DEVELOPMENT OF THE COMPOSITION OF EXTEMPORANEOUS OINTMENT FOR THE TREATMENT OF MUSCULOSKELETAL CONDITIONS

Yuryeva G.B., Shpychak O.S.

National University of Pharmacy of Ukraine

Introduction

A recent analysis of Global Burden of Disease data showed that approximately 1.71 billion people globally have musculoskeletal conditions (MSCs) [1]. While the prevalence of MSCs varies by age and diagnosis, people of all ages everywhere around the world are affected.

MSCs comprise more than 150 conditions that affect the locomotor system of individuals. They range from those that arise suddenly and are short-lived, such as fractures, sprains, and strains, to lifelong conditions associated with ongoing functioning limitations and disability [2]. They are typically characterized by pain (often persistent) and limitations in mobility, dexterity and overall level of functioning, reducing people's ability to work. MSCs include conditions that affect:

- joints (osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis);
- bones (osteoporosis, osteopenia and associated fragility fractures, traumatic fractures);
- muscles (sarcopenia);
- the spine (back and neck pain);
- multiple body areas or systems (regional and widespread pain disorders and inflammatory diseases) [2, 3].

NSAIDs are the first-line drugs for symptomatic treatment of MSCs. The main mechanism of action of NSAIDs is associated with their ability to inhibit cyclooxygenase and especially cyclo-oxygenase-2 (COX-2), which is involved in the formation of pro-inflammatory halogens - prostaglandins [4-6].

For greater safety of therapy in patients with MSCs, especially the elderly, it is recommended to use specific inhibitors of COX-2. The first representative of new selective NSAIDs, meloxicam, is gaining increasing popularity [7].

Meloxicam belongs to the group of enolic acid derivatives, like piroxicam, but differs from the latter in a slight structural change. Meloxicam easily penetrates the synovial fluid, where its concentration is 45-57% of the concentration in blood plasma. Meloxicam predominantly (selectively) suppresses COX-2 and only in high doses - physiological COX-1, with inhibition of which NSAIDs are associated with gastropathy, deterioration of renal blood flow, etc. Meloxicam is the body does not interact with other medications, including cytostatics, cardiac glycosides , diuretics and others, which is of great importance for the rational therapy of patients with concomitant diseases, especially in old age [8, 9].

Meloxicam blocks an enzyme that plays a key role in the synthesis of prostaglandins, substances that trigger inflammation and lower the pain threshold. It selectively acts on the formation of prostaglandins, which appear only during inflammation, and therefore causes fewer side effects from the digestive system compared to the so-called "traditional" or non-selective NSAIDs.

Meloxicam has been used in most countries of the world in medical practice since the end of the 20th century. Wide clinical practice has confirmed the effectiveness of analgesic therapy with minimal risk of adverse reactions to this group of drugs.

The main area of meloxicam application is joint diseases: all types of arthritis, including rheumatoid and gout, ankylosing spondylitis, as well as myalgia, neuralgia, osteochondrosis. Due to its pronounced anti-inflammatory effect, it relieves pain well, relieves swelling, restoring joint mobility. At the same time, meloxicam, unlike some anti-inflammatory drugs, is chondroneutral: it does not destroy cartilage and does not suppress the activity of chondrocytes, substances that ensure its renewal [10-13].

Meloxicam is now commercially available as a tablet, orally disintegrating tablet, dispersible tablet, suspension, capsule, granule, gel, cream, and injection. These data were obtained from the databases of the United States Food and Drug Administration (US FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA) and China Food and Drug Administration (CFDA). Meloxicam gel 5% is only commercially available in China in concentration 5% [14].

Meloxicam-based drugs are registered on the Ukrainian market as 52 trade names of one component [15, 16]. The quantitative distribution of dosage forms with meloxicam is shown in Fig. 1.

