ANNOTATION

dissertation work on the topic: **"Experimental justification for the use of a new drug in ophthalmology",**

for the degree of Doctor of Philosophy (PhD) in the specialty 8D10103-"Medicine"

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Relevance of the research topic

As part of the implementation of the National Project "Healthy Nation" for 2021-2025, the main task of the domestic pharmaceutical industry is import substitution, which consists in the development and creation of domestic drugs with a full production cycle in the country and bringing the share of domestic pharmaceutical products from 17% to 50%.

As part of the implementation of the Comprehensive Plan for the Development of the Pharmaceutical Industry for 2020-2025, the issue of organizing the production of medicines using medicinal plants growing on the territory of the Republic of Kazakhstan has received the status of a state priority.

Currently, 225 out of 7546 drugs for the treatment of eye diseases are registered in the country, which are produced by 47 pharmaceutical companies from different countries. The range of industrially produced ophthalmic preparations is very wide and is represented by 48 active substances.

In clinical practice, infections of the skin of the eyelids, conjunctiva, and lacrimal organs are common. Anti-infectives used to treat eye infections (S01A) account for 24.89% (56) of all registered ophthalmic drugs, of which 46 are prescription drugs.

In recent years, dry eye syndrome has become one of the most common chronic diseases. This pathology occurs in 18-67% of adults worldwide. Dry eye syndrome develops through two main mechanisms: decreased production and increased evaporation of tear fluid. At the heart of the pathogenesis of this disease is a violation of the stability of the tear film. The problem of diagnosis and treatment of patients with dry eye syndrome has become increasingly important for many years. Destabilization of the tear film leads to a cascade of pathological changes, including inflammation, resulting in the production of pro-inflammatory cytokines.

The search for promising medicinal plants as sources of biologically active substances and the development of herbal pharmaceutical substances based on them is relevant.

In this regard, of particular interest is the safflower plant (Carthamus Tinctorius L.), which grows on the territory of the Republic of Kazakhstan, is a valuable source of biologically active compounds, many of which are used in traditional medicine and the food industry. As a result of phytochemical studies, 85 complexes were identified. It was revealed that it contains a very large amount of linoleic acid - 63.7%, tricosan - 93% and vitamin E - 3.3%.

Based on the foregoing, the pharmaceutical development and pharmacological study of drugs from safflower extract in ophthalmology is promising.

Purpose of the study: Experimental study of the use of ophthalmic dosage forms of safflower extract.

Research objectives:

1) pharmaceutical manufacturing of ophthalmic dosage forms based on safflower extract

2) experimental determination of the safety and toxicity of dosage forms for the eyes based on safflower extract

3) study of the antibacterial activity of ophthalmic dosage forms of safflower extract in vitro

4) determination of the pharmacological action of ophthalmic dosage forms of safflower extract

Objects of research: the object of research of this dissertation work are 92 rabbits of the "Chinchilla" breed, weighing 2500-3500 grams, without external signs of the disease.

Research methods: pharmaceutical, microbiological, pharmacological, ophthalmological, immunological and statistical methods.

Scientific novelty: Based on the results of scientific work, 2 patents of the Republic of Kazakhstan for a utility model were obtained: 1. Method for obtaining eye drops from the seeds of tinting safflower (Carthamus Tinctorius L.) (Patent No. 6168 dated 06/25/2021); 2. Method for obtaining an eye emulsion from safflower flowers (Carthamus Tinctorius L.) (09/16/2022 Patent No. 7448). An application for a patent for an invention has been submitted: A device for immobilizing laboratory rabbits with a special block for fixing the ears Reg. Application No. 2022/0488.1 dated 10.08.2022. The following copyright certificates have also been obtained on entering information into the state register of rights to objects protected by copyright:

- Analysis of the level of interleukins in the simulation of the "dry eye" syndrome in experimental animals after treatment with a new innovative drug from safflower (Carthamus tinctorius L.) No. 26659 dated 05/31/2022.
- Study of the antimicrobial effect of an eye emulsion based on safflower flowers (Carthamus tinctorius L.) No. 29057 dated 09/27/2022;
- Determination of the component composition of the eye emulsion from safflower extract No. 29058 dated 09/27/2022;
- Histomorphological features of the eyes of laboratory animals after applying an eye emulsion from safflower extract No. 29397 dated 12/10/2022.
- The study of intraocular pressure indicators after the use of developed dosage forms based on safflower extract (Carthamus Tinctorius L) Copyright certificate No. 29589 dated 10/20/2022.

The main provisions of the dissertation research submitted for defense:

- pharmaceutical preparation of medicines for the eyes based on CO2-extract of safflower

- substantiation of the effectiveness of antimicrobial treatment of dry eye syndrome by pharmacological studies.

Practical significance of the research: The significant contribution of the dissertation work to science was confirmed by the implementation of the results obtained in production and the educational process from the point of view of the possibility of practical application: the reliability of the results was introduced into the production proposed by JSC "Scientific Center for Anti-Infectious Drugs" and at the Departments of Pharmacology and Ophthalmology of Moscow State University. M.V. Lomonosov. As well as the introduction into the educational process of the Department of Clinical Pharmacology of the Kazakh National Medical University. S.D. Asfendiyarov.

Conclusion.

1. The components of ophthalmic dosage forms with safflower extracts are physically and chemically compatible. Based on the fat extract obtained by subcritical CO2-extraction, 5 different models of ophthalmic ointment were made, the optimal composition, technological process and hardware design were developed. The antimicrobial activity of the ophthalmic ointment was studied by a serial method in the laboratory of JSC "Scientific Center for Anti-Infectious Drugs". For the first time, the composition and technological process of eye drops based on CO2 - an extract of safflower seeds under supercritical conditions (17 MPa, 31°C, 60 min) were compiled. The quality index of the obtained preparation was studied in accordance with the requirements of the Ministry of Finance, the EP of the RK and its compliance was proved. It was established that the extract contains a large amount of vitamins A, E. A feasibility study for eye drops was carried out.

