

Aerosolized THC for medical use: assessing the potential of vaping technology as a drug delivery device

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ABSTRACT

Background: Cannabinoid-based therapies, particularly those using Δ^9 -tetrahydrocannabinol (THC), have demonstrated clinical benefit in the treatment of chronic pain and neurological disorders. However, current methods of administration suffer from inconsistent bioavailability and limited control of onset of action. Inhaled administration via the lungs offers rapid systemic absorption and could improve therapeutic outcomes.

Purpose: This study evaluates the in vitro performance of two vaping technologies for the delivery of THC aerosols intended for medical use: a CE-marked medical device (BIKY Breathe) and a commercial vape pen.

Methods: Four THC formulations (20 and 40 mg/mL in 1,3-propanediol; neat cannabis distillate and terpene-supplemented THC distillates) were tested. The aerosol mass per puff was measured using a validated puffing protocol. Respirable dose was determined using a Glass Twin Impinger and aerosol particle size distribution was assessed using a Next Generation Impactor. In addition, the fine particle fraction (FPF) was calculated from the impactor data.

Results: All formulations produced aerosols with a submicroscopic mass median aerodynamic diameter (MMAD: 0.89–0.99 μ m) consistent with deep lung deposition. The FPF ranged from 99.17 % to 100 %, confirming that most of the aerosol mass was lower than 5 μ m. The BIKY Breathe device produced a consistent aerosol mass (~6 mg/puff) with low variability, and respirable THC doses of 50 or 95 μ g/puff, depending on the initial concentration used. In contrast, the vape pen produced higher respirable THC doses (1.7–2.0 mg/puff), but with greater variability between puffs. Both devices showed similar THC delivery efficiency (~45–54 %), indicating effective aerosolization regardless of concentration.

Conclusion: This study shows that vaping devices can produce fine aerosol particles with a good transfer efficiency of THC. While vape pens deliver larger doses of THC, the CE-marked BIKY Breathe offers better dose reproducibility and may be more suitable for controlled clinical applications. The exclusive in vitro nature of this study represents a limitation. However, it provides an essential first step for designing *in vivo* pharmacokinetic and clinical investigations. These results support the development of regulated vaping technologies as viable inhalation platforms for medical THC by inhalation.

1. Introduction

Cannabinoids, in particular Δ^9 -tetrahydrocannabinol (THC), are bioactive compounds derived from *Cannabis sativa* that exhibit significant therapeutic potential. Indeed, cannabinoids are increasingly investigated for various therapeutic applications including chronic neuropathic pain, spasticity, chemotherapy-induced symptoms, and various neurological diseases such as epilepsy (drug Epidiolex®/

Epidyolex®), multiple sclerosis (Sativex®, the trademark of a cannabis drug called nabiximols) or tic disorders [1–3]. Cannabinoids are used in medical applications including synthetic or isolated CBD and THC, nabiximols (THC:CBD = 1.08:1.00), and synthetic nabilone [2]. THC mediates analgesic effects primarily via CB₁ receptor agonism in the central nervous system, and CB₂ receptor modulation of peripheral inflammation [4,5]. In addition, THC interacts with non-cannabinoid targets such as TRPV1 channels and PPAR- γ receptors, which also

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contributes to its analgesic and anti-inflammatory effects [6,7].

Clinical data, including meta-analyses, confirm a possible pain relief from cannabinoid-based treatments such as nabiximols, particularly in neuropathic and cancer-related pain [8,9]. In particular, some authors showed in a randomized, double-blind, placebo-controlled study [10] that inhaled THC at low doses (0.5–1 mg) reaches a plasma C_{max} of 14–34 ng/ml within ~4 min and provides significant pain relief without cognitive impairment. Meta-analyses confirm moderate to large analgesic effects in neuropathic pain, with 20–30 % of patients achieving pain relief of more than 30 % [2]. In addition, THC has the potential to save opioids, with the opioid dose being reduced by 20–40 % with concomitant treatment [1]. However, the psychoactive side effects (euphoria, dizziness) and heterogeneous pharmacokinetics continue to pose a challenge for widespread clinical use [4]. Despite these limitations, THC represents a promising alternative to opioids or other analgesic drugs in pain therapy. Tailored delivery systems that ensure reproducible dosing, maximize analgesia, and limit psychoactivity therefore remain a key pharmacological challenge.

The route of administration of THC and the pharmaceutical formulations are a growing issue. Indeed, the pharmacokinetics and therapeutic efficacy of THC depend crucially on the route of administration. THC can be administered by inhalation, orally, sublingually/oromucosally and by alternative routes such as rectally, transdermally or ocularly [2,4]. Oral administration of THC (capsules/oils) offers a longer duration of action but suffers from a potential low bioavailability (~4–20 %), delayed T_{max} (~1–4 h) and high inter-patient variability due to first-pass metabolism leading to 11-hydroxy-THC, which has a stronger psychoactive effect [5,11]. Sublingual/buccal administration offers an intermediate bioavailability with a faster onset of action than oral administration. Indeed, sublingual/oromucosal sprays (e.g. Sativex®) bypass part of the hepatic metabolism and achieve a T_{max} ~30–60 min and a bioavailability of ~2–20 % [12]. Rectal and transdermal routes are alternative strategies but face challenges in formulation and patient acceptance.

By contrast, inhaled THC (including smoking, vaporization or aerosol administration from liquids/powders) offers a rapid onset of action (T_{max} ~3–10 min) and an important pulmonary bioavailability until 35 % [4]. Preclinical and early clinical results with inhaled THC show rapid analgesia (within 10–15 min) and minimal side effects, even if cough and throat irritation persist [10]. However, combustion-based administration methods, such as smoking, generate toxic by-products and result in uncontrolled dosing. This highlights the need for a combination of medical-grade aerosol systems and a characterized pharmaceutical formulation specifically adapted to the medical device to ensure purity, microdosing, and reproducibility.

The limitations of each route show that, all things considered, inhalation via optimized aerosol systems is required to combine rapid onset of action, precise dosing and patient tolerability. There are various medical aerosol technologies for the administration of cannabinoids. Indeed, some aerosol delivery systems have been developed for the targeted administration of cannabinoids that aim to optimise clinical outcomes through site-specific deposition in the airways [13–15]. Aerosol device performance must consider dose accuracy, respirable fraction, patient compliance, sterility and safety of excipients. Nevertheless, published studies still provide limited quantitative data on aerosol particle size distribution and respirable dose of THC aerosols, leaving major knowledge gaps for the design of safe and efficient inhalation therapies.