As can be seen from Fig. 1 at present, meloxicam on the Ukrainian market is mainly available in solid dosage forms, accounting for 63.5 % and liquid dosage forms (solutions for injections) for 36.5 %. Solid dosage forms are mainly tablets, which is 57.7 %. The remaining 5.8 % are drugs in the form of rectal suppositories.

The distribution of drugs among domestic and foreign manufacturers is 59.6% and 40.4 %, respectively. Foreign manufacturers are represented by companies from Germany (43%), Turkey (14 %), Cyprus (14%), Poland (14 %), Greece (10%), Canada (5%).

Meloxicam is presented on the world market in the form of 1 % gel (Exel, Movalis, Ocam Gel). Also, scientists from different countries are developing external combined dosage forms with meloxicam in the form of cream and patches [12, 13, 17-19].

Meloxicam penetrates well into the synovial fluid, and this is an indicator that the drug contributes to the suppression of the inflammatory process in the tissues of the joint, and therefore it is rational to use it in topical dosage forms. Recent developments have now shown that local, targeted drug delivery might be possible and effective [13, 20-25].

Based on the data obtained and taking into account the etiology, pathogenesis and existing schemes in the treatment of diseases of MSCs, it is expedient to create a combined ointment.

DOI: 10.5281/zenodo.8046263

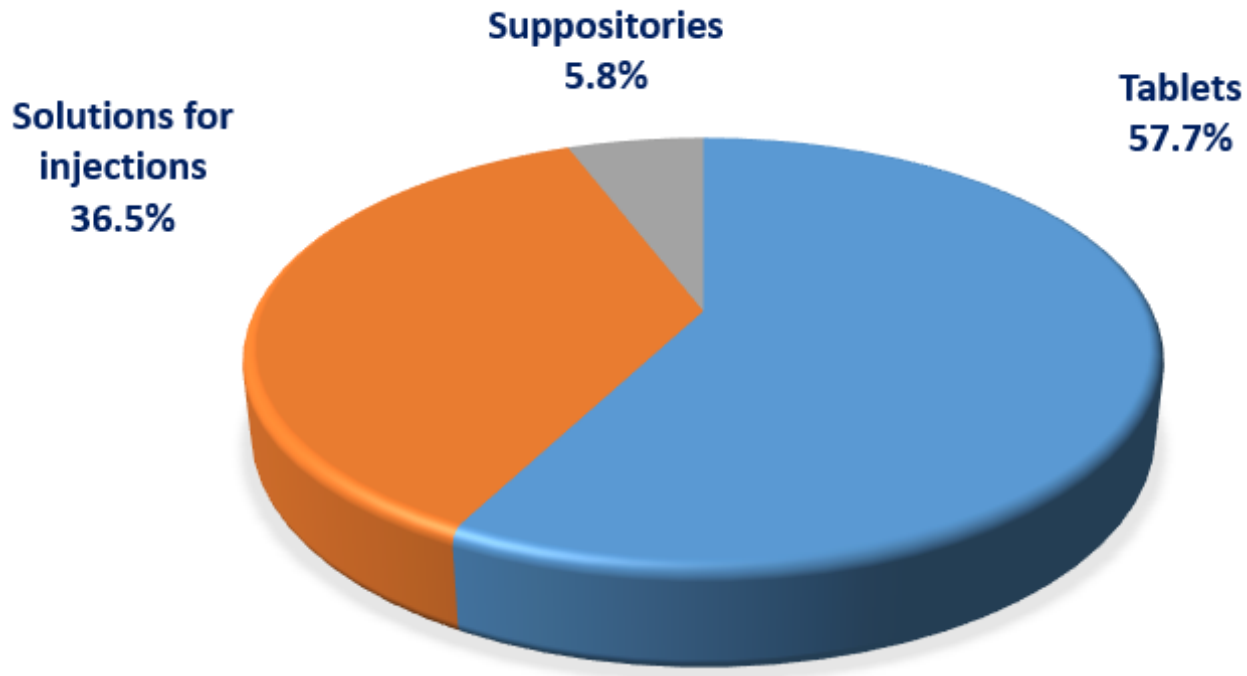

Fig. 1. The quantitative distribution of dosage forms of meloxicam on the Ukrainian market

