

Inhalable cannabidiol dry powders with enhanced solubility

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Summary

Inhalation is a promising administration method for cannabidiol (CBD) due to its higher bioavailability than that from oral delivery. The low solubility of CBD poses a delivery challenge. In this study, spray freeze dried CBD powders with enhanced solubility were produced with dipalmitoylphosphatidylcholine and a hydrophilic bulking agent (mannitol or trehalose dihydrate), referred to as Formulation M and Formulation T, respectively. Formulation M was crystalline, while Formulation T was amorphous. Both showed higher CBD solubility than raw CBD, with Formulation T having the highest value (raw CBD vs Formulation M vs Formulation T: 3.8 µg/mL vs 11.17 µg/mL vs 16.30 µg/mL). The mass median aerodynamic diameter of Formulation T was smaller than that of Formulation M (4.47 µm vs 5.56 µm), as reflected in its higher fine particle fraction < 5 µm (42.7% vs 33.6%). Formulation T may thus be further tested *in vivo* and adapted to deliver other cannabinoids by inhalation.

Key Message

Both the spray freeze-dried cannabidiol dry powders with mannitol (crystalline) and with trehalose dihydrate (amorphous) were dispersible and with enhanced cannabidiol solubility.

Introduction

Cannabis sativa has been used as an herbal medication for millennia. Cannabidiol (CBD) is the second most prevalent cannabinoid in cannabis and is non-psychoactive [1]. Its potential pharmacological actions have attracted much attention in recent years, for example, it is effective for treating seizures associated with Lennox-Gastaut and Dravet syndromes [2]. The United States FDA approved Epidiolex®, an oral CBD solution, for these indications in June 2018 [3]. However, CBD has a low oral bioavailability of about 6%, making ingestion an inefficient route of administration [4]. Pulmonary delivery is a promising alternative [4]. Inhalation via smoking and vaporising are currently the most common delivery methods for cannabis. More importantly, the pulmonary bioavailability of CBD is approximately 31%, which is 5-fold higher than that from oral delivery [4]. Hence, the inhaled doses can be lowered and thus potentially reduce systemic adverse effects.

Problems with aqueous solubility and chemical stability must be overcome to deliver CBD efficiently. The reported aqueous solubility of CBD is approximately 0.1 µg/mL [1]. One approach to improve solubility is to form micelles to entrap and keep the drug in solution by using surfactants [5]. There are endogenous surfactants in the lungs, which mainly consist of phospholipids [6]. One of them is dipalmitoylphosphatidylcholine (DPPC), which is also an active ingredient for treating respiratory distress syndrome in preterm infants and an excipient for improving powder dispersion [7]. This surfactant was utilised as a solubility and dispersion enhancer for the dry powders in this study. Formulating CBD as dry powders may also improve its chemical stability. CBD is prone to degradation by light, temperature, and oxygen during storage [8]. Studies have shown that CBD was more stable when stored in a powder form at room temperature than in solutions, regardless of the type of solvent [9]. Therefore, formulating CBD as dry powders is better than as solutions.

In this study, inhalable dry powder formulations of CBD with DPPC were produced. Mannitol and trehalose dihydrate were added as hydrophilic bulking agents to improve the wetting of the powders. Their crystallinity, CBD solubility, and aerodynamic particle size distribution were investigated.

Experimental methods

Materials

CBD was bought from THC Pharm (Frankfurt, Hesse, Germany). Trehalose dihydrate, Tween 80 and *tert*-butanol were purchased from Sigma-Aldrich (St. Louis, Missouri, United States). Mannitol was bought from Roquette (Geneva, New York, United States), while DPPC was supplied by Cayman Chemical (Ann Arbor, Michigan, United States). Ethanol and phosphate buffered saline (pH 7.4) were purchased from Chem-Supply Pty Limited (Adelaide, South Australia, Australia) and POCD Healthcare (Sydney, New South Wales, Australia), respectively. Ultrapure water was obtained from a Milli-Q® Direct Water Purification System (Millipore, Bedford, Massachusetts, United States).

Methods

Spray freeze drying

Powders of two formulations (Formulation M: CBD+DPPC+mannitol; Formulation T: CBD+DPPC+trehalose dihydrate) were spray freeze dried. The total solute concentration was 20 mg/mL, using 60:40 water:*tert*-butanol by volume as the co-solvent. The CBD-to-DPPC-to-carbohydrate mass ratio was 1:1:3. The solutions were fed at a flow rate of 0.5 mL/min via a syringe pump into an ultrasonic nozzle (Sono-Tek, Milton, New York, United States), which was connected to a Sono-Tek ultrasonic generator for controlling the atomizing frequency and power at 48 kHz and 2 W, respectively. The ultrasonic nozzle was positioned 10 cm above the surface of the liquid nitrogen contained in a stainless-steel collection cup. The liquid nitrogen was allowed to evaporate after finished spraying a solution. The frozen droplets were then lyophilised for 48 h at -20 °C in a freeze dryer (Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Niedersachsen, Germany). After that, the temperature was ramped upwards at a rate of 10 °C per hour until 20 °C was reached, at which point the samples were kept for another 20 h before removal from the freeze dryer.

