

# Regional deposition of mometasone furoate nasal spray suspension in humans

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## ABSTRACT

Nasal deposition studies can demonstrate whether nasal sprays treating allergic rhinitis and polyposis reach the ciliated posterior nasal cavity, where turbinate inflammation and other pathology occurs. However, quantifying nasal deposition is challenging, because *in vitro* tests do not correlate to human nasal deposition; gamma scintigraphy studies are thus used. For valid data, the radiolabel must distribute, as the drug, into different-sized droplets, remain associated with the drug in the formulation after administration, and not alter its deposition. Some nasal deposition studies have demonstrated this using homogenous solutions. However, most commercial nasal sprays are heterogeneous suspensions. Using mometasone furoate nasal suspension (MFS), we developed a technique to validate radiolabel deposition as a surrogate for nasal cavity drug deposition and characterized regional deposition and nasal clearance in humans. Mometasone furoate (MF) formulation was spiked with diethylene triamine pentacetic acid. Both unlabeled and radiolabeled formulations ( $n = 3$ ) were sprayed into a regionally divided nasal cast. Drug deposition was quantified by high pressure liquid chromatography within each region; radiolabel deposition was determined by gamma camera. Healthy subjects ( $n = 12$ ) were dosed and imaged for six hours. Scintigraphic images were coregistered with magnetic resonance imaging scans to quantify anterior and posterior nasal cavity deposition and mucociliary clearance. The ratio of radiolabel to unlabeled drug was 1.05 in the nasal cast and regionally appeared to match, indicating that *in vivo* radiolabel deposition could represent drug deposition. In humans, MFS delivered 86% (9.2) of metered dose to the nasal cavity, approximately 60% (9.1) of metered dose to the posterior nasal cavity. After 15 minutes, mucociliary clearance removed 59% of the initial radiolabel in the nasal cavity, consistent with clearance rates from the ciliated posterior surface. MFS deposited significant drug into the posterior nasal cavity. Both nasal cast validation and mucociliary clearance confirm the radiolabel deposition distribution method accurately represented corticosteroid nasal deposition.

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Nasal delivery is used to directly deliver drugs for local action while also minimizing unintended systemic effects. Alternatively, it may also provide advantages for systemic delivery due to rapid absorption and avoidance of first-pass metabolism.<sup>1–7</sup> The posterior nasal cavity contains local targets, such as the middle meatus and turbinates, that become inflamed in diseases like allergic rhinitis, polyposis, and sinusitis. However, most droplets ( $\approx 50\%$ ) from a nasal spray are filtered into the anterior nasal cavity, with only 25% reaching the posterior regions.<sup>1,4,8–16</sup> Furthermore, due to mucociliary clearance, in the posterior nasal cavity, there is limited residence time in this region.<sup>6,17–22</sup>

Mometasone furoate (MF) is a highly potent glucocorticosteroid exhibiting strong antiinflammatory activity. It is effective in the treatment of seasonal and perennial allergic rhinitis, rhinosinusitis, and nasal polyps. MF has low systemic bioavailability when formulated as a MF nasal suspension (MFS) and delivered by nasal spray (Merck, Whitehouse Station, NJ).<sup>23,24</sup>

Accurately measuring how MF is deposited in the nasal cavity is challenging. Although the Food and Drug Administration lists *in vitro* spray tests,<sup>25</sup> these tests have generated controversy, because they neither predict human nasal deposition nor biologic effect.<sup>2,26–28</sup> Others have examined models such as a glass nose,<sup>29,30</sup> computational models,<sup>8,31,32</sup> and nasal casts.<sup>2,33–38</sup> However, such models have never been validated against *in vivo* deposition with an active drug formulation. Given these concerns about *in vitro* tests, many choose direct *in vivo* assessment of nasal cavity deposition by gamma scintigraphy. The challenge is to ensure the radiolabel deposition can act as a surrogate for drug deposition.<sup>39–41</sup>

For data to be valid, the radiolabel must distribute into different-sized droplets in the same proportions as the drug, remain associated with the drug in the for-

