Research in Pharmaceutical Sciences, June 2018; 13(3): 283-287
Received: June 2017
Accepted: December 2017

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Short Communication

The effect of different coating materials on the prevention of powder bounce in the next generation impactor

Shadi Farshbaf Khalili[1], Saeed Ghanbarzadeh[2], Ali Nokhodchi[3,4], and Hamed Hamishehkar[5,*]

[1]Biotechnology Research Center and Student Research Committee, School of Pharmacy, International Branch-Aras, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.
[2]Zanjan Pharmaceutical Nanotechnology Research Center, Cancer Gene Therapy Research Center, and Department of Pharmaceutics, Faculty of Pharmacy, Zanjan University of Medical Sciences, Zanjan, I.R. Iran.
[3]Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Science, Tabriz, I.R. Iran.
[4]School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QG, United Kingdom.
[5]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.

Abstract

In the process of quality control of pulmonary drug delivery products, aerosolization efficiency is mainly determined using impactors, *e.g.* next generation impactor (NGI). However, particle bounce may interfere with the validity and accuracy of results due to the overestimation of the respirable fraction. It is suggested that the coating of impactor's stages may prevent the particle bounce. Therefore, coating materials may influence the results of the aerosolization indexes of pulmonary dosage forms. The aim of this study was to investigate if the aerosolization indices are affected differently by using the different coating materials. In this study, the effects of using different materials including Span® 85, Tween® 80, silicon® oil, glycerin and Brij® 35/glycerin mixture recommended for the coating of NGI stages on the aerosolization indices such as fine particle fraction, fine particle dose, mass median aerodynamic diameter, and geometric standard deviation of salbutamol emitted from a commercial metered dose inhaler (MDI), were assessed. Three statistically different results were obtained on using Tween® 80, Span® 85 and silicon oil, and glycerin and Brij®35/glycerin mixture. It can be concluded that the type of coating material influenced the aerosolization indices of the examined MDI in NGIs.

Keywords: Metered dose inhalers; Next generation impactor; Coating; Bounce

INTRODUCTION

Numerous approaches have been employed for the treatment of the respiratory diseases like asthma. The pulmonary drug delivery represents an attractive and promising way to localize the treatment. Pharmaceutical products developed to deliver drugs to the lungs should possess two fundamental characteristics namely released mass per actuation and particle size distribution that need to be determined. Impactors are instruments generally used to impact particles on a dry impaction plate or a cup. They are relatively easy to use and comprehensive instructions are available in accredited pharmacopoeias for analyzing all types of pulmonary drug delivery systems such as nebulizers, dry powder inhalers, and metered dose inhalers (MDIs). Impactors possess sharp cutoff chambers for effective particle size perception (1,2,3). However, sometimes particles may bounce to impact when they contact the collection plate. In these veins they are normally re-entrained into the air stream and carried to a lower stage resulting them to be collected on the wrong stage. Furthermore, the sharp cutoff curves require relatively high impactor air jet speeds which increase the risk of bounce. This effect is particularly noticeable when the collection surface is solid and results in overestimation of the amount of fine particle dose and consequently bias occurs in the measured size distribution data toward finer sizes (4).

*Corresponding author: H. Hamishehkar
Tel: +98-4133363231, Fax: +98-4133363231
Email: Hamishehkarh@tbzmed.ac.ir

Access this article online

Website: http://rps.mui.ac.ir

DOI: 10.4103/1735-5362. 228958

In order to eliminate the problem of interanalyst variability various methods are currently used for coating impactor collection surfaces. The routine method for avoidance of this problem is to coat the collection surfaces with a sticky viscous material. Several previous studies have investigated the effects of particle bounce in impactors and showed that the use of uncoated plates results in particle bounce. Hence, selection and application of coating materials are of particular significance when using impactors. Coating of stages is not standardized and different users have applied different materials in various ways (4,5). In this study five different advised next generation impactor (NGI) collection cup coating materials, including Span® 85, Tween® 80, Silicon® oil, Glycerin, and Brij® 35/Glycerin mixture were used to compare the influence of coating material on the aerosolization indices including fine particle fraction (FPF), fine particle dose (FPD), mass median aerodynamic diameters (MMAD), and geometric standard deviation (GSD). The selection of above mentioned coating materials was based on their introduction in pharmacopeias and previously published articles (6). The findings of this study answer the key question of whether the type of coating material should be defined by pharmacopeia or regulatory agencies to harmonize the *in vitro* assessment of pulmonary dosage forms via impactors.

