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XYLOMETAZOLINE BASE SUITABLE FOR USE IN LIPOPHILIC DRUG PRODUCTS: DEVELOPMENT OF PRODUCTION TECHNOLOGY AND ANALYTICAL METHODS FOR QUALITY CONTROL

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The aim: *development of the technology for obtaining the base of xylometazoline, suitable for the development of formulations in combination with essential oils. Development and validation of methods of control of related substances and assay of the obtained base of xylometazoline. Study of the stability of the obtained xylometazoline base under long-term and accelerated conditions.*

Materials and methods: *experimental samples of xylometazoline base were obtained from commercially available xylometazoline hydrochloride and aqueous sodium hydroxide solution. The quality control of the obtained substance was carried out in accordance with the requirements of the internal specification. The analysis of raw materials of xylometazoline hydrochloride was carried out in accordance with the monograph of the European Pharmacopoeia on xylometazoline hydrochloride (Ph. Eur. 10.1, 1162 (01/2008)).*

Results: *a technology for obtaining xylometazoline base from xylometazoline hydrochloride by the action of a 2 % solution of a strong base, namely sodium hydroxide, was developed. Developed and validated methods of quality control of the obtained xylometazoline base according to indicators of related substances and assay. The stability of the substance was studied for 1 year; the results of control under accelerated research conditions meet the requirements of the specification, which allows for establishing a shelf life of 2 years.*

Conclusions: *the technology for obtaining xylometazoline base and quality control methods based on the monograph of the European Pharmacopoeia on xylometazoline hydrochloride was developed. The developed technology ensures the proper quality of the substance in accordance with the requirements of the internal specification. Analytical methods "related substances" and "assay" meet the established criteria during validation. The obtained results were later used to develop a medicine based on xylometazoline and eucalyptus oil – Eukazolin, nasal drops*

Keywords: *xylometazoline, technology, essential oils, stability, liquid chromatography, lipophilicity, chlorides, validation, synthesis*

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1. Introduction

Xylometazoline hydrochloride (2-[4-(1,1-dimethylethyl)-2,6-dimethylbenzyl]-4,5-dihydro-1*H*-imidazole hydrochloride) is a well-established nasal decongestant that belongs to the pharmacotherapeutic group of sympathomimetic drugs and acts selectively on α-adrenergic receptors (alpha-adrenergic agonist) [1].

Xylometazoline hydrochloride has been used in the EU in the treatment of nasal congestion caused by rhinitis/sinusitis since 1959. Since then a large number of preparations containing xylometazoline hydrochloride have been approved and marketed in several European countries [2]. In some countries, it is available as combination products with ipratropium, domiphen or dexpanthenol.

Intranasal administration of xylometazoline and ipratropium in patients with common cold quickly and effectively relieves nasal congestion and rhinorrhea. Both drugs are well tolerated when used alone or in combination [3]. Currently, there is a composition of xylometazoline hydrochloride and ipratropium bromide under the trade name Otrivin Extra.

Also, the results of a controlled clinical study confirm that the combination Xylometazoline-Dexpanthenol is an enlargement and improvement of effective medicinal treatment of rhinitis following nasal operation in comparison to therapy with xylometazoline alone [4]. There are xylometazoline and dexpanthenol preparations on the market, such as Xylazol, Nazik, Galazolin combi, and Tyzin® Panthenol.

For instance, according to patent EP1446119B1, new stable compositions comprising the combination of a topically active vasoconstrictor and a topically active anticholinergic drug are disclosed. Preferably, the composition comprises Ipratropium or a salt thereof in combination with xylometazoline hydrochloride and a salt thereof. Upon topically administering such compositions to nasal mucosa in individuals suffering from the common cold, the symptoms of rhinorrhea are significantly reduced [5].

Patent CN1832726A describes stable aqueous solution comprising oxymetazoline and/or xylometazoline, a zinc salt and a buffer salt. The aqueous solution is particularly suitable for local administration into the nose for decongesting the mucous membrane [6].

The imidazoline-based ophthalmic drugs oxymetazoline and xylometazoline are widely used as ocular decongestants in pharmaceutical preparations [7].

Farmak JSC produces the following assortment of drugs based on aqueous solutions of xylometazoline hydrochloride: Farmazolin, Eukazolin aqua, and Farmazolin with mint and eucalyptus.

Most preparations with xylometazoline are aqueous solutions. According to the instructions for medical use of these drugs, one of the side effects is dryness of the nasal mucosa. However, it can be used in combination with vegetable oils to eliminate nasal dryness.

