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THE STUDY OF THE STABILITY OF SILVER PROTEINATE SOLUTIONS PREPARED IN PHARMACIES

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Today, medicines made in pharmacies are increasingly attracting consumers' attention and are in growing demand in Ukraine. Pharmacy production faces a number of problems, including the study of the stability of extemporaneous dosage forms and the determination of an optimal shelf life. 1 % and 2 % water silver proteinate solutions used in ophthalmology, otolaryngology and nephrology are produced in Ukrainian pharmacies both extemporaneously and as a reserve.

The aim. *The aim of the work is to develop methods for quality support and study the chemical stability of 1 % and 2 % water solutions of silver proteinate, and to study the microbiological purity to extend the storage time of nasal drops.*

Materials and methods. *A study of the chemical stability of 1 % and 2 % water silver proteinate solutions of pharmaceutical production is carried out using chemical identification reactions (to silver and protein), quantitative determination by thiocyanatometric titrimetric method and determination of microbiological purity.*

Results*. The validation characteristics of the method for the quantitative thiocyanatometric determination of silver proteinate were studied (the correlation coefficient r=0.9995 and 0.9996; the systematic error – 0.26 % and 0.03 %, the relative confidence interval – 0.88 % and 0.74 % for 1 % and 2 % solutions, respectively), as well as its suitability for this purpose was proven. "Silver proteinate solution, 1.0 %" and "Silver proteinate solution, 2.0 %" prepared in the pharmacy were studied for 150 days by the "Microbiological purity" indicator and were biologically stable.*

Conclusions*. The chemical identification reactions and methods for the quantitative determination of silver proteinate in an extemporaneous dosage form used to study the chemical stability of the drug have been proposed. The study results of the chemical stability and microbiological purity allow us to recommend pharmacies to extend the shelf life of nasal drops containing silver proteinate as an active pharmaceutical ingredient for 150 days*

Keywords*: extemporaneous dosage forms, titrimetric method of analysis, validation, silver proteinate, chemical stability, microbiological purity*

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1. Introduction

Recently, there has been a certain "renaissance" of extemporaneous compounding of drugs in the world. The rapid development of the pharmaceutical industry and the challenges associated with the pandemic led to the need to replenish the shortage of medicines and quickly respond to the use of unregistered drugs in the country or their off-label use – not only for a different purpose, but also in a different dose or a dosage form.

The same trends as in the whole world are observed in Ukraine [1, 2]. The network of pharmacies manufacturing medicines has stabilized. Still, in recent years there has been a significant expansion of the range, as well as the appearance of a large number of mass-produced drugs. At the present stage, the concept of quality assurance of medicines prepared in pharmacies has been developed in Ukraine [3]. General monographs of the State Pharmacopoeia of Ukraine (SPhU) have been introduced, and the structure and requirements for individual monographs on medicines manufactured in pharmacies have been determined. The development and implementation of monographs began with dosage forms, which pharmacies in Ukraine most often made. Such drugs traditionally include solutions of colloidal silver (protargol) in different concentrations. In the modern scientific literature, new research is provided on the advantages of this medicine and the prospects for its use [4].

Colloidal silver preparations, in particular solutions of silver proteinate, are often prescribed during seasonal illnesses. Long-term practice has proven that silver proteinate exhibits astringent, antiseptic and anti-inflammatory properties [5]. In particular, there is a long-term experience of successful use of silver proteinate in rhinopharyngitis and rhinosinusitis [6]. Silver proteinate does not cause the imbalance of the normal microflora. In addition to antibacterial, fungicidal and antiviral effects, it shows local protective and anti-inflammatory effects. The protective effect is provided by precipitation of proteins with silver, which forms a protective albuminous film on the surface of the damaged mucosa. This

film reduces the permeability of the mucous membrane to bacteria and provides the normal functional state of cells, promoting rapid tissue repair. Local anti-inflammatory and anti-edematous effects are associated with a decrease in the lumen and permeability of the capillaries of the mucous membrane [7, 8].

