GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (364-365) Июль-Август 2025

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
NO 7-8 (364-365) 2025

Содержание:

GEORGIAN MEDICAL NEWS
No 7-8 (364-365) 2025

CURRENT STATUS AND PROSPECTS FOR THE DEVELOPMENT OF PEDIATRIC DOSAGE FORMS BY THE EXAMPLE OF COMBINED MELOXICAM AND VITAMIN B12 TABLETS

Saltanat Imanalieva[1], Bayan Sagindykova[1], Rabiga Anarbayeva[1], Murat Omirali[1], Gulnara Ospanova[1], Murat Ashirov[2]*.

[1]South Kazakhstan Medical Academy, Al-Farabi Square, 1, Shymkent, Kazakhstan.

[2]Asfendiyarov Kazakh National Medical University, 94, Tole Bi str., Almaty, Kazakhstan.

**Corresponding author: Murat Z. Ashirov; E-mail: ashirov.m@kaznmu.kz*

Abstract.

Relevance: In the Republic of Kazakhstan, the pharmaceutical industry is undergoing rapid development. However, there is a significant deficit of specialized dosage forms for children. The majority of pharmaceuticals employed in paediatric practice have not been subjected to clinical trials in children, resulting in irrational prescribing and an elevated risk of adverse effects. The development of paediatric dosage forms for the treatment of socially significant diseases, such as juvenile rheumatoid arthritis (JRA), is of particular urgency. This article discusses the prospect of developing combined meloxicam and vitamin B12 tablets for children, which may improve the efficacy and safety of therapy.

Materials and methods: The study was carried out on the basis of South Kazakhstan Medical Academy and research testing center of JSC "Khimpharm". Physicochemical and technological properties of meloxicam and cyanocobalamin were studied and five model samples of core tablets were developed. Direct pressing methods, as well as dissolution and active substance release tests were used to assess the quality of tablets. The production technology included the stages of mixing, pressing and film coating.

Results: According to the Register of medicines of the Republic of Kazakhstan and the Kazakhstan National Formulary, only 0.3% of the total number of medicines are intended for children. 1.7% of medicines for children are included in the list of medicines for free and (or) preferential outpatient supply to citizens of Kazakhstan. 61 preparations of meloxicam are registered on the pharmaceutical market of Kazakhstan, but there are no preparations for children among them. Combination therapy has advantages over monotherapy, the simultaneous use of several active pharmaceutical ingredients reduces the duration of treatment and reduces the need for additional drugs. The results of determining the physicochemical and technological properties of meloxicam, cyanocobalamin and excipients showed that they meet the requirements of regulatory documents. Taking this into account, the method of direct pressing was chosen as a rational way of tableting meloxicam with cyanocobalamin. The data on quality indicators (by mass, height, diameter, hardness) and dissolution kinetics study showed that the composition no.4 of model samples of meloxicam core tablets is optimal. The technology of production of combined meloxicam tablets for children with an average weight of 62.0 mg ±10% (from 55.8 mg to 68.2 mg) coated was developed, and the pilot technology was tested on 2448.00 g of tablet mass.

Conclusion: The development of combined meloxicam and vitamin B12 tablets for children represents a promising direction in the field of pharmaceutics. This dosage form has the potential to enhance the effectiveness of therapy for juvenile rheumatoid arthritis and other inflammatory diseases in children, whilst concomitantly reducing the likelihood of adverse effects. The results of the study indicate the necessity for additional clinical trials to be conducted, including bioavailability and stability tests, on the developed paediatric dosage form.

Key words. Rheumatic diseases, pharmaceutical development, combination tablets, meloxicam, cyanocobalamin, medicines for children, coated tablets.

Introduction.

In the Republic of Kazakhstan, there has been a notable development in the field of domestic pharmacy over the past decade [1,2]. Consequently, issues pertaining to the development of human resources [3,4], the cultivation of communicative competencies within the context of continuous professional development for pharmacists [5], the establishment of a pharmaceutical cluster [6], the financing of research and educational activities aimed at the development of innovative medicines [7,8], substances [9,10], and other related domains. Of particular note are the development of paediatric medicines [11] and the paucity of officially approved paediatric medicines [12,13]. According to the World Health Organization's (WHO) experts, there is an absence of special pediatric medicines for numerous pediatric diseases [14], a paucity of data on the safety of drugs in children, and an insufficiency of special pediatric dosage forms [15,16]. Consequently, pediatricians are compelled to assume considerable risks by administering medications that have not been specifically approved for use in children [17,18]. This risk is especially increased in early childhood illnesses, as well as in severe, rarely occurring diseases in children. It is a matter of particular concern that the majority of medications prescribed for newborns have not been registered for use in this age group [19,20].

Research has indicated that the prescription of medications to children is often not grounded in scientific rationale [21,22], with a limited number of children receiving long-term drug therapy for chronic or disabling diseases [23]. Furthermore, adverse effects of prescribed medications have been identified as a contributing factor to 18% of all hospital admissions [24]. According to experts in the field, this phenomenon can be attributed to the fact that 70-80% of drugs used in paediatrics have not undergone clinical trials in children [25]. The approach of transferring data from clinical trials conducted on adult

patients to the field of paediatric pharmacology is not always reasonable or accurate. The European Commission has reported that 50-90% of medicines prescribed for children are not tested in this age group and no special studies are conducted to assess the efficacy and safety of the drug for children [26,27].

The World Health Organization has developed the List of Essential Medicines for Children, which includes 350 medicines and is recommended for use in the development of national lists of children's medicines [28].

In recent decades, in many countries of the world serious attention is paid to the development of medicines for children [29]. This may be due to the labor-intensive and peculiarities of the technology of creating medicines for children [30,31], to the generally accepted approach of prescribing the same medicines for children as for adults, only with dose selection taking into account age, body weight and other physiological parameters of the child's body [32], as well as to the disinterest of pharmaceutical business in the production of children's medicines due to insufficient return on financial expenditures [33,34]. One of such pediatric medicines are medicines used for the treatment of socially important diseases in childhood, such as inflammatory diseases of the musculoskeletal system [35,36]. Arthritis is usually considered as an "age-related" disease that is mainly diagnosed in the elderly and arthritis in children was considered impossible until recently [37,38]. However, official statistics indicate that worldwide 1 in 1000 children suffer from inflammatory joint disease [39]. Pediatric arthritis (juvenile arthritis or pediatric rheumatic disease) is a group of rheumatic diseases that have different origins and manifest through lesions of all joint elements [40,41]. Pediatric rheumatology classifies arthritis in children as a group of socially significant diseases, often leading to disability of children [42,43].

In the domain of modern paediatric rheumatology, juvenile rheumatoid arthritis (JRA) has been identified as one of the most prevalent rheumatic diseases [44]. It can be utilised as a paradigm to elucidate the frequency and prevalence of paediatric rheumatologic diseases [45,46]. JRA is defined as a systemic inflammatory disease of connective tissue, manifesting predominantly in the musculoskeletal system. It is characterised by immune system dysfunction and pronounced autoaggression, leading to the development of pathological immune reactions [47,48]. JRA manifests in patients up to the age of 16 years, is characterised by a chronic, severe and progressive course, and generally has an unfavourable prognosis [41,49].

It is estimated that approximately 3 million children and young people worldwide are affected by JRA [50,51]. The incidence of JRA ranges from 3.8 to 400 in different regions of the world, with an incidence of 1.6 to 23 cases per 100,000 children per year [52,53]. The peak incidence of JRA is between the ages of 2-4 years and 10-14 (9-11) years (depending on the clinical manifestation) [54].

Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, immunomodulators, vitamins, antibiotics, antitumor and antirheumatic agents are prescribed for the treatment of arthritis [55,56].

NSAIDs are the mainstay of treatment, with a satisfactory clinical effect observed in 50-70% of cases [57].

The efficacy of NSAIDs in the management of pain syndromes of various localisations has been well-documented, thus classifying them as one of the most effective and popular groups of drugs [58,59]. The principal analgesic effect of NSAIDs is attributable to their capacity to inhibit cyclooxygenases (COX), pivotal enzymes in the synthesis of prostaglandins [60,61]. These enzymes possess robust anti-inflammatory and hyperalgesic characteristics [62]. The prescription of NSAIDs is due to their mechanisms of action, namely anti-inflammatory, antipyretic and analgesic [63,64]. Penetrating the synovial fluid of the affected joint, NSAIDs have been shown to reduce prostaglandin production [65], thereby exerting an anti-inflammatory effect [66,67].

