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RESEARCH ARTICLE

Development of a physiologically relevant method for nasal spray analysis using simulated nasal mucus

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Abstract

Objectives. Current methods for testing nasal spray dosage forms during development fail to fully assess the behavior of the drug following its release from the container, including subsequent distribution, retention, and permeability across the mucosal barrier. Existing *in vitro* models typically overlook the critical factor of drug interaction with nasal mucus, which substantially limits their predictive power and physiological relevance. The study set out to develop a physiologically based analytical method that addresses this gap by employing representative simulated nasal mucus compositions to evaluate the key performance parameters of the spray.

Methods. The pH of the investigated compositions was determined potentiometrically in accordance with the requirements of the 15th Russian State Pharmacopoeia, OFS.1.2.3.0032, using a pH meter (*Econix-Expert*, Russia) equipped with an ESK-10601 glass electrode (*Izmeritelnaya Tekhnika*, Russia). The dynamic viscosity of the compositions was measured using a Brookfield DV2T RV rotational viscometer (*Brookfield*, USA) with a thermostatically controlled measuring unit of the coaxial cylinder type within a temperature range of 25–37°C. The contact angle was determined by the sessile drop method using an EasyDrop Standard instrument (*Krüss*, Germany). The distribution of nasal sprays was evaluated with a silicone model of the human nasal cavity (*Koken Co. Ltd*., Japan).

Results. Representative simulated nasal mucus compositions were developed and characterized that reliably reproduce the key physicochemical and rheological properties of human nasal secretions under both normal and pathologically inflamed conditions. An experimental setup combining an anatomical silicone nasal cavity model with an applied layer of simulated nasal mucus was created and validated. The developed model permits quantitative assessment of key parameters, such as the distribution and coverage area of the drug substance upon contact with mucus of varying viscosity. As such, it provides a physiologically relevant platform for studying nasal sprays during dosage form development.

Conclusions. The proposed approach offers a valuable tool for optimizing the composition and design of nasal sprays, enabling comparative analysis under conditions that closely mimic physiological realities.

Keywords

simulated nasal mucus, nasal drug delivery, intranasal administration, nasal cavity distribution

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НАУЧНАЯ СТАТЬЯ

Разработка физиологически релевантного метода анализа назального спрея с использованием имитированной носовой слизи

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Аннотация

Цели. В настоящее время при разработке лекарственных препаратов в форме назального спрея применяются методы исследования лекарственной формы, которые не позволяют в полной мере оценить поведение лекарственного средства после высвобождения из упаковки, включая его распределение, удержание и проницаемость через слизистую оболочку. Существующие *in vitro* модели, как правило, игнорируют ключевой фактор — взаимодействие препарата с назальной слизью, что значительно снижает их прогностическую способность и релевантность условиям *in vivo*. Целью данной работы являлась разработка физиологически обоснованного метода анализа, который восполняет этот методический пробел за счет использования репрезентативных составов имитированной назальной слизи для оценки ключевых параметров поведения спрея.

Методы. Водородный показатель исследуемых составов определяли потенциометрически в соответствии с требованиями Государственной Фармакопеи Российской Федерации XV издания, ОФС.1.2.3.0032, с использованием pH-метра (*Эконикс-Эксперт*, Россия) с электродом стеклянным ЭСК-10601 (*Измерительная техника*, Россия). Измерение динамической вязкости исследуемых составов проводили на ротационном вискозиметре Brookfield DV2T RV (*Brookfield*, США), снабженном термостатируемой измерительной ячейкой типа коаксиальных цилиндров в диапазоне температур 25–37°C. Измерение угла смачивания исследуемых составов проводили методом лежащей капли с использованием прибора Krüss EasyDrop Standard (Германия). Оценку распределения назальных спреев по модельной поверхности проводили на силиконовой модели человеческого носа (*Koken Co. Ltd*., Токио, Япония)

Результаты. Разработаны и охарактеризованы репрезентативные составы имитированной назальной слизи, которые достоверно воспроизводят ключевые физико-химические и реологические свойства назального секрета человека в состоянии нормы и при патологическом воспалении. Создана и апробирована экспериментальная модель, сочетающая анатомическую силиконовую модель носовой полости с нанесенным слоем имитированной назальной слизи. Показано, что разработанная модель позволяет количественно оценивать ключевые параметры, такие как распространение и зона покрытия лекарственного вещества при контакте со слизью разной вязкости. Данная модель является физиологически релевантной платформой для изучения назальных спреев при разработке лекарственной формы.