Since xylometazoline is in the form of hydrochloride due to its ionic nature, it is hydrophilic and practically insoluble in non-polar solvents, in particular in fatty and essential oils. However, xylometazoline, in the form of a free base, is a lipophilic molecule, practically insoluble in water, which makes it possible to create a formulation with vegetable oils. Lipophilicity refers to the ability of a compound to dissolve in fats, oils, lipids, and non-polar solvents such as hexane or toluene [8]. The biological membrane permeability of a drug is mainly influenced by its lipophilicity. Usually, low-MW lipophilic drugs are well absorbed across the nasal epithelium, whereas peptides and proteins, which are larger hydrophilic drugs, have substantially lower bioavailability [9].

Essential oils have been reported to possess significant antiseptic, antibacterial, antiviral, antioxidant, anti-parasitic, antifungal, and insecticidal activities. Therefore, essential oils can serve as a powerful tool to reduce bacterial resistance. An important characteristic of essential oils and their components is hydrophobicity, which enables them to partition with the lipids present in the cell membrane of bacteria and mitochondria, rendering them more permeable by disturbing the cell structures. This eventually results in the death of bacterial cells due to the leakage of critical molecules and ions from the bacterial cell to a great extent [10]. Thus, the antimicrobial effect of the components of the essential oils is related to the lipophilicity of hydrocarbons and the hydrophilicity of their main functional groups [11]. Eucalyptus is one of the most diverse flowering plants in the world and belongs to the family *Myrtaceae*. Eucalyptus is indigenous to Australia and Tasmania and has spread worldwide [12, 13].

Eucalyptus species are considered pharmaceutical plants because of their biological and therapeutic properties; the *Eucalyptus globulus* has been introduced as the most important and original species of Eucalyptus in international pharmacopoeia [14].

The rising demand for more natural and preservative-free pharmaceutical products reinforces the idea of replacing synthetic preservatives with natural antimicrobials like essential oils [15].

In particular, the literature shows that the combined application of *E. globulus* essential oil and benzalkonium chloride at a concentration of 0.675/0.005 % *v/v*, in nasal spray formulation could decrease the bacterial and fungal populations. This comply with United States Pharmacopoeia criteria, with considerable preservation within 28 days of the study compared to those preserved with only benzalkonium chloride (0.02 %) [16].

According to research [17] essential oils have shown an anti-inflammatory effect and potential in treating patients with allergic rhinitis.

Taking into account the above information about the beneficial properties of eucalyptus oil in the treatment of respiratory diseases, the combination of xylometazoline with eucalyptus oil as an active ingredient is promising.

2. Research planning (methodology)

2. 1. Obtaining of xylometazoline base

Farmak JSC produces a number of drugs with xylometazoline hydrochloride. Therefore, this substance is available at the enterprise and quality control methods have been developed for it (according *to Ph. Eur. 1162* on Xylometazoline hydrochloride), which in turn makes it possible to easily obtain xylometazoline base. To obtain the base of xylometazoline, the base of xylometazoline hydrochloride must be carried out as follows:

– research stages: synthesis is a neutralization reaction with a strong base. Evaluation of the possibility of using NaOH due to its low cost and availability;

– cleaning: rinsing from chloride ions on the filter. To confirm the leaching of chloride ions, it is suggested that the maximum content of chlorides in the final substance be checked with a normalization of no more than 200 ppm;

– drying: choosing the optimal temperature and time mode, which, on the one hand, allows drying the substance, and on the other hand, does not lead to the formation of impurities due to product degradation. At this stage, it is supposed to control the rate of loss in mass during drying with a normalization of no more than 0.5 %.

2. 2. Quality control of the obtained substance and validation

It is planned to determine the following indicators: appearance, melting point, identification, solubility, appearance of solution, chlorides, related substances, loss on drying, sulfated ash, microbiological purity, assay.

In the future, it is necessary to carry out validation of the methods of related substances (*Ph. Eur. 2.2.29, 2.2.46*) and assay (*Ph. Eur. 2.2.20*).

2. 3. Study of the stability of the finished API

To establish the shelf life, it is necessary to investigate the stability of the obtained substance under long-term and accelerated conditions.

3. Materials and methods

Reagents (with an indication of manufacturer and purity): chloroform (Sigma Aldrich, 99.9 %), acetone (Supelco, 99.8 %), anhydrous acetic acid (Sigma Aldrich, 99.9 %), hexane (Honeywell, 98.4 %), *ethanol* (96 %) *R* (SE «Ukrspyrt», 96.3 %), xylometazoline impurity A CRS, xylometazoline WRS of Farmak JSC, acetonitrile (Honey-

well, 99.9 %,), perchloric acid 0.1 M (Merck), acetic anhydride (Honeywell, 99.6 %), phosphoric acid (Sigma Aldrich, >99 %), potassium dihydrogen phosphate (Sigma Aldrich, 99.0 %), sodium hydroxide (Merck, >97.5 %), boric acid (Sigma Aldrich, 99.5 %).

The research was carried out using xylometazoline hydrochloride from the BASF Pharma Chemicalien GmbH & Co. KG company, with an assay of 100.66 %.

