Journal of Drug Delivery Science and Technology 80 (2023) 104206

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Can ENDS technology facilitate the delivery of medicines?

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A B S T R A C T

Over the past decade Electronic Nicotine Delivery System (ENDS) have established themselves commercially as an alternative to tobacco cigarettes. The use of these devices to deliver pharmaceutical active ingredients has also been reported in the literature; however, achievement of the therapeutic dose usually required a large number of puffs. Promisingly, these devices were shown to generate aerosols within the optimal aerodynamic particle size distribution to achieve deep lung deposition. Moreover, they demonstrate the ability to be efficient drug delivery systems for patients with a poor lung function or anatomy, as they can offer a tailored aerosol medicine.

This study was conducted with the aim of successfully delivering free base salbutamol via inhalation using e-liquid salbutamol formulations, aerosolized using the ENDS technology.

E-liquids formulations containing salbutamol as active ingredient were prepared; impaction data were collected using a Next Generation Impactor under laminar flow conditions and aerodynamic particle size distribution evaluated using Copley's Inhaler Testing Data Analysis Software (CITDAS).

This study showed a delivery up to 245 μg/puff of salbutamol with Mass Median Aerodynamic Diameter (MMAD) ranging 1.2–1.4 μm. The results of this study suggest that the use of ENDS technology in inhalation medicine can represent a large innovation, potentially this technology, could close the existing gap in currently available technology, between inhaler design and patients' compliance and adherence.

1. Introduction

Nowadays, inhalation therapy is seldom explored for the delivery of systemic drugs; however, it still remains the best option for the delivery of locally acting drugs, i.e. the treatment and management of lung diseases such as asthma, Chronic Obstructive Pulmonary Disease (COPD) and cystic fibrosis (CF) [1,2]. Compared to other routes of delivery, inhalation therapy presents many advantages: it is non-invasive and provides a fast absorption of active ingredients due to the considerable surface area of the alveolar region, which is characterised by an abundant vasculature and thin air-blood barrier [3]. For these reasons, pharmaceutical companies have developed different inhalation devices to improve pulmonary drug deposition; however, they have made modest differences in the clinical outcome [4]. The efficiency of inhalation therapy is dependent on the nature and amount of the active ingredients reaching the intended site of deposition [5]. It is well known that optimal aerosol delivery requires a harmonic interaction between patient, device and formulation, as illustrated in Fig. 1.

Reaching the harmonised action amongst these three factors is one of the biggest challenges in this field. For instance, there is poor inhaler technique in patients with obstructive pulmonary disease [6]. As a result, only 1 out of 10 COPD patients correctly performs all of the steps required for successful delivery using a metered dose inhaler [7]. As a consequence, there is currently a need for alternative aerosol-generating devices, which are capable of producing small-sized particles, are easy to use, present low costs, are convenient and, most importantly, can be "personalized" to adapt to each patient's need. Despite the development of new devices and formulations to improve the patients' clinical outcome, only a few steps have been taken to tackle other important aspects such as the patient's adherence to the medical plan. On average only 40%–60% of COPD and around 50% of CF patients adhere to the prescribed medical plan [7,8]. There are many factors that affect patient's adherence. In CF patients, the main contributors were: stigma/embarrassment of performing inhalation therapy in the presence of others and the time-consuming procedures to prepare and take the medication [8,9]. The lack of adherence to the medical plan in these two patient populations results in a faster decrement of lung function, increased hospitalization and a larger cost for health care providers [7–11]. To date there are over 230 different devices and drug combination available for inhalation therapy; however, healthcare professionals want to see more innovation that motivates or facilitates their patients to achieve a better adherence to the medical plan [3]. The technology used in ENDS can be a turning point in inhalation medicine, leading towards a more digital innovation that offers a tailored inhalation medicine.