Выводы. Предложен подход, который представляет собой ценный инструмент для оптимизации состава и дизайна назальных спреев, позволяя проводить сравнительный анализ в условиях, максимально приближенных к физиологическим.

Ключевые слова

имитированная носовая слизь, назальный препарат, интраназальное введение, распределение в назальной полости

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INTRODUCTION

The primary physiological barrier of the respiratory tract is the nasal mucosa, which, in a healthy state, produces a certain amount of nasal secretion [1, 2]. Patients suffering from various nasal diseases secrete excessive amounts of nasal mucus, such as allergic rhinitis, sinusitis, and respiratory viral infections. While nasal secretions are approximately 95% water, they also contain about 2.5% of glycoproteins, 1–2% of electrolytes such as lysozyme, lactoferrin, as well as possible liquid fractions similar to surfactants [3–6]. The important parameters of nasal secretion, which include viscosity, hydrogen index (pH), adhesion, and fluidity, are largely determined by the qualitative and quantitative characteristics of glycoproteins [3, 4, 6, 7].

Intranasal drug delivery offers several advantages, such as increased bioavailability and rapid onset of systemic effect, as well as ease and convenience of daily use [3–8]. Therefore, various compositions of nasal medications are currently being actively developed. Nasal sprays are a popular dosage form for delivering local and systemic medications, as well as for delivering medications to the central nervous system [9] and for vaccination. When developing a composition for intranasal administration, it is important to consider not only the structure of the human nose, but also factors such as the interaction of the drug with nasal secretions, the spray pattern, and the characteristics of nasal mucus depending on the type and stage of the patient's disease, for example, from watery and liquid discharge in healthy individuals to thick and viscous discharge in individuals with pathological changes [10, 11].

Currently, possible methods for *in vitro* analysis of the described dosage form include studying the deposition pattern of the nasal spray on paper or a plate with a thin layer of sorbent, as well as investigating the behavior of the nasal spray composition after release from the nozzle on a silicone model of the human nose [12–14]. Approaches to studying the permeability of nasal spray compositions are also known [15]. However, these methods do not sufficiently characterize and predict the behavior of the nasal drug composition when it interacts with human nasal secretions for the following reasons:

1. Neglect of the influence of the key biological barrier. Standard testing media (e.g., distilled water or phosphate buffers) differ radically from real nasal mucus in their rheological, surface, and biochemical properties. The absence of mucins—the main glycoproteins of mucus—leads to an inaccurate assessment of critical parameters such as drug distribution and retention on the nasal mucosa, active substance release, and dosage form stability during administration.
2. Lack of physiological relevance in case of pathologies. The properties of nasal mucus change significantly during disease. In allergic rhinitis or sinusitis, mucus becomes thicker and more viscous due to changes in the composition and concentration of mucins [16]. Thus, the use of a standardized medium does not take into account an assessment of how the spray will perform in a patient in an acute condition, when drug delivery is most critical.
3. Low predictive power for systemic delivery. For drugs intended for systemic action or delivery to the central nervous system, the primary task is overcoming the mucosal barrier and subsequent absorption through the mucosa. Standard methods do not allow for quantitative assessment of this key step.

In light of the above, there is a clear need to create a relevant *in vitro* model that would reproduce not only the anatomy of the nasal cavity but also its primary biological barrier – nasal mucus. The development of a standardized composition of simulated nasal mucus that adequately reflects the key physicochemical properties of both healthy and pathological mucus would fill this existing methodological gap.

