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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
Faculty for training foreign citizens
Department of Pharmaceutical Chemistry

QUALIFYING WORK

on the topic: "**SELECTION OF CONDITIONS FOR THE QUANTITATIVE DETERMINATION OF MELOXICAM IN A COMBINED MEDICINE**"

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ANNOTATION

In the qualification work, the optimal conditions for the quantitative determination of meloxicam in the composition of a combined drug in the form of a powder for oral solution preparation were theoretically substantiated and selected. The validation characteristics of the developed methodology were studied. An analysis of the modern pharmaceutical market for medicines containing meloxicam as the active substance was also conducted.

The total volume of work is 44 pages.

The work contains: figures – 11, tables – 14, literature sources – 42, appendix – 1.

Keywords: meloxicam; quality control; validation; spectrophotometry.

АНОТАЦІЯ

В кваліфікаційній роботі теоретично обґрунтовано та підібрано оптимальні умови для кількісного визначення мелоксикаму в складі комбінованого лікарського засобі у формі порошку для приготування орального розчину; досліджено валідаційні характеристики розробленої методики. Проведено аналіз сучасного фармацевтичного ринку лікарських засобів, діючою речовиною яких є мелоксикам.

Загальний обсяг роботи становить 44 сторінки.

Робота містить: рисунків – 11, таблиць – 14, джерел літератури – 42, додатків – 1.

Ключові слова: мелоксикам; контроль якості; валідация; спектрофотометрія.

CONTENTS

LIST OF SYMBOLS

API – active pharmaceutical ingredients;

ATC – Anatomical Therapeutic Chemical Classification;

COX-2 – cyclooxygenase-2;

DMF – dimethylformamide;

GC – gas chromatography;

NSAID – nonsteroidal anti-inflammatory drug;

MP – medicinal product;

Ph.Eur. – European Pharmacopoeia;

Spectrophotometry – Absorption spectrophotometry in the UV-visible area;

SPhU – State Pharmacopoeia of Ukraine.

INTRODUCTION

Today, medicinal products containing meloxicam as an active ingredient are widely available on the pharmaceutical markets of Ukraine and worldwide. The guarantee of the successful use of medicinal products for pharmaceutical and therapeutic purposes lies in their proven quality, which is ensured, among other factors, during the drug development stage. Given that the modern pharmaceutical market is characterized by a rapid expansion in the range of medicinal products containing meloxicam, selecting optimal conditions for its quantitative determination in new medicinal products is a pressing task.

The purpose of this qualification work is to substantiate and select optimal conditions for the quantitative determination of meloxicam in a combined medicinal product in the form of a powder for oral solution preparation.

To achieve this goal, the following *tasks* were addressed:

– Analyse the literature on the pharmacological properties, medical applications, physicochemical properties, and existing methods of quality control for meloxicam;

– Examine the current pharmaceutical market in Ukraine for medicinal products containing meloxicam;

– Substantiate and select conditions for the quantitative determination of meloxicam in a combined medicinal product in the form of a powder for oral solution preparation using absorption spectrophotometry in the UV-visible area;

– Validate the proposed analytical method.

The object of the study is a combined medicine in the form of a powder for oral solution preparation, with meloxicam as the active pharmaceutical ingredient.

The subject of the study is the optimal conditions for the quantitative determination of meloxicam in the combined medicine using absorption spectrophotometry in the UV-visible area.

Research methods: analysis of literature data, marketing research methods, analysis of competitors and market structure, physicochemical research methods, statistical processing of research results, and validation of analytical methods.

Practical significance. The obtained results can be applied to quality control of meloxicam through the developed method for its quantitative determination by absorption spectrophotometry in the UV-visible area.

Scientific novelty. The study includes the development and validation of a modern spectrophotometric method for the quantitative determination of meloxicam in a combined medicine in the form of a powder for oral solution preparation.

SECTION I
PHARMACOLOGICAL PROPERTIES AND MEDICAL APPLICATIONS OF MELOXICAM. PHYSICOCHEMICAL CHARACTERISTICS AND EXISTING QUALITY CONTROL METHODS

1.1 Overview of meloxicam: pharmacological profile, clinical applications, and safety considerations

Meloxicam is a popular nonsteroidal anti-inflammatory drug (NSAID) used to relieve pain and inflammation related to different musculoskeletal diseases. Meloxicam is a drug that was first introduced in the late twentieth century, gaining popularity due to its selectivity for inhibiting cyclooxygenase-2 (COX-2), thereby reducing stomach-related adverse effects characteristic of non-selective NSAIDs [5-12, 15, 16, 19, 21, 28, 29, 31, 33, 37].

It is highly attracted to synovial tissues and cartilage, which accounts for its use in the treatment of rheumatic and arthropathic conditions. Meloxicam has similar anti-inflammatory, analgesic, and antipyretic effects, but with a marked reduction in peripheral edema when used at higher doses compared to non-selective COX inhibitors [21, 28, 29, 31].

