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Gamma scintigraphy for testing bioequivalence: A case study on two cromolyn sodium nasal spray preparations

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Abstract

The present work was carried out to study the deposition patterns and clearance of technetium-99m (^{99m}Tc) DTPA labeled cromolyn sodium (CS) solutions when administered from two different CS nasal products using gamma scintigraphy. Five healthy volunteers received a single dose with complete crossover design involving treatment A (test formulation) and treatment B (reference formulation). The deposition patterns as well as the changes in distribution of the radiolabeled CS solutions due to the mucociliary transport were monitored by gamma scintigraphy. Primary deposition of the aforementioned nasal solutions occurred in the anterior portion of the nose. After migration into the posterior nasal cavity, the solutions were rapidly cleared by ciliary action into the nasopharynx where it was swallowed. The test product of cromolyn sodium was shown to be equivalent to the reference product with regard to nasal deposition and clearance. The results from this study indicate that external gamma scintigraphy can be used to demonstrate the equivalence of nasal sprays that are intended for local therapeutic action where the drug is not systemically absorbed into the blood circulation. Furthermore, a non-invasive imaging method such as rhinoscintigraphy may prove to be a useful technique to be utilized during the regulatory approval process for local-acting nasal products, and may facilitate the early introduction of these products to the market.

Keywords: Nasal; Deposition; Clearance; Cromolyn sodium; Gamma scintigraphy; Bioequivalence

1. Introduction

The nasal cavity possesses many advantages as a site for drug delivery, such as ease of administration, avoiding first pass hepatic metabolism through direct absorption to the systemic circulation. In recent years growing interest has been paid to the use of the nasal route for the systemic delivery (Cheng et al., 2002; De Ascentiis et al., 1996; Faraj et al., 1990; Humbert et al., 1996; Harris et al., 1986), brain targeting (Al-Ghananeem et al., 2002; Dahlin and Bjork, 2001; Hussain et al., 2000; Kao et al., 2000; Yang et al., 2005), as well as for compounds which impact local pharmacological effects (Meltzer et al., 2002; Hochhaus et al., 2002) such as cromolyn sodium nasal spray.

Intranasal cromolyn sodium efficacy in the treatment of allergic rhinitis has been demonstrated in clinical trials (Meltzer, 2002; Ratner et al., 2001; Handelman et al., 1977). The drug acts by inhibiting the degranulation of sensitized mast cells which occurs after exposure to specific antigens (Ratner et al., 2002). After nasal administration, the drug acts locally with less than 7% of the total dose being absorbed and rapidly excreted unchanged in the bile and urine (Ratner et al., 2002). Since the drug is poorly absorbed from the nasal cavity, a measurement of pharmacological endpoint is difficult, so it would be problematic to demonstrate bioequivalence for this nasally administered compound based on pharmacokinetic parameters. Usually locally acting drugs exhibit low systemic absorption resulting in low blood levels which might result in high standard errors among the readings. Furthermore, due to variability between the drug blood levels and the pharmacologic response of locally acting drugs, which exhibit low systemic blood levels, demonstrating bioequivalence based on pharma-

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cokinetic properties will not reflect a correct bioequivalency correlation.

Classical bioequivalence testing, based upon equal rates and extents of drug absorption, is inappropriate for showing equivalence of products containing nasal allergic drugs, which act directly on nasal mucosa surface such as the mast-cell stabilizer cromolyn sodium. Current Food and Drug Administration (FDA) (2003) guidance (Internet guideline) recommends *in vitro* methods as means of documenting bioavailability (BA) and bioequivalence (BE) for topically acting solution formulations. Furthermore, the FDA recently released draft guidance procedures for the pharmaceutical industry regarding BA and BE studies for locally acting nasal aerosols and nasal sprays. Although the FDA draft proposed that BA/BE to be determined primarily using *in vitro* methods, the draft also mentioned imaging as a potential means for *in vivo* measurements (Internet guideline). In this regard, it is important to know the deposition pattern of nasal formulation within the target organ, since treatment or prophylaxis will be effective only if sufficient drug is delivered directly to the targeted site.

