Comparison of the *In vitro* Deposition of Nasonex® Nasal Spray Product in Two Realistic Nasal Airway Models

Mandana Azimi[1], Michael Hindle[1], P. Worth Longest[1,2] and Ross L. Walenga[2]

[1]Department of Pharmaceutics and [2]Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, Virginia, USA.

Introduction

- After administration of a nasal spray product (NSP), its regional drug deposition within the nasal cavity is dependent upon a number of factors including the formulation spray characteristics, patient use factors and the geometry of the nose.[1]
- Physically realistic nasal airway models have been used widely to assess *in vitro* regional drug deposition of NSPs.[2]
- Investigations of drug delivery efficiency and assessments of bioequivalence of nasal spray products may be aided by the use of physically realistic nasal airway models in combination with simulated patient use to determine *in vitro* spray deposition patterns within the nose.
- The aim of this study is to assess the effects of patient use parameters such as head angle, inhalation timing and actuation force on the *in vitro* regional drug deposition in two nasal airway geometry models.

Methods

***In vitro* experimental components:**

- The test components consisted of an automated nasal spray station, the realistic physical model of the nasal cavity and a programmable breathing simulator (Fig 1).

***In vitro* nasal models**:

- The physically realistic nasal models 1& 2 were segmented into two parts (a) anterior nose and (b) middle passages combined with nasopharynx (Fig 2).[2,3]
- VCU model 2 was characterized by a differing nasal airway geometry compared to VCU model 1, including a smaller nostril hydraulic diameter (10.6 mm vs 12.06 mm), anterior nose volume (2.2 ml vs 3.2 ml), and a larger nostril and nasal vestibule surface area (14.94 cm^2 vs 11.52 cm^2).
- The overall surface area/volume ratio (SA/V) for VCU model 2 was larger than observed in VCU model 1 (1.33 mm^{-1}vs 0.74 mm^{-1}).

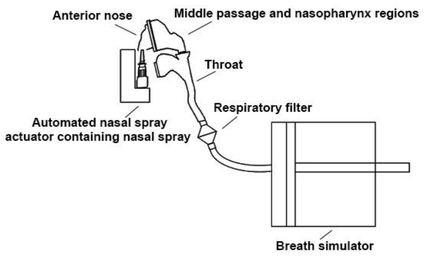

Figure 1. Experimental setup for evaluating the regional nasal deposition of Nasonex® nasal spray

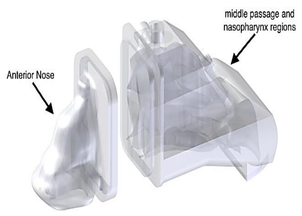

Figure 2. The segmented VCU nasal model

Full factorial design of experiment (DOE):

A 2-level, 3-factor, full factorial design was employed to investigate the *in vitro* nasal deposition of the Nasonex NSP using the following patient use variables:

- Head angle from horizontal (Tilted 30° or 50° forward from horizontal)
- Actuation force (4.5 and 7.5 kg)
- Nasal inhalation-nasal spray actuation timing (actuation of nasal spray occurred during nasal inhalation (D) or inhalation started at the end of nasal spray actuation (E)) (As depicted in Fig 3).

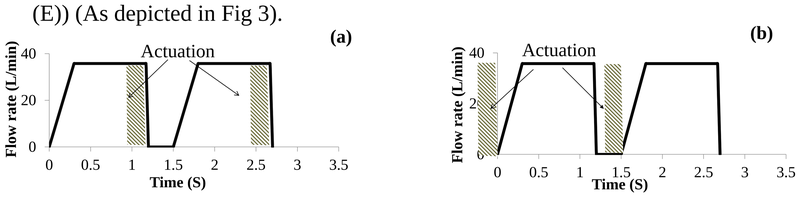

Figure 3. Inhalation timing with respect to nasal spray actuation: (a) during actuation (D), (b) end of actuation (E)

Drug recovery from nasal models:

The regional deposition of the drug was measured at four locations: i) nasal spray device, ii) anterior nose region + formulation dripping from the nose, iii) middle passage and nasopharynx, and iv) throat and inspiratory filter at the exit of the throat, using a high performance liquid chromatography method for mometasone furoate (Fig 1).

Statistical analysis

The outcome measure for analysis was defined as the combined middle passage and nasopharynx deposition. The deposition results from each model were analyzed using full factorial ANCOVA to detect significant main effects or any interactions between the two main effects (p-value < 0.05). Student t-test was used for comparing the regional drug deposition between the nasal models using the different experimental conditions (JMP Pro 12 software) (p-value < 0.05).

Results and Discussion

Regional drug deposition pattern of Nasonex® in VCU models 1 & 2.

- In all studies performed, total drug recovery was greater than 88.0% of the label claim, with the highest mean nasal spray device deposition being 5.3% and in most cases no drug was recovered from the respiratory filter at the end of the throat.