Electronic Nicotine Delivery System (ENDS), also more commonly

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https://doi.org/10.1016/j.jddst.2023.104206
Received 2 September 2022; Received in revised form 18 January 2023; Accepted 23 January 2023
Available online 24 January 2023

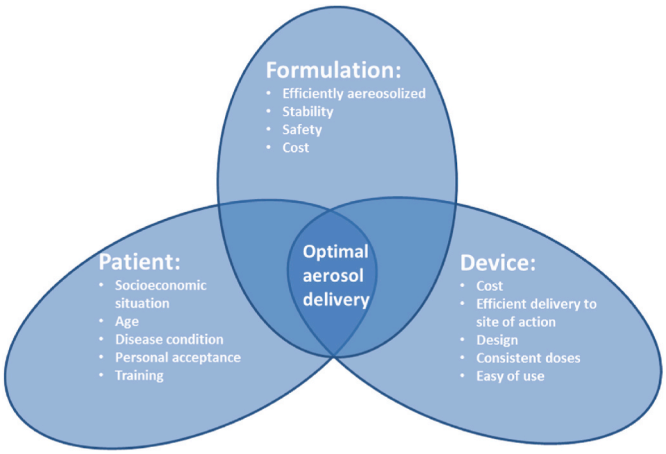

Fig. 1. Optimal combination required to obtain the best aerosol delivery.

referred to as electronic cigarettes or e-cigs, have become increasingly popular over the last decade and have established a significant market. These devices can deliver nicotine to the user without the need of combustion as in conventional tobacco or burners. Driven by commerce and demand, and following complaints about devices performances [12], manufacturers have quickly adapted their products to achieve a more user-tailored experience. For example, they have created a wide range of innovative devices with tuneable settings, such as power output of the battery, airflow intake and resistance of the heating element, among others [13]. The wide range of options and products on offer provides a tailored experience which can be adjusted to fit the user needs. The rapid and unregulated development of these devices also permitted the creation and sale of untested and unsafe products, for example liquids containing substances dangerous to the health [14]; with an outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping (EVALI) observed mainly in the US in 2019 [15]. Data collected from patients in the US showed that the patients were using ENDS containing tetrahydrocannabinol (THC), which were purchased from informal sources like family, friends, or in-person or online. The Centre for Disease Control (CDC) concluded that these products were linked to most EVALI cases and played a major role in the outbreak [16]. Product samples tested by the Food and Drug Administration (FDA) found that Vitamin E acetate was present in these products and tests on the patients lung fluid samples by the CDC also showed the presence of Vitamin E acetate [16]. As a result of these findings authorities have quickly enforced the removal of vitamin E acetate from products, leading to new law enforcement actions being established related to illicit products and increased public awareness of the risk associated with THC-containing e-cigarette [16]. Since the implementation of these points, the number of cases from September 2019 (peak of outbreak), has shown a gradual but persistent decline [16]. Many studies on ENDS are available in the literature focusing on legislation, chemical composition, and side effects to health. There are very few studies related to the application of these devices as drug delivery system. In 2017, a study performed by Pourchez et al. [17] identified and assessed the use of ENDS as inhalers for terbutaline sulphate (a bronchodilator). The authors reported that the device employed in the study was capable of delivering 5.6 μg/puff of active ingredient with a Mass Median Aerodynamic Diameter (MMAD) of 0.78μm[17]. The study concluded that ENDS are very efficient at producing submicron carrier-droplets and most importantly deliver a consistent concentration of active ingredient per puff. Despite the desirable aerodynamic particle size distribution, the results of the study showed that 20–70 puffs were needed to attain a bioequivalence (in terms of emitted dose) to the commercial Bricanyl Turbuhaler ® (500 μg terbutaline sulphate, AstraZeneca) [17]. This number of puffs is too high for an effective and realistic clinical application.

In the meantime, the development of ENDS devices to offer a more tailored experience to users has continued and at present there is a range of easily personalized aerosol devices capable of being adapted to the patient's needs and to be linked to technology, such as apps on mobile phones. Moreover, alongside their efficiency, ENDS technology can play a significant role in patients' adherence. The concept of thermally generated aerosols is still being evaluated also by pharmaceutical companies; recently, a thermal vaporization aerosol device entered the market with the name of STACCATO®. This device has recently been renamed Adasuve® and has been approved by the FDA as a dry powder inhaler (DPI) for the management of agitation associated with bipolar disorder or schizophrenia in adults [18].

The aim of this study was to prove it is possible to successfully deliver free base salbutamol via inhalation using e-liquid salbutamol formulations, aerosolized using the ENDS technology.

