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Short Communication

The Effect of Spacer Morphology on the Aerosolization Performance of Metered-Dose Inhalers

Sepideh Momeni[1,2], Ali Nokhodchi[3], Saeed Ghanbarzadeh[4,5], Hamed Hamishehkar[5]*

[1] *Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2] *School of Pharmacy, International Branch-Aras, Tabriz University of Medical Science, Tabriz, Iran.*
[3] *School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QG, United Kingdom.*
[4] *Zanjan Pharmaceutical Nanotechnology Research Center, and Department of Pharmaceutics, Faculty of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran.*
[5] *Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

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Abstract
Purpose: Respiratory drug delivery has been attracted great interest for the past decades, because of the high incidence of pulmonary diseases. However, despite its invaluable benefits, there are some major drawbacks in respiratory drug delivery, mainly due to the relatively high drug deposition in undesirable regions. One way to improve the efficiency of respiratory drug delivery through metered-dose inhalers (MDI) is placing a respiratory spacer between the inhaler exit and the mouth. The aim of this study was to assess the effect of type and shape of spacer on the aerosolization performance of MDIs.
Methods: A commercial Beclomethasone Dipropionate (BDP) MDI alone or equipped with two different spacer devices (roller and pear type) widely distributed in the world pharmaceutical market was used. The effect of spacers was evaluated by calculating aerosolization indexes such as fine particle fraction (FPF), mass median aerodynamic diameters (MMAD) and geometric standard deviation (GSD) using the next generation impactor.
Results: Although one of the spacers resulted in superior outcomes than the other one, but it was not statistically significant.
Conclusion: The results confirmed that the type and shape of spacer did not substantially influence the aerosolization performance of MDIs.

Introduction

Respiratory drug delivery is currently considered to be the most promising method for directly relieving or treating respiratory diseases such as asthma. As compared with other methods, there are some unique advantages to this type of respiratory drug administration such as quick onset of action and avoided degradation of drug by liver. However, one of the drawbacks attributed to pulmonary drug delivery is considerable deposition of drug particles in undesired locations, which reduces its effectiveness and unfavorable take-up of medication poses health hazards to patients.[1,2] Optimum aerosol particle size is very important for deep lung delivery and is in the range of 1-5 µm. Small particles will be exhaled and large particles deposited on the oropharynx and larynx. Among all pulmonary devices, metered-dose inhalers (MDIs) are undoubtedly the most popular and commonly used devices for pulmonary drug delivery. However, it has been reported that they show low efficacy and only as little as 9 % of the delivered doses are deposited in the lungs.[3,4] It was claimed that to improve the depth of penetration of medication to the lungs, the esophageal impaction and consequently swallowing of the pharmacologic agent should be minimized. For this purpose, the special devices were employed to reduce undesirably high initial momentum which finally decreases the size of primary emitted droplets and unwanted deposition of particles in the oral cavity and upper airways.[1,5] Therefore, it is becoming more and more routine to use some sort of extension, namely respiratory spacers which sometimes called holding chambers, between inhaler outlet and mouth inlet.[6,7] Various spacers with different shapes and volumes were commercially marketed and employed. The aim of this study was to compare the effect of two widely distributed spacer devices pear type and roller type on the *in vitro* performance of a commercial Beclomethasone Dipropionate (BDP) MDI.

Materials and Methods

Materials

Beclomethasone Dipropionate (BDP) anhydrous was provided from Cipla chemical Company (Mumbai, India). HPLC grade acetonitrile was purchased from Duksan Pure Chemicals (Kyungkido, Korea). Ethanol

***Corresponding author:** Hamed Hamishehkar, Tel and Fax: +98 41 33363231, Email: Hamishehkarh@tbzmed.ac.ir

and Tween® 80 were supplied from JATA (Arak, Iran) and Merck Chemicals (Darmstadt, Germany) companies, respectively. Commercialized BDP MDI (Beclotrox® 250 µg/dose) was obtained from Jaber Ebne Hayyan Pharmaceutical Co. (Tehran, Iran). Roller type spacer (Asannafas®) and pear type one (Damyar®) were provided from Tehran Fanavar Teb (Tehran, Iran) and Fanavar Teb Espadana (Isfahan, Iran) Companies, respectively.

Methods

Characteristics of spacers

The characteristics of investigated spacers were mentioned in Table 1. The only difference is shape of the spacers as illustrated in Figure 1, as well.

Table 1. Comparison of spacer's characteristics.