Thus, the aim of this study was to develop a physiologically relevant method for analyzing nasal sprays. This method is based on the use of standardized compositions of simulated nasal mucus that reproduce the conditions of both healthy and pathologically inflammatory mucus.

To achieve this goal, it is necessary to complete the following tasks: to develop and study the characteristics of model compositions of healthy and pathological nasal secretions suitable for testing nasal sprays, and to conduct a study of the interaction of nasal spray drops with simulated nasal secretions.

1. MATERIALS AND METHODS

1.1. Materials

The study was carried out using simulated healthy and pathological nasal mucus, which included the following components: high-molecular hyaluronic acid, 1200 kDa (*Lindera*, China); lactoferrin Proferrin (*Ingredia*, France); lysozyme hydrochloride (*PROQUIGA*, Spain); 0.9% sodium chloride (*Armavir Biofactory*, Russia); locust bean gum (*LBG Sicilia*, Italy); sodium dodecyl sulfate (*Panreac AppliChem*, Spane; *Khimmed*, Russia), as well as antiviral nasal sprays.

Naltrexone hydrochloride nasal spray (hereinafter referred to as spray 1) includes the active substance naltrexone hydrochloride (*Aspen Oss B.V.*, Netherlands) and excipients: poloxamer Kolliphor P 407 (*Geismar*, USA, No. GNA 18721 D, NF-USP/Ph. Eur), citric acid monohydrate, chemically pure (*Khimmed*, Russia),

sodium chloride, chemically pure (GOST 4233-77[1], *Khimmed*, Russia), benzalkonium chloride (*Unilab Chemicals and Pharmaceuticals Pvt. Ltd.*, India, USP), purified water (State Pharmacopoeia of the Russian Federation, FS.2.2.0020) [13].

Antiviral nasal spray (hereinafter referred to as spray 2) based on aminocaproic acid and a copolymer of *N*-vinylpyrrolidone with 2-methyl-5-vinylpyridine includes the following active ingredients: aminocaproic acid (*Polisintez*, Russia), copolymers of 2-methyl-5-vinylpyridine and *N*-vinylpyrrolidone (*IFT*, Russia) and excipients: potassium dihydrogen phosphate (GOST 4198-75[2], *Khimmed*, Russia), disodium hydrogen phosphate (GOST 4172-76[3], *Khimmed*, Russia), benzalkonium chloride (European Pharmacopoeia, *Sigma-Aldrich*, USA), purified water (State Pharmacopoeia of the Russian Federation, FS.2.2.0020) [14].

Nasal spray distribution was assessed on a silicone model of the human nose (*Koken Co. Ltd.*, Tokyo, Japan) using a dosing device with a spray nozzle with a protective cap, volume of released dose 100 μL, model IFP0198-182 (*Bona Pharma*, China), and a 5 mL high-density polyethylene (HDPE) bottle with a snap-on/crimp neck (*Bona Pharma*, China).

Thin-layer chromatography (TLC) plates, CTX-1A silica gel (*Sorbfil*, Russia), and test substrates were additionally used for the studies: polyethylene terephthalate (PETP, GOST R 51695-2000[4]), teflon (GOST 10007-80[5]), and polymethyl methacrylate (PMMA, GOST 17622-72[6]).

Methylene blue (analytical grade, *Khimmed*, Russia) was used as a dye for nasal sprays.

1.2. Methods

The simulated nasal secretion was characterized by the following parameters: pH, dynamic viscosity, wetting angle, surface tension, and work of adhesion.

The pH of the studied compositions was determined potentiometrically in accordance with the requirements of the State Pharmacopoeia of the Russian Federation, 15th edition, OFS.1.2.3.0032, using a pH meter (*Econix-Expert*, Russia) with an ESK-10601 glass electrode (*Izmeritelnaya Tekhnika*, Russia).

