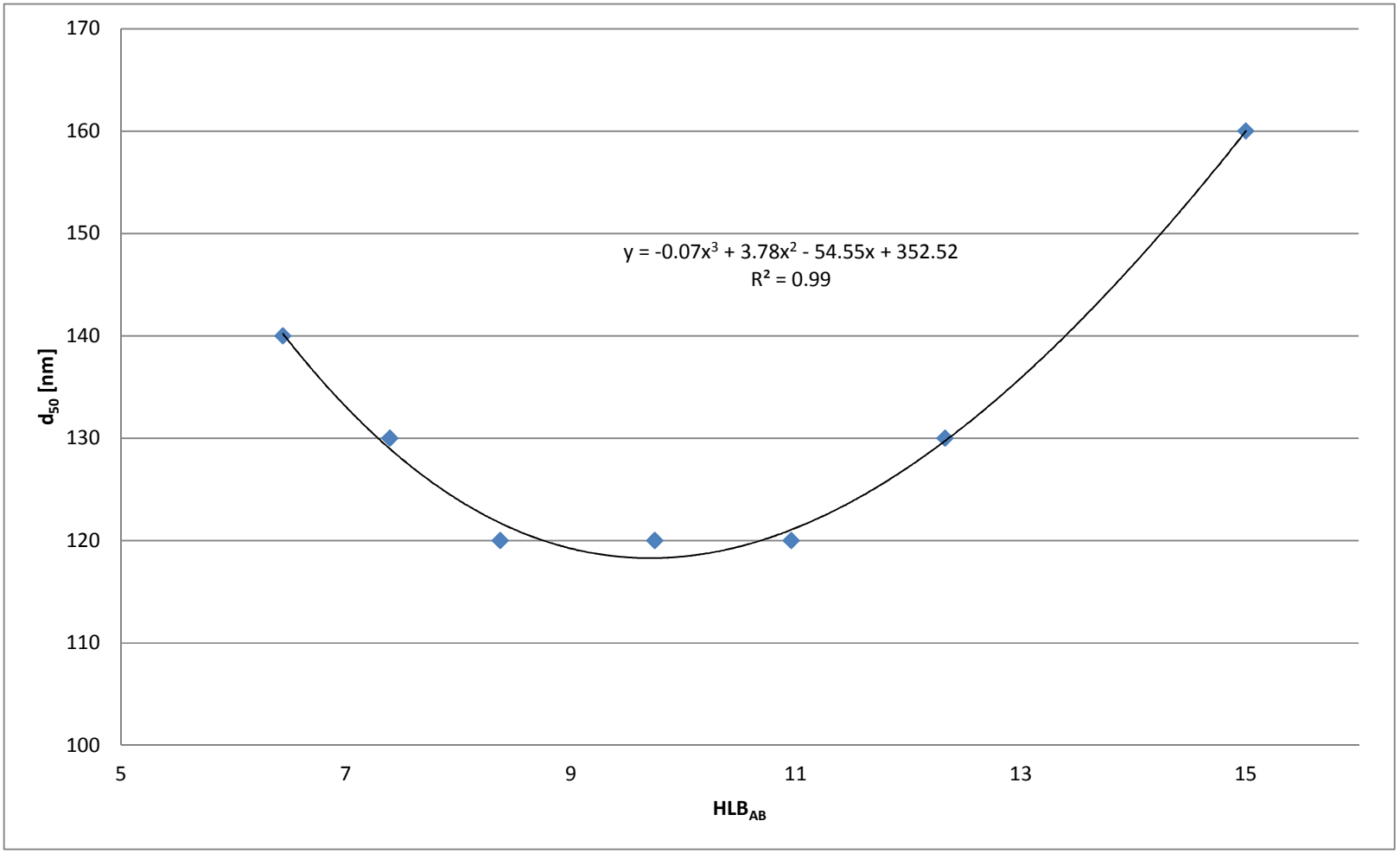


Figure 4. HLB Opt. 2

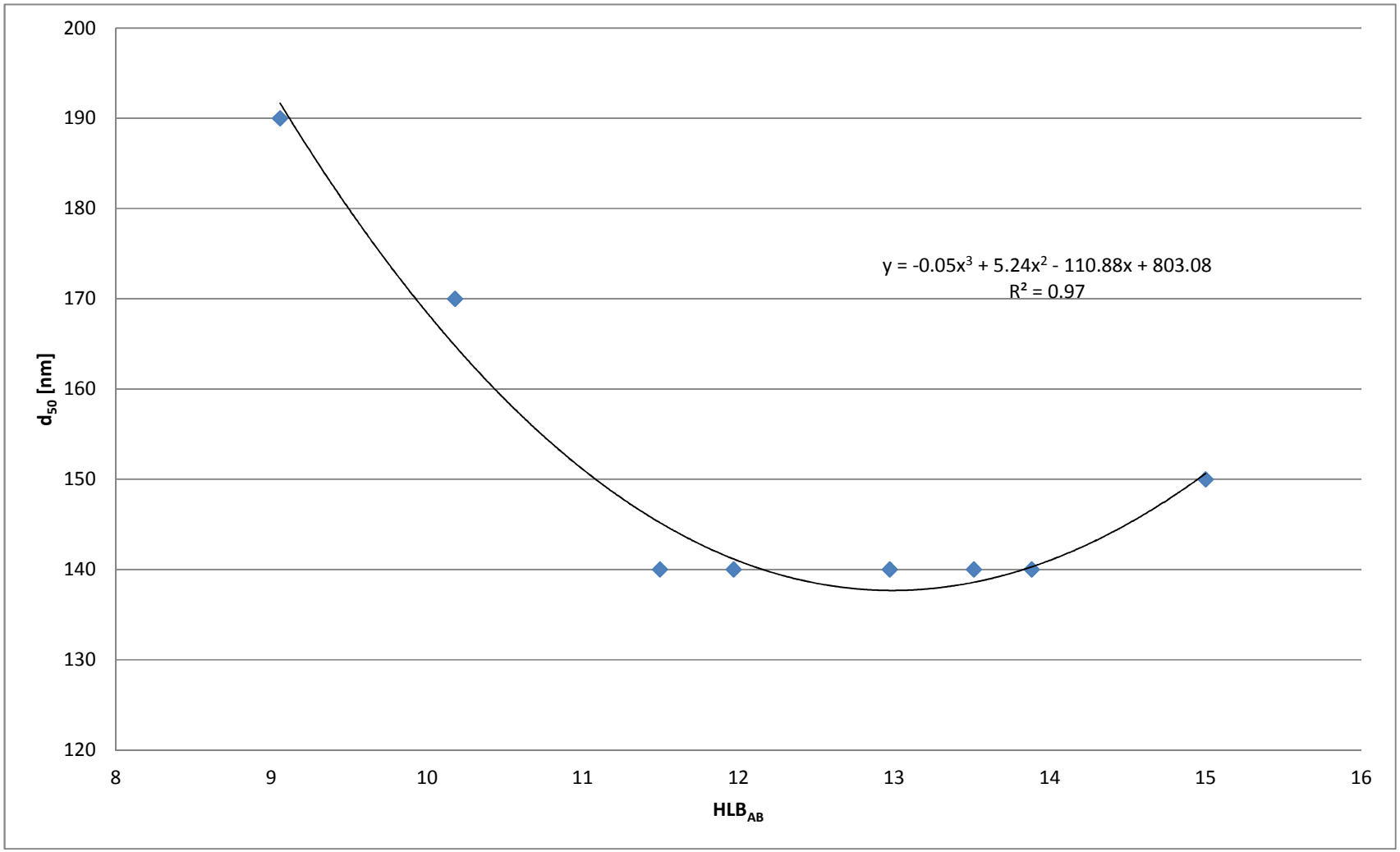


Figure 5. HLB Opt. 3

