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RESEARCH PAPER

Comparison of *In Vitro* Deposition of Pharmaceutical Aerosols in an Idealized Child Throat with *In Vivo* Deposition in the Upper Respiratory Tract of Children

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ABSTRACT

Purpose Deposition of drug emitted from two commercially available inhalers was measured in an *in vitro* child oral airway model and compared to existing *in vivo* data to examine the ability of the child model to replicate *in vivo* deposition.

Methods *In vitro* deposition of drug from a QVAR® pressurized metered dose inhaler (pMDI) and Pulmicort® Turbuhaler® dry powder inhaler (DPI) in an Idealized Child Throat (1) and downstream filter was measured using UV spectroscopy and simulated realistic breathing profiles. Potential effects of ambient relative humidity ranging from 10% to 90% on deposition were also considered.

Results *In vitro* QVAR pMDI deposition in the idealized mouth-throat at 50% RH (39.2 ± 2.3% of delivered dose) compared well ($p > 0.05$) with *in vivo* extrathoracic deposition in asthmatic children age 8 to 14 (45.8 ± 12.3%). *In vitro* Turbuhaler DPI deposition in the idealized mouth-throat at 50% RH (69.0 ± 1.5%) matched *in vivo* extrathoracic deposition ($p > 0.05$) in 6 to 16 year old children with cystic fibrosis (70.4 ± 21.2%). The effects of ambient humidity were found to be insignificant for Turbuhaler and minor for QVAR.

Conclusions The Idealized Child Throat successfully mimics *in vivo* deposition data in school age children for the inhalers tested, and may provide a standard platform for optimizing pediatric treatment with inhaled pharmaceutical aerosols.

KEY WORDS extrathoracic airways · lung delivery · pediatric · QVAR pressurized metered dose inhaler · turbuhaler dry powder inhaler

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ABBREVIATIONS

DPI	Dry powder inhaler
MMAD	Mass median aerodynamic diameter
pMDI	Pressurized metered dose inhaler
RH	Relative humidity

INTRODUCTION

Inhaled pharmaceutical aerosols have been used to great effect in the treatment of respiratory diseases in adult and pediatric patients. A major consideration in the use of inhaled pharmaceutical aerosols is extrathoracic deposition, which plays an important role in determining the total lung dose from pharmaceutical inhalers (2–4). Drug lost to deposition in the extrathoracic region can reduce the efficacy of inhaled medications (5,6) and lead to deleterious side effects (7,8). Furthermore, for many inhaled pharmaceutical aerosols, the total lung dose can often be approximated by the dose delivered distal to the extrathoracic region (4). With these considerations in mind, accurately characterizing extrathoracic deposition is an important step in ensuring that patients receive a consistent and appropriate dose when using marketed inhalation devices.

The fluid mechanic interactions that occur between the oral cavity and flow exiting an inhaler are inherently complex (9,10), making geometric models of the mouth-throat region useful in predicting extrathoracic deposition and total lung dose. *In vitro* methods using realistic oral airway replicas have been shown to successfully predict *in vivo* deposition in adults (4,11,12), though issues stemming from intersubject variability and complex manufacturing of anatomical geometries are often encountered. From the point of view of regulatory compliance and preclinical development, the use of a single standardized geometry is an attractive alternative to realistic replicas (13,14). Historically, the United States Pharmacopeia

Induction Port (USP IP) has been used as a common standard to compare various inhalers, though its simple design, lacking resemblance to a human oral airway, fails to replicate mouth-throat deposition (11,15,16). To address the poor replication of *in vivo* deposition observed with the USP IP, work at the University of Alberta led to the development of the Alberta Idealized Throat (17). This idealized model, incorporating simplified analogues of important geometric features observed in adult extrathoracic airways, has been shown to accurately replicate average deposition in adults (15,16,18), and is commercially available (Copley Scientific, UK). Using an alternative methodology, Delvadia *et al.* recently developed a characteristic mouth-throat and upper airway model based on simplified anatomical data (19). This model captured mean *in vivo* deposition for five commercial dry powder inhalers (20), and together with complementarily scaled versions, replicated the mean and variability of *in vivo* deposition from Budelin Novolizers (19).

Recent interest has turned towards optimizing respiratory drug delivery in pediatric patients. Despite differences in anatomy, physiology, disease processes, pathophysiology, and pharmacokinetics, children are commonly prescribed inhalers and formulations originally designed for adults (21). Young patients may be treated off-label, necessitated by a lack of clinical trial data. Along with the traditional role of managing respiratory disease, recent developments (22–24) have hinted towards the utility of aerosol therapy as a non-invasive path for drug delivery via systemic circulation. Therapies for systemic treatments are often subject to narrow margins between efficacious use and harmful systemic effects, and are thus subject to stringent dose quantification (25). As such, there is a vested interest in developing improved methods for testing pharmaceutical inhalers and formulations in pediatric patients for regulatory compliance and preclinical development.

While a limited number of *in vivo* studies have examined radiolabelled aerosol deposition from pharmaceutical inhalers in pediatric patients (26–30), the ethical concerns associated with these types of investigations make *in vitro* methods a favorable option. *In vitro* methods allow for greater control over the variables that affect deposition of inhaled pharmaceutical aerosols, including environmental conditions such as temperature and humidity. Unfortunately, *in vivo* deposition studies rarely report the environmental conditions under which clinical data is obtained. This absence of such data complicates the validation of *in vitro* work via comparison to *in vivo* deposition, as environmental conditions, humidity in particular, are known to affect the deposition of some pharmaceutical aerosols (31–33). To the authors' knowledge, only one *in vitro* study has examined the effects of humidity on inhaled pharmaceutical aerosol deposition in idealized mouth-throat models: Shemirani *et al.* recently demonstrated that extrathoracic deposition from solution and suspension pMDIs may increase significantly with increasing relative humidity (RH) through experiments with the Idealized Alberta Throat (33).

