SUMMARY

to the doctoral thesis "Pharmaceutical development of a combined drug with iodine adducts"
for the degree of Philosophy Doctor (PhD)
on specialty 6D074800 – Technology of Pharmaceutical Production
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Relevance of the research tittle

The state program for the development of health care of the Republic of Kazakhstan "Densaulyq" for 2025-2025 is aimed at strengthening public health, ensuring the availability of medical and pharmaceutical services, as well as the creation and introduction of competitive import-substituting medicines.

One of the tasks of pharmaceutical science is to purposefully search for new highly effective and safe drugs. The discovery of antibiotics was a major scientific achievement, the significance of which is difficult to overestimate. However, the formation of strains of pathogens resistant to their action, the emergence of multi-resistant forms, the emergence of new types of dangerous pathogens casts doubt on the ability to effectively treat infectious diseases.

Resistance is the result of a number of factors, one of which is the excessive use of antibiotics and their inappropriate use for the treatment of a number of diseases. It should be noted that most of the drugs used now are licensed more than ten years ago. The search and development of new antibacterial drugs continues, but the number of newly registered antibiotics is small, which is associated with financial and time costs.

Thus, the need for new drugs determines the relevance of finding and creating new antimicrobials.

Goal of the study:

Development and investigation of iodine adduct substance D1 as well as pharmaceutical development of a combination drug based thereon.

Objectives of the study:

1. Study of the antimicrobial activity of the original coordination compounds of iodine No. 1-9, determination of samples promising for the development of a new drug;
2. Quality control, determination of conditions and shelf life of iodine adduct substance D1;
3. In vitro efficacy and safety study of iodine adduct substance D1;
4. Development of rational composition and technology of combined dosage form with iodine adduct D1;
5. In vivo efficacy and safety study of the D1 iodine adduct formulation;
6. Conduct quality control and stability study of combined drug product with iodine adduct D1.

Objects of study: coordination compound (adduct) substance of iodine D1 and a combined drug containing iodine adduct and antibiotic chloramphenicol.

Research methods: The development of the technology of laboratory synthesis of study objects (substance D1 and combined drug), the determination of physicochemical properties was carried out at the test center of SCAID (Scientific Center of anti-infectious drugs), accredited according to ISO/IEC 17025-2019 standards (accreditation certificate No. KZ.T.02.1252) and GLP (GLP accreditation certificate dated 12.06.2016).

Scaling of D1 substance and combined drug product manufacturing technology, release of D1 substance batches, determination of pharmaceutical manufacturing process parameters were carried out in accordance with GMP Principles. The safety (toxicology, mutagenicity, cytotoxicity) and efficacy of substance D1 and the combined drug product were studied in accordance with the GLP Principles.

Statistical processing was performed using Statistica 6.0. Software.

Scientific novelty

For the first time by results of a research of antimicrobic activity of original coordination compounds of iodine No. 1-9 concerning 3 museum sensitive strains of *Staphylococcus aureus* ATCC 6538-P, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027, 2 of museum multi-drug resistant strains of *Staphylococcus aureus* ATCC-BAA-39, *Escherichia coli* ATCC-BAA-196 and 1 clinical multi-drug resistant strain of *Pseudomonas aeruginosa* TA2, 3 most perspective connections were revealed: sample No. 5 di-triiodo-3,3 "-dithio-bis-2-aminopropionic acid), sample No. 6 α,α"-di-amino- β,β´"-diphenylpropionic acid monoiodide and sample No. 8 di-triiodide di-2,6-diaminohexanoic acid monohydrate, which showed the greatest antimicrobial activity against sensitive and multi-drug resistant microorganisms.

For the first time, the results of the study of the joint effect of coordination adducts of iodine No. 5, No. 6 and No. 8 with antibiotics revealed synergistic antimicrobial effects of compound No. 8 with antibiotics chloramphenicol, gentamicin and tetracycline, both for Gram-negative multiresistant strains - *E. coli* and *P. aeruginosa*, and for Gram-positive strains - *S.aureus* and *S.pneumoniae*.

For the first time, according to the totality of the results of spectral research methods (UF and IR spectroscopy), it was established that the binary system contains substance D1 and the antibiotic chloramphenicol, there is no data on possible complexation.

For the first time, the technology of obtaining the coordination compound of iodine No. 8 "Substance D1" was developed.

The physicochemical and technological characteristics of substance D1 were studied; quality indicators were developed and substance D1 was standardized.

According to in vitro and in vivo toxicity studies, substance D1 is classified as a class 4 toxicity according to the international GHS toxicity classification system and has no mutagenic effect.

For the first time, an optimal composition and technology for the production of a combined drug (gel) containing substance D1 and the antibiotic chloramphenicol has been developed; stability of substance D1 in combination with antibiotic and excipients has been proven.

The developed combined drug with iodine adduct D1 and antibiotic chloramphenicol exhibits high antimicrobial and wound-healing activity in vivo, under conditions of alloxan-induced experimental diabetes it exceeds the effect of preparations of comparison of ointments "Levomecol" and "Betadin," reducing the wound healing time by 1.5 times; does not have a locally irritating and allergying effect.