Because, quite often diseases of the musculoskeletal system are accompanied by pain, it is desirable to add additional ingredients to the composition of the drug, which helps to reduce this manifestation. Therefore, for analgesia, menthol is introduced into the ointment, which when applied to the skin and mucous membranes causes irritation of cold thermoreceptors, which stimulates the formation and release of endogenous biologically active substances that play an important role in regulating pain, vascular permeability, and analgesic of menthol. When applied topically, menthol has a vasodilating, promoting better penetration of active ingredients through the skin [26]. Typically, the concentration of menthol in external dosage forms varies from 0.5 to 9 %. This menthol concentration is generally considered to be safe for use in topical formulations [27].

This combination of the two APIs, given their pharmacological activity, will provide the new drug with anti-inflammatory, analgesic, cooling effects, which will achieve the desired therapeutic effect in the treatment of MSCs.

All over the world today, the manufacture of medicines in the conditions of pharmacies does not lose its importance. Extemporal production of drugs makes possible an individual approach to the patient, which allows taking into account the characteristics of the organism, the course of the disease, the symptoms of the disease, and its stage. This is the main principle and advantage of making “extempore” preparations. Therefore, the creation of extemporal drugs of combined action for local use based on meloxicam will significantly solve the problems of diseases of the musculoskeletal system of patients and improve their quality of life.

The objective of this work was is to substantiate the composition and technology of extemporaneous ointment with meloxicam and menthol for the treatment of MSCs.

The development of an ointment with meloxicam was based on the following principles: the ointment base should be easily applied to the skin, have stability, the ability to easily perceive and release APIs.

Materials and Methods

The object of researches is ointment samples with meloxicam and menthol prepared on hydrophilic and emulsion bases in pharmacy conditions.

Biopharmaceutical research is carried out according to the method of diffusion into agar gel. It is based on a complexation reaction with the formation of a colored product between the hydroxyl group of the meloxicam molecule and iron (III) chloride introduced into the composition of the agar gel [28].

Preparation of the 2 % agar gel is carried out as follows: agar was placed in a pre-aged glass vessel, poured with purified water for 30 minutes to swell, heated to a boil, and add purified water to the required mass. To the warm gel was added 2 ml of iron (III) chloride and poured into Petri dishes on a strictly horizontal surface of the table. Agar was poured into dishes in two portions: first - 10 and 15 ml of agar (for jellification) and 3 metal cylinders were placed in each dish at an equal distance from each other and the edge of the dish. After jellification the second portion of the agar gel was poured and cylinders were carefully removed. About 2.0 g of ointment samples were placed in the formed wells of the dishes ensuring good contact with the agar. Petri dishes were numbered; placed in a thermostat at the temperature of 37°C. After 1, 2, 4, 8, 12, and 24 hours, dishes were removed and the diameter of the colored zones was measured. The observation time is 24 hours.

The obtained ointment samples were tested for colloidal and thermal stability, pH value.

Colloidal stability was tested after centrifugation at 6.000 rpm for 5 min.

DOI: 10.5281/zenodo.8046263

Thermal stability was determined in the absence of ointment stratification at the different temperatures modes: 7 days in an incubator at 40±2°C, then 7 days in a refrigerator at 10±2°C and 3 days at 20±2°C. Samples were considered stable if they remained homogeneous after thermal exposure [29].

pH determination. 2.5 g of ointment was placed in a beaker with a capacity of 100 mL, 50 mL of purified water R was added and stirred with a glass rod for 10 min; pH determined potentiometric method according to SPhU 2.0.

Results and discussion

Meloxicam was administrated to the extemporaneous ointment in a concentration of 1% which is wildly applied for the topical dosage forms of manufacture preparation.

