

Pharmaceutical equivalence of the combination formulation of budesonide and formoterol in a single capsule with a dry powder inhaler*

Equivalência farmacêutica da formulação combinada de budesonida e formoterol em cápsula única com dispositivo inalador de pó

Marina Andrade-Lima, Luiz Fernando Ferreira Pereira, Ana Luisa Godoy Fernandes

Abstract

Objective: To evaluate the pharmaceutical equivalence of a test formulation (fixed-dose combination of budesonide and formoterol fumarate in a single capsule dispensed in an Aerocaps® inhaler) in relation to a reference formulation (budesonide and formoterol fumarate in two separate capsules dispensed in an Aerolizer® inhaler). **Methods:** This was an in vitro study in which we performed the identification/quantification of the active ingredients by HPLC and determined dose uniformity and aerodynamic particle size distribution in the test and reference formulations. **Results:** In the test formulation, the content of budesonide and formoterol was 111.0% and 103.8%, respectively, compared with 110.5% and 104.5%, respectively, in the reference formulation. In the test formulation, dose uniformity regarding budesonide and formoterol was 293.2 µg and 10.2 µg, respectively, whereas it was 353.0 µg and 11.1 µg in the reference formulation. These values are within the recommended range for this type of formulation (75-125% of the labeled dose). The fine particle fraction (< 5 µm) for budesonide and formoterol was 45% and 56%, respectively, in the test formulation and 54% and 52%, respectively, in the reference formulation. **Conclusions:** For both of the formulations tested, the levels of active ingredients, dose uniformity, and aerodynamic diameters were suitable for use with the respective dry powder inhalers.

Keywords: Asthma; Budesonide; Bronchodilator agents; Drug therapy, combination.

Resumo

Objetivo: Avaliar a equivalência farmacêutica da formulação teste (associação fixa de budesonida e fumarato de formoterol em cápsula única dispensada com o dispositivo Aerocaps®) em relação a uma formulação referência (budesonida e fumarato de formoterol em duas cápsulas distintas dispensadas com o dispositivo Aerolizer®). **Métodos:** Estudo in vitro no qual foram realizadas identificação/quantificação dos ingredientes ativos por HPCL e determinação da uniformidade da dose liberada e da distribuição aerodinâmica das partículas das formulações teste e referência. **Resultados:** Na formulação teste, o teor de budesonida e de formoterol foi de 111,0% e 103,8%, respectivamente, enquanto esse foi de 110,5% e 104,5% na formulação referência. Na formulação teste, a uniformidade das doses de budesonida e de formoterol foi de 293,2 µg e 10,2 µg, respectivamente, enquanto essa foi de 353,0 µg e 11,1 µg na formulação referência. Esses resultados estão dentro da faixa recomendada para esse tipo de formulação (75-125% da dose rotulada). A fração de partículas finas (< 5 µm) para budesonida e formoterol foi de, respectivamente, 45% e 56% na formulação teste e de 54% e 52% na formulação referência. **Conclusões:** As formulações teste e referência apresentaram níveis de ingredientes ativos, uniformidade de doses e diâmetros aerodinâmicos apropriados ao uso com seus respectivos dispositivos inalatórios de pó.

Descritores: Asma; Budesonida; Broncodilatadores; Terapia combinada.

* Study carried out in the *Laboratório T&E Analítica - Centro Analítico e Científico Ltda*, Campinas, Brazil.

Correspondence to: Marina Andrade Lima. Hospital Pró-Cardíaco, Setor Assistência Ventilatória, Rua General Polidoro, 192, Botafogo, CEP 22280-010, Rio de Janeiro, RJ, Brasil.

Tel. 55 21 2528-1411. E-mail: marina.lima@procardiaco.com.br

Financial support: This study received financial support from *Aché Laboratórios Farmacêuticos S.A.*

Submitted: 18 June 2012. Accepted, after review: 21 August 2012.