To analyze the quality of the substances used: titrator (Mettler Toledo, T 70), infrared Fourier spectrometer (Bruker, Alpha), drying oven (SLW, Pol-Eko-Aparatura), liquid chromatograph equipped with a diode-matrix detector (Agilent Technologies, 1260), analytical balance (Mettler Toledo, MS104S), pH-meter (Mettler Toledo, Seven Compact S220), chromatographic column Waters Atlantis C18 (250 mm, 4.6 mm, 5 μm), melting point system (Mettler Toledo, MP 70), muffle furnace (Nabertherm, L3/11/B410), colour reference solutions GY (Merck, 1.00268).

Reagents and titrated solutions for analysis were prepared according to the requirements of the European Pharmacopoeia (*Ph. Eur.*).

The incoming quality control of xylometazoline hydrochloride was carried out in accordance with the monograph of the European Pharmacopoeia (Ph. Eur. 1162 Xylometazoline hydrochloride) [18].

3. 1. Obtaining of xylometazoline base

Purified water *R* (19 kg) is loaded into the reactor, and xylometazoline hydrochloride (1.3 kg) is loaded while stirring. Resulted mixture is stirred at room temperature for 10–15 min until complete dissolution. A 2 % solution of sodium hydroxide is loaded continuously with stirring in a thin stream, and the reaction mixture is stirred for 2–2.5 h for the complete formation of the xylometazoline base and for the complete crystallization. After that, the mass is filtered and washed on the filter with purified water R (21 L) of and squeezed well. The effectiveness of washing is controlled by the content of chloride ions (method in chapter 3.2, allowed content is below 200 ppm). The product is unloaded and dried at a temperature of 25–30 °C until the results of loss on the drying test become less than 0.5 %. The obtained substance is unloaded, sieved and packaged. Process yield is 1.00–1.02 kg of xylometazoline base (89 % of theoretical).

3. 2. Analysis of xylometazoline base

Identification (Ph. Eur. 2.2.24).

The infrared spectrum of a substance predried to a constant mass at a temperature from 100 °C to 105 °C should correspond to the spectrum attached to Fig. 1 (according to internal specification (ISP)).

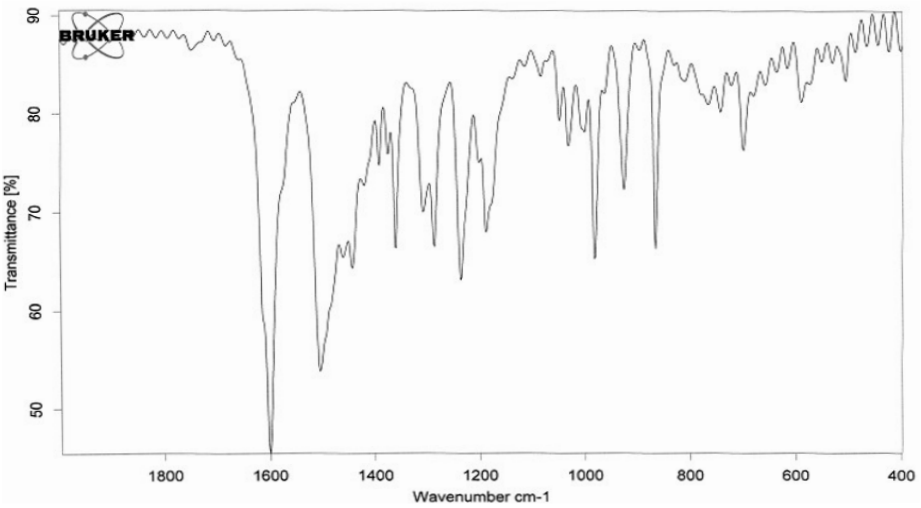


Fig. 1. IR-spectrum of xylometazoline base

2.0.05 g of the substance is dissolved in a mixture of 50 ml of a solution of 12.40 g/l of boric acid P and 2.60 ml of a solution of 8 g/l of sodium hydroxide P. The ultraviolet absorption spectrum (*Ph. Eur. 2.2.25*) of a solution of xylometazoline in the range from 250 nm to 350 nm should have a maximum at wavelengths of (264±2) nm and a minimum at wavelengths of (256±2) nm.

Appearance of solution. Dissolve 1.0 g in 20 ml of *ethanol* (96 %) *R*.

The solution is clear (*Ph. Eur. 2.2.1*) and not more intensely coloured than reference solution GY_6 (*Ph. Eur. 2.2.2*, *Method II*).

Chlorides (Ph. Eur. 2.2.4). Not more than 200 ppm.

Test solution: dissolve 0.25 g of the substance in 7 ml of *ethanol* (96 %) *R*, add 8 ml of water R and mix.

Loss on drying (Ph. Eur. 2.2.32): maximum 0.5 %, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (Ph. Eur. 2.4.14): maximum 0.1 %, determined on 1.0 g.