Taking into account the combined effect of the developed dosage form, we selected a menthol concentration of 1 % to select the optimal ointment base for subsequent research.

At the first stage, 8 compositions were studied as ointment bases - hydrophilic and 6 - of an emulsion nature, since it is known that many NSAIDs show the best pharmacological effect in ointments on hydrophilic and emulsion bases. Based on the screening experiment of these compositions on hydrophilic and emulsion nature in terms of organoleptic and physicochemical indicators, 5 compositions of model samples of meloxicam ointments were selected.

The compositions of the model sample of ointment with meloxicam are represented in table 1.

As can be seen from table 1, model samples of meloxicam ointment were prepared using the following bases: vaseline-lanolin (samples 1, 2), an alloy of polyethylene glycol 400 and 4000 (samples 3, 4), and emulsion base (sample 5).

Table 1. Composition of model samples of ointment with meloxicam

Components	Sample				
	1	2	3	4	5
Meloxicam	1.0	1.0	1.0	1.0	1.0
Menthol	1.0	1.0	1.0	1.0	1.0
Dimethyl sulfoxide		10.0		10.0	10.0
Vaseline	87.0	77.0			
Lanolin	6.0	6.0			
Polyethylene glycol 400			68.6	58.1	
Polyethylene glycol 4000			29.4	24.9	
Emulsifying wax					15.0
Vaseline oil					15.0
Propylene glycol	5.0	5.0		5.0	
Purified water					up to 100.0

The technology of meloxicam ointment on the vaseline-lanolin base (sample 1) consisted of the grinding APIs (meloxicam and menthol) with a part of the lanolin-vaseline base, followed by adding the rest of the base.

It is known that the introduction of dimethyl sulfoxide (DMSO) into medicines composition, as an excipient with dispersing and solubilizing properties, is a rational approach and justified, especially for the local treatment of MSCs [30].

The most popular form of using DMSO in the treatment of these diseases are ointments and gels. Such dosage forms are used to relieve pain in the treatment of rheumatoid arthritis, ankylosing spondylitis, deforming osteoarthritis, arthropathy, radiculitis, for the treatment of bruises, ligament damage, traumatic infiltrates. Thus, the advantages for the patient when using such medicines are the increase of anti-inflammatory and analgesic effect due to synergism and acceleration of the result due to the "conductor function". In addition, DMSO has a positive effect on the skin and enhances the penetration of API through the skin into the blood [31-33]. The technology for making ointment (sample 2) consisted of the preliminary dissolution of meloxicam and menthol in DMSO and the introduction of this solution into a vaseline-lanolin base.

The use of PEG as a base allows to enhance resorption, APIs penetration into the skin, does not leave a greasy feeling [34]. Ointments with meloxicam of samples 3 and 4 were prepared by melting PEG-4000 on the water bath with constant stirring of the base, followed by the addition of PEG-400. At the same time, in sample 3, APIs were dissolved in the base, and in sample 4 - as a solution in DMSO, followed by its introduction into a mixture of PEG 400 and PEG 4000.

As follows from the literature, emulsifying wax, due to the presence of phosphate groups in the molecules of higher fatty alcohols, is close in structure to lecithin and cephalin, which are part of sebum, in this regard, emulsion wax has an effective emollient effect on the skin, preventing, thus, moisture loss and, like PEG bases, does not leave a greasy feeling [35]. Therefore, ointment sample 5 was prepared based on emulsion wax. The preparation of this sample consisted of the dissolution of meloxicam in DMSO, followed by the addition of a base consisting of an alloy of emulsion wax, water, and vaseline oil.

All prepared samples of meloxicam ointment were studied for stability during 1 month in the bottles of dark glass, according to such criteria as: appearance, pH, thermal and colloidal stability (table 2).

