Clinics in Medicine

ISSN: 2688-6731

Research Article

Development of a CBD Nano Formulation

Chauhan A[1], Christopher K[1] and Lanier O[2]*

[1]*Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, CO, USA*

[2]*Department of Chemical and Biological Engineering, University of New Mexico, Albuquerque, USA*

Abstract

Cannabidiol (CBD) is considered to have many medicinal properties which is leading to efforts to develop effective methods of delivery. CBD is a hydrophobic molecule, i.e., it has very limited solubility in water. Therefore, dispersing it in aqueous formulations is not an effective approach for treating diseases. Nanoparticles of CBD or CBD mixed with other inactive components can be dispersed in aqueous formulations to formulate what is typically referred to as "water soluble" CBD, though a more accurate term would be "water dispersible" CBD. These types of formulations retain stability for long periods of time and increase bioavailability when dosed orally compared to control (non-nano) CBD formulations. This paper discloses a novel composition and a method for "water soluble" CBD.

Keywords: Nano formulation; Cannabidiol; Nano emulsions; Microemulsions; Surfactants; Water-Soluble CBD; Emulsification; Nanosuspension

Abbreviations

CBD: Cannabidiol; BCS: Biopharmaceutics Classification System; THC: Δ9-tertahydrocannabinol; PBS: Phosphate Buffer Saline; DCM: Dichloromethane; DLS: Dynamic Light Scattering; PDI: Polydispersity Index

Background

The oral route of drug administration is the least invasive and represents the highest rate of patient compliance. Though about 84% of all medicines are taken orally [1], poor bioavailability is frequently observed when poorly water-soluble drugs are delivered in this way [2]. In order to achieve pharmacologic effect, freely dissolved drug must absorb through the intestinal walls into the bloodstream. Therefore, the bioavailability of drugs, especially low solubility, highly permeable Biopharmaceutics Classification System (BCS) Class II drugs, can be enhanced by reducing the formulation particle size to increase the rate of dissolution [3,4].

Drug micronization through milling is often used to reduce particle sizes to 1-10 microns [5]. Further, techniques such as antisolvent precipitation have been previously used to create drug nanoparticles. Such colloidal nanosuspensions are promising formulations for increased bioavailability with their very small particle sizes (<1 micron diameter) [6]. According to the Ostwald-Freundlich equation, saturation solubility increases with decreased particle size, with a noticeable effect for particle diameters below 1 micron [3,7]. This increase in saturation solubility along with the increased surface area to volume ratio for decreased particle sizes should result in significantly increased dissolution rates as predicted by the Noyes-Whitney equation and demonstrated experimentally by Kocbek et al. [7]. Techniques such as antisolvent precipitation; however, often create unstable formulations and require organic solvents which may be difficult to remove completely [7]. If the drug is hydrophobic and solid at room temperature, colloidal suspensions can be formed via melt emulsification [8]. In this approach, the drug is melted and then emulsified in a solvent, typically water, using suitable surfactants. The emulsions are then cooled to yield a suspension of the drug. This process removes the potential toxic effects of solvents [7] and is a simple process with high reproducibility and scalability. Recent changes in federal regulations have sparked a boom in the cannabis industry. The adoption of cannabis is not as widespread when it comes to products that contain Δ9-tertahydrocannabinol (THC), the psychoactive component of the flower. However, the acceptance of cannabidiol (CBD), has been much more encouraging for the industry. This is because CBD has been found to treat many conditions. The first being that CBD is a natural anti-inflammatory and can be used as a method of pain relief. Second, more clinicians are recommending it for the treatment of anxiety, a condition that afflicts over 15 million Americans. Furthermore, CBD products for the treatment of anxiety have the distinct advantages over traditional medications of not causing withdraws or having serious side effects. Although these are just some of the more mainstream benefits of CBD, additional uses are being found continuously as researchers continue to embrace the use of CBD based products.

