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Aerosol delivery of salbutamol and terbutaline via a CE-marked medical vaping device: aerosol characterization and transfer efficiency compared to nebulization

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ABSTRACT

Pulmonary delivery of bronchodilators remains challenging due to dose variability and suboptimal deposition with conventional inhalers and nebulizers. Thermal aerosolization via vaping devices has emerged as a promising alternative for controlled and reproducible delivery of active pharmaceutical ingredients (APIs). This study evaluates a CE-marked medical-grade vaping device (BIKY Breathe) for pulmonary delivery of salbutamol sulfate and terbutaline sulfate, assessing aerosol performance, particle size, and transfer efficiency, with comparison to a standard pneumatic nebulizer (Cirrus™2). Aerosols were generated under standardized puffing conditions and analyzed using a Glass Twin Impinger (GTI) and a Next Generation Impactor (NGI). Four API concentrations were tested to determine respirable dose, mass median aerodynamic diameter (MMAD), and emitted-dose reproducibility. The Cirrus™2 nebulizer served as reference. The tested device produced aerosols with MMADs of 1.10 ± 0.10 µm (terbutaline) and 1.13 ± 0.14 µm (salbutamol) indicating suitability for deep-lung deposition. Average aerosol mass per puff was ~ 6 mg for both APIs with low inter-puff variability. Terbutaline achieved a maximum transfer efficiency of ~ 40% at 1.35–1.80 mg/mL, whereas salbutamol did not exceed 10%, likely due to physicochemical constraints. Compared with the Cirrus™2 nebulizer, the vaping device generated more efficient micron aerosols and provided higher reproducibility of respirable doses. Overall, the CE-marked device demonstrates robust and reproducible aerosolization of bronchodilators, with particle size appropriate for deep-lung delivery. Terbutaline shows strong translational potential, while salbutamol would benefit from further formulation optimization. These *in vitro* results support the use of medical-grade vaping devices as promising platforms for pulmonary delivery of conventional and novel APIs.

1. Introduction

Over the past decade, drug vaping has emerged as an innovative strategy for pulmonary drug delivery, providing an alternative technical solution to traditional inhalation devices such as pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers. Initially developed for nicotine and recreational use (Farsalinos & Polosa, 2014; Lindson et al., 2024), these devices based on thermal aerosol generation have gained increasing attention for the controlled delivery of active pharmaceutical ingredients (APIs) (Bruneau et al., 2024; Chaoui et al., 2023). Compared with conventional inhalers, Vaping Drug Delivery Systems (VDDS) enable precise control over aerosol droplet size in the micron range, offering potential for patient-specific treatments and improved pulmonary bioavailability of compounds with limited oral absorption (Chaoui et al., 2022a; Chaoui et al., 2022b; Herbert et al., 2021; Khaled et al., 2022). Previous studies from our research group, including investigations into bronchodilators (terbutaline and salbutamol), beclomethasone dipropionate, and Δ^9-tetrahydrocannabinol (THC), have demonstrated the feasibility of delivering pharmaceutical-grade compounds under standardized, clinically relevant conditions. Collectively, these works highlight the translational potential of VDDS for diverse therapeutic applications (Bruneau et al., 2024; Chaoui et al., 2023; Mercier et al., 2025; Pourchez et al., 2017).

The pulmonary route remains highly efficient for both local and systemic drug administration, particularly for molecules requiring rapid onset, such as β_2-agonists. However, conventional inhalation devices

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suffer from several limitations, including dose variability, inspiratory flow dependence, hand-lung coordination and limited formulation flexibility (Labiris & Dolovich, 2003). These challenges have prompted exploration of alternative aerosolization technologies capable of generating fine-particle fractions optimized for deep lung deposition while maintaining formulation integrity. Drug vaping platforms have therefore emerged as promising technological solutions, offering controlled heating of liquid formulations without propellants or complex mechanical systems. This results in reproducible particle size distributions below 1 μm and minimal thermal degradation of thermolabile compounds (Laube, 2014). This emerging technology may also help address sustainability challenges associated with inhalation systems. Specifically, VDDS operates without propellants, in contrast to conventional pMDIs that rely on hydrofluoroalkanes with a significant global warming potential and may therefore align with current efforts to reduce the carbon footprint of inhaled therapies. In addition, unlike pMDIs or DPIs, which require a full device for each delivery, the VDDS body is dispensed only once and reused by the patient, with only the drug container replaced for subsequent deliveries, thereby reducing material consumption and waste.

