การศึกษาคุณสมบัติละอองฝอยของซัลบูทามอล ซัลเฟต โดยใช้อุปกรณ์พ่นรุ่นใหม่ที่อาศัยหลักการการสั่นของเมมเบรน
Aerosol Characterisation of Nebulised Salbutamol Sulfate Produced by A Recent Nebuliser with Modern Vibrating Membrane Technology

นิพนธ์ต้นฉบับ

Original Article

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2565;17(1):1-8.

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลของสารละลาย 0.9% โซเดียมคลอไรด์ (NaCl) ที่มีต่อประสิทธิภาพในการสร้างละอองฝอยด้วยเนบูไลเซอร์รุ่นใหม่ (PARI VELOX®) ที่อาศัยหลักการการสั่นของเมมเบรน และคุณสมบัติการกระจายขนาดของละอองฝอยซัลบูทามอล ซัลเฟต ด้วยเครื่อง Next Generation Impactor (NGI) ซึ่งจำลองระบบทางเดินหายใจ **วิธีการศึกษา:** ศึกษาความสัมพันธ์ระหว่างของเหลวที่ปริมาตรต่าง ๆ ที่ใส่ลงเนบูไลเซอร์กับระยะเวลาที่ใช้ในการพ่นจนไม่มีละอองยาหลงเหลือออกมา ตลอดจนมวลและร้อยละของละอองฝอยทั้งหมดที่ออกจาก PARI VELOX® nebuliser คำนวณจากความแตกต่างของน้ำหนักเนบูไลเซอร์กับของเหลวก่อนและหลังพ่น โดยทดสอบกับน้ำและสารละลาย 0.9% NaCl จากนั้นพ่นสารละลายยาซัลบูทามอล ซัลเฟต ที่ผสมกับ 0.9% NaCl ปริมาตร 2.5 มิลลิลิตร ด้วย PARI VELOX® nebuliser ผ่านเครื่อง NGI ที่ความเร็วลม 15 ลิตรต่อนาที นาน 2 นาที 30 วินาที แล้วเก็บตัวอย่างยาที่กระจายตามส่วนต่าง ๆ ของ NGI เพื่อประเมินคุณสมบัติและการกระจายขนาดของละอองฝอยด้วยเครื่องโครมาโทกราฟฟีของเหลวสมรรถนะสูง **ผลการศึกษา:** สารละลายที่มีเฮไลด์ไอออนช่วยเพิ่มมวลและร้อยละของละอองฝอยทั้งหมดที่ออกมาจากอุปกรณ์พ่นอย่างมีนัยสำคัญ (*P*-value < 0.05) เนื่องจากไอออนลดประจุของน้ำทำให้ของเหลวเกาะติดพื้นผิวอุปกรณ์พ่นลดลง ปริมาณละอองฝอยมากขึ้น เนบูไลเซอร์รุ่นใหม่สามารถผลิตละอองฝอยของซัลบูทามอล ซัลเฟตที่เหมาะต่อการนำส่งไปปอด จากค่ากลางขนาดเส้นผ่านศูนย์กลางของละอองยา (3.95 ไมครอน) และร้อยละ 44 ของตัวยาที่มีขนาดเล็กกว่า 5 ไมครอน **สรุป:** แฟรี วีล็อค เนบูไลเซอร์ เป็นอุปกรณ์พ่นที่สามารถผลิตละอองฝอยยาซัลบูทามอล ซัลเฟตที่ผสมกับ 0.9% NaCl โดยละอองกระจายตามส่วนต่าง ๆ ของทางเดินหายใจเหมาะต่อการนำส่งไปยังปอด เนบูไลเซอร์ดังกล่าวอาจเป็นประโยชน์สำหรับนำส่งสูตรตำรับอื่น ๆ ที่พัฒนาในรูปแบบละอองฝอยได้

คำสำคัญ: ไวเบรติ้ง เมช, เนบูไลเซอร์, เน็คเจอเนเรชัน อิมแพ็คเตอร์, ร้อยละของตัวยาที่มีขนาดเล็กกว่า 5 ไมครอน, ซัลบูทามอล ซัลเฟต