Before it is incorporated into other edible products, many orally administered CBD products are available in the forms of oils, isolate powders, and nanosuspensions that are deemed "water-soluble" CBD. Although the oral route of administration is the most appealing to users, it is met by several key drawbacks. The first is the bioavailability of the oils and isolates which has a maximum value of 19% but is typically much lower. That is due to CBD being highly hydrophobic and having a poor solubility in water, much like hydrophobic drugs and thus all approaches developed for hydrophobic drugs have been adopted for developing nano-formulations of CBD.

Since CBD is solid at room temperature but oil above its melting point, melt emulsification is a potentially useful approach for forming nano emulsions. This approach has the drug melted and emulsified in a solvent, typically water, using suitable surfactants. Another issue with CBD formulations is flavor. Typically, hemp oil is the standard

Citation: Chauhan A, Christopher K, Lanier O. Development of a CBD Nano Formulation. Clin Med. 2025; 7(1): 1069.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 05th, 2025

***Correspondence:** Anuj Chauhan, Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, USA, Tel: 3032733539

vehicle for delivering CBD sublingually, but it is unpleasantly bitter and earthy which results in many users to find alternative methods to consume CBD which has contributed to the rapid growth of the industry.

Here, we explore the possibility of creating CBD microemulsions through melt emulsification that minimalize unpleasant tastes while simultaneously prolonging shelf life and increasing the amount of CBD loading into the emulsion. We look to achieve this through the incorporation of a common food additive, ethyl maltol. Ethyl maltol has been used as a flavor additive in beverages, cakes, and fruit products because it is inherently sweet, but it can also act as an emulsifier. In this study, we evaluate a range of solid and surfactant concentrations to create stable CBD nanosuspensions through melt emulsification. We then evaluated the stability of these suspensions over time and after lyophilization. The purpose of incorporating ethyl maltol was as a flavor additive but it had an unexpected effect of improving stability of CBD nanoparticles.

Methods and Materials

The CBD was purchased from a local supplier (Infinite CBD, Lakewood, CO). Ethyl maltol (>99%) and Pluronic F68 (poloxamer 188) were purchased from Sigma-Aldrich. All aqueous solutions were made with Dulbecco's phosphate buffer saline (PBS) without calcium and magnesium and were obtained from Sigma-Aldrich.

Suspensions were made by first adding the CBD to the PBS in a 5mL scintillation vial. The solution was then heated to 75˚C to melt the CBD. Once liquified, a 15% Pluronic F68 solution was added until the proper concentration was obtained and was immediately sonicated for 60s. The solution was then left to cool at room temperature.

In addition to forming the suspension through melt emulsification, a solvent technique was developed. The CBD was solubilized in 200 µL of dichloromethane (DCM). Then the PBS and surfactant solution were added and immediately sonicated for 60s. The suspensions were then left uncapped overnight to allow for solvent (DCM) evaporation.

The resulting nanosuspensions were characterized in several ways. First, visual observation was used to record whether the nanosuspension formed was a visibly transparent (microemulsion) solution, a translucent solution, or an opaque solution. Once cooled to room temperature, the particle size distribution was measured using dynamic light scattering (DLS), (Malvern Nano-ZS). Several select nanosuspensions which formed transparent solutions were lyophilized. Liquid nanosuspensions were initially frozen at -80oC for several hours before being placed in a vacuum chamber and dried. For all lyophilized samples, it is assumed that the only component removed was water. The dried samples could then be simply rehydrated by adding the measured amount of PBS to match the initial concentrations of the components. The rehydrated suspensions were analyzed for particle size and distribution using DLS.

Results and Discussion

The solid components were rapidly melted when the mixtures of the drug, additive, and PBS were heated above the highest melting point of the system. Then the surfactant was added to the predetermined concentration and sonicated. Whether the system composition formed a visually transparent nanosuspension was evident within the first 15 minutes after sonication while in molten form. If the solution was not visibly transparent after 15 minutes, the system would never form a stable microemulsion, even with prolonged mixing. Table 1 shows the formulations that were prepared with varied amounts of CBD, ethyl maltol, and surfactant. The table expresses the initial stability and shelf life of the emulsions along with the initial particle size and polydispersity index (PDI).