The nomenclature of NSAIDs authorized in pediatric practice is severely limited. Selective NSAIDs authorized in pediatric practice include nimesulide and meloxicam [68,69]. However, in the USA, Canada, the UK, Austria, nimesulide is not allowed for registration due to hepatotoxicity, in Japan, Israel and Spain the use of nimesulide is prohibited [70,71]. Among NSAIDs for the treatment of these diseases, especially juvenile idiopathic arthritis, a number of authors show the effectiveness of meloxicam (0.125-0.25 mg/kg) for children from 2 to 16 years of age compared to other drugs [72,73]. In addition, it should be taken into account that in the complex therapy of patients, B vitamins with a wide range of neurotropic properties (thiamine, pyridoxine, cyanocobalamin) contribute to the activation of reparative processes in damaged nerve trunks subjected to compression or ischemia, and potentiate the effect of analgesics [74]. Combination therapy (nonsteroidal anti-inflammatory drugs (NSAIDs) and B vitamins) has advantages over NSAID monotherapy; their simultaneous use with analgesics and NSAIDs shortens the treatment period and reduces the need for additional use of analgesics [75].

Numerous studies have shown that the combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and B-group vitamins, in particular cyanocobalamin (vitamin B12), may produce a synergistic analgesic effect [57,65,74]. Cyanocobalamin is involved in nerve regeneration, myelin synthesis, and has neurotropic properties that enhance the analgesic activity of NSAIDs [65,74]. Moreover, no clinically relevant interactions have been reported between meloxicam and vitamin B12, which supports the safety of their co-administration. Evidence in pediatric and adult populations suggests that this combination can enhance analgesia and reduce the required NSAID dose, thereby minimizing adverse effects [68,73].

Thus, the development of combination dosage forms with meloxicam is relevant [76]. Studies show that such combination can improve drug dissolution [77], show good stability (drug content, disintegration time, solidity and in vitro dissolution properties) [78,79], increase drug solubility [80,81] and improve bioavailability of meloxicam [82].

Taking into account the above-mentioned, we aimed to study the current state of drug supply of children in the pharmaceutical market of the Republic of Kazakhstan and to consider the prospects for the development of combined tablets of meloxicam with cyanocobalamin for children.

Materials and Methods.

The article consists of several parts. In the first part we consider the relevance of the problem and the current state of drug supply for children, in the second part - the methodology of the study, in the third part - the results of prospective development and testing of tablets, in the fourth part - discussion of the obtained data and their significance for pharmaceutical practice.

To assess the current state of drug supply and production of medicines for children in the pharmaceutical market of the Republic of Kazakhstan (RK), we studied the main regulatory documents [83] governing drug supply to the population, including children [84,85]. The State Register of Medicines and Medical Devices of the Republic of Kazakhstan, the List of Medicines and Medical Devices for free and (or) preferential outpatient provision of certain categories of citizens of Kazakhstan, and the Kazakhstan National Formulary were used in the study.

As a base for conducting prospective study was chosen the Department of Drug Technology of South Kazakhstan Medical Academy (SKMA) and Joint Stock Company "Khimpharm" (Member of Polpharma Group, Shymkent). In addition, the results of scientific research of the authors H. Hosseinzadeh and M. Magaña-Villa were used.

For the research we studied the possibilities of using cyanocobalamin as a component that enhances the analgesic effect of meloxicam, determined the optimal technological properties of the main medicinal and auxiliary substances to develop the composition of combined meloxicam tablets for children, developed the composition and determined some quality indicators of combined meloxicam core tablets with cyanocobalamin for children for further research. The study was conducted at the Department of Technology of Dosage Forms of South Kazakhstan Medical Academy (Protocol No. 5a of 15.01.2024).

Determination of the optimal composition and technology of combined tablets of meloxicam with cyanocobalamin for children was carried out on the basis of research testing center of Joint Stock Company (JSC) "Khimpharm" (Member of Polpharma Group, Shymkent). The objects of the study were meloxicam - produced by "Pharmacutical LTD" (China) and cyanocobalamin - produced by "Xi'an ZB Biotech Co., Ltd" (China).

To determine the physicochemical and technological properties of the main medicinal (meloxicam and cyanocobalamin) and auxiliary substances for the development of the composition of combined tablets meloxicam for children were used Temporary Analytical Normative Document (VAND 42-3843-07) and the State Pharmacopoeia of the Republic of Kazakhstan (II volume, p. 557).

In developing model samples of meloxicam core tablets, we studied the possibility of using as dry binders: povidone K-25, croscarmellose sodium; leavening agents: sodium citrate, anhydrous silicon dioxide; sliding agents: microcrystalline cellulose 102, mannitol, hydroxypropylmethylcellulose 4000 (Sheffcel 75 HD 15000CR), hydroxypropylmethylcellulose 4000 (Sheffcel 75 HD 4000CR), magnesium stearate and other excipients. In accordance with the requirements, we determined the technological properties of the selected auxiliary substances: particle size, friability, bulk density.

Using different combinations of the amounts of the main medicinal and auxiliary substances, calculated for one load of 200 g, we prepared the prescriptions of 5 model laboratory samples of meloxicam core tablets. The doses of medicinal substances were selected taking into account the age of children: for meloxicam the dose was chosen at the rate of 0.125 mg/kg of child weight (the weight of a 10-year-old child is approximately 30-32 kg) or 50% of the adult dose and for cyanocobalamin - the generally accepted dose of vitamin B12 administration for children. Thus, the calculated meloxicam dose per tablet was 3.75 mg. Given the limited ability of younger children (e.g., <6 years) to tolerate solid dosage forms and the challenges of accurately dividing small tablets, this dosage form is primarily intended for children aged 10 years and older with body weight approximately 30-32 kg. The possibility of splitting or adjusting the dose for younger children remains limited and would require the development of alternative dosage forms (e.g., dispersible tablets or suspensions), which is the subject of future work.

For preparation of tablet mass in laboratory conditions meloxicam, cyanocobalamin, aerosil were sieved through a vibrating screen, sieving was carried out twice. Then a sieved mixture of microcrystalline cellulose, povidone K-25, sodium croscarmellase and sodium citrate was added. The mixture was sieved twice, then transferred to a mixer and stirred for 30 minutes. Pre-sieved magnesium stearate was added to this mixture and mixed for an additional 5 minutes. Tablets were pressed from the prepared mass on a tablet press model ADEPT MINI PRESS "MUMBAI" (India). Studies were carried out in the research testing center of JSC "Khimpharm" (Member of Polpharma Group). The punch diameter was 5 mm, spherical shape, height 2.80 mm. Tablet machine automatically determines mass, height, diameter, hardness of core tablets.

One of the quality indicators of tablets is the release of the drug substance from the dosage form. For tablets such a test is the study of tablets by the test "Dissolution". Determination of meloxicam release from core tablets by the test "Dissolution" was carried out on the dissolution tester "ERWEKA DH1520" in accordance with the requirements of GF RK (Volume 1, page 236). Dissolution medium - phosphate buffer solution with pH 6.8; dissolution medium volume - 900 ml; basket rotation speed - 100 rpm; dissolution time - 45 min, dissolution medium temperature - (37.0 ± 0.5) °C.

We used Opadray® 03F28446 (Calarcon Ltd., England), a film-forming agent, which is a fine powdery finished mixture of excipients, to coat the core tablets. Two film coating systems were used during the process: Opadry® 03F28446 (a base coating formulation) and Yellow Opadry® grade 86F32004, a coloured film-coating formulation specifically used for imparting the final yellow opaque appearance. For standardisation and clarity, the term Yellow Opadry® 86F32004 will be used throughout this article to describe the coating material used for the final batch.

Core tablets were loaded into the rotary drum of BG 10 coating machine (Germany) through a direct feeder, and the tablets were dedusted for 20 minutes at a drum rotation speed of 6 rpm, then the tablets were heated to a temperature of 30°C. Next, a

suspension of film-forming agent was sprayed onto the rotating warm core tablets at a drum rotation speed of 20-24 rpm using a spray gun to increase the weight of the tablets to 2.5- 3%. Simultaneously with the suspension supply, heated air of 40-50°C temperature is injected through the bottom of the drum, which ensures fast drying of tablets and uniform distribution of coating on the core tablets.