X-ray powder diffraction (XRD)

An X-ray diffractometer (X'Pert Powder; Malvern Panalytical Ltd., United Kingdom) was employed to characterise the diffraction patterns of the samples. The powders were spread on zero diffraction plates and subjected to Cu K α radiation under ambient temperature. The current and voltage were 45 mA and 40 kV, respectively. The scattered intensity was recorded from 5 to 50° by a detector with a scan speed of 0.04° 2 θ per second.

Solubility test

An excess amount of a spray freeze dried powder was added into 10 mL of 0.002% w/v Tween 80 in phosphate buffered saline at pH 7.4. Tween 80 was chosen because it was used in previous studies to differentiate the dissolution profiles of lipophilic basic drugs [10-12], of which CBD is an example. The concentration of Tween 80 should be as low as possible to minimise artefacts in increasing the solubility of CBD, and was therefore used at its critical micelle concentration in water [13]. The solution was stirred continuously at 37 °C for 2 hours, during which the degradation of solubilised CBD was not significant. After it was centrifuged at 29756 $\times g$ for 10 min, the supernatant was taken as a sample for the quantification of CBD by high pressure liquid chromatography. The solubility test of raw CBD was conducted in the same dissolution medium as a control. The test was performed in triplicate.

Cascade impaction

The aerodynamic particle size distributions (APSDs) of the two formulations were determined using the Next Generation Impactor (Copley, Nottingham, United Kingdom), in which all eight stages were coated with 0.6% w/v Tween 80 in ethanol. Five milligrams of powder was loaded into a Size 3 hydroxypropyl methylcellulose capsule (Capsugel, Sydney, New South Wales, Australia). One capsule per run was dispersed from a low resistance Osmohaler® (Pharmaxis, Frenchs Forest, New South Wales, Australia). The flow rate and duration of dispersion were 95 L/min (equivalent to a 4 kPa drop across the inhaler) and 2.5 s, respectively, allowing 4 L of air to pass through the inhaler. The mass of CBD collected on each part and stage of the Next Generation Impactor was quantified by high pressure liquid chromatography. The emitted fraction (EF), fine particle fraction (FPF), mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) were calculated. The EF and FPF were defined as the emitted dose and fine particle dose with respect to the recovered dose, respectively. MMAD was the aerodynamic diameter that divided the particle size distribution by mass in half. The GSD was the square root of the ratio of the aerodynamic diameter at 84% undersize to that at 16% undersize. The experiments were carried out in triplicate.

Statistical analysis

Jamovi (Sydney, New South Wales, Australia) was used to conduct statistical analyses. The statistical tests for analysing the significance of the aerosolisation performance and solubility were Student's *t*-test and ANOVA with the Tukey *post hoc* test, respectively. The significance level was $p \leq 0.05$ for the *t*-test and ANOVA, and $\alpha \leq 0.05$ for the *post hoc* test.

Results and Discussion

The XRD patterns of the raw materials and both formulations are depicted in Figure 1. The raw materials and Formulation M were crystalline, as confirmed by the distinct diffraction peaks. Most of the peaks of Formulation M corresponded to those of mannitol as it was the major composition. However, raw mannitol and the mannitol in Formulation M did not share the same peaks. Their peaks indicated that the raw mannitol and the mannitol contained in Formulation M were in beta and delta form, respectively [14]. The polymorphic change of mannitol may be attributed to its rapid precipitation during spray freeze drying [15]. The peaks of DPPC and CBD in Formulation M were either low in intensity or they overlapped with other peaks, thus it was difficult to determine their crystal form in this powder. The halo pattern of Formulation T indicates that it was amorphous.