Related substances.

Related substances in the xylometazoline base are controlled with subsequent limits:

– impurity A – not more than 0.2 %;

– any other impurities – not more than 0.1 %;

– total: not more than 0.5 %.

Standard solutions and test solutions were analyzed using the LC technique using the following conditions (Tables 1, 2).

Table 1

Chromatographic conditions

Parameters	Descriptions
Column size	*l*=0.25 m, ⌀=4.6 mm
Stationary phase	End-capped octadecylsilyl silica gel for chromatography with *embedded polar groups R* (5 μm)
Mobile phase A	1.36 g/L solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with *phosphoric acid R*
Mobile phase B	*Acetonitrile R*
Flow rate	1.0 ml/min
Detection	At 220 nm
Injection volume	10 μL

Table 2

Gradient program

Time, min	Mobile phase A, %, *v/v*	Mobile phase B, %, *v/v*
0–5	60	40
5–20	60→15	40→85
20–35	15	85
35–37	15→60	85→40
37–47	60	40

Preparation of solutions.

Solvent: mobile phase A – mobile phase B (60:40).

The concentration of the test solution: 1.0 mg/ml in a solvent.

Concentration of the reference solution (a): 0.001 mg/ml (prepared from the test solution).

Concentration of the reference solution (b): Mixture of 0.02 mg/ml of xylometazoline impurity A CRS and 0.02 mg/ml of xylometazoline WRS (working reference standard) of Farmak JSC.

Concentration of the reference solution (c): Mixture of 0.002 mg/ml of xylometazoline impurity A CRS and 0.002 mg/ml of xylometazoline WRS of Farmak JSC (prepared from the reference solution b).

System suitability: reference solution (b):

– resolution: minimum 2.5 between the peaks due to xylometazoline impurity A and xylometazoline.

Assay.

Dissolve 0.200 g of the previously dried substance in 20 mL of *anhydrous acetic acid R* and add 5 mL of *acetic anhydride R* using as an indicator 0.15 ml of crystal *violet solution R* or titrate with 0.1 M perchloric acid, determining the end-point potentiometrically (2.2.20).

1 mL of 0.1 M perchloric acid is equivalent to 24.44 mg of $C_{16}H_{25}N_2$.

3. 3. Validation of methods

3. 3. 1. Related substances

The following characteristics were considered to confirm capability of the analytical procedure: specificity, linearity, range, limit of detection and limit of quantitation. The range of applications of the analytical technique is presented in Table 3.

Table 3

Range of application of the analytical technique

Substance	Limit of impurities	The studied range
Xylometazoline	Not more than 0.1 %	0.02–0.12 %
Xylometazoline impurity A	Not more than 0.2 %	0.04–0.024 %

Preparation of model solutions for studying linearity.

Solvent: mobile phase A – mobile phase B (60:40)

Solution for linearity (RS). The mixture of 0.1 mg/ml of xylometazoline impurity A CRS and 0.05 mg/ml of xylometazoline WRS of Farmak JSC. Dissolve aliquots of the RS according to Table 4 in solvent and dilute to the volume according to Table 4 with the same solvent.

Table 4

The studied model solutions

Solution	Concentration level, %		Theoretically calculated concentration, mg/ml		Aliquot of RS, ml	The volume of flask, ml
	Imp A	xylometazoline	Imp A	xylometazoline		
L1	0.04	0.02	0.0004	0.0002	0.4	100.0
L2	0.08	0.04	0.0008	0.0004	0.8	100.0
L3	0.12	0.06	0.0012	0.0006	1.2	100.0
L4	0.16	0.08	0.0016	0.0008	1.6	100.0
L5	0.20	0.10	0.0020	0.001	2.0	100.0
L6	0.24	0.12	0.0024	0.0012	2.4	100.0

3. 3. 2. Assay

The following characteristics were considered to confirm capability of the analytical procedure: specificity, linearity, accuracy, precision, range. The range of applications of the analytical technique is presented in Table 5.

Table 5

Range of application of the analytical technique

Substance	Requirements according to ISP	The studied range
Xylometazoline	99.0–101.0 %	80–120 %

Preparation of model solutions.

Weights of the studied substance according to Table 6 were dissolved according to the assay method given in p. 3.2.

Table 6

The studied model solutions

Model solutions	Weight of API, m_i, mg	The given amount of API is relative to the nominal weight, *Xi*, %
M1	159.7	79.89
M2	169.7	84.89
M3	179.9	89.99
M4	189.7	94.90
M5	199.9	100.00
M6	209.7	104.85
M7	219.6	109.85
M8	229.6	114.86
M9	239.8	119.96

3. 4. Study of the stability of xylometazoline

To establish the shelf life, it is necessary to study the stability of the obtained substance. Stability studies were carried out under long-term (25±2) °C/(60±5) % RH and accelerated conditions (40±2) °C/(75±5) % RH. For this, API samples were placed for stability studies in climatic chambers according to the following design:

– under long-term conditions (25±2) °C/(60±5) % RH samples were analyzed every 3 months for 1 year;

– under accelerated conditions (40±2) °C/(75±5) % RH samples were analyzed every 3 months for 6 months.

