

ANNOTATION

of the dissertation work on the topic

«Technology of obtaining phytosubstance from the seeds of tobacco (*Nicotiana tabacum* L.) and the creation of a dosage form on its basis»

for the degree of Doctor of Philosophy (PhD) on speciality

6D074800 – «Technology of pharmaceutical production»

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Relevance of the research topic. As part of the Comprehensive Plan for the Development of the Pharmaceutical and Medical Industry of Kazakhstan for 2020-2025, several large pharmaceutical production facilities are planned to be launched. These measures will increase the output of medicines, as well as train highly qualified specialists, create permanent jobs and strengthen the potential of domestic production. In the Address of the Head of State Kasym-Jomart Tokayev to the people of Kazakhstan «Economic Leadership of Fair Kazakhstan», the key priority for the country is to create a strong industrial base, develop new domestic industries and bring the country's economy to the level of full self-sufficiency.

The small number of enterprises for the production of essential drug substances in Kazakhstan and dependence on foreign raw materials determine the importance of considering medicinal plants as an alternative source of raw materials. This direction not only ensures pharmaceutical independence, but also allows the development of domestic production and efficient use of natural resources.

In addition, herbal medicines are leading the international pharmaceutical market. This is due to the important advantages of herbal medicines, such as naturalness, availability and absence of side effects. The production of pharmaceuticals based on domestic herbal raw materials contributes to Kazakhstan's competitiveness in the pharmaceutical sector and improves the health of the population.

There is currently a steady trend of increasing consumer demand for medicinal plants. According to the WHO, about 80% of the world's population uses natural remedies. Herbal medicines account for about 50% of the global phytopharmaceutical market and are expected to account for more than 60% of the total volume of medicines in a few years.

Recently, there has been a growing interest in the use of new species of cultivated plants with traditional traits and useful properties. One of such plant raw materials, tobacco seeds, is of particular interest to world researchers.

Research results of foreign scientists prove that tobacco seeds contain various biologically active substances such as antioxidants and flavonoids. These components may have antioxidant and antimicrobial properties, being of interest for research as antiseptic and anti-inflammatory components.

Tobacco seeds are a rich source of nutrients, including omega-3 and omega-6 fatty acids, linoleic, linolenic acid and folic acid. They also contain vitamins A, E, C, K, and essential minerals such as potassium, calcium, magnesium, zinc, copper, manganese, iron, phosphorus and sodium.

The high biological activity of tobacco seed oil is due to the bioflavonoids it contains, such as oligomeric proanthocyanidin. This compound is a powerful antioxidant that prevents cell degradation. Clinical studies have found that the antioxidant properties of tobacco seed procyanidins are 20 times stronger than vitamin C and 50 times stronger than vitamin E. In addition, tobacco seed oil acts as a synergist of vitamin P source vitamin E and inhibits lipoperoxidation of polyunsaturated fatty acids, affecting membrane phospholipids. The plant pigment chlorophyll, which determines the intense green colour of tobacco seed oil, has a regenerative effect, improves metabolism and stimulates granulation and epithelialisation of damaged tissues. It also has a hepatoprotective effect, has a positive effect on the kidneys and prevents cancer.

The use of tobacco seed oil in the treatment of skin diseases is due to its various therapeutic effects and rich composition. Tobacco seed oil has softening, anti-ageing, regenerating, rejuvenating and moisturising properties. In addition, this product has bactericidal, anti-inflammatory, antioxidant, immunostimulating, antimicrobial, choleric, tonic and diuretic properties.

To date, tobacco seed oil has been mainly used for technical purposes in the paint and chemical industries.

In recent years, more and more tobacco seed oil has appeared on the global parapharmaceutical market. Tobacco seeds are rich in polyunsaturated fatty acids and therefore are of great interest as biologically active lipid complexes for the creation of therapeutic and preventive agents.

To date, the possibility of obtaining a pharmaceutical substance from a local variety of tobacco seeds and using it as a source of medicinal raw materials has not been studied in our republic. There is not enough research in this area in Kazakhstan, and such studies are found mainly only in the works of foreign scientists. In this regard, the novelty of research in Kazakhstan is the study of the pharmacological properties of tobacco seeds, taking into account local climatic and environmental characteristics, and the development of scientific foundations for its use in domestic pharmaceutical production.