To prepare the slurry for film coating, 4,200 l/kg of purified cold water (20-25°C) and 800.0 g of yellow opadraya grade 86F32004 were prepared. Subsequently, 4,200 l/kg of purified cold water was loaded into the solution preparation apparatus and the stirrer was turned on at 15Gc. Opadray yellow 86F32004 in an amount of 0.8 kg was slowly poured in with the stirrer on. The solution was stirred for 50 minutes with the stirrer on. Ready slurry for coating should be in the apparatus with constant stirring. Tablets - kernels pre-dusted and at the tested quality of atomization of the suspension are loaded into the drum of the BG 80 coating machine (Germany). Control of the film coating process was carried out every 30 minutes.

When spraying the opadraya suspension, the average tablet weight was checked every 30 minutes. The application of yellow opadraya suspension was carried out until the tablets of the required weight were obtained.

To determine the promising technology of production and tested pilot technology of combined coated meloxicam tablets for children, the quality of tablets was assessed and the main technological parameters of meloxicam core tablets in the process of coating were determined. The study was conducted in the laboratory of the research testing center and in the tablet shop of JSC "Khimpharm" (Member of Polpharma Group), Shymkent, Kazakhstan (Protocol series PP №11123 from 01.11.2023), as well as in the testing center of LLP "BioEtica", Shymkent, Kazakhstan (Test Protocol №671 from 16.06.2024).

Scientific novelty of the research is confirmed by the application №2024/0779.2 from 23.07.2024 on the issuance of a patent for a utility model of the Ministry of Justice of the Republic of Kazakhstan "Composition of the core of a solid dosage form for children with anti-inflammatory, analgesic and antipyretic action".

Results.

Study of the current state of drug supply and production of medicines for children in the pharmaceutical market of the Republic of Kazakhstan:

When analyzing the State Register of Medicines and Medical Devices of the Republic of Kazakhstan, we found that this document registered only 7987 medicines authorized for use in the country, of which only 23 medicines are intended for children's practice in special dosage and dosage form for children, which is about 0.3% of the total number of registered medicines.

The list of medicines and medical devices for free and (or) preferential outpatient provision of certain categories of citizens of Kazakhstan with certain diseases (conditions) includes 1100 names of medicines, of which only 19 (1.7%) medicines are intended for children.

The "Kazakhstan National Drug Formulary (KNLF)" includes 6852 drugs, of which 25 (0.36%) are used in pediatric practice. The results of the research are presented in Figure 1.

The pharmaceutical industry of Kazakhstan practically does not produce children's medicines; there is one drug on the market - syrup "Ambro" for children, produced by JSC "Khimpharm" [86,87].

The results of studies indicate the need to determine the nomenclature of drugs, in special pediatric dosage forms and the development of drugs for children, taking into account anatomo-morphological, technological features of drugs for this age group of patients [88].

The analysis has shown that on the pharmaceutical market of the Republic of Kazakhstan registered preparations of meloxicam: in ampoules - 23 items; in tablets of 7.5 mg and 15 mg - 31 items; in the form of suppositories - 2; gels - 2; cream - 3 items. Drug preparations of meloxicam for children are absent in this list, especially with a coated coating.

Thus, in Kazakhstan there is progress in the development of the pharmaceutical industry, the number of registered pediatric dosage forms remains extremely low (0.3% of the total number of drugs). For comparison, in the European Union and the USA, the share of pediatric dosage forms is about 5-10%, which is due to active government support and legislative initiatives, such as Pediatric Research Equity Act (PREA) in the USA and Pediatric Regulation in the EU [28,29]. These programs encourage pharmaceutical companies to conduct clinical trials involving children, which leads to an increase in the number of safe and effective drugs for pediatric practice.

Consideration of the prospects for the development of the formulation of combined meloxicam tablets with cyanocobalamin for children:

Meloxicam is a selective COX-2 inhibitor [89,90], and studies in adult patients have shown a relatively low incidence of side effects of the drug compared with other NSAIDs [91]. Meloxicam is used in the practice of treatment of children aged from 2 years at a dose of 0.125 mg/kg orally once a day with a maximum oral dose of 7.5 mg per day. The drug is approved for use in more than 80 countries for the treatment of OA, rheumatoid arthritis and ankylosing spondylitis [92].

Meloxicam has the properties of a selective COX-2 inhibitor and has a pronounced anti-pain effect, its use is characterized by a low risk of side effects, the absence of damaging effect of the drug on the state of cartilage tissue [93,94]. Therefore, meloxicam is one of the safest drugs of this class [95,96].

At the same time, the safe use of most NSAIDs, including meloxicam, in children is still poorly understood, and the list of recommended anti-inflammatory drugs for children is very limited [97,98]. In addition, most of these drugs have side effects, which limits their use in clinical practice [99,100]. In this regard, at present, the use of a combination of NSAIDs and B vitamins remains relevant [101,102] and may be a safe and inexpensive strategy for postoperative analgesia [103].

Exploring the potential use of cyanocobalamin (vitamin B12) as a component that enhances the analgesic effects of meloxicam is an interesting and potentially significant area of research. According to Drugs.com, which includes sources Micromedex (updated July 7, 2024), Cerner Multum™ (updated July 14,

2024), ASHP (updated July 10, 2024) and others, no interactions between meloxicam and vitamin B12 have been found. A total of 390 drugs are known to interact with meloxicam. It should be considered that Vitamin B12 may prove to be complementary or integrative in the treatment of pain conditions [104,105].

Before the research we analyzed the quality indicators of meloxicam powder in accordance with VAND RK 42-3843-07 [106]; cyanocobalamin - in accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan [107]. Quality indicators of meloxicam and cyanocobalamin fully comply with the requirements of regulatory documents.

The results showed that meloxicam is 4-hydroxy-2-methyl-N-(5-methyl-1,3- thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxyamide 1,1 dioxide, fine yellow colored powder in the form of sticks, crystalline powder anisometric shape, the size of the main fraction from 0.5 mm to 1 mm.

The results of physicochemical and technological properties of meloxicam are summarized in Table 1.

The results of determining the optimal variant of technological properties of auxiliary substances: particle size, friability, bulk density, are presented in Table 2.

Based on the study of various combinations of the amounts of the main drug and excipients, we formulated 5 model laboratory samples of meloxicam core tablets with cyanocobalamin, which are summarized in Table 3.

Taking into account the composition of model samples of core tablets, as well as the studies of some authors [77,108], we chose the direct pressing method as the tabeling method [82,109].

Statistically processed data of quality determination of the developed tablet in terms of mass, height, diameter, hardness of model sample of meloxicam core tablets with cyanocobalamin are presented in Table 4.

The results of studying the release kinetics of meloxicam from the model core tablet samples are shown in Figure 2.

On the basis of the above-mentioned technological indicators, we have chosen composition No. 4 for further research, as this model is optimal (Table 5).

Consideration of the prospects for the development of technology to create combined meloxicam and cyanocobalamin coated tablets for children:

We in the laboratory of Research and Development Testing Center of JSC "Khimpharm" (Member of Polpharma Group) developed a technology for production of combined meloxicam tablets for children with an average weight of 62.0 mg, coated (Figure 3).

In the tablet shop of JSC "Khimpharm" (Member of Polpharma Group) for testing the pilot technology of combined meloxicam tablets for children we calculated the necessary amounts of drugs and auxiliary substances for loading of 2500 g of tablet mass. The corresponding calculations are presented in Table 6.

The quality assessment data of meloxicam combination tablets (n = 10) during pressing are summarized in Table 7.

2448.00 g of core tablets were obtained, which were further directed to be coated with a film coating

Table 8 summarizes the experimentally selected main process parameters that were controlled during the coating process.

The obtained yellow-colored, coated tablets have a round shape with a biconvex surface. The average tablet weight is 62.0 mg ±10% (55.8 mg to 68.2 mg).

Discussion.

The development of pediatric dosage forms is an urgent problem, in particular, meloxicam and vitamin B12 combination tablets. The insufficient range of medicines for children forces pediatricians to use drugs that have not passed clinical trials in the pediatric population. This increases the risks of side effects and irrational use of medicines.

Meloxicam, as a selective COX-2 inhibitor, has a pronounced anti-inflammatory and analgesic effect, which makes it promising for the treatment of juvenile rheumatoid arthritis in children. However, its use in pediatrics is limited due to the lack of safety studies. The combination of meloxicam with vitamin B12 may enhance the analgesic effect and shorten the treatment period.