The non-invasive imaging technique of gamma scintigraphy provides a surrogate measure to the local drug exposure at the site of action in the nasal cavity. Nasal deposition data is likely to be correlated with clinical response to such drugs. Therefore if two nasal spray products that are true solutions have the same nasal deposition, then it is probable that they will be therapeutically equivalent. In the case of assessing the equivalence of nasal allergic medications, gamma scintigraphy determines *in vivo* drug delivery more precisely than *in vitro* testing, and is more expeditious than traditional clinical efficacy studies. The approach requires fewer patients as compared to studies which rely on clinical outcome, provides appropriate data in less time, and all with the likelihood of definitive endpoints.

Gamma scintigraphy has been applied extensively in the development and evaluation of pharmaceutical drug delivery systems. It is an elegant way to gain insights on the actual *in vivo* distribution pattern of dosage forms; it has been used particularly for monitoring formulations in the gastrointestinal (Digenis and Sandefer, 1991; Marathe et al., 1998; Digenis et al., 1998; Honkanen et al., 2004), respiratory tracts (Barker et al., 1994; Cheng et al., 2001; Niu et al., 2005), and to study nasal deposition in order to evaluate a variety of delivery systems (Illum et al., 1987; Chang et al., 1996; Soane et al., 1999; Mao et al., 2004; Tafaghodi et al., 2004). This technique relies on the use of radioactive tracers included into the medicament and selected so as to enable an optimum detection by a gamma camera. When radiolabeling nasal preparations, an appropriate technetium-99m or indium-111 labeled radiopharmaceutical is usually incorporated into the formulation although other isotopes may be used as well.

We have aimed in this work to study the nasal deposition of cromolyn sodium by differentiating nasal regions to include the anterior, posterior, and the nasopharynx regions using external gamma scintigraphy to monitor the deposition pattern and clearance rate. Furthermore, although the *in vitro* characterization of the nasal sprays was performed in another study and was shown to be equivalent, it was the objective of this investigation to demonstrate *in vivo* equivalency by comparing nasal deposition patterns and clearance rates of cromolyn sodium solution when administered from a brand nasal product versus a generic nasal product of cromolyn sodium which were radiolabeled with technetium-99m diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA).

2. Materials and methods

^{99m}Tc-DTPA ($t_{1/2}$ = 6.0 h; γ = 140 keV) was supplied by Syncor International (Lexington, KY) on each acquisition day. Cromolyn sodium test formulation was the product of Bausch and Lomb Pharmaceutical (Tampa, FL), 13 mL, 40 mg/mL (treatment A). Cromolyn sodium reference product was the product of Fisons Pharmaceuticals (Rochester, NY), 13 mL, 40 mg/mL (treatment B). The nasal spray devices were 13 mL white plastic containers equipped with plastic actuators and covers, all resin materials were FDA approved.

Each milliliter of CS formulation solutions contains 40 mg cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution. Cromolyn sodium nasal solution possesses a natural pH of 4.5–6.5 and negligible titratable acidity.

3. Clinical trial material preparation and radiolabeling

Radiolabeled stock solutions of cromolyn sodium formulation A and formulation B were prepared by adding 13 mCi of ^{99m}Tc-DTPA (∼0.1 mL) to one vial of each formulation (13 mL) such that the specific activity was 1 μCi/1 μL at a calibrated time of day. A 130-μL actuation therefore contained 130 μCi ^{99m}Tc-DTPA immediately after addition of the radioactive material. Aliquot parts of each stock solution (3 mL) were transferred into four separate vials and the corresponding actuators were replaced. Each actuator was primed seven times by spraying into separate inverted vials with absorbent tissue at the bottom. The spray actuator was then administered to the subject on the 8th actuation and after dose administration the actuator was primed at least a 9th and 10th time into separate inverted vials to confirm the amount of ^{99m}Tc dispensed per actuation. The level of ^{99m}Tc in each vial was determined on a dose calibrator (Capintec, Pittsburgh, PA), and the radioactive dose administered to each subject was calculated as the average of the 7th, 9th and 10th actuation and decay corrected to the time of dosing.