Measurements of the dynamic viscosity of the test compounds were performed using a Brookfield DV2T RV rotational viscometer (*Brookfield*, USA) equipped with a measuring cell of the coaxial cylinder type over a temperature range of 25–37°C. A 5-mL sample was transferred to the measuring cell and thermostated for 15 min. After this the viscosity was measured at a constant shear rate. The test was conducted using SC_4-18 and SC_4-16 spindles at shear rates of 29 and 18 s^{-1}, respectively.

The contact angle of the test compounds was measured using the sessile drop method using a Kruss EasyDrop Standard instrument (*KRÜSS*, Germany). The study was conducted on six substrates: PETP, teflon, silica gel, silicone, and PMMA. The test conditions were: volume 4 μL, dosing rate 0.16 mL/min, and temperature 25.0–28.0°C. The results were processed and surface free energy was calculated using the Owens–Wendt–Rabel–Kaelble model[7]. The work of adhesion W of the simulated mucus to the test substrates was calculated using formula (1)

$$W = \gamma_{liq}^{\Sigma}\left(1+\cos\theta\right), \quad (1)$$

where γ_{liq} is the surface tension of the liquid or simulated mucus, and θ is the wetting angle.

Dyed nasal spray solutions were prepared by adding 0.5 mL of methylene blue dye to 5 mL of the spray compositions, followed by mixing until homogeneous.

In this study, the following substrates were characterized: PETP, teflon, silica gel, silicone, and PMMA. A Kruss EasyDrop Standard contact angle meter was used according to the sessile drop contact angle method. The study was conducted using test liquids—distilled water and diiodomethane—under the following parameters: volume of 4 μL, dosing rate of 0.16 mL/min, temperature of 25.0 ± 1°C.

1 GOST 4233-77. Interstate Standard. Reagents. Sodium chloride. Specifications. Moscow: Standartinform; 2008 (in Russ.).

2 GOST 4198-75. Interstate Standard. Reagents. Potassium dihydrogen phosphate. Specifications. Moscow: Standartinform; 2010 (in Russ.).

3 GOST 4172-76. State Standard of the USSA. Reagents. Disodium hydrogen phosphate dodecahydrate. Specifications. Moscow: Izdatelstvo standartov; 1977 (in Russ.).

4 GOST R 51695-2000. State Standard of the Russian Federation. Poly(ethylene terephthalate). General specifications. Moscow: Standartinform; 2008 (in Russ.).

5 GOST 10007-80. Interstate Standard. Polytetrafluoroethylene. Specifications. Moscow: Standartinform; 2005 (in Russ.).

6 GOST 17622-72. State Standard of the USSR. Industrial organic plastic. Specifications. Moscow: USSR State Committee on Standards; 1972 (in Russ.).

7 Zhavoronok E.S., Domnina Yu.M., Kedik S.A. *Physicochemical methods for studying biologically active compounds and auxiliary materials:* Laboratory workshop. Moscow: MIREA – Russian Technological University; 2023 (in Russ.).

The nasal spray distribution study was conducted by spraying colored nasal sprays onto a pre-prepared silicone nose model. The silicone nose model was prepared by uniformly applying mucus (healthy simulated mucus, pathological simulated mucus) using a brush. The nasal spray was manually actuated at a 45° angle to the horizontal surface on which the silicone nose model was mounted, with the nozzle inserted 5 mm into the nasal orifice. Photo and video recording of nasal spray distribution on the silicone model was conducted using a vertically mounted video camera. The obtained data were processed using Adobe Photoshop version 21, 2020.

In order to evaluate the behavior of nasal spray solutions, a test was conducted to determine the nasal spray droplet flow rate on PMMA substrates with and without nasal mucus. Simulated healthy and pathological nasal mucus was applied with a brush in a uniform layer over the substrate surface. The droplet placement location and a fixed distance of two centimeters were pre-marked on the substrate. A drop of nasal spray was then applied with the substrate in a horizontal position. The substrate was then rotated 90° so that it was positioned vertically. A digital camera was positioned vertically opposite the substrate at a fixed distance and used to record the nasal spray flow rate. The flow rate was taken as the ratio of the path traveled by the drop to the flow time.