Physicochemical and technological characteristics were studied, quality indicators were developed and the combined antimicrobial gel was standardized.

The practical significance of the study

- for the first time, the coordination compound of iodine No. 8 di-triiodide di-2,6-diaminohexanoic acid monohydrate) is recommended as a promising substance for the development of antimicrobial drugs;
- for the first time, the technology of obtaining D1 pharmaceutical substance was developed and introduced into production on the basis of the JSC Scientific Center for Anti-Infectious Drugs;
- for the first time, a technology for preparing a combined antimicrobial gel containing D1 substance and the antibiotic chloramphenicol was developed and introduced into production on the basis of the JSC Scientific Center for Anti-Infectious Drugs;
- draft normative document on drug product quality for substance D1 and for combined antimicrobial gel have been developed;
- technological instructions for substance D1 and combined antimicrobial gel have been developed.

Implementation of research results in practice

The results of the work were introduced into the pilot production of the Scientific Center for Anti-Infectious Drugs JSC (Act on Introduction of 2021), as well as into the educational process of the Federal State-Financed Educational Institution of Higher Professional Education Saint-Petersburg State Chemical and Pharmaceutical University of the Ministry of Health of the Russian Federation (Act on Introduction of 2018).

The work formed the basis of methodological recommendations on the use of adducts in technology and pharmaceutical development.

The main provisions of the dissertation research submitted to the defense:

Possibility and perspective of using iodine adducts in pharmacy.

The structure of substance D1, the results of studying physical, physicochemical and technological characteristics, as well as the synergistic effect of substance D1 and the antibiotic chloramphenicol in the composition of a combined antimicrobial agent (gel).

Composition and technology of combined drug containing substance D1 and antibiotic chloramphenicol.

Results of Safety and Specific Pharmacological Activity of Substance D1 and Combination Drug Containing Substance D1 and Antibiotic Chloramphenicol.

Approbation of work

The main materials of the dissertation work were reported and discussed at 5 international conferences:

- International scientific conference "Topical Problems of modern science" (2017, Warsaw, Poland);

- VI international scientific conference of young scientists and students, initiated by the Foundation of the First President of Kazakhstan - Elbasy and the South Kazakhstan Medical Academy, "Prospects for the development of biology, medicine and pharmacy" (2018, Shymkent, Kazakhstan);

- International scientific and practical conference dedicated to the memory of Professor R. Dilbarkhanov "Formation and prospects for the development of a scientific school of pharmacy: continuity of generations" (2018, Almaty, Kazakhstan);

- International scientific and practical conference of students, young scientists and teachers "Akanov reading: the role of PHC in achieving universal health coverage" (2019, Almaty, Kazakhstan).

- LX-LXI International Scientific and Practical Conference "Scientific Discussion: Medical Issues" (2017, Moscow, Russia).

Publication Information

According to the results of the research, 11 publications were published, including:

- article in the international journal included in the Scopus database - 1,

- articles recommended by Committee for Control of Education and Science of Ministry of Education and Science of Republic of Kazakhstan - 5,

- abstracts of reports at international scientific and practical conferences (Kazakhstan, Poland, Russia) - 5.

A patent application has been filed for the invention "Antimicrobial Pharmaceutical Composition." State Registration No. 2020/0707.1 dated 14.10.2020

Connection of research tasks with the plan of scientific programs

The dissertation work was carried out in accordance with the research plan of KazNMU named after S.D. Asfendiyarov and within the framework of the research program on the topic: "Development of new anti-infectious drugs" (Scientific Technical Programme Code No. O.0671 for 2015-2017, 2018-2020, 2021-2023) JSC "Scientific Center for Anti-Infectious Drugs" Ministry of Industry and Infrastructure Development of the Republic of Kazakhstan.

Author's contribution

The dissertation is a completed scientific and qualification independent work performed at a high scientific level. During his doctoral studies, the author achieved high competencies in GLP research methods as the head of research (Study Director) and GMP standards of pharmaceutical production and has appropriate certificates. This provided a high methodological level of dissertation work.

The author personally developed and validated the research methods (quantitative determination of chloramphenicol in a medicinal product, assessment of the mutagenic potential of the pharmaceutical substance, calculation algorithms, methodological provisions, etc.), obtained analytical (empirical) dependencies, such as the field of existence of technological parameters, established the boundaries of change of significant variables. The author directly participated in the collection and analysis of initial data, scientific experiments, testing of the results of the study, the preparation of

the main publications on the work performed. The author of the dissertation work is the main developer of pharmaceutical technologies for the production of a new API and a new combined drug.

The scope and structure of the thesis

The dissertation is presented on 172 pages of typewritten text in a computer set, contains 53 tables, 63 figures, a list of references, including 118 titles, 10 applications. The work consists of an introduction, a review of the literature, a section on the materials and methods of the study, 4 sections of their own research, conclusions.