Some researchers, to explain the mechanism of action of silver on the cell, pay special importance to physicochemical processes, in particular, the oxidation of bacterial protoplasm and its destruction by oxygen dissolved in water, and silver plays the role of a catalyst. There is evidence of the formation of nucleic acid complexes with heavy metals, resulting in the destruction of DNA and, consequently, the viability of bacteria. It is assumed that one of the reasons for the broad antimicrobial action of silver ions is the inhibition of transmembrane transport of Na^+ and Ca^{2+} cations caused by silver and respiratory chain enzymes, as well as the separation of oxidation and oxidative phosphorylation processes in microbial cells, which eventually leads to death of the latter [9, 10].

According to the authors [11], it can be used to prevent acute respiratory syndrome; clinical studies have proven the effectiveness of a topical nasal spray in severe rhinosinusitis [12]. It is safe for use during pregnancy, breastfeeding and for newborns [13].

Doctors often prescribe 1 % and 2 % protargol solutions made in pharmacies despite the fact that at the pharmaceutical market, there are a number of medicines with silver proteinate of industrial production, for example, nasal/ear drops "Protargol" (manufacturer Sella, Italy), "Knoxpray" (manufacturer JV LLC Sperko Ukraine, Ukrainian-Spanish), a powder for the solution for intranasal use with a solvent (water for injections) produced under the trade names "Protargol Baby" and "Protargol" (manufacturer LLC "Istok-Plus", Ukraine). Such European country as Poland continues to make extemporaneous silver proteinate solution for use in otolaryngology [14], in Romania 1 % silver proteinate solution in combination with Peruvian balm is used to treat such a complication of diabetes as "diabetic foot" [15].

Solutions of silver proteinate of industrial production are prepared with the addition of excipients; among them there are preservatives, such as imidurea. Extemporaneous compounding allows the physician to vary the dosage of silver proteinate and avoid the use of excipients and preservatives, which, in turn, ensures the effectiveness of treatment and the predictability of the therapeutic effect.

2. Planning of the research

In Ukraine, to ensure the quality of medicines manufactured in pharmacies for future use, it is necessary to develop methods of analysis for quality control and study the chemical stability of the dosage form. These requirements are regulated by the SPhU, which contains a separate section, "Medicines manufactured in pharmacies" [16, 17].

Aqueous solutions of silver proteinate made by individual formulations according to the requirements of the SPhU are non-sterile dosage forms and should be stored for 10 days. At the same time, 2 % solutions of protargol prepared as a reserve can be stored at a temperature of 15 °C to 25 °C for no longer than 30 days [16]. Considering these contradictory requirements and the antimicrobial activity of silver proteinate, it is advisable to experimentally study the chemical and microbiological stability of 1 % and 2 % solutions of pharmacy-made protargol to extend the shelf life of the dosage form.

Such studies have not been performed for silver proteinate solutions before but are very important. Requirements for the quality of the silver proteinate solution are given in the monograph of the Japanese Pharmacopoeia "Silver Proteinate Solution" [17]. This document was used for the transfer of quality control methods with their subsequent validation and application to study the stability of 1 % and 2 % silver proteinate solutions of pharmacy production.

The research stages:

– substantiation of the choice of quality control methods;

– validation/verification of the analytical methods selected;

– determination of critical parameters for the shelf life of the dosage form and the quality assurance of medicines;

– study of the chemical and microbiological stability.

3. Material and methods

For our research, 1 % silver proteinate solution (batches: 6, 15, 247, 285, 394, 407, manufacturer Leda pharmacy, Kharkiv) and 2 % silver proteinate solution (batches: 1, 7, 104, 106, 158, 160, manufacturer Leda pharmacy, Kharkiv) were used. Model mixtures were prepared using the silver proteinate substance (batch PTOR19-0646, manufacturer Laboratorios Argenol SL, Spain). The quantities of substances for the preparation of model solutions and reagents were weighed on AXIS analytical scales (Poland). The study was performed using measuring glassware of class A meeting the ISO standards, and the requirements of the SPhU harmonized with the European Pharmacopoeia [16, 18].

Identification. Method.

