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RESEARCH ARTICLE

Cannabidiol and Hydroxypropyl-β-Cyclodextrin for the Development of Deflated Spherical-Shaped Inhalable Powder

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Abstract

In addition to the known therapeutic indications for cannabidiol, its administration by inhalation appears to be of great interest. Indeed, there is evidence of cannabidiol's efficacy in several physiological pathways, suggesting its potential for a wide range of applications for both local and systemic pulmonary administration like cancers. Significant advances in pulmonary drug delivery have led to innovative strategies to address the challenges of increasing the respirable fraction of drugs and standardizing inhalable products. Among different devices, dry powder inhalers offer significant advantages including high stability and ease of use. Particle engineering using techniques such as spray drying is now the focus of research and is expected to improve upon, rather than completely replace, traditional carrier-based formulations. The development of carrier-free powders (without lactose-carrier) is mainly used for medicines with low active ingredient doses, which limits the technology. Previously, we demonstrated the benefits of using a cyclodextrin to obtain deflated spherical-shaped powders by spray drying. In this study the potential of this excipient with a very poorly water-soluble active molecule was investigated. Inhalable cannabidiol powders were developed by spray drying, using the solubility enhancers hydroxypropyl-beta-cyclodextrin and ethanol to optimize cannabidiol water-solubility. Electron microscopy images revealed consistent deflated spherical shapes, while particle size analysis showed low polydispersity and suitable sizes for deep lung deposition (2 µm). The selected engineered powders (without ethanol) had very high fine particle fractions (> 60%) due to their deflated surface. Finally, the powder was instantly solubilized leading to drug dissolution, which is important for therapeutic efficacy. In conclusion, this study successfully develops a cannabidiol inhalation powder by particle engineering having suitable aerosolization behavior. Due to the speed of the process and the performance of the finished product, this work opens the door for future studies. It has been shown that active molecules that are only slightly soluble in water can be formulated effectively as a powder for inhalation. Other molecules could be tested and subsequent *in vivo* studies conducted to demonstrate correlation with these *in vitro* results.

Keywords cannabidiol · dry powder inhaler · hydroxypropyl-beta-cyclodextrin · inhalation · spray drying

Abbreviations

API	Active pharmaceutical ingredient
APSD	Aerodynamic particle size distribution
ARDS	Acute respiratory distress syndrome
BCS	Biopharmaceutics Classification System
C	Corrugation
CBD	Cannabidiol
Cc	Cunningham slip correction
COPD	Chronic Obstructive Pulmonary Disease
D	Deflation
d	Physical diameter
Da	Aerodynamic diameter
Dd	Depth of dimples
DPI	Dry powder inhaler
ED	Emitted dose
EF	Emitted fraction
EtOH	Ethanol
FPD	Fine particle dose
FPF	Fine particle fraction
GDS	Geometric standard deviation
HPLC	High performance liquid chromatography

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HP-β-CD	Hydroxypropyl-beta-cyclodextrin
ICH	International Council for Harmonization
IH	Hausner index
MDI	Metered-dose inhaler
MMAD	Median mass aerodynamic diameter
ND	Number of dimples
NGI	Next generation impactor
PTFE	Polytetrafluoroethylene
RD	Recovery dose
RF	Recovery fraction
SD	Standard deviation
SEM	Scanning electron microscopy
SMI	Soft-mist inhaler
TGA	Thermogravimetric analysis
UV	Ultraviolet
Δ9THC	Delta-9-tetrahydrocannabinol
ρp	Particle density

Introduction

The herbaceous plant *Cannabis sativa*, classified by Linneo in 1753, has significant medicinal potential, with diverse therapeutic properties attributed to its rich composition of secondary metabolites, including terpenoids, flavonoids, alkaloids, lignans and approximately 113 phytocannabinoids (1, 2). In particular, Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) are the major constituents, detected in cannabis extracts at proportions of 17.3% and 9.6%, respectively (3). The biological effects of CBD and Δ9-THC on the human body have remarkable differences. Δ9-THC primarily induces behavioral effects, including paranoia, memory impairment, and an increased risk of psychotic illness and dependence (4). In contrast, CBD exhibits diverse therapeutic effects ranging from anxiety and inflammation reduction to neuropathic pain management and epilepsy treatment, possibly due to its interactions with different molecular targets (5).

