Comparative analysis of the dispersion quality of oxymetazoline nasal sprays

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INTRODUCTION

Decongestants are the most widely used preparations for symptomatically treating rhinitis.[1] Metered-dose nasal sprays (MDNS) are the most popular ones, which is explained by the ease of use, accurate dosage, and rapid therapeutic effect.[2]

A typical MDNS package consists of a spray vial with a dosing pump (microsprayer). Its design, including the micropump and the trigger mechanism, determines the spraying form of a metered-dose preparation, and it must ensure the best combination of qualities, particularly safe use, full irrigation of the processed surface, good sedimentation in nasal cavity (NC). Dispersion increases

ABSTRACT

Metered-dose nasal sprays (MDNS) are the most widely used for treating rhinitis. Medicinal preparations in the pharmaceutical market vary in their characteristics. To identify the most effective drug, it is necessary to compare the preparations regarding various parameters. The purpose of the research was to compare oxymetazoline MDNS of different brands regarding their dispersion qualities. To that end, nine oxymetazoline sprays available in the Russian market were chosen and analyzed considering their dynamic characteristics and the spraying dispersion composition. The research was conducted with the shadow photography method, the selection of which was justified by its simplicity, the possibilities for detecting the spray jet composition, the process of its formation in dynamics, and the possibility for measuring droplets of all forms. Momentary images of spray activation phases, as well as an averaged image of 100 shots of the spraying main phase, were obtained. According to a range of characteristics, such as spraying duration, a cone angle and cone structure, all the preparations were grouped into three categories. It was found out that the sprays from Group 2 had the best dynamic rates of dispersion, with Vicks Sinex having the best results. Regarding the distribution of particles of different size, the most optimal composition was found for the drugs from Group 2, particularly, Vicks Sinex and Afrin preparations. Hence, Vicks Sinex spraying regimen and microsprayer design were found the most effective for delivering the medicinal substance to the destination.

Key words: Metered-dose spray preparations, oxymetazoline, shadow photography method, spraying dispersion composition, spraying dynamic characteristics
the drug contact surface, which leads to the higher pharmacological activity of the medicinal preparation.\[3-5\]

It seems relevant to study and analyze comparatively the spraying parameters of oxymetazoline MDNS for choosing the best option among a large assortment of such preparations. Most oxymetazoline MDNS are aqueous solutions of oxymetazoline hydrochloride and other substances, including auxiliary ones. The only exception is the Afrin products that contain white gel-like suspension.\[6,7\]

It is important to regard spraying as a process of formation of an aerosol jet with certain characteristics that ensure effective delivery of a preparation onto the nasal mucosa. Earlier, the authors developed and published planar simulation models that allowed to visualize the results of metered-dose preparation spraying from MDNS.\[3\] These models became the basis for defining the quantitative parameters used for comparing the spraying qualities of xylometazoline and oxymetazoline preparations of different brands.\[8\]

The size of droplets produced during spraying is one of the main factors determining effective nasal delivery of preparations. The microsprayer design must ensure the formation of such droplets, the size of which would contribute to their sedimentation on the nasal mucous membrane. Microsprayers commonly used in pharmaceutical vials are known to produce droplets the size of which is in the range from 20 to 120 \(\mu\)m.\[3-6\] Droplets of up to 10 \(\mu\)m – highly dispersed aerosol – sediment slowly and penetrate through nasal passages into deeper airways. The presence of such droplets in nasal sprays leads to penetration of such medicinal preparations into lungs which are not intended to be absorbed by the lung tissue. Medium-dispersed aerosol droplets (10–30 \(\mu\)m) and low-dispersed aerosol ones (30–100 \(\mu\)m) almost completely sediment in NC. Aerosol with droplets larger than 100 \(\mu\)m is unstable because large droplets tend to merge and become an ordinary solution again very fast. Thus, studying the dispersion composition of a spray jet is an important factor for understanding how the medicinal preparation sediment in NC.\[7,8,9\]

To get full information about the drug delivery effectiveness determined by the microsprayer functioning of a specific medicinal preparation, apart from dispersion qualities, it seems reasonable to examine dynamic characteristics of spraying, namely the geometry of a spray jet and duration of different phases of spray activation. Studying and assessing quantitatively the impulse spraying of pharmaceutical preparations will allow to contribute greatly to improving the device for delivering drugs and, as a result, increasing the effectiveness of nasal preparations.