To 3 ml of 1 % solution or 1.5 ml of 2 % solution, add water and dilute to the volume of 10 ml, shake 2 ml of dilute hydrochloric acid for 5 minutes and filter. To 5 ml of the filtrate solution add the sodium hydroxide solution (1:10) and 2 ml of the copper (II) sulfate solution (2:25); a purple color is formed.

To 5 ml of the solution obtained in the previous test, add dropwise the iron (III) chloride solution; a brown precipitate is formed.

Place 3 ml of the solution in a crucible, heat carefully, evaporate almost to dryness, and gradually burn when heated. Dissolve the residue by heating in 1 ml of nitric acid and add 10 ml of water. To the resulting solution, add 0.3 ml of hydrochloric acid (250 g/L); a white cheesy precipitate is formed, which dissolves when adding 3 ml of a dilute ammonia solution.

Assay.

Place 20.0 ml of 1 % or 10.0 ml of 2 % solution to a 100 ml Kjeldahl flask, add 10 ml of the concentrated

sulfuric acid, cover the flask with a funnel, and boil the mixture for 5 minutes. After cooling, gradually add 5 ml of the concentrated nitric acid, heat on a water bath for 45 minutes, stirring periodically and cool. Add 2 ml of the concentrated nitric acid, boil gently, and cool. The procedure of adding nitric acid is repeated until the solution becomes colourless when cooling.

Transfer the mixture to a 250 ml conical flask, and add 100 ml of distilled water. Boil the mixture for 5 minutes, cool, and titrate to 0.02 M ammonium thiocyanate solution (the indicator is 3 ml of the iron (III) ammonium sulfate solution).

1 ml of 0.02 M ammonium thiocyanate solution is equivalent to 2.158 mg of silver, which should be not less than 0.07 %/0.14 % and not more than 0.09 %/0.18 % in the silver protein solution, depending on the concentration.

To calculate the quantitative content of silver proteinate in the dosage form, the following conversion factor of the titer was used, taking into account the actual amount of silver in the substance:

$$T = \frac{0.002158 \cdot 100}{8} = 0.0269 \text{ g/ml.}$$

The content of silver proteinate, g, in the dosage form was calculated by the formula:

$$x, \text{g} = \frac{V_{NH_4SCN} \cdot K_{NH_4SCN} \cdot T \cdot V_{prescr}}{V_{analisis}},$$

where V_{NH_4SCN} is the volume of 0.02 M ammonium thiocyanate solution spent on titration of the dosage form, ml;

K_{NH_4SCN} is the correction factor to 0.02 M ammonium thiocyanate solution;

T is the titer of the titrated solution by silver proteinate, g/ml;

V_{prescr} is the volume of the dosage form according to the prescription, ml;

$V_{analisis}$ is the volume of the dosage form for the quantitative determination, ml.

1 ml of 0.02 M ammonium thiocyanate solution is equivalent to 26.9 mg of protargol, which in dosage forms of the appropriate concentration should be not less than 0.09 g/0.18 g and not more than 0.11 g/0.22 g.

Stability study.

The test samples of the drug (nine of each concentration) were stored in cool conditions (8–15 °C). Chemical indicators (appearance, identification, quantitative content) and microbiological purity were determined immediately after the drug preparation, then in 30, 60, 90, 120 and 150 days of storage.

Microbiological purity.

When analyzing the microbiological purity of the dosage form, the method of the SPhU was used [16]. All studies were performed under aseptic conditions using a laminar box (AC2-4E1 "Esco" biosafety box, Indonesia).

The following thick and liquid nutrient media were used in the tests: casein soyabean digest agar (to determine the total aerobic microbial count (TAMS), Sabouraud dextrose agar (to determine the total yeast and mold count (TYMC), casein soybean pre-incubation to determine the presence of certain species of microorganisms), mannitol salt agar (to detect *Staphylococcus aureus*), cetrimide agar (to detect *Pseudomonas aeruginosa*) according to the SPhU 2.0 [12] To check and eliminate the antimicrobial action of the drug samples a dilution of the dosage form of 1:10 was used and a typical neutralizing liquid (3 % polysorbate solution-80, 0.3 % soy lecithin solution, 0.1 % histidine hydrochloride solution) was added.