Despite potential hurdles, medical vaping may offer a compelling strategy to capitalize on the pharmacokinetic benefits of inhaled THC, rapid analgesia, deep pulmonary delivery and dose adaptation, potentially transforming clinical practice. Evaluation of THC inhalation devices, such as vaping devices, could expand therapeutic options and increase physician confidence in aerosol-based pain management. Importantly, CE-certified medical vaping devices are now available, providing regulated technological platforms that comply with safety and

quality standards and can be paired with pharmaceutically characterized formulations.

Therefore, this study aims to investigate and compare the *in vitro* aerosol performance of two representative vaping technologies, each with a drug formulation specifically adapted to the device: (i) a CE-marked medical device (BIKY Breathe) designed for controlled drug delivery, and (ii) a commercial vape pen typically used for recreational purposes. The comparison focuses on emitted aerosol mass, respirable THC dose, aerosol particle size distribution, and transfer efficiency of THC from the refill liquid to the aerosol particles, parameters critical for evaluating potential medical use. To assess the potential for clinical application, particular attention is given to the reproducibility of the emitted dose between puffs and between cartridges. Although the two systems differ in liquid capacity and THC concentration, both represent relevant vaping technologies for assessing how formulation–device coupling affects aerosol generation and consistency.

It should be noted that this investigation was conducted exclusively *in vitro*, and the results must therefore be interpreted as preclinical performance data rather than clinical outcomes. Nevertheless, the *in vitro* evaluation of aerosol features remains an essential step for predicting *in vivo* deposition of aerosol and guiding subsequent pharmacokinetic studies.

2. Material and methods

2.1. Vaping devices

Two vaping technologies were evaluated:

- (i) BIKY Breathe (BIKY Pharma company, France), a CE-marked medical device designed for reproducible drug delivery. It complies with European Regulation 2017/745, ensuring its conformity and safety. The device uses sealed, single-use cartridges with a capacity of 2 ml, which can be filled with a suitable low-viscosity formulation (*i.e.*, a formulation very different from pure THC distillate, which is highly viscous and cannot be aerosolized by this device).
- (ii) A vape pen (CELL, Shenzhen, China), typically used for recreational purposes. The Vape Pen is a commercially available electronic cigarette device consisting of a 1 mL refillable TH2-EVO cartridge (CELL) connected to an M3 battery (CELL).

We must keep in mind that the two vaping technologies differ in liquid capacity and thermal conditions, which may impact aerosol stability.

2.2. THC formulations

Four THC formulations were tested: (i) 20 mg/mL in 1,3-propanediol, (ii) 40 mg/mL in 1,3-propanediol, (iii) neat cannabis distillate, and (iv) terpene-supplemented THC distillate. The formulations with THC in 1,3-propanediol (PDO) have been specially developed for use in BIKY Breathe. The formulations with THC distillate have been used for use in the vape pen device. The neat cannabis distillate corresponds to a THC content of 77.62 wt % (776.2 mg/mL). The cannabis distillate supplemented with terpenes corresponds to a THC extract of 71.55 wt % (715.1 mg/mL). All formulations were characterized in terms of homogeneity, concentration, and viscosity prior to nebulization, based on the physicochemical characteristics required for aerosolization with the respective devices to be used.

2.3. Aerosol generation and collection

The methodology used for aerosol generation was previously developed and validated [16,17]. In brief, the aerosols were generated using a modular puffing machine based on an automated and

programmable double syringe pump (Burghart, Germany (PE_MOD, Burghart, Germany)). This puffing machine consists of two identical pump modules consisting of a simple linear piston pump with a glass cylinder. A motor drives these pumps to mimic the inhalation and exhalation of a vaping device. Both vaping devices are activated by inhalation. Device operation parameters (puff volume, duration, and flow rate) were standardized using a validated puffing protocol to minimize variability between puffs.

The puffing programme complied with the guidelines of the AFNOR standard XPD-90–300–3, which prescribes certain parameters, including a puff volume of 55 mL, a duration of 3 s for each puff, an interval of 30 s between puffs, two series of 20 puffs and an interval of 5 min between each series. The cartridges of both devices were weighed before and after each experiment to determine the amount of aerosol produced. Due to their viscosity, the THC distillate had to be pre-charged for four puffs prior to the standard draw test to ensure complete aerosol formation with the vape pen device. These four puffs were not collected and considered in the emitted dose and aerodynamic size distribution experiments, but were used to calculate the aerosol mass generated.

Aerosols were generated using each device according to assess the following parameters:

- The aerosol mass per puff (mg/puff), measured gravimetrically.
- Respirable THC dose (μg of particles $<6.4 \mu\text{m}$ /puff), determined using a Glass Twin Impinger to separate particles likely to deposit in the deep lungs,
- Aerosol particle size distribution and mass median aerosol diameter (MMAD in μm), assessed using a Next Generation Impactor.
- Fine particle fraction (FPF, % of particles $<5 \mu\text{m}$) was calculated from the impactor data to quantify alveolar deposition potential,
- Transfer efficiency of THC from the refill liquid to aerosol particles (expressed in %) was calculated as the wt ratio of emitted THC dose to total THC loaded in the device.

2.4. Drug respirable dose

Aerosols were collected using a Glass Twin Impinger (GTI) (MC2, France) to separate particles by size, as per the previously developed and validated methodology for aerosols from vaping devices [16,17]. The GTI consists of two chambers connected in series: an upper chamber for the non-respirable dose fraction, and a lower chamber for the respirable dose fraction as defined by the EU Pharmacopoeia. This two-chamber system mimics a lung model in an extremely simplified way and separates the aerosol fractions on the basis of an aerodynamic cut-off diameter of $6.4 \mu\text{m}$. The lower chamber represents the lower airways and allows the collection of the respirable dose destined for the lungs, while the upper chamber corresponds to the upper airways and captures the non-respirable fraction that would not reach the target site of action. Prior to the experiments, 30 mL and 7 mL of n-butanol were filled into the lower and upper chambers, respectively, to ensure the collection of aerosols. To ensure accurate particle collection, a vacuum pump (LCP5, Copley) with a flow rate of $60 \pm 5 \text{ L/min}$ was connected to the system, which complies with the requirements of the European Pharmacopoeia (Ph. Eur.). Twenty puffs were generated with the puffing machine in accordance with the AFNOR standard and aspirated into the GTI via a plastic tube. The contents of both chambers were then collected and stored at -20°C prior to analysis.