Thus, given the pharmacological properties of tobacco seed oil, an urgent issue for pharmaceutical technology is the development of domestic effective and safe natural medicines that make the skin smooth, soft and velvety, promote rapid regeneration of epidermal cells as a powerful antioxidant.

Purpose of the dissertation research: pharmacognostic and technological studies of seeds of *Nicotiana tabacum* L. as a source of raw materials, obtaining of phytosubstances and development of technology of dosage form on its basis.

Objectives of the research:

- pharmacognostic and phytochemical analysis of plant raw materials *Nicotiana tabacum* L.;
- development and standardisation of optimal technology of phytosubstances production from plant raw materials of *Nicotiana tabacum* L.;
- determination of component composition, acute toxicity and pharmacological activity of phytosubstance *Nicotiana tabacum* L.;

- development and standardisation of technology for obtaining a dosage form (ointment) on the basis of phytosubstance *Nicotiana tabacum* L.;
- development of feasibility study of ointment preparation.

Methods of research: pharmaceutical-technological,, pharmacognostic, physical, physico-chemical, pharmacological and statistical.

Objects of research: plant raw material - tobacco seeds (*Nicotiana tabacum* L.) from the *Solanaceae* family; phytosubstances obtained from plant raw material - tobacco seeds (*Nicotiana tabacum* L.); extracts obtained by ultrasonic, carbon dioxide method; oil obtained by cold pressing and ointment prepared on the basis of this oil.

Subject of the study: Analysis of the growing area, determination of the pharmacognostic characteristics of the plant raw material *Nicotiana tabacum* L. and its standardisation, development of the technology for obtaining extracts by ultrasound, carbon dioxide method, oil phytosubstances obtained by cold pressing and study of their phytochemical composition and biological activity. Study of safety and pharmacological properties of phytosubstances obtained by cold pressing. Development and standardisation of the technology of ointment production with the phytosubstance *Nicotiana tabacum* L.

The main provisions of the thesis research put to the defense:

- 1) results of pharmacognostic studies and standardisation of plant raw materials *Nicotiana tabacum* L.;
- 2) the results of development and standardisation of technology for obtaining phytosubstances from plant material *Nicotiana tabacum* L.;
- 3) the results of research of safety and pharmacological effectiveness of phytosubstance *Nicotiana tabacum* L.;
- 4) results of technological, biopharmaceutical research and preparation of ointment with phytosubstance *Nicotiana tabacum* L.

Description of the main results of the study

A comprehensive pharmacognostic and technological investigation of the plant *Nicotiana tabacum* L. as a source of medicinal raw materials was conducted. The seeds of this plant, which had not previously been the subject of research, were selected for study. Works on identifying plant raw materials of tobacco were undertaken, and an expert opinion was obtained.

The technology of collection, drying and storage of raw materials was introduced into production of «Zerde Fito» LLP (Shymkent).

The study encompassed both macroscopic and microscopic analyses of the seeds of *Nicotiana tabacum* L., culminating in the establishment of fundamental anatomo-morphological characteristics of the plant. The research findings were instrumental in determining the most efficacious extraction method for the plant raw materials, thereby ensuring the complete extraction of biologically active substances. The pharmaceutical-technological parameters identified during the study were utilised in the selection of the most appropriate extraction method, as well as in the calculation of the necessary quantity of raw materials and extractant.

In accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan, a commodity analysis of herbal raw materials was carried

out. The results of the analysis showed that the commodity science indicators of the seeds of *Nicotiana tabacum* L. meet the requirements of the regulatory documents. The raw material has undergone official procedures in accordance with the requirements of the State Inspection Committee in the agro-industrial complex of the Ministry of Agriculture of the Republic of Kazakhstan and is registered as complying with current phytosanitary regulations and free from declared quarantine harmful organisms.

Phytochemical research of the seeds of *Nicotiana tabacum* L.

