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Review Article

Technical Advance: Development of a Micellar Full Spectrum Hemp Formulation and *ex vivo* Characterization

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Abstract

Phytocannabinoids, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), are highly lipophilic compounds with poor aqueous solubility and bioavailability. Several formulation techniques have been explored to enhance the solubility and bioavailability of phytocannabinoids, including liposomal encapsulation, nano-sizing, and micellization. Among these, micellization presents distinct advantages, supported by emerging clinical validation. *Cannabis sativa* is the predominant strain used in cannabinoid-based products today, and clinical studies on micellar formulations primarily focus on this strain. However, the principles of micellar solubilization are applicable across other cannabis species/strains. This study investigates a proprietary micellization process, Purzorb® technology, which solubilizes full-spectrum hemp oil for oral and topical administration. An animal model using a Franz diffusion apparatus demonstrated 85% absorption through the intestinal lining, significantly outperforming traditional CBD oil. Two human pharmacokinetic studies assessed bioavailability, with one showing rapid onset within 15 minutes and sustained circulation over 6 hours, and a 60-day trial confirming 86% bioavailability alongside reductions in inflammation and improvements in sleep, anxiety, and pain. These findings suggest micellar formulations offer superior bioavailability, faster onset, and prolonged effects, with potential applications in metabolic disorders, neuroinflammation, pain management, sleep disorders, and oral health.

Keywords: Bioavailability; Cannabidiol; Full-spectrum hemp; Micellization; Purzorb technology

Abbreviations & Acronyms

CBD: Cannabidiol; THC: Tetrahydrocannabinol; CMC: Critical Micelle Concentration; ECS: Endocannabinoid System; THCV: Tetrahydrocannabivarin; CBDV: Cannabidivarin; MCT: Medium-Chain Triglycerides; TNF-α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin-6; CRP: C-reactive Protein; LDL: Low-Density Lipoprotein

Introduction

Phytocannabinoids, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), are highly lipophilic compounds with poor aqueous solubility and bioavailability [1,2]. Several formulation techniques have been explored to enhance the solubility and bioavailability of phytocannabinoids, including liposomal encapsulation, nano-sizing, and micellization. Among these, micellization presents distinct advantages, supported by emerging clinical validation.

Cannabis sativa is the predominant strain used in cannabinoid-based products today, and clinical studies on micellar formulations primarily focus on this strain. However, the principles of micellar solubilization are applicable across other cannabis species/strains. Optimal delivery of supplements and pharmaceuticals is an ongoing important area of research spanning academics and industry. Delivery of orally absorbable formulations have well documented unique advantages over systemic delivery via pills, capsules and the like. Development of advanced chemistry technologies has progressed quickly with a number of strategies which are often lumped together under the umbrella terminology of nanochemistry or nano formulations. Delivery of a single active component can be progressed rather quickly and efficiently. An example of this is represented in this special issue by two papers where nanoemulsions of a CBD isolate was developed [3] and subsequently shown to have significant efficacy across a number of dental applications [4]. Utilization of this technology approach was an important, efficient strategy to evaluate the potential efficacy and safety of phytocannabinoid based formulations for application in dentistry.

Historically whole plant extracts from cannabis have been the most intensely and widely studied clinical formulations developed. Significant interest across the breadth of plants utilized for developing phytochemical formulations remains with a focus on understanding how in pharmacological terms plant-based medicinal and dental product polypharmacy in general is understood (e.g. synergistic interactions and bioenhancement). Equally challenging to understanding how this polypharmacy in general works is developing water soluble nano formulations from complex mixture of phytochemicals which include molecules of varying size, charge, fat and water solubility. This is not an easy task. Therefore, the importance of the development of stable, water soluble full spectrum

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micelles which include components from all major and minor classes of cannabis/hemp molecules and for which substantial data attests may be the optimum formulation design to take full advantage of this plant's natural medicinal components.

Micelles: structure and function

Micelles are colloidal dispersions with diameters typically ranging from 5 to 100 nm, depending on surfactant composition and alkyl chain length [5,6]. They are formed by amphiphilic molecules, including cationic, anionic, zwitterionic, and non-ionic surfactants [7]. In aqueous environments, micelles arrange with hydrophobic tails forming a core, while hydrophilic heads interface with water, enabling the encapsulation of lipophilic compounds like cannabinoids (Figure 1) [8].