DOI: 10.5281/zenodo.8046263

Table 2. Quality indicators of the studied samples of meloxicam ointments

Sample	Appearance	pH	Colloidal stability	Thermal stability
1	A homogeneous mass of yellowish color, with a specific odor of menthol	5.5-5.7	+	+
2		5.5-6.1	-	-
3		5.8-6.4	+	+
4		5.6-6.3	+	+
5		5.9-6.5	+	+

Notes: 1) "-" – not stable; 2) "+" – stable.

As studies have shown, while storage, the ointment sample 2 prepared on a vaseline-lanolin base with DMSO exhibited delamination. Therefore, it was decided to exclude these compositions.

Biopharmaceutical studies of 1 % ointments with meloxicam were carried out by similar diffusion methods into an agar gel]

The results of the release of meloxicam from 1 % ointment samples (1, 3, 4, 5) are presented in Fig. 2.

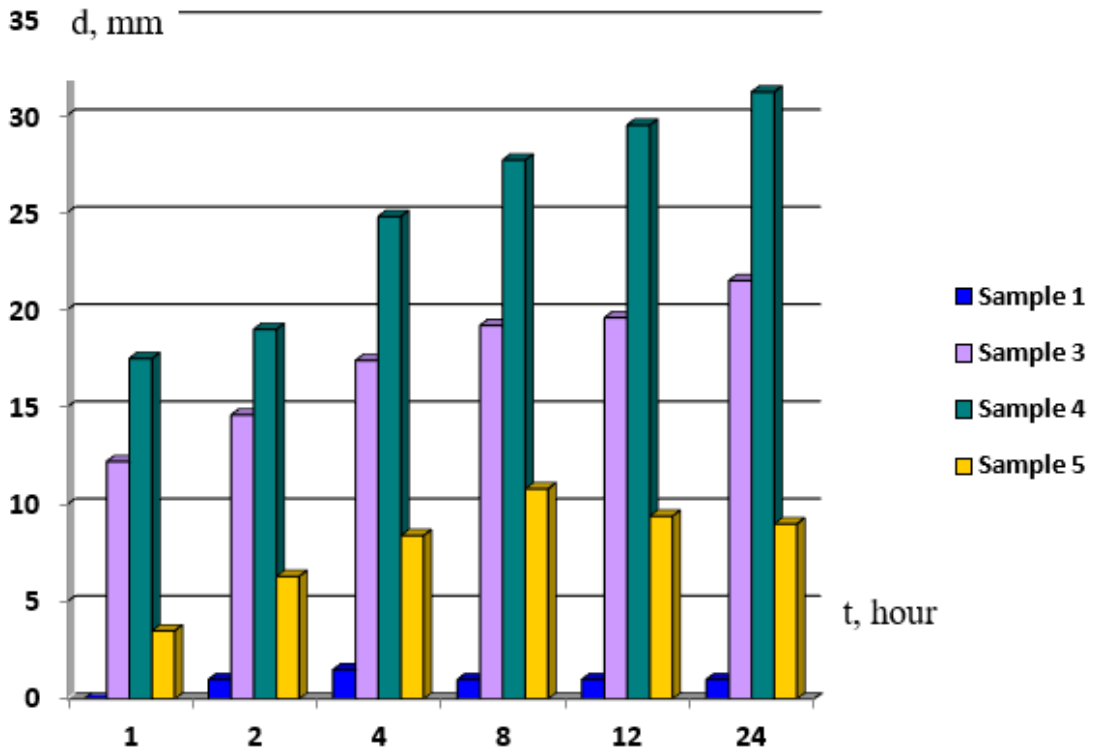

Fig. 2: Results of the meloxicam release from 1% ointment samples *(n = 5, P = 0.95)*

The study showed that, - the maximum release of meloxicam is achieved after 24 hours from the beginning of the "in vitro" experiment. As can be seen from the diagram, the release of meloxicam from the composition of sample 4 (an alloy of PEG base with DMSO) was much higher than the release of meloxicam from the other bases (the diameter of the colored zone, in this case, was 31.2 ± 0.3 mm).