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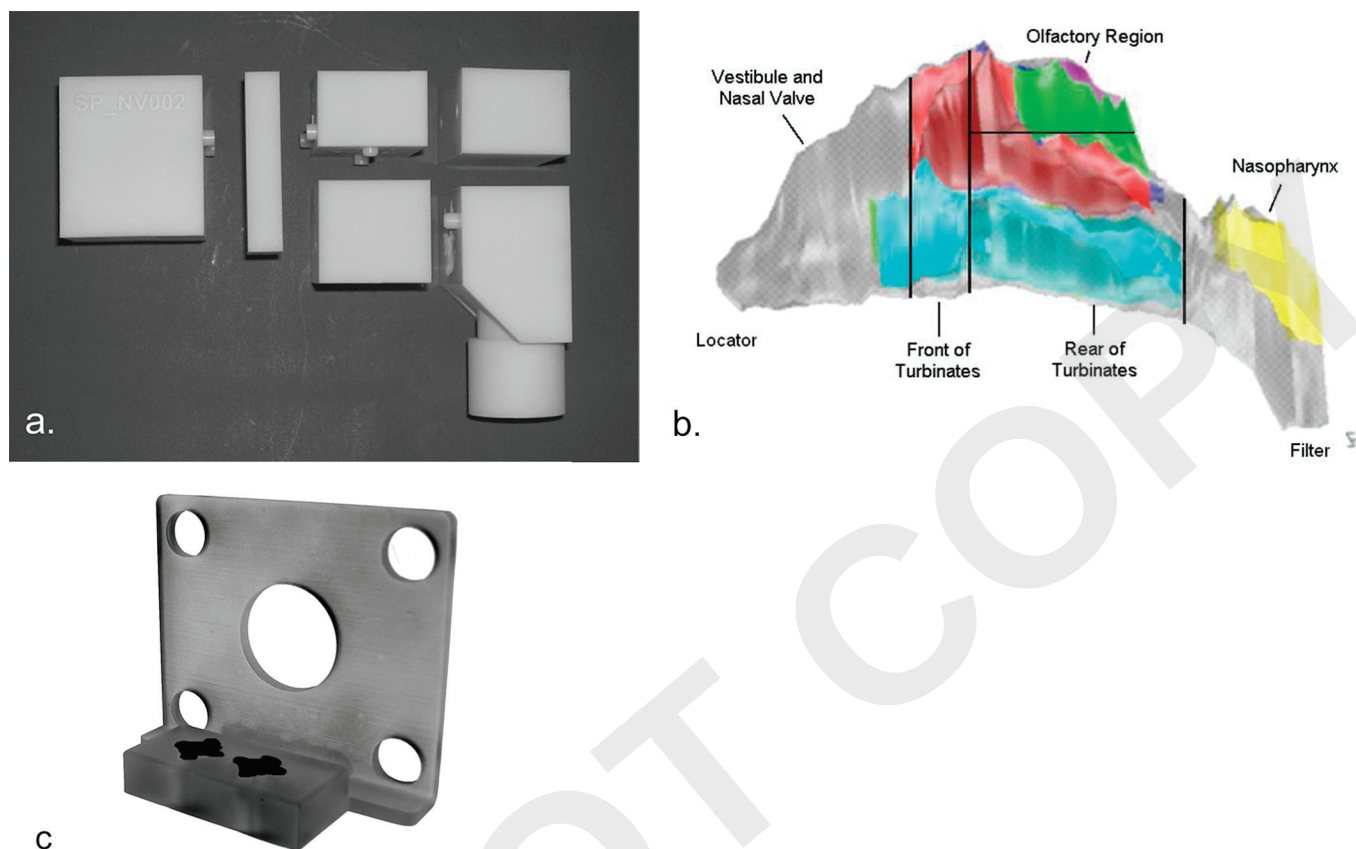


**Figure 1.** (a) Nasal cast sections and (b) corresponding regions in the nasal cavity. (c) Nozzle locators that position the nasal spray at a range of set nozzle insertion angles. (Source: Ref 47, used with permission.)

mulation, and not alter its deposition in the nasal cavity.<sup>39–41</sup> One option, radiolabeling the individual drug molecule, is challenging for corticosteroids.<sup>2,39,40,42</sup> Another option is to use solution formulations containing a dissolved radioactive tracer.<sup>10,12,15,43–46</sup> However, most commercial nasal formulations are suspensions, not solutions. Although a radiolabel can be added, concerns exist as to whether the radiolabel would remain associated with the drug, because the liquid breaks up into spray droplets because the radiolabel and drug are not covalently bonded.

For suspensions, lung deposition studies ensured the radiolabel indicated drug deposition by following Newman's recommendations of using an Anderson cascade impactor (ACI) to show similar aerodynamic particle-size distributions.<sup>40</sup> Unfortunately, droplets from a nasal spray are too large to be measured using an ACI. In this study, we first ensured radiolabel deposition in the nasal cavity represented MF deposition in the nasal cavity using an anatomically similar nasal cast. This cast was more suitable for larger droplets from a nasal spray.<sup>47</sup> Knowing that radioactive deposition represented MF deposition when delivered as a nasal spray, to a nasal cavity replica, we advanced to the clinic. This study assessed regional human nasal deposition and mucociliary clearance of MFS, quanti-

fied the deposition within regions of the anterior and posterior nasal cavity, and then confirmed the deposition location based on measured product clearance and known mucociliary clearance behavior in the nasal cavity.

## MATERIALS AND METHODS

### Validation Using Nasal Cast and ACI

**Nasal cast.** The nasal cast (Bespak, Milton Keynes, UK)<sup>36,47</sup> was divided into five regional areas of interest (Fig. 1):

- nasal vestibule and nasal valve
- front of the turbinates
- rear of the turbinates
- olfactory region
- nasopharynx

Material deposited on the actuator or adaptor, or that dripped out, was measured, and a terminal filter caught material that would deposit in the upper airway.

**Drug device/formulation.** MF monohydrate nasal spray suspension (Merck, Summit, NJ) was used in this study. Each spray delivered 100 mg of formulation

containing 50  $\mu\text{g}$  of MF. The spray characteristics of this formulation,<sup>48</sup> and a similar formulation,<sup>49</sup> have been reported.

*Radiolabeling of formulations.* Each MFS formulation was transferred to an empty nasal spray bottle and spiked with diethylene triamine pentacetic acid ( $^{99\text{m}}\text{Tc}$ -DTPA) solution before crimping the pump into place. The  $^{99\text{m}}\text{Tc}$ -DTPA radiolabel was prepared by adding required  $^{99\text{m}}\text{Tc}$  elution (Qados, Torquay, UK) into a DTPA Technescan kit (Mallinckrodt, St. Louis, MO). Approximately 1% of the resulting  $^{99\text{m}}\text{Tc}$ -DTPA solution was added into the formulation so that less than 5 megabecquerel radioactivity was present in 400 mg of formulation.

*Characterization of nasal spray delivery to a nasal cast.* Two sprays of each MFS nasal spray were administered into each nostril in the nasal cast as previously described,<sup>47</sup> delivering a total of 200 mcg of MF in 400 mg of formulation.

