Clinically relevant *in vitro* tests for the assessment of innovator and generic nasal spray products

Mandana Azimi[1], P. Worth Longest[1, 2], Jag Shur[3], Robert Price[3] & Michael Hindle[1]

[1]Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, 23298, USA

[2] Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, 23298, USA

[3]Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK

Summary

In order to establish equivalence between innovator and generic nasal spray suspension products, similar regional drug deposition at their site of action in the nasal cavity needs to be ensured. The use of realistic models of the nasal airways together with testing using simulated patient use conditions may provide a rapid and inexpensive *in vitro* assessment of these nasal spray products. The regional deposition of an "in house" mometasone furoate nasal spray and a commercially available generic fluticasone propionate nasal spray test products were compared with their respective innovator products using realistic *in vitro* testing methods. Three sets of simulated patient use experimental conditions were chosen to compare regional deposition in two realistic nasal airways models (VCU models 1 and 2) in an attempt to simulate *in vivo* variability and to provide a range of expected middle passage nasal depositions. Based on the *in vitro* experiments, the middle passage and nasopharynx drug deposition of the "in house" mometasone furoate and fluticasone propionate generic nasal sprays were not significantly different than their respective innovator products, Nasonex® and Flonase® across the three different experimental conditions in the two nasal airway models. The developed *in vitro* test methods may offer a useful, and realistic way to differentiate nasal spray products. Future studies will evaluate the effect of nasal spray plume characteristics (droplet size, plume geometry) on the regional nasal drug deposition to assess the sensitivity of these methods to detect differences in nasal sprays.

Introduction

The use of realistic physical nasal airway models has become an emerging tool to investigate and compare locally acting nasal spray products. In order to establish equivalence between innovator and generic nasal spray suspension products, similar regional drug deposition at their site of action in the posterior part of the nose or nasal middle passages needs to be ensured[1, 2]. Realistic *in vitro* testing methods may offer a rapid and inexpensive means of screening nasal spray products compared to radiolabelled imaging and clinical studies. Furthermore, compared to the currently employed *in vitro* nasal spray product characterization methods which focus on the device and formulation performance, realistic *in vitro* test methods may also consider the interplay between device, formulation, patient use variables and the resulting nasal drug deposition[3]. Previously, an *in vitro* regional deposition testing method was described that revealed the importance of patient use factors and the geometry of the nasal cavity in determining the *in vitro* regional nasal deposition of the Nasonex® nasal spray product. A full factorial design of experiment approach was used to assess the effects of patient related factors, including nasal spray position in the nose, head angle, the nasal spray actuation-nasal inhalation timing and applied actuation force and their interactions, together with the influence of nasal airway geometry on regional nasal drug deposition[4, 5]. Nasal middle passage deposition was observed to vary from 16.6 to 57.1% in VCU model 1 and 46.6 to 77.4% in VCU model 2 when tested in this realistic manner for the Nasonex® nasal spray product. The utility of this realistic *in vitro* nasal deposition method will now be investigated using an "in house" and a commercially available generic nasal spray product, that have similar droplet size and plume characteristics compared to their respective innovator products. Therefore, the objective of this study is to compare the regional nasal drug deposition of these generic and innovator nasal spray products using previously developed realistic *in vitro* testing methods with a series of realistic experimental conditions in two nasal airways.

Materials and Methods

The regional nasal deposition of an "in house" mometasone furoate nasal spray, 50 µg (University of Bath, Bath, UK BN# MFM11T F9) was characterized and compared with the innovator product, Nasonex®,50 µg (Merck & Co. Inc., Whitehouse Station, NJ, USA) in the VCU nasal models 1 and 2. The "in house" formulation was designed for experimental purposes to be a generic copy of the innovator product with respect to droplet size and plume characteristics. The regional nasal deposition was tested using the experimental set-up shown in Figure 1, that includes an automated nasal spray actuator (Mighty Runt, InnovaSystems Inc., Moorestown, NJ, USA), the VCU nasal model (VCU model 1 or 2) and a programmable breath simulator (ASL 5000-XL, IngMar Medical, Pittsburgh, PA). The VCU nasal model 2 has a larger nasal vestibule surface area compared to VCU model 1 (14.94 cm^2 vs 11.52 cm^2), and the overall surface area/volume ratio for VCU model 2 was also larger than observed in VCU model 1 (1.33 mm^{-1}vs 0.74 mm^{-1})[5]. Based on previous studies, test conditions for VCU nasal model 1 and 2 were selected to produce low, intermediate and high combined middle passage and nasopharynx drug deposition (Table1)[4, 5]. For VCU model 2, only one nasal spray position was identified for testing due to its smaller nostril hydraulic diameter.

