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ORIGINAL CONTRIBUTION

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Nasal cast deposition for xylo- and oxymetazoline formulations using two different nasal pumps*

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Abstract

Background: Allergic rhinitis, rhinosinusitis, and upper respiratory tract infections, including the common cold, are caused by inflammation of nasal cavity areas. A key symptom is nasal congestion, which can be relieved with nasal spray medications. A key goal in developing a nasal spray medication delivery device for the relief of nasal congestion is delivering a fine mist to the inflamed areas while providing user comfort and convenience.

Methodology: Using a Koken nasal cast model, we studied the deposition patterns of 2 xylometazoline and 1 oxymetazoline formulations with 2 different nasal pumps, the currently marketed Freepod and the investigational laterally actuated device. Effects of nasal tip orientation and breathing were investigated. Additionally, the degree of xylometazoline and oxymetazoline dripping down the back of the cast was assessed.

Results: The largest coverage overall was observed with the xylometazoline formulation with the laterally actuated pump and without breath simulation. The laterally actuated pump used at a 30° angle resulted in deposition to the inferior, middle, and superior turbinates of the nasal cast, with less variability than the Freepod. Drippage at the back of the cast was observed with the Freepod device but not with the laterally actuated device.

Conclusions: Using a nasal cast model, the laterally actuated pump used at a 30° angle produced a full mist covering areas inflamed with the common cold, allergic rhinitis, and rhinosinusitis with no dripping at the back of the cast, an improvement compared with the Freepod pump. In vivo studies are needed to confirm nasal cast results.

Key words: nose, rhinitis, rhinosinusitis, respiratory system, turbinates

Introduction

Allergic rhinitis, rhinosinusitis, and upper respiratory tract infections, including the common cold, are caused by inflammation of nasal cavity areas. Human rhinoviruses are the most common cause of upper respiratory tract infections, including colds and rhinosinusitis [(1)]. With the common cold, human rhinovirus can be detected in nasopharynx, where it is replicated in airway epithelial cells and then spreads to the middle and inferior turbinates and septum [(1-4)]. Areas affected by rhinosinusitis and allergic rhinitis include the middle meatus, superior turbinates and posterior regions of the nasal cavity, and the sinuses [(5)].

Nasal congestion caused by mucosal inflammation is one of the key symptoms of allergic rhinitis, rhinosinusitis, and upper respiratory tract infections [(6)]. Mucosal inflammation reduces the size of the nasal passages by widening blood vessels, increasing vascular permeability, and increasing blood flow. This results in engorgement of nasal venous sinusoids, swelling of the inferior and anterior turbinates, and obstruction of nasal airflow, which leads to nasal congestion [(6)].

The imidazoline derivatives xylometazoline hydrochloride (HCL) and oxymetazoline HCL are commonly used decongestants

that quickly and effectively relieve nasal congestion in patients with common cold and rhinitis [7,8]. Topical xylometazoline and oxymetazoline act on α1- and α2-adrenergic receptors in the nasal cavity. They constrict blood vessels in the nasal mucosa and reduce swelling and airway resistance, thereby relieving nasal congestion [7,8].

A key goal in developing a nasal spray medication delivery device is to deliver a fine mist with a nasal deposition pattern that matches the inflamed areas in the nasal cavity to temporarily relieve congestion symptoms. Comfort and convenience to the user is another key goal of nasal spray delivery. Sensory properties are an important factor in nasal spray tolerability and patient preference among formulations, including odour, aftertaste, and the amount of drippage down the throat [9-13]. Ideally, nasal spray is limited to treatment areas with no leakage to the back of the throat, as 'drippage' of spray medication to the back of the throat can have a negative sensory impact, such as aftertaste [12,14,15].

The nasal spray deposition pattern is dependent on multiple factors including device characteristics, drug formulation, and administration technique of patients [15,16]. Device factors include emitted dose volume, spray pattern and plume geometry, droplet size distribution, and velocity of emitted droplets [15,16]. Administration techniques affecting deposition include administration angle, head orientation, spray nozzle insertion depth, and breathing profile [15]. Formulation factors include viscosity, thixotropic property, and surface tension [15]. Formulation viscosity differences can influence interaction with pump characteristics to affect size/shape of spray plume and therefore deposition patterns and the likelihood of dripping behaviour of formulations [14]. Spray droplet size significantly affects deposition, with larger droplets deposited at the anterior area of the nasal cavity, and smaller droplets depositing in the inner area of nasal cavity [15].