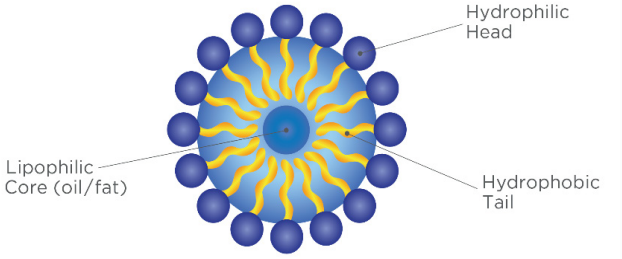

Figure 1: Micelle structure.

Micelles are characterized by their critical micelle concentration (CMC), the threshold concentration required for micelle formation. Above the CMC, micelles self-assemble through hydrophobic interactions and Van der Waals forces, ensuring stable dispersion [6]. Studies indicate that cannabinoid micelles exhibit a low CMC (i.e., they initiate formation at low concentrations), reducing sensitivity to dilution and enhancing systemic circulation [9]. CBD, with a molecular weight of 314.5 g/mol, forms micelles approximately 22 nm in diameter [10].

CBD and THC: properties and mechanisms

Cannabis sativa has been cultivated for millennia for its fibers, oils, and medicinal properties. It contains over 100 cannabinoids, collectively termed phytocannabinoids. The two most studied cannabinoids are THC (Δ9-tetrahydrocannabinol) and CBD (cannabidiol). THC is responsible for the psychoactive effects of cannabis, whereas CBD is non-psychoactive and exhibits a broad pharmacological profile [11]. CBD interacts with the endocannabinoid system (ECS) by modulating CB1 and CB2 receptors, which are distributed throughout the central nervous system and peripheral tissues [12]. Additionally, CBD influences non-cannabinoid receptors and ion channels, contributing to its anti-inflammatory, analgesic, anxiolytic, and neuroprotective effects [13]. The "entourage effect" has been used historically within the cannabis industry and its scientists to describe the synergistic interactions between cannabinoids, terpenes, and flavonoids, enhancing their therapeutic potential [14]. This term has come under criticism for its use is viewed by traditional pharmacologists as primarily for marketing purposes by the cannabis industry [15]. Other natural plant-based multiple compound product's effects have been explained by common pharmacologic terms, i.e. synergistic, antagonistic interactions, additive effects, and bioenhancement [16].

Terpenes, flavonoids and other lipids

Terpenes contribute to the aroma and flavor of cannabis while also exerting therapeutic effects through synergistic interactions with cannabinoids. However, terpenes are volatile and prone to degradation during extraction or storage, which can impact the consistency and efficacy of cannabis oil. Their lipophilic nature further complicates absorption, although some terpenes may enhance cannabinoid permeability across biological membranes [17]. When present in full-spectrum oil, terpenes increase the complexity of micellization.

Cannabis flavonoids, such as Cannflavins A and B, exhibit anti-inflammatory and neuroprotective properties. However, their absorption is hindered by extensive metabolism in the gut and liver, reducing systemic bioavailability. Flavonoids also possess diverse solubility profiles, making their incorporation into micellar formulations as challenging as terpenes [18].

The presence of additional lipids in cannabis oil further complicates micellization and absorption. While lipids can enhance cannabinoid solubility in the gastrointestinal tract, their micelles differ in structure from those formed by cannabinoids, terpenes, and flavonoids, leading to variable pharmacokinetics and formulation stability challenges [19].

Challenges in cannabinoid bioavailability

Oral bioavailability of cannabinoids is poor, with CBD and THC exhibiting absorption rates of 4% to 12% due to extensive first-pass metabolism in the liver [1,2]. Inhalation achieves higher bioavailability (~30%) with peak plasma concentrations reached within 10 minutes [20]. However, inhalation is not always practical or desirable, necessitating alternative delivery systems.

Micellar Full-Spectrum CBD formulation

Purzorb® technology: Purzorb® is a proprietary micellization process that solubilizes decarboxylated full-spectrum hemp oil for oral and topical administration. The resulting micelles, approximately 22 nm in size, enhance aqueous permeability and bioavailability. The formulation includes a standardized ratio of cannabinoids, such as: ≥70% CBD, ≥2% THCV (tetrahydrocannabivarin), ≥5% CBDV (Cannabidivarin), ≤1% Δ9-THC. Purzorb® has been granted a composition of matter patent [21], indicating its novelty and potential therapeutic applications. The process involves dissolving full-spectrum hemp oil in an amphipathic solvent or surfactant, followed by controlled aqueous dispersion to yield a stable micellar suspension.