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Abstract

Objective: To study effects of 0.9 % sodium chloride solution (NaCl) on the performance of a PARI VELOX® vibrating-mesh nebuliser (total mass output and output efficiency of nebulised fluids) compared to the ion-free water, and to determine aerodynamic properties of nebulised salbutamol sulfate using the Next Generation Impactor (NGI) to simulate respiratory tract. **Method:** Certain volumes of fluid filled in the PARI VELOX® nebuliser was nebulised to dryness. Dryness time, total mass output, and output efficiency were recorded. To determine the properties of nebulised salbutamol sulfate, the NGI was operated at 15 L/min with 2.5 mL of salbutamol sulfate solution with 0.9% NaCl. After 2 min 30 sec of nebulisation, the samples were recovered and assayed by a high performance liquid chromatography (HPLC) analysis for aerosolization key parameters. **Results:** The aerosol mass output and output efficiency were significantly higher when halide ion was included (*P*-value < 0.05). This may be because halide suppresses the electrostatic charge in water, resulting in less liquid adherence to the surfaces of mesh membrane and more droplets. This new nebuliser generated aerosols of salbutamol sulfate with 0.9% NaCl with desired pulmonary delivery characteristics such as the mass median aerodynamic diameter of 3.95 µm and high fine particle fraction (44% particles with < 5-µm diameter). **Conclusion:** The properties of nebulised salbutamol sulfate with the addition of 0.9% NaCl emitted from PARI VELOX® vibrating-mesh nebulisers are desirable for pulmonary delivery in terms of aerodynamic particle size distribution. The performance of this device may be proposed as particularly suitable nebuliser for the delivery of various novel formulations.

Keywords: vibrating-mesh nebuliser, Next Generation Impactor (NGI), fine particle fraction (FPF), salbutamol sulfate

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Introduction

Asthma with acute exacerbation has remained a globally serious disease affecting both children and adults, with high morbidity.[1,2] Salbutamol sulfate is a short acting β_2-adrenoreceptor agonist (SABA) usually used for acute asthma attack, Chronic Obstructive Pulmonary Disease (COPD) and other conditions associated with reversible airways obstruction. This molecule binds to β_2-receptor in the lungs and causes relaxation of smooth muscles around the respiratory airways, i.e., bronchodilation, which makes it easier to breathe.[3,4] As salbutamol sulfate relieves the

symptoms of asthma and COPD i.e. coughing, wheezing and breathlessness, this molecule has been therefore recommended as the first choice of drug for asthma according to the guidelines of Global Initiative for Asthma (GINA) and been one of the most common prescribed medicines for several decades.[1]

Nebulised drug delivery has advantages of delivering relatively larger doses/volumes of liquid formulations with less additional procedures as compared to dry powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs).[5,6] The drug is available for inhalation into the lungs by conversion of the drug solutions or suspensions into aerosol droplets. Nebulisers require little to no coordination of breathing and actuation during normal tidal breathing through a mouthpiece or facemask, and hence are widely used for children, elderly and patients who may have trouble using inhalers.[1,5,7] 10 to 20% of the dose can reach the lower respiratory tracts when given by nebulisation.[8] The remainder is retained in the drug delivery system or is swallowed and absorbed from the gut.[9]

Currently, salbutamol nebuliser liquid is available in the market as salbutamol sulfate 2.5 mg/2.5 mL and 5 mg/2.5 mL nebuliser liquid single dose unit. Doses of drug for adults, elderly and children are in the range of 2.5 - 5mg up to four times daily.[10,11] Nebuliser solutions of salbutamol are clear, colourless to pale yellow. They generally would contain other excipients such as sodium chloride (NaCl) as isotonicity agent, and sulfuric acid for pH adjustment.[12,13] The excipients do not affect the therapeutic effect of salbutamol. Salbutamol sulfate solution should be administered by an appropriate nebuliser.