The CE-marked BIKY Breathe device perfectly illustrates this new generation of VDDS. Its modular liquid chamber and optimized heating mechanism enable efficient and reproducible aerosolization of diverse APIs—including β_2-agonists, corticosteroids, and cannabinoids. For Δ^9-tetrahydrocannabinol, experimental data show mass median aerodynamic diameters (MMAD) ranging from 0.89 to 0.99 μm and fine particle fractions (FPF), particle smaller than 5 μm, between 99 and 100% of the emitted dose, values fully consistent with deep lung deposition. Moreover, the device generates a consistent aerosol mass of approximately 6 mg/puff with low variability, corresponding to respirable THC doses of 50–95 μg/puff, depending on the formulation concentration (Mercier et al., 2025). Compared with conventional e-cigarettes and inhalers, which often exhibit variable outputs and poorly characterized aerosol properties (Talih et al., 2017), the BIKY Breathe device ensures standardized micron aerosolization, precise dose calibration, and reproducibility compliant with medical device regulatory standards. These characteristics enable reliable translational studies linking laboratory aerosol characterization to clinical and patient-centered applications. Building on previous work from our group, this device confirms the capacity of vaping technologies to generate stable, reproducible aerosols suitable for medical-grade delivery of APIs (Bruneau et al., 2024; Chaoui et al., 2023; Chaoui et al., 2022a; Chaoui et al., 2022b; Pourchez et al., 2017). Extensive aerosol deposition research indicates that particles with aerodynamic diameters in the respirable range (approximately 1–5 μm) deposit most efficiently in the lower respiratory tract, including the bronchial and alveolar regions, through a balance of inertial impaction, gravitational sedimentation, and diffusion (Heyder et al., 1986). Within this range, smaller and extrafine particles (<2 μm) have been shown to further enhance deposition in the small airways, which are key targets in obstructive airway diseases (Usmani et al., 2005). Although no single optimal cutoff at exactly 1 μm can be defined, these findings provide a strong physiological rationale for targeting the lower end of the respirable size range to maximize deep lung deposition and therapeutic relevance.

Capitalizing on these technological advances, the present study aims to evaluate the feasibility, reproducibility, and aerosol size characteristics of salbutamol and terbutaline aerosols generated by the CE-marked BIKY Breathe medical-grade device. The key objectives include quantifying emitted dose and fine particle fraction, assessing aerosol particle size distribution for optimized deep lung targeting, and verifying formulation stability during vaporization. By capitalizing on the device's performance, this work provides robust pharmacotechnical data supporting its translational potential for personalized pulmonary therapy. Extending prior investigations on Δ^9-tetrahydrocannabinol aerosolization (Mercier et al., 2025), these findings further illustrate the broader applicability of VDDS for conventional therapeutic compounds, contributing to the development of next-generation inhalation therapies for both local and systemic indications.

2. Materials and methods

2.1. Inhalation devices

Two inhalation devices were used in this study: a jet nebulizer (Cirrus™2, Intersurgical, France) as a reference and the CE-marked BIKY Breathe medical-grade device (BIKY Pharma, France). The battery of the device is certified under the European Medical Device Regulation (MDR 2017/745, Class I), ensuring conformity and safety. It operates using a rechargeable lithium battery (USB-C charging) and sealed single-use 2 mL cartridges filled with the desired solution (Fig. 1). Aerosol generation is triggered either automatically upon inhalation or manually via a button-activated resistor heating element.

The nebulizer was filled with 2.5 mL of Salbutamol Viatris® (5 mg/2.5 mL) or 2 mL of Terbutaline Arrow® (5 mg/2 mL) and operated until complete aerosol depletion.

For the thermal aerosol system, puffs were generated using a programmable dual syringe pump (PDSP®, Burghart Messtechnik®, Germany) connected to either the Glass Twin Impinger (GTI) or Next Generation Impactor (NGI) via airtight tubing. Testing parameters followed AFNOR XP D90-300–3 standards: 55 mL puff volume, 3 s puff duration, 30 s interpuff interval, with 20 puffs per run (one series for GTI and two consecutive series for NGI, separated by a 5-min interval).

2.2. E- liquid composition for the vaping device delivery system (VDDS)

Liquid formulations were prepared using pharmaceutical-grade salbutamol hemisulfate (Thermo Fisher Scientific, USA) and terbutaline sulfate (Abcam, UK) dissolved in sterile saline (0.9% NaCl, Aguettant,

Fig. 1. Image of the BIKY Breathe device composed of a rechargeable battery CE-marked as medical device and sealed cartridge.

France) to obtain stock solutions at 0.45, 0.9, 1.35, and 1.80 mg/mL. These concentrations were selected based on previous studies demonstrating a plateau in respirable dose above 1 mg/mL (Chaoui et al., 2022b). Each compound was accurately weighed using an analytical balance (Adventurer Pro, OHAUS, USA).

The final refill liquids consisted of 10% (v/v) API stock solution mixed with 90% (v/v) 1,3-propanediol (PDO, supplied by BIKY Pharma). PDO was selected as the vaping solvent in this study instead of conventional Propylene Glycol / Glycerol (PG/VG) mixtures commonly used in vaping devices. Although PDO is recognized as Generally Recognize As Safe (GRAS) by the FDA for oral use, its inhalation use is not formally approved and requires dedicated toxicological evaluation. Nevertheless, available data suggest a low acute toxicity profile following inhalation exposure under experimental conditions. In addition, PG has been reported to cause respiratory irritation, and both PG and VG can generate aldehydes upon excessive heating. PDO was therefore selected as a pragmatic formulation compromise for this *in vitro* evaluation. All solutions were freshly prepared on the day of testing, protected from light with aluminum foil, and used immediately to ensure chemical stability. Cartridges were filled with 1.9 mL of solution (device capacity = 2 mL).