4. Dose administration and *in vivo* gamma scintigraphy

Five healthy male volunteers (22–30-year-old) were enrolled into the study. The research followed the tenets in the Declaration of Helsinki promulgated in 1964, and the protocol was approved by the Institutional Review Board and Radioactive Drug Research Committee at the University of Kentucky. The study was a balanced, single dose, complete crossover design involving two treatment conditions: formulation A (test product) and formulation B (reference product). Each observation session was separated by 1 day and all doses were administered over a 2-day period.

A complete medical history and physical exam was obtained prior to enrollment of the subject into the study. Fasting blood and urine samples were taken for clinical testing which included routine blood chemistry, hematology, and urine drug screen.

Blood and urine analysis was also completed at the end of the second treatment day. Pre-study images for background determinations were taken prior to dose administration with and without the subject in front of the gamma camera. This was done to assure that no residual activity remained in the subject on the second dosing day. The spray solution was administered to the healthy volunteers who were free of nasal congestion, and were not suffering from allergies or colds. Doses were administered to the nostril which appeared to be the most clear on the first dosing day, and the same nostril was administered on the second dosing day. Subjects were in an upright sitting position with the gamma camera taking a left lateral view of the head. The applicator tip was inserted approximately 1 cm into the nostril, the contra lateral nostril was closed and the dose was administered as the subject was instructed to deeply inhale through the open nostril and exhale through the mouth. All doses were administered by the same trained technician and subjects continued to breathe through their noses after dose administration.

5. *In vivo* nasal clearance studies

The deposition, distribution and subsequent clearance of the two nasal formulations were evaluated by gamma scintigraphy. The gamma scintillation camera (Siemens BasiCamera, Chicago, IL) was equipped with a low energy parallel collimator, and the pulse analyzer was set to detect the 140 keV gamma ray of ^{99m}Tc (15% window width). Immediately upon dose administration, 40 continuous 30 s frames were acquired from the left lateral view through the first 20 min post-dosing. Subjects tolerated this restricted movement with the exception of some minor neck stiffness, but this was necessary in order to accurately determine all regions of interest for this study and fully characterize the initially rapid kinetics of nasal clearance. After the initial 20 min scanning sequence, subjects were scanned for 5 min (10 frames, 30 s/frame) at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5 and 3 h post-nasal administration. When imaging was not required, subjects were instructed to not clear their nose, and if at all possible to avoid sneezing. After the image at 3 h post-dose, each subject cleansed their nose of residual radioactivity by self-administering 100–200 μL of saline (1–2 pumps of 100 μL actuator) to each nostril and blowing into a tissue and thoroughly wiping the inside of the nose with tissue. The level of ^{99m}Tc on the tissue(s) was determined in the dose calibrator, corrected for decay, and reported as a percent of the originally administered dose. A final image was recorded at approximately 187 min post-dose after subjects had cleared the nose of residual activity.

6. Data analysis

The sequential computer generated images were reviewed for each subject and regions of interest (ROI) were drawn to represent the anterior part of the nasal cavity, posterior nasal activity, and nasopharynx (Scinwin™ Scintigraphy Analysis software, GammaForge, Louisville, KY). All counts were corrected for radioactivity decay and background, and the relative fraction of radioactivity in each of the three regions was determined by summing the counts in all three ROIs for the first several complete frames of data acquisition (i.e., frames 1–3), and then using this base value as the denominator for all determinations:

$$\text{fraction of activity in ROI}_x = \frac{\text{decay corrected counts in ROI}_x \text{ at time } t}{\text{total counts in all ROIs immediately post-dose}} \quad (1)$$

ROI_x represents the region of interest (i.e., anterior part of the nasal cavity, posterior nasal activity, or nasopharynx). Plots were generated for individual subjects and mean data which depicted the deposition and clearance of radioactivity in the three regions versus time. A fourth curve was also generated showing the relative fraction of radioactivity versus time for the summation of the three regions. Area under the nasal clearance curves (AUC 0–3 h) were determined by linear trapezoidal rule. Statistical analysis of nasal clearance between the two treatments were made using a paired Student's *t*-test with a significance of $p < 0.05$.