Nebulisers are divided into three main categories including air-jet, ultrasonic and vibrating-mesh. Ultrasonic nebulisers use a piezoelectric crystal pulsation at high frequency to provide energy necessary to atomise liquids. The vibrations cause a wave to be created in the chamber resulting in aerosol formation. This nebuliser may use a fan to blow the respirable droplets out of the device or the patient may need to inhale to allow the droplets to leave the device.[14] They generate heat during aerosol generation; therefore they are not suitable for delivering heat-labile products or delicated formulations such as liposomes, nucleic acids or proteins.[15,16] The air-jet nebulisers have been previously reported to be the most appropriate device for delivering aqueous aerosols. [17] Air-jet devices use a compressed air supply to atomise liquid into a fine mist. The high velocity gas is passed through a narrow aperture. Once the gas emerges in an area of negative pressure, the Bernoulli effect is responsible for drawing the liquid up through a feed tube from the reservoir of fluid. Surface tension causes the liquid to collapse into aerosolised droplets. A portion of the resultant aerosol directly leaves the nebuliser, the remaining droplets, which are large and non-respirable are recycled in the reservoir fluid.[18] However, the air compressors are usually noisy, bulky and require an electricity supply to work, making jet nebulisers less portable compared to the ultrasonic and vibrating-mesh nebulisers.[19] Nebulisers with vibrating mesh technology have been developed to overcome some drawbacks of air-jet and ultrasonic devices due to the most advanced design. These devices are silent and are operated by batteries and hence are more portable compared to air-jet and ultrasonic nebulisers. Based on their designs, these devices are divided into two modes, which was active vibrating-mesh nebulisers, e.g., Aeroneb®, eFlow®, Micro-based technology (MBTC) and passive machines, e.g., Omron®.[20,21] However, both modes of action have the same mechanism of aerosol generation. Generally, the aerosol is generated by passing through a vibrating-mesh or plate with multiple apertures. The aerosol created has a high FPF, it delivers fluid rapidly with small residual volumes, giving an increased output efficiency compared to air-jet and ultrasonic nebulisers. Vibrating-mesh nebulisers also have been suggested for the delivery of various pharmaceutical products, e.g., liposomes, nucleic acids, suspensions and niosomes.[15,22,23]

Currently, PariGmbH launched the Velox® mesh nebuliser in 2015, based on the proven eFlow technology platform with the intention of improving convenience and appeal to the user.[22] It consists of two main parts such as a vibrating element and a mesh plate containing 4000 electroformed dome-shaped apertures. The energy of vibration comes from a vibrating element that reduces and expands on application of an electric current and subsequently transports the vibrations to the micro-perforated plate, causing the aerosol production.[20,21] For this specific model, it differs from other commercial brands in terms of shape of the mesh, main metal used in its construction (stainless steel), the mode of vibration (micropump effect) as well as aerosol direction (vertically sprayed into aerosol chamber). These factors can widely vary the performance of the mesh devices between commercial brands.[22] Also, 0.5 – 1 mL of drug solutions/suspensions can be loaded in this vibrating-mesh reservoir as compared with 2 – 5 mL required for a jet nebuliser, reflecting significant cost

savings for the expensive pharmaceutical products.[22] Due to improvements in administration time, dose delivery and device portability of mesh nebuliser with micro-perforated vibrating membrane technology, this recent device considerably enhances patient adherence and tolerability throughout the treatment period.[22,24]

In terms of characterising nebulised products, the cascade impactor, e.g., the Next Generation Impactor (NGI) is the gold-standard apparatus as it can differentiate the particle size measurement of the active pharmaceutical ingredients (API) from other components in the sample resulted from the chemical analysis, i.e., HPLC assay.[14,25] Orally inhaled and nasal products (OINPs) including nebulisers, require measurement of their aerodynamic particle size distribution (APSD) at various stages throughout their development and manufacture. The APSD of an aerosol cloud express where the particles or droplets in that cloud are likely to be deposited within the airways following inhalation. It hence determines the percentage of the total emitted dose that actually gets into the peripheral lung during inhalation. It is therefore therapeutically effective to the user.[26,27]