Micelle penetration and delivery pathways: Micelles, self-assembling nanoscale structures formed by amphiphilic molecules, play a crucial role in drug delivery by encapsulating hydrophobic drugs within their core. The penetration and cellular uptake of micelles primarily occur through endocytic pathways, including clathrin-mediated and caveolae-mediated endocytosis, depending on their surface charge, size, and composition [23]. Some micelles can also facilitate membrane fusion, allowing drug transfer directly into cells. For example, poloxamer-based micelles exhibit concentration-dependent uptake, with high concentrations favoring clathrin-mediated pathways and low concentrations relying on caveolae-mediated endocytosis [24]. Once inside the cell, micelles are trafficked to endosomes, where pH changes or enzymatic activity promote drug release. Certain formulations, such as poloxamer-based micelles, can also trigger endosomal escape, further enhancing drug bioavailability [25].

Specific surfactants form micelles that enhance the solubility and absorption of hydrophobic drugs. These micelles exhibit prolonged retention (i.e. retained as intact micelles) in solution, allowing for extended absorption time and interaction with biological membranes, leading to improved oral bioavailability [26]. While research suggests that these micelles may merge with cellular membranes for drug release, their role in transdermal penetration is still being explored. Similarly, nonionic surfactant micelles can facilitate drug transport through the stratum corneum, enhancing topical and transdermal delivery [27]. Micelle stability, size, and surface charge are critical factors that influence penetration efficiency and systemic absorption. In the context of oral mucosal drug delivery, the buccal membrane, which is more permeable than the keratinized epithelium of the hard palate, serves as an important absorption site. However, due to the permeability barrier, penetration enhancers such as bile salts and surfactants are often employed to improve drug transport across the oral mucosa [28].

Permeability enhancers, particularly surfactants and bile salts, play a significant role in improving drug absorption through the buccal mucosa, allowing medications to bypass first-pass metabolism and directly enter systemic circulation. Bile salts function by fluidizing membranes, disrupting lipid and protein structures, initiating reverse micellization, and creating aqueous channels, all of which enhance drug penetration [29]. The oral mucosa's permeability varies among different regions, with the sublingual area exhibiting the highest permeability, followed by buccal and palatal regions [30]. Compared to intestinal epithelium, which has tight junctions limiting paracellular transport, the buccal mucosa's larger intercellular domain can facilitate improved drug penetration [31]. By incorporating micelle-based drug carriers alongside penetration enhancers, researchers can optimize drug delivery for oral, transdermal, and systemic applications, enhancing bioavailability and therapeutic effectiveness.

Results

Absorption and bioavailability studies: Purzorb® absorption animal model study

A Franz diffusion apparatus was used to evaluate the intestinal absorption of micellized full-spectrum hemp oil in an *ex vivo* animal model. Results demonstrated 85% absorption through the intestinal lining, significantly outperforming traditional CBD oil formulated with MCT [22]. The micellar formulation exhibited superior permeability, likely due to its nanoscale size and amphiphilic properties, which facilitate transcellular and paracellular transport across the intestinal epithelium.

Human bioavailability studies

Two single dose human pharmacokinetic studies assessed the bioavailability of Purzorb®-formulated CBD over a 12-hour period [32]. In the first study, fourteen participants received either a 7.35 mg or an 8.95 mg oral dose of micellized CBD, with plasma CBD levels measured at intervals to determine systemic uptake. Key findings include: rapid onset with 50% of the maximum concentration of CBD detected in plasma within 15 minutes, peak plasma concentration achieved within 45 minutes, significantly faster than traditional lipid-based formulations, and extended systemic circulation with plasma CBD levels remaining near peak concentrations for over 6 hours.

In a separate 60-day study [33], 150 participants received 3 mL/day of Purzorb®-formulated CBD (Med7®) to evaluate long-term safety and efficacy. CBD was measured arterially following 60 days of daily dosing. The overall bioavailability of this formulation following oral administration was greatly improved relative to standard CBD oil. Subjects also exhibited significant reductions in inflammatory markers (TNF-α, IL-6, CRP) and improvements in metabolic and cardiovascular health parameters, including reduced fasting glucose levels and lower LDL cholesterol. Subjective reports also indicated improved sleep quality, reduced anxiety, and decreased chronic pain scores.

