



An *In Vitro* Aerosolization Efficiency Comparison of Generic and Branded Salbutamol Metered Dose Inhalers

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ABSTRACT

Background: Due to the high rate of pulmonary diseases, respiratory drug delivery systems have been attracted excessive attention for the past decades. Because of limitations and growing drug bill, physicians are encouraged to prescribe generically whenever possible. The purpose of this study was to evaluate whether there was any significant difference in aerosolization performance between a reference brand Salbutamol (A) Metered Dose Inhalers (MDIs) and two generic products (B and C).

Methods: The aerosolization performance of MDIs was evaluated by calculating aerosolization indexes including fine particle fraction (FPF), fine particle dose (FPD), geometric standard deviation (GSD) and mass median aerodynamic diameters (MMAD) by using the next generation impactor.

Results: Although aerosolization indexes of MDI A were superior than the Iranian brands, but the differences were not statistically significant.

Conclusion: These results verified that generic MDIs deliver similar quantities of Salbutamol to the reference brand and aerosolization performance parameters of generic Salbutamol MDIs did not differ significantly from the reference brand.

Introduction

Asthma is a common long term hypersensitivity and inflammatory disease and is described by reversible airflow obstruction, bronchospasm and other variable recurring symptoms.¹ Various approaches can be used as treatments of respiratory diseases like asthma, however, the pulmonary drug delivery route represents an appealing and encouraging way to localize drug delivery.^{2,3} The main advantages of the pulmonary administration in comparison with other drug delivery routes are related to the large alveolar surface area and extensive vascularization which is suitable for drug absorption.^{4,5} Salbutamol is one of a group of medicines called bronchodilators which helps to open up the airways and so relieve chest tightness and cough resulting more easily breathe. Salbutamol stimulates receptors in the lung called beta 2 receptors and causes the muscles in the airways to relax and makes it easier to breathe.⁶ Inhaling the medicine allows it to act directly in the lung where it is most needed and among the

pulmonary drug delivery systems, metered dose inhalers (MDIs) are undoubtedly the most widespread and popular used devices for pulmonary delivery.⁷ MDIs developed in 1956 and are the most widely used devices for aerosol therapy and used by over 70 million worldwide. An MDI consists of a canister holding suspension or solution containing drug and surfactants, propellant and lubricants. MDIs are easy to use, handy and relatively low-cost which designed for delivery of multiple drug doses in a sequence. The particles aerodynamic diameter should be lower than 5 μm to effective particle deposit in the lower airways. The size of delivered particles by MDIs is influenced by a range of factors, such as: inside pressure of the canister, propellant's physicochemical properties, type and concentration of drug, as well as design of valve and delivery outlet.^{8,9} Some physicians are reluctant to accept that generic salbutamol device is really as effective as the reference brand. To clarify this issue, a few studies have been carried out in different countries

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by universities to not only test the domestic products but also to encourage the physicians to choose more cost benefit way of treatment if the domestic products passed from their examinations.¹⁰⁻¹⁵

Anecdotally, there is no evidence to support that generic inhaled salbutamol is inferior to the branded product. Therefore, *in vitro* aerosolization efficiency analysis of domestic products are necessary to show that generic Salbutamol MDIs possess similar aerosolization efficiency to the reference brand ones.¹⁶ This study aimed to assess whether a commonly prescribed generic Salbutamol MDIs (B and C) are as similar as (A) as a reference brand in the case of aerosolization efficiency.

Materials and Methods

Materials

Salbutamol sulphate was provided from Zahravi Pharmaceutical Company (Tabriz, Iran). HPLC grade Methanol was obtained from Duksan Chemicals (Kyungkido, Korea). Tween[®] and Ethanol 80 were purchased from Merck Chemicals (Darmstadt, Germany) and JATA (Arak, Iran) Companies, respectively.

In vitro aerosolization assessment

The aerodynamic particle size distribution of three Salbutamol MDIs was studied according to the USP monograph (using USP apparatus 6) by next generation impactor (NGI) (Copley Scientific, Nottingham, UK).¹⁷ To connect the NGI device to MDI the induction port was employed. To confirm an efficient particle capture and inhibit inter-stage losses caused by particle bounce, the surface of each stage was coated with Tween[®] 80. For this aim, the NGI's collection cups were soaked into ethanolic solution of Tween[®] 80 (1 %) and placed under the hood until the complete ethanol evaporation. The impactor lid was closed with the sealed body and the handle was used to lock the impactor together. The induction port was linked to the first NGI's stage. The flow rate was calibrated by a flow meter (DFM 2000, Copley Scientific, Nottingham, UK) and fixed at 30 L/min. After checking of the assembly and ensuring of airtight, as well as shaking up and down for ten seconds, A, B and C MDIs had been placed in into the mouthpiece attached to the USP induction port. The vacuum pump (HCP5, Copley Scientific, Nottingham, UK) was turned on and let it to increase to the steady flow rate (30 L/min). Finally, the dose was released for two times with the five seconds interval and the pump was turn off after five seconds of the second actuation. After two doses firing into the apparatus, the throat and stages were washed with 15 mL of methanol: PBS pH= 4 (40: 60, v/v) solution, and the amount of Salbutamol was evaluated using our developed and validated HPLC method for six times and the results are shown as averages \pm standard deviations. Fine particle dose