2.3. Respirable dose fraction

The Glass Twin Impinger (GTI) (Copley Scientific, UK) was used to quantify the respirable and non-respirable aerosol fractions in compliance with the European Pharmacopoeia and AFNOR standards. The system applies a 6.4 μm aerodynamic cut-off, whereby particles above this threshold are retained in the upper chamber (oropharyngeal region) and smaller particles pass to the lower chamber (pulmonary fraction).

The upper and lower chambers contained 7 mL and 30 mL of Milli-Q grade water, respectively. Aerosols were generated under standardized conditions (20 puffs per run, 55 mL puff volume, 3 s puff duration, 30 s interval) using the PDSP® system. Airflow was maintained at 60 ± 0.5 L/min and calibrated with a DFM3 flowmeter (Copley). Aerosols were generated using a programmable puffing machine under AFNOR-standardized conditions (20 puffs per run) and directed into the GTI via a sealed tubing system. For nebulizer assays, aerosol generation continued until complete depletion of the liquid formulation.

After aerosol collection, the chamber volumes were adjusted to 10 mL (upper) and 50 mL (lower) before analysis. Samples were stored at − 20 °C until quantification by HPLC. Each experiment was performed in triplicate.

2.4. Particle size distribution

The Next Generation Impactor (NGI) (Copley Scientific, UK) was employed to determine the aerodynamic particle size distribution of the emitted aerosols. This eight-stage cascade impactor separates particles according to their aerodynamic diameter and inertia, enabling calculation of the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) by log-probability analysis. In the context of inhalation therapy, aerodynamic particle size is the key determinant of respiratory deposition, accounting for particle size, density, and shape. Optical droplet sizing was not performed, as it is less physiologically relevant than aerodynamic measurements for inhalation studies.

Experiments were performed at controlled flow rates of 15 ± 0.5 L/min for the pneumatic nebulizer and 60 ± 0.5 L/min for the thermal aerosol device, in accordance with pharmacopeial recommendations. The nebulizer was operated until complete aerosol exhaustion, while the thermal device was tested with two consecutive 20-puff series separated by a 5-min interval. After each run, each NGI stage was rinsed with 5 mL of Milli-Q water, and the collected samples were stored at − 20 °C until analysis. Measurements were conducted in triplicate.

2.5. Quantification of salbutamol and terbutaline by mass spectrometry

Salbutamol and terbutaline concentrations were determined using an Acquity UPLC system coupled to a Xevo TQS micro triple quadrupole mass spectrometer (Waters, Saint-Quentin-en-Yvelines, France). Samples were diluted with the internal standard (IS) prepared in acetonitrile and centrifuged. Chromatographic separation was carried out on a Kinetex HILIC column (30 mm × 3 mm, 2.6 μm; Phenomenex, France) under a 2 min gradient elution. Quantification of salbutamol was based on the mass to charge (m/z) transitions 240.21 → 148.04 for salbutamol and 243.18 → 150.99 for the IS salbutamol-d3. For terbutaline and its IS terbutaline-d9, the following transitions were monitored m/z 226.19 → 151.97 and 235.23 → 152.96, respectively.

2.6. Data analysis

Data processing and statistical analyses were performed using GraphPad Prism 10.0 (GraphPad Software, USA). Results of each biological assay are expressed as mean ± standard deviation (SD) of 3 independent experiments, each performed in triplicate. Differences between groups were evaluated by nonparametric Mann-Whitney test, with $p < 0.05$ considered statistically significant.

3. Results

3.1. Generated aerosol mass

Both APIs aerosolized using the medical-grade VDDS exhibited comparable average aerosol masses per puff—6.02 mg/puff for salbutamol sulfate and 6.27 mg/puff for terbutaline sulfate—with no statistically significant difference between the two formulations. This finding indicates that the nature of the API did not influence the total aerosol mass generated under standardized operating conditions, thereby enabling valid inter-formulation comparisons in terms of emitted dose. The low standard deviations observed (1.18 mg for salbutamol and 0.60 mg for terbutaline) reflect high inter-puff reproducibility, underscoring the technical reliability and consistency of the device. Such reproducibility is a critical attribute for therapeutic applications, ensuring minimal dose variability during repeated administrations under controlled puffing parameters (fixed volume and duration).

3.2. Distribution of APIs in non-respirable and respirable dose

Both APIs showed a negligible non-respirable dose ranging from 0.002 μg/puff to 0.089 μg/puff. Therefore, the vaping device generates a respirable aerosol corresponding to particles with aerodynamic diameters < 6.4 μm. The average respirable dose increased Fig. 3 in a non-linear fashion with initial API concentration: 0.23–0.56 μg/puff for salbutamol and 0.36–2.07 μg/puff for terbutaline. Interestingly, respirable terbutaline stabilized above 1.35 mg/mL (2.07 → 2.02 μg/puff), whereas salbutamol continued to increase almost twofold (1.35 → 1.80 mg/mL). Across all concentrations, respirable salbutamol was lower than terbutaline. For example, at 0.45 mg/mL, terbutaline delivered twice the respirable dose, and at 1.35 mg/mL, eightfold higher. Since total aerosol masses were similar (Fig. 2), this reflects a lower transfer efficiency for salbutamol (Fig. 4).