In vitro deposition has been examined in child (34–37) and infant (38–42) physical airway replicas, but the need for a standard idealized model for predicting average pediatric deposition remains. Bickmann *et al.* modified the Alberta Idealized Throat based on magnetic resonance imaging scans of 5-year-old children, altering the dimensions of the oral cavity, pharynx, larynx, and trachea to match that observed in younger patients (43). This idealized throat, representative of preschool children, was used to examine deposition from a Respimat® Soft Mist™ Inhaler and a pressurized metered dose inhaler (pMDI) plus spacer. More recent work with this geometry has focused on deposition measurements with Respimat Soft Mist Inhalers (44), and SalbuHexal® Easyhaler® and Salbu Novolizer® dry power inhalers (45). Whether this 5-year-old child idealized throat replicates *in vivo* deposition in preschool children has not, to the authors' knowledge, been determined.

With inhaler use being more common among children and adolescents over the age of 5, an idealized throat representative of children 6 to 14 years old has recently been developed by uniformly scaling the Idealized Alberta Throat to match the average characteristic diameter, defined as the airway volume divided by surface area, measured in nine child oral airway replicas (1). This Idealized Child Throat has been shown to match average *in vitro* deposition under constant flow rates (1) and tidal breathing (37), but has yet to be compared to *in vivo* data.

The present study thus aims to validate the Idealized Child Throat with *in vivo* deposition data for inhalers commonly used in children. Specifically, a pMDI delivering beclomethasone dipropionate for asthma prophylaxis and maintenance treatment (QVAR®, Medicis Pharmaceutical Corporation, Scottsdale, AZ, USA) and a multidose dry powder inhaler (DPI) delivering budesonide for the same indication (Pulmicort® Turbuhaler®, AstraZeneca Canada Inc., Mississauga, Ontario, Canada) were tested with the Idealized Child Throat using simulated breathing profiles for comparison with published scintigraphic *in vivo* deposition studies (26,28). To account for potential discrepancies arising from differences in humidity between *in vitro* measurements in the present study and previously reported *in vivo* data, experiments were performed in an environmental chamber at various RH, thus allowing for an analysis of the effects of ambient humidity on deposition in the Idealized Child Throat.

MATERIALS AND METHODS

Idealized Child Throat

The Idealized Child Throat was developed by uniformly scaling down the Alberta Idealized Throat by a factor of 0.62 to match the average characteristic diameter, defined

as the airway volume divided by its surface area, of nine oral airway replicas of children age 6 to 14 years old (1). This mouth-throat geometry contains simplified analogues of anatomical features that heavily influence the transport and deposition of aerosols in the extrathoracic airways (13), and has been shown to replicate the *in vitro* deposition of micrometer-sized particles under constant flow rates (1, 36) and tidal breathing (37). A rapid prototyped model of the Idealized Child Throat was made using stainless steel (Linear Mold & Engineering, Livonia, MI, USA), the use of which reduces artificial electrostatic surface charging effects and avoids solvent contamination issues during chemical assay.

Selected Inhalers

Two commercially available inhalers were selected for use in the present study, including a pMDI delivering beclomethasone dipropionate for asthma prophylaxis and maintenance treatment (label claim of 100 μg beclomethasone dipropionate, QVAR® pMDI, manufactured by Medicis Pharmacetuical Corporation, Scottsdale, AZ, USA, distributed by Medicis Canada, Ltd., Toronto, Ontario, Canada) and a multidose DPI delivering budesonide for the same indication (label claim of 200 μg budeonside, Pulmicort® Turbuhaler®, manufactured AstraZeneca Canada Inc., Mississauga, Ontario, Canada), owing to the availability of *in vivo* scintigraphic deposition data for comparison purposes (26,28). Devadason *et al.* examined deposition of radiolabeled budesonide delivered via Pulmicort Turbuhaler in children 4 to 16 years old with cystic fibrosis (26). A later study by the same group examined the deposition of radiolabeled QVAR administered via Autohaler™, a breath-actuated inhaler, in asthmatic children 5 to 14 years old (28). QVAR pMDIs have been shown to achieve the same deposition as QVAR Autohalers for adult patients demonstrating proper inhalation techniques (46), and equivalent clinical efficacy for these inhalers has been demonstrated in children (47); thus, the use of a pMDI rather than an Autohaler in the present study was considered a negligible source of error. To replicate patient use, inhalers were handled and operated according to product insert instructions. Prior to testing, the QVAR pMDI was primed by firing to waste four times at 1 min intervals.

Experimental Setup

Schematic diagrams of the experimental setup for the QVAR pMDI and Turbuhaler DPI are shown in Fig. 1. The Idealized Child Throat was coupled to a collection filter with a pore size of 0.3 μm (Respirgard II™ bacterial/viral filters; Vital Signs Inc., Englewood, CO, USA) and placed within a modified environmental chamber with glove ports (CEO-910 W-4; Lunair Environmental, Williamsport, PA, USA) and an integrated compressed dry air line (<1% RH). Conditions within the chamber were monitored using a humidity and temperature meter (Vaisala HUMICAP® HM70; Helsinki, Finland) accurate to ±1% RH of reading for 0–90% RH and ±0.2°C at 20°C. Inhalers were attached to the Idealized Child Throat prior to being placed in the environmental chamber using custom-built adapters.