Molten macroemulsions had poor stability when cooled to room temperature and led to the formulations demonstrating rapid precipitation of CBD and a complete phase separation within a couple days of shelf storage. Most solutions did not stay stable upon cooling. CBD is highly insoluble in aqueous solutions and, when cooled to room temperature, the nanosuspensions are highly supersaturated due to the very small particle size. The formulations then tend to crystallize into macroscopic particles. The ethyl maltol additive mitigates the supersaturation. In addition to helping stabilize the solution, the ethyl maltol is a common sweetening agent that has the added benefit of improving taste.

At lower surfactant concentrations, the formulations demonstrated no stability and all except the 10% w/w surfactant formulations never resulted in stable emulsions. Additionally, no formulation without ethyl maltol formed a stable solution. All unstable emulsions resulted in the components precipitating out and forming solids within the system. The absence of the ethyl maltol and the low surfactant concentrations resulted in the flocculation of the emulsion and the sedimentation of the species. The solutions with 0.8% and 0.875% CBD formed briefly stable emulsions that formed precipitates after less than two days, forming particles that were roughly 200 nm. As the CBD decreased to 0.75%, the system became more stable and was able to last for a month with particles that were 141 nm and a similar PDI. Finally, below 0.75% CBD, all the systems formed highly stable emulsions that have been stable for 6 months. The particle size has also decreased to below 100 nm with similar PDIs. All the formulations had PDIs that were below 0.3 which is the recommended limit for pharmaceutical formulations. Furthermore, the use of solvent evaporation had a minimal effect on the system compared to the melt emulsification method. As it can be seen in Figure 1, the size distribution is nearly identical with the solvent method having a slight shift of only 5nm larger particles on average and similar PDI (Table 1), demonstrating that both methods can be used to consistently fabricate the stable CBD emulsions.

After 30 days, the particles sizes were reexamined to measure the stability of the emulsion over time, but only for the five formulations that demonstrated significant stability after the one week (Table 2). The particle sizes of Formulations 1-4 slightly increased over time, but all stayed below 100nm and mostly retained the low PDI. However, with formulation 5, the particle size decreased and the PDI more the doubled after only 30 days likely suggesting aggregation and settling. The system became unstable and the coalescence of the particles led to a bias in the mean hydrodynamic diameter and a greater disparity in the particle size distribution.

While liquid nanosuspensions are attractive for concentrated packs that can be easily and rapidly consumed, the liquid systems can exhibit shorter shelf-life stability and lower concentrations than dried solutions. Commercial products with liquid nanosuspensions that have concentrations of roughly 1mg/mL CBD or about 0.1% w/w, which is one-fifth the concentration that we were able to encapsulate with a relatively high stability and shelf life. Once these formulations are dehydrated, the concentrations of CBD, ethyl maltol, and surfactant will increase significantly and provide a stable and easily dissolvable system. Freeze drying, or lyophilization, was therefore examined for

Table 1: Formulations prepared.