Introduction

Inhalation is the preferred method for administration of drugs for the treatment of obstructive respiratory diseases, in accordance with national and international guidelines.⁽¹⁻⁴⁾ Inhaled drug therapy is much more complex than is oral drug therapy. To be effective, it requires an inhaler containing the proposed drug, in the amount specified for each dose, and producing appropriately sized particles that will reach the lower airways. Aerodynamic size diameter is usually the most important particle-related factor, affecting aerosol deposition, which is determined by impaction, sedimentation, and Brownian motion. Particles more than 5 μm in diameter deposit by impaction onto the oropharynx and are swallowed. The percentage of particles less than 5 μm in diameter in an aerosol is designated the fine particle fraction (or fine particle dose, which is expressed as the absolute mass of such particles). Particles of 4-5 μm deposit primarily in the bronchi and large airways, whereas smaller particles remain in the air stream and are carried into the peripheral airways and the alveolar region, where the airflow rate is reduced and particles deposit by sedimentation. In contrast, particles between 0.1 μm and 1.0 μm diffuse by Brownian motion and deposit when they collide with the airway wall. A longer residence time in the smaller airways translates to greater deposition from sedimentation and Brownian motion.⁽⁵⁾

There are three basic systems for administration by inhalation: metered dose inhalers; dry powder inhalers; and nebulizers. The treatment of persistent asthma implies continuous use of controller medications. Current evidence shows that the use of the combination of an inhaled corticosteroid and a long-acting β_2 agonist bronchodilator, when compared with the use of an inhaled corticosteroid alone, improves current control and reduces future risk.⁽²⁾

Various combinations of inhaled corticosteroids and long-acting β_2 agonists, administered via different inhalers, have been approved and are available for use in the treatment of asthma and COPD in Brazil. The combination of budesonide and formoterol for dry powder inhalation can be dispensed in a multiple-dose inhaler (Turbuhaler[®]), in a single-dose inhaler with separate capsules containing budesonide and formoterol (Aerolizer[®]), or in an inhaler with a single capsule containing

a fixed-dose combination (Aerocaps[®]). There is not sufficient evidence in the medical literature to support the use of this fixed-dose combination dispensed in an inhaler manufactured in Brazil. For this reason, we designed the present in vitro study.

The objective of the present study was to evaluate the pharmaceutical equivalence of a test formulation (fixed-dose combination of budesonide and formoterol fumarate in a single capsule dispensed in an Aerocaps[®] inhaler) in relation to a reference formulation. The test formulation used was the drug commercially known as Alenia[®] (Aché Laboratórios Farmacêuticos S.A., São Paulo, Brazil), whereas the reference formulation was that containing budesonide and formoterol fumarate in separate capsules dispensed in a dry powder inhaler (Aerolizer[®]); in the latter case, the drug commercially known as Foraseq[®] (Novartis Biociências S.A., São Paulo, Brazil) was used. The batch numbers used in the present study, as well as their manufacture date and expiration date, are as follows: Alenia[®], batch number 0702213, manufactured in May of 2007 and good through November of 2008; and Foraseq[®], batch number U0173, manufactured in October of 2006 and good through September of 2008.

Methods

The present study was conducted in 2007, when there was no specific legislation on regulatory issues related to dry powder inhalers by the *Agência Nacional de Vigilância Sanitária* (ANVISA, Brazilian National Health Oversight Agency). However, the ANVISA required that the following procedures be performed: drug identification; determination of the average capsule content weight; determination of the active ingredient content (dosing); determination of content uniformity; determination of delivered dose uniformity; determination of aerodynamic particle size distribution; microbiology testing; determination of the water content; and determination of volume variability; all of which were performed in accordance with the specifications of the U.S. and Brazilian pharmacopeias.^(6,7) Throughout the process, two ANVISA technicians directly supervised the procedures, which were performed in an accredited laboratory (T&E Analítica; Campinas, Brazil).

Chart 1 shows the definitions of the main technical terms and norms used in the

present study. The details of each method are available in the online appendix (http://www.jornaldepneumologia.com.br/portugues/artigo_detalhes.asp?id=1943).

In summary, the methods used were as follows: drug identification was performed by HPLC column elution; dosing was performed by HPLC with UV detection (HPLC-UV); content uniformity determination, the aim of which is to investigate variability in the concentrations of active ingredients in a pharmaceutical formulation, was also performed by HPLC-UV⁽⁷⁾; delivered dose uniformity was determined with a dosage unit sampling apparatus for dry powder inhalers (DUSA-DPIs; Westech Scientific Instruments, Bedfordshire, UK; Figure 1)⁽⁶⁾; aerodynamic particle size distribution was determined with an Andersen cascade impactor (ACI; model 8301-60; Copley Scientific Ltd., Nottingham, UK),⁽⁸⁾ by means of which the ingredient content in the discharged spray from the inhaler is drawn by vacuum at a controlled flow rate through a set of filters that mimic in vitro the airways up to the pulmonary alveoli (Figure 2); the water content was determined by the Karl Fischer method; microbiology testing included bacterial and fungal counts and detection of total and fecal coliforms; and variability in the volumes of the

test formulation with low inspiratory volumes (simulating a patient with breathlessness) was determined by testing of aerodynamic particle size distribution with a multistage liquid impinger (Astra Draco MSLI; Erweka, Heusenstamm, Germany), which assesses in vitro the effect of inhalation on particle size distribution.