In the seeds of the plant raw material, the mineral composition was studied by the method of atomic absorption spectroscopy, and the composition of amino acids and fatty acids was studied by the method of gas chromatography. The analysis of the mineral composition of the seeds of *Nicotiana tabacum* L. revealed the presence of 9 macro and micro elements, and the content of minerals such as potassium (271.4250 µg/ml), magnesium (87.30 µg/ml), and calcium (42.50 µg/mL).

The composition of amino acids in seeds of *Nicotiana tabacum* L. was investigated by gas chromatography. The analysis revealed the presence of 20 amino acids in the studied object, 10 of which are considered essential (leucine, valine, isoleucine, threonine, methionine, phenylalanine, lysine, tryptophan, ornithine, histidine).

The fatty acid composition of *Nicotiana tabacum* L. seeds was determined using a gas chromatograph (GC-1000; Chromos, Russia). Saturated fatty acids, such as palmitic and stearic acids, as well as monounsaturated fatty acid oleic acid, were detected in the seeds of the plant. The main share of fatty acids is unsaturated acids, among which linoleic acids predominate.

The investigation aimed to ascertain the safety of *Nicotiana tabacum* L. seeds. The analysis revealed that the concentration of radionuclides in the plant material does not exceed the established standards. Furthermore, the concentration of heavy metals in the seeds did not exceed the normative indicators defined in the sanitary and epidemiological requirements «Ensuring radiation».

It has been determined that the microbiological purity of plant raw materials conforms to the criteria outlined in GF RK I, vol. 1, 5.1.4, category 4 B.

The qualitative and quantitative composition of organic compounds present in the seeds of *Nicotiana tabacum* L. has been ascertained through the analysis of a chromatogram obtained by high-performance liquid chromatography. This analysis has revealed the presence of both polar and non-polar substances, thereby indicating their complete separation. The chromatogram obtained at an absorption wavelength of 254 nm in a 70% ethanol extract revealed the presence of polar compounds within the first 6 minutes and the subsequent 10 to 18 minutes. The identification of flavonoids, glycosides and sugars was predominantly focused in this region. The range of 20 to 25 minutes was characterised by the presence of non-polar compounds, including monoterpenes, sesquiterpenes, aliphatic compounds and fatty substances.

Standardisation of *Nicotiana tabacum* L. seeds was conducted, and quality indicators for the plant raw material were developed.

Determination of the stability and shelf life of tobacco seeds was conducted under conditions of long-term storage for 24 months. During the experiment, in three series of tobacco seeds, no significant changes were revealed, with controlled indicators remaining stable throughout the 24-month storage period. The findings of this study thus established a 24-month (2-year) storage period for plant raw materials (seeds of *Nicotiana tabacum* L.). Subsequent studies focused on the development of technology for the isolation of biologically active substances from the seeds of *Nicotiana tabacum* L. Dense extracts were obtained by ultrasonic extraction and superextraction.

A study was conducted on the development of technology for the extraction of biologically active substances from the seeds of *Nicotiana tabacum* L. The study involved the extraction of dense extracts by ultrasonic extraction and supercritical carbon dioxide extraction, as well as tobacco oil by cold pressing.

A comparative analysis of the technologies of obtaining extracts and tobacco oil, as well as their yield, was then carried out. The analysis yielded the following results: an extraction yield of 0.35% was obtained after 8 hours of ultrasonic extraction; 0.72% was obtained after 11 hours of extraction with carbon dioxide; and 7.25% was obtained after 1 hour of cold pressing.

The qualitative parameters of herbal pharmaceutical substances obtained from tobacco seeds were determined in accordance with the requirements of regulatory documents.

A comparative analysis of the component composition of plant substances obtained from the seeds of *Nicotiana tabacum* L. was conducted, revealing 31 components in the ultrasonic extract, 41 components in the supercritical extract, and 49 components in the tobacco oil. The study concluded that the content of biologically active compounds is the highest in *Nicotiana tabacum* L. oil.