Spacer	Shape	Length(cm)	Volume (mL)	Expiratory valve
Damyar®	Roller	10.5	130	√
Asannafas®	Pear	10.5	150	√

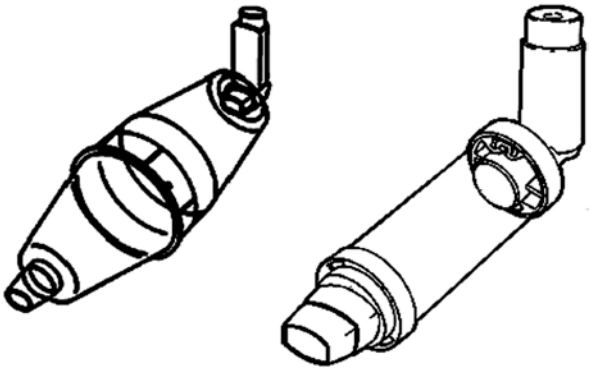

Figure 1. Pear type spacer (left) and Roller type (right).

In vitro aerosolization assessment

The aerodynamic particle size distribution of BDP MDI with and without spacers was analyzed according to the USP monograph using the next generation impactor (NGI) (Copley Scientific, Nottingham, UK).[8] The induction port was used to connect the NGI device to MDI. To ensure an efficient particle capture and prevent inter-stage losses due to particle bounce, the particle collection surface of each stage was coated with Tween® 80. For this purpose, every eight collection cups of the NGI were soaked into Tween® 80 ethanolic solution (1 %) and placed under the fume hood until the complete evaporation of ethanol. The cups were placed into the apertures in the cup tray and the cup tray was located into the bottom frame and lowered into place. The impactor lid was closed with the sealed body attached and the handle was operated to lock the impactor together. The induction port was connected to the first stage of the NGI. The flow rate was calibrated using a flow meter (DFM 2000, Copley Scientific, Nottingham, UK) and fixed at 30 L/min. Once the assembly had been checked and found to be airtight, after shaking and one actuation to out, a Beclotrox® MDI had been inserted into the rubber mouthpiece attached to the USP induction port of the NGI. The vacuum pump (HCP5, Copley Scientific, Nottingham, UK) was switched on and let it to reach the steady flow rate (30 L/min), and finally the dose was released for two times in the interval of 5 seconds. The pump was switched off after 5 seconds of the second actuation. After firing 2 doses into the apparatus, spacer, throat and stages were rinsed with 15 mL of acetonitrile: water (60: 40, v/v) solution, and the amount of BDP was analyzed using a validated HPLC method. Assays were repeated six times with or without each spacer and the results are presented as averages with standard deviations. Fine particle fraction (FPF), mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) indexes were calculated using the Copley Inhaler Testing Data Analysis Software (CITDAS, version 3.10). The MMAD is defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller, whereas the FPF corresponds to the fraction of drugs carried in particles with a diameter of <5µm.[7]

High performance liquid chromatography analysis

The amount of BDP was analyzed using a reversed-phase HPLC system employing Knauer apparatus (Germany) consisted of a model 1000 HPLC pump and a model 2600 tunable absorbance detector. BDP was separated at room temperature by a C18 column (4.6 mm×250 mm, 10 µm, 125 A°) (Germany). The mobile phase was consisted of acetonitrile and water (60:40). The flow rate was 2 mL/min and sample injection volume was 20 µL. The detecting wavelength was set at 254 nm. The retention time was approximately 5 min and the area under the curve of BDP peak was calculated by apparatus software (ChromGate Client/Server, version 3.1.7) where responses were linear in the range of 1–40 µg/mL (r^2=0.9981).

Statistical analysis

Data are expressed as a mean value ± standard deviation (SD). Statistical analysis was performed using a one-way analysis of variance (ANOVA) with multiple comparisons between deposition data using a Tukey-Kramer HSD test by SPSS software (version 13.0, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results and Discussion

The clinical effects of inhaled asthma drugs are determined by the total amount of drug deposited in the lungs, and its distribution amongst airways with different sizes. MDIs have been the traditional means of delivering inhaled asthma drugs. For inhaled corticosteroids such as BDP, it is recommended that MDIs are used in conjunction with a large volume spacer device for the delivery of any dose especially in children.[9-11] Spacer devices reduce the total body dose of inhaled drugs, which may result in fewer local and systemic side effects. In addition, spacers are able to reduce the problems of co-ordination that some patients have with MDIs.[11,12] In 1997, a group of pharmaceutical companies involved in the development and manufacturing inhalers formed an association to develop a new impactor specifically