The purpose of the study is to compare oxymetazoline MDNS of different brands regarding their dispersion qualities, including dynamic characteristics and the spraying dispersion composition.

**MATERIALS AND METHODS**

Nine oxymetazoline MDNS available in the pharmaceutical market of Russia were selected for this study. Eight of them are approved for pediatric use for children over the age of 6, and one preparation is approved for children aged 1–6 [The parameters of the nine drugs analyzed in the article are presented in Appendix 1].

All the experiments were conducted on a basis of the Shadow Photography method (ShPhM) with the use of the related equipment [Figure 1] and techniques developed for analyzing xylometazoline MDNS.\[4,5,11\] ShPhM with digital processing of images is a method of quick and simple screening of pharmaceutical sprays regarding the spray dynamics and dispersion with the spraying process visualization. It was of particular interest to apply the ShPhM to assess the dispersion characteristics of oxymetazoline drugs. The selection of the method is justified by its simplicity, the possibilities for detecting the spray jet composition and the process of its formation in dynamics, as well as the possibility for measuring droplets of a nonspheric form which is typical of droplets over 40 \(\mu\)m in size.

The working principle of the ShPhM is as follows. The researched object was photographed with a digital camera equipped with a lens and an optical filter. The photograph was taken against the background of a bright screen that is back-illuminated with a light source equipped with a light diffuser which provides higher lighting uniformity. While making the measurements, vials with the preparations were installed and fixed on a platform one by one, as it is presented in Figure 2.

Two series of measurements were made. The first series was completed using high-speed imaging with low optical magnification. It was aimed at detecting the structure and dynamics of the spray jet, whereas the second series with

**Figure 1:** Shadow photography method scheme
high optical magnification was made to assess the size of the produced droplets. The images were processed with the use of the software package ActualFlow. In the first series, the shooting frequency was 5 kHz. Due to low optical magnification and short exposure time (2.5 µs), it was possible to use continuous illumination from a 1 kW halogen lamp.

In the second series, the experiments on measuring the size of the droplets were conducted with camera Imperx Bobcat B2020 equipped with long-distance microscope Infinity K2. As illumination, a specially manufactured fluorescent liquid screen was used that was lit with pulsed Nd: YAG laser Quantel Evergreen. The laser ray was transformed into a diverging cone with a desired angle with the help of a lens system.

The image resolution depends on several parameters, including the pixel size of the camera sensor and the optical magnification provided by the lens (the long-distance microscope).

Compared to the microscope used earlier, the design of the long-distance microscope was supplemented with magnifying optical element CF-tube, which allowed to achieve the image resolution of 0.92 µm/pixel.

The use of laser illumination allowed to ensure ultra-short exposure and avoid the motion blurring of droplets edges in the image, while the use of the fluorescent screen allowed to avoid nonhomogenous speckled images occurring when directly using a coherent laser light for illumination.

The imaging frequency was 30 Hz, the exposure time was 10 ns (determined by the laser pulse duration and fluorescent dye lifetime). The obtained images and processing procedures allowed to measure the size of the droplets from 5 µm (plus or minus 2 µm). The droplets smaller than 5 µm were marked as having the size from 1 to 5 µm.

RESULTS

Comparative analysis of the sprays regarding their dynamic characteristics

As a result of the experiment with the ShPhM, videos were produced that showed the whole process of the spray jet formation and attenuation taking approximately 50–200 ms.