Nasal casts (biomimetic models of the human nasal passage) can be used to evaluate intranasal drug deposition [5,14,17-20]. Advantages of using nasal cast models include low cost and speed of in vitro evaluation as compared with testing in vivo [17].

In this study we examined deposition patterns of 3 formulations using 2 different nasal pumps, the current Freepod® device (Aptar Pharma, Switzerland) and the investigational laterally actuated device (Haleon [formerly GSK Consumer Healthcare], Switzerland). The objectives of this study were, first, to compare the deposition of 3 nasal spray formulations, 0.1% weight/volume (w/v) xylometazoline HCL (F3), 0.1% (w/v) moisturizing xylometazoline HCL (F5), and 0.05% (w/v) oxymetazoline HCL, to the turbinate region of the nasal cast, using the Freepod and laterally actuated nasal pumps; second, to confirm the importance of the nasal pump insertion angle and breathing simulation using the laterally actuated nasal pump; and third, to assess dripping behaviour at the pharynx of the nasal cast with each formulation, comparing the Freepod with the laterally actuated nasal pump.

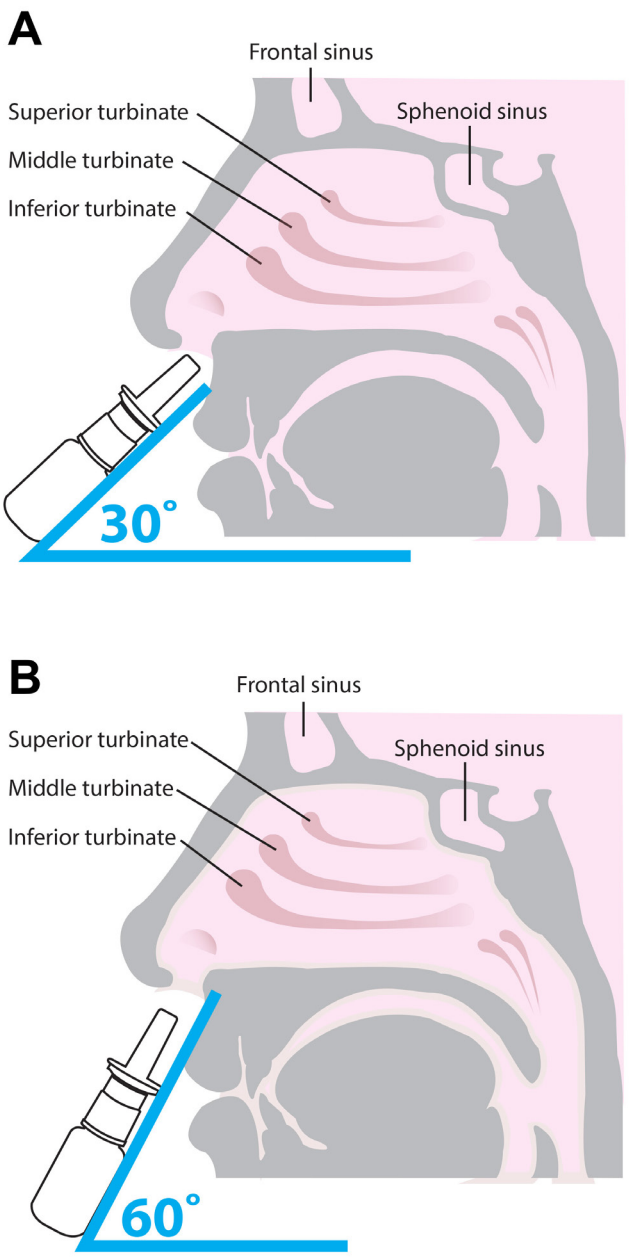

Figure 1. Nasal cast setup (example images). Illustration of the nasal pump application angles used are shown in A. (30° angle position) and B. (60° angle position).