RESULTS AND DISCUSSION

In the first stage, nasal mucus prototypes were selected and prepared [17–19] (Table 1). The components of the nasal mucus composition were taken from the work by Ilyin *et al*. [19]. Then, the composition was adjusted to achieve the required properties of healthy and pathological [20, 21] mucus. Healthy nasal mucus was imitated by adding hyaluronic acid 3.5 mg/mL, lysozyme hydrochloride 2.5 mg/mL, and lactoferrin 5.0 mg/mL to an isotonic 0.9% sodium chloride solution. Pathological nasal mucus was imitated by preparing sodium dodecyl sulfate 1.73 mg/mL and locust bean gum 8 mg/mL in a saline solution.

Preliminary studies showed that the compositions exhibited near-Newtonian behavior (Fig. 1). Therefore, further viscometric studies were conducted at various shear rates, with the torque ranging from 10 to 90%.

Table 1. Prototypes of model compositions of simulated healthy and pathological mucus

Component	Concentration, mg/mL	
	Simulated healthy mucus	Pathological mucus
Hyaluronic acid, high-molecular weight	1.0	–
Lactoferrin	5.0	–
Lysozyme hydrochloride	2.5	–
Locust bean gum	–	8.0
Sodium dodecyl sulfate	–	1.73
Sodium chloride 0.9%	1.0	1.0

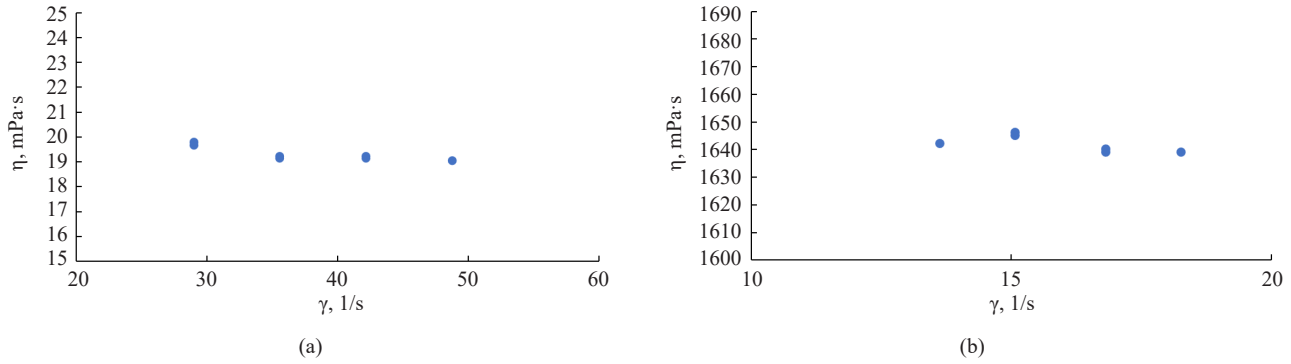


Fig. 1. Dependence of dynamic viscosity on shear rate at a temperature of 35°C: (a) for healthy simulated nasal mucus, (b) for pathological simulated mucus

For the selected prototypes, the pH and dynamic viscosity values at 35°C were determined (Table 2).

It is known from the literature [20] that the dynamic viscosity of healthy nasal mucus is about 13 mPa · s, while in the case of pathological nasal mucus it is about 1400 mPa · s. The pH for healthy nasal mucus is in the range from 4.5 to 6.5; in case of pathological nasal mucus, it increases to 7.95 [21]. Therefore, it was necessary to adjust the compositions to achieve optimal values of dynamic viscosity. For this purpose, the compositions were prepared in accordance with Table 3, and the dynamic viscosity and pH were measured.