Results

The results of the in vitro analyses, which were performed using HPLC, a DUSA, and an ACI, are shown in Table 1. In accordance with

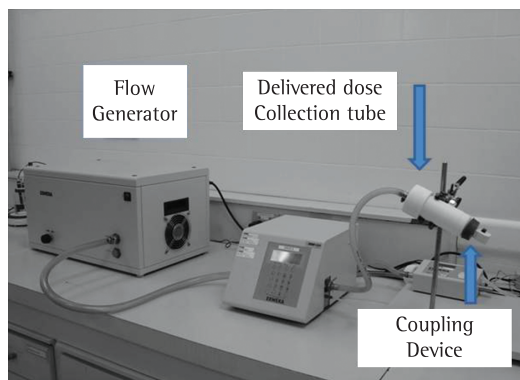


Figure 1 – Dosage unit sampling apparatus, used for determining dose uniformity of samples.

Chart 1 – Terms, definitions, and norms used in the study.^a

Term	Definition/norm
Aerosol	Suspension of solid particles and liquid droplets in air
Labeled dose or nominal dose	The mass of drug that is available within the device per actuation
Delivered dose	The mass of drug delivered per actuation that is actually available for inhalation at the mouth
Fine particle dose	The mass of particles < 5 µm in size within the total delivered dose
Fine particle fraction	The fine particle dose divided by the total delivered dose.
Mass median aerodynamic diameter	The diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller
Tests for delivered dose uniformity	They are used to assess delivered dose uniformity of inhaled medications containing the active ingredient or active ingredient formulations, packaged in reservoirs or in premetered dosage units where these containers are labeled for use with a named inhalation device. For dry powder inhalers, the specified target-delivered dose is usually less than the label claim. Its value reflects the expected mean active ingredient content for a large number of delivered doses collected from the product, using the specified method.
Acceptance criteria	The test results are considered satisfactory if not less than 9 of the 10 doses tested are within the range of 75% to 125% of the specified target-delivered dose and none is outside the range of 65% to 135% of the specified target-delivered dose. If the content of a maximum of 3 doses is outside the range of 75% to 125% of the specified target-delivered dose, but is within the range of 65% to 135%, another 20 capsules are selected and one minimum dose from each is analyzed as described elsewhere. ⁽⁶⁾

^aIn accordance with the U.S. Pharmacopeial Convention⁽⁶⁾ and the Brazilian Pharmacopeia.⁽⁷⁾