Separate flow systems were used to draw air through the setup owing to differences in device operation for press-and-breath QVAR pMDIs and breath-actuated Turbuhaler DPIs. The QVAR pMDI was examined under a constant flow rate, generated by a vacuum pump (Model 0523; Gast Manufacturing Inc., Benton Harbor, MI, USA) and measured using a digital mass flow meter (Model 4043; TSI Incorporated, Shoreview, MN, USA) accurate to 2% of reading. In contrast, the Turbuhaler DPI was tested using a time-variant inhalation flow profile, generated by a pulmonary waveform generator (MH Custom Design & Mfg. L.C., Midvale, UT, USA), as discussed below.

In Vitro Deposition Testing

Prior to each test run, the two halves of the Idealized Child Throat were coated with silicone oil (Molykote 316; Dow Corning Corporation, Midland, MI, USA) to minimize particle bounce. After allowing 15 min for solvent evaporation, the idealized throat was assembled, connected to the inhaler and downstream filter, and placed within the environmental chamber. The chamber was closed, and conditions were set to the desired temperature and RH; deposition from each inhaler was examined under several RH values (10, 30, 50, 70, 90% RH) at a temperature of 23.5°C. After allowing for a sufficient period of time for conditions to stabilize within the chamber, approximately 5 min, inhalers were actuated into the Idealized Child Throat under simulated breathing. To achieve realistic *in vitro* assessment of deposition in the Idealized Child Throat, breathing parameters were chosen to closely mirror those observed *in vivo* for each inhaler. As previously noted, different setups were used to test the QVAR pMDI and Turbuhaler DPI. A summary of simulated breathing parameters is presented in Table I.

QVAR Procedure

Deposition from the QVAR pMDI was examined using a constant inhalation flow rate, set to equal the average inhalation flow rate generated by patients examined in the Devadason *et al.* study on radiolabeled QVAR deposition (28). Reported heights of subjects from this study (weighted average of 136.8 cm, all male patients) were used to estimate the average inspiratory capacity of enrolled patients, 1.6 L, via the reference equations of Stocks and Quanjer (48). The average *in vivo* inhalation flow rate was estimated using this measure of average inspiratory capacity and reported data

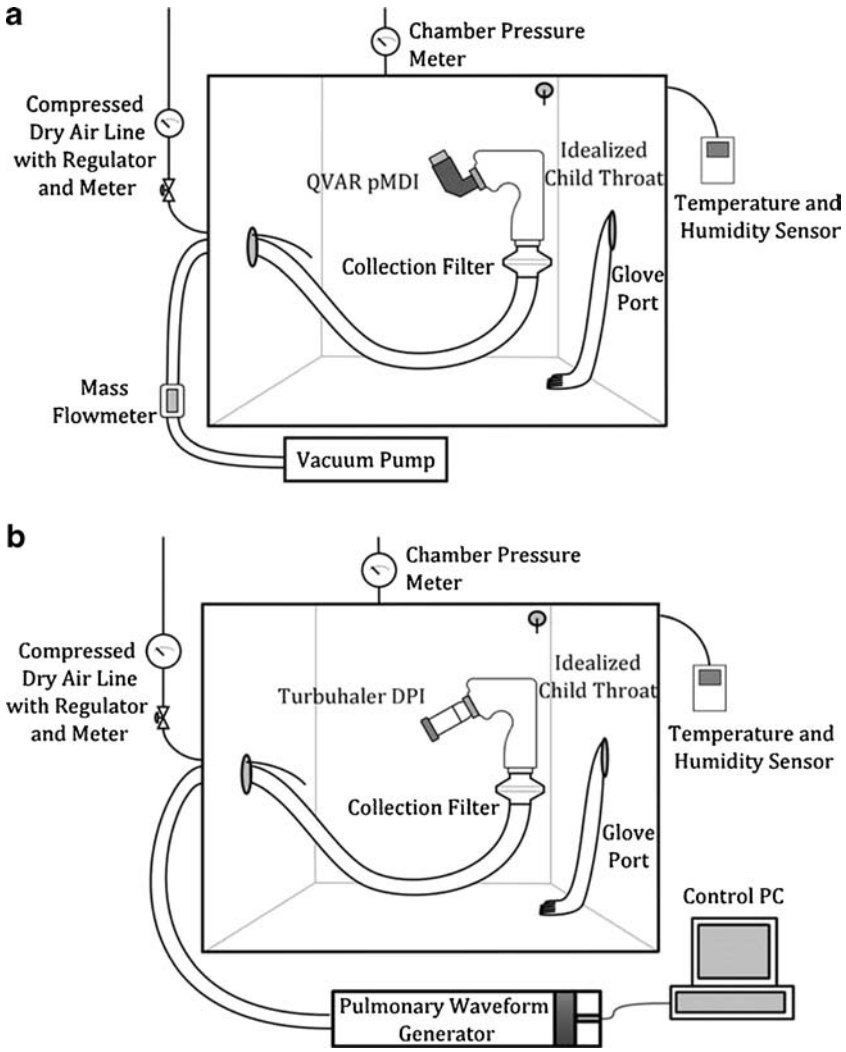

Fig. 1 Experimental setup for (**a**) QVAR pMDI with a constant flow rate set by a vacuum pump and (**b**) Turbuhaler DPI with a time-variant flow profile supplied by a pulmonary waveform generator.

concerning inspiratory time (28); mean inspiratory time, 2.12 s, was calculated by subtracting the time to actuation of the Autohaler, 0.31 s, from the total inspiratory time, 2.43 s. From these values of inspiratory capacity and inspiratory time, the average *in vivo* flow rate was calculated to be approximately 45 L/min. Thus, for QVAR, the vacuum pump was set to draw air at a constant rate of 45 L/min through the Idealized Child Throat.

