The Effect of Altitude on Inhaler Performance

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ABSTRACT: The purpose of the study is to understand the effect of altitude on the performance of selected pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). A testing apparatus that created consistent breath profiles through the Alberta Idealized Throat was designed to test five pMDIs and two DPIs at altitudes of 670, 2450, 3260, and 4300 m. Both gravimetric and chemical assays were conducted to determine the *in vitro* lung dose. Additionally, spray duration and shot weight for pMDIs and device resistance for DPI were measured. There was no significant change in *in vitro* lung dose for any of the pMDIs tested. Shot weight and spray duration were unaffected. The device resistance of the DPIs decreased with increasing altitude and was successfully modeled as a function of ambient pressure. The *in vitro* lung dose of both DPIs showed no significant change when operated with an inhaler pressure drop of 4 kPa, but for the Bricanyl® Turbuhaler®, a significant decrease occurred when matching the volumetric inspiratory flow rate to that of the baseline altitude. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

Patients suffering from asthma commonly use bronchodilators and corticosteroids for the relief and prevention of their symptoms.[1,2] These medications are taken as daily preventative measures, and during asthma exacerbations in rescue situations. They are generally administered using pressurized metered dose inhalers (pMDIs) or dry powder inhalers (DPIs). Both types of inhalers are developed and tested mainly in air-conditioned buildings, set to room temperature and a comfortable humidity, and at sea level or moderate altitudes. Little is known about their performance when operated outside of these conditions. Individuals who participate in outdoor activities such as mountaineering, skiing, or snowmobiling, or who may be either temporarily or permanently residing at high altitudes, may need to use their inhalers at conditions differing from those tested by the manufacturer. Human populations permanently reside at altitudes ranging from 360 m below sea level, such as near the city of Jericho, to 5100 m above sea level, such as in the city of La Rinconada in the Peruvian Andes.[3] Hypsographic demography data show that globally more than 20 million people live at an altitude of greater than 4000 m and more than 175 million people live at an altitude of greater than 2000 m.[4] Asthma prevalence in populations living at moderate altitude may be reduced compared with the sea level because of the typically reduced allergen exposure, whereas asthma at high altitudes >2500 m is expected to worsen because of hypoxia.[5] Asthma patients traveling to high altitudes also tend to have increased symptoms, especially while adjusting to the reduced ambient pressure and typical cold air climate of high altitudes.[6] Exposure to low pressure and low relative humidity environments is also frequent in air travel. The permissible cabin pressure in commercial passenger aircraft is limited by the United States Federal Aviation Agency to a pressure equivalent to an altitude of 2438 m (8000 ft) with most airlines selecting cabin pressures in a range corresponding to 1500–2500 m altitude.[7,8] The air in aircraft cabins is typically very dry. The relative humidity decreases during the flight and levels as low as 2% have been reported on long-haul flights.[9] With such a large range of inhabited and traveled altitudes, it is important to determine the functionality of inhalers to ensure that they operate properly under realistic patient use conditions.

Rescue inhalers are available in DPI and pMDI formats. As the mechanisms for drug delivery are different for DPIs and pMDIs, ambient pressure may affect pMDIs and DPIs differently. Furthermore, for each of these formats, various formulations of medications, excipients, and propellants exist. In pMDIs, propellants create the driving force to expel a spray upon actuation. The most common propellants after the ban of chlorofluorocarbons are tetrafluoroethane (HFC-134a) and heptafluoropropane (HFC-227ea).[10] Excipients in pMDIs include surfactants to prevent particle aggregation and help with lubrication of the valve, and cosolvents, for example, ethanol, to either help dissolve surfactants or dissolve the active ingredient. PMDIs are available in both solution and suspension formulations.[11] Solution pMDIs consist of the drug molecularly dispersed throughout the propellant, creating a solution.[12] Suspension pMDIs consist of the drug forming a particulate suspension within the propellant, necessitating proper shaking to ensure a consistent distribution of drug through the canister prior to actuation.[11,13] DPIs use the patients' inhalation effort to disperse and deliver the dry powder dose from the device. Several formulation formats for DPIs exist, for example, spray-dried formulations or micronized drug particles alone or mixed with coarse particles known as carriers.[14] During inhalation, most of the active ingredients detach from the carriers in

Abbreviations used: pMDI, pressurized metered dose inhaler; DPI, dry powder inhaler; MMAD, mean mass aerodynamic diameter.

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Table 1. List of Inhalers Used, with Active Ingredients and Other Relevant Information from the Product Monographs[21–27]

Product	Label Dosage[a] (μg)	Propellant	Format
Symbicort®	Budesonide 160[a] Formoterol 4.5[a]	HFC 227ea	Suspension pMDI with Povidone K25 and PEG 1000
QVAR™	Beclomethasone Dipropionate 100	HFC 134a	Solution pMDI with Ethanol
Ventolin®	Salbutamol Sulfate 100	HFC 134a	Suspension pMDI without excipients
Airomir™	Salbutamol Sulfate 100	HFC 134a	Suspension pMDI with Ethanol and Oleic Acid
Apo-Salvent	Salbutamol Sulfate 100	HFC 134a	Suspension pMDI with Ethanol and Oleic Acid
Ventolin® Diskus®	Salbutamol Sulfate 200	NA	DPI with Lactose carrier
Bricanyl®	Terbutaline Sulfate 500	NA	DPI without excipients