7. Results and discussion

The nasal clearance and deposition of cromolyn sodium nasal delivery formulations were studied using gamma scintigraphy. Through comparison of the images recorded during this study it was possible to ascertain the approximate shape of the subjects nasal cavity and, therefore, the area of deposition after dosing. Fig. 1 illustrates the ROI investigated in this study where the head of one subject is outlined, and as indicated in the figure, region 1 represents the anterior nasal cavity, region 2 is the posterior nasal cavity and region 3 is the nasopharynx region.

The clearance and deposition of cromolyn sodium formulation A (test formulation) after nasal spray dosing from each of the ROI is shown in Fig. 2. As expected, only the solution that reaches the ciliated nasal cavity moves with time. The nasal mucosa proximal to the nasal valve and directly at the nasal valve is non-ciliated. Any solution that fails to penetrate this area does not move with time and stays in the vestibule where it was initially delivered. Therefore, this gamma scintigraphy imaging technique can readily assess the proportion of delivered solution that penetrates the nasal valve. The proportion of solution to reach the nasopharynx, esophagus, stomach and lower respiratory tract, both directly and via subsequent mucociliary action can also be assessed by gamma scintigraphy. In our experiment, the defined ROIs were the anterior nasal cavity, the posterior nasal cavity and the nasopharynx region.

The anatomy of the human nose favors internal impaction in the anterior third of the nasal cavity, especially when a dose is administered from a high velocity pressurized aerosol (Newman et al., 1987) or from lower velocity pumps which produce a fine mist (Aoki and Crawley, 1976; Hardy et al., 1985; Harris et al., 1986; Pennington et al., 1988; Illum et al., 1987). The localization of the dose in the anterior part of the nose should not be too surprising if one consider that the nasal valve is just 1.5 cm