MATERIALS AND METHODS

Materials

Salbutamol was provided from Cambrex Company (Italy). Methanol and glycerin were purchased from Duksan Pure Chemicals Company (Korea). Span® 85, Silicon® oil, and Brij® 35 were obtained from Sigma Aldrich (USA), Sigma Aldrich (Germany), and Sigma Aldrich (UK) Companies, respectively. Tween® 80, HCl, n-hexane, acetone and N, N -dimethylformamide were procured from Merck Chemicals Company (Germany).

Coating of collection cups and in vitro aerosolization assessment

The aerodynamic parameters of salbutamol MDI with different coating materials were analyzed according to the USP monograph, using the NGI (Copley Scientific, Nottingham, UK), equipped with a USP induction port (7). To compare the effects of different coating materials on particle capture and to prevent inter-stage losses due to the particle bounce, the particle collection surface of each stage was coated with Span® 85 (1% w:v in hexane), Tween® 80 (1% w:v in ethanol), Silicon® oil (1% w:v in hexane), glycerin and Brij® 35 (1% w:v in glycerin). Brij® was dissolved in small amounts of ethanol (less than 5% of glycerin) to be simply dissolved in glycerin. For this purpose, every eight collection cups were soaked into coating materials and placed under the fume hood until the complete evaporation of the solvents. 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 and attached; the handle was operated to lock the impactor together. The flow rate was calibrated using a flow meter (DFM 2000, Copley Scientific, Nottingham, UK) and fixed at 30 L/min. Once the assembly was checked and found to be airtight, after shaking and one actuation to out, a generic salbutamol MDI (Ventalex®, Sina daru, Tehran, Iran) was shaken for 5 sec and discharged one delivery to waste. With the vacuum pump (HCP5, Copley Scientific, Nottingham, UK) running at the steady flow rate of 30 L/min, MDI was inserted into the mouthpiece adapter and immediately fired into the cascade impactor. After firing 10 doses into the apparatus, throat and stages were rinsed with 15 mL of mobile phase, and the amount of salbutamol was analyzed using a validated HPLC method employing Knauer apparatus (Germany) comprising of a model 1000 HPLC pump and a model 2600 tunable absorbance detector. Salbutamol was separated at room temperature by a C_{18} column (4.6 mm × 150 mm, 10 µm, 125 Å) (Germany). The mobile phase consisted of methanol and 1-heptane sulphonic acid sodium salt (45:55). The flow rate was 1 mL/min and sample injection volume was 20 µL. The detecting wavelength was set at 200 nm. The retention time was approximately 3 min and the area under the curve of salbutamol peak was calculated by apparatus software (ChromGate Client/Server, version 3.1.7) where responses were linear in the range of 1-20 µg/mL ($r^2 = 0.99986$).

Assays were repeated at least six times and the results were presented as averages with standard deviations. FPF, FPD, MMAD and GSD indices were calculated using the Copley inhaler testing data analysis software (CITDAS, version 3.10) (8,9). 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 16, Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

RESULTS

The *in vitro* parameters which were measured to evaluate the effect of different coating materials used to prevent the particle bounce are shown in Fig. 1. Results showed that the type of coating materials affects the aerosolization indices of examined MDI in NGIs. The statistical analysis showed that Tween® 80 in ethanol demonstrated significantly different FPF (Fig. 1a) and FPD (Fig. 1b) values in comparison with Span® 85 and Silicon oil in hexane as well as glycerin and Brij® 35/glycerin. In addition, glycerin and Brij® 35/gly resulted in higher GSD values (Fig. 1c) than Tween® 80 in ethanol, Span® 85 in hexane and Silicon oil in hexane. Although there was no statistical differences in the case of MMAD (Fig. 1d) among the different coating materials ($p > 0.05$), glycerin showed considerably higher MMAD than others. The high standard deviations associated with using glycerin and Brij® 35/glycerin resulted in erratic and unrepeatable values.