Table I Summary of Simulated Breathing Parameters used to Examine Deposition in the Idealized Child Throat

	Inhaled Volume (L)	Inspiratory Flow Rate (L/min)	Flow Increase Rate (L/sec^2)
QVAR pMDI	1.6	45	-
Turbuhaler DPI	1.5	53[a]	2

[a] Corresponds to peak inspiratory flow rate generated by the pulmonary waveform generator for the Turbuhaler DPI

With the idealized throat, QVAR pMDI, and collection filter connected to the flow system inside the environmental chamber, the vacuum pump was turned on, and the flow rate was allowed to stabilize at 45 L/min. The pMDI was then actuated into the Idealized Child Throat, and a stopwatch (accurate to ±0.1 s) was used to manually measure the time required for 1.6 L of air to be drawn through the idealized throat, equal to 2.1 s for the 45 L/min inhalation flow rate. The vacuum pump was then turned off, and the idealized throat, inhaler, and collection filter were removed from the chamber for deposition analysis.

Turbuhaler Procedure

As the Turbuhaler DPI is a breath-actuated device, a pulmonary waveform generator was used to generate a time-variant, nearly trapezoidal inhalation profile, consisting of a constant flow increase rate from zero to peak inspiratory flow rate, followed by a period of constant inhalation, then a linear decrease back to zero flow. Studies have demonstrated the

performance of the Turbuhaler as being heavily dependent on flow parameters including peak inspiratory flow rate and flow increase rate (49–53). Therefore, to closely approximate *in vivo* breathing parameters, the pulmonary waveform generator was configured to deliver appropriate values of flow increase rate and peak inspiratory flow rate for the patients under consideration in the Turbuhaler study on children with cystic fibrosis by Devadason *et al.* (26). From reported data of patient-specific peak inspiratory flow rate, the average peak inspiratory flow rate of children in the study was calculated to equal 53 L/min. An estimate of average flow increase rate generated by children with cystic fibrosis through the Turbuhaler, 2 L/s^2, was obtained from available literature; data from Tiddens *et al.* (54) suggest that a majority of children between the ages of 6 and 18 years old with cystic fibrosis can generate a flow increase rate of 2 L/s^2 in inhalers with device resistances similar to that of Turbuhaler. Patient demographics and age-appropriate estimates of body height (average age of 10 years, average height of 136 cm, male and female patients) allowed for an estimation of average inspiratory capacity using the equations of Stocks and Quanjer (48), equal to 1.5 L. These values for peak inspiratory flow rate, flow increase rate, and inspiratory capacity were used to fully define the time-variant inhalation profile supplied by the pulmonary waveform generator.

After connecting the Turbuhaler, Idealized Child Throat, and filter to the experimental setup, sufficient time was allowed for the environmental conditions to stabilize after which the Turbuhaler was primed. Immediately after priming, the pulmonary waveform generator was used to deliver the simulated breathing profile through the inhaler. The idealized throat, Turbuhaler, and filter were then removed from the environmental chamber for deposition analysis.

Quantification of Deposition

Following inhaler actuation into the Idealized Child Throat and removal from the environmental chamber, the idealized throat and filter were rinsed, respectively, with 10 mL and 5 mL of methanol. The solution collected from each deposition site was transferred to volumetric flasks, and adjusted to volume using methanol. Samples were subjected to chemical assay by UV spectroscopy (Model 8452A; Hewlett Packard, Greely, Ontario, Canada) at wavelengths of 238 nm for beclomethasone dipropionate and 244 nm for budesonide to determine the mass of drug depositing in the Idealized Child Throat and collection filter.

The mass of drug depositing in the Idealized Child Throat was considered an *in vitro* measure of extrathoracic deposition. Because only inspiratory flow was considered with the present setup, dose depositing on the collection filter was considered analogous to *in vivo* lung deposition plus exhaled dose. The delivered dose was calculated as the sum of active pharmaceutical ingredient recovered from the Idealized Child Throat and collection filter. Mouth-throat deposition was defined as the dose depositing in the Idealized Child Throat, while the dose collected on the filter was defined as the lung dose. This *in vitro* lung dose, the dose delivered distal to the extrathoracic region, is an approximation of the total lung dose measured *in vivo* (4). For the initial *in vitro* analysis of the effects of humidity, the delivered dose, mouth-throat deposition, and lung dose were reported as a percentage of the label claim for each inhaler as reported in Canada, equivalent to the ex-valve dose for pMDIs. However, mouth-throat deposition was also reported as a percentage of delivered dose for further *in vitro* analysis to be comparable with *in vivo* data sets from Devadason *et al.*, which were reported as the percentage of the total recovered dose within the body (26,28). Experimental conditions were not explicitly reported in the *in vivo* studies by Devadason *et al.* (26,28). However, assuming these studies were performed in a heated, ventilated, and air-conditioned location, typically designed to maintain humidity ranging from 40% to 60%, a reasonable estimate of 50% RH can be assumed. Therefore, for comparisons to *in vivo* data were performed with *in vitro* deposition measurements obtained at 50% RH.