Transfer efficiency was calculated as Equation (1). Salbutamol did not exceed 10%, whereas terbutaline reached up to 40% at higher concentrations (1.35 and 1.80 mg/mL).

$$Transferefficiency(\%) = \frac{Measuredrespirabledose}{Maximumtheoreticaldose} \times 100 \quad (1)$$

Equation (1). Transfer efficiency calculation

The Cirrus™2 nebulizer delivered a respirable dose of 427.1 ± 49.6 μg terbutaline (out of 2125 μg total, 20.1 ± 2.3%) and 613.1 ± 111.7 μg

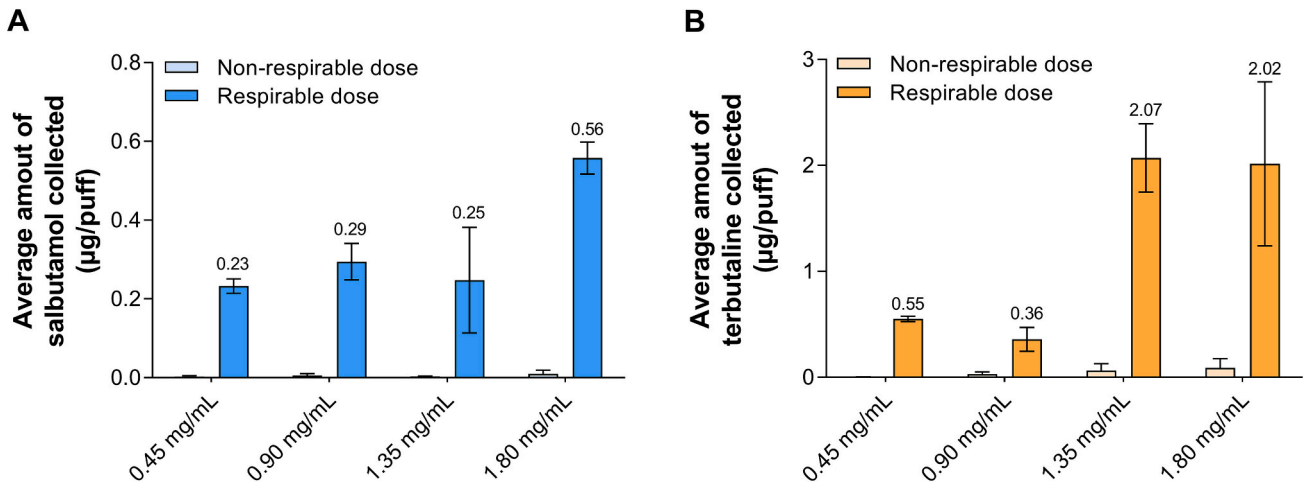

Fig. 3. Average amount of (A) salbutamol and (B) terbutaline collected per puff from the respirable and non-respirable fraction of GTI for the BIKY Breathe device. Results are presented as the mean of three independent experiments ± standard deviation (SD).

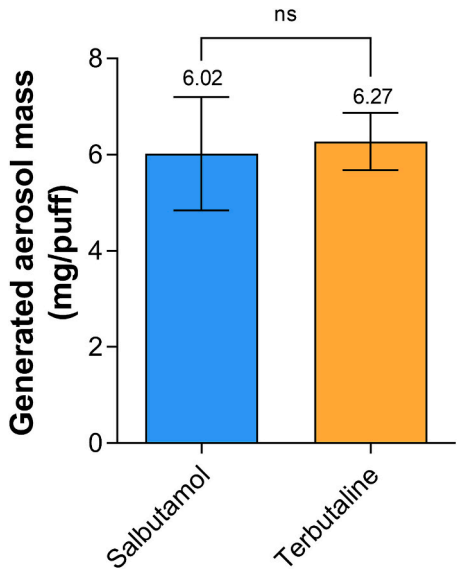

Fig. 2. Average amount of active ingredients per puff generated by the tested device. Results are presented as the mean of three independent experiments ± standard deviation (SD). ns: not significant. Mann-Whitney non-parametric statistical test.

salbutamol (out of 1700 µg total, 36.1 ± 6.6%) (Table 1). These results highlight substantial drug loss during nebulization, mainly due to low nebulizer efficiency, exhalation, and residual volume retention of large droplets.

3.3. Particle size distribution of APIs

The aerodynamic particle size distribution profiles obtained from the impactor analyses are presented in Fig. 5. Both aerosol delivery systems produced particles within the respirable range, and comparable results were observed across all tested concentrations for both active ingredients. For terbutaline sulfate, the reference nebulizer (Cirrus™2) generated aerosols with a Mass Median Aerodynamic Diameter (MMAD) of 1.73 ± 0.06 µm and a Geometric Standard Deviation (GSD) of 1.59 ± 0.02, whereas the vaping device produced an MMAD of 1.10 ± 0.14 µm and a GSD of 1.92 ± 0.07 (Fig. 6). Similarly, for salbutamol hemisulfate, the nebulizer yielded an MMAD of 1.78 ± 0.08 µm with a GSD of 1.60 ± 0.02, while the VDDS produced smaller particles, with an MMAD of 1.13 ± 0.14 µm and a GSD of 2.10 ± 0.11 (Fig. 6). Cumulative distribution curves (Figs. 5C and D) further demonstrated that the VDDS generated approximately 40% of particles with diameters below 1 µm, compared to only ≈8% for the nebulizer, independent of the active ingredient or tested concentration. Conversely, the nebulizer emitted a larger proportion of particles exceeding 10 µm, which are more likely to deposit in the oropharyngeal region rather than reaching the lower respiratory tract.