Table 2. pH and dynamic viscosity values for prototype model compositions

Prototype	pH	Dynamic viscosity, mPa·s
Simulated healthy mucus	4.9	19
Pathological mucus	7.0	1430

Table 3. Composition of healthy and pathological simulated nasal mucus

Simulated healthy mucus					Parameters	
Component	Hyaluronic acid, mg/mL	Lactoferrin, mg/mL	Lysozyme hydrochloride, mg/mL	Sodium chloride 0.9%, mg/mL	pH	Dynamic viscosity, mPa·s, T = 35°C
Composition 1	1.0	5.0	2.5	1.0	4.7	1.3
Composition 2	3.0	5.0	2.5	1.0	4.9	9.8
Composition 3	3.5	5.0	2.5	1.0	4.9	18.6
Composition 4	4.0	5.0	2.5	1.0	4.8	28
Pathological mucus					Parameters	
Component	Locust bean gum, mg/mL		Sodium dodecyl sulfate, mg/mL	Sodium chloride 0.9%, mg/mL	pH	Dynamic viscosity, mPa·s, T = 35°C
Composition 1	2.0		1.73	1.0	6.7	90
Composition 2	10.0		1.73	1.0	7.2	1980
Composition 3	20.0		1.73	1.0	7.0	≥4000
Composition 4	6.0		1.73	1.0	6.8	872
Composition 5	7.0		1.73	1.0	6.9	1235
Composition 6	8.0		1.73	1.0	7.0	1430

Thus, compositions 3 (healthy simulated mucus) and 6 (pathological simulated mucus) exhibit optimal pH and dynamic viscosity values.

The next step consists in evaluating the wettability of the developed nasal mucus compositions with nasal spray fluids. Since this is a rather complex task, we divided it into several stages. First, we characterized the substrates using standard test fluids (water and diiodomethane). The substrates, in turn, served as test substrates to determine the surface energy of the nasal mucus. Based on information on the surface energy of the mucus and the surface tension of the spray fluid, the spray contact angle with the mucus can be calculated to evaluate the adhesion characteristics of their interactions, which are essential for assessing spray retention on the mucosal surface.

In the first stage of this work, the contact angles of droplets of test liquids on polymer substrates were measured, and the free surface energies of the substrates and their polar and dispersion components were determined (Table 4). A TLC plate of a kind typically used to evaluate the runoff of nasal sprays was used as an additional substrate [22].

Next, simulated compositions were applied to each substrate, contact angles were measured, free surface energies and the work of adhesion to the substrates were calculated (Table 5).

It can be seen that, while the pathological simulated mucus is more polar than healthy mucus, its total surface energy is significantly lower than that of healthy mucus due to a reduction in the dispersion component. This results in different values of the work of adhesion between

Table 4. Free surface energy of substrates and its polar and dispersion components at 25°C

Parameter	PETP	Teflon	TLC plate	Nose model silicone	PMMA
γ_{sol}^{P}, mN/m	8.24	1.51	29.40	29.26	1.05
γ_{sol}^{D}, mN/m	42.35	30.36	50.80	1.53	40.80
γ_{sol}^{Σ}, mN/m	50.59	31.87	80.2	30.79	41.85

Table 5. Characteristics of simulated mucus and work of adhesion *W* to various substrates

Parameter	Simulated healthy mucus	Pathological mucus
γ_{liq}^{P}, mN/m	14.0	27.1
γ_{liq}^{D}, mN/m	62.1	19.2
γ_{liq}^{Σ}, mN/m	76.1	46.3
W (PETP), mN/m	5.2	43.5
W (teflon), mN/m	151.3	77.0
W (TLC plate), mN/m	28.3	21.6
W (silicone nose model), mN/m	125.2	77.6
W (PMMA), mN/m	138.1	39.7

the mucus samples and the model substrates (Table 5). Note that the work of adhesion of the TLC plates to the simulated mucus compositions is the lowest; for this reason, they cannot be considered suitable as mucus carriers in subsequent experiments.