The therapeutic potential of CBD without psychotropic effects is very promising. However, our understanding of its neuro-molecular mechanisms remains limited, leaving a gap for further exploration and discovery of additional therapeutic applications (6). Moreover, CBD has low oral bioavailability, with only 6% reaching the bloodstream limiting their clinic utilization. Despite its promising therapeutic properties, CBD faces formulation challenges due to its low water solubility and high lipophilicity, being considered a class II drug in the Biopharmaceutics Classification System (BCS) (7–9). Various strategies to improve its oral bioavailability have been investigated, such as using the amorphous form of CBD by hot melt extrusion or supercritical fluid technology. Jennotte *et al*. have recently developed an extruded filament loaded with amorphous CBD to print personalized drug doses by fused deposition modelling (9). In addition, Koch *et al.* compared two new oral solid dosage forms as impregnated mesoporous silica and a lipid-based formulation after oral administration in piglets (10). Both formulations increased the bioavailability of CBD by 10.9-fold and 6.8-fold for the amorphous and lipid formulations, respectively, compared to the crystalline form. In addition, cyclodextrins such as hydroxypropyl-beta-cyclodextrin (HP-β-CD) or methyl-beta-cyclodextrin (CH3-β-CD) have been used to develop solutions of CBD. HP-β-CD has shown the greatest improvement in water solubility (11).

In parallel with oral formulations, inhalation is the preferred route of administration for the delivery of drugs to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) (12, 13). Recently, it has been shown that the administration of CBD via the pulmonary route significantly increases bioavailability to 31%, leading to faster absorption and higher peak concentrations in the bloodstream (14). This observation is encouraging for systemic therapeutic effect following pulmonary absorption (15). Hesam *et al.* demonstrated promising potential for future treatments aimed at alleviating cancer-related symptoms and possibly inhibiting tumor progression, as observed in glioblastoma (GBM) following lung delivery of CBD (16). Inhalation is favored due to its advantages such as bypassing first-pass metabolism, increasing bioavailability, achieving faster absorption and requiring lower doses (17). The human pulmonary airways are functionally divided into two distinct zones: the conducting channels and the respiratory zone (13). These airways are lined with respiratory epithelium and mucosa, allowing for drug delivery and absorption throughout the airways. However, the deepest regions offer the best opportunities for dissolution and absorption of inhalable particles (18).

In the modern era, drug aerosolization for pulmonary delivery can be achieved by four primary systems: nebulisers, metered dose inhalers (MDIs), soft mist inhalers (SMIs) and dry powder inhalers (DPIs) (19). DPIs are designed to deliver solid formulations and consist of three integral components: the powdered drug formulation, the drug dose measurement system, and a mechanism to disperse the formulation (20). Compared to other inhalable devices, DPIs offer several advantages: improved product stability due to lower water content, environmental friendliness without the need for propellant, ease of use without coordination between inhalation and device actuation, and high dose delivery capability (13, 21). Most DPIs use carrier excipients such as lactose, mannitol or trehalose to prevent powder aggregation, add bulk, and facilitate dosing, delivery and handling (20, 22, 23). Inhalable dry powder formulations for DPIs can be produced using a variety of techniques, including milling and spray drying. Less common methods such as spray freeze drying and supercritical fluid drying are also promising, as are emerging

processes such as thin film freezing and hot melt extrusion (24). The resulting micronized products often exhibit poor aerosolization properties, characterized by pronounced cohesiveness and aggregation tendencies due to significant surface free energy at the microscopic scale (25). Particle engineering has emerged as a strategic approach to address these challenges by optimizing the bulk forces of dry powders for improved stability during processing, storage and inhalation (26, 27). By tailoring physicochemical attributes such as size and morphology, particle engineering ensures reproducible product properties through precise control of equipment operating parameters (28, 29).

Spray drying is the most widely used technique for developing powders for inhalation without a carrier (30). It efficiently converts liquid solutions, suspensions or emulsions into dry powders and is recognized for improving aerosol performance by tailoring material properties (31). Spray drying offers advantages such as precise control of particle size, shape and density through manipulation of process parameters, enabling a single-step process for different feed forms and providing highly dispersible particles (32). The size of aerosolized particles is critical to their penetration of the respiratory tract as well as the particle shape (33). Lechanteur *et al.* showed that deflated spherical shape particles induce very good aerosolization behavior when specific spray drying parameters are used and when the feed solution contains at least 50% HP-β-CD as the carbohydrate component (34). This was explained by the high Peclet value of the excipient. In addition, Gresse *et al.* recently showed that the combination of the engineered powder (with a particle size below 2.5 µm) and coarse lactose resulted in a stable blend with suitable flow properties for further industrial processes (35).

Concerning the development of engineered particle loaded with CBD, Devinsky *et al*. have used spray drying technique to develop inhaled powder with CBD (36). A suspension of CBD was prepared with 1,2-distearoyl-sn-glycero-3-phosphocholine, piperazinedione, ethanol and water. The morphology of atomized powder was not analyzed but results showed low emitted fraction and low fine particle fraction (30%). In comparison, we aimed to atomize a solution using specific excipients such as cyclodextrins. Another very recent publication showed the production of inhaled powder using spray-freeze drying. In this case, authors use a solution prepared with dipalmitoylphosphatidylcholine, mannitol, and trehalose dihydrate and CBD dissolved in 60:40 (v/v) water:tert-butanol mixture. We only use water in our optimized formulation for ecological reasons. Although the proportion of loaded CBD in the powder is high, the diameter of the powders found is greater than 10 µm, which also results in a low FPF (close to 30%) (37).