2.5. Aerosol particle size distribution

As recommended by the EU Pharmacopoeia guidelines, a next generation impactor (NGI) (Copley Scientific, Nottingham, UK) was used to assess the aerodynamic distribution characteristics of the generated particles, including MMAD (mass median aerodynamic diameter), FPF (fine particle fraction, i.e. particles $< 5 \mu\text{m}$), and GSD (geometric

standard deviation) of the particles size distribution. The experimental protocol used was previously developed and validated [16,17]. The separation of the particles depends on the velocity and the aerodynamic particle size. The NGI consists of different stainless-steel stages with different sized holes placed above the collection cup. The airflow passes through the device as the particles move and reach the stages where they reach the appropriate separation diameter. NGI was connected to a vacuum pump with a flow rate of $60 \pm 5 \text{ L/min}$ and two series of 20 puffs with a 5-min pause between series were drawn with the puffing machine. Each NGI stage was rinsed with 2 mL of absolute ethanol and the samples were stored at -20°C prior to analysis.

2.6. Quantification of THC

THC was quantified by HPLC-UV detection at 222 nm. The HPLC system consisted of a LC-2050C compact model (Shimadzu, Kyoto Japan) with PDA detector. A stainless-steel column 0.15 m long and 4.6 mm internal diameter packed with Cortecs Shield[®] RP18 (Waters, Milford, PA, USA) was used. As mobile phase, a mix of 41 vol of water with 0.1 per cent (V/V) Trifluoroacetic acid for chromatography RS and 59 vol of acetonitrile with 0.1 per cent (V/V) trifluoroacetic acid for chromatography RS (41:59 V/V), at a flow rate of 1.5 mL per minute was used. The injection volume was 10 μL . This method was validated for the quantification of cannabinoids in GTI and NGI samples. Samples were diluted in a mix of methanol and ethanol (80:20 V/V) and prepared in triplicate. LOD of 0.40 mg/L and LOQ of 2.00 mg/L were validated for GTI and NGI samples.

2.7. Statistical analysis

All results are expressed as mean $\pm$ standard deviation (SD) of 3 independent experiments, each performed in triplicate. Data were processed using GraphPad Prism 9 software (GraphPad Software, San Diego, CA). Kruskal-Wallis test followed by a Dunn's test and Two-way ANOVA followed by a Tukey's test were used when testing differences between 3 or more groups. p-value <0.05 was considered statistically significant.

3. Results

The main results obtained are summarized in Table 1 and described in detail in the following sections.

3.1. Aerosol mass per puff

When tested with the BIKY Breathe device, both THC formulations (20 mg/mL and 40 mg/mL) produced a similar average aerosol mass per puff ($5.88 \pm 0.36 \text{ mg/puff}$ and $6.07 \pm 0.13 \text{ mg/puff}$, respectively; Fig. 1 and Table 1). This demonstrates that increasing THC concentration in PDO solution does not affect the total aerosol mass generated, highlighting the device's consistent aerosol generation performance. The low coefficients of variation ($<10\%$) for both formulations indicate excellent inter-puff and inter-cartridge repeatability. This finding is critical for ensuring low dose variability in therapeutic settings.

In contrast, the vape pen's aerosol mass per puff varied with THC mass in the distillate ($4.29 \pm 0.67 \text{ mg/puff}$ for neat THC distillate vs. $5.23 \pm 0.60 \text{ mg/puff}$ for terpene-supplemented distillate), with terpenes causing a non-significant $\sim 20\%$ increase. However, higher coefficients of variation (15.6 % and 11.4 %) were observed for both formulations, reflecting greater variability. This inconsistency, combined with the need for a 3-5-puff initialization sequence, risks dose irregularities. This finding is particularly problematic for microdosing purposes in a therapeutic context (Supplementary Fig. 1 and Table 1).

Table 1

Summary of the main results obtained for emitted mass, respirable THC dose and transfer efficiency.

Device	THC formulation	Emitted mass (mg/puff)	Respirable THC dose ($\mu\text{g/puff}$)	Transfer efficiency (%)	Mass Median Aerodynamic Diameter (μm)
Biky Breathe	20 mg/mL	5.88 ± 0.36	50.3 ± 4.4	48.6 ± 2.7	0.95 ± 0.02
Biky Breathe	40 mg/mL	6.07 ± 0.13	94.7 ± 4.9	45.0 ± 2.1	0.95 ± 0.04
Vape pen	THC content of 776.2 mg/mL	4.29 ± 0.67	1714 ± 241	54.2 ± 3.6	0.89 ± 0.04
Vape pen	THC content of 715.1 mg/mL	5.23 ± 0.60	2016 ± 82	51.6 ± 4.8	0.99 ± 0.08

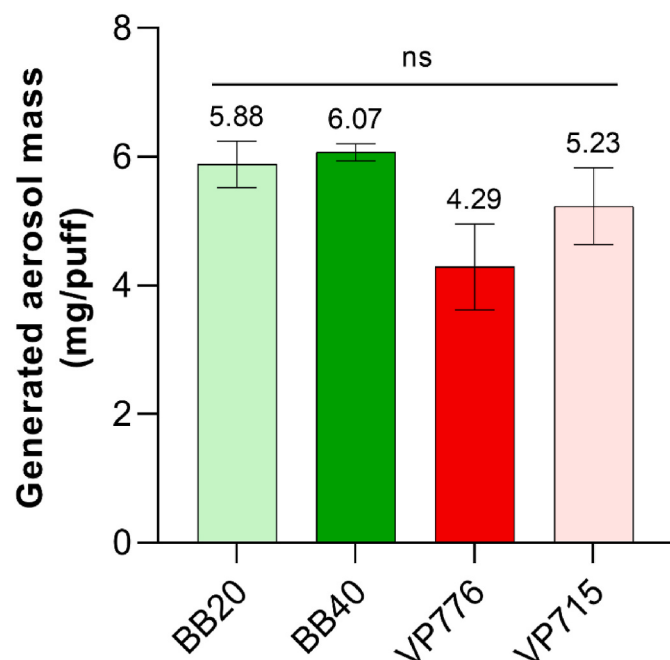


Fig. 1. Average aerosol mass generated for the four formulations tested. BB20: BIKY Breathe/PDO/THC 20 mg/mL; BB40: BIKY Breathe/PDO/THC 40 mg/mL; VP776: Vape Pen/Neat cannabis distillate/THC 776.2 mg/mL; VP715: Vape Pen/Terpene-supplemented THC distillate/THC 715.5 mg/mL. Results are presented as the mean of three independent experiments $\pm$ standard deviation (SD). ns: non-significant. Kruskal-Wallis test followed by Dunn's multiple comparisons test.