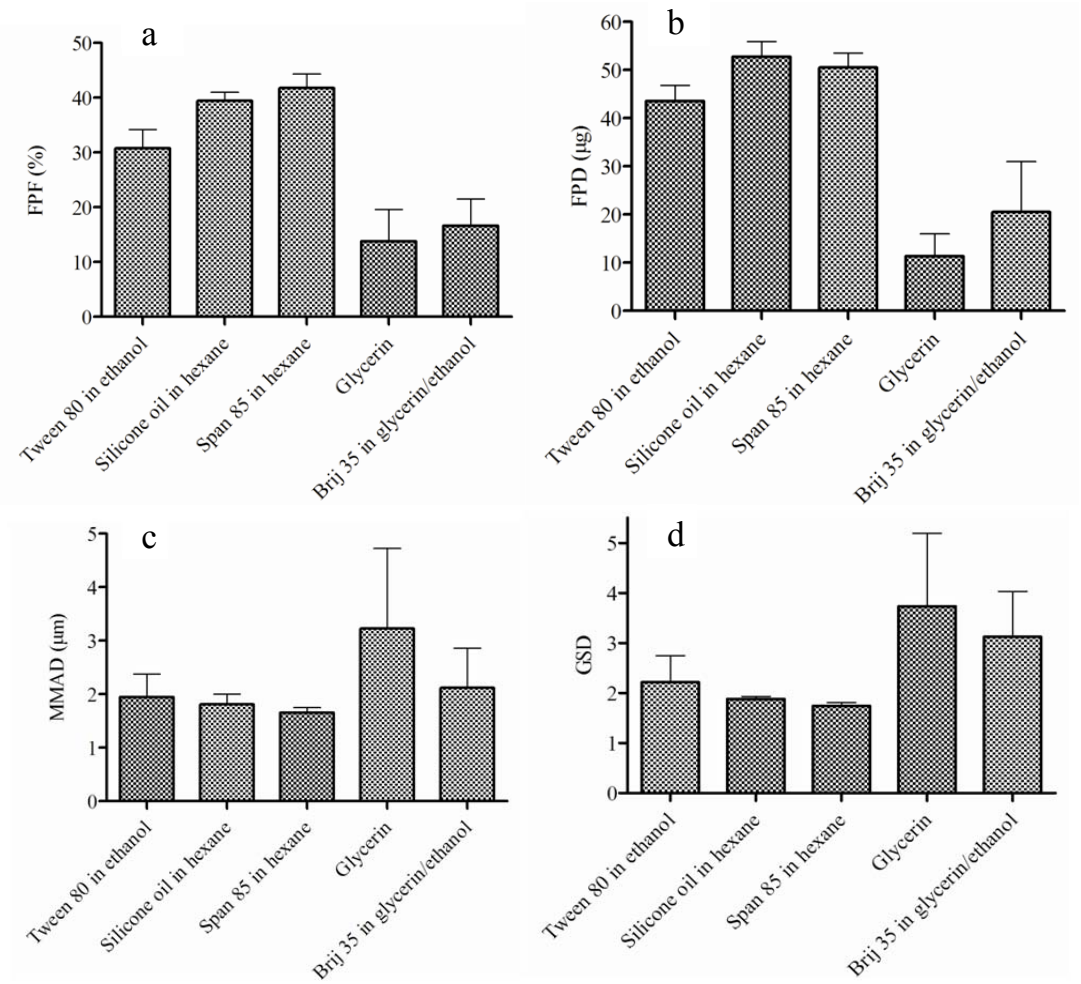

Fig. 1. Aerosolization parameters (fine particle fraction (FPF), fine particle dose (FPD), mass median aerodynamic diameters (MMAD), and geometric standard deviation (GSD)) of salbutamol metered dose inhaler sprayed in next generation impactor coated with different coating materials.

DISCUSSION

The clinical effects of inhaled drugs effective in the treatment of asthma are analyzed by the total amount of drug deposited in the lungs and its distribution through airways with different sizes (10,11). MDIs have been the traditional means of delivering inhaled drugs used in the treatment of the asthma. The traditional particle size analysis methods for medical inhalers in the USP and European Pharmacopeias require drug assays in the collected size fractions, so that there would be a direct relationship between calculated particle size and the mass of active ingredient (12). NGIs were designed and developed for examining pharmaceutical inhalers based on the very newest and modern designed theory. In practice, its flexibility of use and high productivity are making NGIs the most popular testing device in many inhaler research laboratories. NGI was launched in 2000 and was subsequently accepted by the European Pharmacopeia as apparatus E and in the United States Pharmacopeia as apparatus 6 in 2005 (13). It is well known that impactors are vulnerable to particle bounce, biasing particle size distribution data toward finer sizes (12). Particle bounce happens when the impulse of an impacting particle is larger than the adhesion strength. Overload takes place when large volumes of particles are placed, modifying the collection efficacy of the impaction surface. Particle bounce, re-entrainment and stage overload are collaborating properties and are difficult to identify independently and therefore, they are usually denoted to as bounce effects (14). Various methods have been proposed to lessen this effect, including coating of the collection surfaces with grease or using nonvolatile agents that create a sticky surface (15). It has been shown that due to the dissolving of particles in hydrophilic coating materials and capillary action, using hydrophilic coating materials could reduce the particle bounce effect in comparison with hydrophobic coating materials (16).