The Next Generation Impactor (NGI) was designed by the pharmaceutical industry to meet all pharmacopoeia standards specifically for OINPs testing. It consists of three predominant parts. The eight collecting cups gather samples for analysis. The bottom frame supports the plates. The lid contains the inter-stage passageways and a handle clamping system. Air-flow passes through all the stages of NGI in a saw tooth pattern as the jet diameter gets progressively smaller.[28] It separates a formulation into various fractions on the basis of inertial impaction, which is a function of aerodynamic diameter.[29] Larger and/or dense particles deposit higher in the impactor whereas smaller and/or less dense particles deposit lower in the impactor. As recommended in the European Pharmacopeia, the NGI is operated at the flow rate of 15L/min for nebulisers. Deposited drug particles would be recovered by dissolving in a suitable solvent or water and are analysed using validated analytical method to quantify the amount of drug present on each stage of the impactor and any remaining on the nebuliser reservoir. From the data analysis, the fine particle dose (FPD), fine particle fraction (FPF), emitted dose (ED), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the emitted dose, which are considered as key parameters of aerosolisation, can be determined.

The physicochemical properties of nebulised fluids including surface tension, viscosity and ion concentrations largely affect the properties of aerosol droplets particularly vibrating-mesh devices.[16] Previous studies have demonstrated the comparability of formulations with various halides and electrolytes, i.e., NaCl, NaBr, NaI, NaF, mannitol and glycerol delivered by different designs of mesh devices.[15,16,24] However, the aerosol properties of nebulised formulations with the inclusion of electrolyte produced by this modern vibrating membrane technology have received very little attention. NaCl was chosen in this study as preparation of salbutamol sulfate solution is commonly diluted with normal saline before nebulisation; for example, Ventolin®.[12] Therefore, the aims of this research were to study the effect of the inclusion of 0.9% sodium chloride solution (NaCl) on the performance of a PARI VELOX® vibrating-mesh nebuliser in terms of total mass output and output efficiency of nebulised fluids as compared to the ion-free water, and further determine the aerodynamic properties of nebulised salbutamol sulfate characterised by the Next Generation Impactor (NGI).

Methods

Materials

Salbutamol sulfate (Micro Technologies, UK) was used as a model hydrophilic drug. Sodium chloride (NaCl) was obtained from Sigma-Aldrich, Pool, UK. The following reagents and solvents were obtained from Sigma-Aldrich (Pool, UK): acetronitrile (99.9%, gradient grade for HPLC), HPLC grade water and trifluoroacetic acid (TFA, > 99.0%) were used for the HPLC analysis.

A PARI VELOX® vibrating-mesh nebuliser (PARI Medical Ltd, Byfleet, UK) was used to produce the aerosol of salbutamol sulfate (Micro Technologies, UK), and the properties of nebulised salbutamol sulfate were characterised by the Next Generation Impactor (NGI) (Copley Scientific, UK).

Determination of time taken to nebulise water to dryness and aerosol mass output

This study involved weight and dryness time tests which were carried out with water (HPLC grade, UK). This was done to determine the nebulisation time to dryness using diffrent volumes; 2 mL, 2.5 mL, 4 mL and 6 mL. The test was repeated with sodium chloride solution (NaCl, Sigma Aldrich, UK) 0.9% w/v to observe any difference in total mass output (g) and

output efficiency (%) as research papers have shown that halides may increase mesh nebuliser output efficiency.[15,23]

The European Pharmacopeia recommends that the vacuum pump (Copley instruments, UK) is switched on 10 s before the nebuliser and switched off 5 s after the nebuliser is operated.[30] Time taken to nebulise to "dryness" was determined after complete cessation of aerosolization.[31] For mass output, the weight of the nebuliser was measured before and after nebulisation[31] and calculated through the weight difference using the following equations:

$$\text{Total mass output (g)} = \text{Weight difference of nebuliser before and after nebulisation}$$

$$\text{Output efficiency (\%)} = \frac{\text{Weight difference of nebuliser before and after nebulisation}}{\text{Weight of fluid placed into the nebuliser reservoir}} \times 100\%$$