CBD Concentration (wt%)	Ethyl Maltol Concentration (wt%)	Surfactant Concentration (wt%)	Method of Emulsification	Stable	Shelf-Life Stability	Initial Particle Size (nm)	PDI
0.5	0	1	Melt	No	None	-	-
1	0	1	Melt	No	None	-	-
0.25	0.25	1	Melt	No	None	-	-
0.375	0.125	1	Melt	No	None	-	-
0.375	0.125	1	Solvent Evap.	No	None	-	-
0.25	0.75	1	Melt	No	None	-	-
0.5	0.5	1	Melt	No	None	-	-
0.75	0.25	1	Melt	No	None	-	-
0.5	0	2	Melt	No	None	-	-
1	0	2	Melt	No	None	-	-
0.25	0.25	2	Melt	No	None	-	-
0.375	0.125	2	Melt	No	None	-	-
0.25	0.75	2	Melt	No	None	-	-
0.5	0.5	2	Melt	No	None	-	-
0.75	0.25	2	Melt	No	None	-	-
0.75	0.25	2	Solvent Evap.	No	None	-	-
0.5	0	4	Melt	No	None	-	-
1	0	4	Melt	No	None	-	-
0.25	0.25	4	Melt	No	None	-	-
0.25	0.25	4	Solvent Evap.	No	None	-	-
0.375	0.125	4	Melt	No	None	-	-
0.25	0.75	4	Melt	No	None	-	-
0.5	0.5	4	Melt	No	None	-	-
0.75	0.25	4	Melt	No	None	-	-
0.5	0	6	Melt	No	None	-	-
1	0	6	Melt	No	None	-	-
0.25	0.25	6	Melt	No	None	-	-
0.375	0.125	6	Melt	No	None	-	-
0.25	0.75	6	Melt	No	None	-	-
0.5	0.5	6	Melt	No	None	-	-
0.5	0.5	6	Solvent Evap.	No	None	-	-
0.75	0.25	6	Melt	No	None	-	-
0.5	0	10	Melt	No	None	-	-
0.75	0	10	Melt	No	None	-	-
1	0	10	Melt	No	None	-	-
0.25	0.25	10	Melt	Yes	> 6 months	89 ± 1	0.2
0.375	0.125	10	Melt	Yes	> 6 months	95 ± 9	0.13
0.25	0.75	10	Melt	Yes	> 6 months	86 ± 1	0.22
0.25	0.75	10	Solvent Evap.	Yes	> 6 months	91 ± 2	0.24
0.5	0.5	10	Melt	Yes	> 6 months	86 ± 1	0.18
0.75	0.25	10	Melt	Yes	1 month	141 ± 12	0.18
0.8	0.2	10	Melt	Yes	< 2 days	204 ± 12	0.2
0.875	0.125	10	Melt	Yes	< 1 day	208 ± 8	0.22
1	0.5	10	Melt	No	None	-	-
1.25	0.25	10	Melt	No	None	-	-
1.5	0.25	10	Melt	No	None	-	-
1.5	0.5	10	Melt	No	None	-	-
1.75	0.25	10	Melt	No	None	-	

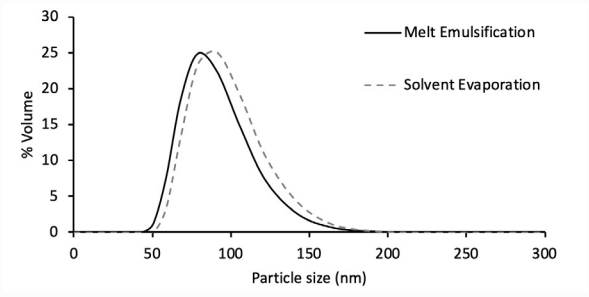

Figure 1: Particle size distribution of CBD Nano dispersions prepared by melt emulsification or solvent evaporation, the formulations had 0.25% CBD, 0,75% ethyl maltol and 10% surfactant.

several of the proposed nanosuspension formulations that yielded considerable initial stability. Table 3 lists the concentrations of these solutions before and after dehydration.

These dried particles can be pressed into tablet form and coated for protection against the gastric conditions or encapsulated in gelatin which only dissolves at neutral pH such as those in the small intestine which is common for over-the-counter drugs. However, for these dehydrated systems to maintain their increased bioavailability and rapid onset, the particles must retain favorable properties once rehydrated. Table 4 shows the initial particle size before drying and after rehydration and Figure 2 shows the optical results before dehydration and after rehydration. Formulations 1-4 all retained favorable optical quality, having similar appearances to before they were dehydrated. Additionally, the particles sizes increased slightly

Table 2: Formulations demonstrating significant stability for at least one week.

Formulation	CBD Concentration (wt%)	Ethyl Maltol Concentration (wt%)	Surfactant Concentration (wt%)	Initial Particle Size (nm)	Initial PDI	Particle Size After 30 Days (nm)	PDI After 30 Days
1	0.25	0.25	10	89 ± 1	0.2	98 ± 2	0.23
2	0.375	0.125	10	95 ± 9	0.13	99 ± 1	0.21
3	0.25	0.75	10	86 ± 1	0.22	95 ± 1	0.22
4	0.5	0.5	10	86 ± 1	0.18	91 ± 1	0.18
5	0.75	0.25	10	141 ± 12	0.18	115 ± 4	0.4

Table 3: Concentrations of the formulations before and after dehydration.