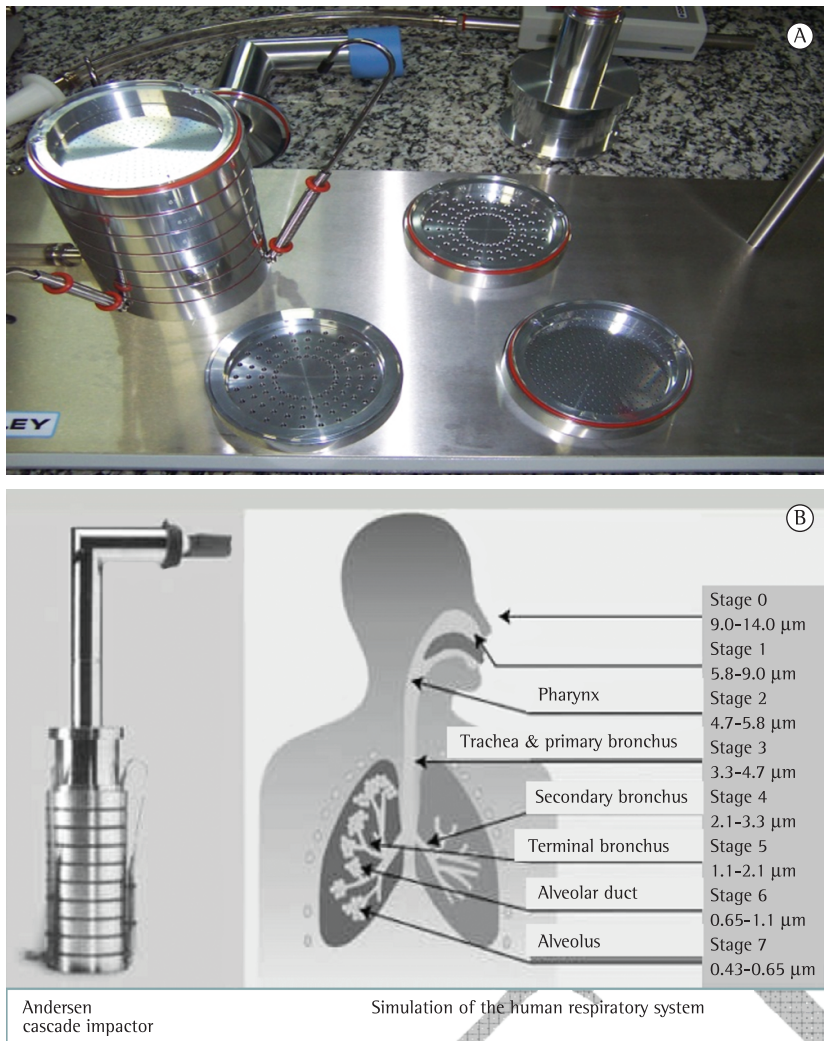


Figure 2 – In A, image of the Andersen cascade impactor, which simulates the aerodynamic particle size distribution in the human respiratory system. In B, the assembled device and the correspondence between its stages and the different parts of the human respiratory system.

the parameters laid down by the pharmacopeias, there were no differences between the test and reference formulations regarding drug identification (Figure 3), active ingredient content, content uniformity, delivered dose, or aerodynamic particle size distribution. Figure 4 shows that the portion of active ingredient collected on each ACI stage, corresponding to the estimated median mass diameter, was very similar for the two formulations.

For the test formulation (Aerocaps® inhaler), the delivered doses of budesonide and formoterol were, respectively, 73% and 85% of the labeled doses, compared with 88% and 92%, respectively, for the reference formulation (Aerolizer® inhaler),

The results of the microbiological analyses for the test and reference formulations were < 10 CFU/g for bacteria and fungi (recommended specification, < 100 CFU/g) and absence of pathogens and fecal coliforms. The water content of the test formulation was 4.76%, as determined by the Karl Fischer method, whereas the water content of the capsules of formoterol and budesonide of the reference formulation was 5.00% and 5.12%, respectively.

The comparative profile of the aerodynamic particle size distribution of budesonide and formoterol, with inspiratory volumes of 1 L and 4 L, was similar, demonstrating the good

Table 1 – Capsule weight, active ingredient content, content uniformity, delivered dose uniformity, and fine particle distribution in the test and reference formulations.^a

Variable	Formulation			
	Test		Reference	
	Budesonide	Formoterol	Budesonide	Formoterol
Capsule weight ^b , mg	25.56 ± 0.79 [25.3 (24.2-27.1)]		25.35 ± 1.08 [25.5 (23.0-27.3)]	25.19 ± 0.70 [25.3 (23.8-26.3)]
Active ingredient content, %	111.41	103.80	110.59	104.51
Delivered dose uniformity ^c , µg	293.24 ± 12.91 [292.32 (271.80-320.39)]	10.23 ± 0.47 [10.33 (9.20-11.05)]	353.04 ± 11.48 [352.98 (322.40-378.24)]	11.07 ± 0.60 [11.06 (10.10-12.38)]
Delivered dose uniformity, % ^d	92.69-109.25	89.63-108.01	91.31-107.14	91.32-111.83
Content uniformity ^e , %	103.68 ± 1.68 [103.68 (101.40-106.59)]	97.93 ± 1.98 [98.38 (95.00-100.77)]	107.20 ± 5.83 [107.16 (97.20-117.76)]	100.00 ± 3.23 [99.80 (95.80-105.33)]
Fine particle dose ^f , µg (%)	140.67 (44.71)	6.18 (56.13)	181.53 (53.56)	5.46 (52.05)

^aValues expressed as mean ± SD [median (min-max)], except where otherwise indicated. ^bOn the basis of 20 capsules. ^cOn the basis of 30 capsules. ^dIn mean percent variation. The recommended specification is 75-125% in at least 9 of the 10 samples tested. ^eOn the basis of 10 capsules. ^fOn the basis of 10 capsules.