3.4. Duration of administration

Based on respirable doses delivered by the nebulizer (613.1 µg salbutamol, 427.1 µg terbutaline), the number of VDDS puffs required varied from 2634 to 212. As expected, the higher the initial dose in the e-liquid, the lower the number of puffs required to achieve the nebulizer equivalent API dose. Once the number of puffs had been established, we estimated the inhalation time required according to two scenarios: AFNOR vs. Patient. The first follows the standard recommended by AFNOR XP-90–300-3 for thermal inhalation devices, with a puff duration of 3 s and an inter-puff interval of 30 s, corresponding to one puff every 33 s. Based on this definition, the total administration time was calculated by multiplying the number of puffs required to reach the target respirable dose by 33 s. The second scenario considers actual use by patients, who would take a 3-second puff with an inter-puff interval of 3 s, corresponding to one puff every 6 s. Based on these two assumptions, the results showed the given administration times: (i) Salbutamol: 1448–604 min (AFNOR) vs. 263–109 min (Patient) and (ii) Terbutaline: 654–116 min (AFNOR) vs. 119–20 min (Patient). At equivalent doses, nebulization took 13 min (salbutamol) and 11 min (terbutaline). Considering practical administration times, only terbutaline at 1.35 or 1.80 mg/mL is feasible for routine use with VDDS but remains long and number of puffs required need to be considerably decrease.

4. Discussion

Overall, this study demonstrates that the investigated medical-grade thermal inhalation device can efficiently generate aerosols of therapeutic interest, with particle sizes in the optimal range for deep lung deposition (MMAD ≈ 1 µm). The reproducibility of emitted puffs and the similarity of aerosol masses generated between formulations highlight the technical robustness of the tested device. However, differences in drug transfer efficiency between terbutaline and salbutamol underline the impact of both physicochemical properties of the API and

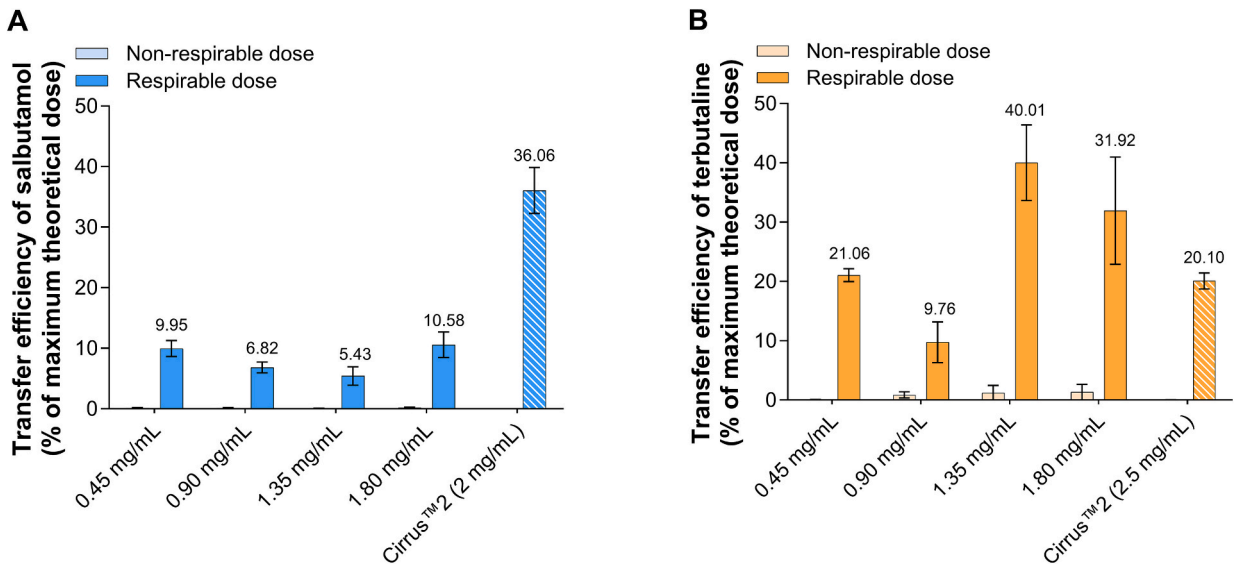

Fig. 4. Transfer efficiency of salbutamol sulfate (A) and terbutaline sulfate (B) as a percentage of maximum theoretical dose for both the BIKY Breathe device and the Cirrus™2 nebulizer. Results are presented as the mean of three independent experiments ± standard deviation (SD).