After actuation, the nasal cast was disassembled into its regions. The radioactivity in each region was measured using a gamma camera (General Electric Maxicamera, Milwaukee, WI). MF in each region was measured as previously described.<sup>47</sup> All experiments were repeated three times. The data were reported as the percentage of the radioactivity or MF.

*Characterization of nebulizer delivery of MFS to an ACI.* Approximately 3 mL of the MFS radiolabeled formulation were transferred into the nebulizer (LC Plus, PARI Respiratory Equipment, Inc., Midlothian, VA), which was fitted to the ACI. The flow was started at a rate of 28.0 L/min and remained until the chamber was exhausted. Radioactivity in each stage was detected using a gamma camera. The stages of the ACI were then analyzed to quantify the percentage of MF on each stage.

#### *Clinical evaluation.*

**Subjects.** Healthy subjects from a single center were administered open-label MFS. Approval was obtained by the Capenhurst Independent Research Ethics Committee. Informed consent was obtained from all subjects.

**Drug formulations and drug delivery devices.** In the human study, MFS was radiolabeled as described in the earlier section.

*Scintigraphy registration.* Subjects had a magnetic resonance imaging (MRI) scan of the head before admission for the study. This MRI provided an outline of the nasal cavity, nasopharynx, and other anatomic structures so that the deposition pattern could be assigned

to specific regions. Before scanning, external markers were applied so that coregistration with the scintigraphic images could be performed.

*Drug administration.* Before dosing, subjects were trained to become familiar with and able to reliably reproduce the techniques described in the package insert. Subjects were instructed to blow their noses before dosing.

Each unit was primed 10 times. A technician administered the spray: two 100- $\mu\text{L}$  sprays into each nostril, alternating, for a total dose of 200  $\mu\text{g}$  of MF, following the package insert instructions. After dosing, subjects were not allowed to blow their noses until all imaging was completed. Tissues were provided for subjects to wipe their noses, and these were retained and then imaged. The first dosing was approximately two months after the nasal cast validation, within the recommended time frame.<sup>41</sup>

*Scintigraphy.* Two anatomic markers containing 0.1 MBq  $^{99\text{m}}\text{Tc}$  were used. Both of the markers were taped in line with the nose, one on the hairline and the other on the tip of the chin.

The next scintigraphic images were acquired immediately after dosing:

- left lateral head (nasal cavity and nasopharynx)
- anterior head (sinuses)
- anterior and posterior images of the lungs
- anterior and posterior images of the stomach

After dosing, radioactivity in the devices, exhaled air filter, and any associated tubing or nasal wipes were monitored as the scheduled allowed.

Subsequently, left lateral images of the head (nasal cavity and nasopharynx) were acquired at 15-, 20-, 30-, 45-, 60-, 90-, 120-, 180-, and 360-minute postdose. The images were acquired using a Maxicamera gamma camera with a 40-cm field of view and fitted with a low-energy, all-purpose, parallel-hole collimator. All the images were acquired with the subjects sitting in front of the gamma camera using a support frame to ensure correct and consistent positioning of the subjects, as appropriate. Image recording was by a Micaxplus computer system (Bartec Technologies Ltd., Camberley, Surrey, UK).

To correct for attenuation of gamma rays by overlying tissues, each subject underwent a transmission scan of the head and the thorax, using a flood field source containing  $^{57}\text{Co}$ .

*Scintigraphy analysis.* Scintigraphic data were corrected for background radiation, radioactive decay, and tissue attenuation of gamma rays. Where appropriate, the geometric mean of anterior and posterior counts was calculated.

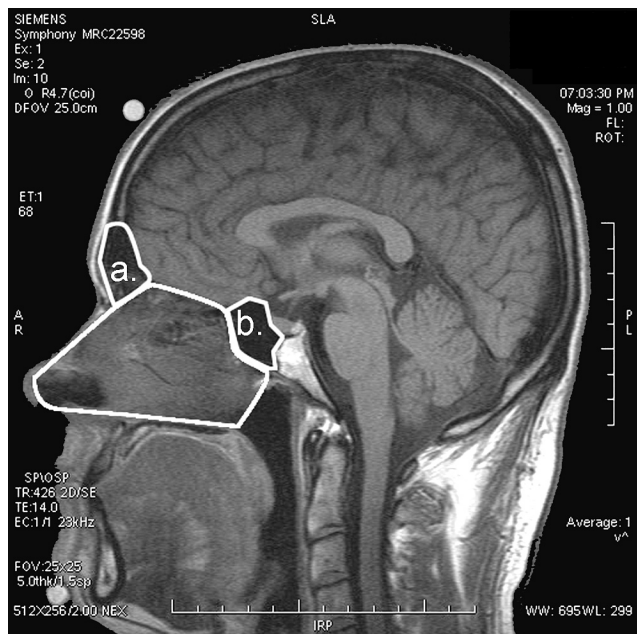


**Figure 2.** Sagittal section from MRI to define the (a) frontal and (b) sphenoid sinus region of interest.

**Drug delivered.** The amount of formulation delivered on each administration was assessed gravimetrically. The calculation was carried out as follows:

$MF (\mu g) = \text{formulation weight loss (mg)} \times 0.5 \mu g/mg$  (based on concentration).

**Nasal cavity deposition analysis.** Deposition of radioactivity (% of the metered dose) in the nasal, nasopharynx, lungs (whole), and swallowed (esophagus plus stomach) was measured in the lateral (sagittal) head, and thoracic postdose images acquired immediately after delivery of the product. The amount of radioactivity deposited on device nozzle wipes and nasal wipes was also determined.

Metered dose was the sum of counts in all measurable regions in images acquired immediately after dosing.