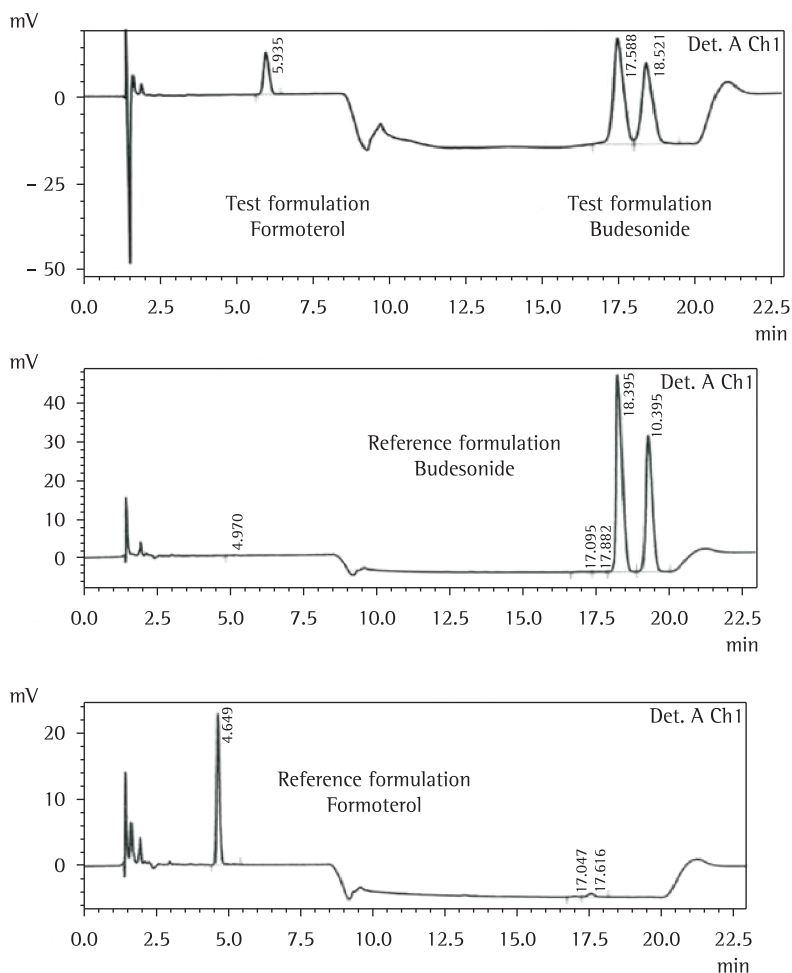


Figure 3 – Chromatography for identification of the drugs contained in the capsules of the test and reference formulations.

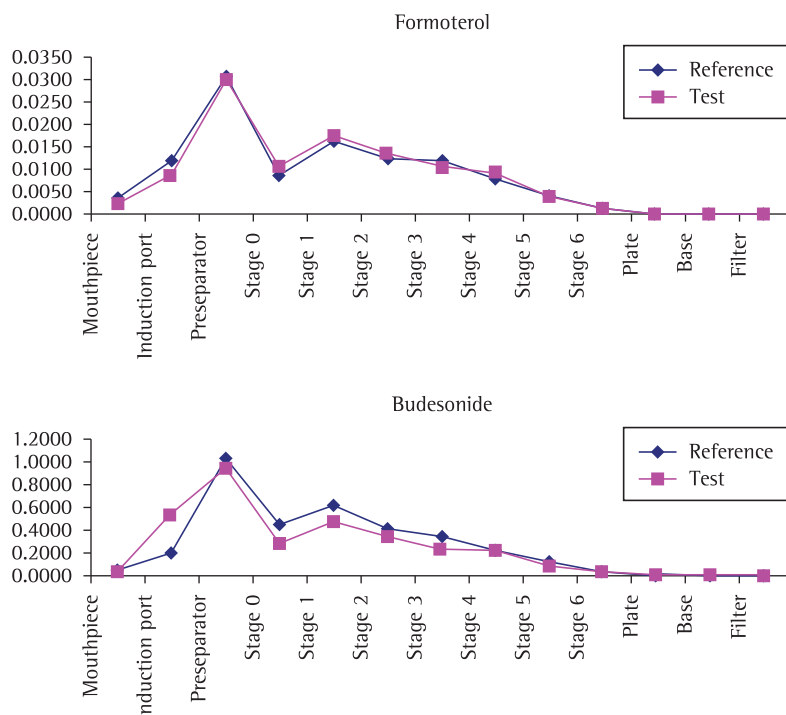


Figure 4 – Comparison of the reference and test formulations regarding aerodynamic particle size distribution of formoterol and budesonide on the different stages of the Andersen cascade impactor.

performance of the test formulation even with low volumes (Figure 5).