For the analysis, 1.0 ml of the test sample was taken, a sterile buffer solution with sodium chloride and peptone (pH 7.0) and a neutralizing liquid was added, and the volume was diluted to 10 ml (dilution of 1:10).

Statistical processing of the results of the physicochemical and microbiological studies obtained was performed according to the requirements of the SPhU.

4. Result

The monograph of the Japanese Pharmacopoeia "Silver Proteinate Solution" [14] is recommended 3 % solution of silver proteinate made with the addition of 10 % glycerin and a sufficient amount of peppermint water for the analysis. In comparison, domestic pharmacies most often prepare 1 % and 2 % aqueous solutions. Changing the concentration of the active pharmaceutical ingredient (API) in the dosage form requires making changes in the analytical methodology, which, in turn, requires studying such validation characteristics as linearity, accuracy and precision.

Silver and protein residue determination reactions have traditionally been used to identify silver proteinate [19, 20]. After the destruction of the protein part, colloidal silver is converted into silver nitrate, which is determined by pharmacopoeial reactions. The protein residue after the acid hydrolysis is identified by the biuret test or the reaction with the solution of iron (III) chloride [19].

Tests for the silver proteinate identification in the composition of an extemporaneous drug were performed according to the monograph of the Pharmacopoeia [21] using the same concentrations of API. To increase the reliability of the results obtained, the effect of the reactions was compared with the effect of a sample of the silver proteinate substance. To prevent a false negative effect, a "blank" experiment was performed in parallel.

Methods for the quantitative determination of silver proteinate in solutions are known, namely after mineralization and transition of silver to the ionic state, the salts formed are titrated with ammonium thiocyanate. These methods are given in the Ukrainian and Soviet scientific and reference literature [19, 20]. Still, unfortunately, they exceed the criteria of the maximum allowable uncertainty of the method even in preliminary calculations, and some of them are not reproduced at all. For experimental studies, we chose a method for the quantitative determination of silver proteinate in solution given in the monograph of the Japanese Pharmacopoeia as a prototype. The destruction of the protein part of the silver proteinate molecule is carried out with concentrated sulfuric acid. Further addition of nitric acid leads to the formation of silver nitrate, which is determined by titration with the ammonium thiocyanate solution.

Taking into account the change in the content of API in the extemporaneous dosage form, the transfer of the quantitative determination method to further use in the pharmacy quality control occurred with such changes in indicators as reducing the weighed sample of the dosage form for testing and the molar concentration of the titrated solution. When studying the validation characteristics of the quantitative determination method the tolerance of the API content was chosen ±10 % [16, 22, 23].

According to the SPhU requirements, the uncertainty of the analysis results (ΔAs) was calculated taking into account the standardization of 0.02 M ammonium thiocyanate solution and the quantitative determination of silver proteinate with the reduced weighed sample proposed. It was found that the calculated total uncertainty of the method proposed of 0.76 % and 0.77 % for solutions of the appropriate concentration did not exceed the maximum allowable uncertainty of the analysis results (ΔAs_{max} 3.20 %).

The linearity of the titrimetric method for the quantitative determination of the extemporaneous dosage form was performed on model mixtures in the concentration range of 80-120 % (step – 10 %) of the nominal amount of silver proteinate in the solutions studied [16, 23]. The preparation of a model mixture of silver proteinate solutions was carried out in accordance with the Guidelines ST-N MOH 42-4.5: 2015 "Requirements for the manufacture of non-sterile drugs in pharmacies" establishing the provisions (principles and rules) of Good Pharmacy Practice (GPP) for the manufacture and quality control of non-sterile extemporaneous medicines not subjected to official registration according to the current legislation and intended for retail sale through pharmacies and their structural units [24]. According to the results of the linearity study, it was found that the method was linear, the correlation coefficients r=0.9995 (1 % solution) or 0.9996 (2 % solution) did not exceed the value of the SPhU (Table 1, Fig. 1).