**Regional nasal cavity deposition.** Exploratory analysis investigated differences in the deposition pattern within the nasal cavity. The nasal cavity defined in the sagittal sections of the MRI scan was divided into anterior and posterior regions by drawing regions of interest for each subject after the locating the nasal valve and other anatomic structures on the coregistered MRI, similar to previous reports to segment the nasal cavity (Fig. 2).<sup>6</sup> An example of the area segmented as the posterior region is shown in Fig. 3.

**Mucociliary clearance.** The radioactivity counts remaining in the nasal cavity in images after the initial images were quantified as a percentage of the original counts at  $t = 0$ .

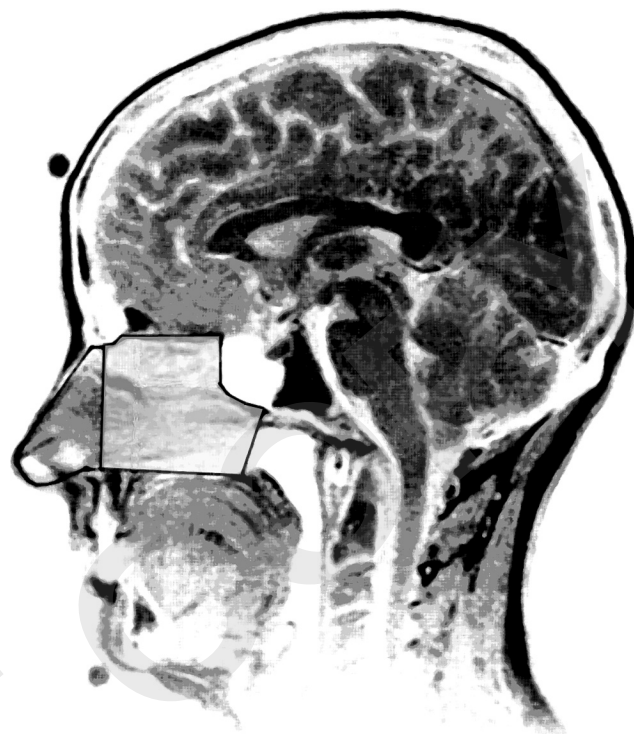


**Figure 3.** Approximate segmented region deemed the posterior nasal cavity; anatomic regions of interest were drawn for each subject based on the MRI image of that subject.

**Sample size.** Approximately 12 subjects were enrolled. The sample size was based on empiric rather than statistical considerations, because no previous background deposition information existed.

## RESULTS

### *In Vitro* Deposition Characterization

**Characterization of formulations with the nasal cast.** Table 1 and Fig. 4 show the deposition pattern. The ratio of drug (unlabeled) delivered to the nasal cast and drug (radiolabeled) was calculated as 1.04. For the percentage depositing to the nasal cavity, the ratio of both drug (labeled) and radiolabel to drug (unlabeled) was calculated to be 1.05. Within each region, the confidence intervals overlap.

**Characterization of MFS delivery to an ACI.** Table 2 shows the deposition pattern when delivered by jet nebulizer to an ACI. Within regions, stages one, four, and five showed that the radiolabel did not follow the drug, because the confidence intervals barely overlapped. The apparent fine particle fraction based on radiolabel from the jet nebulizer was greater than that seen with the drug, with a ratio of 1.74. It appeared that MF deposited on the upper stages (by larger droplets) and the radioactivity distributed on the lower stages (by smaller droplets).

Table 1. Deposition as mean percentage of metered dose (90% confidence interval) of drug (unlabeled), drug (labeled), and radiolabel of MFS when delivered by nasal spray to the nasal cast

| Stage                    | Drug (Unlabeled)       | Drug (Labeled)         | Radiolabel           |
|--------------------------|------------------------|------------------------|----------------------|
| External wipe (%)        | 9.57 (5.94–13.19)      | 5.46 (0.00–14.82)      | 5.20 (0.00–14.05)    |
| Nasal valve (%)          | 58.20 (54.24–62.16)    | 53.93 (50.25–57.61)    | 55.40 (51.31–59.49)  |
| Front turbinate (%)      | 14.67 (9.15–20.18)     | 18.23 (11.15–25.32)    | 18.20 (9.17–27.23)   |
| Rear turbinate (%)       | 13.87 (7.64–20.09)     | 19.97 (16.83–23.10)    | 18.57 (14.57–22.56)  |
| Olfactory region (%)     | 0.00 (0.00–0.00)       | 0.40 (0.00–1.57)       | 0.47 (0.00–1.40)     |
| Nasopharynx (%)          | 3.73 (0.07–7.40)       | 2.07 (0.00–5.09)       | 2.17 (0.00–5.05)     |
| Filter (%)               | 0.00 (0.00–0.00)       | 0.00 (0.00–0.00)       | 0.00 (0.00–0.00)     |
| Nasal cavity (%)         | 86.73 (82.76–90.70)    | 92.53 (81.53–100.00)   | 92.63 (81.63–100.00) |
| Drug recovery ( $\mu$ g) | 182.22 (175.37–189.07) | 189.67 (183.44–195.90) |                      |
| Formulation removed (mg) | 388.03 (386.91–389.16) | 384.13 (382.07–386.19) |                      |