Discussion

The use of regular doses of maintenance medication is a key element in asthma management. Current guidelines recommend continuous medication use for achieving asthma control and minimizing future risks,^(3,9) and, therefore, it is important that tests be conducted to validate the active ingredient content of commercial formulations of the drugs prescribed in Brazil.

The tests for determination of the active ingredient content by HPLC demonstrated that the capsules of the test and reference formulations contained budesonide and formoterol. The present in vitro study is of relevance because it allows the determination and validation of the drug content of a formulation, as well as allowing sequential weighing of capsules, all of which ensure formulation homogeneity during production. It was also demonstrated that the test formulation was equivalent to the reference formulation in terms of fine particle fraction.

The results obtained regarding the doses of active ingredients delivered by the inhalers of the test and reference formulations indicate that both were in compliance with the guidelines for the acceptance of such devices by the ANVISA, which are based on the recommendations of the U.S. and Brazilian pharmacopeias.^(6,7) Although the absolute values were lower for the delivered doses of the ingredients of the test formulation than for those of the reference formulation, caution should be exercised in this analysis. First, because both formulations, as previously mentioned, are within the accepted range for this type of test by the pharmacopeias and are therefore equivalent from a pharmaceutical standpoint. Second, because these tests, when repeated, usually show significantly different results: another dosage with other capsules could invert the situation, with the values for the reference formulation being lower than those for the test formulation. For this reason, there is the equivalence acceptance range. Finally, this was an in vitro study: we do not know what the consequences are under in vivo conditions. To answer this question, we would need clinical trials. A study that was recently published in the

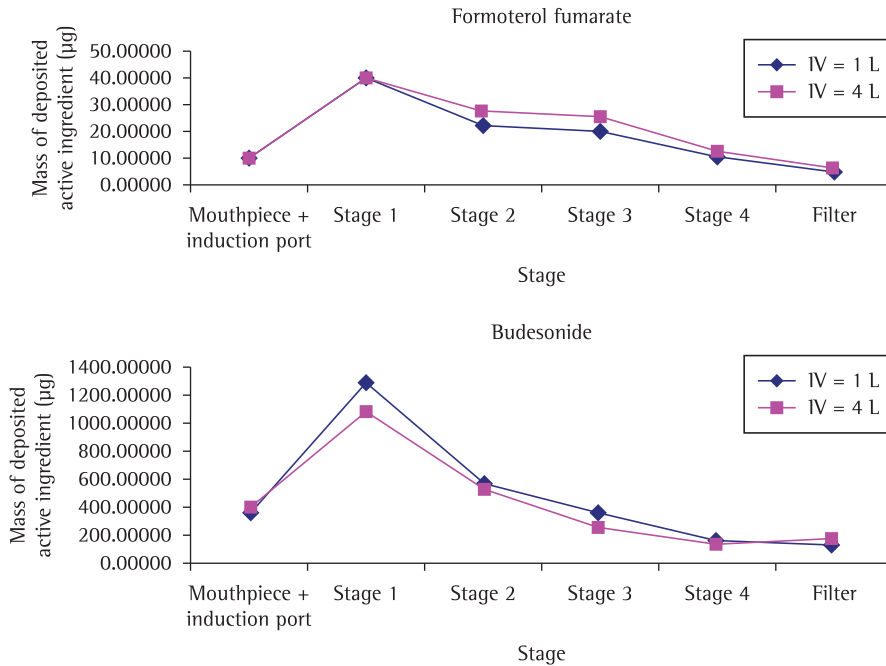


Figure 5 – Aerodynamic particle size distribution of formoterol and budesonide in the test formulation with inspiratory volumes (IVs) of 1 L and 4 L.

Brazilian Journal of Pulmonology⁽¹⁰⁾ showed the clinical efficacy of budesonide alone and of the budesonide/formoterol combination contained in a test formulation. To date, there have been no clinical studies directly comparing the ingredients of a test formulation with those of a reference formulation.