Five measurements were performed at each RH, for a total of 25 runs with each inhaler. Deposition results were subjected to one-way ANOVA with post-hoc Tukey's Honestly Significant Difference for a comparison of deposition at different RH, and unpaired Student's t-tests with Welch's correction for comparisons between *in vitro* and *in vivo* data (Prism 6.02; GraphPad Software, Inc., La Jolla, CA, USA), where a p value < 0.05 was considered significant.

RESULTS

Effect of Humidity

The delivered dose, deposition in the idealized throat, and lung dose for the QVAR pMDI and Turbuhaler DPI under varying RH are shown in Fig. 2, expressed as percentage of label claim. For the QVAR pMDI, no significant difference was observed in the delivered dose ($p = 0.722$) for increasing RH, while significant differences were noted in mouth-throat deposition ($p = 0.015$) and lung dose ($p < 0.0001$). Average delivered dose was $77.4 \pm 2.4 \mu$g beclomethasone dipropionate ($n = 25$), equal to $77.4 \pm 2.4\%$ of label claim. For Turbuhaler, no significant differences were noted in the delivered dose ($p = 0.727$), mouth-throat deposition ($p = 0.567$), or lung dose ($p = 0.774$) for increasing RH. Average delivered dose was $116.7 \pm 27.5 \mu$g budesonide ($n = 25$), equivalent to $58.4 \pm 13.7\%$ of label claim. In terms of dose variability, the coefficient of variation of the average delivered dose was 0.032 for the QVAR pMDI, and 0.235 for the Turbuhaler.

Mouth-throat deposition in the idealized model, expressed as a percentage of the delivered dose, is shown in Fig. 3. For the QVAR pMDI, significant differences in mouth-throat deposition were noted for varying RH ($p < 0.0001$ via ANOVA), with a slight trend of increasing mouth-throat deposition for increasing RH. For QVAR, the lowest mouth-throat deposition (36.2±1.2%) was measured at 10% RH, while the highest (42.6±2.0%) was measured at 90% RH. Post-hoc analysis showed that for moderate ranges in humidity (30% to 70%), the effect of humidity on mouth-throat deposition was not significant, except for a slight difference between 30% and 70% RH ($p = 0.014$). This indicates that the deposition measured at 50% RH provides a good estimate of the typical deposition values expected in air conditioned spaces. At 50% RH, mouth-throat deposition of beclomethasone dipropionate via QVAR pMDI was 39.2± 2.3% of delivered dose ($n = 5$).

For Turbuhaler, no significant differences in mouth-throat deposition were observed for increasing RH ($p = 0.210$ via ANOVA). The lowest deposition measured in the mouth-throat (64.1±4.2% of delivered dose) was measured at 10% RH, while the highest was observed at 70% RH (69.0±5.3%). Mouth-throat deposition of budesonide via Turbuhaler at 50% RH was 69.0±1.5% ($n = 5$).

In Vitro – In Vivo Comparison

Devadason *et al.* reported deposition of radiolabeled QVAR in children age 5 to 14 in terms of the total dose depositing in the body or exhaled, equivalent to the delivered dose defined in the present work. Extrathoracic deposition was measured to be 59.7±8.2% ($n = 5$), 48.9±12.3% ($n = 7$), and 40.3±11.8% ($n = 4$) of delivered dose, respectively, for children age 5 to 7, 8 to 10, and 11 to 14 (28). No significant difference was observed between *in vitro* mouth-throat deposition at 50% RH and *in vivo* extrathoracic deposition for children age 11 to 14 ($p = 0.865$) and 8 to 10 ($p = 0.084$), while a significant difference was observed for deposition in children age 5 to 7 ($p = 0.004$). Pooling the two oldest age groups, which are similar to the range of subjects upon which the Idealized Child Throat was based (1), mouth-throat deposition of QVAR in the Idealized Child Throat at 50% RH agreed well with the *in vivo* average for children age 8 to 14 of 45.8±12.3% ($p = 0.113$).

For the *in vivo* study on Turbuhaler, Devadason *et al.* reported extrathoracic deposition separately in terms of the oropharynx and the stomach (26). From their reported data, equivalent extrathoracic deposition was recalculated by adding deposition in the oropharynx and stomach; this gave estimates of *in vivo* extrathoracic deposition equal to 70.4± 20.5%, 75.6±24.5%, and 65.1±21.1% of delivered dose in children age 6 to 8, 9 to 12, and 13 to 16, respectively. No significant difference was observed between *in vitro* and *in vivo* deposition for these age groups of 6 to 8 ($p = 0.874$), 9 to 12 ($p = 0.539$) and 13 to 16 ($p = 0.670$); mouth-throat deposition in the Idealized Child Throat thus compares well with *in vivo* deposition in children age 6 to 16 with cystic fibrosis of 70.4± 21.2% ($p = 0.424$).

A summary of these comparisons is shown in Fig. 4, where *in vitro* mouth-throat deposition is compared to *in vivo* extrathoracic deposition in children age 8 to 14 using QVAR and children age 6 to 16 using Turbuhaler.