3.2. THC dosing and transfer efficiency from the refill liquid to aerosol particles

The initial THC concentrations in the BIKY Breathe cartridges were measured at 18.65 mg/mL (initial target: 20 mg/mL) and 36.72 mg/mL (initial target: 40 mg/mL). No non-respirable THC dose was detected (Figs. 2A and 3A; Supplementary Table 2), confirming that the aerosol generated corresponds only to the respirable fraction ($<6.4 \mu\text{m}$).

It is important to note that the mass of THC collected in the two chambers of the GTI are lower than the maximum theoretical dose delivered by the device. This dose is calculated assuming 100 % transfer efficiency between the initial THC concentration in the liquid filling the cartridge, and the THC contained in the liquid aerosol particles produced. We used the following equation: maximum theoretical dose ($\mu\text{g/puff}$) = ([THC]initial $\times$ aerosol mass loss)/number of puffs). The maximum theoretical THC dose per puff, assuming 100 % transfer efficiency, was 103.54 μg (for formulation at 20 mg/mL) and 201.35 μg (for formulation at 40 mg/mL) for the BIKY Breathe, and 3329.90 μg (for the formulation using neat distillate) to 3741.16 μg (for the formulation using terpene-supplemented distillate) for the vape pen (Figs. 2A and 3A). Transfer efficiency, calculated as the ratio of respirable THC to the theoretical dose, ranged from 45.02 % (BIKY Breathe associated with formulation at 40 mg/mL) to 54.24 % (vape pen associated with formulation using terpene-supplemented distillate) (Figs. 2B and 3B; Supplementary Table 3).

The average respirable THC doses were $50.3 \pm 4.4 \mu\text{g/puff}$ (formulation at 20 mg/mL) and $94.7 \pm 4.9 \mu\text{g/puff}$ (formulation at 40 mg/mL) for the BIKY Breathe (Table 1), demonstrating a possible linear relationship between initial concentration and emitted dose, with no saturation effect. Indeed, the observed near-doubling of respirable THC between 20 and 40 mg/mL supports a concentration-dependent trend, although the relationship may not be strictly linear across broader ranges. For the vape pen, respirable doses reached $1714 \pm 241 \mu\text{g/puff}$ (neat distillate) and $2016 \pm 82 \mu\text{g/puff}$ (+terpenes), a ~ 20 % increase attributed to reduced viscosity and higher aerosol mass per puff.

Interestingly, the ratio of 21 between THC concentration in neat distillate (776.2 mg/mL) and THC concentration in PDO solution (36.72 mg/mL) closely matched the ratio of 18 between respirable doses using these formulations (1714 μg vs. 94.7 μg). This finding suggests that respirable THC depends more on formulation features (*i.e.*, initial THC concentration and viscosity) than vaping device performance. However, the vape pen's initialization puffs (*i.e.* 3-5 puffs, not accounted for here) could significantly alter this correlation in clinical use.

3.3. Aerosol particle size distribution

Fig. 4A describes the aerosol size distribution for the four formulations tested and the two devices (each replicate is shown in Supplementary Figs. 2, 3, 4 and 5). Overall, the Gaussian distribution of particle sizes shows that most of the particles produced have an aerodynamic diameter of 0.5–1 μm , regardless of the formulation with an average GSD ranging from 1.58 ± 0.01 (terpene-supplemented THC distillate) to 1.78 ± 0.04 (THC 20 mg/mL) (Supplementary Table 4). Excellent repeatability of the particle size distribution was observed for both formulations aerosolized with the BIKY Breathe device. The two THC formulations aerosolized with the Vape Pen device showed a slightly larger standard deviation and dispersion without a significant shift in mean aerodynamic diameters. In addition, the fine particle fraction (FPF) was calculated from the impactor data to better characterise the proportion of aerosol particles within the respirable size range. Under all experimental conditions, the fine particle fraction ranged from 99.17 % to 100 %, confirming that most of the aerosol mass was less than 5 μm when using vaping devices. To sum up, Mass median aerodynamic diameter (MMAD) ranged from 0.89 to 0.99 μm for all formulations, with a geometric standard deviation (GSD) < 1.2 , indicating narrow particle size distribution conducive to deep lung deposition. Fine particle fraction (FPF) was 99.17–100 %, demonstrating that nearly all aerosolized THC is respirable. No significant differences in MMAD or FPF were observed between the four THC formulations, indicating that particle size and respirable fraction are primarily driven by device performance rather than formulation properties.

3.4. Reproducibility across puffs and formulations

Multiple consecutive puffs ($n = 5$) were analyzed to assess reproducibility. BIKY Breathe showed low puff-to-puff variability in aerosol mass, MMAD, FPF, and respirable THC dose. By contrast, the commercial vape pen exhibited greater variation. These findings emphasize the clinical relevance of using a CE-marked device (such as the BIKY Breathe) for precise dosing, regarding variability in puff delivery and clinical applicability.