The following critical quality parameters were investigated: solubility, melting point, chlorides, related substances, loss on drying and assay.

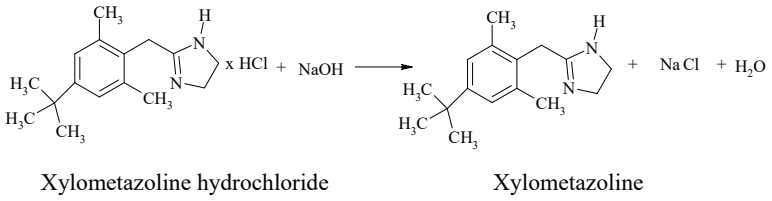
4. Research results

4. 1. Obtaining of xylometazoline base

The scheme for obtaining xylometazoline base is shown in Fig. 2.

Xylometazoline hydrochloride was chosen as the raw material for the production of the xylometazoline base as a commercially available raw material, the quality of which can be easily checked according to the available ISP at Farmak JSC. The preparation of the base is carried out by the action of an aqueous alkali solution, namely, sodium hydroxide was chosen due to its availability and higher solubility of both the hydrochloride itself and the resulting sodium chloride. The resulting paste of xylometazoline base was filtered and washed with water from sodium chloride residues on the filter. An analysis of the chloride indicator was carried out in accordance with the ISP of Farmak JSC. The chloride content did not exceed 200 ppm.

Next, the washed paste was dried at a temperature of 25–30 °C until the loss on drying was no more than 0.5 %. At this drying temperature, product degradation does not occur (see Fig. 3). The finished base of xylometazoline has the form of a fine white crystalline powder. The yield is about 89 %.



Xylometazoline hydrochloride Xylometazoline

Fig. 2. Obtaining of xylometazoline base

4. 2. Quality control of the obtained substance and validation

After obtaining the xylometazoline base, a full analysis of the substance was carried out in accordance with the requirements of the ISP. Since xylometazoline hydrochloride is described in a monograph of the European Pharmacopoeia [18], the quality indicators were adapted according to this monograph for the analysis of xylometazoline base.

Solubility for this API was tested in water, because after conversion to the base, the xylometazoline molecule becomes a lipophilic molecule. Solubility in 96 *% ethanol R*, *acetone R*, *chloroform R* and *hexane R* was also investigated.

Identification. As with xylometazoline hydrochloride, IR spectroscopy was used as an identification method. However, due to the lack of a standard sample for this API, a reference IR spectrum was obtained, which was added to the ISP. The second method of identification was carried out according to *Ph. Eur. 2.2.25* (UV and visible spectrophotometry).

Appearance of solution. According to the monograph on xylometazoline hydrochloride, the substance is dissolved in water, which is not suitable for dissolving the base. Therefore, it was necessary to choose another solvent in which the base of xylometazoline is easily soluble and another colour reference solution (p. 3.2.).

Chlorides and related substances. Analysis of chlorides is carried out in accordance with *Ph. Eur. 2.4.4*. To determine related substances, the methodology according to the monograph on xylometazoline hydrochloride was adapted for the base, since the test solution of xylometazoline hydrochloride is prepared in water, which is not suitable for the xylometazoline base. Therefore, another solvent was selected, and the gradient optimized; namely, the volume of the aqueous phase, in this case, phosphate buffer, was slightly reduced from 70 volumes to 60 volumes, and the volume of acetonitrile was correspondingly increased from 30 volumes to 40. Mobile phase A – mobile phase B in the ratio of 60:40 is used as a solvent for the preparation of the investigated solutions, i.e. the same as the initial ratio of mobile phases in the gradient (p. 3.2).

Loss on drying and sulfated ash. Control of these quality parameters is carried out in the same way as in accordance with the monograph on xylometazoline hydrochloride.

Microbiological purity and assay. According to the monograph on xylometazoline hydrochloride, control of the assay parameter is carried out potentiometrically, using a mixture of acetic acid and acetic anhydride as a solvent. To control xylometazoline base, it is necessary to determine the optimal ratio of these solvents.

The most critical parameters in this analysis are solubility and chlorides since these indicators indicate the complete conversion of xylometazoline hydrochloride into its base.

The obtained substance was analyzed according to ISP. The obtained data are shown in Table 7. Also according to the chromatogram shown in Fig. 3 drying API does not lead to its degradation.