DISCUSSION

Humidity Effects

While the delivered dose from the QVAR pMDI remained consistent at varying RH, significant differences in regional deposition were observed. The relatively weak trend of increasing mouth-throat deposition with increasing RH, illustrated in Fig. 3, mirrors the results of a recent study in which the deposition of a beclomethasone dipropionate pMDI (100 μg beclomethasone dipropionate per dose, 13% w/w ethanol, 1.3% w/w glycerol, in HFA134a - a similar formulation to QVAR) was examined in the Alberta Idealized Throat (33). In that study, Shemirani *et al.* found no difference in deposition for the HFA-134a beclomethasone dipropionate pMDI between 0% and 35% RH, but a significant difference between 35% and 80% RH, at a temperature of 20°C and flow rate of 60 L/min. Between 35% and 80% RH, mouth-throat deposition increased from 43.5% to 50.8%, while the lung dose decreased from 56.5% to 48.0%, reported as a percentage of recovered dose (including retained dose within the pMDI actuator). This effect of humidity on deposition from pMDIs is believed to relate to the condensation of water onto propellant-cooled residual dry particles (31). As noted by Shemirani *et al.*, higher RH would likely cause an increase in particle diameter, leading to increased throat deposition and a correspondingly lower lung dose (33). In the Idealized Child Throat, this effect was observed in the relatively minor 6% increase in mouth-throat deposition for RH increasing from 10% to 90%.

Unlike QVAR, regional deposition with Turbuhaler showed no significant dependence on humidity, with mouth-throat deposition and lung dose remaining consistent between 10% and 90% RH. As evident in Fig. 2, the Turbuhaler yielded a high variability in delivered dose compared to QVAR. This reflects the considerable variability of Pulmicort Turbuhaler performance documented in the literature (32,52,55,56).

Despite a high variability in delivered dose, percentage deposition in the mouth-throat and the lung dose remained consistent across all examined RH for the Turbuhaler. For QVAR, no significant difference in delivered dose was measured at varying RH, while mouth-throat deposition increased

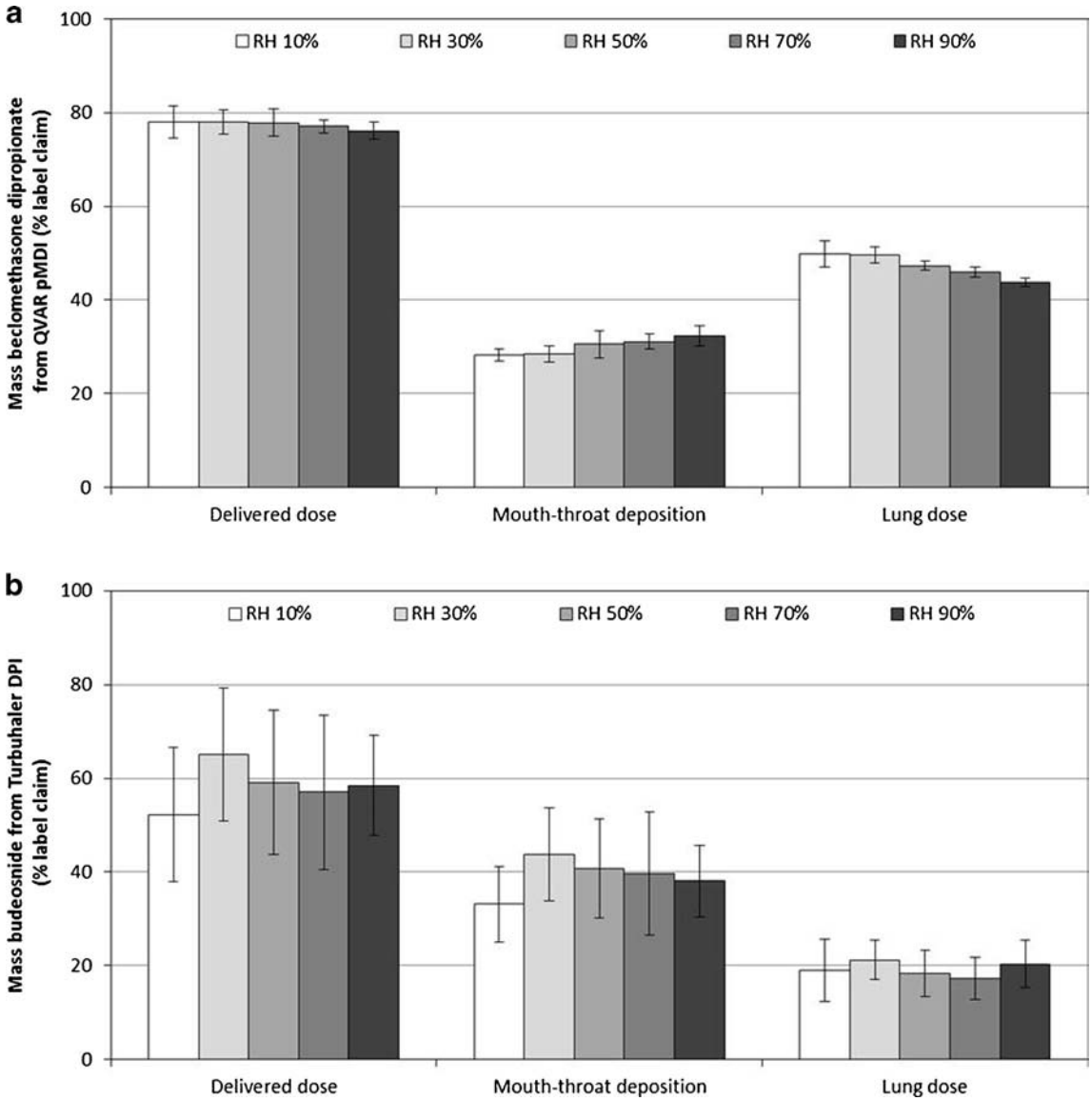

Fig. 2 Mean deposition of (**a**) the QVAR pMDI and (**b**) the Turbuhaler DPI measured in the Idealized Child Throat under varying RH. Delivered dose, mouth-throat deposition, and lung dose are expressed as a percentage of the label claim for each device. Error bars denote standard deviation ($n = 5$).