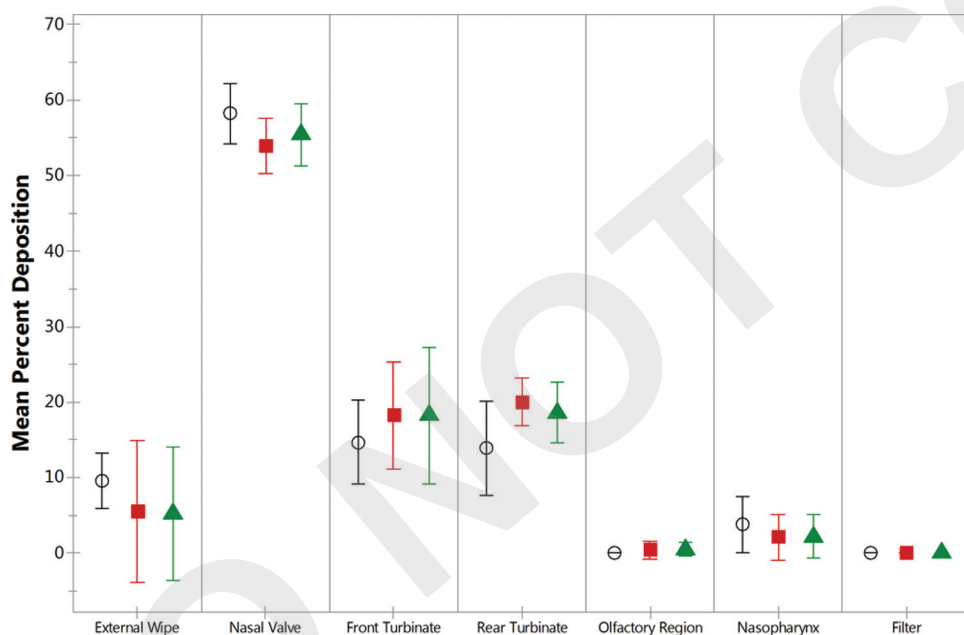


Figure 4. Drug and radiolabel distribution of MFS in regions in the nasal cast showing overlap of (○) drug from unlabeled formulation, (■) drug from labeled formulation, and (▲) radiolabel. Interval bars show 90% confidence interval.

## Human Deposition Characterization

**Patient demographics.** Of the 12 subjects in this study, 10 were female and 2 were male. All subjects were Caucasian. The mean age was 45.1 years (median = 46.0 years), with an age range of 23 to 64 years.

**Delivered dose.** The amount of MF delivered by the nasal spray is shown in Table 3. Almost 95% of the label claim of MF was delivered.

**Initial deposition.** Images for two subjects are shown in Fig. 5, and initial deposition data for 12 subjects are summarized by region in Fig. 6.

On average, approximately 60% of the radioactivity deposited in the posterior nasal cavity, with 26% in the anterior nasal cavity, approximately 10% swallowed, and less than 2% in the nasopharynx and lungs. Approximately 86% of the radioactivity was deposited in the nasal cavity.

**Mucociliary clearance.** Table 4 and Fig. 7 show the average percentage of radioactivity remaining in the nasal cavity as a function of time. The radioactivity deposited by MFS was removed quickly, with approximately 60% cleared after 15 minutes.

**Adverse effects.** MFS was well tolerated. One subject (8%) reported a mild headache, which was assessed as unrelated to treatment. No serious adverse events or deaths occurred. No clinically significant laboratory or vital sign findings were observed.

## DISCUSSION

In this study, we demonstrated that MFS deposited 60% of the formulation in the posterior nasal cavity, exceeding previous reports of nasal spray deposition. This deposition was measured by quantifying the anterior and posterior *in vivo* human nasal deposition

Table 2. Deposition as mean percentage of metered dose (90% confidence interval) of drug (unlabeled), drug (labeled), and radiolabel of MFS when delivered by jet nebulizer to an ACI\*

| Stage          | Drug (Unlabeled)%   | Drug (Labeled)%     | Radiolabel%         |
|----------------|---------------------|---------------------|---------------------|
| Induction Port | 3.34 (2.79–3.90)    | 4.23 (0.00–14.03)   | 4.73 (0.00–18.31)   |
| Stage 0        | 23.03 (20.77–25.29) | 26.54 (16.39–36.69) | 8.55 (3.34–13.77)   |
| Stage 1        | 31.32 (27.52–35.12) | 30.45 (27.94–32.97) | 13.31 (9.95–16.67)  |
| Stage 2        | 14.38 (12.62–16.14) | 14.96 (4.75–25.18)  | 10.25 (10.14–10.35) |
| Stage 3        | 16.25 (14.90–17.59) | 14.66 (0.00–33.65)  | 18.78 (12.26–25.31) |
| Stage 4        | 7.92 (4.98–10.87)   | 6.36 (3.54–9.19)    | 16.90 (15.14–18.66) |
| Stage 5        | 2.87 (1.35–4.39)    | 2.49 (0.60–4.39)    | 19.54 (16.62–22.46) |
| Stage 6        | 0.67 (0.00–1.62)    | 0.30 (0.00–2.19)    | 6.03 (4.55–7.52)    |
| Stage 7        | 0.04 (0.00–0.15)    | 0.00 (0.00–0.00)    | 1.51 (0.64–2.39)    |
| Filter         | 0.00 (0.00–0.00)    | 0.00 (0.00–0.00)    | 0.40 (0.26–0.53)    |
| FPF            | 42.14 (37.70–46.57) | 38.78 (36.61–40.95) | 73.41 (68.41–78.41) |

\*These types of inertial impactors segregate droplets that are aerodynamically less than 9  $\mu\text{m}$ ; droplets larger than this size typically deposit in the entry port or preseparator before the size-discriminating portions of the impactor.