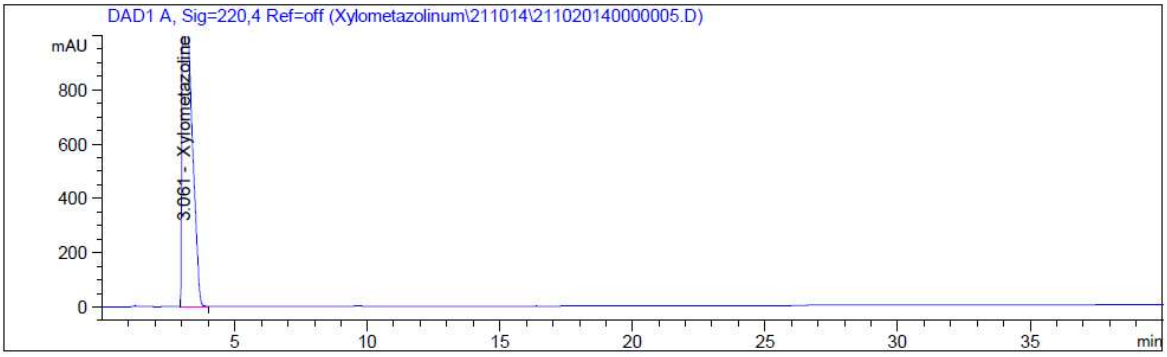


Fig. 3. Chromatogram of xylometazoline base

Table 7

Quality of xylometazoline base according to ISP

Parameter	Requirements of ISP	b. 10413	b. 10215
Appearance	Fine crystalline powder of white or almost white colour	conforms	conforms
Solubility	Very soluble in *ethanol* (96 %) *R,* freely soluble in *chloroform R*, soluble in *acetone R*, slightly soluble in *hexane R*, practically insoluble in *water R*	conforms	conforms
Identification	IR spectrophotometry	conforms	conforms
	UV and visible spectrophotometry	conforms	conforms
Melting point	135 °C to 140 °C	135.9 °C	138.0 °C
Appearance of solution	The solution is clear and not more intensely coloured than RS GY_6	conforms	conforms
Chlorides	Not more than 200 ppm	<200 ppm	<200 ppm
Related substances	Impurity A – NMT 0.2 %; any other impurities – NMT 0.1 %; total – NMT 0.5 %	BDL BDL BDL	BDL BDL BDL
Loss on drying	Not more than 0.5 %	0.24 %	0.26 %
Sulfated ash	Not more than 0.1 %	0.0 %	0.0 %
Microbiological purity	TAMC: not more than 1000 CFU; TYMC: not more than 100 CFU	Conforms; conforms	Conforms; conforms
Assay	From 99.0 % to 101.0 %	99.02 %	100.2 %

Note: NMT – not more than; BDL – below detection limit.

4. 3. Validation of methods

4. 3. 1. Related substances

Specificity. System suitability.

The results of the chromatographic system suitability are shown in Table 8.

Table 8

System suitability test

Parameter	Criterion	Result
Resolution between the peaks due to xylometazoline impurity A and xylometazoline	Minimum 2.5	3.5

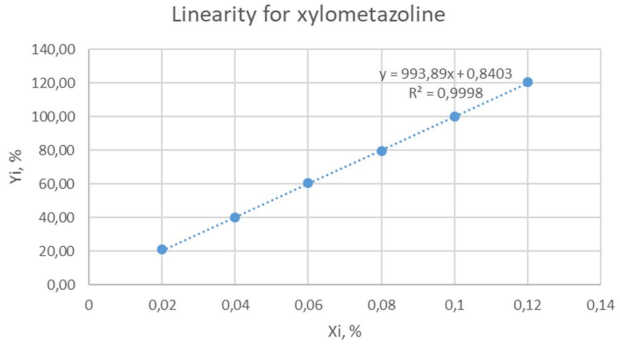
The system suitability requirements are met.

It is shown that there is no interference between the peaks of API impurities and the peaks of the solvent.

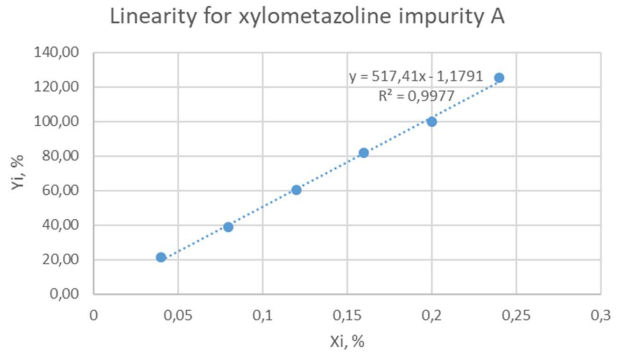
The specificity of the analytical procedure is sufficient.

Linearity.