The delivered dose is the dose that is actually available for inhalation at the mouth, and, for the test formulation, the mean delivered dose was obtained after 30 analyses, collected from many inhalers of the chosen product. These procedures ensure device regularity and reproducibility in delivering a certain amount of drug for inhalation. The effectiveness of the inhaled medication also depends on the size of the particles produced following actuation of the device.

The results of the in vitro tests, which, in the present study, were performed with an ACI, showed that the fine particle (diameter < 5 µm) fraction was similar in the test and reference formulations (Figure 4). The use of an ACI for this purpose is validated and recommended by the U.S. and Brazilian pharmacopeias for quality control of medications dispensed in dry powder inhalers.^(6,7) The device used in the test is the most comprehensive, because it is applied to dry powder

inhalers and metered dose inhalers, allowing an evaluation equivalent to that performed in the respiratory tract. It is considered the only technique for measuring particle size that can differentiate the active ingredient from the other components of the formulation, measuring the mass median aerodynamic diameter, a parameter that is particularly relevant to understanding the behavior of the particles during inhalation.

Recommendations for validation of particulate quality control advocate the use of a standard flow rate of 90 L/min. However, it should be borne in mind that inspiratory flow, when the patient is using the device, varies depending on disease state, age, postural position, and patient-device interaction.⁽¹¹⁾

In a study of the Turbuhaler® inhaler, at flow rates of 30 L/min, 60 L/min, and 90 L/min, the mean delivered dose was 37.5%, 64.4%, and 107.4%, respectively. The authors emphasized the importance of flow rate in drug discharge from the inhaler.⁽¹²⁾

In the present study, the delivered fine particle fraction of budesonide and formoterol was 45% and 56%, respectively, when using the Aerocaps® inhaler at a standard flow rate of 90 L/min, compared with 54% and 52%,

respectively, when using the Aerolizer® inhaler. In the study of the Turbuhaler® inhaler, the fine particle fraction was found to be 11.9% and 28.6% of the labeled dose at flow rates of 28.3 L/m and 60 L/m, respectively, confirming that the emitted dose from the inhaler is dependent on patient inhalation flow rates.⁽¹²⁾

Radiolabeling has also been employed to study the regional deposition of inhaled particles. A study of mannitol labeled with ^{99m}technetium-diethylenetriamine pentaacetic acid was conducted in which the Aerolizer® inhaler was used. The deposited lung dose of mannitol particles decreased with increasing particle diameter. For particles measuring 2.7 µm, 3.6 µm, and 5.4 µm in diameter, the mean (standard error) lung deposition was 44.8 ± 2.4%, 38.9 ± 0.9%, and 20.6 ± 1.6%, respectively; *p* < 0.0001). The sites of deposition of particles measuring 2.7 µm and 3.6 µm were similar.⁽¹³⁾ These studies demonstrate the importance of knowing the mean particle diameter of the drugs to be prescribed.

Under in vivo conditions, aerosol particle deposition can be limited by collision with a solid wall or by the aerodynamic characteristics of the particles, which are affected by laminar and turbulent flows, typical of the anatomical features of the airways.^(14,15) To simulate flow variations, the inhalers were tested with a flow volume simulator with inspiratory volumes of 1 L and 4 L, and were shown to perform similarly.

The regional deposition of aerosols is also dependent on temperature and humidity, as well as on the presence of secretions in the airways. All these limitations mean that validation studies of drug formulations must be conducted in clinical research settings in order to prove the therapeutic effectiveness of such formulations.

A study comparing patient handling of various types of inhalers demonstrated that 76% of the patients who used metered dose inhalers made at least one error when using it, whereas the same was true for 49% and 55% of those who used breath-actuated inhalers. Errors compromising treatment efficacy were made by 11.5% of the patients using Aerolizer®, Autohaler®, or Diskus® inhalers, by 28% of those using metered dose inhalers, and by 32% of those using Turbuhaler® inhalers.⁽¹⁶⁾

It is also important to emphasize that the inhalation technique must be reviewed at all visits and that systematic training on the correct

use of the medication contributes to asthma control.⁽¹⁷⁾

In summary, the present in vitro study confirmed that the test and reference formulations were quite similar in terms of active ingredient content and that the delivered dose uniformity of both formulations was within the range recommended by ANVISA. The fine particle fraction at a standard flow rate was approximately half of the delivered dose, which is similar to that of other inhalers commonly used in the treatment of obstructive lung diseases.