Thus, optimal nasal mucus compositions suitable for *in vitro* testing were selected and characterized, and these compositions were used for further studies of nasal spray compositions.

In order to evaluate the interaction of nasal sprays with simulated nasal mucus samples using the sessile drop method on the previously characterized test substrates (Table 4), the polar and dispersion components of the free surface energy of the sprays under study were calculated (Table 6).

Table 6. Free surface energy of nasal sprays and its polar and dispersive components at 25°C

Parameter	Spray 1	Spray 2
γ_{liq}^{P}, mN/m	27.2	39.7
γ_{liq}^{D}, mN/m	39.8	19.6
γ_{liq}^{Σ}, mN/m	67.0	59.3

Using the data of Tables 5 and 6, the contact angles of simulated mucus by nasal sprays were estimated according to formula (2), and the work of adhesion was calculated according to formula (1) (Table 7).

$$\frac{\cos\theta+1}{2\sqrt{\gamma_{liq_0}^{D}}}=\frac{\sqrt{\gamma_{liq}^{P}}}{\gamma_{liq}^{\Sigma}}\cdot\frac{\sqrt{\gamma_{liq_0}^{P}}}{\sqrt{\gamma_{liq_0}^{D}}}+\frac{\sqrt{\gamma_{liq}^{D}}}{\gamma_{liq}^{\Sigma}}, \quad (2)$$

where θ is the contact angle, γ_{liq} is the surface tension of the liquid (nasal sprays), γ_{liq_0} is the surface energy of healthy simulated mucus or pathological mucus, γ_{liq}^{Σ} is the free surface energy of the sprays. The superscripts D, P, and Σ denote the dispersion and polar components, as well as their sum.

Table 7. Contact angle θ and work of adhesion *W* of nasal sprays on simulated nasal mucus

Parameter	Simulated healthy mucus	Pathological mucus
θ°, Spray 1	5.4	50.9
θ°, Spray 2	13.6	45.5
W, mN/m, Spray 1	133.7	109.2
W, mN/m, Spray 2	116.9	104.4

Table 7 shows that both types of simulated mucus are well wetted by the spray compositions (contact angle is less than 51°), while the adhesion of the sprays to both types of simulated mucus is quite high. This ensures retention of the dosage form on the surface of the simulated mucosa.

Finally, not only the equilibrium wetting characteristics of the spray composition on the mucosal surface are important, but also the behavior of these sprays under dynamic conditions, which approximate real conditions in the body. To evaluate this behavior, the droplet runoff velocity of the sprays was determined on the surface of simulated nasal mucus as compared to the surface of unmodified polymers (using PMMA as an example). These polymers are used to make nasal cavity models. The droplet rates of flow results for the studied compositions on various substrates are presented in Table 8.

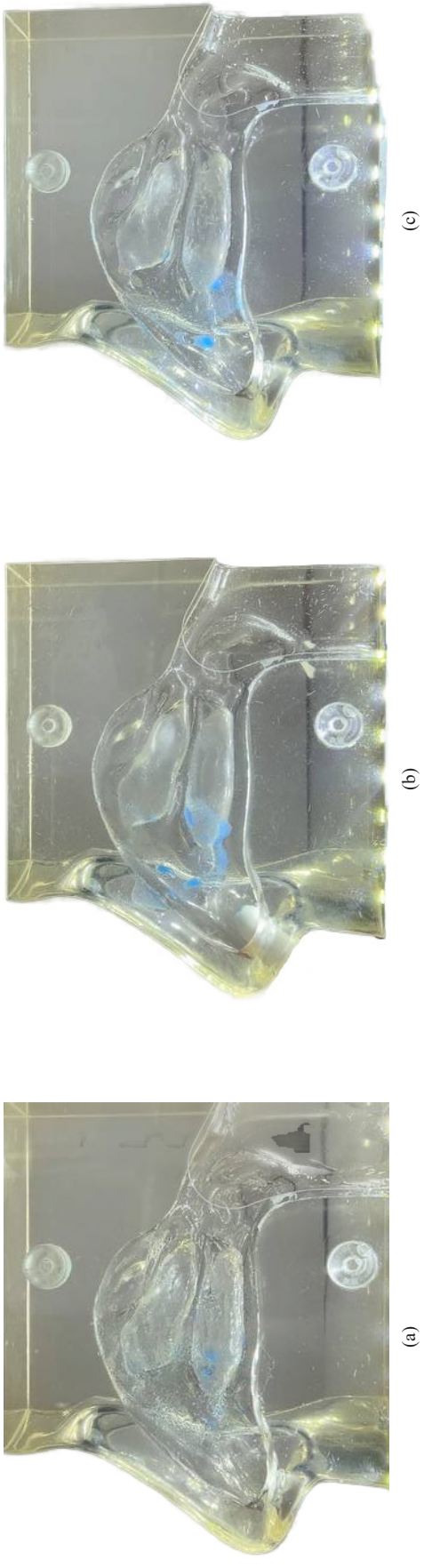
It can be concluded on the basis of the obtained values that when testing nasal spray droplets on a substrate using simulated mucus, the time of flow (or contact) increases,