Development of high performance liquid chromatography (HPLC) method for quantification of salbutamol sulfate

The HPLC method was developed by adapting existing approaches.[32-34] HPLC system with UV/Vis detector (Agilent 1100 Series, USA) at the wavelength of 276 nm was used to determine the amount of salbutamol sulfate deposited on each stage of the impactor and any remaining on the vibrating-mesh membrane. The phenyl column was used as the stationary phase, with isocratic elution 80:20 (by volume) of 0.1% v/v trifluoroacetic acid (TFA) in HPLC grade water and 100% v/v acetonitrile (ACN). The mobile phase was degassed before pumping through the column at 1 mL/min. Each run was set for 6 min at 30 °C with injection volume of 10 µL.

The HPLC method was validated for analysis of salbutamol sulfate according to the ICH Q2 guideline.[35] The limit of quantification (LOQ) and limit of detection (LOD) were derived from calibration curve of salbutamol sulfate for HPLC analysis plotted using serial concentrations of 100, 50, 25, 12.5, 6.25 and 3.125 µg/mL.

Aerodynamic particle size characterisation using the Next Generation Impactor (NGI)

The NGI (Copley Scientific, UK) was set up according to the methods described in the European Pharmacopoeia [26, 30]. Collection cups were positioned into the cup tray that holds the cups at the bottom of the NGI. An internal filter holder with 7 mm diameter glass microfibre filter (Whatman®, UK) fitted was placed in the cup below the Micro-Orifice Collector (MOC) to collect any extra-fine particles as shown in Figure 1A.[28,36,37] As demonstrated in Figure 1B, a standard NGI induction port was used to mimic the throat and a mouthpiece adaptor was used to connect the nebuliser to the induction port. NGI was connected to a vacuum pump (Copley Scientific, UK) and the air-flow rate through the NGI was monitored using a flow meter (Copley Scientific, UK).

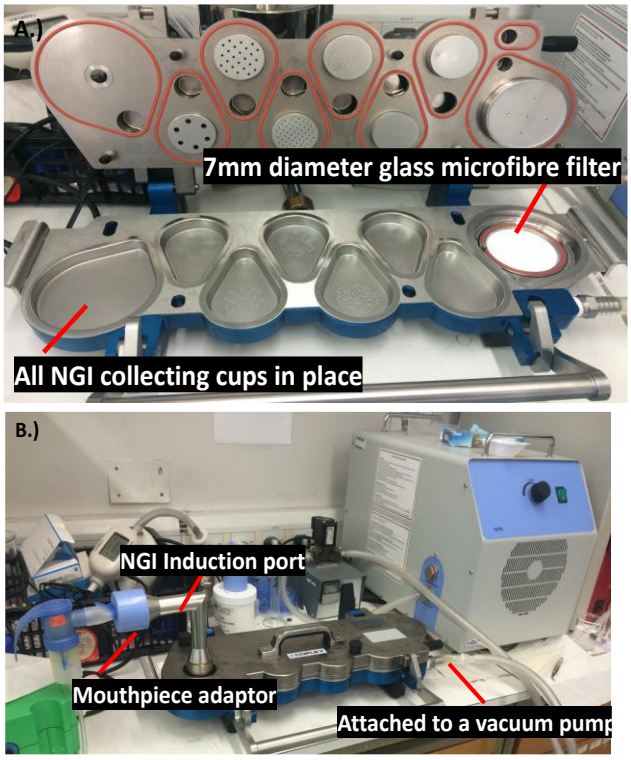

Figure 1 Next Generation Impactor (NGI) (A) the interior structure of the NGI (B) the experimental setup.