Similarly, the regional nasal deposition of fluticasone propionate nasal spray 50 µg (Roxane Laboratory, Ohio, USA) was characterized and compared with Flonase® Nasal Spray, 50 µg, (GlaxoSmithKline, Research Triangle Park, NC, USA) using the experimental conditions and models described in Table 1, with only a single actuation force of 5.8kg employed which was derived from the studies of Doughty et al[6].

For each *in vitro* deposition experiment, 2 actuations of the nasal spray were delivered into a single nostril, the regional deposition of the drug was measured at four locations, (i) the nasal spray device, (ii) the anterior nose region + the amount of formulation dripped from the nose, (iii) middle passages + nasopharynx and (iv) throat + low resistant inspiratory filter at the exit of the throat. Validated HPLC assays were employed to determine the amount of drug deposited at each location and results were expressed as a percentage of recovered dose.

Student t-test was used to compare the regional drug deposition of the "in house" mometasone furoate nasal spray with its innovator product and the generic fluticasone propionate with its innovator nasal spray product across the range of experimental conditions in the two nasal models (JMP Pro 12 software; p-value < 0.05).

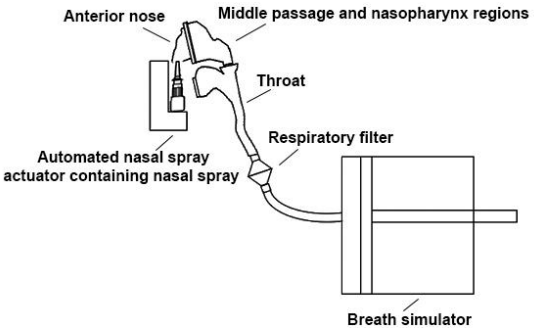

Figure 1. Schematic diagram of experimental setup for the realistic *in vitro* nasal deposition studies

Table 1. Experimental conditions for testing of nasal spray products using VCU nasal models 1 and 2.

Expected combined middle passage and nasopharynx regions drug deposition	Actuation force (kg)	Nasal spray position (mm)[a]	Head angle	Inhalation and actuation timing[b]
VCU Model 1				
Level 1- Low (~ 20%)	7.5	9	50°	E
Level 2- Intermediate (~40%)	7.5	5	30°	D
Level 3- High (~60%)	7.5	5	50°	D
VCU Model 2				
Level 1- Low (~ 50%)	7.5	NA	30°	E
Level 2- Intermediate (~60%)	4.5	NA	30°	D
Level 3- High (~77%)	4.5	NA	50°	D

[a] Distance between nasal spray applicator and the tip of the nose[4]
[b] Inhalation-actuation timing: E - inhalation started at the end of actuation, D - actuation during inhalation[5]

Results and Discussion

Middle passage and nasopharynx nasal drug deposition for the "in house" mometasone furoate and Nasonex® nasal spray products in the VCU nasal models are summarized in Table 2 for low, intermediate and high, deposition conditions. The total drug recovery for these experiments ranged from 85.0 to 100.8%. The amount of drug deposited on the nasal spray device was lower than 3.0% and no drug recovered from filter positioned at the end of the nasal model. As shown in Table 2, there were no statistical differences for the amount of drug that deposited in the middle passage + nasopharynx region for paired experiments with the "in house" mometasone furoate and innovator product using the three different experimental conditions performed with VCU nasal models 1 and 2. Depending upon the experimental conditions, drug delivery to the middle passages varied from 20.2% to 59.1% (2.9-fold change) for the "in house" product and 16.6% to 57.1% (3.4-fold change) for the innovator product using VCU nasal model 1. Similar values in VCU nasal model 2 were 49.6-70.9% (1.4-fold change) and 46.6-77.4% (1.7-fold change), respectively. For comparison, conventional *in vitro* characterization of the spray droplet particle size distribution showed mean (SD) median volume droplet diameters of 47.2 (1.7) µm and 44.5 (2.7) µm, respectively, for the "in house" mometasone furoate and innovator nasal spray products while measured at actuation force of 7.5kg.

Table 2. Mean (standard deviation) *in vitro* middle passage and nasopharynx nasal drug deposition (expressed as a percentage of recovered dose) for the "in house" mometasone furoate and its innovator nasal spray product in VCU models 1 and 2.

Expected middle passage + nasopharynx drug deposition	**Model 1**		**Model 2**	
	"In house" mometasone furoate	**Nasonex®**	**"In house" mometasone furoate**	**Nasonex®**
Level 1-Low	20.2 (3.2) %	16.6 (2.4) %	49.6 (10.7) %	46.6(10.0) %
Level 2-Intermediate	37.0. (9.9) %	34.1 (3.1) %	62.1 (13.8) %	61.6 (9.6) %
Level 3-High	59.1 (6.8) %	57.1 (9.4) %	70.9 (6.5) %	77.4 (8.5) %