References

1. Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro sobre Doença Pulmonar Obstrutiva Crônica - DPOC - 2004. *J Bras Pneumol.* 2004;30(Suppl 5):S1-S42.
2. Global Initiative for Asthma. Bethesda: Global Initiative for Asthma. [cited 2012 Jun 18]. Global Strategy for Asthma Management and Prevention 2011. [Adobe Acrobat document, 124p.]. Available from: http://www.ginasthma.org/uploads/users/files/GINA_Report2011_May4.pdf
3. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o Manejo da Asma - 2012. *J Bras Pneumol.* 2012;38(Suppl 1):S1-S46.
4. Global Initiative for Chronic Obstructive Lung Disease. Bethesda: Global Initiative for Chronic Obstructive Lung Disease. [cited 2012 Jun 18]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. Revised 2011. [Adobe Acrobat document, 90p.]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf
5. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J.* 2011;37(6):1308-31. PMID:21310878. <http://dx.doi.org/10.1183/09031936.00166410>
6. U.S. Pharmacopeial Convention. Rockville: The United States Pharmacopeial Convention. [cited 2012 Jun 18]. Available from: <http://www.usp.org>
7. Agência Nacional de Vigilância Sanitária. Farmacopéia brasileira, 4ª edição, São Paulo: Atheneu; 1988.
8. Wong W, Crapper J, Chan HK, Traini D, Young PM. Pharmacopeial methodologies for determining aerodynamic mass distributions of ultra-high dose inhaler medicines. *J Pharm Biomed Anal.* 2010;51(4):853-7. PMID:19932579. <http://dx.doi.org/10.1016/j.jpba.2009.10.011>
9. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J.* 2008;31(1):143-78. PMID:18166595. <http://dx.doi.org/10.1183/09031936.00138707>
10. Stirbulov R, Fritscher CC, Pizzichini E, Pizzichini MM. Evaluation of the efficacy and safety of a fixed-dose, single-capsule budesonide-formoterol combination in uncontrolled asthma: a randomized, double-blind, multicenter, controlled clinical trial. *J Bras Pneumol.* 2012;38(4):431-7. PMID:22964926. <http://dx.doi.org/10.1590/S1806-37132012000400004>

11. Byron PR, Hindle M, Lange CF, Longest PW, McRobbie D, Oldham MJ, et al. In vivo-in vitro correlations: predicting pulmonary drug deposition from pharmaceutical aerosols. *J Aerosol Med Pulm Drug Deliv.* 2010;23 Suppl 2:S59-69. PMID:21133801. <http://dx.doi.org/10.1089/jamp.2010.0846>
12. Tarsin W, Assi KH, Chrystyn H. In-vitro intra- and inter-inhaler flow rate-dependent dosage emission from a combination of budesonide and eformoterol in a dry powder inhaler. *J Aerosol Med.* 2004;17(1):25-32. PMID:15120010. <http://dx.doi.org/10.1089/089426804322994433>
13. Glover W, Chan HK, Eberl S, Daviskas E, Verschuer J. Effect of particle size of dry powder mannitol on the lung deposition in healthy volunteers. *Int J Pharm.* 2008;349(1-2):314-22. PMID:17904774. <http://dx.doi.org/10.1016/j.ijpharm.2007.08.013>
14. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para teste de função pulmonar. *J Pneumol.* 2002;28(3):S2-S238.
15. Sameshima K. Relação fluxo-resistência no sistema respiratório: aspectos teóricos. *J Pneumol.* 1987;13(Suppl 1):S10-S20.
16. Molimard M, Raheison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med.* 2003;16(3):249-54. PMID:14572322. <http://dx.doi.org/10.1089/089426803769017613>
17. Costa Mdo R, Oliveira MA, Santoro IL, Juliano Y, Pinto JR, Fernandes AL. Educational camp for children with asthma. *J Bras Pneumol.* 2008;34(4):191-5.

About the authors

Marina Andrade-Lima

Coordinator for Pulmonology Clinical Research. *Hospital Pró-Cardíaco*, Rio de Janeiro, Brazil.

Luiz Fernando Ferreira Pereira

Coordinator. Outpatient Smoking Cessation Clinic, Pulmonology Residency Program, Federal University of Minas Gerais *Hospital das Clínicas*, Belo Horizonte, Brazil.

Ana Luísa Godoy Fernandes

Tenured Associate Professor. Federal University of São Paulo/Paulista School of Medicine, São Paulo, Brazil.