FPF and FPD values show the fraction and the dose of the drug particles reached the lower parts of the lung. The higher values of FPF and FPD indicate better aerosolization performance of MDI. The MMAD is defined as the diameter at which 50% of the particles, by mass, are larger and the rest are smaller. Ideal MMAD value for pulmonary drug delivery should lie between 1 and 5 μm. Although, all the results were in the acceptable range, glycerin resulted in the lowest FPF, FPD, and MMAD which might be attributed to the high solubility of hydrophilic drug (salbutamol) compared to hydrophobic coating materials. GSD exhibits the aerodynamic size distribution of aerosolized particles through the MDIs which was calculated from drug deposition in the various stages of NGI. The lower GSD values indicate narrower size distribution which guarantees reproducible and predictable therapeutic results. Glycerin showed the lowest GSD probably because of high viscosity and sticky characteristic. Therefore, it seems that glycerin is not a suitable coating material. On the other hand, due to the toxicity of hexane for laboratory staffs, Tween® 80 in ethanol is a more suitable and safer coating material to be used in NGIs.

CONCLUSION

This study has compared the effect of various coating materials in the prevention of particle bounce and aerosolization parameters of MDI once analyzed by NGIs. Results confirmed that the type of coating materials would influence the aerosolization indices of the examined MDI using NGIs. Due to the great impact of coating materials on the *in vitro* output of impactors, their type and application procedure should be specified in the pharmacopeias or regulatory agencies. Because of reproducible and safe characteristics, Tween® 80 in ethanol seems to be more promising agent for coating of the impactors plates.

ACKNOWLEDGEMENT

The content of this paper is extracted from the Pharm.D thesis (No. 66) submitted by Shadi Farshbaf Khalili which was financially supported by the Drug Applied Research Center of Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.

REFERENCES

1. Momeni S, Nokhodchi A, Ghanbarzadeh S, Hamishehkar H. The Effect of spacer morphology on the aerosolization performance of metered-dose inhalers: spacer shape effect on aerosolization performance. Adv Pharm Bull. 2016;6(2):257-260
2. Faramarzi P, Haririan I, Ghanbarzadeh S, Yaqoubi S, Hamishehkar H. Development of carrier free montelukast dry powder inhalation formulation. Pharm Ind. 2015;77(10):1535-1542.
3. Varshosaz J, Taymouri S, Hamishehkar H, Vatankhah R, Yaghubi S. Development of dry powder inhaler containing tadalafil-loaded PLGA nanoparticles. Res Pharm Sci. 2017;12(3):222-232.
4. Bateman AP, Belassein H, Martin ST. Impactor apparatus for the study of particle rebound: Relative humidity and capillary forces. Aerosol Sci Technol. 2014;48(1):42-52.
5. Jain S, Petrucci GA. A new method to measure aerosol particle bounce using a cascade electrical low pressure impactor. Aerosol Sci Technol. 2015;49(6):390-399.
6. Mitchell JP. Practices of coating collection surfaces of cascade impactors: a survey of members of the european pharmaceutical aerosol group (EPAG). Drug Deliv Lung. 2003;14:75-78.
7. The United States Pharmacopoeia, 35th rev, and The National Formulary, 30th ed. Vol. 1, Rockville, MD: USP Convention; 2015, General Chapter 601.
8. Yazdani A, Normandie M, Yousefi M, Saidi MS, Ahmadi G. Transport and deposition of pharmaceutical particles in three commercial spacer-MDI combinations. Comput Biol Med. 2014;54:145-155.
9. Hassanpour Aghdam M, Ghanbarzadeh S, Javadzadeh Y, Hamishehkar H. Aggregated nanotransfersomal dry powder inhalation of itraconazole for pulmonary drug delivery. Adv pharm bull. 2016;6(1):57-64.
10. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β2-agonist particle size. Am J Respir Crit Care Med. 2005;172(12):1497-1504.
11. Emami J, Mohiti H, Hamishehkar H, Varshosaz J. Formulation and optimization of solid lipid nanoparticle formulation for pulmonary delivery of budesonide using Taguchi and Box-Behnken design. Res Pharm Sci. 2015;10(1):17-33.
12. Mitchell J, Nagel M. Particle size analysis of aerosols from medicinal inhalers. KONA Powder Part J. 2004;22:32-65.
13. Aghdam MH, Ghanbarzadeh S, Javadzadeh Y, Hamishehkar H. Aggregated nanotransfersomal dry powder inhalation of itraconazole for pulmonary drug delivery. Advanced pharmaceutical bulletin. 2016;6:57.
14. Dunbar C, Kataya A, Tiangbe T. Reducing bounce effects in the Andersen cascade impactor. Int J Pharm. 2005;301(1-2):25-32.
15. Anderson CW, Carlson MA. A time-of-flight mini-mass spectrometer: Aerosol collection, capture, and load-lock system. Johns Hopkins APL Tech Dig. 1999;20:352-362.
16. Winkler P. Relative humidity and the adhesion of atmospheric particles to the plates of impactors. J Aerosol Sci. 1974;5(3):235-240.