To compare the sprays regarding their dynamic qualities, each characteristic was divided conditionally into two categories: short (<85 ms) and long (>115 ms) spraying duration, a narrow (≤45°) and wide (≥50°) cone angle, hollow and filled cone structure. According to these parameters, three groups of preparations with the same qualities were formed out of all the nine studied drugs:

1. Group 1: A filled narrow cone, short duration (Nasivin Sensitive (11.25 µg/dose), Nasivin Sensitive (22.5 µg/dose), Nesopin, Nazol)
2. Group 2: A hollow wide cone, short duration (Nazol Advance, Vicks Sinex);
3. Group 3: A filled wide cone, long duration (Afrin, Afrin Moisturizing, Afrin Extro).

Three-stage mechanism of spray activation was observed for all the preparations, which corresponds with the literature. The initial stage (the jet speed and pressure generated by the pump are still low) involves the cone formation in the form of a film or large particles. The main phase of a fully formed spraying cone and achieved proper pressure is the stage of formation of the jet with droplets of optimal size. In the final stage, the jet speed generated by the pump decreases, and the film contracts or twists into a jet, and large droplets form.

Instant images of all the spraying phases, as well as an averaged image of 100 shots of the spraying main phase for the representatives of the three groups of preparations are presented in Figure 3.

The spraying process dynamics were characterized by the following parameters: the spraying total duration, duration of different stages, the angle of the jet cone. Total duration was measured as the time from the beginning of the spraying to the total ending of the fluid supply, information about the cone angle was obtained through assessing the cone outer contour from the average image of the main stage. Distribution of droplets within the jet was described with two different types of structures: “a hollow cone” or “a filled cone.” Data on the dynamic characteristics of the nine studied oxymetazoline sprays are summarized in Appendix 2.
Comparative analysis of sprays regarding dispersion composition

To characterize dispersion composition of the spray jet, the researchers obtained data on distribution of the droplets regarding their size (quantity and mass parameters) and measured average and average mass diameters of the particles. The results of assessing the dispersion composition are presented in Appendix 3.

DISCUSSION

Comparative analysis of the sprays regarding their dynamic characteristics

The analysis of those videos allowed to measure the duration of the spray activation phases, geometric parameters of the spray jet (the angle of the spray) and make conclusions about uniformity of the distribution of droplets in the spray jet.

To explain long spraying duration of the Afrin preparations, spraying duration was correlated with the dose mass of each drug (the latter figure was obtained as a result of the test on the dose mass uniformity). The sprays, the dose mass of which was approximately 0.05 g, were characterized by short spraying duration, whereas long duration was detected for all the preparations of the Afrin line, the dose mass of which was about 0.1 g. Aerosol sedimentation in airways depends on the movement speed of the aerosol particles. The higher the speed is the less particles sediment in NC. The jet speed of each preparation was calculated as the ratio of the dose mass to the spraying main phase duration [Appendix 2]. It was found out that the jet speed rates were rather comparable (approximately 1 g/s). It is therefore obvious that longer spray activation duration is due to the fact that it takes more time to deliver larger dose mass to the destination. The sprays from Group 2, namely Nazol Advance and Vicks Sinex demonstrate the best dynamic rates of dispersion.

As is clear from Figure 3, during the initial and final stages, dispersion produces a film or a distorted jet with large droplets, rather than finely dispersed particles. The longer these stages are the larger the losses of the effective dose part (which sediments on the nasal mucosa in the form of active finely dispersed particles) of the preparation are. Data in Appendix 2 show that the preparations differ in the ratio of the main phase duration (effective spraying) to the initial and final stage duration (ineffective spraying). Thus, to compare dispersion of the preparations, a new indicator was introduced as an additional dynamic characteristic, namely “the share of the spraying effective phase” \(T_{eff}\) which is in fact a “performance coefficient” of the sprayer. \(T_{eff}\) was calculated as the ratio of the main phase duration \(T_{main}\) to the total spraying duration \(T\). \(T_{eff}\) values vary from 0.59 for Nazol to 0.93 for Vicks Sinex. Comparing \(T_{eff}\) of the preparations of Group 2, which are the leaders regarding their dynamic qualities, demonstrates that the most effective dispersion of the oxymetazoline dose was registered for Vicks Sinex.
Comparative analysis of sprays regarding dispersion composition