2. Material and method

Salbutamol was selected as it is one of the most prescribed drug used in both primary and secondary care [19]. Formulations were prepared by dissolving salbutamol base free (100 mg) within an e-liquid composed of propylene glycol and vegetable glycerol (4.5 ml each), water (1 ml) and ethanol (2.5 ml). Formulations were vaporised in triplicate using a KangerTech® Subox Nano, equipped with a 3.7 V battery with a capacity of 4500 mAH. The device is of variable voltage and variable wattage which allows variation of these two parameters between 3.0 and 9.0 V and 6.0–60 W, respectively. For each formulation a new coil (cotton 0.5 Ω) was used in order to ensure reproducibility. Formulations were vaporised using three different wattage setting 20, 30 and 40 W. Aerodynamic particle size distribution was studied using a Copley Next Generation Impactor (NGI) coupled with a Copley HCP 5 high vacuum and a Copley TPK 2000 Critical Flow Controller; the flow was set up and calibrated at 15 L/min using a Copley DFM 2000 flow meter. The device was attached to the NGI via a custom-made adapter produced by Copley, which sealed the interface between the two components. Each run consisted of 30 puffs and the duration of each puff was 4 s for a total volume of 1L. Each NGI tray was weighted before and after each test to evaluate the total amount of deposit present in each tray. A pre-metered volume (5 ml) of methanol was dispensed in each NGI cup tray using an automatic pipette in order to dissolve the impacted content on each tray. Where necessary, samples were diluted by a factor of 10. Samples were analysed by Cary 7000 Universal Measurement Spectrophotometer system at 278 nm. The analytical method was fully validated according to ICH guidelines a summary of method validation is available as supplementary information. All absorbances and weight recordings for each respective tray were then fed into CITDAS (Copley inhaler testing data analysis software) for particle size distribution analysis. This software provided details of the MMAD, particle size distribution patterns, fine particle fraction (%) and geometric standard deviation (GSD).

3. Results & discussion

The total mass of the active ingredient delivered per puff against the device wattage output (ranging from 20 to 40 W) was investigated; an increase in the level of drug delivered with increasing battery power output (in W) can be observed (Fig. 2).

These findings indicate the ability of this device to deliver a range of doses of drug per puff by simply changing the wattage output on the device. Moreover, the relatively small standard deviation indicates a reproducible dose delivered with each puff. The small delivery dose of salbutamol per puff (79.51 ± 1.68 μg) at 20 W can be explained as a result of insufficient heating from the coil due to lower wattage. This is because all the experiments were ran by using a low resistance 0.5 Ω, or to be more specific the experiments were ran as "Sub-ohm vaping", also

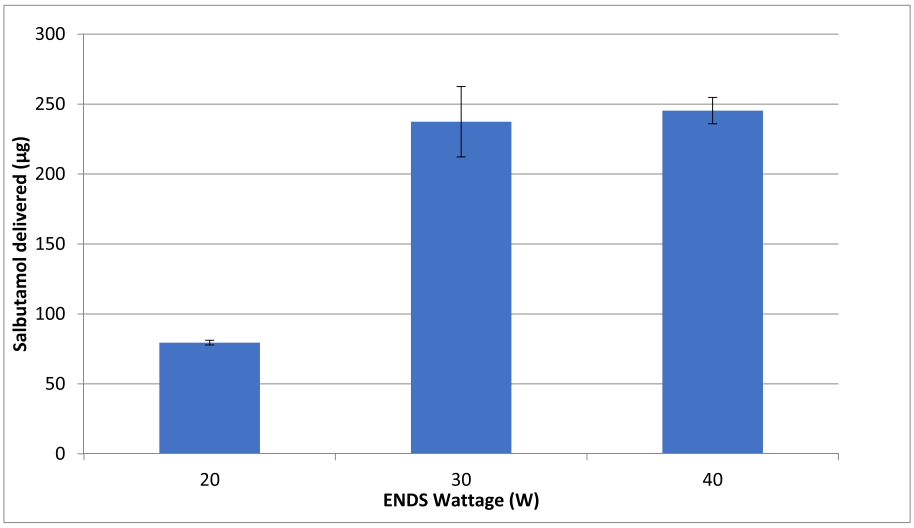

Fig. 2. Total emitted dose per puff against power output (W) of device, the relative standard deviation observed at 20, 30 and 40W was 2.10, 10.6 and 3.84% respectively.