To assess the linearity, the model solutions L1–L6 were analyzed in the chromatographic conditions specified by the method (Table 4). Three parallel chromatograms were obtained for each solution, and the average value of the peak areas was calculated to evaluate the results. Linearity regression data, summarized in Table 9, show a good linear dependence between concentration and peak areas over a concentration range of 20–120 % for impurity A and unspecified impurities (Fig. 4).



a



b

Fig. 4. Graph of the dependence of the analytical signal on the concentration: xylometazoline (*a*), impurity A (*b*)

Table 9

The results of determining linear regression parameters

–	|*a*|	*b*	*r*	s_b	s_a	s_r	LOD, %	LOQ, %
xylometazoline	0.84	993.89	0.9999	6.4	0.5	0.54	0.0017	0.005
impurity A	1.18	517.41	0.9988	12.45	1.94	2.08	0.0012	0.0037
Criterion	≤5.0	–	≥0.990	–	–	–	–	–

4. 3. 2. Assay

According to 9 model solutions (Table 6), the dependence of the found amount of API (Y_i, %) on the given amount of API (X_i, %) was calculated, that is, the dependence of the form $Y=B\cdot X+A$ was calculated. The obtained values are shown in Tables 10, 11 and Fig. 5.

Table 10

The results of determining linear regression parameters

Parameter	The obtained values	Criteria	Conclusion
$\|A\|$	0.65	≤1.0	Corresponds
R	1.000	≥0.999	Corresponds
Z_{aver}	100.1	99.5 %≤Z_{aver}≤100.5 %	Corresponds
Z_{min}	99.9	≥99.0 %	Corresponds
Z_{max}	100.3	≤101.0 %	Corresponds

Table 11

Result of the analysis of model solutions and their statistical processing

Parameter	Value	Conclusion
Z average, %	100.1	Corresponds
SD_{-}, %	0.15	Corresponds
RSD_{-}, %	0.15	Corresponds
Relative confidence interval: Δz %=t(95 %, 8)*RSD_{-}	0.28<1.0 %	Corresponds
Systematic error: δ=|Z–100|, %	0.10	Corresponds
Criterion of significance of systematic error: δ≤max δ=0.32 %	0.10<0.32 %	Corresponds

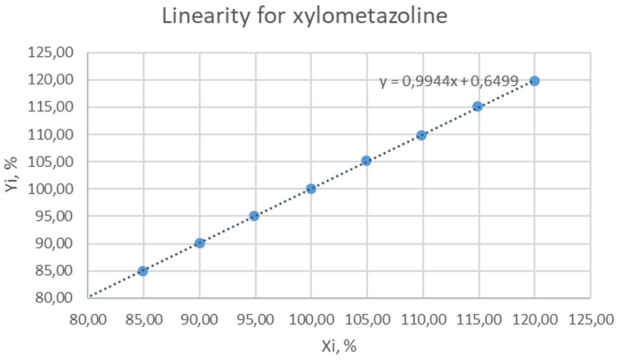


Fig. 5. Graph of the dependence of the amount of API found (Y_i, %) on the given amount of API (X_i, %)

4. 4. Study of the stability of xylometazoline

The results of the study of the stability of xylometazoline base in long-term and accelerated testing are given in Table 12 for the main parameters of substance quality.

Table 12

Stability of xylometazoline base

b. 10413	Long-term testing					Accelerated testing		
Storage conditions	(25±2) °C/(60±5) % RH					(40±2) °C/(75±5) % RH		
Months								
–	0	3	6	9	12	0	3	6
Solubility	Complies					Complies		
Melting point	135.9	136.0	136.1	136.0	136.2	135.9	136.1	136.2
Chlorides	<200 ppm					<200 ppm		
Related substances	BDL					BDL		
Loss on drying	0.24	0.27	0.28	0.27	0.30	0.24	0.28	0.32
Assay	99.02	99.2	99.7	99.9	99.8	99.02	99.4	99.7

5. Discussion of research results

As already mentioned in the introduction, xylometazoline is used in the form of hydrochloride and not in the form of a base. Therefore, synthesis routes are described in the literature for xylometazoline hydrochloride. For instance, one of the inventions (CN101928247A) relates to a method for synthesizing a xylometazoline hydrochloride compound. In the method, 1,3-dimethyl-5-butyl benzene is used as an initiative material, and the xylometazoline hydrochloride is obtained by chloromethylation, cyanation, cyclization and salification. The synthesis method has the advantages of simplicity, readily available raw materials, safe operation and high yield and is suitable for industrial production [19].