Table 3. Mean MF delivered (standard deviation) and percentage of the radiolabel metered dose deposited into each region (standard deviation) of MFS when delivered by nasal spray to human subjects

| MF Delivered (mcg) | In Vivo Deposition (%) |            |            |             |           |            |
|--------------------|------------------------|------------|------------|-------------|-----------|------------|
|                    | External               | Anterior   | Posterior  | Nasopharynx | Swallowed | Lung       |
| 190.2 (6.0)        | 3.1 (4.2)              | 26.0 (9.8) | 60.1 (9.1) | 1.54 (2.2)  | 7.4 (7.4) | 1.58 (1.2) |

pattern. We confirmed our findings based on the rapid mucociliary clearance (60% in 15 minutes) of the radiolabel, indicating deposition in the ciliated posterior nasal cavity. We further validated initial deposition using a nasal cast. This is the first human nasal deposition study to validate that radiolabel deposition accurately represented drug deposition using an active formulation and separating deposition by region. Our validation approach followed recommendations by Newman<sup>40</sup> and provided data recommended by Devadason *et al.*<sup>41</sup>

Few recent human nasal deposition studies exist in the literature, and none that we found characterized the regional deposition of suspensions. The challenge has been ensuring that the radiolabel distributes in the droplets, and therefore in the nasal cavity, in the same proportions as the drug.<sup>39–41</sup> Because our formulation was an aqueous suspension, our approach was to spike the formulated suspension with a radiolabel.

Droplets from a nasal spray are reported to have mass median aerodynamic diameters of 50  $\mu\text{m}^2$  and 65  $\mu\text{m}$ .<sup>19</sup> These sizes are much larger than droplets from lung delivery devices, and therefore, Newman's methods to show radiolabel deposition matched drug deposition<sup>40</sup> using an ACI are not applicable to nasal formulations. After our studies were already complete, Devadason *et al.* provided recommendations to validate radiolabeling for lung deposition studies, which

included using at least a four-stage *in vitro* system, using an air flow rate comparable with those used by patients, comparing both the overall dose and deposition in each region, displaying 90% confidence intervals, and providing the data in a form to allow easy comparison between radiolabeled and unradiolabeled formulations.<sup>41</sup>

The nasal cast met the first two requirements, because it had six regions and we had optimized the cast for air flow rates used by patients.<sup>47</sup> We further show that the data in Table 1 allows calculation of ratios of labeled and unlabeled drug dose, and radiolabel, all of which were close to 1. Within each region, there was significant overlap in the confidence intervals (Fig. 4) between the unlabeled drug, radiolabeled formulation, and radiolabel. We have presented the data as recommended<sup>41</sup> to demonstrate that radiolabel deposition accurately represented nasal drug deposition in humans.

In humans, MFS delivered on average 95% of its label claim (Table 3). Of the formulation emitted from the nasal spray, 86% delivered to the nasal cavity. Although deposition in the anterior nasal cavity was expected (25%), it was surprising that 60% of the formulation deposited into the posterior nasal cavity. Most other nasal spray deposition studies showed less than 25% in the posterior nasal cavity, with more than 50% in the anterior regions<sup>1,4,8–12</sup> due to the inertial

