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Original Research Article

Comparison between air-jet and vibrating-mesh nebulizers in the delivery of nebulized salbutamol sulfate determined using an abbreviated impactor

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Abstract

Purpose: *To investigate the aerodynamic properties of nebulized droplets from nebulizers for delivery of salbutamol sulfate.*
Methods: *Drug deposits were collected from fast screening impactor (FSI). Parameters of aerosolization such as dryness time and salbutamol sulfate characteristics were determined using chilled FSI at a flow velocity of 15 L/min, with salbutamol sulfate solution nebulized to dryness. An optimized HPLC procedure was used to analyze the deposited salbutamol sulfate across the FSI. Parameters comprising mass balance, FPD and FPF were determined.*
Results: *Statistical analysis showed that the performance of vibrating-mesh was more efficient than that of air-jet device, as depicted in significantly higher values FPF of aerosolized droplets (60 and 40 %, respectively; $p < 0.05$).*
Conclusion: *The performance of aerosol generation using vibrating-mesh was more superior to that of air-jet nebulizer. However, there is need for further investigations on various physicochemical properties of nebulizer fluid as well as improvement in percentage FPF.*

Keywords: *Air-jet nebulizer, Fast screening impactor (FSI), Salbutamol sulfate, Vibrating-mesh nebulizer*

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INTRODUCTION

Cascade impactors are currently the gold standard for aerosol characterization of nebulizers [1,2]. There is need for measurement of aerodynamic particle size distribution of orally-inhaled products (such as nebulizers) at various stages throughout their development and manufacture, in order to evaluate their therapeutic effectiveness [2]. Orally-inhaled products should produce particle size less than 5 μm. This allows droplets to reach the periphery of the lungs, and all particles within this range constitute the fine particle fraction (FPF) [3,4].

Unfortunately, the application of cascade impactors is laborious and time-unfriendly. In an attempt to deal with these challenges, the abbreviated impactor measurements (AIM)

incorporating Fast-Screening Impactor (FSI) has attracted the interest of a number of researchers. Nebulizers work via administration of inhalation. They deliver relatively large volumes of drug solutions or suspensions, and can therefore provide substantial therapeutic doses, when compared to conventional inhalers such as pressurized metered-dose inhalers (pMDIs) and dry power inhalers (DPIs). During normal breathing pattern, the liquid solution or suspension is converted into aerosol droplets [3,4]. Air-jet nebulizer is more common than ultrasonic and vibrating-mesh nebulizers for atomization of compressed air into a fine mist. Mesh nebulizers are products of very advanced design. The aerosol is generated by passing liquids through a vibrating mesh or plate with multiple apertures. It contains a vibrational element which generates the aerosol via contraction and expansion [5].

In the present investigation, the performances of air-jet and vibrating-mesh nebulizers were compared using a simple solution of salbutamol sulfate, characterized by FSI.

EXPERIMENTAL

Materials

A PARI LC® Sprint nebulizer and a PARI VELOX® vibrating-mesh nebulizer (PARI Medical Ltd (Byfleet, UK) were used to produce aerosols from a 1 mg/mL solution of salbutamol sulfate (Micron Technologies, UK). The aerodynamic properties of nebulized salbutamol sulfate were determined using Fast Screening Impactor (FSI; Copley Scientific, UK). High-purity acetonitrile, HPLC-quality H_2O, and TFA (products of Sigma-Aldrich, Pool, UK) were used for HPLC analysis.

Quantification of salbutamol sulfate with HPLC

An adaptation of the conventional HPLC method was used for quantification of salbutamol sulfate [6,7]. The features of the optimized HPLC method used in the studies are shown in Table 1.

A calibration curve was made using serial dilution of salbutamol sulfate. This allowed for the use of area under the curve (AUC) from the HPLC peaks for calculation of drug concentrations. The calibration curve allowed for calculations of the limit of quantification (LOQ) and limit of detection (LOD) in accordance with the International Conference of Harmonisation guidelines [8]. The curve was plotted using salbutamol sulfate at concentrations of 3.125, 6.25, 12.5, 25, 50 and 100 µg/mL, in triplicate.