Materials and methods

Nasal cast

The drug deposition pattern was studied using an anatomically

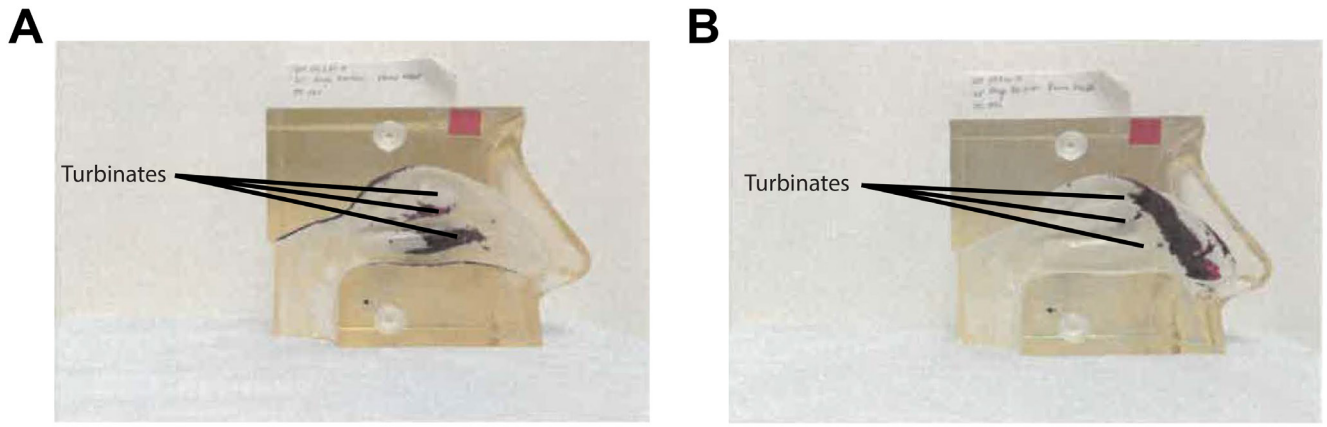

Figure 2. Angle positions (example images). Laterally actuated nasal pump filled with moisturizing xylometazoline (140 µL). A. 30° angle position. B. 60° angle position.

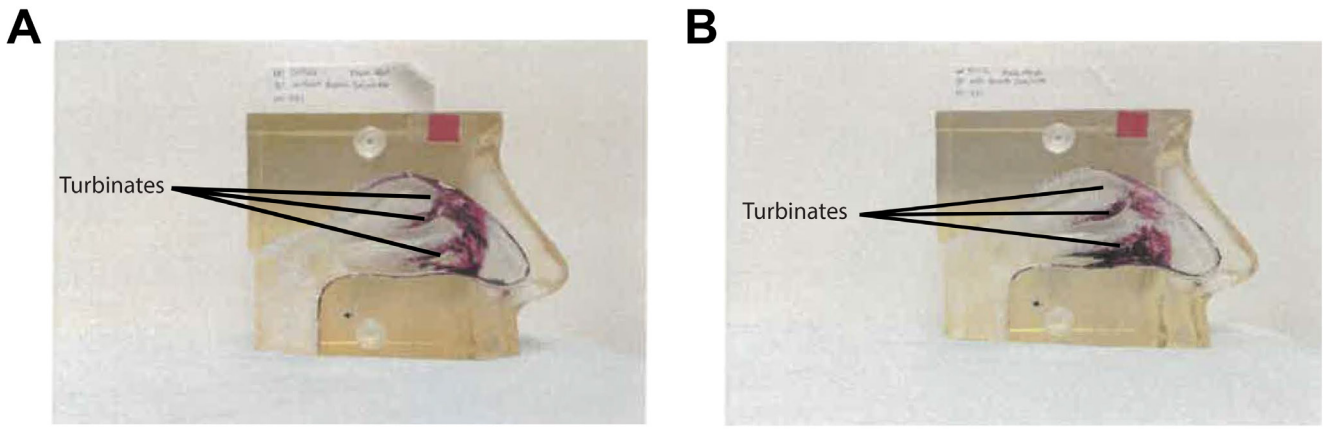

Figure 3. Breath simulation (example images). Laterally actuated nasal pump filled with xylometazoline (140 µL) at a 30° angle position. A. Without application of breath simulation. B. With application of breath simulation.

correct, transparent nasal cast model (Koken Co., Ltd., Tokyo, Japan) made of silicone rubber and approximately 10.5 cm (length) x 9 cm (width) x 9 cm (height) [14,21]. Location and area of drug deposition were determined using Sar-Gel® (Sartomer Company Inc., Exton, PA, USA), a clear paste that changes colour when exposed to the water contained in the drug formulation [19-22].

During the nasal cast sample collection, each nasal spray unit was manually administered into the nasal cast and the nozzle was aimed toward the centre of the eye pupil of the nasal cast (turbinate region), which was equivalent to a 45° angle position.