The aim of this study was to formulate a CBD-loaded powder for pulmonary administration having high aerosolization performance. The investigation focused primarily on the complexation of CBD with HP-β-CD. After solution formulation, atomization was performed by spray drying technology and CBD powders were characterized. In addition, it was aimed to understand the effect of the formulation on the physicochemical properties of the collected particles. The binary combination of CBD with HP-β-CD was compared with a ternary formulation containing ethanol as a solubilization enhancer. The dissolution speed of the selected inhalable powder was also assessed.

Materials and Methods

Materials

Hydroxypropyl-β-cyclodextrin (HP-β-CD) (Kleptose HPB-molar substitution = 0.63) were provided by Roquette (Lestrem, France). Cannabidiol (CBD) was obtained from THCPharm GmbH (Frankfurt, Germany). Ethanol (EtOH) absolute was supplied by Thermo Fisher Scientific (Loughborough, England). Ultrapure water was produced by a Rephile PURIST PRO water purification system.

Preparation of the CBD Solutions Before Atomization

First, a solution of HP-β-CD with 15% solid content (w/v) was prepared either in water or an aqueous medium with 10% (v/v) of EtOH. An excess CBD powder was added to each solution and underwent 5 min of ultrasounds waves, followed by placement in a thermostated bath set to 37 °C with continuous agitation for 24 h. The volume of each solution was standardized at 10 ml. CBD particles that remained unsolubilized were eliminated using a syringe membrane filter made of PTFE with a pore size of 0.45 µm. These two solutions were prepared in triplicate and were made following the same procedure.

Spray Drying

The equipment used in this operation was a Procept 4 M8-Trix Formatrix spray dryer (Procept, Zelzate, Belgium) with a bi-fluid nozzle. The parameters of the process are based on previous study and shown in Table I (33, 34). The process yield was calculated for each powder obtained with the following formula:

$$\text{Process yield}(\%) = \frac{\text{Mass of obtained spray dried powder (g)}}{\text{Mass of total dissolved powder before spray drying (g)}} \times 100$$

CBD Quantification

High performance liquid chromatography (HPLC) was used to quantify CBD using an HPLC Agilent serie1100 with OpenLab CDS LC ChemStation version C.01.05 as

Table I Parameters of Spray Drying Process

SD parameter	Specification
Solid content	15% (w/w)
Cyclone gas pressure	0.4 bar
Inlet gas flow	0.4 m^3/min
Inlet temperature	160 ℃
Pump speed	100 rpm
Flow rate	3.85 g/min
Nozzle gas pressure	3 bar
Nozzle diameter	0.4 mm

the software, UV detector operating at 240 nm and with a Zorbax® C18 300 SB 4.6*150 mm analytical column filled 3.5 µm C18 (X Bridge BEH C18). The mobile phase was composed of a mixture of water and acetonitrile [38/62% (v/v)]. The flow rate was set at 1.0 ml/min and the column was kept at 30 ℃. A volume of 20 µL of each sample was injected at room temperature and the run time of process was set to 10 min.

The process was fully validated based on the total error as a decision criterion. The acceptance limits were set at 10%. All validation results were computed using the Enoval software V3.0 (Arlenda, Liege, Belgium).

Particle Size Distribution (PSD) Measurement

To assess the size of the generated powder particles, a laser diffraction particle size analyzer, specifically the Mastersizer 2000, coupled to Scirrocco powder feeder (Malvern, UK), was employed. A dispersion pressure of 4 bars was used, with a measurement duration of 10 s. Approximately 150 mg of powder was utilized for each sample to achieve the desired obscuration within the range of 0.5% to 5%.

Scanning Electron Microscopy

The particulate morphology was observed by scanning electron microscopy (SEM) using either a Philips XL30 ESEM or a FEI Quanta 600 after metallization with Au (~ 50 nm). Representative micrographs were captured, and four particles were sampled for each powder to measure their diameter and characterize their shape. For each powder, the average number of dimples was manually counted (the visible dimples can be assumed to be half the total number of a particle), and dimple depth (normalized to the diameter d of the particle) was estimated.

Thermogravimetric Analysis

The quantification of residual moisture in the obtained powders was performed using thermogravimetric analysis (TGA 2—Mettler Toledo, Switzerland). Powder samples ranging from 6 to 12 mg were placed into a platinum sample pan. The method began at 25°C and increased to 200°C at a rate of 10°C/min. Additionally, TGA was utilized to evaluate the degradation temperatures of CBD raw materials. Approximately 5 mg of API was placed in aluminum pans and heated from 25°C to 500°C at a rate of 20°C/min, under a nitrogen flow rate of 20 mL/min.