(FPD), fine particle fraction (FPF), geometric standard deviation (GSD) and mass median aerodynamic diameter (MMAD) indexes were calculated using the Copley Inhaler Testing Data Analysis Software (CITDAS, version 3.10). The MMAD is expressed as the diameter at which 50 % of the particles (by mass) are larger and 50 % are smaller. Whereas the FPF and FPD are defined as the fraction and doses of drugs carried in particles with a diameter of $<5\mu\text{m}$.^{18,19}

High performance liquid chromatography (HPLC) analysis

The amount of Salbutamol was evaluated using a reversed-phase HPLC system (Knauer apparatus, Germany) involved of 1000 and 2600 tunable HPLC pump and absorbance detector models. Salbutamol was separated at room temperature by a C18 column (4.6 mm \times 150 mm, 10 μm , 125 A[°]) (Germany). The mobile phase was consisted of methanol and PBS pH=4 (40:60) and flow rate was set at 1 mL/min. The sample injection volume and detecting wavelength were set 20 μL and 254 nm, respectively. The retention time was about 6 min and the area under the curve of Salbutamol peak was computed by apparatus software (ChromGate Client/Server, version 3.1.7) (Responses were linear in the range of 1–20 $\mu\text{g/mL}$, $r^2=0.9982$).

Statistical analysis

Data are shown as a mean \pm standard deviation (SD). Statistical analysis was done using a one-way analysis of variance (ANOVA) using a Tukey-Kramer HSD test by SPSS software (version 13.0, Chicago, IL, USA). A P value <0.05 was considered as statistically significant.

Results and Discussion

The clinical effects of inhaled drugs used for asthma are determined by the total amount of deposited drug in the lungs and its distribution in the airways with different sizes. MDIs are the traditional and recommended means of delivering inhaled drugs used for asthma such as Salbutamol due to the easy to use and portability for the delivery of any dose especially in children.²⁰⁻²² In 1997, some pharmaceutical companies tried to develop and manufacture inhalers and formed an association to progress a new impactor which specifically designed for testing pharmaceutical inhalers by using the new and modern designed theory. Flexibility of use and high productivity make NGIs the most popular analysis machine among many inhaler research laboratories. Subsequently, NGIs were accepted into the United States Pharmacopeia as Apparatus 5 and 6 in 2005 and into the European Pharmacopeia as Apparatus E in 2000. The *in vitro* parameters which should be measured for each MDI including FPF, FPD, GSD and MMAD are exhibited

in Table 1. The details of Salbutamol deposition in different stages of NGI are presented in Figure 1. FPF and FPD values show the fraction and amount of Salbutamol particles reach to the lower respiratory tract. The higher values indicate the better aerosolization performance of MDIs.

The results of FPF and FPD values indicated that the aerosolization efficacy of reference Salbutamol MDI was higher than B and C MDIs, however, the differences were not significant ($P>0.05$). GSD displays the aerodynamic size distribution of aerosolized particles through the MDIs which

measured from drug deposition in the various stages of NGI. The lower GSD value specifies the narrower size distribution which warrants predictable and reproducible therapeutic outcomes. As shown in Table 1, C MDI showed better GSD values than A and B MDIs. The Ideal MMAD value for pulmonary drug delivery systems is considered between 1 to 5 μm . In the case of MMAD results, like previous parameters, although A MDI showed the better results in comparison with other brands, the differences were not significant.

Table 1. Aerosolization efficiency indexes of A, B and C MDIs (4 batches) analyzed by the NGI (data presented as mean \pm SD, n= 3).