Table 1

The results of studying the linearity of the method for the quantitative determination of silver proteinate by thiocyanatometry

Validation parameters	Value		Requirements of the SPhU
	1 % solution	2 % solution	
b	1.0067	0.9956	–
S_b	0.0991	0.0076	–
a	|-0.4000|	0.3922	≤5.10
S_a	0.9212	0.7695	–
S_o	0.4996	0.4173	≤1.69
r	0.9995	0.9996	≥0.9924

The precision and accuracy of the method were evaluated on model mixtures prepared to determine the linearity by performing three parallel titrations of each concentration. The method is characterized by acceptable accuracy and precision. The value of the systematic error of the method (ε, %) for the quantitative thiocyanatometric determination of silver proteinate solutions was 0.26 % and 0.03 %, for 1 % and 2 % solutions, respectively. The relative confidence interval was 0.88 % and 0.74 % for 1 % and 2 % solutions, respectively. The method meets the requirements of the SPhU [16].

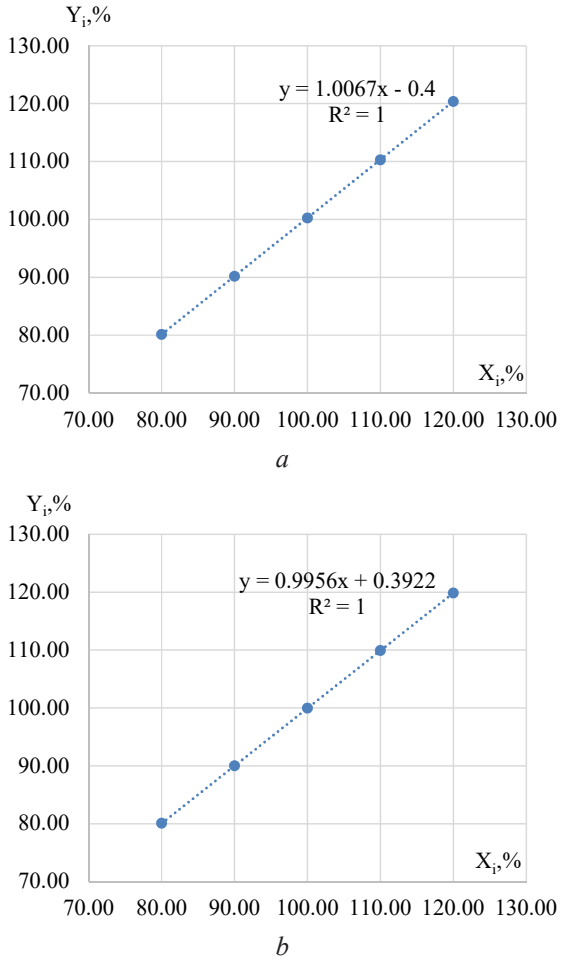

Fig. 1. Graphs of the linear dependence of the volume of the titrated solution on the concentration of silver proteinate in normalized coordinates: *a* – 1 % solution; *b* – 2 % solution

The method was tested on six batches of 1 % and 2 % solutions of silver proteinate of extemporaneous compounding. The content of silver proteinate in the solution was calculated both by the percentage of silver (according to the requirements of the pharmacopoeial monograph) and by the amount of silver proteinate in the dosage form (taking into account the requirements for the extemporaneous formulation analysis). The results of the quantitative determination of silver/silver proteinate obtained in the test solutions using thiocyanometry are shown in Table 2.

The results of the quantitative determination of silver proteinate in the dosage form were subjected to statistical processing. Metrological characteristics of the average result of the quantitative determination of silver proteinate by thiocyanatometry are given in Table 3.

To check the microbiological purity, the suitability of the method for determining the total aerobic microbial count and total yeast and mold count in the test samples in a dilution of 1:10 (Tables 4, 5) was tested.

The results of the study presented in Table 4 showed that the test samples of the extemporaneous dosage forms "Silver proteinate solution, 1.0 %" and "Silver proteinate

solution, 2.0 %" under the conditions of testing for the microbiological purity on the casein soyabean digest agar in a dilution of 1:10 did not exhibit the antimicrobial action against bacterial cultures of such microorganisms as *S. aureus* ATCC 6538, *P. aeruginosa* ATCC 9027, *B. subtilis* ATCC 6633.