Bulk and Tapped Density

Based on previous experiments and research, it was already established that powders containing HP-β-CD would present poor flowability (33). Bulk and tapped density were performed according to European Pharmacopoeia Procedure 2.9.34 with few adaptations, which were also adopted by other researchers (38–40). A 10 ml graduated cylinder was used to measure a certain volume of powder. The bulk volume used for the calculation of the bulk density was directly read from the cylinder.

$$\text{Bulk density } (g/cm^3) = \frac{\text{Weight of powder (g)}}{\text{Bulk volume of powder } (cm^3)}$$

The tapped density was determined by mechanically tapping a graduated cylinder containing the powder sample. The value of the tapped volume was read after 10 and 500 taps at a tapping height of 3 mm.

$$\text{Tapped density } (g/cm^3) = \frac{\text{Weight of powder (g)}}{\text{Tapped volume of powder } (cm^3)}$$

The Hausner (IH) index is used to express flowability of powders. This was calculated based on tapped and bulk densities.

$$\text{IH} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Homogeneity and Drug Recovery

For each formulation, homogeneity was assessed by analyzing five spray dried powder samples from every batch. Each sample was dissolved in a fixed volume of a 62:38 (v/v) of acetonitrile and water solution. After a brief sonication, the resulting solutions underwent filtration using a 0.45 µm PTFE membrane filter and were subsequently subjected to HPLC analysis (as detailed in Section CBD Quantification). After each production run of powder, homogeneity was evaluated, and CBD recovery was quantified using the following formula.

$$\text{Recovery } (\%) = \frac{\text{Total mass of CBD in spray dried powder}}{\text{Total mass of CBD in solution (before SD)}} \times 100$$

In vitro Aerodynamic Performance Evaluation

Aerodynamic particle size distribution was characterized for each batch of produced powder through *in vitro* analysis conducted using a Next Generation Impactor (NGI) equipment. The dry powder inhaler (DPI) used was the Aerolizer® device, which was connected to a mouthpiece that was attached to an induction port and a preseparator. This cascade impactor comprises eight stages, each demarcated by a pore diameter that encompasses a particle size range spanning from 0.206 µm to 12.8 µm. The pressure and flow rate parameters were controlled through a pump system interlinked with the equipment.

For each batch, twelve size 3 capsules were manually filled with a 30 mg quantity of spray dried powder and subjected to a one-hour deionization step. In particular, capsules were placed between two electrodes with opposite charges to adsorb ions through electrostatic interactions. To minimize errors and ensure statistical reliability, 12 capsules were used in order to be able to quantify the drug by HPLC, even in low stages of the apparatus where very few quantity of powder is collected." Subsequently, one capsule at a time was punctured using the inhaler and exposed to a controlled airflow of 100 L/min for precisely 2.4 s. Following the introduction of all twelve capsules, the powder deposited at each of the defined stages was recovered utilizing a solution composed of 62% acetonitrile and 38% water, and subsequently subjected to HPLC analysis.

The resulting mass located in the throat and stages 1 to 8 was designated as the recovery dose (RD). Therefore, the recovery fraction (%) was calculated by considering the total dose encompassed within the twelve capsules. The fine particle dose (FPD) was specifically quantified as the aggregate mass of particles with dimensions of up to 5 µm. Furthermore, the fine particle fraction (FPF) was derived by dividing the FPD by RD, expressed as a percentage. The mass median aerodynamic diameter (MMAD) was meticulously calculated from the cumulative curve of aerosol mass distribution, representing the diameter at which 50% of the total mass can pass. Finally, the geometric standard deviation (GSD) was computed employing the relation GSD = D84/D50.

In vitro Dissolution Assay

The *in vitro* dissolution system consisted of a USP II apparatus (Sotax®, Thun, Switzerland) at a temperature of 37°C and at a stirring rate of 100 rpm. Dissolution medium (900 ml) was composed of saline phosphate buffer (pH 7.4) supplemented with 0.5% sodium lauryl sulfate. Medium was sampled at a volume of 2 mL and replaced with fresh media at intervals of 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 90 min and 120 min. An equivalent of 3.5 mg of CBD was used. After the dissolution testing, all samples were filtered with a PTFE filter (0.45 µm) and diluted adequately before being analyzed by HPLC. The powder was put into capsules with a size of 000. To avoid the capsule floating on the surface of the dissolution medium, Japanese baskets sinkers were used to ensure the immersion of the capsules at the bottom of the bath. Testing was performed in sink conditions. The tests were run in triplicate and the results obtained are the mean and standard deviations of three determinations.

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism 9 software.