The European Pharmacopoeia recommends that the NGI should be refrigerated at 5 °C for 90 min before nebulisation to reduce aerosol droplet evaporation due to heat from the impactor.[36-38] This could lead to reduction of droplet size, giving inaccuracies in the aerodynamic particle size assessment results [38]. Nebulisation should be started within 5 min of NGI removal from the fridge. The flow rate of the vacuum pump was set at 15 ± 5% L/min.[36,37,39]

To prepare nebuliser solution, 2.5 mL of a stock solution of salbutamol sulfate (2mg/mL) was diluted to a final volume of 5.0 mL with 0.9% w/v NaCl solution. Afterwards, 2.5 mL of the clear mixture (2.5 mg of salbutamol sulfate) was placed into the PARI VELOX® reservoir. The solution was then nebulised for 2 min 30 sec and directed into the NGI operated at 15 L/min. Triplicate measurements were taken. After 2.5-min nebulisation, salbutamol sulfate was recovered by rinsing with HPLC grade water starting from the nebuliser reservoir, induction port, all collecting cups and ending with the back-up

filter placed after the final stage of the NGI. The quantification of salbutamol sulfate was determined by validated HPLC analysis and the aerosolisation parameters in this study were calculated as directed below.[40]:

$$\text{Mass balance (\%)} = \frac{\text{Mass of drug collected from nebuliser to filter}}{\text{Mass of drug initially placed into the nebuliser}} \times 100$$

$$\text{Emitted dose (\% ED)} = \frac{\text{Mass of drug collected from induction port to filter}}{\text{Mass of drug collected from nebuliser to filter}} \times 100$$

For the distribution characteristics, Fine Particle Dose (FPD) was defined as drug mass less than 5 µm determined from the plot of cumulative mass of active substance versus cut-off diameter; Fine Particle Fraction (FPF) as percentage cumulative fraction of drug less than 5 µm from the plot of cumulative fraction of active substance versus cut-off diameter; Mass Median Aerodynamic Diameter (MMAD) as the diameter in which 50% of the aerosol droplets are larger or smaller than the stated size, derived from the plotted graph of log cumulative fraction of salbutamol sulfate versus stage cut-off diameter; and Geometric Standard Deviation (GSD) as the variability of the aerosol particle size distribution.

Statistical analysis

The results of mass output (g) and output efficiency (%) of nebulised ion-free water and 0.9% NaCl solution produced by a PARI VELOX® vibrating-mesh nebuliser were presented as the mean and standard deviation (SD) using a Student's t-test. A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistic 22 Software.

Results and Discussions

Determination of salbutamol sulfate

The concentration of salbutamol sulfate was highly proportional to the area under the curve (AUC) with R^2 of 0.9999. Based on the ICH Q2 guidelines, the limit of quantitation (LOQ) and the limit of detection (LOD) were 3.53 µg/mL and 1.17 µg/mL respectively.

Determination of dryness time

The mesh nebuliser was tested with a range of volumes of water to observe the relationship between the fill volume and the time taken to nebulise to dryness. A longer time for aerosolisation to dryness was required when increasing fill volumes of HPLC grade water from 2 mL to 6 mL in the PARI VELOX® mesh nebuliser reservoir (Figure 2). From previous studies, it took more than double the time compared to this study (2 min 30 sec) to nebulise to dryness when using a fill volume of 2.5 mL with a vibrating-mesh nebuliser.[34,41] This reflects the higher performance of this modern membrane technology in terms of shorter nebulisation time to dryness as compared with other models of vibrating-mesh devices.

Table 1 shows very low mass output and the percentage aerosolised since the aerosol droplets deposited on the base of the device housing, causing the minimal output of droplets. This was consequently done to determine the total mass output and output efficiency by using the impactor alongside the nebuliser.[24]