known as "sub-ohming"; which, is a style of vaping that generates large clouds of vapour, this style of vaping uses resistance coils that are less than 1 Ω. Furthermore, to achieve a direct lung inhalation during sub-ohm the devices needs to have enough airflow, but most importantly they need to be capable of putting out a minimum of 40W. Hence at 20W there is not enough power to generate sufficient volumes of vapour, to reach the desired dose of 100 µg. The relative standard deviations, obtained from each condition, indicates that the device shows good reproducibility in terms of emitted dosage. A one-way ANOVA was performed to compare the effect of wattage on the emitted dose.

The ANOVA test revealed that there was not a statistically significant difference in emitted dose between at least two groups ($F(8, 63) = 0.72$, $p = 0.68$, 95% C·I.).

The aerodynamic particle size distribution of the emitted dose is summarised in Table 1.

Plotting the percentage mass distribution against the aerodynamic diameter (Fig. 3), it is possible to observe a good match between the data obtained at 20 and 30 W, whereas a different distribution was observed with the data obtained at 40 W. As a consequence of different mass distribution, a slight increase in MMAD was observed from 1.25 ± 0.01 µm at 20 W to 1.41 ± 0.039 µm at 40 W.

To establish if there was the generation of carrier-free droplets by the device, the plates of the NGI were weighed before and after the experiment to establish the MMAD, to evaluate the mass distribution percentage of the aerosol itself. The values obtained from this experiment were then plotted against the one obtained from salbutamol in Fig. 4.

The almost perfect overlap between the two set of data suggest that carrier-free aerosol was not generated during the experiment.

The results of this study show that ENDS are able to deliver drugs within the microgram range per puff, therefore they are potentially suitable for the delivery of medicines which have a prescribed dosage within the same range. There are different advantages in using such devices which include their ability to generate the optimal MMAD in the range of the micron (1.2–1.4 µm) and, the emitted dose can be simply adjusted by the user changing the power output or the flow intake. The range of MMAD obtained by these formulation and device is very close to 1.5 µm, which according to Usmani et al. [20] is the optimal size for greatest total lung deposition; 56% of the total emitted dose.

These devices are efficient for all the type of patients with different anatomy, lung function or obstruction. However, analogously to other inhalers, patients need to receive training on how to use the device by healthcare professional who will counsel the patient on understanding the technology and usage. One of the main drawbacks for employing these devices in drug delivery is the potential thermal degradation of the active ingredient during the generation of the aerosol. Another problem reported in literature by Pourchez et al. [17] was the efficiency of ENDS to deliver a desired emitted dose of terbutaline sulphate. The author reported that 20–70 puffs of their formulation were required to reach the pharmacological dose. The results of this study suggest that this issue can be overcome by simply using the free-base of the drug, in this case salbutamol. The use of a salt free drug allowed a higher emitted dose compared to salbutamol sulphate. One of main disadvantages of using a free-base version of a drug is that this may degrade easier than the salt form, an issue that can be easily adjusted by adding a preservative to the formulation. To date, marketed salbutamol inhalers have a labelled emitted dose of 100 µg or 200 µg per puff and patients might increase this to 400 µg as needed by taking two puffs to achieve relief from symptoms. In this study, the total emitted dose of the formulation can reach this range of values via a single puff. Moreover, it shows that the amount of drug and the emitted MMAD of the emitted particles can be easily adjusted by changing the wattage output of the device opening up the possibility of easily adjusting the dosage and fine particle fraction, which can be beneficial in patients with airways obstructions [21]. However further studies are needed to assess the stability of salbutamol in both e-liquids and in the emitted vapour from ENDS.

Table 1
Summary of the aerodynamic particle size distribution obtained by vaporizing formulations at different wattages.