designed for testing pharmaceutical inhalers using the very newest and modern designed theory. In practice, its flexibility of use and high productivity are making NGI the most popular testing machine within many inhaler research laboratories. NGI was launched in 2000 and was subsequently accepted into the European Pharmacopeia as Apparatus E and into the United States Pharmacopeia as Apparatus 5 and 6 in 2005. The *in vitro* parameters which should be measured for each spacer including FPF, MMAD and GSD are shown in Table 2. The details of BDP deposition in different stages of NGI are presented in Figure 2. Although both spacer devices improved all aerosolization indexes, only the difference of FPF value was statistically significant (P_{value} < 0.01). FPF value shows the fraction of BDP particles reach to the lower parts of lung. The higher FPF value indicates the better aerosolization performance of MDI. The results illustrated that the efficacy of BDP MDI increased by 58 and 70 % when pear and roller type spacers were used, respectively. Although it seems that the increase in FPF value by using roller type spacer was higher than pear type but it was not statistically significant (P_{value} = 0.412). Ideal MMAD value for pulmonary drug delivery is between 1 to 5 µm. All the results even without using spacer were in the acceptable range. GSD exhibits the aerodynamic size distribution of aerosolized particles through the MDIs calculated from drug deposition in the various stages of NGI. The lower GSD values indicates the narrower size distribution which guarantees reproducible and predictable therapeutic outcomes. Only roller type spacer improved GSD value of BDP MDI (P_{value} = 0.046). Although pear type spacer improved GSD value, as well but it was not statistically significant (P_{value} = 0.956).

Table 2. In vitro characteristics of Beclomethasone Dipropionate delivered from Beclotrex® MDI alone and in combination with spacers. Data are presented as mean ± standard deviation.

Device	FPF[a] (%)	MMAD[b] (µg)	GSD[c]
Beclotrex®	42.90±11.18	2.77±0.54	2.55±0.612
Beclotrex®+Asannafas®	67.87±10.68	2.64±0.40	2.45±0.32
Beclotrex®+Damyar®	72.93±6.33	2.07±0.26	1.93±0.13

a: Fine Particle Fraction
b: Mass Median Aerodynamic Diameter
c: Geometric Standard Deviation

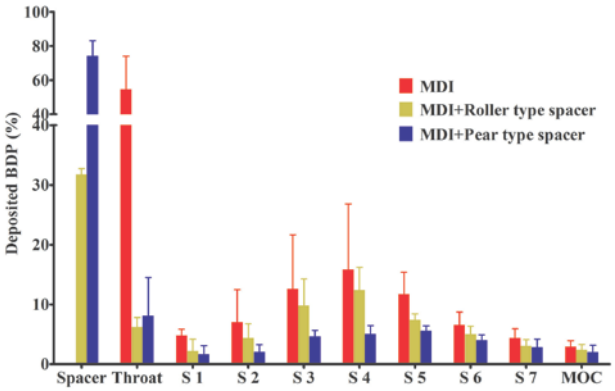

Figure 2. Comparison of the amount of Beclomethasone deposited in various stages of NGI (Data presented as mean ± SD, n= 3)

The change from oral to inhaled medications as the preferred route of administration has been one of the most important developments in asthma treatment and chronic obstructive pulmonary disease. Unfortunately, patients with asthma have been shown to have poor inhaler technique which is an important cause of poor asthma control. The inhalation method is an important variable in the delivery of inhaled drugs. Furthermore, although several spacers and holding chambers are available, numerous studies showed that healthcare devices have poor inhaler technique and dose delivery varies considerably depending on the design.[3,13,14] The most important factors influencing output from MDI plus add-on device are: spacer material and volume, dead space between inlet and outlet, inlet and outlet valve controls, drug formulation, propellants, evaporation rate and humidity.[11,15,16] Each brand of spacer device has different drug delivery characteristics and the impaction plane and deposition curves with distinct cut-off sizes could be altered. Therefore, the specific design should be chosen to guarantee passing favorable particles through the spacer.[1,17,18] Last but not least, keeping flow turbulence down to a minimum is recommended to diminish particle deposition which suited to the preferred particle size criteria and a sharper cut-off curve. The disadvantages of spacers are that they are bulky, and difficult to carry out. In addition, the valves sometimes stick or become otherwise faulty.[7,18] But as shown in the present study, the use of spacers for efficient drug delivery into the lung and consequently effective therapeutic outcome is necessary.

Conclusion

The esophageal impaction and consequently swallowing of the pharmacologic agent which causes side effects in oropharynx and gastrointestinal tract is the main disadvantages of MDIs that can be prevented by the use of a suitable spacer. The results of the present study confirmed the importance, beneficial and advantages of using spacers with MDIs. The results showed that the performance of MDIs could even be improved up to 70%, however the shape of spacer did not affect the aerosolization performance of MDI significantly. Due to the great impact of spacer on the outcomes of MDI, further investigations on the designing of new spacers or exploring the factors affecting the performance of spacers such as length, shape, and volume of spacers are opened to be discovered.

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Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest.

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