The regional drug deposition for the generic fluticasone propionate and innovator nasal spray products are summarized in Table 3. There were no statistical differences found in the amount of drug delivered to the middle passage and nasopharynx in paired experiments for these two nasal spray products using three different experimental conditions performed in VCU nasal models 1 and 2. Depending upon the experimental conditions, drug delivery to the middle passages varied from 17.5% to 39.5% (2.2-fold change) for the generic product and 21.0% to 47.2% (2.2-fold change) for the innovator product using VCU nasal model 1. Similar values in VCU nasal model 2 were 64.6-78.6% (1.2-fold change) and 55.6-79.6% (1.4-fold change), respectively. For comparison, conventional *in vitro* characterization of the spray droplet particle size distribution showed mean (SD) median volume droplet diameters of 69.4 (2.1) μm and 70.8 (1.4) μm, respectively, for the generic and innovator fluticasone propionate spray products at actuation force of 5.8kg.

Comparing all the nasal spray products, there were no statistical differences in the recovered drug dose when tested using the low, intermediate and high deposition conditions in VCU models 1 and 2. Across both drug products, the variability in drug deposition in the middle passages appears more sensitive to the patient use testing parameters in VCU model 1, and overall there was a trend towards higher middle passage drug deposition observed in VCU model 2, both of which may be reflective of *in vivo* variability.

Table 3. Mean (standard deviation) *in vitro* middle passage and nasopharynx nasal drug deposition (expressed as a percentage of recovered dose) for the generic fluticasone propionate and its innovator nasal spray product in VCU models 1 and 2.

Expected middle passage + nasopharynx drug deposition	**Model 1**		**Model 2**	
	Generic fluticasone propionate	**Flonase®**	**Generic fluticasone propionate**	**Flonase®**
Level 1-Low	17.5 (1.0) %	21.0 (3.8) %	64.6 (4.8) %	55.6 (7.3) %
Level 2-Intermediate	42.7 (4.1) %	41.7 (8.4) %	74.5 (3.3) %	68.1 (10.8) %
Level 3-High	39.5 (5.9) %	47.2 (10.4) %	78.6 (5.6) %	79.6 (0.3) %

Conclusions

The regional drug deposition of innovator and generic nasal spray products of two drugs, mometasone furoate and fluticasone propionate, were characterized using realistic *in vitro* test methods. An 'in house' mometasone furoate nasal spray product was not significantly different from its innovator product with respect to drug deposition at the local sites of action within the middle passages of two realistic nasal airway geometries. Similarly, there was no deposition differences observed for a generic fluticasone propionate nasal spray product and its innovator using the realistic *in vitro* testing method. The range of local deposition observed using the patient use testing parameters and the two nasal models may be reflective of potential *in vivo* variability in nasal deposition. These realistic testing methods could have utility as an inexpensive tool for early evaluation of regional nasal deposition and with future *in vivo* validation may offer an efficient means of evaluating equivalence of nasal spray products.

Acknowledgments

Funding was provided by Contract # HHSF223201310220C, from the Department of Health and Human Services (DHHS), Food and Drug Administration. The content is solely the responsibility of the authors and does not necessarily reflect the official policies of the DHHS; nor does any mention of trade names, commercial practices or organizations imply endorsement by the United States Government. The technical support of IngMar Medical (ASL 5000-XL Breath Simulator) and InnovaSystems Inc (Mighty Runt Actuator Station) is gratefully acknowledged. The authors wish to thank Guenther Hochhaus, Renish Delvadia, Bhawana Saluja and Mohammad Absar for their assistance and useful discussions during the planning of this study.

References

1 Shah S A, Berger R L, McDermott J, Gupta P, Monteith D, Connor A, Lin W: *Regional deposition of mometasone furoate nasal spray suspension in humans*, Allergy Asthma Proc 2015; 36: pp48-57.

2 Djupesland P G: *Nasal drug delivery devices: characteristics and performance in a clinical perspective-a review*, Drug Deliv Transl Res 2013; 3: pp42-62.

3 FDA Draft Guidance (2003) Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action.

4 Azimi M, Longest P W, Hindle M: *Towards clinically relevant in vitro testing of locally acting nasal spray suspension products*. In: R N Dalby, P R Byron, J Peart, J Suman, P Young and D Traini (eds): *Respiratory Drug Delivery Europe 2015*. DHI Publisher, River Grove, IL; pp121-130, 2015.

5 Azimi M, Longest P W, Hindle M, Walenga R L: *Comparison of the in vitro deposition of nasonex nasal spray product in two realistic nasal airway models*. In: R N Dalby, P R Byron, J Peart, J Suman, P Young and D Traini (eds): *Respiratory Drug Delivery 2016.* DHI Publishing, River Grove, IL; pp617-622, 2016.

6 Doughty D V, Vibbert C, Kewalramani A, Bollinger M E, Dalby R N: *Automated actuation of nasal spray products: determination and comparison of adult and pediatric settings*, Drug Dev Ind Pharm 2011; 37: pp359- 366.