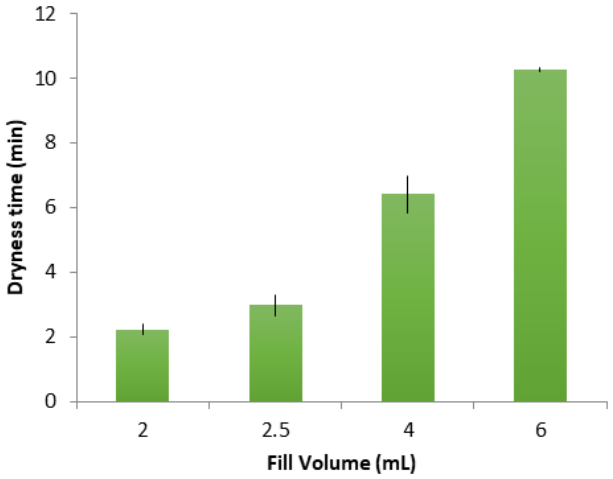

Figure 2 Effect of fill volumes of water on time to nebulise to dryness for the vibrating-mesh nebuliser (n = 3, mean ± S.D.).

Table 1 Mass output determined for a range of fill volumes of water (n = 3, mean ± S.D.).

Volume (mL)	Mass output during nebulisation (g)
2	0.027 ± 0.006
2.5	0.030 ± 0.017
4	0.157 ± 0.124
6	0.730 ± 0.052

Aerosol output with HPLC grade water and NaCl 0.9% w/v solution

To observe any differences in mass output and output efficiency, two separate tests were carried out. The first one involved using HPLC grade water and the second used a halide solution (NaCl 0.9%). Fill volume of 2.5 mL was chosen as it represents the available marketed product (Ventolin®). Throughout this study, these tests were done with the Next Generation Impactor (NGI), using 2.5 mL of each solution and

nebulising for 2 min 30 sec as confirmed previously (Determination of dryness time).

The study with water demonstrated a comparatively smaller percentage of mass output compared to the NaCl (0.9%) solution (*P*-value < 0.01) (Table 2). Previously, the influence of characteristic properties of nebulised fluid, e.g., viscosity, surface tension, and ion concentrations on the effectiveness of aerosol delivery using vibrating-mesh devices has been evaluated.[15,31,42] Aerosol droplet size is inversely proportional to the viscosity of nebulised formulation, whilst a direct relationship between surface tension and aerosol droplet diameter has been observed.[16,42] Changes in physicochemical properties of nebulised fluid noticeably affect aerodynamic parameters of those collected from the two-stage impinger, e.g., aerosol output and FPF.[31] In this study, the presence of NaCl may increase the fluid viscosity, causing smaller aerosol size and a consequent increase in FPF and output efficiency (%) as compared to ion-free water. Moreover, this may be because the halide suppresses the electrostatic charge in water, which in turn increases conductivity and allows this charge to flow back into the liquid before being aerosolised. The droplets produced are of a lower charge so there is less liquid adherence to the inner surfaces and mesh holes which ultimately increases the amount of water being converted into droplets.[15,24] When considering the surface tension, it has been previously shown that the addition of salbutamol sulfate or NaCl had no significant effect on the measurement of surface tension compared with ion-free water.[24,31] All observations indicated that changes in viscosity as a result of NaCl inclusion had a significant impact on aerodynamic properties of nebulised fluid. Nebulisation of 2.5 mL of salbutamol sulfate in the presence of normal saline for 2 min 30 sec was accordingly considered appropriate for the further assessment of aerosol properties using the Next Generation Impactor (NGI).

Table 2 Mass output from nebuliser attached to the Next Generation Impactor for 2.5 mL water and 2.5 mL of 0.9% NaCl solution (n = 3, mean ± S.D.).

	Water	0.9% NaCl solution
Mass output (g)	0.60 ± 0.16	0.96 ± 0.14
Output efficiency (%)	24.00 ± 6.40	38.40 ± 5.60