In particular, it was superior from sample 3 prepared on the same base, but without DMSO in this case, the diameter of the colored zone was equal to 21.5 ± 0.4 mm).

Thus, it was proved that the presence of DMSO contributes to an increase in the release of meloxicam from ointments. If you carry out a comparative assessment of the release of meloxicam into an agar gel from the rest of the studied samples, it should be noted that samples 1 and 5 provide a lower degree of drug release from ointments. Thus, the diameter of the staining of the zones of sample 5 (emulsion wax base) was significantly less than samples 3 and 4 and amounted to 11 ± 0.3 mm. And release meloxicam from sample 1 (lanolin-vaseline base), was almost not observed.

Thus, the best release of meloxicam into the agar gel from the developed ointment samples is provided by the PEG base.

Thus, based on a complex of physical-chemical, biopharmaceutical studies, we have determined that sample 4 (based on an alloy of PEG) is the most optimal and is recommended for further study "in vivo".

Conclusions

For the MSCs treatment, the composition of the extemporaneous ointment which contains meloxicam and menthol has been proposed. The technology of ointment on a hydrophilic base with the introduction of dimethyl sulfoxide has been developed. Thermal and colloidal

DOI: 10.5281/zenodo.8046263

stability, pH values were studied. The conducted biopharmaceutical studies made it possible to verify the rationality of the choice of the base and auxiliary substances of the ointment, which was characterized by the best release of meloxicam.

Development of the Composition of Extemporaneous Ointment for the Treatment of Musculoskeletal Conditions

Yuryeva G.B., Shpychak O.S.

Introduction. Approximately 1.71 billion people worldwide have musculoskeletal conditions (MSCs), which include over 150 conditions. They range from the sudden onset and short-lived conditions to lifelong conditions associated with ongoing functional limitations and disabilities. Usually they are characterized by pain and limited mobility, which reduces the ability of people to work. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs for symptomatic treatment of MSCs. Skin delivery of NSAIDs offers several advantages over the oral route associated with potential side effects. The efficacy and safety profile of meloxicam is largely determined by the mechanism of its action and makes it a promising ingredient to treat diseases of MSCs, namely for the creation of topical dosage forms of combined action. Meloxicam, unlike some other anti-inflammatory medicines, is chondroneutral: it does not destroy cartilage and does not suppress the activity of chondrocytes, substances that ensure its renewal. It is also known that meloxicam in the body does not interact with other drugs, which is of great importance for the rational therapy of patients with concomitant diseases, especially in old age. **The aim** of this work is to develop an extemporaneous ointment with meloxicam of combined action to treat musculoskeletal conditions. **Material and methods.** Ointment samples were made on hydrophilic and emulsion bases, considering the solubility of the active pharmaceutical ingredients. Thermal and colloidal stability, pH values, biopharmaceutical research were determined by accepted methods. **Results and discussion.** Samples of the ointment containing meloxicam are a homogeneous mass of soft consistency with yellowish color and specific odor of menthol. While valuating the thermal stability of five samples of ointment to treat MSCs, it was found that this indicator did not match for sample 2. When centrifuging this sample; the ointment was separated into a fatty and aqueous phase. The pH value for all ointment samples corresponded to the pH of the skin. When studying release of meloxicam from the ointment using the agar gel diffusion method, it was found that an ointment containing dimethyl sulfoxide based on a PEG alloy provides the best release within 24 hours. **Conclusion.** For the MSCs treatment has proposed the composition of the extemporaneous ointment which contains meloxicam and menthol. The technology of ointment on a hydrophilic base with introducing dimethyl sulfoxide has been developed. Thermal and colloidal stability, pH values, were studied. The conducted biopharmaceutical studies made it possible to verify the rationality of the choice of the base and auxiliary substances of the ointment, which was characterized by the best release of meloxicam.

Keywords: nonsteroidal anti-inflammatory drugs, musculoskeletal conditions, ointment, technology, stability.