Table 1: Optimized parameters of the HPLC method used

Parameter	Details
HPLC column	Phenyl column (Agilent 15cm x 4.6mm x 5µm, USA)
Flow rate (mL/min)	1
Injection volume (µL)	10
Temperature (ºC)	30
Mobile phase	80:20 (v/v) ratio of 0.1 % TFA in HPLC water and 100 % acetonitrile
Wavelength (nm)	276
Retention time (min)	2-3 min

Time taken to nebulize to dryness

The nebulizers were tested using various volumes of water to determine the relationship between the fill volume and the time taken to nebulize to dryness.

In accordance with the European Pharmacopeia [9], the vacuum pump (Copley Instrument, UK) was switched on for 10 sec prior to nebulization. Then, the pump was switched off 5 sec after activation of the nebulizer. Nebulization time was determined as the time taken for total cessation of aerosol generation [10].

Aerodynamic particle size characterization using FSI

Fast Screening Impactor (FSI), a two-phase impactor, was used for the characterization of aerosols, with some modifications. The additional insert of the instrument which was calibrated at a flow velocity of 30 L/min for aerodynamic diameter of 5 µm, was adapted through alternate closing of 3 of the 6 outlets with a damp glass microfiber sieve, as shown in Figure 1 [11,12]. The aim of this modification was to retain the stage cut-off diameter of 5 µm at a flow velocity of 15 liters per min. This flow rate for nebulized products is recommended in the European Pharmacopoeia [9]. Indeed, studies have indicated that the flow rate of 15 L/min resulted in better approximation of the normal tidal breathing conditions of an adult during *in vivo* use of nebulizer, and it reduced solvent evaporations which usually affect the sizes of aerosol droplets [13]. A diameter of 5 µm was used for fine particle dose (FPD) and for the calculation of fine particle fraction (FPF) [14,15].

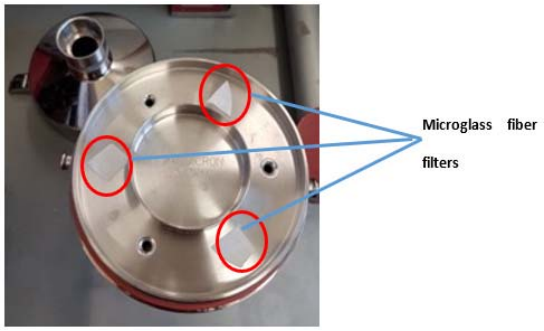

Figure 1: FSI size-fractionator setup using six-nozzle fine-cut insert

The impactor was chilled at 2 - 8 ºC for 90 min before use, to minimize aerosol droplet evaporation due to heat from the FSI, and it was run at 15 L/min in each experiment [16,17]. The effects of attachment of air-jet and vibrating-mesh nebulizer (to FSI) on aerosol properties (Figure 2) were also studied. The nebulizers were operated as indicated in the dryness time studies. Two volumes of the stock solution (2.5 and 4 mL) were pipetted into the vibrating-mesh and air-jet nebulizers, followed by nebulization for 2 min 30 sec and 10 min, respectively. After each nebulization, the amounts of drug deposited on various parts of the impactor were quantified by rinsing with HPLC water, and the rinsed drug solutions were collected in volumetric flasks and quantified with HPLC analysis.

Aerosolization parameters, including mass balance (MB), FPD and FPF were determined and reported as mean ± SD [12]. The aerodynamic properties were then calculated as indicated in Eqs 1 and 2.

$MB\ (\%) = (M_1/M_0)100$ …..... (1)

where M_1 = mass of drug from nebulizer to the filter and M_0 = mass of drug initially placed in nebulizer.

Fine particle dose (FPD) was defined as the amount/mass of drug deposited on the lower stage of the FSI, while fine particle fraction (FPF) was calculated as in Eq 2.