Table 1. *Physicochemical and technological properties of meloxicam and cyanocobamine.*

Indicators	**Determination results**	
	Meloxicam	**Cyanocobalamin**
Description	Yellow crystals	Dark red crystalline powder or dark red crystals
Solubility	Soluble in dimethylformamide, slightly soluble in acetone, very slightly soluble in 96% ethyl alcohol and methanol, practically insoluble in water.	Moderately soluble in water and in 96% alcohol, practically insoluble in acetone. The anhydrous substance is very hygroscopic.
Particle structure (Malvern Instruments Ltd Morphologi G3S automated particle structure and volume analysis system)	Flat plates	Flat plates
Particle size, μm (Mastersizer 3000 laser particle size analyzer from Malvern Instruments Ltd)	D10=2.26± 0.071; D50=6.02± 0.262; D90=12.3± 0.390;	D10=5.46± 0.102; D50=10.23± 0.018; D90=21.14± 0.024;
Bulk density, g/(cm)^3 (Erweka SVM-121) (before compaction)	0.38± 0.02	0.36± 0.02
Bulk density, g/(cm)^3 (Erveka SVM-121, instrument) (after compaction) 0.51±0.02	0.51±0.02	0.49±0.02
Bulk density, g/s (Erweka GTL apparatus)	0.2± 0.02	0.3± 0.02
Pressability, kg/s (Erweka TBH-30)	1.9± 0.05	1.7± 0.05

Table 2. *Technological properties of auxiliary substances.*

Auxiliary substances	**Manufacturer**	**Particle sizes**	**Bulk density, g/s**	**Bulk density, g/см□**
Microcrystalline cellulose	DFE Pharma	15% <63 microns 60-80%<150 μm 99%<250 microns	4.4	0.72±0.02
Povidone K-25	DFE Pharma	5-13% <75 μm 25-45%<150 microns 60-80%<250 μm 98%<600 microns	5.1	0.81±0.02
Sodium starch glucolate	DFE Pharma	15% <45 μm 30-60%<150 μm 98%<250 microns	5.7	0.60±0.02
Sodium citrate	DFE Pharma	30% <75 μm 40-70%<150 μm 90%<355 microns 100%<500 μm	6.2	0.54±0.03
Anhydrous colloidal silicon dioxide (aerosil) 200	Dow Chemical Company	110-225 μm	1.4	0.15±0.02
Magnesium stearate	DFE Pharma	7-13% <75 μm 20-45%<150 μm 60-80%<250 μm 94%<600 microns	5.0	0.75±0.02
Mannitol	DFE Pharma	18% <45 μm 30-60%<150 μm 97%<250 microns	5.5	0.64±0.02

Table 3. *Compositions of model samples of meloxicam core tablets.*

Components	**Number of components per 1 load**				
	1	2	3	4	5
Active ingredients					
Meloxicam	12.50	12.50	12.50	12.50	12.50
Cyanocobalamin	0.0067	0.0067	0.0067	0.0067	0.0067
Auxiliary substances					
Microcrystalline cellulose type 200	124.160	66.67	116.16	129.49	128.69
Pregelatinized starch	-	-	40.00	-	-
Mannitol	-	57.49	-	-	
Povidone k-25	40.00	40.00	8.00	36.0	-
Croscarmellose sodium	-	-	-	8.0	-
Lactose anhydrous	-	-	-	-	40.0
Sodium starch glycolate	8.00	8.00	8.00	-	8.00
Sodium citrate	11.334	11.334	11.334	10.0	6.8
Silicon dioxide anhydrous	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	2.00	2.00	2.00	2.00	2.00
Weight per 1 load	200.0	200.0	200.0	200.0	200.0
Weight of 1 tablet (core)	60.0	60.0	60.0	60.0	60.0

Table 4. *Quality indicators of core tablets during pressing of laboratory samples.*

Laboratory sample models	**Statistical processing**	**Weight**	**Height**	**Hardness**	**Diameter**
Model No. 1	X min X max X max-min X everage X S X rel	51.5 mg 57.0 mg 5.2 mg 55.04 mg 1.90 mg 3.44 %	2.72 mm 2.82 mm 0.10 mm 2.78 mm 0.03 mm 0.98 %	72 N 108 N 36 N 83.5 N 10.00 N 11.98 %	4.90 mm 4.96 mm 0.06 mm 4.92 mm 0.02 mm 0.50 %

Model No. 2	X min X max X max-min X everage X S X rel	58.8 mg 60.8 mg 2.0 mg 59.79 mg 0.77 mg 1.28 %	2.83 mm 2.87 mm 0.04 mm 2.86 mm 0.02 mm 0.53 %	55 N 70 N 15 N 61.80 N 4.94 N 7.99 %	4.87 mm 4.93 mm 0.06 mm 4.91 mm 0.02 mm 0.33 %
Model No.3	X min X max X max-min X everage X S X rel	59.1 mg 64.9 mg 5.8 mg 62.82 mg 1.80 mg 2.86 %	2.89 mm 3.10 mm 0.21 mm 3.02 mm 0.06 mm 1.98 %	35 N 57 N 22 N 46.50 N 7.18 N 15.45 %	4.89 mm 4.94 mm 0.05 mm 4.91 mm 0.02 mm 0.32 %
Model No.4	X min X max X max-min X everage X S X rel	59.0 mg 61.6 mg 2.6 mg 60.28 mg 0.84 mg 1.39 %	3.13 mm 3.18 mm 0.05 mm 3.15 mm 0.02 mm 0.58 %	40 N 56 N 16 N 46.80 N 4.52 N 9.65 %	4.91 mm 4.94 mm 0.03 mm 4.92 mm 0.01 mm 0.23 %
Model No.5	X min X max X max-min X everage X S X rel	54.8 mg 61.0 mg 6.2 mg 58.14 mg 1.75 mg 3.00 %	2.79 mm 2.84 mm 0.05 mm 2.82 mm 0.02 mm 0.56 %	51 N 78 N 27 N 61.30 N 9.80 N 15.98 %	4.87 mm 4.91 mm 0.04 mm 4.89 mm 0.01 mm 0.22 %

Table 5. *Composition of meloxicam core tablets No. 4.*

Components	**quantity in mg.**
Active ingredients	
Meloxicam	3.75
Cyanocobalamin	0.002
Auxiliary substances	
Cellulose Microcrystalline type 200	38.848
Povidone K-25	10.8
Croscarmellose sodium	2.4
Sodium citrate	3.0
Silicon dioxide anhydrous	0.60
Magnesium stearate	0.60
Tablet mass - core	60.0

Table 6. *Quantity of medicinal and auxiliary substances for production of pilot series of meloxicam tablets for children.*

Components	**Composition per 1 tablet**		**Composition per load 2500 g.**
	B %	**In mgmt.**	**In g.**
Active ingredient			
Meloxicam	6.25	3.75	153,00
Cyanocobalamin	0.003	0.002	0.0833
Auxiliary substances			
Cellulose microcrystalline type 200	64,747	38.848	1584,9
Povidone k-25	18.0	10,8	440,7
Croscarmellose sodium	4.0	2.4	97,9
Sodium citrate	5.0	3.0	122,40
Anhydrous silica (aerosil)	1.0	0.6	24,5
Magnesium stearate	1.0	0.60	24,5
Tablet weight (core)	100.0%	60.0	2448,00
Opadray yellow			2.00

Note: *The term "Opadray yellow" refers to Yellow Opadry® 86F32004 used for film coating of the tablets.*

Table 7. *Quality control of meloxicam combination tablets during tabletting process.*

Quality indicators			
Weight	**Height**	**Hardness**	**Diameter**
60.5 mg	3.22 mm	47 N	5.01 mm
61.2 mg	3.22 mm	56 N	5.01 mm
63.5 mg	3.25 mm	67 N	5.01 mm
59.8 mg	3.21 mm	45 N	5.00 mm
60.5 mg	3.22 mm	52 N	5.00 mm
63.4 mg	3.24 mm	68 N	5.02 mm
63.7 mg	3.23 mm	66 N	5.02 mm
58.5 mg	3.22 mm	44 N	5.01 mm
60.5 mg	3.22 mm	52 N	5.00 mm
61.0 mg	3.23 mm	49 N	5.00 mm
Statistical			
n= 10 58.5 mg 63.7 mg 5.2 mg 61.3 mg 1.7 mg 2.8%	n=10 3.21 mm 3.25 mm 0.04 mm 3.23 mm 0.01 mm 0.4%	n=10 44 N 68 N 24 N 55 N 9,3 N 17 %	n=10 5.00 mm 5.02 mm 0.02 mm 5.01 mm 0.01 mm 0.22 %