In the course of the research, the seeds of *Nicotiana tabacum* L. were subjected to a process of extraction of the plant pharmaceutical substance, with consideration being given to the technological yield of the substance and the full extraction of biologically active compounds. The oil from *Nicotiana tabacum* L. was selected for further research, and the experimental technology of obtaining oil from the seeds of *Nicotiana tabacum* L. was implemented at the enterprise «Fitoleum» LLP. The identification, solubility, relative density, refractive index, oxidation number, saponification number, iodine number, foreign oil content, free fatty acids, hydroxyl number, microbiological purity, packaging and quantitative content of γ -tocopherol in plant pharmaceutical substance from seeds of *Nicotiana tabacum* L. were determined. The quantitative content of γ -tocopherol in *Nicotiana tabacum* L. oil was determined using an Agilent 7890B gas chromatograph equipped with an Agilent 5977A dual channel mass spectrometer.

The present study constitutes an inaugural investigation into the qualitative indicators of *Nicotiana tabacum* L. oil, with the objective of incorporating these indicators into regulatory documentation as quality markers for the aforementioned herbal pharmaceutical substance.

The study encompassed the analysis of the component composition of *Nicotiana tabacum* L. oil, utilising the gas chromatography-mass spectrometry

method. This method revealed the presence of 49 components within the plant pharmaceutical substance. The investigation further identified the following main pharmacologically active compounds: Vitamin E (2.08%), Stigmasterol (0.87%), γ -Sitosterol (1.33%), Stigmasterol-3,5-dien (0.63%), Cholesta-6,22,24-triene, 4,4-dimethyl (0.30%), Squalene (0.90%).

The functional groups in the composition of the plant pharmaceutical substance *Nicotiana tabacum* L. were determined by Fourier transform Raman spectroscopy, including aliphatic series (731 cm⁻¹); C-O-C bonds of esters and esters (849, 875 and 920 cm⁻¹); and carboxylic acids (976 cm⁻¹). cm⁻¹); aromatic rings (1072 and 1079 cm⁻¹); salts of carboxylic acids (1270 and 1304 cm⁻¹); methyl and methylene groups (1439 cm⁻¹); C=C bond (1658 cm⁻¹); aldehyde group (1748 cm⁻¹).

The fatty acid composition of the *Nicotiana tabacum* L. plant pharmaceutical substance was determined using gas chromatography, with the total content of saturated and unsaturated fatty acids determined to be 11.7% and 85.5%, respectively. Of the unsaturated fatty acids, linoleic acid (71.73%) and oleic acid (13.77%) were predominant, while among the saturated fatty acids, palmitic acid (8.06%) was the most abundant.

Subsequent studies on the safety, harmlessness, and efficacy of the *Nicotiana tabacum* L. plant pharmaceutical substance were conducted, and the pharmacological activity of tobacco oil was demonstrated to be significant in terms of antioxidant, anti-inflammatory, and antimicrobial properties.

Chronic toxicity studies established that the plant pharmaceutical substance has low toxicity (Class V – slightly toxic substances), and furthermore, morphological and anatomical studies of animal organs and tissues revealed no toxic effects from the substance. The results confirm the potential use of the *Nicotiana tabacum* L. plant pharmaceutical substance as a biologically active pharmaceutical substance (BAPS).

The stability testing and shelf life determination of the *Nicotiana tabacum* L. plant pharmaceutical substance were conducted over a 24-month period, encompassing a comprehensive set of parameters. These included description, identification, qualitative reactions, the presence of foreign impurities, weight loss on drying, quantitative determination, and microbiological purity.

The study found that the main quality indicators of the plant pharmaceutical substance remained stable during the long-term storage period, and the shelf life was determined to be 24 months (2 years).

To analyse the market for soft medicinal forms used in the Republic of Kazakhstan, a study of the range of pharmaceutical products registered in the State Register of the Republic of Kazakhstan was conducted. The study revealed that 92% of all registered soft medicinal forms on the Kazakh pharmaceutical market are imported from neighbouring and distant foreign countries. The register of medicinal products in Kazakhstan includes 417 soft medicinal forms, accounting for only 5% of the total number of registered pharmaceutical products.

Among soft medicinal forms, ointments hold the leading position (39%), followed by creams (28%), gels (29%), liniments (2%), and pastes (2%).

It is evident that no ointments containing the *Nicotiana tabacum* L. plant pharmaceutical substance are registered in the State Register of Medicinal Products

of Kazakhstan. Furthermore, such pharmaceutical forms are neither produced in Kazakhstan nor imported by foreign pharmaceutical manufacturers.