$FPF\ (\%) = (M_2/M_3)100$ …….... (2)

where M_2 = mass of drug from the filter, and M_3 = mass of drug from deposited drug on upper and lower stage of FSI.

Statistical analysis

All experiments were carried out in triplicates, and the results are expressed as mean ± standard deviation (SD). Data analyses were done using student's t-test and analysis of variance (ANOVA). Statistical significance of difference was assumed at $p < 0.05$.

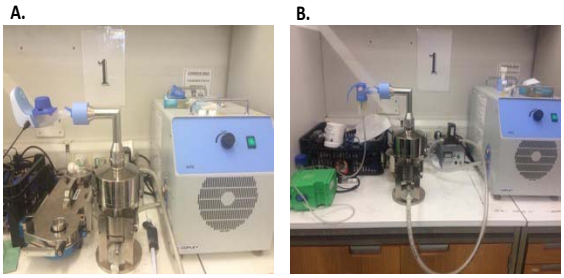

Figure 2: Nebulizers attached to FSI. (A) vibrating-mesh nebulizer; (B) air-jet nebulizer

RESULTS

Characteristics of salbutamol sulfate

Figure 3 shows the HPLC peak when salbutamol sulfate (1 mg/mL) was run through a C18 phenyl column. This resulted in an HPLC trace with a good symmetrical peak of retention time between 2 and 3 min. Thus, this method was used for further data collection.

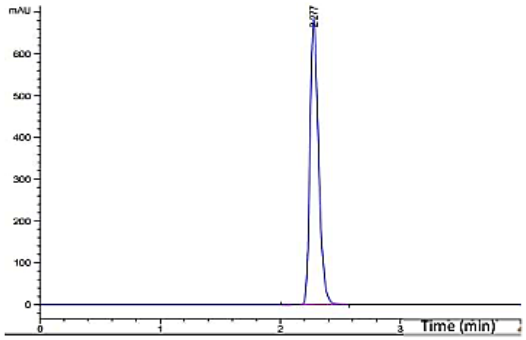

Figure 3: HPLC chromatogram of salbutamol sulfate

Using the calibration curve and the ICH Q2 guidelines [8], the limit of quantitation (LOQ) and the limit of detection (LOD) were determined, resulting in values of 3.533 and 1.166 µg/mL, respectively. These parameters were important to the study because they indicated the range of concentrations for accurate quantification of samples.

Time taken to nebulise to dryness

The experiment was carried out with a wide range of volumes, from the minimum to the maximum fill volume, using nebulizer solution commercially available as Ventolin® Nebulizer

Solution (2.5 mL) [18]. As shown in Figure 4A, increase in the volume of liquid resulted in increase in nebulization time. In a previous study, it took more than double the time (6.1 min), relative to the present study (2.5 min) to nebulize to dryness when using a fill volume of 2.5 mL with a vibrating-mesh nebulizer [19]. This indicated that this model of vibrating-mesh nebulizer was more efficient in generating aerosol, with shorter time for nebulization to dryness, when compared with different designs of mesh devices. For air-jet device (Figure 4B), it required a longer time for nebulization to dryness when fill volumes were increased from 2 to 8 mL in the Pari air-jet nebulizer reservoir. A duration shorter than 10 min is usually preferable for patient convenience. The nebulizer was tapped occasionally when the delivery of the aerosolized material was impeded. The average time taken to nebulize 4 mL of water, which was 10 min, was used for nebulization throughout the experiment.