Brand	FPD ^a (μg)	FPF ^b (%)	MMAD ^c (μm)	GSD ^d
A (1)	30.85 \pm 5.35	34.14 \pm 1.22	3.51 \pm 0.10	2.77 \pm 0.07
A (2)	39.50 \pm 17.14	39.73 \pm 12.63	2.19 \pm 1.14	2.75 \pm 0.88
A (3)	21.86 \pm 1.25	24.19 \pm 0.56	3.07 \pm 0.96	NA
A (4)	49.03 \pm 10.78	56.14 \pm 24.66	1.87 \pm 0.87	NA
B (1)	57.13 \pm 29.28	52.01 \pm 18.50	2.66 \pm 0.56	2.27 \pm 0.21
B (2)	20.83 \pm 2.16	24.34 \pm 1.70	2.50 \pm 0.63	NA
B (3)	33.18 \pm 5.22	33.17 \pm 5.33	2.85 \pm 0.53	3.39 \pm 0.26
B (4)	24.77 \pm 3.03	26.84 \pm 5.87	4.78 \pm 0.92	3.05 \pm 0.99
C (1)	30.85 \pm 5.35	34.14 \pm 1.22	3.51 \pm 0.10	2.77 \pm 0.07
C (2)	39.50 \pm 17.14	39.73 \pm 12.63	2.19 \pm 1.14	2.75 \pm 0.88
C (3)	21.86 \pm 1.25	24.19 \pm 0.56	3.07 \pm 0.96	NA
C (4)	49.03 \pm 10.78	56.14 \pm 24.66	1.87 \pm 0.87	NA

^aFine particle dose (FPD)

^bFine particle fraction (FPF)

^cMass median aerodynamic diameter (MMAD)

^dGeometric standard deviation (GSD)

^eNot available (Could not be measured)

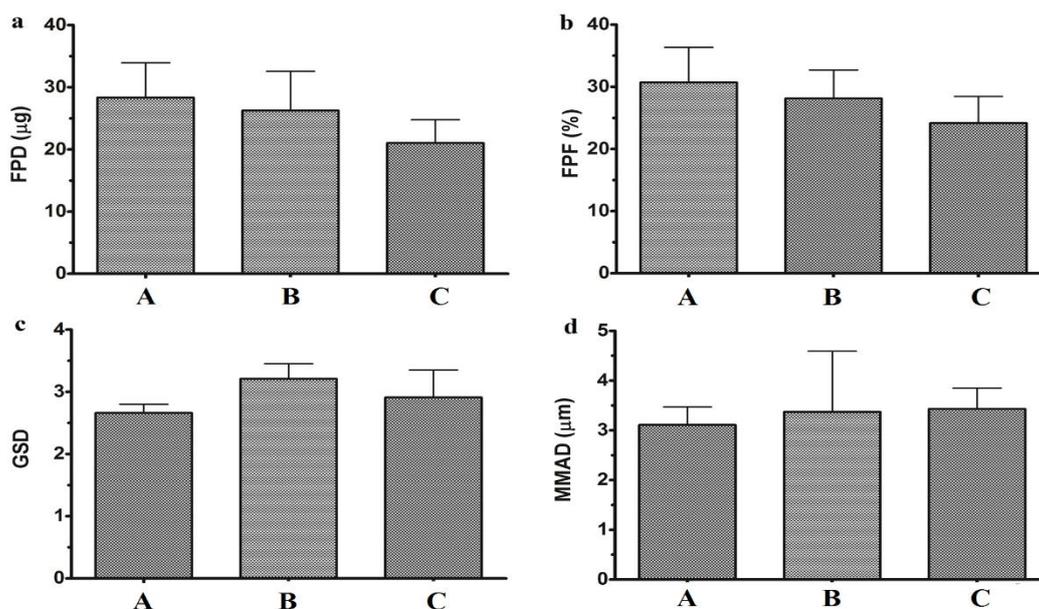


Figure 1. The aerosolization indexes; a) fine particle dose (FPD), b) fine particle fraction (FPF), c) geometric standard deviation (GSD), and d) mass median aerodynamic diameter (MMAD) of A, B and C MDIs (data presented as mean \pm standard deviation, n= 4).

Conclusion

The use of aerosol therapy for pulmonary drug delivery in lung diseases has increased considerably in recent years. Confirming that generic MDIs deliver the same active compound in equivalent amounts to the reference brand product and the absence of any difference in efficacy is critical. This study provides *in vitro* data to show that generic salbutamol is equivalent in efficacy to the reference brand product. Due to the high prices, patients using branded MDIs could have converted to the generic product and save many money per year. For the future *in vivo* assessment on patients was suggested when converting patients from the branded to the generic product. Unfortunately, data is not available showing that different generic products are pharmacologically equivalent to the branded product and this should help convince physicians at least, that the generic product can be prescribed with assurance.

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Conflict of interests

The authors claim that there is no conflict of interest.

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