Table 1
Comparison of duration between nebulization and VDDS at different concentrations for equivalent respirable dose of salbutamol sulfate and terbutaline sulfate. Administration time AFNOR XP-90–300-3 considered a 3-second puff duration following by a 30-second interval between puffs, while administration time Patient considered a 3-second puff duration following by a 3-second interval between puffs. We therefore considered that a puff is emitted each 33 s for AFNOR time and each 6 s for patients' time. Based on this definition, the total administration time was calculated by multiplying the number of puffs required to reach the target respirable dose by the 33 s or 6 s depending on the conditions tested.

		Nebulizer	VDDS 0.45 mg/mL	0.90 mg/mL	1.35 mg/mL	1.80 mg/mL
Respirable dose	Salbutamol	613.1 µg/nebulization of 2,5mL	0.233 µg/puff	0.526 µg/puff	0.248 µg/puff	0.558 µg/puff
	Terbutaline	427.1 µg/nebulization of 2 mL	0.552 µg/puff	0.359 µg/puff	2.071 µg/puff	2.016 µg/puff
Number of puffs to reach nebulizer equivalence	Salbutamol	–	2634	1166	2476	1099
	Terbutaline	–	774	1191	206	212
Administration time (AFNOR)	Salbutamol	13 min	1448 min	641 min	1362 min	604 min
	Terbutaline	11 min	425 min	654 min	113 min	116 min
Administration time (Patient)	Salbutamol	13 min	263 min	116 min	247 min	109 min
	Terbutaline	11 min	77 min	119 min	20 min	21 min

formulation parameters on aerosol performance.

Among the two bronchodilators studied, terbutaline sulfate emerged as a promising candidate for administration with the tested medical-grade VDDS. The emitted respirable dose reached approximately 2 µg per puff at an initial concentration of 1.35 mg/mL, corresponding to a transfer efficiency of ≈40%. This value exceeds typical efficiencies reported for conventional inhalation systems, such as jet nebulizers or dry powder inhalers, which rarely exceed 30% (Chaoui et al., 2023). The plateau observed at concentrations above 1 mg/mL aligns with previous reports on terbutaline formulations (Chaoui et al., 2022a), confirming the existence of a concentration threshold beyond which further increases do not significantly enhance emitted dose. Comparable results observed a respirable dose of 2.98 µg/puff using a JUUL® device filled with a terbutaline solution at 2.5 mg/mL (Chaoui et al., 2023). Despite operating at similar fixed low power (≈ 8 W), the medical-grade VDDS BIKY Breathe used in this work achieved equivalent or higher efficiency at lower API concentrations, highlighting its suitability for medical applications. By contrast, third-generation "tank" e-cigarette devices equipped with adjustable power and larger reservoirs can deliver doses nearly ten times higher up to 20 µg/puff (Chaoui et al., 2022b), but at the cost of increased formation of thermal degradation by-products highly toxic such as acetaldehyde and acrolein, which appear above 14 W and increase substantially beyond 40 W (Uchiyama et al., 2020). While our study demonstrates reproductible aerosol generation and particle sizes appropriate for deep lung deposition, long-term inhalation safety of these formulation has not been established. Chronic exposure studies and dedicated toxicological evaluations are required before advancing to clinical testing. These consideration highlight the need for cautious interpretation of *in vitro* performance data and the importance of comprehensive safety assessments in future work.

Conversely, salbutamol hemisulfate delivered lower respirable doses, not exceeding 0.56 µg/puff at the highest tested concentration (1.8 mg/mL), corresponding to a transfer efficiency below 10%, resulting in a large disparity compared to results obtained with terbutaline. Although this represents an improvement over previous JUUL®-based studies, where no measurable salbutamol was detected in the emitted aerosol (Chaoui et al., 2023), it remains substantially lower than values obtained with high-power third-generation devices, which can reach up to 237 µg/puff using the free base form (Buonocore et al., 2023). While the relative difference between salbutamol and terbutaline is apparent in our VDDS data, the fraction of drug delivered by the nebulizer (20–36% respectively) demonstrates that differences in delivery efficiency are generally modest across devices. The discrepancy likely stems from physicochemical and thermal factors. The sulfate salt, while more water-soluble than the free base (classified as "easily soluble" versus "fairly soluble" in the European Pharmacopoeia), may undergo partial thermal degradation under the heating conditions of the device. Additionally, adsorption phenomena on the impinger glassware, wick, or heating element could reduce the effective collected dose. Finally, a portion of the molecule may transition into the gas phase,

