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In Vitro Investigation of Regional Nasal Drug Delivery using Two Glucocorticoid Nasal Spray Products and Twenty Anatomical Nasal Replicas

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PURPOSE

Nasal sprays are commonly used to deliver locally-acting drugs to treat allergic rhinitis. Among these, glucocorticoids show sustained anti-inflammatory effects. Fluticasone propionate (FP), an androstane carbothioate glucocorticosteroid, is considered a well-established drug to achieve a faster resolution of the acute symptoms and to lower the respiratory symptoms associated with rhinitis and asthma. Fluticasone furoate (FF), which is structurally related to FP, represents a novel enhanced-affinity glucocorticoid [1, 2].

However, quantifying drug delivery to the site of action within the nasal cavity is challenging from a scientific and regulatory perspective and is known to be highly variable and dependent upon patient mode of use, patient anatomical variability, and formulation and device properties. Currently, *in vitro* spray performance studies are used as part of the bioequivalence assessment between a potential generic and its reference product. A model that considers the complexity of the nasal airway anatomy and inter-subject variability may provide a more accurate assessment of regional deposition, and so product performance, which may serve as a potential alternative method for establishing bioequivalence in lieu of conducting comparative clinical endpoint studies, in the context of weight of evidence approach.

OBJECTIVE

This study is the first step to developing the next generation of *in vitro* test methods to quantify the *in vitro* deposition patterns of the active pharmaceutical ingredient from two nasal sprays in a series of twenty anatomical nasal airway replicas and administered using controlled methods.

FUNDING

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METHODS

Physical nasal airway replicas were developed from anonymized computed tomography images of twenty adult subjects with healthy nasal airways (half male and half ≥50 years old) by including the entire nasal cavity and nasopharynx down to the end of C1 vertebra. The models were segmented into two regions of anterior and posterior nasal deposition relative to the internal nasal valve (Figure 1). The anterior section of each replica was rapid prototyped using a flexible rubbery material (TANGO PLUS 27A) in order to easily insert and maneuver the tip of nasal sprays into the nostrils. The posterior section of each replica was rapid prototyped using high clarity rigid plastic (Accura ClearVue).

Nasal spray deposition studies were performed using two test products, Flonase® (fluticasone propionate 50 µg per 100 µl spray), and Flonase® Sensimist™ (fluticasone furoate 27.5 µg per 50 µl spray), with two sprays actuated into the right nostril of each replica. Twenty units of each nasal spray with identical lot number and expiration date were purchased and each replica was tested with a unique spray unit. The positioning of the spray nozzle in the nostril was recorded and characterized across all twenty subjects by the head angle (Flonase®: 57.9±5.1°, Flonase® Sensimist™: 48.3±6.3°), coronal angle (Flonase®: 39.5±10.0°, Flonase® Sensimist™: 36.7±7.3°), and the insertion depth (Flonase®: 15.1±2.6 mm, Flonase® Sensimist™:12.5±0.0 mm). The values are presented as mean±standard deviation. A realistic *in vivo* breathing pattern representing gentle sniffing [3] was simulated using a breathing simulator (ASL5000, Ingmar Medical).

The Mighty Runt Actuation Station (InnovaSystems, Inc.) was synchronized with the breathing simulator and two actuation force (AF) levels, 5.8 and 7.2 kg, were applied to actuate the Flonase® at the start of nasal inhalation [4]. The Flonase® Sensimist™ spray was hand actuated at the beginning of inhalation using the same breathing pattern. Analytical quantification of FP (Flonase®) and of FF (Flonase® Sensimist™), recovered from the nasal models, was performed using a validated high-performance liquid chromatography (HPLC) method. The drug recovery was calculated as the mass of drug in the entire nasal model as a percentage of the labeled dose. The mass of drug reaching the posterior region is also expressed as the percentage of the recovered dose.