The results presented in Table 5 showed that the extemporaneous dosage forms studied under the conditions of testing for the microbiological purity on Sabouraud dextrose agar in a dilution of 1:10 did not exhibit the inhibitory effect on the viability of *C. albicans* ATCC 10231 and *A. brasiliensis* ATCC 16404 fungi.

The data given in Tables 4, 5 indicate the suitability of the method for testing TAMC and TYMC of the extemporaneous dosage form samples in a dilution of 1:10. Therefore, this method can be used to study the microbiological purity of the extemporaneous dosage forms.

The methods of identification and quantification proposed were used to study the chemical resistance of silver proteinate in drops made in a pharmacy. The chemical stability studies were performed by the following indicators: description, identification and the quantitative content of the active substance. In the analysis of the microbiological purity, the pharmacopoeial two-layer method determining TAMC and TYMC was used.

The results of determining the chemical resistance and microbiological purity of the extemporaneous drug samples are given in Table 6.

It was found that the content of the active pharmaceutical ingredient in 1 % and 2 % solutions of silver proteinate remained constant for 150 days.

Incubation of the samples of the extemporaneous dosage forms (dilution 1:10) prepared on mannitol salt agar (temperature – 30–35 °C for 72 hours) and cetrimide agar (temperature – 30–35 °C for 72 hours) showed no colonies. It corresponds to the result – "no bacteria of *Staphylococcus aureus*, *Pseudomonas aeruginosa* in 1 ml of the test samples". It was found that in the samples of the extemporaneous dosage forms "Silver proteinate solution, 1.0 %" and "Silver proteinate solution, 2.0 %" analyzed no bacteria of *Staphylococcus aureus*, *Pseudomonas aeruginosa* were detected for 150 days (Table 6). Determination of the microbiological purity of the extemporaneous dosage form samples for external use by the two-layer method demonstrated that TAMC was up to 10 CFU/ml, and TYMC did not exceed 10 CFU/ml for 150 days.

Table 2

The results of the quantitative determination of silver/silver proteinate in the dosage form

No.	The volume for the quantitative determination, ml	The volume of ammonium thiocyanate spent on titration, ml	Silver found, %	Silver proteinate found, g/10 ml of the dosage form
1 % solution of the drug				
1	20.0	7.50	0.081	0.101
2		7.55	0.081	0.102
3		7.20	0.078	0.097
4		7.30	0.079	0.098
5		7.25	0.078	0.098
6		7.15	0.077	0.096
2 % solution of the drug				
1	10.0	7.40	0.159	0.199
2		7.65	0.165	0.206
3		7.55	0.163	0.203
4		7.45	0.161	0.200
5		7.70	0.166	0.207
6		7.35	0.159	0.198

Table 3

Metrological characteristics of the method for the quantitative determination of silver proteinate

ν	$\overline{x}$	S^2	S	$S_{\overline{x}}$	P	$t(P,\nu)$	$\Delta\overline{x}$	ε, %
1 % solution of the drug								
5	0.099	$5.47\cdot10^{-6}$	0.0023	0.0009	95	2.5706	0.0025	6.09
2 % solution of the drug								
5	0.202	$1.42\cdot10^{-5}$	0.0038	0.0015	95	2.5706	0.0039	4.79

Table 4

The results of checking the suitability of the method for determining the total aerobic microbial count (TAMC)

The study object	The average number of CFU in 1 ml of the sample					
	S. aureus ATCC 6538		*P. aeruginosa* ATCC 9027		*B. subtilis*ATCC 6633	
	experiment	control	experiment	control	experiment	control
	casein soyabean digest agar					
1.0 % silver proteinate solution	102	98	96	98	100	102
2.0 % silver proteinate solution	100	96	102	98	102	100

Table 5

The results of checking the suitability of the method of determining the total yeast and mold count (TYMC)