Results and Discussion

HP-β-CD was chosen for inclusion of CBD in the dry powder inhaler (DPI) formulations due to its well-documented effectiveness in mitigating the low water solubility of drugs through the formation of cyclodextrin-drug complexes (41). Furthermore, HP-β-CD has demonstrated the ability to enhance drug molecule permeability and bioavailability (42). This substance has exhibited safety *in vitro*, specifically in human airway epithelial Calu-3 and A549 cells and has been studied *in vivo* by lung instillation in rabbits. Consequently, its incorporation in the formulation of DPI for inhalation is considered safe from a safety perspective (43–45). Moreover, Dufour *et al.* have previously demonstrated the interest of this excipient upon drying for inhaled powder development (41).

Due to its high Peclet number, HP-β-CD in feed solution promotes the formation of particles with a deflated spherical shape during spray drying, which enhances their aerosolization properties. That HP-β-CD, when combined with up to 50% of other carbohydrates such as raffinose or maltodextrins, facilitates the formation of efficient engineered powders with low dose drugs as budesonide and formoterol fumarate. By modifying the drying parameters in a Design of Experiments, low particle size and a specific morphology were obtained which led to fine particle fraction (FPF) of both active pharmaceutical ingredient (API) greater than 60% (33, 34).

In the first step of the study, it was produced, for the first time, inhaled powder with CBD by spray drying. HP-β-CD

has thus a dual purpose: solubilize CBD before the atomization and promote a deflated shape morphology. In addition, to overcome the challenge of CBD's limited water solubility and potentially increase its solution concentration, an alternate formulation employing ethanol (EtOH) was also analyzed. EtOH has been studied in prior studies for its role in spray dried solutions (46). It has been shown its contribution to the formation of powder particles with a wrinkled morphology, which is advantageous for efficient delivery to the lungs, aligning with the objective of achieving optimal pulmonary administration in our formulation. In terms of safety, EtOH has demonstrated pulmonary tolerance at concentrations of up to 10% (47).

Properties of Spray Dried Powder

Two solutions have been atomized with same drying parameters (Table I) as HP-β-CD/CBD and HP-β-CD/CBD/EtOH. The resulting powders were then subjected to several tests to analyze their properties. As presented in Table II, the process yields across all formulations were notably high, ranging from 61 to 69%. Powder loss was due to powder adhesion to the cyclone and drying chamber walls. Regarding particle size, both powders exhibited average sizes below 2.5 µm, suggesting their capability to reach the deep pulmonary tract effectively. In addition, a span value greater than 3 was observed (irrespective of the type of powder), which corresponds to high size dispersity. This can be explained by the poor flow of the powders and their ability to form self-agglomerates due to their very small sizes and deflated morphology. This behavior has been highlighted previously with same type of engineered powder (27). The potential for deagglomeration during inhalation is a concern, which will be discussed in the section below related to the fine particle fraction.

The determined water content values ranged from 3.52% to 5.22%, with the highest moisture content observed in the spray dried solution incorporating EtOH. Higher moisture levels can impact the flowability of the powder by promoting the formation of liquid bridges. Conversely, excessively low water content could indicate an unstable product due to hygroscopicity. Thus, identifying an optimal water content value remains an ongoing endeavor, striking a balance between adequate flow properties and product stability (48).

Morphology of Spray Dried Particles

In terms of particle morphology, Table III illustrates the key aspects analyzed in samples from each formulation using scanning electron microscopy (SEM). Atomized particles exhibited distinctive dimples, indicating a wrinkled surface. Such wrinkled morphology is commonly observed in spray dried particles designed for lung administration and has been associated with improvement of aerosolization (49). This observation was further substantiated by complementary topographic photographs presented in Fig. 1.

More precisely, based on SEM pictures, two morphological properties were characterized as the number of dimples (ND) and their depth (DepthD/d). This allows the calculation of the deflation ratio ξ as the product of ND and DepthD/d, with a high ξ indicating deflated particles. A previous study showed that powders having a deflation ratio ξ greater than 2.5 have the theoretical appropriate morphology to be deposited deep in the respiratory tract (33). Both powders composed of either HP-β-CD/CBD or HP-β-CD/CBD/EtOH therefore have a morphology that is assumed to be adequate.

It is important to remind that the solid content of atomized solution is 15% and as highlighted by Lechanteur *et al.* this high percentage could compromise drying and lead to a different morphology (27). Effective drying was observed despite this major constraint, which is very promising.

CBD Quantification in Solution and in Spray Dried Powders

First, samples were collected from the solution following CD-complexation to quantify the CBD content. Table IV shows that HP-β-CD and HP-β-CD/EtOH allow to obtain solution with 1.07 ± 0.08 g/L and 0.74 ± 0.25 g/L of CBD, respectively. EtOH was found to adversely affect the solubility of CBD in the solution compared to a medium using only water. It suggests that a possible competition between EtOH and CBD can occur, indicating that the formation of

Table II Characteristics of Spray Dried Powders Composed of HP-β-CD/CBD or HP-β-CD/CBD/EtOH (Mean ± SD, $n = 3$)