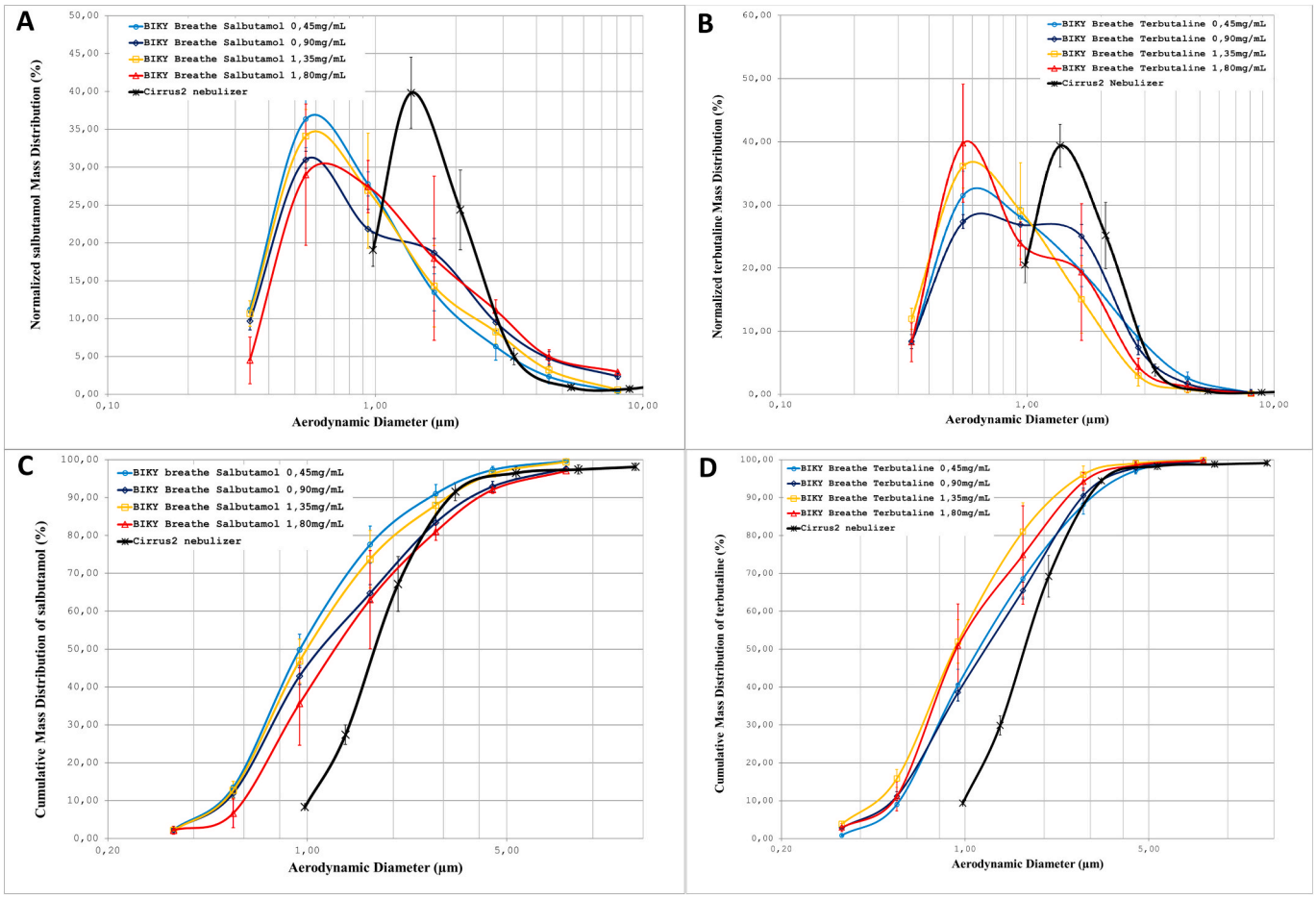

Fig. 5. Average particle size profile of respectively (A) salbutamol sulfate and (B) terbutaline sulfate, and using BIKY Breathe device at various concentration: 0.45 mg/mL (light blue), 0.90 mg/mL (dark blue), 1.35 mg/mL (yellow), 1.80 mg/mL (red), and Cirrus™2 Nebulizer (black) expressed in terms of mass median aerodynamic diameter (MMAD). Average cumulative mass distribution profile of (C) salbutamol sulfate and (D) terbutaline sulfate using BIKY Breathe device at various concentration: 0.45 mg/mL (light blue), 0.90 mg/mL (dark blue), 1.35 mg/mL (yellow), 1.80 mg/mL (red), and Cirrus™2 nebulizer (black). The results are presented as the mean of three independent experiments ± standard deviation (SD).

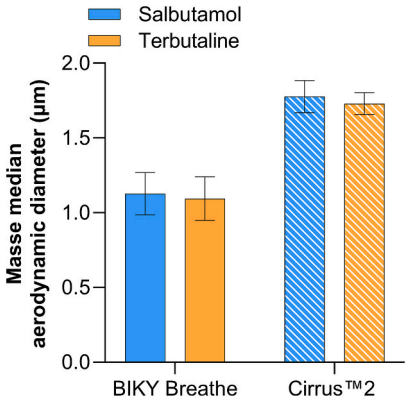

Fig. 6. Mass median aerodynamic diameter (MMAD) of salbutamol and terbutaline using BIKY Breathe device and Cirrus™2 nebulizer. Results are presented as the mean of three independent experiments.

which the GTI does not capture, potentially underestimating the emitted dose. Collectively, these results indicate that formulation optimization is required for salbutamol hemisulfate to achieve transfer efficiencies comparable to terbutaline. Strategies could include using the free base form, alternative solvents, or stabilizing excipients to enhance thermal stability and aerosolization.

