ANNOTATION

The dissertation work of Saltanat Marshalovna Imanaliyeva entitled "Development of Dosage Forms of a Non-Steroidal Anti-Inflammatory Drug for Children and Their Biopharmaceutical Study", submitted for the degree of Doctor of Philosophy (PhD) in the educational program 8D10140 – Pharmacy

Relevance of the research topic. The anatomical and physiological characteristics of each pediatric age group have a significant effect on the course of diseases and on the pharmacokinetic and pharmacodynamic parameters of medicines. Children should receive medicinal products in age-appropriate doses, and their pharmaceutical design should correspond to the intended age group.

At present, the range of medicines intended for pediatric use remains insufficient. According to experts of the World Health Organization (WHO), for 75% of childhood diseases there are still no specific pediatric medicines; data on the safety of drug use in children are very limited, and special pediatric dosage forms are insufficiently available [Volskaya E., 2007].

According to the European Commission, 50–90% of medicines prescribed for children have never been tested in the relevant age groups, and the efficacy and safety of these medicines have not been specifically evaluated in children [Namazova L.S., 2006; Mikirtichan G.L., 2015].

WHO proposes a Model List of Essential Medicines aimed at meeting public health needs for both adults and children. This list includes 350 medicines for children.

The production of specialized pediatric medicinal products in the Republic of Kazakhstan is an urgent problem, since the conducted studies show that not a single domestic medicinal product specifically intended for children is manufactured in the country [B.A. Sagyndykova, S.M. Imanalieva, H.K. Ismailova, 2021].

One of the socially significant diseases in childhood is pathology of the musculoskeletal system, including juvenile rheumatoid arthritis (JRA), which is among the most common rheumatic diseases in pediatric rheumatology [Alekseeva E.I., Litvitskiy P.F., 2007].

JRA develops in children under 16 years of age, is characterized by a chronic severe progressive course, and has an unfavorable prognosis [E.L. Nasonov, A.M. Lila, 2019]. In different countries, the prevalence of JRA ranges from 0.05% to 0.8%, the incidence is from 2 to 16–20 cases per 100,000 children per year, and mortality is up to 0.5–1% [Kozhevnikov A.N., Pozdeeva N.A., Konev M. et al., 2014].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the basis of therapy for this disease and provide a satisfactory clinical effect in 50–70% of cases [E.S. Zholobova, E.I. Alekseeva, 2002].

Meloxicam is considered a selective COX-2 inhibitor and, in adult patients, demonstrates a pronounced analgesic effect compared with other NSAIDs. The use of meloxicam is characterized by a low risk of adverse effects and the absence of damaging

effects on cartilage tissue. Therefore, meloxicam is regarded as one of the safest drugs in this class [N.V. Chichasova, 2018].

Meloxicam is used in children from the age of 2 years at a dose of 0.125 mg/kg once daily, with a maximum oral dose of 7.5 mg per day [A.N. Daniyarova, O.V. Lobanchenko, 2011].

However, the safety of many NSAIDs in childhood, including meloxicam, has still not been sufficiently studied. In addition, the list of medicines with nonsteroidal anti-inflammatory action recommended for children is very limited [N.A. Shostak, A.A. Klimenko, 2013].

In the pharmaceutical market of the Republic of Kazakhstan, the following meloxicam products are registered: 23 ampoule products; 31 tablet products at doses of 7.5 and 15 mg; 2 suppository products; 2 gel products; and 3 cream products. This list does not include meloxicam products for children.

In this regard, the development of pediatric meloxicam medicines and their biopharmaceutical investigation is of considerable importance for pharmaceutical science and practice.

Research aim: to develop pediatric dosage forms of a nonsteroidal anti-inflammatory drug and to conduct a biopharmaceutical investigation.

Research objectives:

- to analyze the state of medicine provision for children in the Republic of Kazakhstan;
- to develop the technology and perform biopharmaceutical studies of film-coated meloxicam tablets combined with cyanocobalamin for use in pediatric practice in musculoskeletal diseases;
- to master the pilot-industrial technology of film-coated meloxicam tablets combined with cyanocobalamin for children and to develop the drug specification;
- to study the anti-inflammatory activity and safety (preclinical) of film-coated meloxicam tablets combined with cyanocobalamin for children;
- to develop the technology of pediatric meloxicam transdermal patches and to conduct technological and biopharmaceutical studies.

Objects of research:

– the State Register of Medicinal Products of the Republic of Kazakhstan;

– the list of medicinal products and medical devices for free and/or concessional outpatient provision of certain categories of citizens of Kazakhstan for specific diseases (conditions);

– the National Drug Formulary of Kazakhstan;

– medicinal substances: meloxicam, cyanocobalamin;

– film-coated meloxicam tablets combined with cyanocobalamin for children;

– transdermal meloxicam patches with chondroitin sulfate for children.

Research methods: sampling method, statistical method, expert assessment method, technological methods, biopharmaceutical methods, physicochemical methods, pharmaceutical methods, pharmacological and other methods.