Table 8. Time and flow rate of the studied compositions

Nasal spray	Spray 1		Spray 2	
Parameter / Base	Time, s	Rate, cm/s	Time, s	Rate, cm/s
PMMA	2.24	0.89	1.04	1.92
PMMA coated with healthy nasal mucus	4.25	0.47	2.39	0.84
PMMA coated with pathological nasal mucus	2.63	0.76	1.44	1.39

(a) (b) (c)

Fig. 2. Distribution of spray solution 1 on a human nose model:
(a) dry model,
(b) model with pre-applied healthy mucus, and
(c) model with pre-applied pathological mucus



(a) (b) (c)

Fig. 3. Distribution of spray solution 2 on a human nose model:
(a) dry model,
(b) model with pre-applied healthy mucus, and
(c) model with pre-applied pathological mucus

and the flow rate accordingly decreases as compared to those on a dry substrate, regardless of the presence of high-molecular-weight thickeners in the spray composition. Thus, by using model nasal mucus compositions in the experiment, it is possible to obtain flow rates for nasal sprays that are as close as possible to those taking into account the physiology of the human nose.

This conclusion is supported by the results of spray studies on a human nasal model using the developed mucus compositions, which are presented in Figs. 2 and 3.

An analysis of the obtained images reveals that if no simulated nasal mucus is used, the spray solutions, after being released from the nozzle, are distributed evenly as fine droplets without the presence of large, visible droplets. However, the presence of simulated mucus on the nasal model allows for a more precise depiction of the area of the test compound application in the nasal cavity due to the higher adhesion of the test compound to the model surface.

CONCLUSIONS

The study developed and characterized representative compositions of simulated nasal mucus to simulate key properties of the nasal mucosa both under healthy conditions and during pathological inflammation. The resulting models were successfully integrated into a silicone model of the human nasal cavity for testing nasal sprays.

Thus, the developed simulated nasal mucus compositions, especially as combined with an anatomical silicone model of the nose, represent a valuable and reliable tool for experimental research. This approach enables reproducible and ethically acceptable comparative testing of nasal sprays under conditions as close as possible to *in vivo* conditions. Its implementation in the development of dosage forms for intranasal use has the potential to significantly simplify and optimize the composition and design of nasal sprays.

The developed method will enable comparative analysis of various nasal sprays using a single, standardized, and physiologically justified protocol, as well as the evaluation of critical parameters of spray behavior:

- spread and coverage area—to study the behavior of nasal spray droplets upon contact with mucus of varying viscosities;
- interaction with nasal secretions—to visualize and analyze mixing or potential stratification processes upon spray contact with mucus.

Authors' contribution

All the authors actively participated in the discussion, analysis, and design of the experiment, processing the results, writing the text of the article, and discussing it.

The authors declare no conflicts of interest.

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