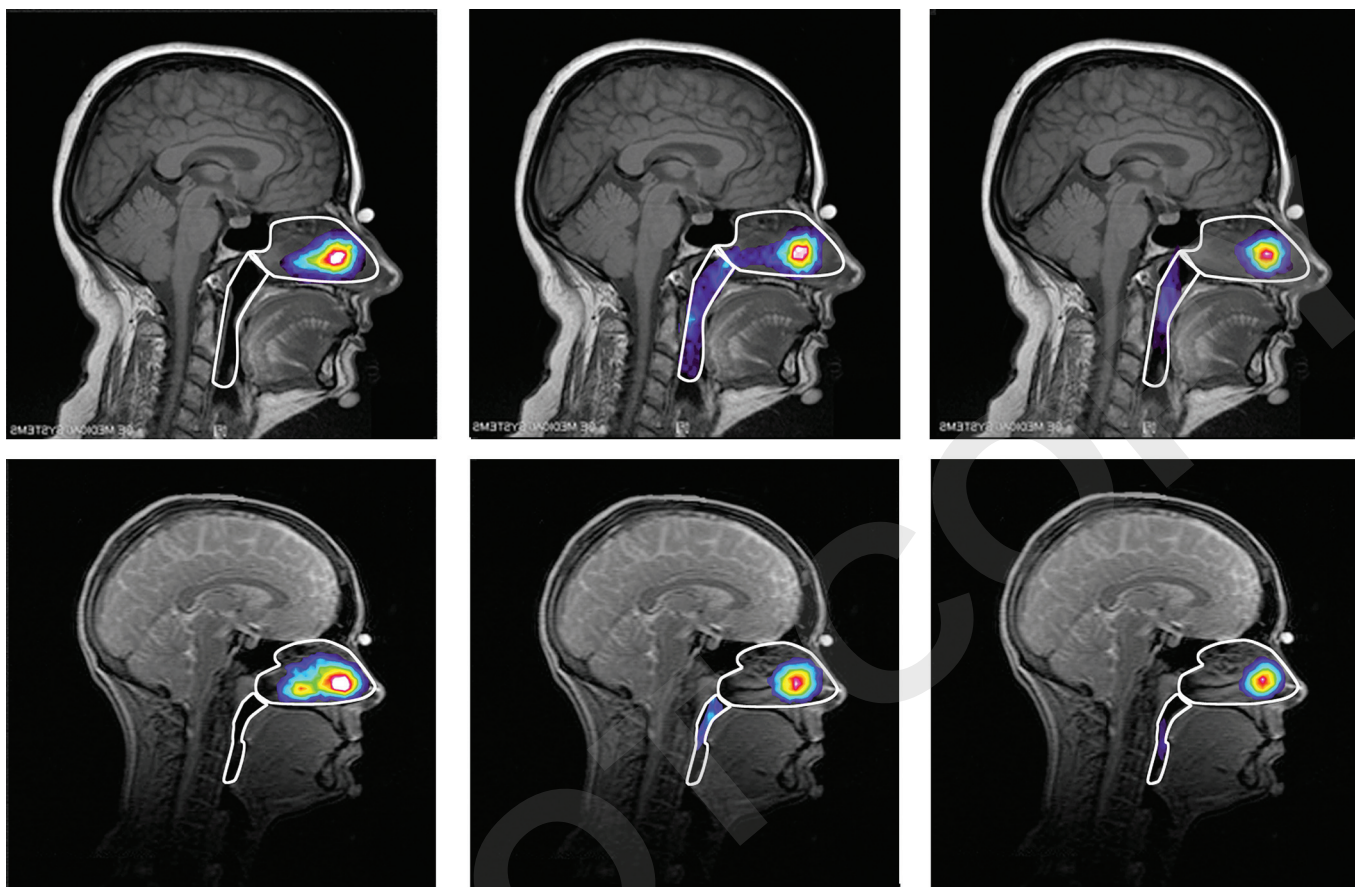


**Figure 5.** Initial human deposition images of MFS radiolabeled formulation (left) and after 20 and 60 minutes (center and right) of two subjects (above, below).

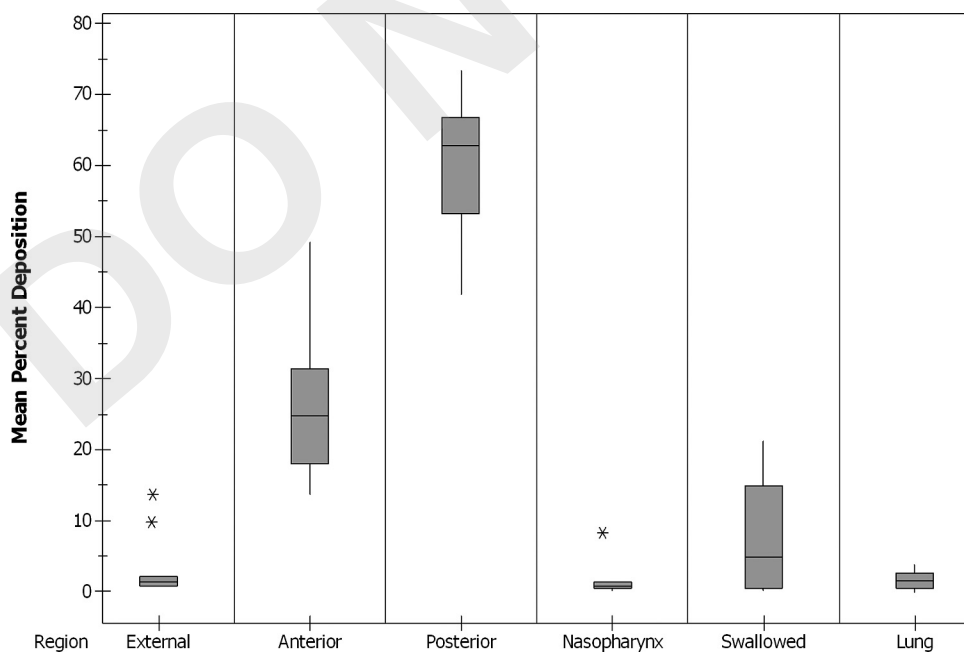


**Figure 6.** Box and whisker diagram showing human deposition of radiolabeled MFS in the nasal cavity as a percentage of metered dose, by region. The top and bottom edges of the box mark the 1st and 3rd quartile; line extends to the furthest data point within 1.5 times the interquartile range.

impaction of the droplets before making the 90° turn after the nasal valve. The nasal spray deposited less than 8% on the device or subject's face. Although some drug was swallowed, an insignificant portion of the

formulation deposited in the lung, consistent with the low percentage of droplets less than 10  $\mu\text{m}$ .<sup>2</sup>

Table 4 shows that material deposited by the nasal sprays was rapidly cleared. Rapid clearance from the

Table 4. Mean radiolabel remaining (standard deviation) in the nasal cavity as a percentage of the initial radiolabel counts in the nasal cavity

| Time (min) | Nasal Spray Suspension |
|------------|------------------------|
| 0          | 100.00 (0)             |
| 15         | 41.11 (18)             |
| 20         | 37.02 (17)             |
| 30         | 30.71 (14)             |
| 45         | 26.42 (11)             |
| 60         | 25.00 (11)             |
| 90         | 23.04 (10)             |
| 120        | 20.54 (9)              |
| 180        | 17.37 (7)              |
| 360        | 13.32 (7)              |

nasal cavity is due to mucociliary transport, a defense mechanism moving material from the posterior nasal cavity to the nasopharynx to be swallowed.<sup>4,50</sup> The initial phase of mucociliary clearance removes material in 15–30 minutes.<sup>4,5</sup> After 15 minutes, we found that 60% of the radioactivity from the nasal spray was removed, consistent with other studies finding that approximately 50% of the formulation had been removed after 15–20 minutes due to mucociliary clearance.<sup>5,19–22</sup> Because the form of radioactivity administered is not absorbed, this removal must be from mucociliary clearance, confirming deposition to the ciliated posterior regions beyond the nasal valve.<sup>5,6</sup>