Characteristics	HP-β-CD/CBD	HP-β-CD/CBD/EtOH
Process yield (%)	60.75 ± 6.17	68.83 ± 3.57
Particle size d50 (µm)	2.05 ± 0.28	2.01 ± 0.10
Span (-)	3.33 ± 0.25	3.36 ± 0.22
Water content (%)	3.52 ± 0.38	5.22 ± 0.17

Table III Evaluation of Spray Dried Particles Morphology by SEM. Number of Dimples (ND), Their Depth Dd (DepthD/d) and the Deflation Ratio ξ Which is the Product Between ND and Dd (DepthD/d) (Mean ± SD, $n = 3$)

Particle properties	HP-β-CD/CBD	HP-β-CD/CBD/EtOH
ND	21.50 ± 4.12	19.00 ± 5.29
Dd	0.14 ± 0.02	0.16 ± 0.07
ξ	2.94 ± 0.38	2.81 ± 0.49

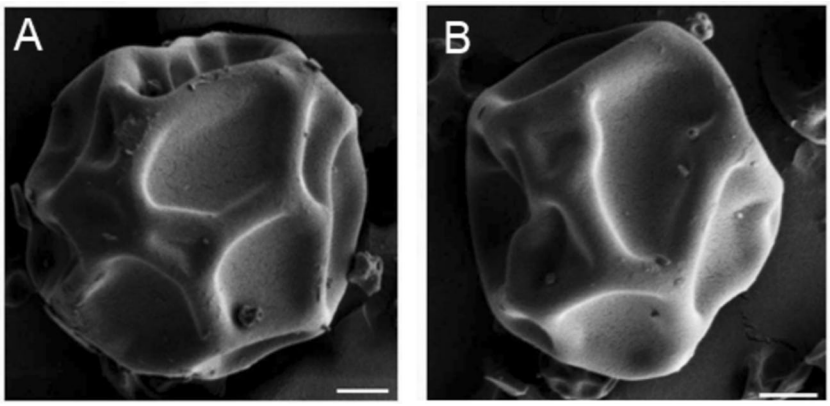

Fig. 1 Scanning electron microscopy (SEM) images of spray dried particles from feeding solutions containing HP-β-CD/CBD (**A**) and HP-β-CD/CBD/EtOH (**B**). Scale bar = 1 µm

Table IV CBD Quantification During Powder's Production (Mean ± SD, $n = 3$)

CBD quantification	HP-β-CD/CBD	HP-β-CD/CBD/EtOH
[CBD] in solution (g/L)	1.07 ± 0.08	0.74 ± 0.25
[CBD] in spray dried powder (mg/g)	7.66 ± 0.40	4.83 ± 0.22
Drug recovery (%)	113.44 ± 9.97	103.27 ± 3.08

EtOH-(HP-β-CD) was more prevalent than the formation of supramolecular complexes composed of CBD-EtOH-(HP-β-CD) (50, 51).

Second, in order to evaluate the CBD concentration in the resulting powders, samples were collected post-atomization and subjected to the same quantification method. The higher CBD concentration of 7.66 mg/g was observed in powders without EtOH, which revealed to have 1.59 times higher quantity of CBD than the ones with EtOH. To explain this observation, drug (CBD) recovery was also evaluated.

The recovery rate of CBD from powder composed of HP-β-CD/CBD is 113.44% whereas the drug recovery with HP-β-CD/CBD/EtOH was 103.27%. According to the degradation temperature of CBD, which is 271°C, the spray drying technique is expected to be suitable (Suppl. Figure 1) (9). Inlet temperature used was 160°C and mean registered column outlet temperatures were 85.1 ± 1.1 and 83.7 ± 2.5 for HP-β-CD/CBD and HP-β-CD/CBD/EtOH, respectively. Therefore, CBD should not be degraded during the process. Moreover, we did not observe any interfering peaks on the chromatogram. Given these results, a question might arise as to why more CBD is harvested in the powder than in the initial filtered solution. The hypothesis is that, during drying, losses in the drying chamber are primarily of the HP-β-CD excipient. Therefore, in relation to a certain quantity of powder weighed, the quantity of CBD in the powder increases proportionally.

With HP-β-CD alone, we found higher quantities of CBD per gram of powder, which will have a significant impact on the quantity of powder to be used to obtain a final dose of CBD. In this case, to minimize the amount of powder used in DPI capsules, it is preferable to use the powder made from HP-β-CD. Finally, it is important to show the homogeneity of the powder which is demonstrated by very low standard deviation in five different powder samples.

Aerodynamic Performance of CBD Powder

The aerosolization performance was assessed using a cascade impactor, due to its unique features. This approach allows for a comprehensive understanding of particle behavior in a moving air stream through aerodynamic particle size distribution which supports the ability to deliver the aerosol to the lungs. In this analysis, a Next Generation Impactor (NGI) was used with samples of powders from both formulations. Aerosolization efficiency is illustrated by different parameters obtained from the analysis of the NGI data and are summarized in Table V.