When sprays (aerosol forms) are described, the size of the dispersed particles depends on the sprayer design and viscosity of the medicinal substances. Finely dispersed and medium dispersed particles are considered optimal for nasal sprays. Such particles have the best sorption qualities and their effective sedimentation on the nasal mucosa leads to faster therapeutic effect of the drug.

Comparison of oxymetazoline preparations regarding the size of the particles shows that all the preparations of Group 1 (both Nasivin Sensitive preparations, Nazol, Nesopin, and Nazol Advance) \((d = 8–11 \, \mu m)\) belong to highly dispersed aerosols. Vicks Sinex and all Afrin preparations \((d = 16–20 \, \mu m)\) belong to medium dispersed aerosols. Fine particles \((1–5 \, \mu m)\) are typical for more severe aerosol medicinal forms, particularly inhalants. Analyzed data on distribution of particles of the studied preparations demonstrate that spraying of the preparations of Group 1 and Nazol Advance is more similar to aerosols because the share of “harmful” particles with the size \(1–5 \, \mu m\) (33%–53%) is higher there, which leads to possible undesirable consequences. As for Afrin preparations and Vicks Sinex, the share of fine particles is much lower (15%–18%), which makes them safer for deeper airways.

In all the studied preparations, large particles \((d > 100 \, \mu m)\), which are almost ineffective due to their weak sorption on the nasal mucosa and tendency to leak from a nose, are not found at all or represent a very low fraction.

Vicks Sinex and Afrin preparations were found the most optimal regarding the size distribution of particles typical of spray drugs: The share of droplets of optimal size \((V10–100, \%)\) in their dispersion was about 70%, while for other preparations, this indicator was only 50%–60% (and only 36% for Nasol).

It is necessary to emphasize that Nasol spraying produced an asymmetric cone with inadequate dispersion degree: in addition to the drops, there were a lot of liquid bridges (ligaments), as can be seen in Figure 4.

CONCLUSION

1. Spraying effectiveness of nine oxymetazoline MDNS of different brands was comparatively analyzed with the ShiPhM
2. Spraying dynamic characteristics and dispersion composition were obtained
3. Regarding delivery of the medicinal preparation into NC, the spraying regimen of Vicks Sinex preparation was found the most effective thanks to the microsprayer design of the primary packaging.

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Conflicts of interest
There are no conflicts of interest.

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### Appendix 1: Characteristics of oxymetazoline preparations