The domestic manufacturers of soft medicinal forms that are available on the Kazakhstani market include JSC «Nobel AFF» (2.4%), LLP «Shansharov-Pharm» (1.91%), and LLP «Pharmacy 2010» (2.4%).

A research study was conducted to develop the composition and technology for an ointment containing the plant pharmaceutical substance *Nicotiana tabacum* L. A range of bases that are widely applied in industrial pharmaceutical technology were used to prepare 10 laboratory samples of ointment with different combinations of excipients. The most optimal base was selected by comparing the ointment samples based on characteristics such as consistency, greasiness, spreadability, and release rate of the active ingredient. Following a thorough evaluation of the study's findings, it was determined that an emulsion-based ointment was the most suitable option due to its exceptional technological properties.

The quality indicators of the ointment were determined in accordance with Order No. MH RK-20 of the Ministry of Health of the Republic of Kazakhstan, dated 16 February 2021, and the general monograph of the State Pharmacopoeia of the Republic of Kazakhstan, Volume I, Section 1, «Soft Dosage Forms for Topical Application». The quality specification for ointments containing the *Nicotiana tabacum* L. plant pharmaceutical substance, as well as permissible deviation limits, were established, and it was determined that the quality indicators of ointments with the *Nicotiana tabacum* L. plant pharmaceutical substance comply with the aforementioned requirements.

The technical and economic indicators of the ointment formulated with the *Nicotiana tabacum* L. plant pharmaceutical substance were calculated. In the process of preparing the techno-economic justification (TEJ) for the production of the ointment, the total cost per unit of production, manufacturing cost, administrative and commercial expenses were determined. It was established that the payback period for the project is 3 years and 5 months, with a net profit margin of 30%. The techno-economic justification confirms the feasibility and profitability of industrial-scale ointment production.

Justification of scientific novelty

For the first time in Kazakhstan:

- pharmacognostic and pharmaceutical-technological study of plant raw materials *Nicotiana tabacum* L., belonging to the *Solanaceae* family, quality and stability indicators were determined and standardised;
- extraction of extract from plant raw material *Nicotiana tabacum* L. by methods of extraction by ultrasound and carbon dioxide in pre-critical conditions, as well as oil from plant raw material by cold pressing method was carried out;
- oil by cold pressing method with a wide range of biologically active compounds and expressed antimicrobial, antioxidant and anti-inflammatory activity was obtained, which was selected as an optimal phytosubstance;
- safety and efficacy studies of the phytosubstance *Nicotiana tabacum* L. were carried out, and in vitro and in vivo studies proved the obvious antimicrobial antioxidant and anti-inflammatory activity of the phytosubstance;

- the optimal technology was developed and qualitative parameters of the ointment with phytosubstance *Nicotiana tabacum* L. were evaluated, the shelf life was determined;

- scientific novelty of the study is confirmed by patents for utility model registration number No. 35232 dated from 04/06/2020 «Method of obtaining carbon dioxide extract from tobacco seeds (*Nicotiana tabacum* L.)» and registration number No.9236 dated from 15/12/2023 «Method of obtaining oil from tobacco seeds *Nicotiana tabacum* L.». RSE «National Institute of Intellectual Property» (Appendixes D, E).

Practical significance of the research:

- the technology of collection and harvesting of plant raw materials *Nicotiana tabacum* L. Plant raw materials were identified by certificate No.64-02, 14/02/2019 from the akim of Masak rural district of Yenbekshikazakh district of Almaty region E. Nurmakhanov and IE «Chebotova A. N.» (Appendix B);

- the state institution of territorial inspection «Committee of State Inspection in the agro-industrial complex of the Ministry of Agriculture of the Republic of Kazakhstan» conducted a phytosanitary examination of *Nicotiana tabacum* L. plant raw materials for the presence of harmful quarantine organisms, phytosanitary certificate number AA No. 1976202 (Appendix A);

- the technology of collecting and harvesting of plant raw materials *Nicotiana tabacum* L. of «Zerde-Fito» LLP was introduced (Appendix V);

- the technology of collection and harvesting of plant raw materials *Nicotiana tabacum* L. was introduced in JSC «South Kazakhstan Medical Academy», at the Department of Drug Technology and Pharmacognosy (Appendix P).