Its pharmacology makes it an optimal choice for chronic management in conditions such as osteoarthritis and rheumatoid arthritis, which are often maintained over a lifetime. Meloxicam also plays a significant role in pharmacy because as is known to improve patient compliance with once-daily dosing and enjoys an excellent safety profile when used in appropriate clinical scenarios [5-12, 21, 22, 24, 32, 38].

Meloxicam is one of the most commonly used NSAIDs for adults and children, because it is not only a powerful analgesic, but also a highly specific and potent inhibitor of the COX-2 enzyme [5-12, 18, 19, 23].

Meloxicam presents with a plethora of pharmacokinetic features rather unique to it such as unpronounced first-pass hepatic metabolism, fast tissue penetration and

high-capacity plasma protein binding, whereas exerting considerable drug interplays over medicines sharing same mechanisms. Because of the traffic jam in bio membranes, cellular structures, organelles and some carrier proteins caused by excretion via biliary-urinary pathway for most metabolites' meloxicam may additionally cause various degrees reversible hepatotoxicity (with or without cholestasis) and nephrotoxicity. Meloxicam is a basic drug which can distribute to its site of action throughout the body due to passive diffusion after partitioning into cytoplasm, enter tissues and be bio transformed in liver for elimination, making it safe as well as efficacious [5-12, 21, 22, 24, 32, 38].

The main metabolic pathway responsible for the pharmacological effect of meloxicam is through inhibition of COX-2 enzyme which results in a decrease in prostaglandins that are involved to inflammation and pain. Meloxicam is considered to be a more selective COX-2 inhibitor than non-selective NSAIDs, and its higher potency relative to older drugs in this class such as diclofenac may translate into fewer adverse gastrointestinal effects. At least at lower doses, this selectivity is due to meloxicam having a higher binding affinity for the COX-2 enzyme, so, this medication is frequently used to treat disorders like arthritis [5-12, 18, 19, 21-25, 32, 38].

The pharmacokinetic of meloxicam is derived from absorption, distributed in the body, metabolized and excreted. Other important features are bioavailability, half-life and systemic exposure. Meloxicam is dosed in a mostly linear fashion (as are other NSAIDs, up to 15 mg/day) with some nonlinearity possibly present at doses > 15 mg/d. The pharmacokinetic parameters of meloxicam may be influenced by age, weight and renal function. Meloxicam should be used at higher doses sparingly in the elderly and obese patients. There is also a need for caution in patients with reduced renal function as the metabolism of meloxicam depends on organ integrity [5-12, 21, 22, 24, 32, 38].

Absorption. The absolute bioavailability of meloxicam capsules was 89 % following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were

shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling [5-12, 18, 19, 23, 22, 24, 32, 38].

Distribution. The mean volume of distribution of meloxicam is approximately 10 L. Meloxicam is ~99.4 % bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to ~99 % in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10 %. Following a radiolabeled dose, over 90 % of the radioactivity detected in the plasma was present as unchanged meloxicam. Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40 % to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown [5-12, 19, 21, 22, 24, 32, 38].

Metabolism. Meloxicam is almost completely metabolized to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxy meloxicam (60 % of dose), from P-450 mediated metabolism was formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9 % of dose). In vitro studies indicate that cytochrome P-450 2C9 plays an important role in this metabolic pathway with a minor contribution of the CYP 3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively [5-12, 18, 21, 22, 23, 22, 24, 38].

Excretion. Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged

parent compound are excreted in the urine (0.2 %) and feces (1.6 %). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5 %, 6 % and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50 %. The mean elimination half-life (t1/2) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 mL/min [5-12, 21, 22, 24, 32, 38].

The pharmacokinetic profile of meloxicam is relatively consistent between different disease states which aids predictability and thus clinical utility in determining optimal dosing intervals. This is why best practice in patients receiving meloxicam often involves personalized pharmacokinetic/pharmacodynamic-guided therapy [5-12, 21, 22, 24, 32, 38].

It also has an efficacy of 24 per 100 patients for pain relief, as a second-line analgesic. Moreover, benefits plateau at this dose and doses higher than 15 mg/day do not increase additional efficacy; even greater levels of activation (approximately two- to fivefold what we tested) are still effective. Key pharmacokinetic–pharmacodynamic studies are needed to predict when the therapeutic effect will occur, and can help in right dose titration. In addition, incapability of meloxicam to modulate its anti-inflammatory activity based upon the employed dosing regimen may contribute towards an increased incandescence in DDIs with other therapies for which co-administration is warranted [21, 22, 24, 32, 38].

Depending on post-marketing research and the route of administration, different therapeutic indications are approved. Guidelines & recommendations for the use of meloxicam are published by different medical institutions [18, 19, 23].