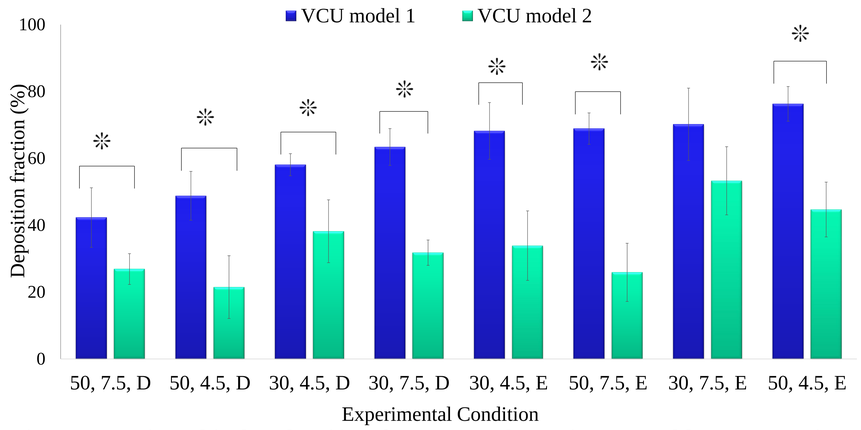

Figure 4. Anterior + drip drug deposition of Nasonex nasal spray in VCU models 1 & 2. Experimental conditions represent head angle (30/50º), actuation force (4.5/7.5 kg) and inhalation timing (end of actuation – E or during actuation – D), respectively. * P<0.05, significant difference (student t-test).

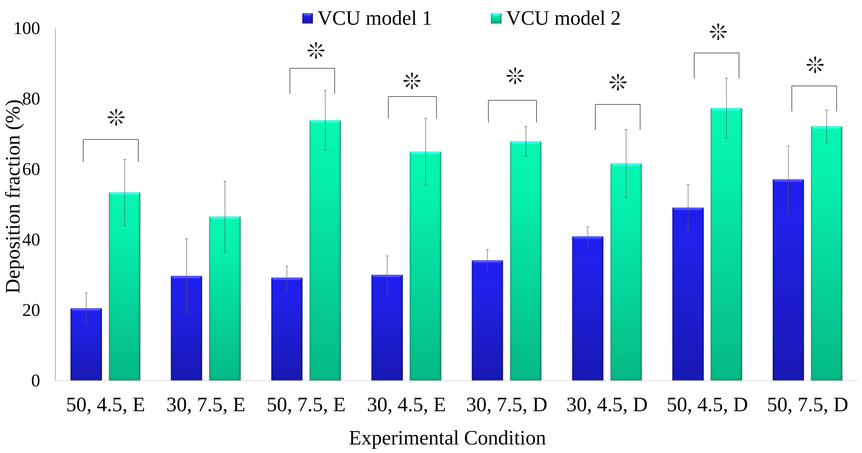

Figure 5. Middle passage drug deposition of Nasonex nasal spray in VCU models 1 & 2. Experimental conditions represent head angle (30/50º), actuation force (4.5/7.5 kg) and inhalation timing (end of actuation – E or during actuation – D), respectively. * P<0.05, significant difference (student t-test).

- Figures 4 & 5 show the mean (error bars are standard deviation) anterior nose + dripped deposition and the combined middle passage and nasopharynx deposition, respectively, in VCU nasal models 1 & 2 ranked in order of increasing deposition for VCU model 1.
- Figure 4 reveals that by varying the patient use experimental parameters the anterior nose dose deposition can vary from 42.3% to 76.3% of the recovered dose in VCU model 1. Lower anterior nose deposition values ranging from 21.5% to 53.3% of the recovered dose were observed using VCU model 2.
- Figure 5 shows that a significantly higher middle passage and nasopharynx deposition was observed for VCU model 2 compared to VCU model 1 for most of the patient use conditions (Table 2; P<0.05), perhaps due to different anatomical geometric features in the anterior nose.

Statistical Analysis:

- Table 1 shows the variables that are included the fitted model together with their significance. Significant interactions were observed between *head angle* and *inhalation timing* (P<0.0002) and *head angle* and *actuation force* (P<0.016) for VCU model 1.
- Table 2 reveals that the effects of *inhalation timing* (p<0.0143) and *head angle* (p<0.0277) resulted in significant changes to the regional nasal drug deposition of Nasonex in VCU model 2.

Table 1. Variables that are included in the fitted model for VCU model 1

Term	Estimate	Prob>|t|
Intercept	20.8	0.0043*
Force	0.8	0.3074
Head angle	0.27	0.0292*
Timing[D]	8.97	<.0001*
Timing[E]	-9	<.0001*
(Force-6)*(Head angle-40)	0.2	0.0166*
(Force-6)*Timing[D]	-0.6	0.4417
(Force-6)*Timing[E]	0.6	0.4417
(Head angle-40)*Timing[D]	0.5	0.0002*
(Head angle-40)*Timing[E]	-0.5	0.0002*

Table 2. Variables that are included in the fitted model for VCU model 2

Term	Estimate	Prob>|t|
Intercept	45.3	0.0004*
Force	0.3	0.8349
Head angle	0.5	0.0277*
Timing[D]	5.0	0.0143*
Timing[E]	-5.0	0.0143*
(Force-6)*(Head angle-40)	0.2	0.0866
(Force-6)*Timing[D]	-0.1	0.9516
(Force-6)*Timing[E]	0.1	0.9516
(Head angle-40)*Timing[D]	0.1	0.7844
(Head angle-40)*Timing[E]	-0.1	0.7844

Conclusions

- Significant differences in the regional drug deposition of Nasonex were observed when tested using experimental parameters designed to reflect "in use" conditions.
- The regional drug deposition of Nasonex was observed to be different when compared using two anatomical nasal models. Differences in the geometry of anterior nose may be responsible for the lower drug deposition in this region of VCU model 2.
- When developing realistic *in vitro* testing methods for nasal spray products it is important to control the patient use experimental conditions, and inter-subject variability can be investigated using nasal model geometries with different anatomical characteristics.

References

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3. Walenga RL et al., *J Aerosol Sci* 2014, 78:11-29.

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