Recovery results indicate that operational losses were not significant, with values ranging from 89.00% to 94.70%. The emitted fractions were also very high since more than 90% of the powder was coming out of the inhaler.

Even though the powder flow was very poor (Hausner index 1.56 ± 0.09), which could compromise the exit of the powder from the DPI, the fine particle fraction ranged from 57.00% to 61.70%, which is considered high compared to other findings (52). It represents the quantity of powder with particles smaller than 5 µm compared to total recovery dose. Consistent with the emitted fraction, the powder produced without EtOH exhibited the highest value of 61.70%, which converted to CBD quantity that reaches the deep lung zone is 125.23 µg per capsule. This indicates that it possesses the most favorable properties for deposition in the deep parts of the lungs.

The MMAD values ranged from 3.83 to 4.01 µm, falling within the acceptable range for respirable particles (1–5 µm). Furthermore, the GSD values for all spray dried powders were consistently below 2.02, indicating a narrow size distribution

Table V Aerodynamic Behavior of Spray Dried Powders (Mean ± SD, $n = 3$)

Aerodynamic properties	HP-β-CD/CBD	HP-β-CD/CBD/EtOH
Recovery dose (µg)	2435.00 ± 187.79	1646.80 ± 53.22
Recovery fraction (%)	89.00 ± 0.42	94.70 ± 1.25
Emitted dose (µg)	2232.45 ± 217.94	1454.00 ± 31.05
Emitted fraction (%)	91.55 ± 1.87	88.45 ± 4.78
FPD (µg)	1502.70 ± 123.35	935.30 ± 151.76
FPF (%)	61.70 ± 0.28	57.00 ± 11.09
Deep delivered CBD/capsule (µg)	125.23 ± 10.282	77.94 ± 12.65
MMAD (µm)	3.83 ± 0.06	4.01 ± 0.55
GSD (-)	2.02 ± 0.01	1.98 ± 0.10

predominantly centered around a fine particle size. This observation suggests an efficient pulmonary delivery, as a tight size distribution enhances aerosol penetration into the respiratory tract (53). It is important to emphasize that, although the dispersion of the geometric diameter is wide (See Section Properties of Spray Dried Powder), the fraction of fine particles is very high. This demonstrates that, even if the powder has the property of self-agglomerating, the forces in force do not hinder deagglomeration during inhalation.

Using the gathered data on the quantity of CBD detected in each part of the impactor, the Fig. 2 was elaborated to illustrate the aerodynamic profile of the particles for each spray dried powder. All capsules contained 30 mg of powder. As explained in the previous section, the quantity of CBD in the powder with HP-β-CD is proportionally higher than in the powder HP-β-CD/EtOH. Therefore, it is logical to observe greater quantities of CBD in the different stages for powder with HP-β-CD. To compare the aerodynamic potential, it is useful to refer to the FPF which were almost similar between powders.

To sum up, in comparison to lactose-carrier powders, our engineered spray dried powder demonstrated very higher aerosolization behavior. Indeed, Molina *et al*. explained that FPF values of lactose-carrier were below 26% (54). Concerning the CBD, Tai *et al*. have very recently developed a high CBD-loading powder by wet ball milling (55). However, the FPF of their powder was low which will ultimately lead to excessive use of powder in capsule or reservoir. Indeed, the ability to develop powders with deeper lung deposition and less upper airway impaction (or loss in the inhaler device) will mean less powder is used, with economic and environmental benefits.

Dissolution Profile of CBD Powder

Due to previous data, the powder composed of HP-β-CD/CBD have been selected. Indeed, whereas properties and aerosolization behavior were almost similar with the powder containing EtOH, a major advantage is the quantity of CBD that can be solubilized. Consequently, the quantity of CBD in the powder was higher when HP-β-CD was used alone.

While the *in vitro* lung deposition is very encouraging, another important parameter is the dissolution of CBD in pulmonary fluids. As explained by Learoyd *et al.* there is no readily available model to predict the rate of drug dissolution in the lung following inhalation (56). Although some authors have proposed interesting models, such as Price *et al.,* who described an aerosol dose collection apparatus for *in vitro* dissolution measurements, there is no standard as there is for solid oral forms (57).

Figure 3 shows that the spray dried engineered CBD powder made with HP-β-CD was immediately dissolved.