The first invention (CN103351343A) discloses a synthetic method for xylometazoline hydrochloride, which includes the following steps: taking m-xylene as a raw material to react with tertiary butanol under the catalysis of Lewis acid, so as to obtain 1,3-dimethyl-5-tert-butyl benzene; generating 2,6 dimethyl-4-tertiary butyl benzyl chloride through 1,3-dimethyl-5-tert-butyl benzene under the combined function of formaldehyde, hydrochloric acid and catalyst; mixing the 2,6 dimethyl-4-tertiary butyl-1-benzyl cyanide to react with quadrol tosilate, heating for ring closure, so as to obtain xylometazoline p-toluenesulfonic acid, and separating in an alkali-out manner to obtain xylometazoline; performing salifying through xylometazoline and hydrochloric acid. According to the invention, the original raw material is easy to obtain, the utilization of poisonous and strong-corrosivity reagents is avoided, the cyanation condition is gentle, the side reaction is few, the operation is simple after treatment is easy, the labour intensity is reduced, the working environment is improved, the purity of products is high, and the yield is high [20].

5. 1. Obtaining xylometazoline base

Xylometazoline hydrochloride is the raw material for obtaining of xylometazoline base. The conversion of the salt into a free base is carried out with an aqueous alkali solution, by which 2 % solution of sodium hydroxide was chosen. Another parameter chosen for this stage is the concentration of the starting substance. It was selected in such a way that, on the one hand, it was maximal, and on the other hand, the precipitate formed did not reduce the intensity of mixing and did not complicate the discharge of the mass onto the filter. Therefore, the final ratio was chosen as 4.5 mol of sodium hydroxide is taken for 4.6 mol of the xylometazoline hydrochloride.

The inprocess control of the obtained paste for content of chloride ions met the requirements of in-house specification (not more than 200 ppm), which indicates that the neutralization reaction has passed completely. Further drying of the washed paste at a temperature of 25–30 °C for about 7–8 h did not lead to product degradation (Fig. 3). The results of loss on drying test met the inhouse specification (no more than 0.5 %).

5. 2. Quality control of the obtained substance and validation

The data in Fig. 3 and Table 7 show that the quality of the obtained xylometazoline base meets the requirements of the ISP.

In the production process of xylometazoline, where the main stage is the neutralization process, inorganic impurities, the presence of which is possible in the substance xylometazoline, is sodium chloride. Sodium chloride appears and is removed during the production process at the neutralization stage. Residual amounts of chloride ions are controlled at the stage of technological control during production.

5. 3. Validation of methods

5. 3. 1. Related substances

According to Table 8, the system suitability requirements are met. It is also shown that there is no interference between the peaks of the API impurities and the peaks of the solvent. Therefore, the specificity of the analytical procedure is sufficient.

The method is linear in the studied range and has a sufficient level of sensitivity both for unidentified impurities and for impurity A (Table 9 and Fig. 4).

5. 3. 2. Assay

No titrant is used for solvent titration, which indicates the specificity of the method.

All studied linear regression parameters are within the acceptance criteria (Table 10 and Fig. 5).

According to Table 11, the method has no significant systematic error (δ) and has sufficient convergence for the analysis results.

5. 4. Study of the stability of xylometazoline

Studies of the stability of xylometazoline base, conducted under the conditions of long-term and accelerated studies, show the absence of noticeable degradation for at least 12 months, which, in the absence of significant changes in the accelerated study, allows extrapolation to a shelf life of up to 24 months (Table 12). This testifies to the stability of the substance and the possibility of its use for obtaining a medicinal product.

Practical relevance. A drug product with active substances such as xylometazoline base and eucalyptus oil – Eukazolin, nasal drops – is included in the drug portfolio of Farmak JSC.

Research limitations. Multistage synthesis of xylometazoline based on starting materials requires additional resources in terms of personnel, materials, and time.

Prospects for further research. In the future, the effect of higher drying temperatures on the quality of the final API is planned to be investigated.

6. Conclusions

A method of obtaining a lipophilic form of xylometazoline, suitable for administration in oil-based formulations, was developed. Xylometazoline hydrochloride was used as a raw material for the synthesis of the xylometazoline base, as it is commercially available. In the process of obtaining the finished product, the salt was converted into a free base. For this, treatment with a strong base solution, namely sodium hydroxide, was carried out. To rinse chloride ions, the base obtained on the filter was washed with several portions of water until the chloride content was less than 200 ppm. Drying of the substance after washing was carried out at a temperature of 25–30 °C until the loss drying was no more than 0.5 %. The obtained substance meets the requirements of the ISP, and the stability of the substance has been studied and proven for a minimum of 12 months, with the possibility of establishing a shelf life of 2 years. Results of "Related substances" and "Assay" tests meet the established criteria during validation and can be used to control the substance xylometazoline produced by Farmak JSC.

Eucalyptus essential oil was chosen as another component of the active substance, which is able to eliminate dryness of the mucous membrane and has anti-inflammatory and antiseptic effects. Medium-chain triglycerides are used as excipient material. The drug product based on this formulation – Evkazolin, nasal drops – is present in the drug portfolio of Farmak JSC.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

Data will be made available at a reasonable request.

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