Nasal spray formulations and pumps

Nasal spray formulations were fitted with the Freepod nasal spray pumps (dosing volume, 70 µL and 140 µL) or the laterally actuated nasal spray pumps (dosing volume, 70 µL and 140 µL). Formulations tested (all Otrivin, Haleon, Warren, NJ, USA) included 0.1% w/v xylometazoline HCL (F3, dosing volume 140 µL), 0.1% w/v moisturizing xylometazoline HCL (F5, dosing volume 140 µL), and 0.05% oxymetazoline HCL (dosing volume 70 µL). These formulations differed in active pharmaceutical ingredient and viscosity. All study variables were tested separately with each formulation.

Administration variables

Effects of factors associated with patient administration techniques were assessed, including nasal tip orientation [18,20] and effect of breathing simulation [23]. Nasal tip orientation was tested at 30° or 60° angle positions relative to the user's chin (Figure 1 and Figure 2). Breath simulator evaluation was tested with or without application of breath simulation (Figure 3).

Assessments

To study the total area of drug deposition in nasal cast cavity, the entire nasal cast (vestibules, nasal cavity, and nasopharynx) was evenly coated with Sar-Gel water indicating paste. Deposition was visualised by colour change in the Sar-Gel coating of the nasal cast cavity (equal amounts per trial) (Figures 1–3). In an initial comparison between the Freepod and laterally actuated

Table 1. Total area of drug deposition (cm2) in nasal cast cavity by formulation.

	Xylometazoline [a]			Moisturizing xylometazoline [a]			Oxymetazoline [a]		
	Mean (SD)	%CV	P-value [c]	Mean (SD)	%CV	P-value [a]	Mean (SD)	%CV	P-value [c]
Nasal pump [a]									
Freepod	6.72 (0.62)	9.2		4.34 (0.75)	17.4		1.05 (0.10)	10.0	
Laterally actuated pump	7.57 (0.73)	9.7	***0.011***	3.90 (0.55)	14.1	0.289	0.84 (0.13)	14.9	***0.0008***
Angle (laterally actuated pump) [b]									
30°	6.97 (0.21)	3.1		2.33 (0.14)	5.8		3.06 (0.16)	5.2	
60°	7.29 (0.31)	4.3	0.114	4.72 (0.39)	8.4	***0.009***	3.34 (0.44)	13.1	0.355
Breath simulation (laterally actuated pump) [b]									
With breath simulation	6.07 (0.03)	0.4		3.13 (0.28)	9.0		3.01 (0.09)	3.0	
Without breath simulation	6.69 (0.14)	2.2	***0.014***	3.23 (0.19)	5.7	0.588	3.33 (0.18)	5.5	0.980

[a] N=10 for each formulation were first used in the Freepod pump and the formulation from the same 10 sets of samples from each lot were then transferred into laterally actuated pump. [b] N=6 replicates. [c] Two-tailed t-test. Bold text indicates statistical significance at P<0.05. SD, standard deviation; %CV, percentage coefficient of variation.

devices, 10 replicates/trials were performed for each formulation. Nasal tip angle and breath simulation were each studied using 6 trials per formulation.

To characterise the spread of deposition, quantity assessment was performed based on density of staining; pixel density (lightness/darkness) was assessed using Adobe Photoshop CS5 software for quantification, comparing the pixel count of the selected area with a calibration area. The exposed nasal cast was photographed, and area of colour change was analysed using photo analysis software (Adobe Photoshop CS5) to quantify the total area of deposition in different locations of the nasal cast. The method for the application of Sar-Gel and sample image analysis was performed per Next Breath Test Method, NB-TM-143, 'Method for Determining Nasal Cast Deposition Using a Sar-Gel and Image Analysis via Adobe Photoshop'. For each trial, the total deposition area (cm^2) was calculated.

Formulation drippage assessment

To evaluate sample formulation drippage on the back of the nasal cast, artificial mucous was applied to the frontal area of the nasal cast cavity to mimic human cavities [24], while the back of the nasal cast cavity was evenly coated with Sar-Gel to identify drippage. Five trials of each formulation were administered with the Freepod nasal pump and 5 with the laterally actuated nasal pump. In each case a 30° angle position into the nasal cast was used, because it produced less variability than a 60° angle, and without breath simulation, because this produced a wider deposition area compared with added breath simulation. Breathing simulation was performed with the breath simulator instrument using the adult breathing pattern method. Drippage of the sample formulation at the back of nasal cast was evaluated by visual assessment of the deposition pattern. A larger area with colour changes at the back of the cast indicated more drippage. Five trials were performed for each formulation.