| Preparation          | Manufacturers/license holder in Russia                                                                 | Concentration of oxymetazoline/dose | Application                                                                                     | Comments                                                                                           |
|----------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Afrin (15 mL)        | Contract Pharmaceuticals Ltd. (Mississauga, ON, Canada)                                               | 0.05%                               | Adults and children >10 years old: 2-3 sprayings into each nasal passage with the interval of 12 h   |                                                                                                    |
|                      | Bayer Inc. (Point-Claire, QC, Canada)/Bayer, closed joint-stock company (Russia)                     |                                     | Children aged 6-10 years old: 1 spraying into each nasal passage with the interval of 12 h        |                                                                                                    |
| Afrin moisturizing (15 mL) | Contract Pharmaceuticals Ltd. (Mississauga, ON, Canada)                                                | 0.05%                               | Adults and children >6 years old: 2-3 sprayings into each nasal passage with the interval of 10-12 h for adults, the frequency may be increased to 3 times per day |                                                                                                    |
|                      | Bayer Inc. (Point-Claire, QC, Canada)/Bayer, closed joint-stock company (Russia)                     |                                     |                                                                                                 |                                                                                                    |
| Afrin extro (15 mL)  | Contract Pharmaceuticals Ltd. (Mississauga, ON, Canada)                                               | 0.05%                               | Adults and children >6 years old: 2-3 sprayings into each nasal passage with the interval of 12 h   |                                                                                                    |
|                      | Bayer Inc. (Point-Claire, QC, Canada)/Bayer, closed joint-stock company (Russia)                     |                                     |                                                                                                 |                                                                                                    |
| Vicks sinex (15 mL)  | Procter and Gamble Manufacturing GmbH (Germany)                                                        | 25 (μg/dose)                        | Adults and children >10 years old: 1-2 sprayings into each nasal passage, at most 2-3 times per day |                                                                                                    |
|                      | Procter and Gamble LLC (Russia)                                                                         |                                     | Children aged 6-10 years old: 1 spraying into each nasal passage, at most 2-3 times per day       |                                                                                                    |
| Nasivin sensitive (10 mL) | Ursapharm Arzneimittel GmbH (Saarbrucken, Germany), Pharmaster (Erstein, France)                     | 11.25 (μg/dose)                     | Children aged 1-6 years old: 1 spraying into each nostril 2-3 times per day                       |                                                                                                    |
|                     | Merck Selbstmedikation GmbH (Germany)                                                                  |                                     | Adults and children >6 years old: 1 spraying into each nostril 2-3 times per day                 |                                                                                                    |
| Nazol (10 mL)        | Istituto De Angeli (Reggello FI, Italy)/Bayer, closed joint-stock company (Russia)                    | 25 (μg/dose)                        | Adults and children >12 years old: 2-3 sprayings into each nasal passage 2 times per day           |                                                                                                    |
|                      |                                                                                                       |                                     | Children aged 6-12 years old: 1 spraying into each nasal passage 2 times per day                  |                                                                                                    |
| Nazol Advance (10 mL) | Istituto De Angeli (Reggello FI, Italy)/Bayer, closed joint-stock company (Russia)                   | 25 (μg/dose)                        | Adults and children >12 years old: 2-3 doses into each nasal passage 2 times per day              | Additional components: Levomenthol, eucalyptol, camphor                                             |
|                      |                                                                                                       |                                     | Children aged 6-12 years old: 1 dose into each nasal passage 2 times per day                      |                                                                                                    |
| Nesopin (10 mL, 20 mL) | Sintez, public joint-stock company (Kurgan, Russia)                                                   | 0.05%                               | Adults and children >12 years old: 2-3 sprayings into each nasal passage with the interval of 10-12 h for adults, the frequency may be increased to 3 times per day | Additional components: Racementhrol, eucalyptus oil                                                 |
Appendix 2: Values of spraying dynamic characteristics and average dose masses of oxymetazoline metered-dose nasal sprays