This nasal deposition study is the first to quantify regional deposition from an active, commercial, suspension formulation. Both Suman *et al.*<sup>12</sup> and Hardy *et al.*<sup>10</sup> found that nasal sprays deposited mostly in the anterior regions, with little of the dose reaching the turbinates. Similarly, Bateman *et al.*,<sup>51</sup> Bergstrom *et al.*,<sup>13</sup> Aoki and Crowley,<sup>43</sup> and McInnes *et al.*<sup>45</sup> found poor to low distribution of drug into the posterior nasal cavity. Newman reported slightly higher posterior nasal cavity deposition of 40%–50% in one study.<sup>11</sup> Other than Bergstrom's, these studies did not need to show the radiolabel and drug matched because they were in solution.<sup>39</sup> However, these decades old nasal deposition studies have limited value today because many nasal sprays are not solutions due to the poor solubility of the compounds administered (*e.g.*, corticosteroids like MF) and/or because they contain viscosity-modifying agents. Emanuel *et al.* recently reported deposition of this formulation, but neither anterior versus posterior deposition nor methods for validation were provided.<sup>52</sup>

Our study's validity rests on the nasal cast validation confirming that initial radioactive deposition represented drug deposition of the MFS. That validation,

and the *in vivo* confirmation by the rapid mucociliary clearance, supports the accuracy of our report of higher deposition in the posterior nasal cavity.

We believe that the MF and the radiolabel remained associated when sprayed from the nasal spray because of its larger droplet sizes. Droplets are created when shear from the pump breaks up the formulation. When delivered by the oral nebulizer, in smaller droplet sizes, the MF and radiolabel did not distribute into droplets in similar proportions. We believe that this mismatch demonstrates that neither an oral nebulizer nor an ACI should be used to validate delivery of nasal sprays. The difference in deposition between the nasal cast and human study also shows the need for more engineering on these casts<sup>53</sup> to ensure realistic nasal casts.

Our study was specific to an aqueous nasal spray; nasal aerosols may show different performance because of different droplet sizes. However, deposition in a healthy human alone cannot show clinical efficacy or equivalence. For local action, systemic delivery, or nose-to-brain delivery, deposition is only one factor in therapeutic effect. The active ingredient, the crystal form, and the formulation can all play roles. Both Costantino *et al.*<sup>54</sup> and Dhuria *et al.*<sup>55</sup> summarized studies showing how changes to a formulation's physicochemical properties affects nasal absorption, transport to the site of action, and initiation of therapeutic molecular signaling pathways. Furthermore, as Newman pointed out, no studies exist relating deposition to biologic action.<sup>2</sup> Additionally, our study was performed on healthy subjects, whose nasal passage characteristics may be different from those with allergic rhinitis or any other chronic condition,<sup>2</sup> a topic of a recent publication.<sup>46</sup> For these reasons, although healthy subject deposition studies suggest greater therapeutic potential of an existing product because of the areas they target, they cannot show that one product is equal to another.

## CONCLUSIONS

MF aqueous suspension deposited more of its metered dose in humans to the turbinates and middle meatus of the nasal cavity than demonstrated in the literature by other nasal sprays. The posterior nasal cavity pathologies are associated with sinusitis, rhinitis, and polyposis inflammation. Using a nasal cast, and methods from lung radiolabel validation, we developed a new technique to confirm that radiolabel remained associated with drug and therefore accurately characterized nasal drug deposition. Furthermore, the rapid mucociliary clearance was consistent with greater posterior nasal cavity deposition. Because these studies were conducted in healthy subjects, further study in diseased patients is merited to better

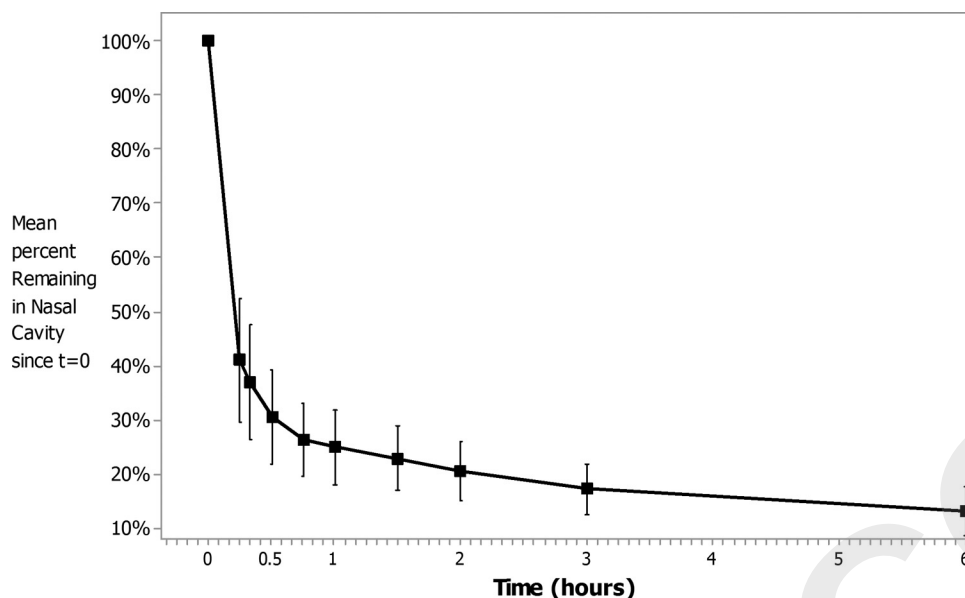


**Figure 7.** Mucociliary clearance of radiolabel from the nasal cavity, expressed as the percent of radioactivity remaining in the nasal cavity. Initial deposition is represented as 100%, and the plotted number is the average percent remaining of all subjects at that time point.

understand MFS deposition and its relationship to efficacy and safety.

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