Table 8. *Control points during the film coating process.*

Film coating mode	**Control time, h**					
	Normative indicators	**13.00**	**13.30**	**14.00**	**14.30**	**15.00**
Temperature of air supplied to the unit, ℃	40-50	45	47	47	47	45
Inlet air temperature,℃ (indicators on the installation panel)	38-52	47.3	49.3	47.9	47.3	49.3
Exhaust Air Temperature,℃	25-35	31.8	31.5	31.3	31.8	31.5
Pill layer temperature , ℃	20-30	24.3	24.2	22.4	24.3	24.2
Optimization pressure to nozzle, kgf/cm^2	max 3	3.0	3.0	3.0	3.0	3.0
Drum rotation speed, rpm	up to 15	6	7	7	7	6
Slurry feed, rpm	1-10	6	5	6	6	5
Tablet weight, g	62.0 ±10%	62.3	62.3	62.6	62.5	62.2

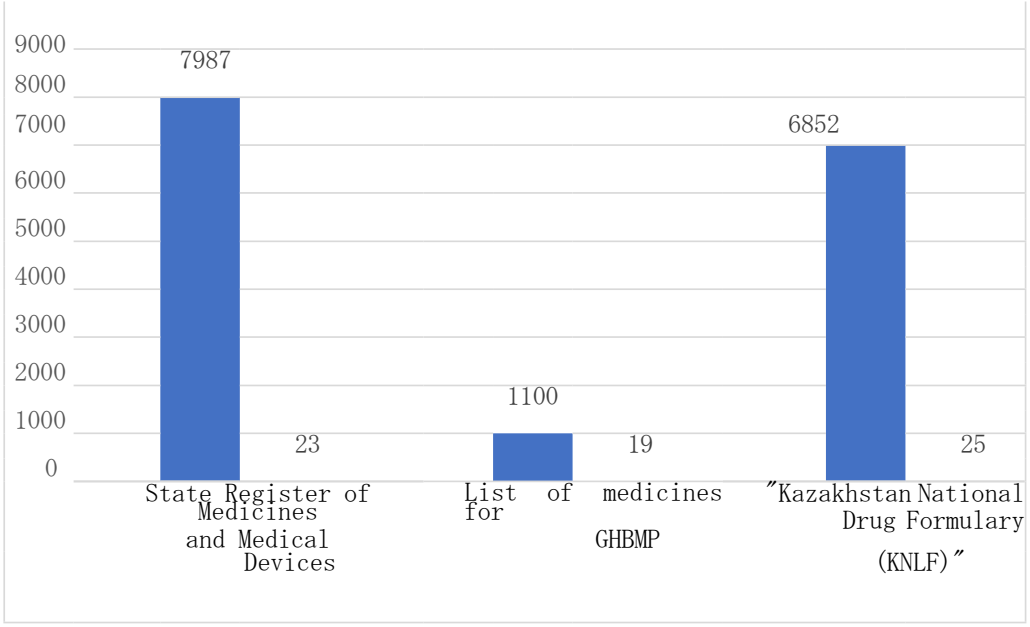

Figure 1. *Total volume of medicines authorized for use in the Republic of Kazakhstan, including for children (as of March 30, 2023).*

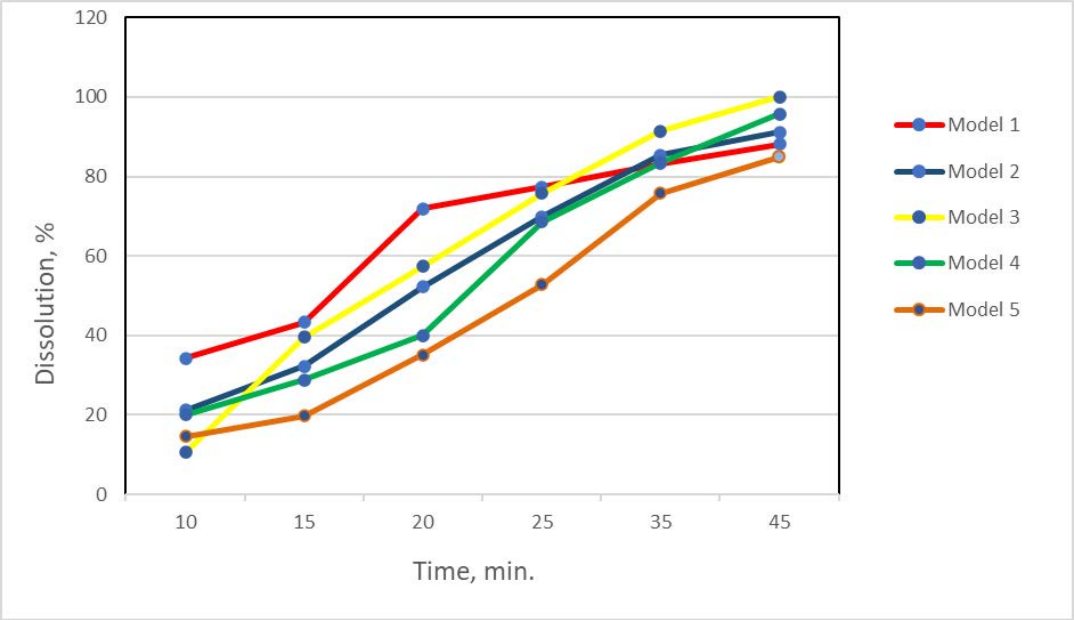

Figure 2. *Results of meloxicam dissolution kinetics in model core tablet samples.*

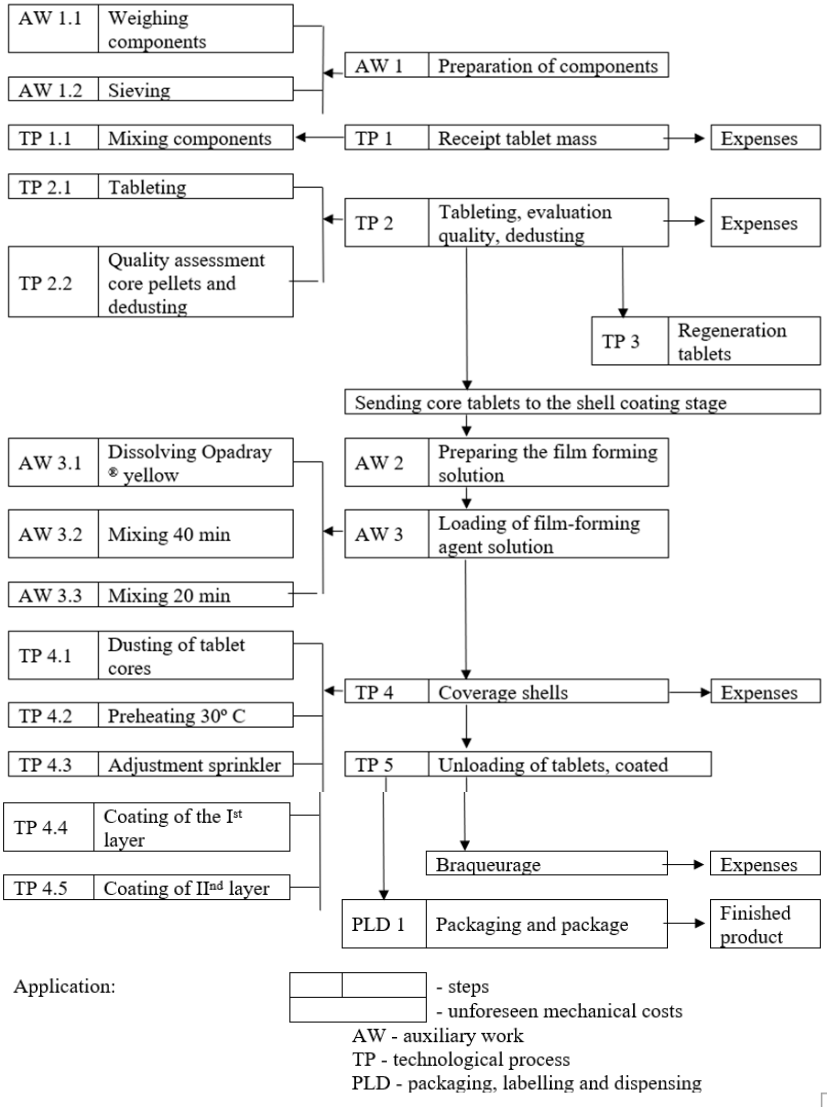

Figure 3. *Technological scheme of meloxicam combination tablets for children with a coated coating.*

Analysis of the pharmaceutical market in Kazakhstan showed an extremely low share of pediatric dosage forms (0.3% of the total number of drugs). This emphasizes the need to develop new dosage forms that take into account the anatomical and morphological features of children.