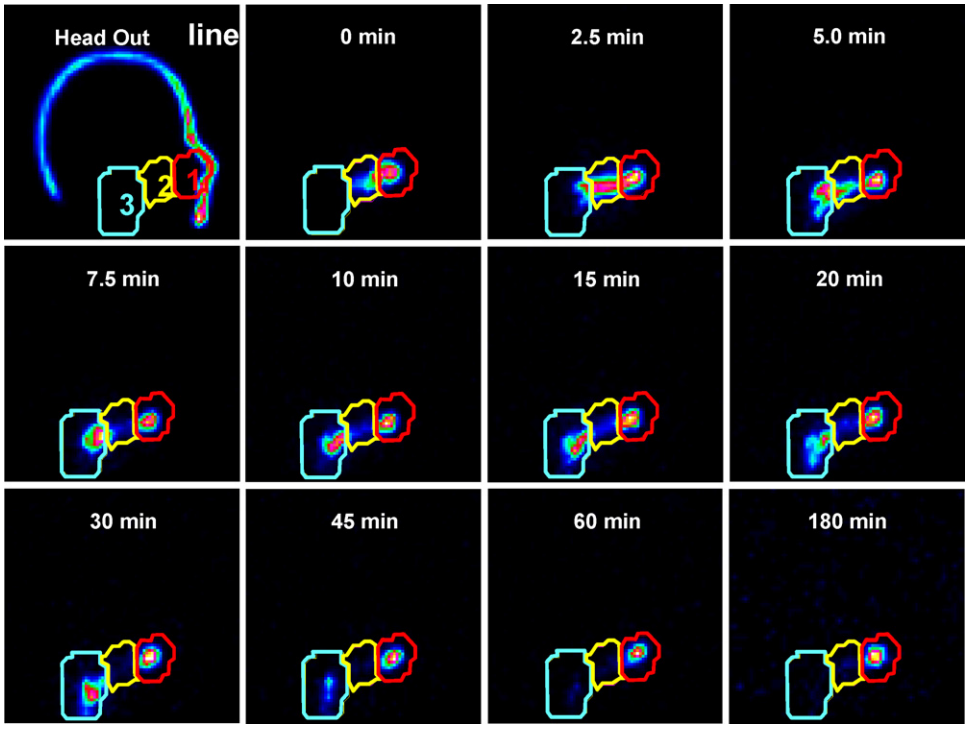

Fig. 1. The deposition sites of cromolyn sodium nasal spray particles in the nasal cavity of human volunteer: region 1 represents the anterior nasal cavity; region 2 is the posterior nasal cavity; region 3 is the nasopharynx region.

from the outer nostril and constricts the airway cross-section to 0.3–0.4 cm^2; this represents the smallest passage for total airflow in the respiratory tract (Newman et al., 1987). In the present study, the same type of nasal pump actuator was used for both formulations and the dose was administered to the subjects using identical techniques in order to minimize potential variables. Cromolyn sodium and the radiotracer (^{99m}Tc-DTPA) forms a true solution, thus, a freely water-soluble drug is anticipated to deposit and clear from the nasal cavity in a similar fashion as a freely soluble surrogate radioactive marker. Furthermore, the use of gamma scintigraphy has been established previously whereby surrogate gamma emitting isotopes have been used to represent the deposition, migration and *in vivo* transit patterns of a wide variety of drug formulations (Theodorakis et al., 1983; Vidgren et al., 1991; Newman, 1996). The scintigraphic analysis was validated by plotting of the administered dose (μCi) and the measured counts representing the denominator in Eq. (1) which was resulted in linear correlation ($R^2 = 0.99$).

The mean data from Figs. 3–6 show the nasal clearance and deposition for each formulation from regions 1 to 3 and all regions of interest. The area under the curves for all individual regions and summation of all regions were determined and

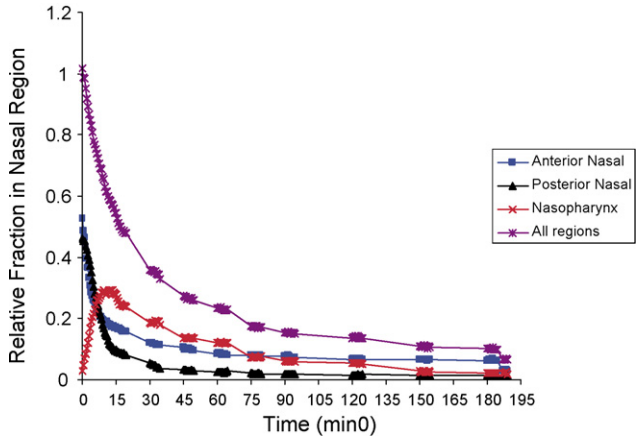

Fig. 2. The clearance characteristics of radiolabeled cromolyn sodium formulation A from anterior nasal cavity, posterior nasal cavity, the nasopharynx region and all ROI in human nose ($n = 5$).

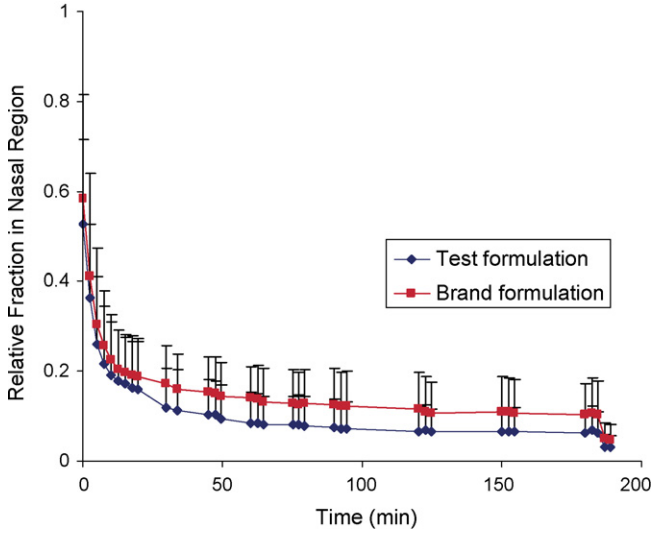

Fig. 3. The clearance characteristics of radiolabeled cromolyn sodium formulations (test and brand formulation) from the anterior part in human nose.