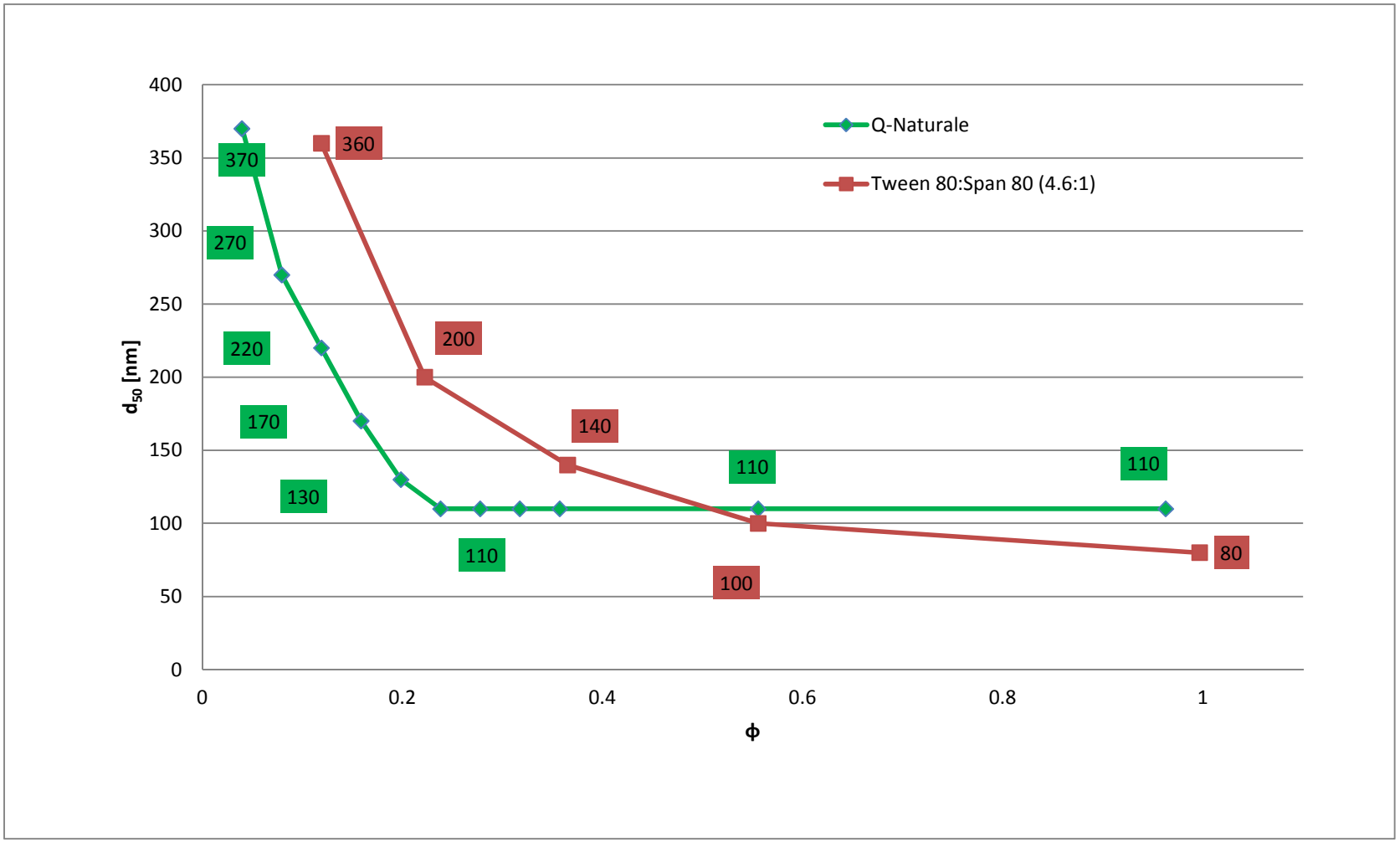


Figure 6. Translucency Approach

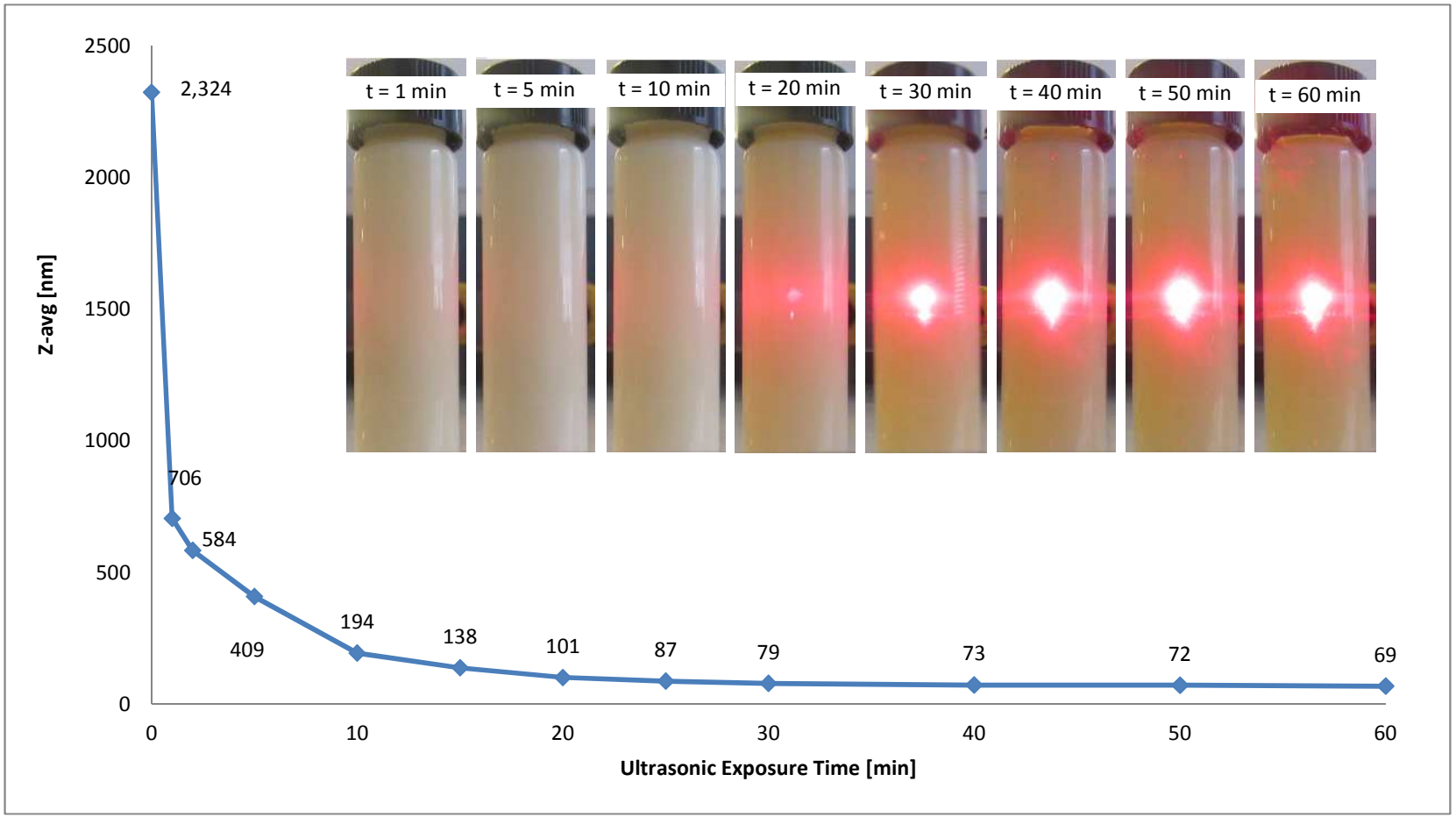


Figure 7. Scaled-up Ultrasonic Nano-emulsification

Highlights:

- Nanoemulsions, as drug delivery vehicles are discussed.
- A translucent, cannabinoid-loaded nanoemulsion was prepared.
- Commercial-scale production of cannabinoid-loaded nanoemulsions is demonstrated.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.