The developed combined tablets of meloxicam with cyanocobalamin showed good basic physicochemical and technological properties. Despite the lack of directly comparable studies on the development of pediatric dosage forms combining meloxicam and cyanocobalamin, several studies support the rationale behind such formulations. For instance, combination therapies involving NSAIDs and B vitamins have demonstrated enhanced analgesic and anti-inflammatory efficacy in adult patients with neuropathic or musculoskeletal pain [110,111]. Moreover, the use of B vitamins such as cyanocobalamin in conjunction with NSAIDs has shown a potential to reduce the required dosage of NSAIDs, thereby mitigating associated side effects. Although no prior pediatric formulations exactly match the one developed in this study, this indirect evidence supports the hypothesis that combining meloxicam and cyanocobalamin may yield synergistic effects, particularly relevant for juvenile rheumatoid arthritis. Therefore, the absence of identical analogs in the literature underscores the originality of our approach, while the existing evidence base from adjacent domains provides sufficient grounds for further clinical investigation. The results of the study confirm the prospectivity of this development for pediatric practice, and require further clinical studies

The article does not consider the pharmacological effects of use (clinical efficacy studies) and stability of combined meloxicam tablets with cyanocobalamin (safety of the proposed combination) coated in pediatrics, which limits the possibility of direct introduction of the drug into medical practice without additional trials. These aspects will be the subject of further studies.

It is important to note that although the developed tablet contains 3.75 mg of meloxicam, which corresponds to the recommended dose for a 10-year-old child weighing approximately 30-32 kg, this dosage form may not be suitable for younger or lighter children due to the difficulty in ensuring precise dose titration. Therefore, the current formulation is optimized for older pediatric patients, and further studies are required to assess the feasibility of dose flexibility or to create alternative age-appropriate forms.

Thus, the study emphasizes the importance of developing safe and effective dosage forms for children, especially in conditions of insufficient assortment on the pharmaceutical market. Combined meloxicam tablets with vitamin B12 represent a promising area for further research with subsequent introduction into clinical practice.

One of the key considerations in pediatric drug formulation is ensuring the acceptability of the dosage form by the child patient. In this regard, the application of a film coating to the meloxicam and vitamin B12 tablets serves multiple functions. Firstly, meloxicam has a distinctly bitter taste, which may negatively affect adherence in children. The film coating acts as a taste-masking layer, thereby improving the palatability of the tablets. Secondly, it enhances the physical and chemical stability of the dosage form by protecting the active pharmaceutical ingredients from external factors such as moisture, light, and oxygen. Finally, coated tablets are generally perceived as more aesthetically appealing and easier to swallow, which is particularly important for pediatric patients and contributes to improved compliance.

These considerations are critical for ensuring the therapeutic effectiveness of pediatric treatment regimens and must be prioritized in the development of child-friendly dosage forms.

Comparison with Existing Studies.

The results obtained in the current study can be better appreciated through comparison with previous research on the use of meloxicam in pediatric monotherapy and combined NSAID treatments with B vitamins. Meloxicam has been studied in children with juvenile idiopathic arthritis (JIA), where its efficacy at doses of 0.125-0.25 mg/kg demonstrated satisfactory safety and therapeutic outcomes [72]. However, despite its selective COX-2 inhibition and lower gastrointestinal side effects, long-term monotherapy in pediatric patients may require additional analgesic support.

Several clinical studies [105] indicate that the use of B-group vitamins, especially cyanocobalamin, in combination with NSAIDs such as diclofenac and ibuprofen enhances analgesic efficacy and may reduce treatment duration and side effects. Though such combinations have been tested predominantly in adult patients, the analgesic potentiation by B vitamins – via modulation of nerve conduction and anti-inflammatory mechanisms – uggests similar potential in pediatric applications.

Compared to existing formulations, our proposed combination of meloxicam and vitamin B12 in tablet form offers technological advantages (e.g., optimized dissolution and stability) as well as a pharmacological rationale for reduced polypharmacy. This study, therefore, bridges a gap between monotherapy limitations and the potential for rational combination therapy in pediatric rheumatology, warranting further clinical exploration.

Conclusion.

The development of pediatric dosage forms, in particular, combined meloxicam and vitamin B12 tablets for the treatment of juvenile rheumatoid arthritis is an urgent problem. The paper presents the results of development of composition and production technology of tablets, as well as evaluation of their physicochemical and technological properties. The developed technology for the production of coated tablets shows promise for further studies, including stability, bioavailability and clinical efficacy. The article emphasizes the need to develop pediatric pharmaceuticals and increase the share of specialized dosage forms for children in the pharmaceutical market, especially in the context of their current deficit in Kazakhstan. However, the developed dosage form is primarily intended for older children due to fixed-dose limitations, and further development of flexible pediatric formulations for younger age groups is warranted.

Conflicts of interest.

The authors declare that they have no conflict of interest in connection with this study, whether financial, personal, author or otherwise, that could influence the research and its results presented in this article.

Financing.

The study has no external sources of funding.

Data availability.

Data will be made available upon reasonable request.

Confirmation.

The authors would like to thank JSC "Khimpharm" (Member of Polpharma Group) and "BioEtica" LLP for support in conducting the research.

REFERENCES

1. Turgumbayeva A, Zhanat T, Zhakipbekov K, et al. A review on the medicinal plant Echinops ritro species: phytochemistry and biological activity. Farmacia. 2023;71:455-462.
2. Shertaeva C, Tulemissov S, Botabayeva R, et al. Improvement of medicine provision of patients with chronic obstructive lung disease on the basis of pharmaceutical and economic investigations. Life Sci J. 2014;11:16-23.
3. Umurzakhova G, Zhakipbekov K, Sultanbekov A, et al. Analyzing the ways to improve personnel management in the pharmaceutical industry of Kazakhstan. J Glob Pharma Technol. 2017;9:223-237.
4. Datkhayev U, Shopabaeva A, Zhakipbekov K, et al. Determination of seasonal demand for pharmaceutical staff. Int J Pharm Sci Rev Res. 2016;36:105-111.
5. Umurzakhova G, Sultanbekov A, Issatayeva N, et al. Communication skills as one of the main competences of pharmacists. Ann Trop Med Public Health. 2018;11:62.
6. Serikbayeva EA, Zhakipbekov KS, Umurzakhova GZh, et al. Methods of assessing the possibility of forming a branch regional clusters in RK. Sys Rev Pharm. 2020;11:425-434.
7. Zhakipbekov K, Posylkina O, Zhumabayev N, et al. Analysis of the current state of the pharmaceutical market of the Republic of Kazakhstan. ScienceRise: Pharm Sci. 2023;2:57-67.
8. Kozhanova K, Alimanova A, Datkhayev U, et al. Unlocking the potential: exploring pharmacological properties from Apiaceae family. Pharmacia. 2025;72:1-14.
9. Tleubayeva MI, Abdullabekova RM, Datkhayev UM, et al. Investigation of CO_2 extract of Portulaca oleracea for antioxidant activity from raw material cultivated in Kazakhstan. Int J Biomater. 2022;2022:6478977.
10. Turgumbayeva A, Zhakipbekov K, Shimirova Z, et al. Study of phytochemical compounds of Plantago major leaves grown in Kazakhstan. Pharmacia. 2022;69:1019-1026.
11. Ward RM, Benjamin DK Jr, Davis JM, et al. The need for pediatric drug development. J Pediatr. 2018;192:13-21.
12. Domingues C, Jarak I, Veiga F, et al. Pediatric drug development: reviewing challenges and opportunities by tracking innovative therapies. Pharmaceutics. 2023;15:2431.
13. Petkova V, Georgieva D, Dimitrov M, et al. Off-label prescribing in pediatric population: literature review for 2012–2022. Pharmaceutics. 2023;15:2652.
14. Field MJ, Boat TF, eds; Committee on Pediatric Studies Conducted Under BPCA and PREA; Institute of Medicine. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Washington (DC): National Academies Press (US); 2012.
15. Galande AD, Khurana NA, Mutalik S. Pediatric dosage forms-challenges and recent developments: a critical review. J Appl Pharm Sci. 2020;10:155-166.
16. Zahn J, Rascher W, Neubert A. How significant is the lack of formulations for paediatric inpatients? Arch Dis Child. 2019;104:e62.
17. Conroy S, McIntyre J, Choonara I, et al. Drug trials in children: problems and the way forward. Br J Clin Pharmacol. 2000;49:93-97.
18. van der Zanden TM, Mooij MG, Vet NJ, et al. Benefit–risk assessment of off-label drug use in children: the BRAvO framework. Clin Pharmacol Ther. 2021;110:952-965.
19. Neubert A, Wong IC, Bonifazi A, et al. Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res. 2008;58:316-322.
20. Gonçalves ACS, Reis AMM, Marçal ACG, et al. Use of unlicensed and off-label drugs in neonates in a Brazilian university hospital. Braz J Pharm Sci. 2017;53.
21. Ofori-Asenso R, Agyeman AA. Irrational use of medicines: a summary of key concepts. Pharmacy (Basel). 2016;4:35.
22. Suyunov N, Umurzakhova G, Blatov R, et al. Pharmacoeconomic research of medicines used for allergic rhinitis in children. J Appl Pharm Sci. 2024.
23. Turkel S, Pao M. Late consequences of chronic pediatric illness. Psychiatr Clin North Am. 2007;30:819-835.
24. Arnold MJ. Key potentially inappropriate drugs in pediatrics: the KIDs list. Am Fam Physician. 2021;103:633-636.
25. Hoppu K. Can we get the necessary clinical trials in children and avoid the unnecessary ones? Eur J Clin Pharmacol. 2009;65:747-748.
26. Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: serving children's needs? Arch Dis Child. 2007;92:808-811.
27. Schrier L, Hadjipanayis A, Stiris T, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by EAP and ES-DPPP. Eur J Pediatr. 2020;179:839-847.
28. World Health Organization. Model List of Essential Medicines for Children, 9th List (2023): Web Annex B. Geneva: WHO; 2023.
29. Shukar S, Zahoor F, Hayat K, et al. Drug shortage: causes, impact, and mitigation strategies. Front Pharmacol. 2021;12:693426.
30. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. Br J Clin Pharmacol. 2015;79:405-418.
31. Moretti F, Ruiz F, Bonifazi F, et al. Health technology assessment of paediatric medicines: European landscape, challenges and opportunities within the conect4children project. Br J Clin Pharmacol. 2022;88:5052-5059.
32. Rocchi F, Tomasi P. The development of medicines for children. Pharmacol Res. 2011;64:169-175.
33. Perkins L. Pharmaceutical companies must make decisions based on profit. West J Med. 2001;175:422-423.
34. Severin T, Corriol-Rohou S, Bucci-Rechtweg C, et al. How is the pharmaceutical industry structured to optimize pediatric drug development? Existing pediatric structure models and