Figure 1. *The front (1) and side (2) view of Model 1 in the final printed form.*

RESULTS

The spray weight values for two sprays were 190.8±4.4 mg, and 193.8±2.6 mg for Flonase® using 5.8 and 7.2 kg AF, respectively, and 108.9±3.0 mg for Flonase® Sensimist™. Across the twenty replica models, the recovered doses were 76.1±9.0% and 78.6±7.2%, respectively, using 5.8 kg and 7.2 kg AF for Flonase®, and 89.1±5.9% for Flonase® Sensimist™ (Figure 2, panel A and B, respectively). The posterior deposition (PD) values across the twenty models were 58.1±22.7% and 57.5±19.8 % for Flonase® using 5.8 kg and 7.2 kg actuation forces, respectively, and 56.5±15.7% for Flonase® Sensimist™ (Figure 3, panel C and D, respectively). The range of PD with Flonase® was 21-89% at 5.8 kg and 24-85% at 7.2 kg. With Flonase® Sensimist™ this range was 29-92%.

Figure 2*. The recovered dose of FP for Flonase® - fluticasone propionate using 5.8 kg and 7.2 kg actuation forces, respectively (A) and for FF Flonase® Sensimist™ - fluticasone furoate (B).*

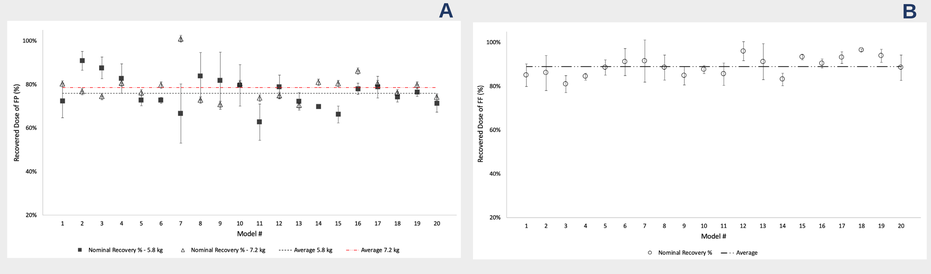
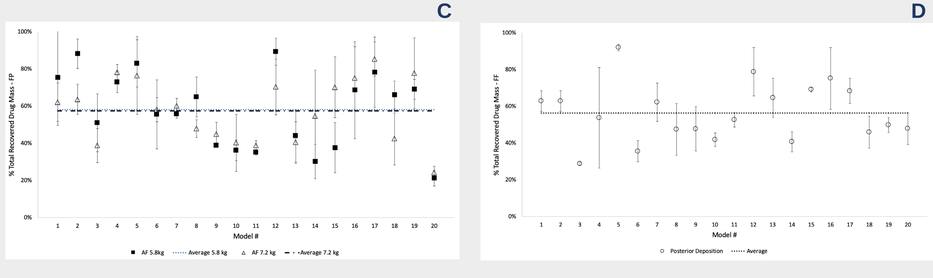


Figure 3*. Recovery percentages in the posterior region across the twenty models for Flonase® - fluticasone propionate (FP) using 5.8 kg and 7.2 kg actuation forces, respectively (C) and for Flonase® Sensimist™ - fluticasone furoate (FF)(D).*



CONCLUSION

Despite using a controlled administration protocol to minimize the anterior losses a wide range of posterior delivery was observed for Flonase® and Flonase® Sensimist™. The results show the importance of the nasal airway anatomy in determining the fraction of delivered dose reaching the posterior region. Thus, to improve the current *in vitro* test methods, anatomical airway geometries and inter-subject variability must be considered.

REFERENCES

[1] Płoszczuk, A., et al., 2018. Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. Ther. Adv. Respir. Dis. 12.

[2] May, J.R., Dolen, W.K., 2019. Evaluation of Intranasal Corticosteroid Sensory Attributes and Patient Preference for Fluticasone Furoate for the Treatment of Allergic Rhinitis. Clin. Ther. 41, 1589–1596.

[3] Doughty, D. V. et al., 2011. Automated actuation of nasal spray products: determination and comparison of adult and pediatric settings. Drug Dev. Ind. Pharm. 37, 359–366.

[4] Guo et al., 2008. Assessment of the influence factors on in vitro testing of nasal sprays using Box-Behnken experimental design. Eur. J. Pharm. Sci. 35, 417–426.