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Assessment of new-generation high-power electronic nicotine delivery system as thermal aerosol generation device for inhaled bronchodilators

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ABSTRACT

Purpose: A need remains for alternative devices for aerosol drug delivery that are low cost, convenient and easy to use for the patient, but also capable of producing small-sized aerosol particles. This study investigated the potential of recent high power electronic nicotine delivery systems (ENDS) as aerosol generation devices for inhaled bronchodilators.
Methods: The particle size distribution was measured using a cascade impactor. The delivery of terbutaline sulfate, a current bronchodilator used for asthma or COPD therapy by inhalation, was studied. This drug was quantified by liquid chromatography coupled with tandem mass spectrometry.
Results: The particle size distribution in terms of mass frequency (in two ways, gravimetrically and quantitatively through drug assay on each stage) and the terbutaline sulfate concentration in the aerosol were elucidated. The mass median aerodynamic diameter (MMAD) and the drug delivery rose when the power level increased, to reach 5.6 ± 0.4 μg/puff with a MMAD of 0.78 ± 0.03 μm at 25 W.
Conclusion: New generation high-power ENDS are very efficient to generate carrier-droplets in the submicron range containing drug molecules with a constant drug concentration whatever the size-fractions. ENDS appear to be highly patient-adaptive.

1. Introduction

Drugs can be delivered to the human body through a variety of routes such as oral intake, parenteral administration or inhalation. The pulmonary route has proven to be effective in local and systemic delivery of miscellaneous medications to treat pulmonary but also non-pulmonary diseases. A pulmonary drug administration requires a successful interaction between the pharmaceutical formulation, the patient and the aerosol device. In the last decade, various innovations have been devoted to develop aerosol technologies generating smaller airborne particles (Albuquerque-Silva et al., 2014; Leclerc et al., 2014; Perinel et al., 2016) compared to usual devices used in clinical practice like nebulizers, pressurized metered-dose inhalers and dry-powder inhalers. These technological breakthroughs aim at improving the drug delivery via the deep lung for systemic administration (*e.g.* insulin delivery), or local administration in patients suffering from obstructive lung diseases like asthma, cystic fibrosis and chronic obstructive pulmonary disease (COPD) (Dolovich et al., 2005; Sims, 2011). However, it remains a need for an alternative means of generating aerosols for drug delivery that is low cost, convenient and easy to use for the patient, and capable of producing small-sized aerosol particles with aerodynamic diameter ranging from 500 nm to 1 μm.

Smokers of tobacco have implicitly found out that aerosols from thermal generation can reach the alveoli and are at least partially deposited upon inhalation. From a pharmaceutical perspective, of

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course smoking has never been considered as a viable drug delivery process because of uncontrolled production of numerous carcinogens, and also because of lack of consistent or desirable aerosol particle size. But new aerosol devices, electronic nicotine delivery systems (ENDS), have appeared on the market for a decade already. Currently, they are regulated as general consumer products and not as medical devices. The popularity of these devices has dramatically increased since approximately 2009. They have become a widespread smoking reduction or cessation tool ("E-cigarettes," n.d.; Fagerstrom et al., 2015). The ENDS market has grown from several thousand users in 2006 to several million worldwide in 2016.

Basically, ENDS are battery-powered personal vaporizers. The physic principle shared by all ENDS is an electrically-powered heating element which enables to vaporize a liquid solution so that aerosol is produced for the user to inhale. Therefore, ENDS are undoubtedly thermal aerosol generation devices. They exhibit a close working principle to that of some medical devices, already on the drug delivery technology market for various clinical applications like schizophrenia or bipolar disorder in adults, the delivery of anti-panic or anti-migraine agents (Ibrahim et al., 2015; Rabinowitz et al., 2006, 2004). The refill liquid used in ENDS contains nicotine, humectants (*i.e.* glycerol and propylene glycol) and other ingredients in small quantities (water, ethanol, flavorings, etc.). Since its emergence the ENDS industry continuously evolved. Nowadays new generation of high-power ENDS perfectly demonstrate that they can deliver very high levels of aerosol nicotine (Farsalinos et al., 2016, 2014). Their effectiveness in delivering a drug (*i.e.* nicotine) for systemic administration thanks to small-sized aerosol particles, their capacity in developing user-friendly and customer-oriented technology, make ENDS a potential promising aerosol device for clinical purposes.

In this frame, this study proposes to assess the potential of new-generation high-power ENDS as aerosol generation device for inhaled therapy. As a proof of concept in order to emphasize the main advantages and drawbacks of this class of devices, this work focuses on the delivery of an inhaled bronchodilator. To the best of authors' knowledge, this paper studies for the first time: the thermal stability of a drug after ENDS vaporization (*i.e.* to proceed at the vaporization of a bronchodilator without thermal degradation), the aerosol features (*i.e.* according to usual standards in the aerosol therapy field: mass median aerodynamic diameter (MMAD), cumulative and frequency mass distributions *vs.* aerodynamic diameters), the aerosol output (defined as the mass of fluid and the mass of drug contained in aerosol for different size fractions) using recent ENDS technology.