Assessment of aerosol properties using the NGI

Mass balance of all runs was within European Pharmacopoeia acceptance limit of 75 - 125%.[43] However, mass balance is difficult to obtain 100% due to technical errors during transferring and rinsing for HPLC analysis. Data of aerosol parameters is summarised in Table 3. Looking at the emitted dose (ED), the ED determined from the mass obtained with HPLC analysis, against the ED calculated from weight differences had shown no significant difference (*P*-value > 0.05). The ED obtained from the mass collected via HPLC method (drug output), 39.24 ± 9.49% is slightly higher than that determined by weight difference (aerosol mass output), 38.40 ± 5.60% (*P*-value > 0.05). This indicates no effect of water evaporation during aerosol generation, unlike jet-nebulisation. To be more specific, a drop in temperature can be observed for droplets emitted from air- jet nebuliser whereas the temperature is constant throughout the period of nebulisation for vibrating-mesh device. Differences in temperature between inlet and outlet aerosols lead to the water loss. This effect results in higher concentration of drug in the air-jet nebuliser reservoir as compared to the initial concentration.[34] Therefore, the aerosol mass output is generally higher than drug output in the case of air-jet device.

Table 3 Aerosol parameters for the nebulised salbutamol sulfate with the inclusion of 0.9% NaCl solution produced by a PARI VELOX® vibrating-mesh device and characterised by the Next Generation Impactor (n = 3).

Aerosolisation parameters	Mean ± S.D.
Mass balance (%)	94.90 ± 1.05
ED (%)	39.24 ± 9.49
FPD (mg)	0.41 ± 0.09
FPF (%)	44.14 ± 0.01
MMAD (μm)	3.95 ± 0.04
GSD	1.64 ± 0.01

The optimum particle size required for drug deposition in the lungs is in the range of 2 - 6 μm. The MMAD for the NGI is approximately 3.95 μm, allowing for good deposition in the lungs.[31] The GSD indicated polydispersed aerosols (GSD > 1.2).[44] Based on the plotted graph of cumulative mass of salbutamol sulfate deposited versus cut-off diameter of the respective stage of the NGI derived from interpolation of the graph, the cumulative fraction of salbutamol sulfate under 5 μm (fine particle fraction) was approximately 44% as seen in

Figure 3. This value was slightly higher than other previous reports using different models of vibrating-mesh devices for producing the aerosols of salbutamol sulfate.[31,34,41]

The data suggest the PARI VELOX® vibrating-mesh nebulisers have great utility as a promising device for the delivery of salbutamol sulfate with the addition of 0.9% NaCl, and this thus could initially push the growth of asthma and other therapeutic effects related to respiratory diseases market.

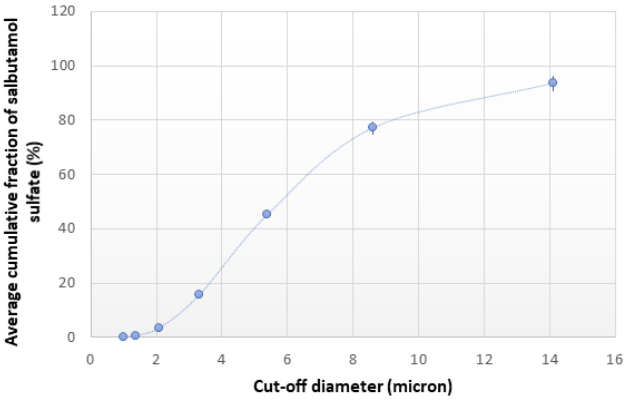

Figure 3 Cumulative fraction of salbutamol sulfate deposited versus cut-off diameter of the respective stage of the NGI (n = 3, mean ± S.D.).

Conclusion

To sum up, the properties of nebulised salbutamol sulfate with the addition of 0.9% sodium chloride solution produced from PARI VELOX® vibrating-mesh nebulisers are desirable for pulmonary delivery in terms of aerodynamic particle size distribution (APSD) as expected. Additionally, the performance of this device may be proposed as particularly suitable nebuliser for the delivery of various novel formulation approaches. Other future research could evaluate the effect of changes in formulation, i.e., change in viscosity, surface tension, and types of ion and ion concentrations of nebuliser liquids, on the ability of the performance of PARI VELOX® vibrating nebuliser. Comparison of the performance between this recent device and other mesh nebulisers requires further investigation. The study could also test for level of variations from multiple operators to check for sensitivity.

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Declaration of interest

The author does not have any competing interests with regards to the use of this nebuliser in this work.

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