proposed recommendations for structural enhancement. Ther Innov Regul Sci. 2020;54:1076-1084.
35. National Academies of Sciences, Engineering, and Medicine. Selected Health Conditions and Likelihood of Improvement with Treatment. Washington (DC): National Academies Press (US); 2020 Apr 21. Chapter 5: Musculoskeletal Disorders. 2020.
36. Humphreys JH, Verstappen SMM. The burden of musculoskeletal disease. Medicine (Abingdon). 2022;50:82-84.
37. Pavlov-Dolijanovic S, Bogojevic M, Nozica-Radulovic T, et al. Elderly-onset rheumatoid arthritis: characteristics and treatment options. Medicina (Kaunas). 2023;59:1878.
38. Lites TD, Foster AL, Boring MA, et al. Arthritis among children and adolescents aged <18 years-United States, 2017–2021. MMWR Morb Mortal Wkly Rep. 2023;72:788-792.
39. McLaughlin D, Keir M, Foster H, et al. Chronic arthritis in children and young people. Medicine (Abingdon). 2022;50:149-158.
40. Axford J. The impact of glycobiology on medicine. Trends Immunol. 2001;22:237-239.
41. Thatayatikom A, Modica R, De Leucio A. Juvenile idiopathic arthritis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
42. Moorthy LN, Peterson MG, Harrison MJ, et al. Physical function assessment tools in pediatric rheumatology. Pediatr Rheumatol Online J. 2008;6:9.
43. Lupini F, Rubinstein TB, Mackey ER, et al. Behavioral health outcomes and social determinants of health in children with diabetes and juvenile arthritis. Res Sq [Preprint]. 2023:rs.3.rs-3610878.
44. Bhattad S, Mohite RS, Singh N. Growth and development in children with rheumatic diseases: maintaining a balance between drugs and disease activity. Indian J Rheumatol. 2023;18:S38-S43.
45. Abdwani R. Pediatric rheumatology. In: Almoallim H, Cheikh M, eds. Skills in Rheumatology. Singapore: Springer; 2021. Chapter 24. 2021.
46. Zaripova LN, Midgley A, Christmas SE, et al. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol. 2021;19:135.
47. Marwa K, Anjum F. Undifferentiated connective tissue disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
48. Sapkota B, Al Khalili Y. Mixed connective tissue disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
49. Sudoł-Szopińska I, Matuszewska G, Gietka P, et al. Imaging of juvenile idiopathic arthritis. Part I: Clinical classifications and radiographs. J Ultrason. 2016;16:225-236.
50. Dave M, Rankin J, Pearce M, et al. Global prevalence estimates of three chronic musculoskeletal conditions: club foot, juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. Pediatr Rheumatol. 2020;18:49.
51. McHugh J. Increased risk of self-harm in fibromyalgia. Nat Rev Rheumatol. 2020;16:408.
52. Thierry S, Fautrel B, Lemelle I, et al. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81:112-117.
53. Oberle EJ, Harris JG, Verbsky JW. Polyarticular juvenile idiopathic arthritis-epidemiology and management approaches. Clin Epidemiol. 2014;6:379-393.
54. Tsujioka Y, Nishimura G, Sugimoto H, et al. Imaging findings of juvenile idiopathic arthritis and autoinflammatory diseases in children. Jpn J Radiol. 2023;41:1186-1207.
55. InformedHealth.org (IQWiG). Rheumatoid arthritis: Learn More-Painkillers for rheumatoid arthritis. In: InformedHealth.org. Cologne, Germany: IQWiG; 2006.
56. Bobek D, Banić Stipetić A, Franić M, et al. Use of non-steroidal anti-inflammatory drugs in patients with advanced active rheumatoid arthritis. Acta Clin Croat. 2022;61:588-598.
57. Burgos-Vargas R, Foeldvari I, Thon A, et al. Pharmacokinetics of meloxicam in patients with juvenile rheumatoid arthritis. J Clin Pharmacol. 2004;44:866-872.
58. Ghlichloo I, Gerriets V. Nonsteroidal anti-inflammatory drugs (NSAIDs). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
59. Wong RSY. Disease-modifying effects of long-term and continuous use of NSAIDs in spondyloarthritis. Adv Pharmacol Sci. 2019;2019:5324170.
60. Gunaydin C, Bilge SS. Effects of nonsteroidal anti-inflammatory drugs at the molecular level. Eurasian J Med. 2018;50:116-121.
61. Rouzer CA, Marnett LJ. Structural and chemical biology of the interaction of cyclooxygenase with substrates and non-steroidal anti-inflammatory drugs. Chem Rev. 2020;120:7592-7641.
62. Osafo N, Agyare C, Obiri DD, et al. Mechanism of action of nonsteroidal anti-inflammatory drugs. In: Nonsteroidal Anti-Inflammatory Drugs. London: InTech; 2017.
63. Qandil AM. Prodrugs of nonsteroidal anti-inflammatory drugs (NSAIDs), more than meets the eye: a critical review. Int J Mol Sci. 2012;13:17244-17274.
64. Low M, Suresh H, Zhou X, et al. The broad spectrum anti-inflammatory activity of andrographolide in comparison to NSAIDs: a promising therapeutic compound against the cytokine storm. PLOS ONE. 2024;19:e0299965.
65. Magni A, Agostoni P, Bonezzi C, et al. Management of osteoarthritis: expert opinion on NSAIDs. Pain Ther. 2021;10:783-808.
66. Ding C. Do NSAIDs affect the progression of osteoarthritis? Inflammation. 2002;26:139-142.
67. Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. Am J Med. 1987;83:29-34.
68. Ziesenitz VC, Welzel T, van Dyk M, et al. Efficacy and safety of NSAIDs in infants: a comprehensive review of the literature of the past 20 years. Paediatr Drugs. 2022;24:603-655.
69. Cavkaytar O, Arga M. NSAID hypersensitivity in the pediatric population: classification and diagnostic strategies. J Asthma Allergy. 2022;15:1383-1399.
70. Traversa G, Bianchi C, Da Cas R, et al. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ. 2003;327:18-22.
71. Kwon J, Kim S, Yoo H, et al. Nimesulide-induced hepatotoxicity: a systematic review and meta-analysis. PLoS One. 2019;14:e0209264.