References

1. Cieza A., Causey K., Kamenov K., Hanson S. W., Chatterji S., Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020. 396 (10267). P. 2006-2017.
2. Pereira P. M.; Amaro J., Ribeiro B. T.; Gomes A., De Oliveira P., Duarte J., Ferraz J., Baptista J. S., Costa J. T. Musculoskeletal Disorders' Classification Proposal for Application in Occupational Medicine. Int. J. Environ. Res. Public Health. 2021. 18. P 8223. https://doi.org/10.3390/ijerph18158223
3. Hamilton B., Valle X., Rodas G., Til L., Grive R. P., Rincon J. A. G., Tol J. L. Classification and grading of muscle injuries: A narrative review. Br. J. Sports Med. 2015. 49. P. 306.
4. Gomaa Mahmoud R. S. Rheumatoid Arthritis: Diagnosed and Treatment. Acta Rheuma 2022. Vol. 9 No. 4. 14 p.
5. Barkin R. L. Topical Nonsteroidal Anti-Inflammatory Drugs: The Importance of Drug, Delivery, and Therapeutic Outcome. Am. J. Ther. 2015. 22 (5). P. 388-407. doi: 10.1097/MJT.0b013e3182459abd. PMID: 22367354
6. Jorge L. L., Feres C. C., Teles V. E. Topical preparations for pain relief: efficacy and patient adherence. J. Pain Res. 2010. 4. P. 11-24
7. Warksman J. C. Nonselective nonsteroidal anti-inflammatory drugs and cardiovascular risk: are they safe? Ann. Rharmacother. 2007. 41. P. 1163–1173.
8. Wen Z. H., Tang C. C., Chang Y. C. et al. Intra-articular injection of the selective cyclooxygenase-2 inhibitor meloxicam (Mobic) reduces experimental osteoarthritis and nociception in rats. Osteoarthritis Cartilage. 2013. 21 (12). P. 1976–1986.
9. Yocum D., Fleischmann R., Dalgin P.et al. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple doses, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. Arch Intern Med. 2000 Oct 23. 160(19). P. 2947.
10. Ohtori S., Inoue G., Orita S. et al. Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. Yonsei Med. J. 2013. 54 (5). P. 1253–1258.
11. Hasçicek C., BediZ-Ölçer A., Gönül N. Preparation and evaluation of different gel formulations for transdermal delivery of meloxicam. Turk. J. Pharm. Sci. 2009. 6. P. 177–186.
12. Bachhav Y. G., Patravale V. B. Formulation of meloxicam gel for topical application: In vitro and in vivo evaluation. Acta Pharm. Zagreb Croat. 2010. 60. P. 153-163.
13. Jianmin Chen, Yunhua Gao. Strategies for meloxicam delivery to and across the skin: a review. Drug Delivery. 2016. 23.8. 3146-3156. DOI: 10.3109/10717544.2016.1157839.