Power output of the battery (W)	MMAD of Salbutamol (µm)	Delivery of Salbutamol (µg/puff)	Fine Particle Fraction (%)
20	1.25 ± 0.01	79.51 ± 1.68	91.79 ± 1.58
30	1.22 ± 0.04	237.38 ± 25.17	93.61 ± 2.42
40	1.41 ± 0.039	245.34 ± 9.42	83.49 ± 2.52

4. Conclusion

This research has examined the potential use of the technology currently employed in ENDS as aerosolization devices for drug delivery via inhalation. Driven by a booming market, technological advances have resulted in a large variety of available devices; however, the literature suggests only few works explored the opportunity for technology transfer to deliver medicines. Modern ENDS devices can be easily adapted to patients' needs, to offer more tailored treatments, which can in turn improve patience adherence. The results in this study showed

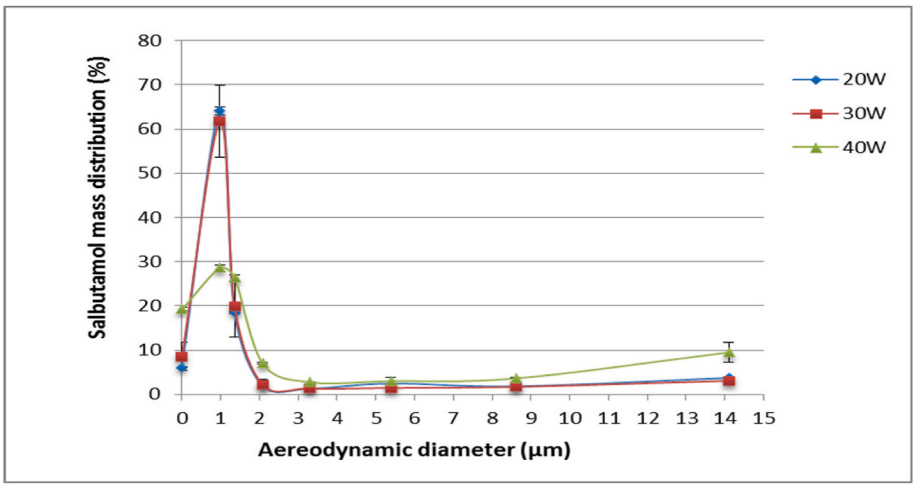

Fig. 3. Plot of the mass distribution % per dose of salbutamol against the aerodynamic diameter of the aerosol.

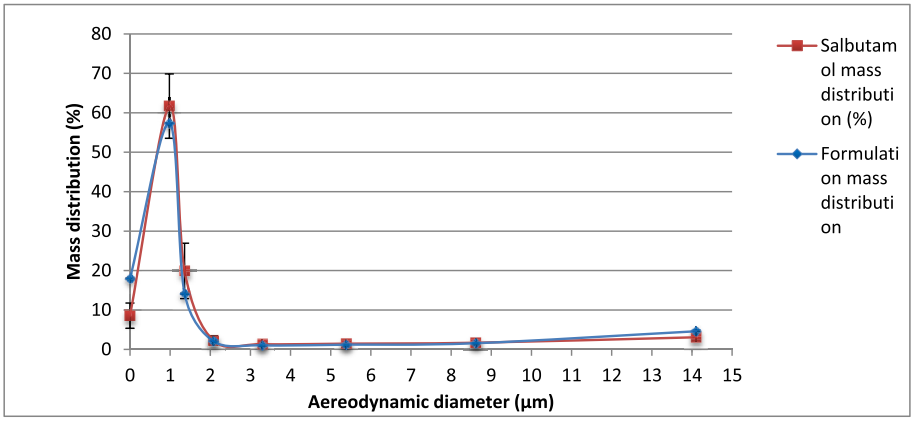

Fig. 4. The percentage mass distribution of salbutamol and formulation mass distribution against the aerodynamic diameter (30 W).

that this technology can be successfully used for pulmonary drug delivery for drugs that have a prescribed dose in the range of the micrograms such as salbutamol. This study finds that these devices are capable of delivering consistent levels of active ingredients when operating at optimal settings.

Declaration

All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

F. Buonocore: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **S. Barton:** Writing – review & editing, Validation. **S. Nabhani-Gebara:** Writing – review & editing. **G. Calabrese:** Conceptualization, Writing – review & editing, Supervision.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2023.104206.

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