slightly from 36.2% to 42.6% for RH increasing from 10% to 90%. Considering deposition in the mouth-throat and the lung dose, with no significant differences for Turbuhaler and minor differences for QVAR, environmental conditions under which *in vivo* studies on the QVAR pMDI and Turbuhaler DPI were performed likely played a minor role on regional deposition measurements. This may not always be the case however, as demonstrated by the 30% decrease in lung dose from the Flixotide Evohaler measured by Shemirani *et al.* for RH increasing from 0% to 80% at a temperature of 20°C (33). Thus, it is recommended that authors of *in vivo* studies report the environmental conditions under which experiments are performed to aid in proper drug delivery comparisons.

In Vivo – In Vitro Comparison

Deposition in the Idealized Child Throat compared well with the *in vivo* measurements by Devadason *et al.* (28) for children age 8 to 14 using the QVAR pMDI. Extrathoracic deposition in children age 11 to 14, at 40.3±11.8% of delivered dose, matched mouth-throat deposition measured in the idealized throat at 50% RH, 39.2±2.3%. Good agreement was also found for *in vivo* extrathoracic deposition in children age 8 to 10. However, children age 5 to 7 demonstrated considerably higher mouth-throat deposition compared to older patients, with average extrathoracic deposition in this young age group equaling 59.7±8.2%, resulting in a poor comparison to

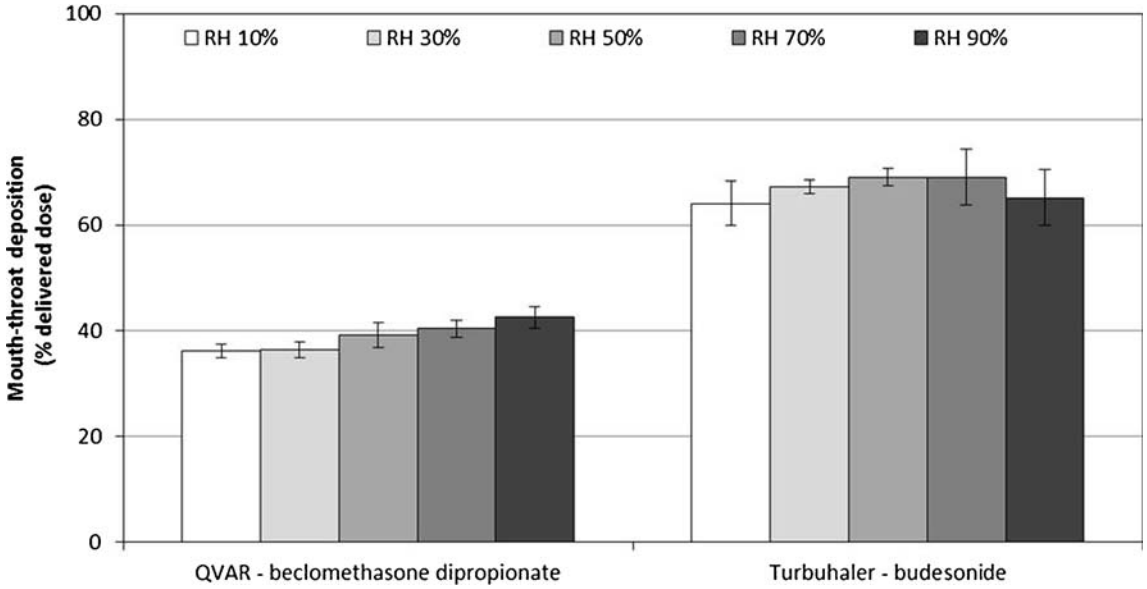

Fig. 3 Mouth-throat deposition for the QVAR pMDI and Turbuhaler DPI in the Idealized Child Throat setup at varying RH, expressed as a percentage of delivered dose. Error bars denote standard deviations ($n = 5$).

deposition in the Idealized Child Throat. This likely stems from age-related differences in the size of the extrathoracic region. The average age of children used to develop the Idealized Child Throat was 11 years (1), and as such the size of the Idealized Child Throat is more in line with the dimensions of the extrathoracic regions of older patients in the Devadason *et al.* (28) study. Increased impaction of the spray emitted from the QVAR pMDI would be expected in younger patients due to the decreased distance between the back of the throat and the mouthpiece of the inhaler, resulting in the increased extrathoracic deposition observed *in vivo*. Measurements in the larger Alberta Idealized Throat support this theory; in an examination of deposition from a QVAR pMDI in the Alberta Idealized Throat, Zhang *et al.* (15) measuring a mouth-throat deposition of $25.8 \pm 4.2\%$ of delivered dose, considerably lower than that observed here in the Idealized Child Throat. *In vivo* deposition measurements of $100\,\mu$g QVAR in older patients also support this trend, with Leach *et al.* reporting an extrathoracic deposition of $29.0 \pm 18.0\%$ of delivered dose in adult males age 18 to 55 (57).