Subject of research: investigation of the state of medicine provision for children in the Republic of Kazakhstan; development of the technology for obtaining and standardizing film-coated meloxicam tablets combined with cyanocobalamin for children; mastering the pilot-industrial technology of film-coated meloxicam tablets combined with cyanocobalamin for children and developing the drug specification; determination of tablet shelf life; validation of quantitative analytical methods for drug substances; preclinical pharmacological studies; development of the technology for obtaining transdermal meloxicam patches with chondroitin sulfate for children and their pharmaceutical study.

Scientific novelty of the research:

- the current state of medicine provision for children in the Republic of Kazakhstan was studied.

For the first time:

- the technology of film-coated meloxicam tablets combined with cyanocobalamin for children was developed and their quality indicators were determined;
- the pilot-industrial technology of film-coated meloxicam tablets combined with cyanocobalamin for children was mastered and the drug specification was developed;
- a preclinical study of film-coated meloxicam tablets combined with cyanocobalamin for children was carried out;
- the shelf life of film-coated meloxicam tablets combined with cyanocobalamin for children was established;
- the technology for producing transdermal patches for children using meloxicam and chondroitin was developed, and their quality indicators were determined.

An initiative project entitled “Development of pediatric dosage forms of a nonsteroidal anti-inflammatory drug and biopharmaceutical investigation” was registered at the National Center for State Scientific and Technical Expertise. State registration number: 0123RKI0297, approved on 23.06.2023.

A utility model patent No. 9490, “Composition of the core of a solid dosage form for children with anti-inflammatory, analgesic and antipyretic effects,” was approved at the National Institute of Intellectual Property.

A certificate of entry of information into the state register of rights to copyright-protected objects was obtained. On July 23, 2024, No. 48562, “Development of transdermal patches with anti-inflammatory and analgesic effects for children.”

Main provisions of the dissertation research submitted for defense:

- results of the study of the current state of medicine provision for children in the Republic of Kazakhstan;
- results of developing the technology of meloxicam tablets combined with cyanocobalamin for children and determining their quality indicators;
- results of mastering the pilot-industrial technology of film-coated meloxicam tablets combined with cyanocobalamin for children and developing the drug specification;

- results of determining the shelf life of film-coated meloxicam tablets combined with cyanocobalamin for children and validating the analytical methods;

- results of developing the technology of transdermal patches for children using meloxicam and chondroitin;

- results of studying the pharmacological activity and harmlessness of film-coated meloxicam tablets combined with cyanocobalamin for children.

Practical significance of the research:

- the current state of medicine provision for children in the Republic of Kazakhstan was studied, and a conclusion was made about the need to manufacture domestic medicinal products for children;

- at the Research Testing Center of JSC “Khimpharm,” the technology of film-coated meloxicam tablets combined with cyanocobalamin for children was developed;

- on the basis of JSC “Khimpharm,” the pilot-industrial technology of film-coated meloxicam tablets combined with cyanocobalamin for children was mastered and the drug specification was developed;

- the shelf life of film-coated meloxicam tablets combined with cyanocobalamin for children was established, and the analytical methods were validated;

- the technology of transdermal patches for children using meloxicam and chondroitin was developed and their quality indicators were determined;

- the pharmacological activity and harmlessness of film-coated meloxicam tablets combined with cyanocobalamin for children were proven;

- a draft regulatory document for film-coated meloxicam tablets combined with cyanocobalamin for children was prepared;

- the technology of transdermal patches for children prepared using meloxicam and chondroitin was introduced into the educational process at the Department of Drug Technology and Pharmacognosy of SKMA JSC.

An act on the implementation of the topic "Technology for producing transdermal patches with analgesic and anti-inflammatory action" into the educational process under the educational program "Pharmacy" at the Department of Drug Technology and Pharmacognosy of JSC SKMA was received.

Author’s personal contribution. Within the dissertation topic, the doctoral candidate independently carried out a review and analysis of domestic and foreign literature, and the experimental studies were performed with the author’s full personal participation. At the Department of Drug Technology of SKMA and at the Research Testing Center of JSC “Khimpharm,” the doctoral candidate personally conducted the work on obtaining laboratory samples of meloxicam tablets combined with cyanocobalamin for children.

The production of the pilot-industrial batch of film-coated meloxicam tablets combined with cyanocobalamin at JSC “Khimpharm” was carried out with the direct participation of the doctoral candidate. The studies on selecting the composition of

pediatric transdermal patches, preparing laboratory samples, and evaluating their quality were personally performed by the doctoral candidate.

The reliability and validity of the research results are confirmed by the fact that the performed scientific work is aimed at solving urgent current problems, was carried out in accredited research centers and at the production sites of JSC “Khimpharm” and LLP “EkoFarm,” and was accompanied by the preparation of a draft regulatory document for the medicinal product.

Connection of the work with state and scientific programs.