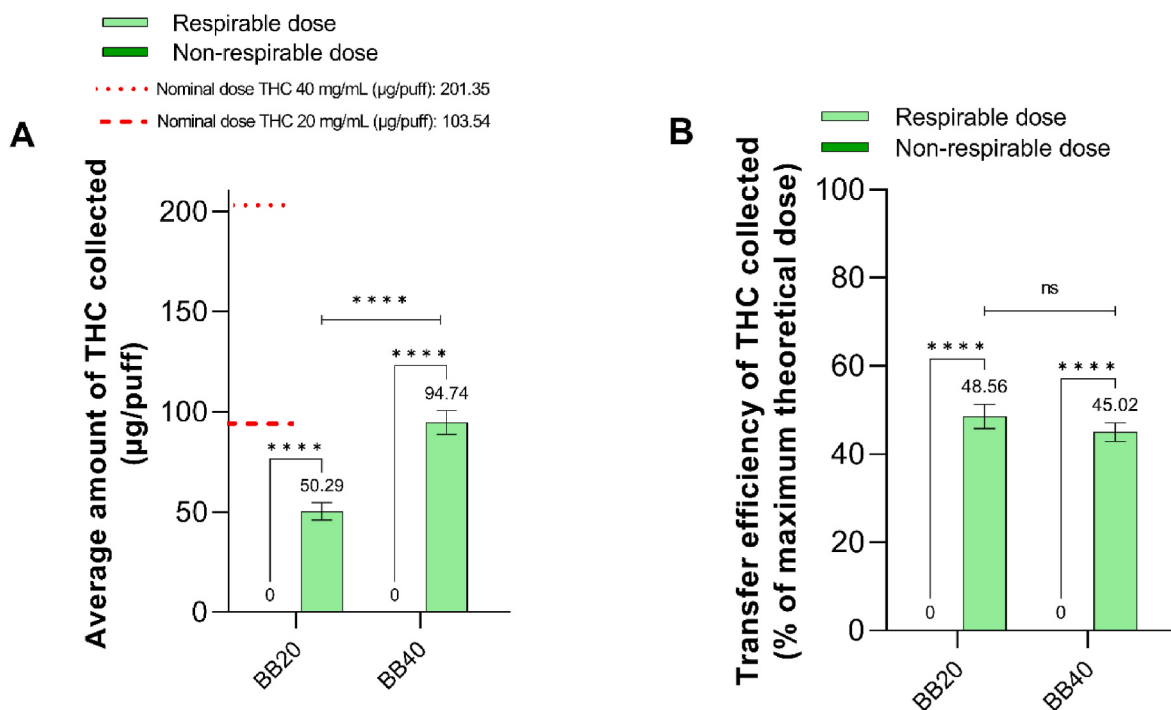


Fig. 2. (A) Average amount of THC collected per puff from the respirable and non-respirable fraction of GTI and (B) transfer efficiency of THC for respirable and non-respirable fraction expressed as a percentage of the maximum theoretical dose for the BIKY Breathe device. BB20: BIKY Breathe/PDO/THC 20 mg/mL; BB40: BIKY Breathe/PDO/THC 40 mg/mL. Results are presented as the mean of three independent experiments $\pm$ standard deviation (SD). ns: non-significant; ****: $p < 0.0001$. Two-factor ANOVA followed by Tukey's multiple comparisons test.

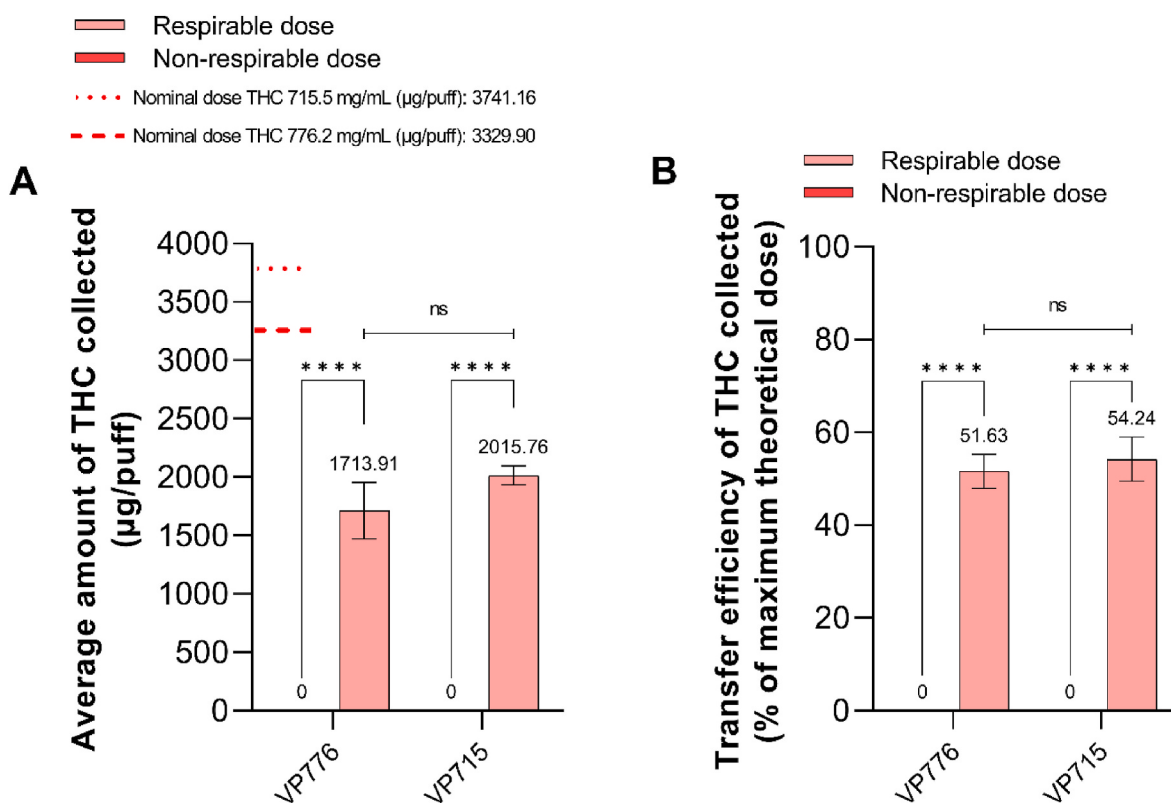


Fig. 3. (A) Average amount of THC collected per puff from the respirable and non-respirable fraction of GTI and (B) transfer efficiency of THC for respirable and non-respirable fraction expressed as a percentage of the maximum theoretical dose for the Vape Pen device. VP776: Vape Pen/Neat cannabis distillate/THC 776.2 mg/mL; VP715: Vape Pen/Terpene-supplemented THC distillate/THC 715.5 mg/mL. Results are presented as the mean of three independent experiments $\pm$ standard deviation (SD). ns: non-significant; ****: $p < 0.0001$. Two-factor ANOVA followed by Tukey's multiple comparisons test.