72. Ruperto N, Nikishina I, Pachanov ED, et al. A randomized, double-blind trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. Arthritis Rheum. 2005;52:563-572.
73. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010;2:299-316.
74. Baltrusch S. The role of neurotropic B vitamins in nerve regeneration. Biomed Res Int. 2021;2021:9968228.
75. Magaña-Villa M, Rocha-González H, Fernández del Valle-Laisequilla C, et al. B-vitamin mixture improves the analgesic effect of diclofenac in patients with osteoarthritis: a double-blind study. Drug Res (Stuttg). 2013;63:289-292.
76. Agarwal V, Alayoubi A, Siddiqui A, et al. Powdered self-emulsified lipid formulations of meloxicam as solid dosage forms for oral administration. Drug Dev Ind Pharm. 2013;39:1681-1689.
77. Samprasit W, Akkaramongkolporn P, Ngawhirunpat T, et al. Formulation and evaluation of meloxicam oral disintegrating tablet with dissolution enhanced by combination of cyclodextrin and ion exchange resins. Drug Dev Ind Pharm. 2015;41:1006-1016.
78. Nalluri BN, Chowdary KP, Murthy KV, et al. Tablet formulation studies on nimesulide and meloxicam-cyclodextrin binary systems. AAPS PharmSciTech. 2007;8.
79. Li S, Kou L, Qin Y, et al. A ternary system of meloxicam with matching hydrophilic polymer and cyclodextrin for improved stability in liquid preparations. RSC Adv. 2024;14:21260-21268.
80. Awasthi SS, Kumar TG, Manisha P, et al. Development of meloxicam formulations utilizing ternary complexation for solubility enhancement. Pak J Pharm Sci. 2011;24:533-538.
81. Hareeja MM, Abbas KI, Madiha F, et al. Solubility enhancement of meloxicam by binary and ternary solid dispersion. J Pharm Negative Results. 2022;13:116-124.
82. Ghorab MM, Abdel-Salam HM, El-Sayad MA, et al. Tablet formulation containing meloxicam and beta-cyclodextrin: mechanical characterization and bioavailability evaluation. AAPS PharmSciTech. 2004;5:e59.
83. Ministry of Health of the Republic of Kazakhstan. Order № KR DSM-11 of February 4, 2022: On amendments to Order № KR DSM-75 of August 5, 2021 "On approval of the list of drugs and medical devices for free and/or concessional outpatient provision…". 2022.
84. National Center for Expertise and Medicines & Medical Devices (NCELSIMI), MH RK. Database of the State Register of Medicines and Medical Devices. Almaty; 2023. http://register.ndda.kz/category/Gosudarstvennyi_reesttr.
85. Ministry of Health of the Republic of Kazakhstan. Kazakhstan National Drug Formulary (KNF). Astana; 2023. https://www.knf.kz/ru/site/about.
86. Sagindykova BA, Imanalieva SM. Study of the state of drug supply and nomenclature of medicines for children in the pharmaceutical market of the Republic of Kazakhstan. Pharmacia Kazakhstan. 2023.
87. Sagindykova B, Imanalieva S, Niyazbek A. Development of transdermal patches with anti-inflammatory, analgesic action for children. Eurasian J Med Nat Sci. 2024;4:116-118.
88. Spadoni C. Pediatric drug development: challenges and opportunities. Curr Ther Res Clin Exp. 2018;90:119-122.
89. Budsberg SC. Nonsteroidal anti-inflammatory drugs. In: Gaynor JS, Muir WW, eds. Handbook of Veterinary Pain Management. 3rd ed. St. Louis: Mosby; 2015:142-160.
90. Buvanendran A, Reuben SS. Nonsteroidal anti-inflammatory drugs, acetaminophen, and COX-2 inhibitors. In: Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE, eds. Raj's Practical Management of Pain. 4th ed. St. Louis: Mosby; 2008:671-692.
91. Furst DE. Meloxicam: selective COX-2 inhibition in clinical practice. Semin Arthritis Rheum. 1997;26:21-27.
92. Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. Arch Intern Med. 2000;160:2947-2954.
93. Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin. 2015;31:2331-2343.
94. Hussaini A, Solorio D, Young C. Pharmacokinetic properties of low-dose SoluMatrix meloxicam in healthy adults. Clin Rheumatol. 2016;35:1099-1104.
95. Chopra A, Bichile L, Rajadhyaksha AG, et al. Randomized double-blind clinical drug trials of meloxicam in rheumatoid arthritis and osteoarthritis knees: an Indian experience. APLAR J Rheumatol. 2004;7:108-116.
96. Prieto A, De Barrio M, Martín E, et al. Tolerability to nabumetone and meloxicam in patients with nonsteroidal anti-inflammatory drug intolerance. J Allergy Clin Immunol. 2007;119:960-964.
97. Levy DM, Imundo LF. Nonsteroidal anti-inflammatory drugs: practices and concerns of pediatric specialists and summary of safety data. Pediatr Rheumatol Online J. 2010;8:7.
98. Chichasova NV. General medical aspects of the use of meloxicam (Movalis®) in clinical practice: efficacy and safety. Sovremennaya Revmatologiya = Modern Rheumatology Journal. 2012;6:76-85.
99. Ivani G, Tonetti F. Postoperative analgesia in infants and children: new developments. Minerva Anestesiol. 2004;70:399-403.
100. Beck A, Salem K, Krischak G, et al. NSAIDs in the perioperative phase in traumatology and orthopedics: effects on bone healing. Oper Orthop Traumatol. 2005;17:569-578.
101. Curatolo M, Sveticic G. Drug combinations in pain treatment: review of evidence and a method for finding the optimal combination. Best Pract Res Clin Anaesthesiol. 2002;16:507-519.
102. Calderon Ospina CA, Nava Mesa MO, Arbelaez Ariza C. Effect of combined diclofenac and B vitamins (thiamine, pyridoxine, and cyanocobalamin) for low back pain management: systematic review and meta-analysis. Pain Med. 2020;21:1-16.
103. Ponce-Monter HA, Ortiz MI, Garza-Hernández AF, et al. Effect of diclofenac with B vitamins on acute pain from lower-limb fracture and surgery. Pain Res Treat. 2012;2012:104782.
104. Buesing S, Costa M, Schilling JM, et al. Vitamin B12 as a treatment for pain. Pain Physician. 2019;22:E45-E52.

105. Hosseinzadeh H, Moallem SA, Moshiri M, et al. Anti-nociceptive and anti-inflammatory effects of cyanocobalamin (vitamin B12) in mice. Arzneimittelforschung. 2012;62:324-329.
106. Sagindykova BA, Omarbekova AA. Evaluation of pharmaceutical characteristics of meloxicam tablets. Sciences of Europe. 2016;8-1:93-96.
107. State Pharmacopoeia of the Republic of Kazakhstan. Vol. 2. Almaty: Zhibek Zholy. 2009:804.
108. Shaikh R, O'Brien DP, Croker DM, et al. The development of pharmaceutical oral solid dosage forms. In: Singh R, Yuan Z, eds. Computer Aided Chemical Engineering. Amsterdam: Elsevier; 2018;41:27-65.
109. Obaidat AA, Obaidat RM. Development and evaluation of fast-dissolving tablets of meloxicam-β-cyclodextrin complex prepared by direct compression. Acta Pharm. 2011;61:83-91.
110. Delgado-García P, Alcocer-Herrera JB, Urenda-Quezada A, et al. A randomized controlled trial of dexketoprofen/vitamin B fixed-dose combination in post-traumatic grade I–II cervical sprains. Clin Drug Investig. 2024;44:413-424.
111. Algarni I, Alfayez AA, Alharbi HA, et al. Efficacy and safety of combining NSAIDs with vitamin B for musculoskeletal pain: a systematic review and meta-analysis. SJEMed. 2025;6:52-64. 1