- developed a method of obtaining oil from plant raw materials *Nicotiana tabacum* L. by cold pressing method and introduced draft ND for pilot production of «Ardo Fito» LLP (Appendix J);

- the method of extraction from plant raw materials *Nicotiana tabacum* L. by carbon dioxide extraction in pre-critical conditions was developed and the technological regulations were introduced for pilot production of PLP «Zhanafarm» LLP (Appendix G);

- optimal technology for obtaining phytosubstances from the seeds of tobacco (*Nicotiana tabacum* L.) introduced in the State Budgetary Educational Institution «Kazakhstan-Russian Medical University», Department of Pharmacy (Appendix R);

- the optimal composition and technological scheme of ointment production with phytosubstance *Nicotiana tabacum* L. was developed and implemented by 'DOSFARM' LLP (Appendix L);

- the project of ND ointment obtained on the basis of phytosubstance *Nicotiana tabacum* L. has been developed (Appendix M);

- draft technological instruction for the production of ointment based on phytosubstances *Nicotiana tabacum* L. and approved by «DOSFARM» LLP (Appendix N);

- the project of feasibility study of ointment production with obtaining phytosubstance from the seeds of *Nicotiana tabacum* L. and the addition of phytosubstance introduced in the Department of Organisation, Management and

Economics of Pharmacy and Clinical Pharmacy NAO «S.D. Asfendiyarov KazNMU» (Appendix O).

Author's personal contribution

All experimental studies presented in the thesis work were performed personally by the author, which confirms his significant contribution to the development of pharmaceutical science.

The doctoral student independently reviewed and analysed the domestic and foreign literature, conducted experimental studies in accordance with the set tasks. This is confirmed by the results of research obtained in laboratory and production conditions using modern equipment and literature.

Reliability and validity of the research results are confirmed by the fact that the performed works are aimed at solving the actual problem of pharmaceutical science and practice on the development of new drugs for domestic production, the performance of studies in modern research centres and the development of draft regulatory documents.

Conclusions

The present dissertation work is devoted to the complex pharmacognostic and pharmaceutical-technological research, standardisation, as well as proper development of plant pharmaceutical substance from raw materials *Nicotiana tabacum* L. A deep study and introduction of new types of medicinal plant raw materials, as well as the development of plant pharmaceutical preparations on its basis, is an important direction in the production of import-substituting medicines by creating competitive drugs.

A particularly promising source of biologically active substances is the plant *Nicotiana tabacum* L., cultivated in the territory of Kaztay Utlarakov village of Masak rural district of Yenbekshikazakh district of Almaty region, which has a sufficient raw material base for industrial use.

The collection and harvesting of *Nicotiana tabacum* L. plant raw materials was conducted in accordance with the fundamental principles of the «Good Agricultural and Collection Practice» (GACP) requirements, as well as a pharmacognosy analysis of *Nicotiana tabacum* L. seeds. In order to determine an effective extraction technology for maximum retrieval of biologically active substances, the pharmaceutical-technological parameters of the plant raw materials were studied.

The qualitative and quantitative analysis of *Nicotiana tabacum* L. raw materials revealed the presence of flavonoids, alkaloids, polysaccharides, coumarins, free organic acids, and phenolic compounds. Furthermore, studies of the mineral and amino acid composition of the medicinal plant raw material were conducted.

Utilising the findings from these analyses, the quantitative content of biologically active substances and the specific compounds of interest within *Nicotiana tabacum* L. seeds were determined. The seeds were found to contain vitamin A at 9.7%, vitamin E at 12.6%, and other notable nutrients. Furthermore, the qualitative characteristics and quality indicators of *Nicotiana tabacum* L. seeds were identified. The findings of a long-term stability study of *Nicotiana tabacum* L. plant raw materials at a temperature of (25 ± 2) °C and a relative humidity of (60 ± 5) % revealed that the shelf life is 24 months.