Formulation		CBD Concentration (wt%)	Ethyl Maltol Concentration (wt%)	Surfactant Concentration (wt%)
1	Liquid	0.25	0.25	10
	Freeze Dried	2.4	2.4	95.2
2	Liquid	0.375	0.125	10
	Freeze Dried	3.6	1.2	95.2
3	Liquid	0.25	0.75	10
	Freeze Dried	2.3	6.8	90.9
4	Liquid	0.5	0.5	10
	Freeze Dried	4.55	4.55	90.9
5	Liquid	0.75	0.25	10
	Freeze Dried	6.8	2.3	90.9

Table 4: Particle size before drying and after rehydration.

Formulation	Particle Size Before (nm)	PDI Before	Particle Size After (nm)	PDI After
1	89 ± 1	0.2	102 ± 13	0.2
2	95 ± 9	0.13	117 ± 9	0.15
3	86 ± 1	0.22	93 ± 16	0.22
4	86 ± 1	0.18	103 ± 12	0.14
5	141 ± 12	0.18	177 ± 4	0.41

Table 5: Effect of dilution on particle size.

Formulation	Particle Size Before (nm)	PDI Before	Particle Size Diluted (nm)	PDI Diluted
1	89 ± 1	0.2	163 ± 4	0.32
2	95 ± 9	0.13	196 ± 11	0.3
3	86 ± 1	0.22	178 ± 4	0.13
4	86 ± 1	0.18	205 ± 4	0.12
5	141 ± 12	0.18	225 ± 3	0.17

but with PDI comparable to the original formulations. Formulation 5 did not retain optical quality but instead formed a slightly opaque solution. When the particles size was tested, there was a noticeable increase of more than 35nm and the PDI more than doubled.

The results of this study demonstrate that melt emulsification can be used to obtain relatively small particles with favorable size distributions that may be used to increase the bioavailability of CBD formulations while simultaneously increasing stability, drug loading, and promoting better taste. The lyophilized particles can be rehydrated. Once rehydrated, the formulations maintain a size distribution similar to what they were prior to being dried.

Although the loading of CBD can be 5 times that of what is commercially available, there is still the option for consumers to dilute the system into larger drinks as an additive or enhancer. For those reasons, we explored the effects of diluting the system by a factor of 5 and observed the properties of the nanosuspension after 5 minutes. The results of the study can be seen in Table 5 and demonstrated that lower overall loading volumes like in formulations 1 and 2 yield a PDI that borders on the acceptable limits of a nanosuspension and the size of the particles roughly doubled in both cases. However, when the formulations with higher loading were diluted, the PDI decreased slightly and the particle sizes roughly doubled as well except for formulation 5 which only increased by 60%. While the effect of dilution increases particle size, it still remained within an acceptable range that the benefits of increased bioavailability over pure isolate products and is still easily consumed if diluted. However, the particles retain the more favorable PDI when the initial solution has a higher loading concentration which may make our systems more favorable as a flavor enhancer or additive to other drinks that other commercial products.

Conclusion

The result presented in this study demonstrate that melt emulsification and solvent evaporation can be used to create stable CBD nanosuspensions. Without the inclusion of ethyl maltol, no CBD formulation resulted in a stable emulsion. Although the original intent of ethyl maltol was to mask taste, it had the indirect effect of increasing stability. When ethyl maltol was added to the solution, several formulations with 10% surfactant yielded nanosuspensions that were stable for periods longer than 6 months. Formulations with a CBD loading of 0.5% w/w and another was 0.75% w/w CBD and was stable for roughly a month. The stable solutions that were lyophilized and increased the concentration of the CBD up to 5% w/w and when they were rehydrated, the 0.375%, 0.25%, and 0.5% CBD solutions retained reasonable particle sizes and stability. These nanosuspensions are 5 times more concentrated than what is normally seen commercially and the dried powders that further increase the