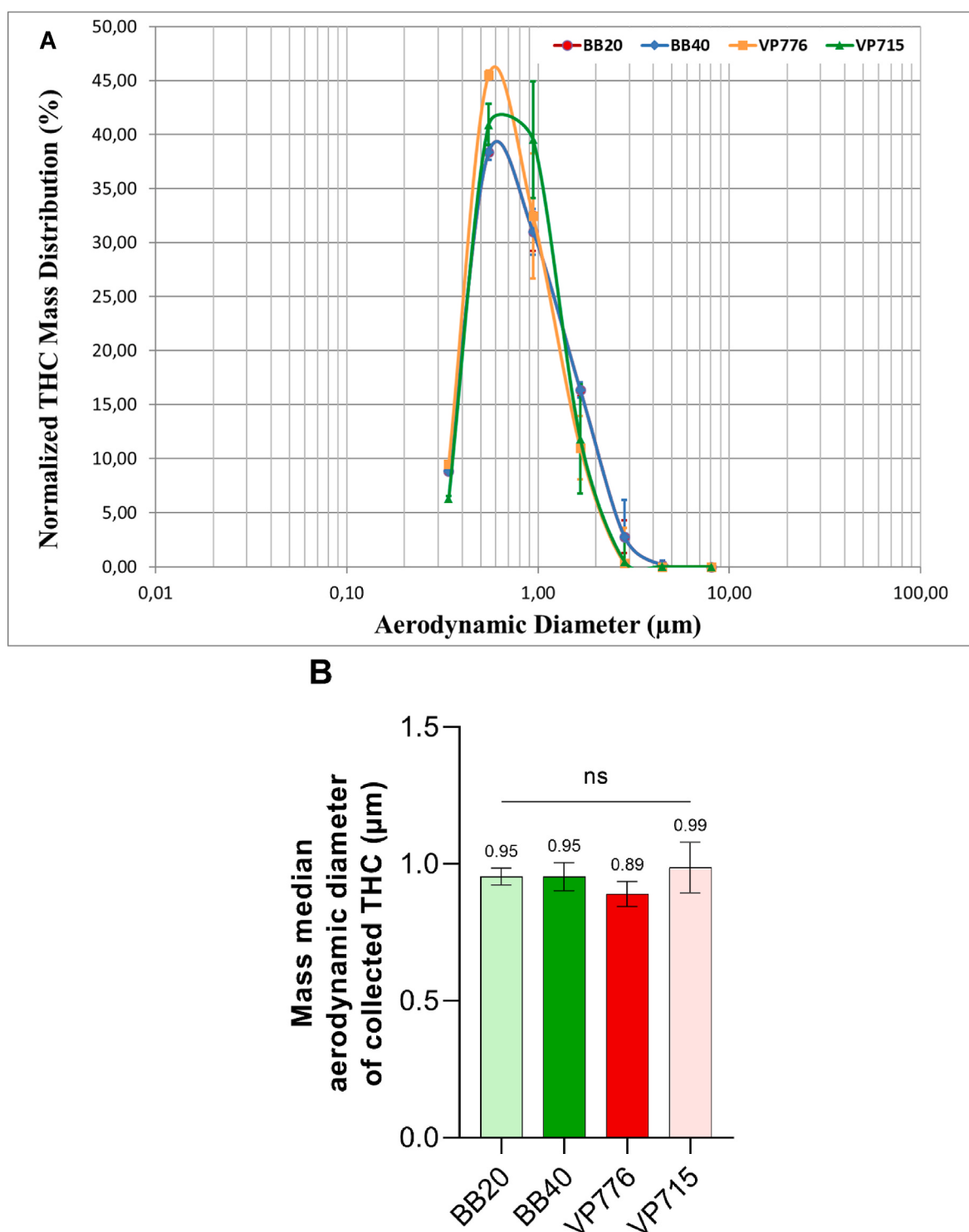


Fig. 4. (A) Normalized mass distribution of THC and (B) mass median aerodynamic diameter of THC (MMAD) in the four formulations. BB20: BIKY Breathe/PDO/THC 20 mg/mL; BB40: BIKY Breathe/PDO/THC 40 mg/mL; VP776: Vape Pen/Neat cannabis distillate/THC 776.2 mg/mL; VP715: Vape Pen/Terpene-supplemented THC distillate/THC 715.5 mg/mL. Results are presented as the mean of three independent experiments $\pm$ standard deviation (SD). ns: non-significant. Kruskal-Wallis test followed by Dunn's multiple comparisons test.

4. Discussion

4.1. Available technologies for the administration of THC aerosols

Various technologies have been explored for cannabinoid delivery, including oromucosal sprays, nebulisers, dry powder inhalers (DPIs) and pressurized metered dose inhalers (pMDIs) [10]. Each presents specific

limitations regarding droplet size, reproducibility, and compound stability. Oromucosal sprays ($\sim 30\text{--}60\ \mu\text{m}$) mainly deposit in the oropharynx, resulting in variable absorption and low pulmonary efficiency [12], while jet nebulisers generate respirable droplets ($2\text{--}5\ \mu\text{m}$) but are inefficient and cumbersome for chronic use. DPIs and pMDIs offer dosing precision and portability. However, these devices require slow deep inspirations and hand-mouth coordination. Additionally,

THC's poor thermal and chemical stability in propellants or carriers remains a challenge [18,19].

Heating-based systems such as the Volcano® vaporizer or SyqeAir® inhaler have shown clinical efficacy but struggle to ensure reproducible dosing and may produce thermal degradation products [21,22]. Conversely, liquid-based aerosol devices generating fine droplets (~1 µm) can target alveolar deposition, improving both onset and bioavailability [20]. In this context, the BIKY Breathe device combines CE certification, controlled microdosing, and consistent aerosol generation, offering a scalable therapeutic platform. Compared to consumer vape pens or herbal vaporizers, it ensures reproducible delivery (~50–100 µg/puff) and precise titration, which could facilitate personalized dosing and enhance clinical safety [23–27].

4.2. The use of vaping devices for cannabinoids delivery

Vaping devices have gained attention as potential platforms for cannabinoid administration [2,28]. CBD vaping is increasingly used legally in several countries, offering acceptable bioavailability (30–45 %) and good tolerability [29–31], though rigorous clinical data remain scarce. THC vaping, however, often involves unregulated devices and concentrated distillates, exposing users to toxic impurities such as vitamin E acetate or thermal degradation products, factors implicated in the EVALI outbreak [32–36]. Experimental studies confirm that vaping can achieve pulmonary deposition efficiencies comparable to smoking, with THC plasma levels of similar magnitude [33–35], but variability in device design and formulation compromises reproducibility and safety [37]. Medical-grade vaping platforms, by contrast, provide regulated engineering, stable formulations, and temperature control [34], addressing these risks while preserving the pharmacokinetic advantages of inhalation (rapid onset, deep lung delivery, dose adjustability). This distinction underscores the need for a combination of medical-grade aerosol systems and a characterized pharmaceutical formulation specifically adapted to the medical device to ensure consistent, clinically relevant THC administration.

4.3. Vaping as a medical aerosol technology

Recent advances in e-cigarette engineering have accelerated their transformation into therapeutic aerosol devices. Studies on nicotine and bronchodilator aerosols demonstrate accurate dosing, rapid systemic uptake, and favorable user adherence, supporting the feasibility of drug delivery via controlled vaping technologies [16,38,39]. Medical vaping systems such as BIKY Breathe represent a new class of CE-marked medical devices containing pharmaceutical formulations specially developed for this type of device, ensuring reproducible aerosol generation (~1 µm MMAD), reduced degradation, and improved safety [40]. This integrated “device–formulation” approach minimizes variability linked to coil temperature and excipient interaction. Key benefits include rapid onset, titratable dosing, improved compliance, and elimination of combustion by-products. Remaining challenges involve thermal stability of cannabinoids, long-term inhalation safety, regulatory harmonization, and GMP validation [34]. Despite these hurdles, medical-grade vaping offers a promising route toward safe, standardized, and patient-adapted THC inhalation therapies.