A comprehensive study was conducted on the chemical composition and biological activity of plant pharmaceutical substances derived from *Nicotiana tabacum* L. seeds. The extraction process utilised both ultrasonic extraction and supercritical carbon dioxide extraction methods, in conjunction with cold pressing of tobacco oil.

The research findings indicated that the plant pharmaceutical substance obtained by cold pressing exhibited antiviral, antioxidant, and anti-inflammatory activity. This substance was then selected for further development as an ointment.

A comprehensive quality specification for the plant pharmaceutical substance obtained from *Nicotiana tabacum* L. seeds was formulated, encompassing the following parameters: description, vitamin E identification, solubility, loss on drying, heavy metal content, microbiological purity, quantitative determination of vitamin E, packaging, labeling, transportation, storage conditions, shelf life, and key pharmacological effects.

Following extensive testing over a prolonged period (at a temperature of 25 ± 2 °C and humidity of 60 ± 5 %), a shelf life of 2 years was determined for three batches. The validation of the quantitative determination method for vitamin E was conducted, with assessment of validation characteristics such as linearity, specificity, accuracy, and reproducibility.

In the study of the chronic toxicity of the plant pharmaceutical substance *Nicotiana tabacum* L., it was determined that it belongs to Class V of low-toxicity substances. Morphological and anatomical studies of the organs and tissues of animals revealed no toxic effects of the substance.

Research was conducted on the formulation and technology for producing an ointment containing the plant pharmaceutical substance *Nicotiana tabacum* L. Based on the nomenclature of bases widely used in industrial technology and various combinations of excipients, 10 laboratory samples of the ointment were prepared.

To select the optimal base, the ointment samples were compared in terms of consistency, greasiness, application properties, and drug release rate. Based on technological characteristics, the ointment prepared on an emulsion base was selected.

The quality indicators of the ointment comply with the requirements of the Order of the Ministry of Health of the Republic of Kazakhstan dated February 16, 2021, No. MH RK-20, and the General Monograph of the State Pharmacopoeia of the Republic of Kazakhstan I, Vol. 1, «Soft Dosage Forms for Topical Use». The quality specification for the ointment containing the plant pharmaceutical substance *Nicotiana tabacum* L. and permissible deviation limits were established. It was confirmed that the quality indicators of the ointment comply with the specified requirements.

The techno-economic analysis was conducted on the ointment containing the plant pharmaceutical substance *Nicotiana tabacum* L., and the results were then used to calculate the cost-effectiveness of its production. The cost per unit of product, the manufacturing cost, administrative and commercial expenses were determined in the cost-effectiveness analysis. It was established that the payback period of the project

is 3 years and 5 months, with a net profit of 30%. The economic feasibility study thus confirms the profitability of industrial-scale ointment production.

Approbation of the results of the dissertation

The main results of the dissertation research are published and presented in the materials of the VI International Scientific Conference of Young Scientists and Students «Prospects for the development of biology, medicine and Pharmacy», organized by the Foundation of the First President of Kazakhstan – Elbasy and the South Kazakhstan Medical Academy (Shymkent, 2018), the International Scientific and Practical Conference «European Research: Innovations in Science, Education and Technology» (London, 2019), the international scientific and practical conference «Modern Aspects of Medicine and Pharmacy: Education, Science and Practice» (Shymkent, 2019), International scientific and practical conference «Akanov Readings: The Role of primary health care in achieving universal health coverage» (Almaty, 2019), International Scientific Conference of young scientists and students «Prospects for the development of biology, medicine and Pharmacy» (Shymkent, 2020).

Publications

The results of the dissertation research have been published in 17 scientific papers, including:

- in an article in a journal included in the international database Scopus – 1;
- abstract in an International journal included in the Web of Science Core Collection database – 1;
- in publications recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan – 7;
- abstracts in the materials of international scientific and practical conferences – 5;
- patent for invention and utility model – 2;
- copyright certificate – 1.

Scope and structure of the dissertation

The dissertation work covers 178 pages of machine text in a computer set, 61 tables, 47 figures, 163 domestic and foreign literature, as well as applications. The work consists of an introduction, a literature review, materials and methods, 4 sections of the experimental part, conclusions by sections and conclusions.