Table 1
Area under the nasal clearance curves for treatment A (cromolyn sodium test formulation) and treatment B (cromolyn sodium reference formulation)

Value measured	Anterior nasal cavity		Posterior nasal cavity		Nasopharynx		All regions of interest	
	Reference	Test	Reference	Test	Reference	Test	Reference	Test
Mean	26	17.9	7.5	8	17.2	17.6	50.7	43.4
CV	0.53	0.69	0.24	0.26	0.44	0.52	0.21	0.24
Range	37.4	31.2	4.6	5.2	16.8	20	26.7	25.6

none were shown to be statistically different (Table 1), paired t-test, $p < 0.05$.

Both treatments demonstrated biphasic elimination with a significant and variable amount of radioactivity (5.1–27.7%) which remained in the anterior nasal cavity at the end of the last imaging sequence (Table 2).

Examination of Figs. 2–6, which describe the mean activity of the two formulations within the nasal cavity as a relative fraction of administered dose versus time, and show that the clearance characteristics of both formulations did indeed exhibit biphasic-like patterns, as suggested by initial deposition pictures and the literature (Fig. 6). The clearance of inhaled materials from the nasal cavity *in vivo* has been shown to follow a biphasic pattern (Aoki and Crawley, 1976; Hardy et al., 1985; Harris et al., 1986; Illum et al., 1987; Pennington et al., 1988). This biphasic pattern is the result of an initial fast rate of clearance of material from the ciliated regions of the nose, followed by a comparatively slow second phase of clearance associated with material deposited on the non-ciliated anterior region of the nose.

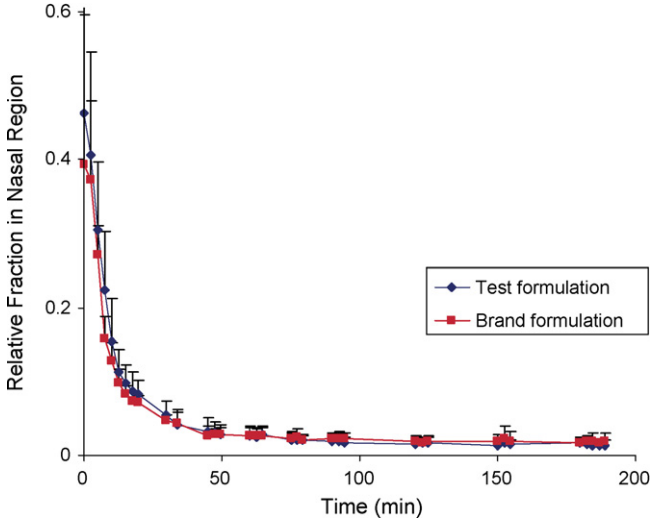

Fig. 4. The clearance characteristics of radiolabeled cromolyn sodium formulations (test and brand formulation) from the posterior part in human nose.

Table 2
Fraction of the radioactive Tc-99m DTPA, remaining in the anterior nasal cavity (region 1) at 180 min post-dose

Subject	Percentage of Tc-99m DTPA remaining in anterior nasal cavity (region 1) at 180 min post-dose	
	Treatment A: cromolyn sodium (test formulation product, %)	Treatment B: cromolyn sodium (reference formulation product, %)
1	14.5	14.5
2	5.1	12.2
3	16.3	10.3
4	7.7	8.7
5	6.5	27.7
Mean	10.0	14.7
Median	7.7	12.2
S.D.	5.0	7.6