For the Turbuhaler DPI, deposition in the Idealized Child Throat compared well with that observed in children age 6 to 16 with cystic fibrosis (26). Devadason *et al.* also measured deposition in two patients 3 to 5 years old, measuring a rather large average extrathoracic deposition of 86.8% of delivered dose (recalculated from reported deposition in the oropharynx and stomach). However, these two patients were much younger than the age represented by the Idealized Child Throat, and a proper statistical comparison to *in vitro* data could not be performed with only two subjects. For the time-variable flow

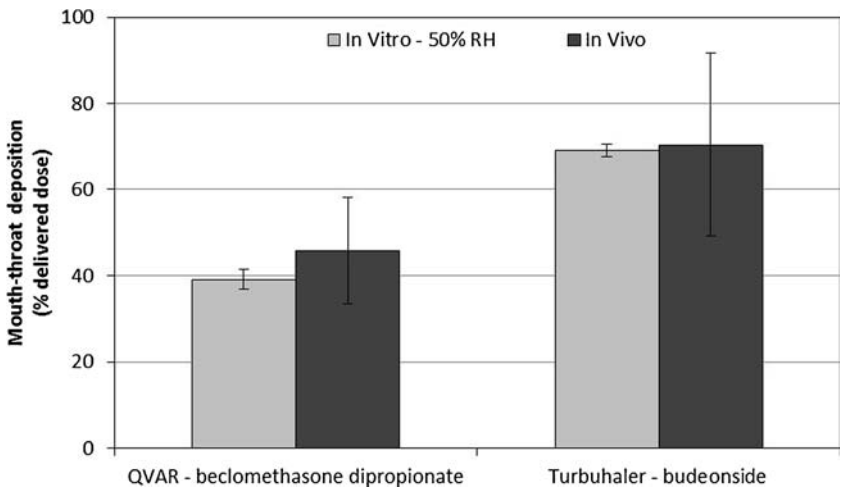

Fig. 4 Mouth-throat deposition in the Idealized Child Throat at 50% RH compared to *in vivo* extrathoracic deposition in children age 8 to 14 for QVAR (28) and 6 to 16 for Turbuhaler (26). Error bars denote standard deviation ($n = 5$).

profile used in the present work, flow increase rates and peak inspiratory flow rates representative of appropriate *in vivo* values for children with cystic fibrosis capture average *in vivo* deposition effectively. However, the parameters of flow increase rate and peak inspiratory flow rate are patient dependent, and given the dependence of Turbuhaler performance on these parameters (48–53), it is important to use values representative of the patient group under consideration in rigorous *in vitro* analyses. This importance is illustrated by a comparison of deposition in the Idealized Child Throat to that measured by Wildhaber *et al.* (27) for radiolabel budesonide via Turbuhaler in asthmatic children age 6 to 16. The asthmatic patients in that *in vivo* study generated a peak inspiratory flow rate of 65 L/min, notably higher than that obtained by the cystic fibrosis patients of Devadason *et al.* (26), though no data was reported concerning flow increase rate. The extrathoracic dose was recalculated as a percentage of the delivered dose from reported data (delivered dose equaling oropharyngeal deposition plus lung deposition), yielding an average of 55.4% of delivered dose, considerably less than the mouth-throat deposition measured in the Idealized Child Throat at 50% RH (69.0±1.5%) and the average extrathoracic deposition measured *in vivo* for children with cystic fibrosis at 70.4± 21.2% (28). As evident by the increased average peak inspiratory flow rate, the asthmatic patients in the study by Wildhaber *et al.* (27) were able to generate more energy through the breath-actuated Turbuhaler DPI, resulting in better aerosolization performance of the budesonide powder and improving delivery to the lungs. From this difference in deposition among two patient groups of similar ages, it is clear that realistic *in vitro* breath parameters for the patient group under consideration must be employed to achieve a good comparison to *in vivo* data.

The simulated breathing patterns in the present study were relatively simple, with a constant flow rate for the pMDI and a trapezoidal time-variant flow profile for the DPI. Other authors have suggested the use of more realistic profiles to obtain closer matches between *in vivo* and *in vitro* deposition. For example, Delvadia *et al.* recently demonstrated a good comparison of deposition in an adult mouth-throat and upper airway model with *in vivo* data for five commercial dry powder inhalers using a breathing simulator and flow profiles more typical of patient use (20). While the methods employed in the present study were successful in replicating *in vivo* deposition in school age children, there remains room to study the effect of realistic breathing profiles on deposition in idealized pediatric geometries, as has been examined previously in the adult Alberta idealized Throat (58).

CONCLUSION

The recently developed Idealized Child Throat has been compared with *in vivo* scintigraphic deposition data in school age children. For QVAR pMDIs, mouth-throat deposition in the Idealized Child Throat at 50% RH (39.2±2.3% of delivered dose) compared well with *in vivo* deposition in asthmatic children age 8 to 14 (45.8±12.3%). For Turbuhaler DPIs, *in vitro* mouth-throat deposition at 50% RH (69.0±1.5%) matched *in vivo* deposition in 6 to 16 year old children with cystic fibrosis (70.4±21.2%). Humidity ranging from 10% to 90% RH was found to have a small effect on the deposition from the QVAR pMDI and an insignificant effect on deposition from the Turbuhaler DPI at a temperature of 23.5°C. It is recommended that *in vivo* studies report the environmental conditions under which data is collected to aid in future comparisons between *in vivo* and *in vitro* data.

The current focus on pediatric respiratory drug delivery has outlined the need for improved *in vitro* methods for predicting aerosol deposition in young patients. The Idealized Child Throat, here shown to mimic *in vivo* deposition data, may provide a standard platform for optimizing the treatment of school age children with inhaled pharmaceutical aerosols.

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