[a]All listed label dosages are the Canadian label strengths (metered dose) except Symbicort® which follows USA labeling conventions (ex-actuator dose).

carrier DPIs, while powder agglomerates disperse into smaller fragments and separate drug particles in drug-only DPIs.[15] Because the energy for the dispersion mechanism is provided by the inhalation air flow, some DPIs exhibit flow rate dependent performance.[16] The breathing profiles of patients inhaling from a DPI at high altitudes have not been studied to the best of our knowledge. It is hypothesized that patients adjust by either maintaining the volumetric inhalation flow rates they are accustomed to at sea level conditions, resulting in a decreased mouth pressure drop, or by matching the mouth pressure drop to that of sea level conditions, resulting in a higher flow rate.

Very few studies have been conducted on the performance of pMDIs and DPIs at altitude: Küpper et al.[17] suggested, without presenting supporting evidence, that both "spray and powder application systems provide constant dosages," even at high altitudes. This study prompted Röggla and Moser[18] to test four different pMDI to exhaustion at altitudes of 171 m and in a mountain hut at 3100 m. These authors counted the total number of available actuations per canister and found a decrease of 8%–12% at the higher altitude, which raises the question of whether the shot weight, that is, the mass of propellant metered by the metering chamber of the pMDI, is affected by changes in ambient pressure. Cogo and coworkers[5,19] recommended that patients use a spacer with metered dose inhalers at high altitudes, hypothesizing that the reduced pressure and different air density at altitude may affect drug delivery. The effect of altitude on spray duration[20] of pMDIs is also currently unknown.

In the present work, we examine the effect of altitude on drug delivery to the lungs with selected pMDIs and DPIs using *in vitro* measurements performed at various altitudes.

MATERIALS AND METHODS

Inhaler Devices

Seven different inhalers were used for this study, including two DPIs: Bricanyl® Turbuhaler® (lot #3510310B00; AstraZeneca, Inc., Mississauga, Ontario, Canada) and Ventolin® Diskus® (lot #1055, #1019-A, #1033-2; GlaxoSmithKline, Inc., Mississauga, Ontario, Canada), and five pMDIs: Symbicort® 160/4.5 (lot #3000598C00; AstraZeneca, Inc.), Ventolin® (lot #3ZP5854; GlaxoSmithKline, Inc.), Airomir™ (lot #GNJ017A; Medicis now Valeant, Laval, Quebec, Canada), Apo-Salvent (lot #GNH036A; ApoTex Inc., Toronto, Ontario, Canada), and QVAR™ (lot #GNG058A; Medicis now Valeant). Further description of the inhalers is provided in Table 1. For each selected inhaler, five different devices were tested, with the exception of Symbicort® for which three devices were tested.

The inhalers were selected based on a number of criteria. For the DPIs, the Bricanyl® Turbuhaler® was selected because it is free of carrier powder and contains only drug, whereas Ventolin® Diskus® was selected because it contained a lactose carrier. For the pMDIs, a variety of combinations of propellant, solution mixture, and excipients were chosen. The respective formats are listed in Table 1. Apo-Salvent CFC free, a rescue inhaler that is claimed to be identical to Airomir™,[28] was added because little information about its performance has been published.

Test Apparatus

The test apparatus, shown in Figure 1, was designed based on well-known methods for inhaler testing. The apparatus consisted of custom built adapters attached to an Alberta Idealized Throat, to give a tight seal around each inhaler; a filter holder (XX4404670; Millipore, Billerica, Massachusetts) to hold a 47 mm filter (TX40HI20-WW, lot: #T14418GW; Pall Corporation, Port Washington, New York) for collecting particles; a flow meter (4043 E; TSI, Shoreview, Minnesota); a critical flow controller (0001-01-8760A-X; Copley Scientific Limited, Nottingham, UK); and a system of vacuum pumps (0523-101Q-G582DX, Gast, Benton Harbor, Michigan; A65301906, Edwards, Sanborn, New York; KSV16, Kinney, Springfield, Missouri) in parallel. A modified filter holder top plate was manufactured that allowed for a direct connection between the Alberta Idealized Throat and the filter holder. After the filter holder, all components of the test apparatus were connected using vacuum tubing.

The inhaler adapters were rapid prototyped using a 3D printer (Eden350v; Objet, Rehovot, Israel), using designs drawn in Solidworks 2013® (Dassault Systèmes SolidWorks Corporation, Waltham, Massachusetts). To create a tight seal, any spaces that remained between the adapter and inhaler, or between the adapter and the Alberta Idealized Throat, were filled using vacuum grease (Molykote Silicone 557; Dow Corning, Midland, Michigan) and Parafilm®.

Aerosol performance has often been assessed using a United States Pharmacopeia induction port, however, as noted by Zhang et al.,[29] the Alberta Idealized Throat provides a more accurate representation of the administered *in vitro* lung dose. As this study is concerned with the impact that reduced pressure will have during patient use, it is preferable to use a test apparatus that accurately mimics deposition in human upper airways.

The critical flow controller was used in order to generate a consistent flow profile. This device has a solenoid valve with a flow rate response time of 25 ms. As shown by De Boer et al.,[30] the shape of the flow curve can have an impact on delivered