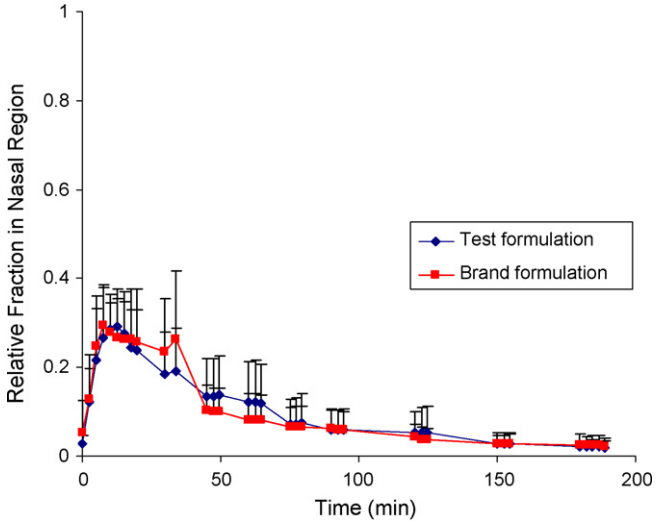

Fig. 5. The clearance characteristics of radiolabeled cromolyn sodium formulations (test and brand formulation) from the nasopharynx in human nose.

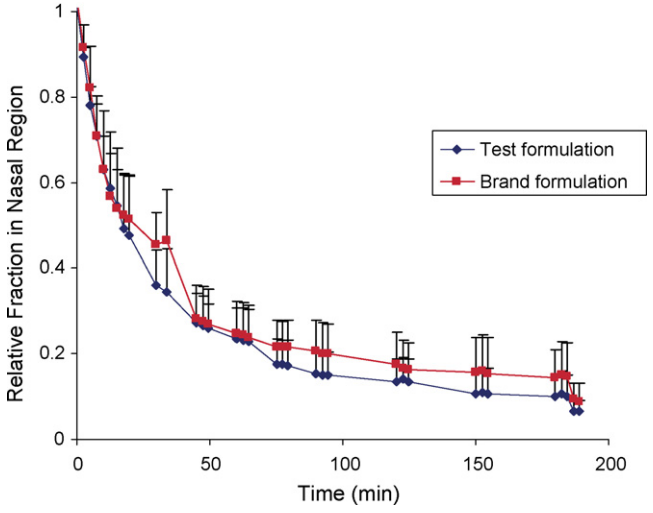

Fig. 6. The clearance characteristics of radiolabeled cromolyn sodium formulations (test and brand formulation) from all ROI in human nose.

Although the *in vitro* characterization of the two nasal sprays was shown to be equivalent, the *in vivo* migration as well as the residual amount of the nasal formulation retained at its original site of deposition is ultimately more relevant to its *in vivo* efficacy. This is due to the fact that the mucociliary transport in the nasal cavity affects the movement of the formulation in the posterior nasal passages as a function of time. The overall residence and rate of movement can possibly be affected by several factors such as formulation viscosity, intersubject differences in nasal patency, and the fluidity of the epithelial surface.

The data obtained in the present study suggested that there is little or no difference in nasal deposition and clearance from the three regions between the two formulations of cromolyn sodium, and the two formulations were considered equivalent in their *in vivo* performance.

8. Conclusion

Presently, there are limited ways to demonstrate bioequivalence of nasal drugs which are intended for topical treatment. Gamma scintigraphy (Rhinoscintigraphy) was evaluated as a rapid and more definitive method to establish *in vivo* equivalence between reference and test nasal products for drugs that are not systemically absorbed. It is assumed that products having similar *in vivo* nasal deposition and clearance should also show equivalence with regard to their *in vivo* topical treatment. Thus, the two cromolyn sodium formulations (reference and test) showed equivalence. The clearance profiles of the preparations from their initial site of deposition and through the nasopharynx region were identical. Therefore, it was interpreted that as soon as the spray droplets were dislocated from their initial deposition area, they were rapidly cleared and their following interactions with mucus layer in the rest of the nasal cavity did not have a significant role on the total clearance-time. The described methods suggest that gamma scintigraphy can determine local delivery of nasal products, and should play a key role in the regulatory approval process for new allergy products, helping to facilitate the early introduction of these products to the market.

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