| Preparation         | \( T_{\text{eff}} \) | \( T_{\text{ini}} \) | \( T_{\text{main}} \) | \( T_{\text{fin}} \) | Average dose mass (g) | jet speed (g/s) | \( \phi \) | Cone structure                                                                 |
|---------------------|----------------------|---------------------|---------------------|---------------------|-----------------------|-------------------|--------|--------------------------------------------------------------------------------|
| Nasivin sensitive   | 0.62                 | 17                  | 51                  | 14                  | 0.04665               | 0.91              | 44     | Filled cone, fine and medium fractions predominate                               |
| 11.25 (μg)          |                      |                     |                     |                     |                       |                   |        |                                                                                  |
| Nasivin sensitive   | 0.73                 | 17                  | 45                  | 10                  | 0.04215               | 0.94              | 45     | Filled cone, fine and medium fractions predominate                               |
| 22.5 (μg)           |                      |                     |                     |                     |                       |                   |        |                                                                                  |
| Nesopin             | 0.73                 | 9                   | 44                  | 7                   | 0.05305               | 1.2               | 42     | Filled cone, fine and medium fractions predominate                               |
| Nazol               | 0.59                 | 4                   | 41                  | 25                  | 0.05240               | 1.2               | 40     | Hollow asymmetric cone, multiple liquid bridges (ligaments), fine fraction predominates |
| Nazol advance       | 0.75                 | 5                   | 53                  | 15                  | 0.05250               | 0.99              | 52     | Hollow cone, fine and medium fractions predominate                               |
| Vicks sinex         | 0.93                 | 1                   | 53                  | 3                   | 0.05105               | 0.96              | 57     | Hollow cone, medium fraction predominates                                         |
| Afrin moisturizing  | 0.78                 | 6                   | 106                 | 24                  | 0.1045                | 0.99              | 63     | Filled cone, medium fraction predominates                                         |
| Afrin               | 0.80                 | 9                   | 97                  | 15                  | 0.1025                | 1.06              | 63     | Filled cone, medium fraction predominates                                         |
| Afrin extro         | 0.85                 | 3                   | 117                 | 14                  | 0.1049                | 1.05              | 62     | Filled cone, medium fraction predominates                                         |

\( T_{\text{eff}} \): Proportion of the main phase to the total duration of spraying, \( T_{\text{ini}} \): Total spraying duration, \( \phi \): Cone angle, degree, \( T_{\text{main}} \): Duration of spraying initial phase, \( T_{\text{fin}} \): Duration of spraying final phase

Appendix 3: Average and average mass size of the droplets, distribution of the droplets regarding their size in oxymetazoline metered-dose preparations

| Preparation         | \( d_{a} \) (μm) | \( d_{b} \) (μm) | \( V_{<5} \) (%) | \( V_{10} \) (%) | \( V_{10-30} \) (%) | \( V_{10-100} \) (%) | \( V_{>100} \) (%) |
|---------------------|------------------|------------------|-----------------|-----------------|-------------------|---------------------|----------------------|
| Nasivin sensitive   | 10.57            | 20.71            | 40.64           | 45.57           | 32.13             | 53.34               | 1.09                 |
| 11.25 (μg)          |                  |                  |                 |                 |                   |                     |                      |
| Nasivin sensitive   | 11.29            | 24.05            | 33.44           | 39.98           | 27.73             | 60.02               | 0.00                 |
| 22.5 (μg)           |                  |                  |                 |                 |                   |                     |                      |
| Nesopin             | 11.26            | 23.01            | 33.14           | 38.89           | 35.18             | 59.72               | 1.39                 |
| Nazol               | 8.60             | 20.52            | 53.44           | 60.75           | 26.09             | 36.44               | 2.81                 |
| Nazol advance       | 10.89            | 21.95            | 35.55           | 42.31           | 31.63             | 57.05               | 0.64                 |
| Vicks sinex         | 17.52            | 37.22            | 18.35           | 21.42           | 22.55             | 70.90               | 7.69                 |
| Afrin moisturizing  | 16.24            | 38.03            | 23.50           | 25.66           | 24.13             | 67.57               | 6.77                 |
| Afrin               | 16.24            | 35.47            | 20.45           | 24.02           | 23.26             | 69.63               | 6.35                 |
| Afrin extro         | 20.45            | 34.73            | 15.04           | 22.18           | 20.53             | 71.20               | 6.62                 |

\( d_{a} \): Average particle diameter (μm), \( d_{b} \): Average mass particle diameter (μm), \( V_{<5} \): Mass fraction of particles with diameter 1-5 μm (%), \( V_{10} \): Mass fraction of particles with diameter <10 μm (%), \( V_{10-30} \): Mass fraction of particles with diameter 10-30 μm (%), \( V_{10-100} \): Mass fraction of particles with diameter 10-100 μm (%), \( V_{>100} \): Mass fraction of particles with diameter >100 μm (%)