2. The study of the component composition of CO2-extract of safflower (Carthamus Tinctorius L.) was carried out by gas chromatography (KR MF I, vol. 1, 2.2.28) with mass spectrometric detection method (Agilent 7890A/5975C).), resulting in linoleic acid (63.7%), tricosan (93%) and others. It is established that there are biologically active substances. Linoleic acid has been proven to be highly effective in dry eye syndrome.

3. During the experiment, it was found that the obtained ophthalmic preparations did not have a cytotoxic effect in vitro and did not show a local allergic effect on rabbits and did not have a toxic effect in vivo. Intraocular pressure in experimental animals after application of ophthalmic ointment, eye drops and ophthalmic emulsion in Friedman's intragroup analysis with Bonferroni correction was $p=0.453$; $p=0.370$ and $p=0.577$ showed statistically insignificant differences.

The median value in the group after eye drops with silver nanoparticles were changes from 0 to 1 hour, statically significant 20 (19-21) and 21 (21-22) (Friedman's test, $p=0.01$), in the group after application of eye drops with gold nanoparticles - differences between eye pressures were statistically significant from 0 to 24 hours 21 (20-21) and 23 (22-24) (Friedman's test, $p<0.001$), respectively, from 0 to 6 hours was 23 (22-24) (Friedman's test, $p=0.06$).

4. As a result of studying the antimicrobial effect by disk diffusion and serial dilution methods, the effect of the in vitro eye emulsion was the highest among 5 types of eye preparations.

5. When comparing the indicators of the groups of the Preparation and Cationorm, higher median values were found for the indicators "Total tear production" and "Stability of the tear film", as well as lower ones for "Staining of the epithelium of the ocular surface with lyssamine green solution according to the vanBijsterveld scale" in the group of the Preparation, but statistically there were significant differences only on days 7, 14 and 21 in terms of "Total tear production" (Mann-Whitney test, p=0.036; p=0.0362 and p=0.015; respectively).

When analyzing the production of the anti-inflammatory cytokine IL-10 in the lacrimal fluid of animals with the DES model against the background of a decrease in tear production, despite the reduced level of this indicator by 1.12 times during eye emulsion therapy, no significant differences were found in comparison with the control group of animals. And in animals with DES model against the background of meibomian gland dysfunction during therapy with Eye emulsion, the level of IL-10 production was significantly lower (P = 0.02) by 1.5 times compared with the control group of animals.

The results of the study showed significant differences in the level of production of the chemokine IL-8 in animals with DES and during therapy with Eye emulsion and Cationorm, both in animals with the DES model against the background of a decrease in tear production, and in the group of animals with the DES model against the background of dysfunction of the meibomian glands (table 1 or figure 1.2). Thus, in animals with DES, against the background of a decrease in tear production, the level of IL-8 production was 10.03 pg/ml, which exceeds the level of this indicator in comparison with the control group of animals by 1.5 times (P = 0.007). And during therapy with eye emulsion in animals with a DES model, against the background of a decrease in tear production, the level of IL-8 was significantly lower (P = 0.03) by 2.4 times compared with control animals, and also 3.6 times lower in compared with the group of animals with confirmed DES (P < 0.0001). A similar picture was observed in the group of animals with the DES model against the background of meibomian gland dysfunction, where there was also a significant (P = 0.0005) increase in IL-8 in animals with confirmed DES by 1.6 times and a significant decrease (P = 0, 02) by 2.4 times this indicator during therapy with eye emulsion compared to the control. Therapy with Cationorm also led to a decrease in IL-8 both in animals with DES against the background of a decrease in tear production and against the background of dysfunction of the meibomian glands, but not in comparison with the control, but in comparison with animals with confirmed DES (P = 0.001).

Personal contribution of the author. All the results of the dissertation work were obtained by the author independently, which indicates the personal contribution of the researcher to science in the field of ophthalmopharmacology.

The correctness of the results formulated in the dissertation, the basic rules to be defended, conclusions and conclusions is fully confirmed by the results of our own research, based on a large number of experimental materials, in laboratory and production conditions, using modern devices. and precise measurement methods, as well as by comparing them with literature data.

Approbation of work.

The basic rules for conducting dissertation work are described and published in the materials of international scientific and practical conferences: X All-Ukrainian scientific and practical conference with the participation of international experts in the field of clinical pharmacology. Vinnitsa, Ukraine, November 7-8, 2019; VIII scientific and practical conference with international participation "Priorities of pharmacy and dentistry: from theory to practice" in memory of K.A.Abdullin. November 11, 2019; III Central Asian Congress "Current state of clinical pharmacology and development prospects" Bishkek, Kyrgyzstan, October 28-29, 2021

Information about publications.

Based on the results of the research, 23 scientific papers were published, including 1 article in an international peer-reviewed scientific journal included in the Scopus (52 percentile) and Web of Science Core Collection databases; 4 articles in journals recommended by the Committee for Quality Assurance in Education and Science of the Republic of Kazakhstan; 8 articles and abstracts in collections of international conferences (Russian Federation, Ukraine, Kazakhstan); Received 2 monographs, 2 patents for a utility model, positive results for 1 patent for an invention, 5 copyright certificates on entering information into the State Register of rights to objects protected by copyright.

The volume and structure of the dissertation.

The dissertation work includes 124 pages of machine text, 45 tables, 31 figures, a bibliography of 157 literary sources and 17 appendices. The work consists of an introduction, a literature review, a chapter on research materials and methods, three chapters of individual studies, a conclusion.