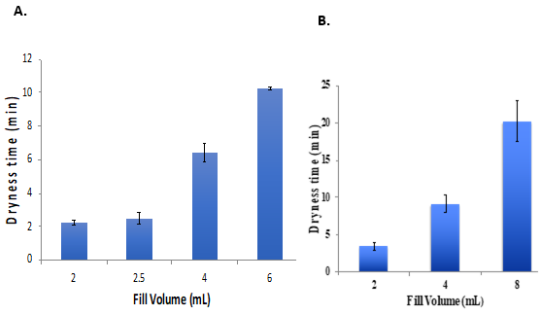

Figure 4: Dryness time for a range of water fill volumes delivered by vibrating-mesh nebulizer (A) and air-jet nebulizer (B)

Parameters of nebulized aerosols administered via the two nebulizers

Results from comparison of drug distributions in the FSI produced by the air-jet and vibrating-mesh nebulizers, are presented in Table 2. Mass balance values were consistent with the acceptable range stated in the European Pharmacopeia, i.e., 75 - 125 % [9]. The FPF generated from the vibrating-mesh device (60%) was significantly higher than that from the air-jet nebulizer (40 %) ($p < 0.05$). These data showed that stage 2 had a higher deposition. This was due to the effective ceiling diameter of 5 µm between the two phases. It was expected that stage 2 would have a larger mass deposition since it was the stage where fractions below 5 µm in diameter were collected (FPF). However, FPD was not compared between these two inhaler devices due to different loading doses mentioned above.

Table 2: Aerosol parameters for the nebulized aerosols determined using air-jet and vibrating-mesh nebulizers (n = 3, mean ± SD)

Nebulizer	FPD (mg)	FPF (%)
Vibrating-mesh	0.50 ± 0.09	57.00 ± 6.08
Air-jet	0.94 ± 0.18	43.0 ± 1.20

DISCUSSION

The retention time of HPLC analysis was shorter, when compared to other reported assays [20,21]. This was due to the interaction with TFA in the mobile phase. The increased polarity in the mobile phase increased the affinity of salbutamol sulfate, which in turn shortened the retention time due to faster elution. An increase in TFA:CAN ratio to 80:20 (v: v) resulted in a good symmetry HPLC peak with a late retention time between 2 and 3 min. Thus, this method was used for further data collection.

An experiment was done to determine the time taken to nebulize a wide range of HPLC grade water to dryness using the nebulizer which was subjected to occasional tapping whenever the aerosol production decreased. The average time taken to deliver 2.5 mL of HPLC grade water (2 min 30 sec) at a speed of 1 mL/min, and time taken to nebulize 4 mL of HPLC grade water (10 min) at a flow rate of 0.4 mL/min, were used for nebulization throughout the experiment. These results suggest that vibrating-mesh device was more efficient than the air-jet device in generating aerosol up to 2.5-fold higher output rate (mL/min).

The abbreviated impactor was used to compare air-jet and vibrating-mesh nebulizer with respect to aerodynamic characterization of aerosolized salbutamol sulfate. The results indicated that vibrating-mesh nebulizer was more appropriate for delivering salbutamol sulfate solution (1 mg/mL), based on the significantly higher % FPF. This implies that most of the aerosolized drug will be delivered to the alveolar regions of human respiratory tract, as expected.

It was previously demonstrated that FSI could be an alternative impactor for nebulizer characterization during product development and quality control processes [12]. Based on published report on the delivery of liposomes containing erlotinib and genistein, the quality of the air-jet nebulizer seems better than that of the vibrating-mesh device. This is possibly because the viscous formulation and inappropriate surface tension might affect the efficiency of output, especially in the case of the vibrating-mesh device. Moreover, aggregation or degradation of liposomes may block the mesh pore of the

membrane due to heat generation over the 10 min aerosolization period [11,22,23]. These two factors resulted in the lower output efficiency of this inhaler device. Consequently, a simple solution was used in this study for better understanding of the phenomenon.

The characteristics of liquid formulations influence the aerodynamic properties of nebulized aerosols. This may be due to the use of various nebulizer fluids with different physicochemical properties. Further studies are required to unravel this effect.

CONCLUSION

In terms of nebulizers, the performance of aerosol generation using vibrating-mesh was more efficient than that of air-jet device. The former produce higher percentage FPF of aerosolized solutions than the latter. However, FPD was not compared between the two methods of aerosol production. There is need for further investigations on improvement of percentage FPF as well as various physicochemical properties of nebulizer fluids. The levels of variations from various technicians also need to be checked for sensitivity.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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