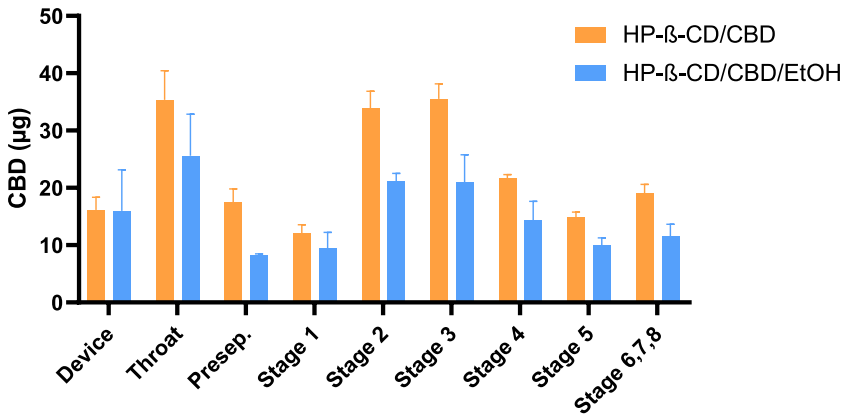

Fig. 2 Aerodynamic particle size profile of CBD of the two spray dried powders HP-β-CD/CBD and HP-β-CD/CBD/EtOH evaluated with the Next Generation Impactor (NGI). Data were presented as mean ± standard deviation from 3 test runs

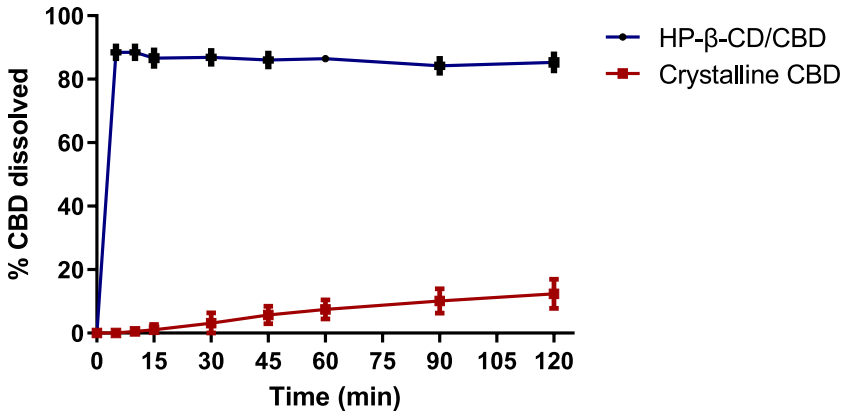

Fig. 3 Dissolution profile (% CBD dissolved) obtained with the selected HP-β-CD/CBD powder over the time. Data were presented as mean ± standard deviation from 3 test runs ($n = 3$)

Indeed, after 5 min, more than 85% of CBD in the powder was already solubilized. In comparison to crystalline form, the dissolution speed is faster which can be explained by the presence of HP-β-CD, which promote a very high solubilization in water. Tai *et. al* have evaluated the solubility enhancement instead of the dissolution of CBD over the time but they also showed an improvement of the water-solubility when dipalmitoylphosphatidylcholine is added. These observations demonstrate the importance of the formulation on the bioavailability of this molecule (55).

Rapid dissolution enhances the absorption and therapeutic efficacy of the active molecule, making it essential to demonstrate this increase in solubility *in vitro* before moving on to subsequent stages of development. Cyclodextrins have been described as an excipient for improving solubility, but this study also highlights their significant aerosolization capacity associated with the behavior of this excipient during drying.

Conclusion

In this study, we embarked on the development of an inhalable powder aimed at achieving deep lung deposition of cannabidiol (CBD). Our results underscore the crucial role of hydroxypropyl-β-cyclodextrin (HP-β-CD) in enhancing the solubility of CBD, thus enabling the production of powders with high concentrations of the drug. In addition, the formation of a ternary complex with the addition of ethanol did not result in a significant improvement in CBD solubilization.

Furthermore, the spray dried particles exhibited favorable aerosolization properties due to a suitable morphology. Deflated spherical-shaped particles with a small particle size promoted a fine particle fraction of up to 60%. The spray drying process was found to be well suited to produce this powder, ensuring consistent and reproducible powder characteristics without causing any degradation of the final product. In addition, the solid content of the feed solution was very high at 15%. As the atomization rate was also very fast, this formulation was achieved very quickly, which is important from an industrial process perspective.

Finally, the dissolution rate was almost instantaneous, which can be attributed to the cyclodextrin excipient in the formulation. In conclusion, the obtained CBD powder, with a deflated spherical morphology and high aerodynamic performance, holds promise for the treatment of pulmonary or systemic pathologies due to the deep lung deposition of the molecule. The CBD therapeutic potential could benefit several conditions such anxiety, schizophrenia, Parkinson's and Huntington's disease and acute respiratory distress syndrome (ARDS) (58, 59).

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- Substantial contributions to the conception or design of the work: Bernardo Gomes.
- Acquisition, analysis, or interpretation of data for the work: Bernardo Gomes, Nathan Koch, Laure-Anne Bya.
- Drafting the work or revising it critically for important intellectual content:
- Final approval of the version to be published: Anna Lechanteur, Brigitte Evrard, Helena Cabral-Marques.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Anna Lechanteur.

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Declarations

Conflict of Interest All the authors declare that they have no conflict of interest.

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