Statistical analysis

To calculate the total area of drug deposition, the mean (standard deviation) area of deposition and coefficient of variation (%CV) were calculated for each variable. Effects of nasal pump (Freepod vs laterally actuated pump), angle (30° vs 60°), and breath simulation (with vs without) were assessed for each formulation separately using 2-tailed t-tests.

Results

Drug deposition area

When assessing the total area of drug deposition, the largest coverage overall was observed for the xylometazoline formulation with the laterally actuated pump and without breath simulation (Table 1). Using the xylometazoline formulation, total area of drug deposition was significantly greater for the laterally actuated pump compared with the Freepod pump (P=0.011, Table 1). For moisturizing xylometazoline, which has a higher viscosity than xylometazoline, the area of deposition did not differ between the pumps (P=0.289, Table 1). Using the oxymetazoline formulation, total area of drug deposition was significantly greater for the Freepod pump versus the laterally actuated pump (P=0.0008, Table 1).

When comparing the effects of nasal tip orientation, the 60° angle produced a significantly greater mean spray deposition area compared with the 30° angle for the moisturizing xylometazo-

Table 2. Drippage assessment [a] by pump and formulation.

Number of trials, n/N [b]	Xylometazoline	Moisturizing xylometazoline	Oxymetazoline
Freepod	5/5	4/5	1/5
Laterally actuated pump	0/5	0/5	0/5

[a] Drippage was defined as a stream/trickle. [b] Number of trials assessing drippage.

line formulation (P=0.009, Table 1). No significant differences were seen for the xylometazoline or oxymetazoline formulations (Table 1). Whereas the 30° angle resulted in deposition in the inferior turbinate, middle turbinate, and superior turbinate of the nasal cast, the 60° angle deposited formulation more so in the frontal cavity of the nasal cast (Figure 2). The 30° angle also resulted in less variability (%CV) for all 3 formulations (Table 1).

Breath simulation significantly reduced deposition area with the xylometazoline formulation compared with no breath simulation (Figure 3), but no effect of breath simulation was observed for moisturizing xylometazoline or oxymetazoline formulations (Table 1).

Drippage assessment

No drippage was seen with the laterally actuated pump, with 0/5 observations of drippage for all 3 formulations (Table 2). Using the Freepod pump, drippage was observed at the back of the nasal cast cavity with the xylometazoline (5/5 trials) and moisturizing xylometazoline (4/5 trials) formulations and with the oxymetazoline formulation (1/5 trials) (Table 2).

Discussion

In this study we successfully quantified the nasal spray deposition area in the nasal cast cavity for 2 xylometazoline formulations and 1 oxymetazoline formulation. We found that deposition area varied depending on pump used and by formulation, but the overall best results were obtained with the laterally actuated pump, particularly when used with the xylometazoline formulation. Both devices produced a fine mist, but visually, the spray area from the laterally actuated pump appeared to have a slightly wider spread than that from the Freepod pump.

Spray angle and breath simulation also affected deposition. A 30° angle position without breath simulation provided deposition at the inferior turbinate, middle turbinate, and superior turbinate of the nasal cast, whereas a 60° angle deposited medication more in the frontal cavity of the nasal cast. Moreover, a 30° angle position produced a more consistent coverage area for all 3 formulations and was therefore considered the optimal position. A significantly larger area was covered without breath simulation versus with breath simulation for the xylometazoline formulation only. No difference was observed for the moisturizing xylometazoline and oxymetazoline formulations.

This study shows that medication administered using the laterally actuated device or Freepod can reach areas that are affected by the common cold, allergic rhinitis [2-4], and rhinosinusitis [4], including the turbinates, which can become swollen, obstructing nasal flow and contributing to nasal congestion [6]. Using the laterally actuated pump at a 30° angle position relative to the user's chin and without breath simulation, the deposition pattern overlaps with those target areas. Other studies also have observed that administration angle can significantly affect deposition area [20].