Results from the animal absorption study showed a 3 to 4 fold increase in absorption rate for micellized full-spectrum hemp oil, significantly higher than traditional CBD oil (Figures 2 and 3). Human studies revealed rapid CBD uptake, with 50% of the Cmax in plasma achieved by 15 minutes and peak concentrations at 45 minutes, sustaining levels for over 6 hours [32]. The 60-day study demonstrated greatly improved bioavailability, with reductions in TNF-α, IL-6, and CRP, alongside improved metabolic markers and subjective benefits in sleep, anxiety, and pain [33].

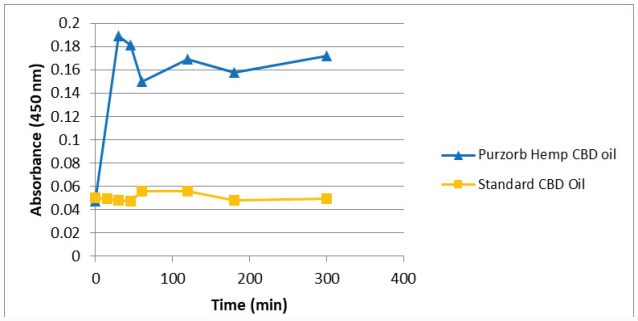

Figure 2: Absorption comparison between Purzorb® micellized CBD oil and standard MCT-formulated CBD oil in an *ex vivo* animal model for intestinal absorption.

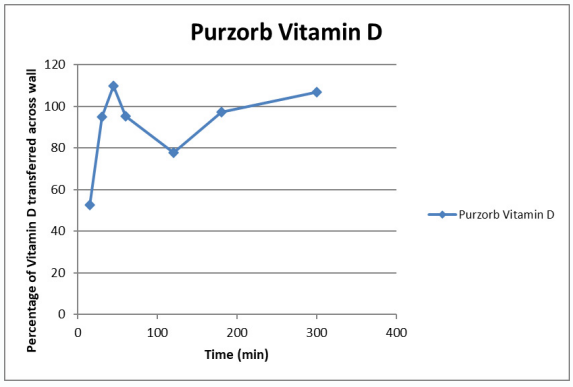

Figure 3: Purzorb Vitamin D3 in an *ex vivo* animal model for intestinal absorption.

Discussion

The enhanced bioavailability of micellar CBD formulations presents significant therapeutic advantages, particularly in medical applications requiring consistent and efficient cannabinoid absorption. Compared to conventional oil-based preparations, Purzorb®-micellized CBD provides greater systemic absorption, leading to improved efficacy at lower doses, more predictable pharmacokinetics; while reducing variability in patient response and extended

circulation times, thereby enabling prolonged therapeutic effects, and potential for lower dosing requirements, minimizing side effects associated with high-dose CBD use. Emerging research suggests that micellar cannabinoid formulations may offer particular benefits for metabolic disorders (e.g., diabetes, insulin resistance, obesity-related inflammation), neuroinflammation and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), pain management (including chronic inflammatory and neuropathic pain), sleep disorders (insomnia and sleep regulation), control of cytokines in hyperinflammatory states (e.g. Cytokine Storm Syndrome in COVID-19) [34] and oral and dental health applications (anti-inflammatory, anti-microbial and wound healing effects). Furthermore, the rapid and consistent absorption of micellar CBD may improve patient adherence and treatment outcomes, particularly for individuals requiring precise cannabinoid dosing for symptom management.

Conclusion

Purzorb® micellar full-spectrum CBD oil demonstrates superior bioavailability, faster onset of action, and extended systemic circulation compared to conventional lipid-based formulations. Clinical and preclinical studies confirm its higher absorption rates, rapid systemic uptake, and longer plasma retention times, supporting its role as an optimized delivery system for cannabinoids. By overcoming the solubility challenges associated with cannabinoids, micellar formulations hold promise for a wide range of therapeutic applications, from chronic pain and inflammation to neurodegenerative conditions and metabolic disorders. Future research should further explore expanded clinical applications, long-term safety, and optimal dosing regimens to fully harness the potential of micellar cannabinoid delivery systems.

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