This dissertation was completed in accordance with a program registered with the National Center for State Scientific and Technical Expertise on the topic "Development and biopharmaceutical study of dosage forms containing a non-steroidal anti-inflammatory drug for children." State registration number: 0123RKI0297, June 23, 2023.

Conclusion

1. An analysis of the key regulatory documents governing the provision of medicines to the population of the Republic of Kazakhstan was conducted. A list of pediatric medicines included in Kazakhstan's regulatory documents was established. It was found that the domestic pharmaceutical industry does not produce specialized medications for children, and this patient group is not provided with a sufficient selection of medications in pediatric dosages.

2. At the Regional Children's Hospital (RCH, Shymkent), studies were conducted to determine the range of medications for children, including those produced by domestic manufacturers. It was found that the healthcare organization's drug formulary includes a significant number of medications, but no medications specifically intended for children were found in the formulary.

3. The research and testing center of JSC Khimfarm conducted research on the development of film-coated combination tablets of meloxicam 3.75 mg with cyanocobalamin 0.002 mg for children. Based on scientific data, the possibility of creating meloxicam tablets combined with cyanocobalamin for children was studied to enhance the analgesic effect of meloxicam.

4. The physicochemical and technological properties of meloxicam and cyanocobalamin were determined. Studies were conducted to produce a tablet mass suitable for direct compression, using excipients to improve the technological properties of meloxicam. Five laboratory samples of combined tablet cores were prepared using various compositions and amounts of excipients to select the composition. Tablet cores were pressed from the prepared tablet mass. During the pressing process, the quality parameters of 10 tablets from each model series were automatically determined.

5. Based on the results of a study of the technological parameters and dissolution profiles of combined meloxicam 3.75 mg tablet cores with 0.002 mg cyanocobalamin, a model sample suitable for coating was selected. Meloxicam 3.75 mg tablet cores combined with 0.002 mg cyanocobalamin were coated with Opadry® 03F28446 film-forming suspension. Laboratory samples of combined meloxicam 3.75 mg tablets with

0.002 mg cyanocobalamin film-coated for children were prepared at the Research Center of JSC Khimfarm.

6. At JSC Khimfarm's Tablet Shop No. 3, a pilot-scale trial of film-coated combination tablets of meloxicam 3.75 mg with cyanocobalamin 0.002 mg for children was conducted in the tablet shop. Tablet compression and coating were carried out in accordance with Standard Operating Procedures in the production shop. Quality control was performed on 10 tablet core samples during the pressing process. The coating process was selected, the required parameters were set on the equipment control panel, and the coating process was carried out in the "dosing-rotation-drying" mode until the average tablet weight increased by 2.5%.

7. The BioEtica testing center (Shymkent, Republic of Kazakhstan) conducted quality testing of the developed tablets. For the first time, a specification was developed and a draft interim analytical regulatory document was prepared for the pediatric-grade meloxicam 3.75 mg/cyanocobalamin 0.002 mg film-coated combination tablets.

8. A method for the quantitative determination of meloxicam and cyanocobalamin in film-coated tablets for children containing 3.75 mg meloxicam and 0.002 mg cyanocobalamin was validated. The validation results fully comply with the requirements of the Eurasian Economic Union Pharmacopoeia and ICH Q2(R1) "Validation of Analytical Procedures" and can be recommended for analytical quality control of dosage forms containing a combination of meloxicam and cyanocobalamin.

9. Stability and shelf life studies were conducted on pediatric-grade meloxicam 3.75 mg and cyanocobalamin 0.002 mg film-coated combination tablets. The results of the stability study under accelerated storage conditions suggest a shelf life of at least 24 months for meloxicam 3.75 mg and cyanocobalamin 0.002 mg film-coated combination tablets when stored in a dry, dark place at a temperature not exceeding 25°C.

10. The safety and specific activity of combined meloxicam 3.75 mg tablets with 0.002 mg cyanocobalamin, film-coated tablets for children, were studied. An acute toxicity study demonstrated that the drug belongs to Class 4 low-toxicity agents.

The results of a specific activity study in aseptic histamine and carrageenan-induced inflammation models demonstrated high anti-inflammatory activity. This suggests an enhanced anti-inflammatory effect due to the effective combination of meloxicam and cyanocobalamin.

11. Research was conducted to develop a technology for transdermal meloxicam patches for children, combined with chondroitin sulfate. Excipients were selected, and 20 laboratory samples were prepared. The functional properties of the resulting laboratory samples were studied, and the most optimal samples for producing patch masses were selected. A technology for patches containing meloxicam and chondroitin sulfate was developed. The functional properties and release rate of meloxicam from the patches were studied.

12. A patch composition with the required functional properties and a high meloxicam release concentration was selected. The quality indicators of combined meloxicam and chondroitin sulfate transdermal patches were determined. The study

results demonstrate the feasibility of developing a combined meloxicam and chondroitin sulfate transdermal patch technology for children.