Previous studies indicated that breathing profile and airflow rate may influence nasal spray deposition depending on the viscosity of the formulation. Increase in airflow rate may induce turbulence and drag the droplets in unpredictable directions, thereby decreasing the nasal deposition [15]. However, not all studies found an effect of breathing rate on drug deposition [15]. Narrow plume angles with smaller droplets (finer mist) were found to promote deposition into the turbinate areas using both nasal cast models and in vivo [16,18,19,23]. Moisturizing xylometazoline has a higher viscosity than xylometazoline, resulting in a narrower plume.

Using the laterally actuated pump, no drippage was observed at the back of the cast after administration of xylometazoline, moisturizing xylometazoline, or oxymetazoline formulations. We investigated drippage of the devices because sensory properties were found to be an important factor in nasal spray tolerability and patient preference among formulations [12,14,15]. Drippage can result in aftertaste and irritation in the throat, which are considered adverse effects that can reduce patient preference for a nasal spray medication [12,14,15]. Formulations delivered using the laterally actuated pump may therefore be more acceptable to patients compared with products that allow more of the spray to reach the throat. In addition, the reduction in drippage using the laterally actuated pump is achieved mechanically by producing a fine mist. In other products, drippage is reduced by modifying the formulation using chemical additives that act as thickening agents [25,26]. Here, no change was made to the formula and the absence of drippage was a consequence of the physical distribution of the spray achieved by the pump. Therefore, the laterally actuated pump appears to have more favourable characteristics and may be the preferred choice compared with the Freepod pump.

Limitations

The study has several limitations. Results were based on a small number of trials (5 to 10) for each condition. Assessment of drippage was conducted using only the 30° angle position without breath simulation, and changing those or other parameters may affect the outcome of that assessment. For these studies we used artificial mucous (Sar-Gel) colourimetry, which has been used in various publications to compare drug deposition in the nose and olfactory region and was found to provide a simple and practical way to visualize and quantify regional deposition [19,20,22]. Compared with gamma scintigraphy, it is considered simpler, more direct, and less expensive, and it does not require radiolabelling [22]. Limitations of Sar-Gel include that it quantifies only visible aerosols and that it requires the same lighting conditions to avoid image colour distortion [22]. Results are in part dependent on the characteristics of the type of nasal cast used [17]. A single Koken model cast was used for all measurements in this study. This is a standardised adult nasal cast and findings are not generalisable to children. Deposition patterns will vary among human patients [18]. In addition, in vivo studies are needed to confirm nasal cast results [5].

One of the challenges of intranasal delivery of drugs using nasal spray pumps is the nasal mucociliary clearance system, which transports the mucus layer that covers the nasal epithelium towards the nasopharynx by ciliary beating [27]. Its function is to protect the respiratory system from damage by inhaled substances. Rapid clearance can limit drug absorption and efficacy [27]. Studies are needed to assess the effects of mucociliary clearance on delivery of drugs using these nasal spray pumps and formulations [27]. In addition, the safety of these drug formulations and delivery devices needs to be tested in vivo [27].

Conclusions

Using a nasal cast model, both the laterally actuated and Freepod pumps, used at a 30° angle, produced a full mist with a wide coverage, including areas typically affected by the symptoms of the common cold, allergic rhinitis, and rhinosinusitis. Target areas varied among angle, formulations, and pumps, indicating that the appropriate pump may depend on the required conditions. The laterally actuated pump produced no drippage at the back of the nasal cast regardless of formulation used and without the need for formula modification, which is predicted to result in less unpleasant aftertaste, indicating an improvement compared with the Freepod pump [12,14,15]. In vivo studies are needed to confirm the nasal cast results.

List of abbreviations

2HCL, hydrochloride; %CV, percentage coefficient of variation; SD, standard deviation; weight/volume (w/v).

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Authorship contribution

MH, SC, GS, and GD designed the study. MH, SC, GS, and GD analyzed and interpreted the data. MH, SC, GS, GD wrote or critically reviewed the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The aggregated data that support the findings of this study are available upon reasonable request from Haleon. Requests must include a research proposal describing the objectives of research and its benefits for patients accompanied by a sufficient description of statistical and publication plans. Each request will be reviewed on an individual basis by Haleon to assess the ability of the proposal to meet the proposed scientific objectives and relevance to patient care.

Conflict of interest

Martina Hagen, Gilbert Shanga, and Gautam Debnath are employees of Haleon (formerly GSK Consumer Healthcare).
Sophie Caron was an employee of GSK Consumer Healthcare (now Haleon) at the time of study.

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