DOI: 10.5281/zenodo.8046263

14. Directory of medicines. Available at: https://www.vidal.ru/drugs/amelotex__42722
15. State Register of Medicines of Ukraine. Available at: http://www.drlz.com.ua
16. Compendium 2022 – drugs. Available at: https://compendium.com.ua
17. Abdul Rasool K. B., Gareeb R. H., Fahmy S. A., et al. Meloxicam β-cyclodextrin transdermal gel: physicochemical characterization and in vitro dissolution and diffusion studies. Curr Drug Deliv. 2011. 8. P. 381–91.
18. Barhate S. D. Development of meloxicam sodium transdermal gel. Int J Pharm Res Dev. 2011. 2. P. 1–4.
19. 19Duan X-D, Ji C-J, Nie L. Formulation and development of dendrimer-based transdermal patches of meloxicam for the management of arthritis. Trop J Pharm Res. 2015. 14. P. 583–90.
20. Yue Yuan, Xiao-yan Chen, San-ming Li, Xiu-yan Wei, Hui-min Yao, Da-fang Zhong. Pharmacokinetic studies of meloxicam following oral and transdermal administration in Beagle dogs. Acta Pharmacol Sin. 2009. Jul. 30(7). P. 1060–1064. doi: 10.1038/aps.2009.73
21. Singh P., Roberts M. S. Skin permeability and local tissue concentrations of nonsteroidal anti-inflammatory drugs after topical application. J Pharmacol Exp Ther. 1994. 268. P. 144–51.
22. Li Y. J., Pan Y., Xu H., Wei G., Zheng J. M. Pharmacokinetics and local tissue disposition of piroxicam following topical and oral application in rats. J Chin Pharm Sci. 2002. 11. P. 85–90.
23. Suh H., Jun H. W., Dzimianski M. T., Lu G. W. Pharmacokinetic and local tissue disposition studies of naproxen following topical and systemic administration in dogs and rats. Biopharm Drug Dispos. 1997. 18. P. 623–33.
24. Mohammadi-Samani S., Yousefi G., Mohammadi F., et al. Meloxicam transdermal delivery: effect of eutectic point on the rate and extent of skin permeation. Iran J Basic Med Sci. 2014. 17. P. 112–18.
25. Nief R. A., Hussein A. A. Preparation and evaluation of meloxicam microsponges as transdermal delivery system. Iraqi J Pharm Sci. 2014. 23. P. 62–74.
26. Topp Robert, Brosky Joseph A., Pieschel David. The Effect of Either Topical Menthol or a Placebo on Functioning and Knee Pain Among Patients With Knee OA. Journal of Geriatric Physical Therapy. 2013. 36 (2). P. 92-99 doi: 10.1519/JPT.0b013e318268dde1
27. Murat Oz1, Eslam G. El Nebrisi, Keun-Hang S. Yang, Frank C. Howarth, Lina T. Al Kury. Cellular and Molecular Targets of Menthol Actions. Frontiers in Pharmacology. 2017. Vol. 8. P. 1-17. https://doi.org/10.3389/fphar.2017.00472
28. Biopharmacy: a textbook for students of higher education institutions / O. I. Tikhonov, T. G. Yarnykh, I. A. Zupanets. Ed. O. I. Tikhonov. 2nd ed., revised. and additional Kh.: NPhaU: Golden Pages, 2019. 224.
29. State Consumer Standard of Ukraine. Cosmetic Creams. General Technical Conditions. DSTU 4765-2007. Kiev: State Consumer Standard of Ukraine. 2008. P. 7.
30. Otterbach A., Lamprecht A. Enhanced Skin Permeation of Estradiol by Dimethyl Sulfoxide Containing Transdermal Patches. Pharmaceutics 2021. 13. P. 320. https://doi.org/10.3390/pharmaceutics13030320
31. Marren K. Dimethyl Sulfoxide: An Effective Penetration Enhancer for Topical Administration of NSAIDs. The Physician and Sportsmedicine. 2011. 39(3).
32. Shulyak A. V., Goydyk V. S., Gusakovsky S. S., Grygorenko V. N., Mytsik Y. O., Badiuk N.S. Modern aspects of the use of dimethyl sulfoxide (dmso). PharmacologyOnLine. 2021 (1). P. 82-89.
33. Ivkin D. Yu., Okovityy S. V., Anisimova N. A. Dimethyl sulfoxide substance with pleiotropic effects, relevant in diseases of the musculoskeletal system. Attending physician. 2019. Vol. 4. P. 19-22.
34. K McMartin. Propylene Glycol. Encyclopedia of Toxicology. 3rd edition. 2014. P. 1113-1116. http://dx.doi.org/10.1016/B978-0-12-386454-3.01029-01113
35. Handbook of pharmaceutical excipients / edited by Paul J. Sheskey, Bruno C. Hancock, Gary P. Moss, David J. Goldfarb. London. Pharmaceutical Press. Washington. DC. American Pharmacists Association. 9th ed. 2020. 1296 p.

DOI: 10.5281/zenodo.8046263