4.4. Discussion of the performance comparison between the BIKY breathe and a commercial vape pen with their respective formulations

This study presents a detailed in vitro evaluation of THC aerosolization using two vaping devices: a CE-marked medical device (BIKY Breathe) and a commercial vape pen, each with its respective formulation. Our results show that device design significantly affects dose reproducibility, particle size distribution, and the respirable THC fraction, addressing reviewer concerns about clinical applicability and device reliability.

Aerosol features and device performance: The BIKY Breathe device produced aerosols with consistent MMAD (~0.9 µm) and near-complete fine particle fraction (99–100 %), ensuring deep lung deposition and reproducible respirable dose. In contrast, the commercial vape pen delivered higher doses per puff (1.7–2.0 mg THC) but with greater variability and the need of 3–5 puffs of initialization, confirming potential concerns about uncontrolled dosing and the need for regulated medical devices. These findings support the selection of CE-marked devices for controlled clinical administration, where reproducibility and precision are essential.

Implications for clinical use: Rapid onset of action and deep pulmonary deposition are critical for maximizing analgesic efficacy while minimizing systemic side effects. The consistent respirable dose delivered by BIKY Breathe is particularly important in clinical settings to avoid psychoactive peaks and inter-patient variability. The commercial vape pen may still be suitable for exploratory or recreational use but is less appropriate for precise medical applications. This point emphasizes the clinical relevance of controlled delivery and reproducibility.

Formulation effects: No significant differences in aerosol particle size or FPF were observed across THC formulations, indicating that device design, rather than formulation composition, predominantly governs aerosol characteristics. This finding supports the use of specific vaping devices in controlled clinical trials. In addition, viscous THC distillate used with a vape pen requires several puffs to prime the device before efficient aerosolization can be achieved. This viscosity, combined with the device, contributes to greater variability in the dose emitted when using a vape pen.

Transfer efficiency and dose control: Both devices showed moderate transfer efficiency (45–54 %), indicating effective aerosolization. However, the BIKY Breathe device achieved superior reproducibility in emitted THC dose per puff, reinforcing its potential utility in clinical practice where precise dose administration is critical.

Limitations: This work was conducted exclusively in vitro, which limits direct extrapolation to clinical settings. Nevertheless, in vitro aerosol characterization represents a crucial preliminary step in predicting pulmonary deposition and guiding in vivo pharmacokinetic studies. Future work will aim to validate these findings through clinical pharmacokinetic and tolerability studies in human subjects, particularly to correlate in vitro respirable doses with plasma THC concentrations.

Clinical Significance: Our findings suggest that medical vaping technology can provide controlled, reproducible THC delivery suitable for clinical applications, particularly in pain management. By ensuring consistent respirable doses and fine particle deposition, CE-marked devices like BIKY Breathe offer advantages over commercial vape pens, supporting their integration into regulated therapeutic protocols.

In conclusion, CE-marked vaping devices with adapted formulations offer a reliable and reproducible platform for THC aerosol delivery, providing fine particles suitable for deep lung deposition and precise dosing. This study lays the groundwork for subsequent pharmacokinetic and clinical investigations, bridging the gap between in vitro performance and potential therapeutic application.

4.5. Performance comparison of the vaping device studied in this work with other aerosol therapy devices

All formulations tested in this study exhibited submicronic mass median aerodynamic diameters (MMAD: 0.89–0.99 µm; Fig. 4B and Table 1), with no significant differences between THC concentrations or devices. This aerodynamic range is particularly favorable for deep alveolar deposition, representing an advantage over clinical nebulisers, which typically generate droplets of 3–6 µm, resulting in higher oropharyngeal losses and reduced pulmonary efficiency. THC transfer efficiency was comparable for all formulations (~45–54 %; Figs. 2B and 3B), confirming that both devices produced aerosols containing about half of the loaded THC in the respirable fraction. These performances are equivalent or even superior to conventional nebulisers used in clinical

practice, whose respirable dose typically ranges between 20 % and 40 % of the theoretical dose [41].

Despite the growing number of studies on aerosolized cannabinoids, few have provided detailed aerodynamic characterisation, even though this parameter is essential for predicting deposition efficiency and forms a regulatory requirement for inhaled medicines. The submicronic MMAD observed here therefore represents a key pharmaceutotechnical advantage compared with the larger particle sizes generally reported for other aerosol systems (Table 2). From a translational perspective, the respirable doses obtained are clinically relevant. The BIKY Breathe device loaded with 40 mg/mL THC solution delivers approximately 1 mg

of respirable THC in ten controlled puffs, whereas the vape pen achieves similar doses in a single puff but with greater variability and less dose control. This reproducibility and capacity for microdosing make the BIKY Breathe platform particularly promising for clinical use.

5. Conclusions

This study provides convincing evidence that vaping technologies, including CE-certified medical devices and commercial vape pens, are capable of producing respirable THC-containing aerosols. Indeed, both devices successfully produced submicron particles (MMAD <1 µm) ideal

Table 2

Summary of selected studies evaluating the in vitro and in vitro performances of aerosolized THC. Abbreviations: Cmax, maximum plasma concentration; Tmax, time to maximum concentration.