The study object	The average number of CFU in 1 ml of the sample			
	C. albicans ATCC 10231		*A.brasiliensis* ATCC 16404	
	experiment	control	experiment	control
	Sabouraud dextrose agar			
1.0 % silver proteinate solution	96	98	98	102
2.0 % silver proteinate solution	100	94	96	102

Table 6

The results of the study of the chemical resistance and microbiological purity of drugs

The quality indicator	The research conditions	The storage period						Requirements	Conformity
		Freshly prepared	Day 30	Day 60	Day 90	Day 120	Day 150		
Description	a brown liquid	+	+	+	+	+	+	a brown liquid	Meets
Identification	with the copper sulfate solution	+	+	+	+	+	+	a purple color	Meets
	with a solution of iron (III) chloride	+	+	+	+	+	+	a brown precipitate	Meets
The quantitative determination	thiacyano-metry	0.081 g/ 0.215 g	0.082 g/ 0.210 g	0.079 g/ 0.207 g	0.079 g/ 0.215 g	0.078 g/ 0.210 g	0.078 g/ 0.204 g	0.100 g/ 0.200 g	Meets
Microbiological purity									
The two-layer method (the amount of CFU/ml)	TAMC	up to 10	up to 10	up to 10	up to 10	up to 10	up to 10	10	Meets
	TYMC	up to 10	up to 10	up to 10	up to 10	up to 10	up to 10	10	Meets
Microorganisms: *Staphylococcus aureus, Pseudomonas aeruginosa*		Not found	Not found	Not found	Not found	Not found	Not found	Not found	Meets

5. Discussion

Acute rhinosinusitis is an inflammatory disease of the nasal mucosa and paranasal sinuses lasting less than six weeks. Acute rhinosinusitis is one of the most common upper respiratory tract diseases in the practice of general practitioners and otorhinolaryngologists. Silver proteinate prevents the reproduction of bacterial flora on the mucous membranes. As a result of the interaction of silver proteinate with a bacterium, a protective film is formed on the damaged mucous membrane, which helps to reduce the sensitivity of nerve endings and constrict blood vessels, slowing down the inflammatory process. Silver ions also inhibit the reproduction of various bacterial agents, are active against gram-positive and gram-negative microorganisms. In turn, the topical use of silver proteinate does not disturb the balance of normal microflora. Silver proteinate solution is safe and well tolerated by both children and adults [25].

Summarizing the review of literature sources to the quantitative determination of silver proteinate in preparations, various methods of chemical and physico-chemical analysis are used. One of them is an analytical technique known as X-ray fluorescence analysis, which is based on the stimulated emission and spectroscopy of so-called characteristic X-rays. However, the material and staff are exposed to ionizing radiation, and that is why this method cannot be used in pharmacies [26].

Also known are spectral methods like UV, Vis-spectroscopy and titrimetric methods on protein residue, such as the determination of nitrogen after mineralization with sulphuric acid. However, the aim of the study was to verify the methods for further implementation in the monograph of the State Pharmacopoeia of Ukraine, so we considered the methods proposed by the monograph of the Japanese Pharmacopoeia, with the improvement of the conditions of analysis, which can be used in laboratories of different equipment, including in the pharmacy.

Research limitations. The proposed methods for determination of 1 % and 2 % water solutions of silver proteinate can be used considering the modern equipment of pharmacies and laboratories.

Prospects for further research. The next step of the research is to include monographs for 1 % and 2 % water solutions of silver proteinate in the State Pharmacopoeia of Ukraine.

6. Conclusion

According to the results of the research, the chemical identification reactions and methods for the quantitative determination of silver proteinate in an extemporaneous dosage form used to study the chemical stability of the drug have been proposed. It has been experimentally found that the extemporaneous dosage forms “Silver proteinate solution, 1.0 %” and “Silver proteinate solution, 2.0 %” studied are chemically and biologically stable during the study period. The results of the study of the chemical stability and microbiological purity allow us to recommend pharmacies to extend the shelf life of nasal drops containing silver proteinate as an active pharmaceutical ingredient for 150 days.

Conflict of interests

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

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Data availability

Data will be made available on reasonable request.

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