2. Materials and methods

2.1. Materials

A recent high-power ENDS was used (purchased in March 2016 from a local store and online distributor). This ENDS model is made up of a variable lithium-ion battery (iStick TC40W, Eleaf) and an atomizer (GS Tank, Eleaf). Equipped with an internal 2600 mAh battery, the variable wattage can be adjusted up to 40 W (W) of vaping power. The variable wattage/voltage resistance range is 0.15–3.55 ohm. It corresponds to the working range of the battery device. The GS-Tank is a recently engineered atomizer. It presents a resistance of 0.15 ohm, a liquid capacity of 3 mL and requires maximum push power ranging up to 40 W. The amount of airflow can easily be adjusted by the control ring on the atomizer base. Prior to perform particle size assessments, batteries were fully charged, the maximum air inflow position was fixed, and the value of the electrical resistance was checked. Atomizers were changed regularly to avoid biases due to the use of degraded and/or dirty coil. In our study, all combinations of vaping parameters were carefully adjusted to avoid the dry puff phenomenon. The human control feedback of a regular vaper was used to be certain of the absence of unpleasant taste using the ENDS (which proves that the dry puff phenomenon occurs). For all experiments the power level of the battery was fixed at 12.5 W, 18 W or 25 W.

2.2. Refill liquid composition

The composition of the refill liquid used corresponded to a 80% PG + 20% VG base (noted 80 PG/20VG); PG referred to propylene glycol, and VG referred to vegetable glycerin. This formulation was home-made in the laboratory from commercial nicotine-free solutions (purchased in March 2016 from a local store, 100-VG and 100-PG base, A&L company, France). It is important to underline that both formulations of refill liquid used for this study were flavor-free. Although the nominal capacity of the tank-type atomizer is 3 mL, only 2.4 mL of the prepared solution was used to avoid potential overfilling.

The drug chosen for this study was a solution of terbutaline sulfate (5 mg/2 mL, Bricanyl®) usually employed to fill nebulizers for pulmonary administration (composition of the commercial product: water, terbutaline sulfate and excipients such as sodium chloride, sodium EDTA or E385, hydrochloric acid or E507). Terbutaline sulfate is a β2 adrenergic receptor agonist used as bronchodilator. Therapeutic indications of terbutaline sulfate are the treatment or prevention of bronchospasm (wheezing, chest tightness, trouble breathing) in patients with lung conditions such as asthma, bronchitis, COPD or emphysema. A dilution of 12.5% of the terbutaline sulfate solution with 87.5% of the 80 PG/20VG solution was carried out. Thus, a concentration of terbutaline sulfate equal to 0.3125 mg/mL was used to fill the tank-atomizer of the ENDS.

2.3. Particle size distribution: mass distribution and MMAD

Aerosol particle sizing was defined in terms of Mass Median Aerodynamic Diameter (MMAD). Aerodynamic particle size distribution was measured using a cascade impactor, where the aerosolized particles are impacted on different stages depending on their inertia in relation to their aerodynamic diameter. This device allows simultaneous measurements of the aerodynamic size and the mass of aerosol in the different size ranges. The DLPI set-up was used (Low-Pressure Impactor; Dekati Ltd, Finland) to quantify the aerosol output and the particle size distribution of aerosol generated by high-power ENDS. The DLPI allows the collection of nebulized particles from 7 nm to 10 μm into 12 size fractions and operated with an air flow of 10 L min^{-1}. An in-house interface was designed to introduce quickly and reproducibly a well-controlled volume and duration puff into the inlet of the impactor. This interface was composed of a 3L syringe (3 L spirometry calibration syringe, Hans-Rudolph, USA) connected to both the ENDS and the DLPI cascade impactor. Aerosol sampling was carried out considering 4-s puff with a flow rate of 500 mL/s and a dilution ratio of 1.5 (*i.e.* the aerosol was produced in the 3 L syringe applying an inhaling flow rate of 500 mL/s for 4 s to reach a volume of 2 L of aerosol diluted in 1 L of air). 6 syringes of 3 L (2 L of aerosol diluted with 1 L of air) were successively introduced to the impactor. All parameters were chosen from results performed during previous works (Pourchez et al., 2016; Prévôt et al., 2016). Particularly, high flow rate is needed when we introduce aerosol generated by ENDS to the DLPI cascade impactor. This flow rate is totally unrealistic (i.e. no human can apply such a high flow rate). However, previous studies (Pourchez et al., 2016; Prévôt et al., 2016) showed no significant impact on MMAD of this high flow rate (for a dilution ratio of 1.5) compared to highly realistic puffing