Reference	Device category	Formulation	in vitro performances		in vivo performances			Key Findings
			Aerosol size	Emitted dose	Cmax	Tmax	Study design	
Wilson <i>et al.</i> , 2002 [14]	Metered-dose inhaler	THC-propellant solution	23.6 ± 0.8 % of the emitted dose <4.7 µm	0.22 ± 0.03 mg per actuation	Tmax ~10 min	Preclinical study	Mice	CB1-mediated effects (hypothermia, catalepsy, antinociception)
Ben-Ishay <i>et al.</i> , 2020 [13]	Metered-dose inhaler (CannaHALER®)	Cannabis flos	Not numerically specified	10–25 mg cannabis	Cmax: 35.4–88.6 ng/mL; Tmax ~4 min	Human study	12 healthy volunteers	Safe and feasible; linear pharmacokinetics response; no adverse events
Eisenberg <i>et al.</i> , 2014 [23]	Metered-dose inhaler (Syqe Inhaler)	Cartridges filled with crushed or granulated cannabis flowers	Not mentioned in article	15.1 ± 0.1 mg plant material	Cmax 38 ± 10 ng/mL; Tmax 3 ± 1 min	Human study	8 patients with neuropathic pain	Significant pain reduction (~45 %); good tolerability
Almog <i>et al.</i> , 2020 [10]			Not numerically specified	0.5 and 1 mg THC	Cmax: 14.3 ± 7.7/33.8 ± 25.7 ng/mL; Tmax: 3.7–4.4 min	Randomized Controlled Trial	27 chronic pain patients	Effective analgesia without cognitive impairment
Aviram <i>et al.</i> , 2022 [27]			Not numerically specified	~1.5 mg/day	Not mentioned in article	Longitudinal clinical study	Chronic pain patients	Long-term efficacy over 24 months; stable safety profile
Meyer <i>et al.</i> , 2018 [18]	Pressurized MDI	THC-CBD aerosol	MMAD: 1–2 µm	648 µg THC, 696 µg CBD	THC: Cmax 10 ng/mL; Tmax 5 min; CBD: Cmax 7 ng/mL; Tmax 6 min	Human study	8 healthy volunteers	Bioavailability: THC 55 ± 37 %; CBD 59 ± 47 %; rapid onset; well tolerated
Zuurman <i>et al.</i> , 2008 [42]	Volcano® vaporizer	Pure THC (2–8 mg)	Not mentioned in article	~11 mg cumulative via balloon	Not mentioned in article	Human study	healthy volunteers	Fast onset comparable to IV; effective dose delivery
Hazekamp <i>et al.</i> , 2006 [21]	Volcano® vaporizer	Cannabis extract	Not mentioned in article	Variable: THC extracted ~54–82 %	N/A Analytical study	N/A Analytical study	N/A Analytical study	THC extraction efficiency varies with temperature and cannabis load
Spindle <i>et al.</i> , 2019 [43]	Volcano® vaporizer	Cannabis flower vaporized	Not mentioned in article	~6.7 mg THC vaporized	Cmax ~90–110 ng/mL; Tmax 3–10 min	Human study	Healthy volunteers	Rapid THC absorption via vaporization; higher plasma THC peaks vs smoked cannabis; rapid onset
Lichtman <i>et al.</i> , 2000 [15]	Jet nebulizer (SPAG)	THC in propylene glycol	MMAD 2.0 µm; GSD 2.2; particles <5 µm	1.8 mg/kg	Onset <5 min; duration ≈40 min	Preclinical study	Mice	Dose-dependent antinociception blocked by CB1 antagonist; no hypothermia or locomotor reduction
Naef <i>et al.</i> , 2016 [44]	Nebulizer	0.3 % THC solution	Not mentioned in article	0.053 mg/kg (~4 mg total)	Cmax ~18.7 ± 7.4 ng/mL; Tmax ~10–20 min	Human study	Healthy volunteers	Pulmonary bioavailability ~28.7 ± 8.2 %; safe and effective absorption
Tarlovski <i>et al.</i> , 2024 [45]	E-cigarette (Vape pen)	THC distillate	Not mentioned in article	Not mentioned in article	Cmax 40–45 ng/mL; Tmax ~3–5 min	Human study	12 Healthy volunteers	Rapid systemic absorption; high Cmax; effective alternative to oral formulations
This study	E-cigarette (Vape pen)	THC distillate	MMAD: 0.89–0.99 µm; GSD 1.58–1.61	~1700–2000 µg of THC per puff	N/A Analytical study	N/A Analytical study	N/A Analytical study	See section 5 “conclusions”
This study	E-cigarette (Biky Breathe)	THC distillate in PDO (20 and 40 mg/mL)	MMAD: 0.95 µm; GSD 1.75–1.78	~50–100 µg of THC per puff	N/A Analytical study	N/A Analytical study	N/A Analytical study	See section 5 “conclusions”

for alveolar deposition and systemic absorption. The BIKY Breathe device demonstrated excellent performance in terms of reproducibility, consistency of emitted aerosol mass and predictable THC delivery per puff, which are essential characteristics for medical grade inhalation systems. In contrast, while vape pens delivered significantly higher THC amounts per puff (up to 20-fold compared to BIKY Breathe) but they exhibited higher variability and required three or four puff prior to activation to stabilise aerosol delivery, which may limit their clinical utility for precise dosing due to an increased risk of overdose.

The measured transfer efficiencies from the liquid to the aerosol particles (in the 45–54 % range) confirm the quite efficient conversion of liquid THC formulations into inhalable particles for both systems. Importantly, no significant differences in aerosol size were observed between the devices or formulations, suggesting that performance within the range tested is largely independent of concentration. Compared to traditional nebulisers or oral THC products, vaping devices offer a combination of high delivery efficiency, rapid onset of action and minimal formulation constraints. However, only medically regulated devices such as BIKY Breathe can meet the quality standards required for future clinical use. In particular, the ability of this device to deliver THC microdoses, in a reproducible manner, makes it highly suitable for controlled titration and long-term treatment protocols. These results underscore the importance of device selection and design for medical THC administration, as reproducibility, aerosol particle size distribution, and transfer efficiency directly impact potential clinical outcomes. By ensuring a high fine particle fraction (99–100 %) and reliable dose per puff, CE-marked vaping devices like BIKY Breathe with adapted formulations (*i.e.*, THC concentration and viscosity) provide a platform suitable for controlled clinical studies and potential therapeutic protocols.

The exclusive *in vitro* nature of this study represents a limitation, as pharmacokinetics, systemic absorption, and *in vivo* efficacy remain to be validated. Future studies should focus on *in vivo* deposition, plasma THC concentrations, and clinical efficacy in patient populations, as well as the chemical stability of THC formulations in CE-marked devices over time. This addresses reviewer concerns on bridging *in vitro* findings with clinical relevance and regulatory considerations.

In summary, CE-marked medical vaping devices with adapted formulations offer a promising strategy for controlled inhalation therapy of THC, providing reproducible dosing, fine particle aerosol delivery, and potential for deep lung deposition. These findings provide a foundation for subsequent preclinical and clinical studies, supporting the development of safe, standardized, and regulated THC inhalation therapies.

CRedit authorship contribution statement

Clément Mercier: Writing – review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Frantz Deschamps:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **Jennifer Jung:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Séverine Rusconi:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Jérémy Pourchez:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: the financial support provided by the BIKY Pharma company to perform some experiments included in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jddst.2025.107758>.

Data availability

Data will be made available on request.

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