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

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PURPOSE

Traditional methods of characterizing nasal spray products focus on evaluating the fully developed spray plume as it emerges from the spray nozzle mainly for quality control and *in vitro* equivalence purposes [1].

For investigations of local drug delivery efficiency within the nose and for assessments of bioequivalence of nasal spray products, it may be useful to use realistic *in vitro* testing methods.

It is hypothesized that nasal spray delivery into physically realistic nasal airway models used in combination with simulated patient use parameters may be used to estimate regional drug deposition patterns within the nose.

The current study investigates 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 geometries.

METHODS

In vitro experimental components:

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

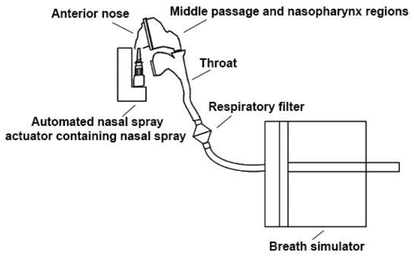

Figure 1. Experimental setup for evaluating the regional nasal deposition of Nasonex® nasal spray

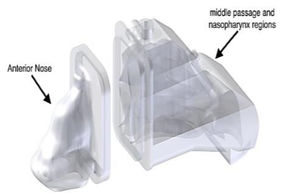

Figure 2. The segmented VCU nasal model 1

In vitro nasal models:

- The physically realistic nasal models 1 and 2 were segmented into two parts (a) the anterior nose and (b) the middle passages combined with the nasopharynx (Figure 2).

- VCU model 2 was characterized by a differing nasal airway geometry compared to VCU model 1, including a larger nostril and nasal vestibule surface area (14.94 cm^2 vs 11.52 cm^2). The 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}) [2].

Drug recovery from nasal models:

- Drug was collected 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, and quantified using a high performance liquid chromatography method for mometasone furoate (Fig 1).

METHODS

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 nasal spray product using the following patient use variables:

i. Head angle from horizontal (Tilted 30° or 50° forward from horizontal)

ii. Actuation force (4.5 and 7.5 kg)

iii. 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 Figure 3).

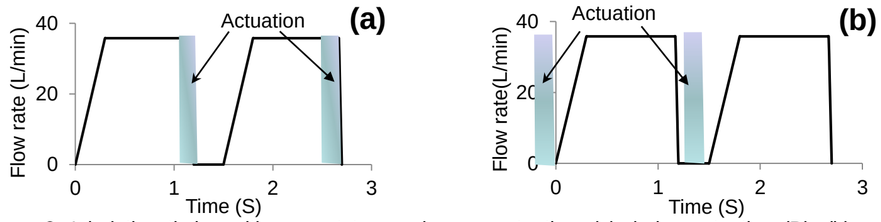

Figure 3. Inhalation timing with respect to nasal spray actuation, (a) during actuation (D), (b) end of actuation (E)

Statistical analysis

- 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

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

- Total drug recovery was greater than 88.0% of the label claim.

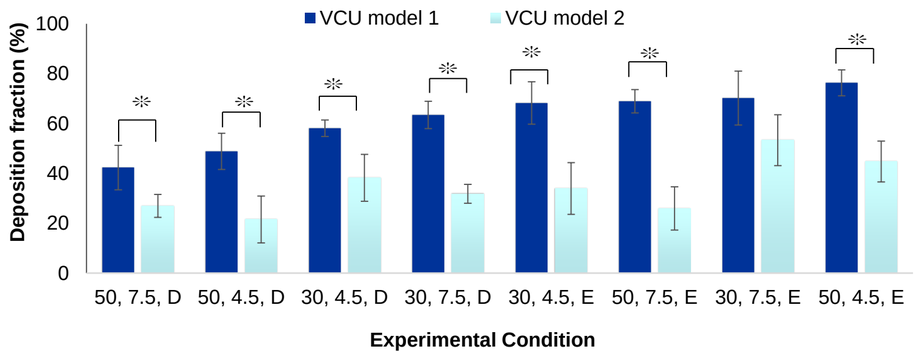

Figure 4. Anterior + drip drug deposition of Nasonex nasal spray in VCU models 1 & 2. Experimental conditions represent head angle (30/50º), actuation force (4.5/7.5 kg) and inhalation timing (end of actuation – E or during actuation – D), respectively. * P<0.05, significant difference (student t-test).

- Figure 4 shows the mean (error bars are standard deviation) anterior nose + dripped deposition VCU nasal models 1 & 2 ranked in order of increasing deposition for VCU model 1. 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. Anterior nose deposition values were lower using VCU model 2, ranging from 21.5% to 53.3% of the recovered dose.

RESULTS

- Figure 5 shows then mean (error bars are standard deviation) for the combined middle passage and nasopharynx deposition.

- 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 (P<0.05), perhaps due to different anatomical geometric features in the anterior nose.

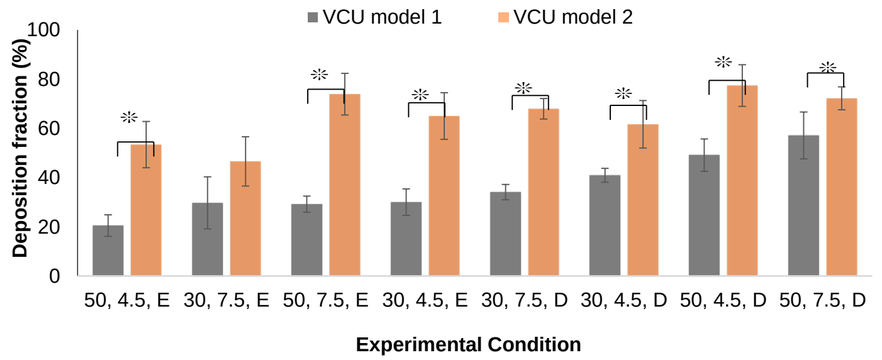

Figure 5. Middle passage drug deposition of Nasonex nasal spray in VCU models 1 & 2. Experimental conditions represent head angle (30/50º), actuation force (4.5/7.5 kg) and inhalation timing (end of actuation – E or during actuation – D), respectively. * P<0.05, significant difference (student t-test).

- 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.

- 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.

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. Inter-subject variability can be investigated using nasal model geometries with different anatomical characteristics.

REFERENCES

1. FDA Draft Guidance (2003) Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action.
2. Walenga RL, Tian G, Hindle M, Yelverton J, Dodson K, Longest PW: J Aerosol Sci. 2014;78:11-29.

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