In addition to achieving an adequate respirable dose, the VDDS must produce particles capable of reaching distal lung regions, where therapeutic action is most effective. The optimal MMAD for inhaled therapies typically ranges between 1 and 5 µm (Pleasants and Hess, 2018). In this study, the VDDS produced aerosols with approximately 40% of particles below 1 µm and with an average MMAD of 1.1 µm for both APIs, within the optimal range, whereas the nebulizer produced larger particles with an MMAD ≈ 1.75 µm and only around 8% of particles below 1 µm. Similar findings were previously reported for terbutaline and beclomethasone dipropionate using various VDDS technology (Bruneau and al., 2024; Chaoui and al., 2023). Notably, the VDDS produced micron particle fraction absent in nebulizer aerosols, which can penetrate distal airways and alveolar regions, enhancing deposition in target zones. As particles significantly below 1 µm may be partially exhaled, deposition models and experimental data indicate thar particles around 1 µm represent a favorable compromise between deep lung deposition and exhalation losses. Conversely, the nebulizer emitted a considerable fraction of particles > 10 µm, prone to oropharyngeal deposition (Forest and Pourchez, 2022). Although this study was conducted solely *in vitro*, *in vitro* aerosol characterization remains a critical step for anticipating pulmonary deposition and guiding the desing of *in vivo* pharmacokinetic and tolerability studies. Future work will aim to validate these findings in humans, with particular attention to correlating *in vitro*-determined respirable doses with plasma API concentrations. Importantly, our previous work using radiolabeled e-cigarette aerosols and *ex vivo* lung models demonstrated regional deposition patterns for aerosols with

particle sizes similar to those generated by the device studies here (MMAD ≈ 1.1 μm). This provides supporting evidence that the pulmonary deposition observed in our current *in vitro* study is likely reflective of real deposition trends (Montigaud and al., 2021).

When comparing dose and administration time with nebuliser treatment, the number of puffs required depends on emitted dose per puff. Higher-powered devices produce larger emitted masses, requiring fewer puffs to achieve nebulizer equivalence. In our study, terbutaline concentrated at 1.35–1.80 mg/mL required 206–212 puffs, outperforming JUUL®-type systems (347 puffs), but still below high-power third-generation devices delivering tens of micrograms per puff (Chaoui and al., 2023). Even if the BIKY Breathe seems to be better than equivalent devices, the number of puffs require is clinically inconceivable for salbutamol and the administration time under realistic patient conditions remains high even for the higher dose emitted with terbutaline (around 20 min). To improve the delivered dose and reduce administration time, several strategies can be considered. Increasing API concentration is a straightforward option, but limited by solubility constraints in the PDO-based vehicle. Incorporation of pharmaceutical excipients, such as poloxamer 188, has been shown to improve solubility and stability for poorly soluble APIs (e.g., beclomethasone dipropionate) (Bruneau and al., 2024). Nanocrystal or surfactant strategies could similarly enhance solubility and transfer efficiency for the bronchodilators studied, provided that excipients meet inhalation-grade safety requirements.

Although the device is easy to use, minimal patient education is required to ensure correct technique. Only a quarter of patients currently receive adequate instruction for DPIs, often leading to incorrect use, reduced inhaled dose, and lower therapeutic efficacy (Laube and al., 2011; Molimard and al., 2017). This device may help address hand–lung coordination issues in children and the elderly due to its low suction resistance. Additionally, its compact and discreet design may improve treatment adherence, mitigating stigma associated with public inhalation. However, it is crucial to distinguish this medical device from recreational e-cigarettes, particularly in public spaces where vaping is prohibited. For pediatric use, enhanced education is essential to prevent confusion between therapeutic and recreational use.

5. Conclusion

In summary, this study demonstrates the potential of a CE-marked medical-grade vaping device as an innovative platform for pulmonary drug delivery. The tested device generated reproducible aerosol puffs and produced micrometer-sized droplets suitable for deep-lung deposition. However, a significant difference in delivery efficiency was observed between the two bronchodilators: terbutaline sulfate achieved a transfer efficiency of approximately 40%, among the highest reported for inhalation devices, whereas salbutamol hemisulfate did not exceed 10%. The lower transfer efficiency of salbutamol is likely attributable to its salt form, which may undergo partial thermal degradation or exhibit limited transfer during aerosolization. These findings indicate that further formulation optimization—such as the use of alternative salts, stabilizers, or excipients—will be necessary to improve its suitability for administration via VDDS.

Although the number of puffs required to achieve a therapeutically equivalent dose to that of a nebulizer remains too high (≈206 puffs, corresponding to a patient administration time of ≈20 min), the device offers clear advantages in terms of aerosol reproducibility, particle size control, and delivery consistency. Increasing the API concentration beyond 1 mg/mL did not further enhance emitted dose, suggesting a plateau effect. Therefore, refinement of formulation, rather than concentration increase appears to be the most effective strategy for improving therapeutic feasibility. Overall, the tested CE-marked medical-grade meets critical requirements for particle size and repeatability and demonstrates strong potential as a safe and efficient alternative to conventional nebulization systems for the pulmonary delivery of bronchodilators which need to be then confirmed by clinical pharmacokinetic and tolerability studies.

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CRediT authorship contribution statement

Faustine Fournel: Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation. **Clément Mercier:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sophie Hodin:** Writing – review & editing, Validation, Investigation, Data curation. **Jérémie Pourchez:** Writing – review & editing, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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