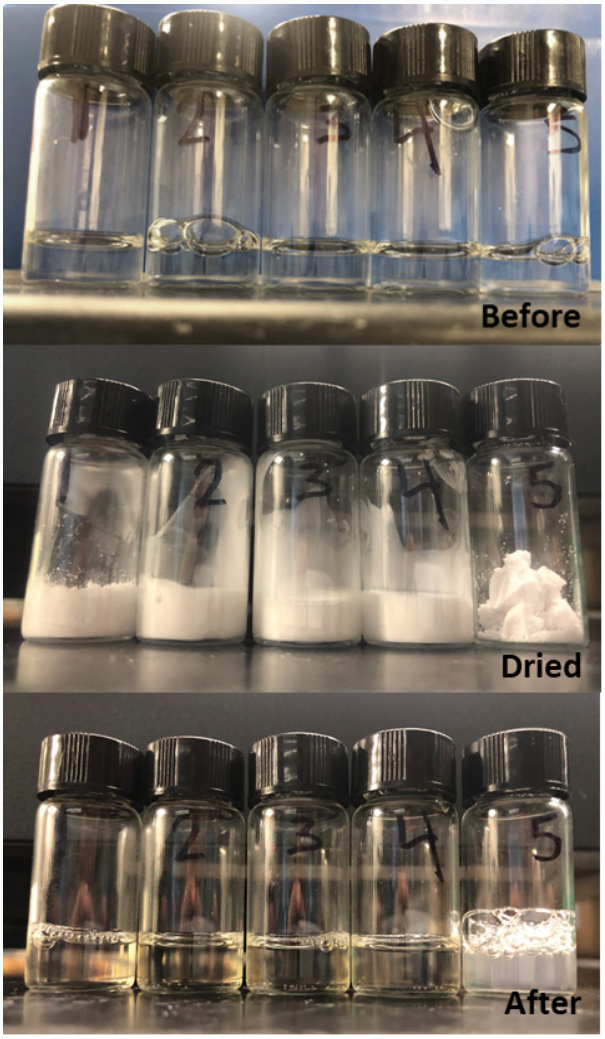

Figure 2: Optical results of the formulations before dehydration, dehydrated and after rehydration Photographs of formulations (top). Photographs of same formulations after freeze drying (middle). Photographs after re-dispersing the freeze-dried formulation in water (bottom). Numbers on vials correspond to the formulations listed in Tables 2-5.

concentrations have the added benefit of maintaining their favorable properties after rehydration. Furthermore, our formulations with higher loading concentrations retain favorable properties better than lower concentration solutions, making them more attractive as a flavor enhancer or additive to an existing drink.

References

1. Waterbeemd HVD, Lennernas H, Abrahamsson B. Drug bioavailability estimation of solubility, permeability, absorption, and bioavailability; Wiley-VCH, 2003;18(27):9783527304387.
2. Waterbeemd HVD, Testa B, Manhold R, Kubinyi H, Flokers G. Drug bioavailability: estimation of solubility, permeability, absorption, and bioavailability. Wiley-VCH. 2009;(2):ISBN: 978-3-527-62386-0.
3. Wise DL. Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. In Handbook of Pharmaceutical Controlled Release Technology. 2000;1:345-57.
4. Lindenberg M, Knopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization model list of essential medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm. 2004;58(2):265-78.
5. Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods Find Exp Clin. Pharmacol. 1998;20(3):211-5.
6. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004;3(9):785-96.
7. Kocbek P, Baumgartner J, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. Int J Pharm. 2006;312(1-2):179-86.
8. Ignjatović J, Đuriš J, Cvijić S, Dobričić V, Montepietra A, Lombardi C, et al. Development of solid lipid microparticles by melt-emulsification/spray-drying processes as carriers for pulmonary drug delivery. Eur J Pharm Sci. 2021;156:105588.