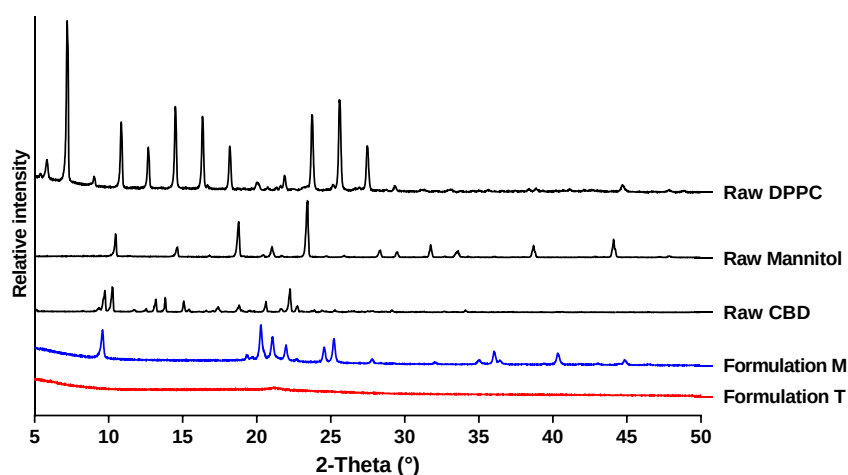


Figure 1. X-ray diffraction patterns of the raw materials and spray freeze dried powders.

The saturated concentrations of CBD from Formulations M and T were significantly higher than that of raw CBD (raw CBD vs Formulation M vs Formulation T: 3.8 $\mu\text{g/mL}$ vs 11.17 $\mu\text{g/mL}$ vs 16.30 $\mu\text{g/mL}$; control vs formulations: $p \leq 0.05$; Formulation T vs Formulation M: $p > 0.05$), showing the effect of DPPC in enhancing solubility. The lower solubility of CBD from Formulation M compared to that of Formulation T might be due to the difference in crystallinity. Mannitol in Formulation M was crystalline and formed an orderly packed structure on its own, leaving DPPC and CBD out of the matrix. Therefore, it provided limited enhancement in the wetting and dissolution of CBD, suggesting that its solubility was increased mainly by DPPC. In contrast, DPPC and CBD fitted well into the glassy matrix of the amorphous Formulation T. Therefore, CBD in that powder was wetted better and dissolved easier, reaching a higher saturated concentration.

The mass recoveries, APSDs, EFs, and FPFs of the powders measured by cascade impaction are shown in Figure 2. The recovery was close to 100%, indicating that almost all the CBD was accounted for in the drug assay. Formulation T had slightly less powder retained inside the capsule than Formulation M, hence the EF for the former was slightly higher but the difference was not statistically significant. Less CBD from Formulation T deposited on Stage 1 but more deposited on the lower stages. Therefore, Formulation T had significantly higher FPFs than Formulation M, suggesting that more particles from Formulation T could reach the deep lung. The MMAD of Formulation M was significantly larger than that of Formulation T (5.56 μm vs 4.47 μm ; $p \leq 0.05$), but their GSDs were comparable (2.51 vs 2.52; $p > 0.05$). Stability study is required to investigate the change in aerosol performance under different storage conditions.

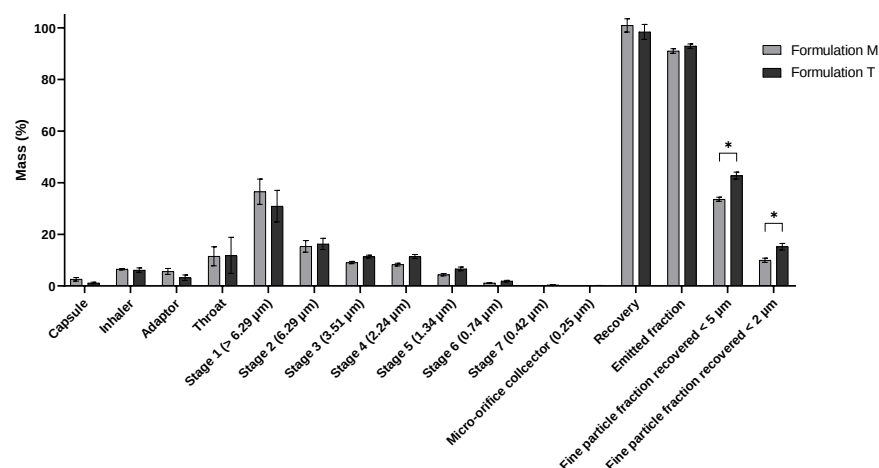


Figure 2. The recovery, APSD, emitted fraction, and fine particle fraction of Formulation M (light grey) and Formulation T (dark grey). ($n = 3$; mean $\pm$ standard deviation; $*p \leq 0.05$)

Conclusion

CBD was spray freeze dried with DPPC and mannitol or trehalose dihydrate to obtain inhalable particles with enhanced solubility. Both formulations showed acceptable aerodynamic performance for pulmonary delivery. Despite the powder having different crystallinity, the significant enhancement of the aqueous solubility of CBD may lead to a higher drug absorption from the lungs. Formulation T performed better overall than Formulation M, owing to its higher FPF and CBD solubility. It may thus be further tested *in vivo* and adapted to deliver other cannabinoids by inhalation.

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