Meloxicam is an FDA-approved medication for the treatment of many inflammatory conditions such as osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis [5-12]. Meloxicam is administered in a number of forms

suitable for various patient populations: oral tablets, capsules and solution injectables are available. Oral formulations are advantageous because of their convenience and extended-release, offering once-daily dosing benefiting patient compliance. There is also ongoing work in the area of topical meloxicam formulation, for targeted pain relief and minimal absorption into the systemic circulation [5-12, 18, 19, 21-25, 32, 33, 38]

Adverse Effects and Contraindications. Meloxicam, as an NSAID, exhibits the following side effects, similar to other agents from its class: gastrointestinal effects, including bleeding, gastric pains, and an increase in hepatic enzymes. When introducing meloxicam, it is essential to assess antecedent cardiovascular episodes in the patient, including arterial hypertension, ischemic attack, and myocardial ischemia. Furthermore, meloxicam could have potential in the development of congestive heart failure. The co-administration of additional corticosteroids, other NSAIDs, and anticoagulants should be approached with prudence because this may enhance their toxicity. As for a contraindication, meloxicam should not be administered to children [5-12, 18, 19, 23, 33].

In conclusion, meloxicam continues to be an important option for the treatment of inflammation and accompanying painful conditions because of its COX-2 selectivity with less gastrointestinal risk.

1.2 Physicochemical characteristics and quality control methods of meloxicam

Meloxicam is a $C_{14}H_{13}N_3O_4S_2$ molecule with the molecular weight of 351.4 g/mol [15-17, 25, 27, 29, 31, 34, 40].

The physical properties of meloxicam include the following: a pale yellow crystalline powder; poorly soluble in water and soluble in polar organic solvents such as dimethylformamide (DMFA), dimethyl sulfoxide, and methanol. Melting point: approximately 255-258°C. Meloxicam exhibits moderate lipophilicity, with a Log P value of around 1.1–1.2. Stability: stable under normal storage conditions;

sensitive to strong acidic or alkaline conditions, which may cause degradation [14, 15, 17, 27, 29, 34, 40].

It has two ionisable functional groups, the 4-hydroxyl group of the thiazine and the N1 of the thiazolyl substituent (Fig. 1.1) [35].

According to its physicochemical properties, meloxicam is an amphoteric compound, as it contains both acidic (hydroxyl) and basic (amino) groups. Depending on the pH of the environment, it can exist in different forms: cationic (in an acidic environment), neutral, or anionic (in an alkaline environment). The acid dissociation constant (pKa) is 4.08 [14-17, 20, 25, 26, 27, 29, 31, 34-36, 40].

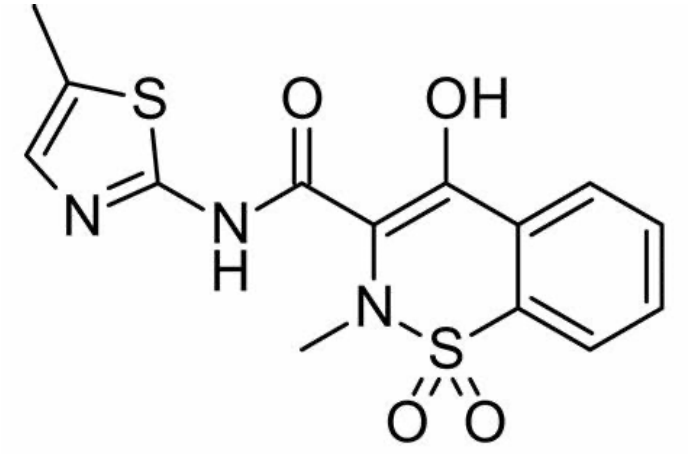

Fig. 1.1 Chemical structure of meloxicam

These physicochemical properties of meloxicam including its pH-sensitivity are essential when used in drug delivery systems. Also in the presence of ultrasound-generated hydroxyl metal ions meloxicam molecular can be degraded. Higher temperatures may increase dissociation of meloxicam, as well as its reactivity, but can form thermoregulated products that do not show any significant changes in the clinical aspect [20, 25, 26, 27, 29].

Solubility is one of the most important factors which decides bioavailability, since a drug can only act when exist in its soluble form as absorption of drugs will always happened when they are in solution. Thus, at a pH of 7.4 (where the drug actually acts), meloxicam existing in its prevailing unionized state brings about and supports activity [14-17, 20, 27, 29, 31, 40].

The current quality control methods for meloxicam and its formulations active principles are necessary during all phases of manufacturing process in order to guarantee that these drugs will have constant pharmaceutical qualities [14-16].

It is essential to test the quality of Meloxicam in pharmaceutical dosage forms as drug potency and purity will influence its functional profile (efficacy, safety) that may result in adherence to regulatory requirements. A literature survey has revealed several methods for the determination of meloxicam and they include the titrimetric method with the most common being the non-aqueous titration. Other methods reported are potentiometric titration, UV-spectrophotometric methods, Visible spectrophotometry, Near infra-red spectroscopy, Voltammetry, Fluorescence spectrometry, Thin layer chromatography and High Performance Thin Layer Chromatography. The use of High-Performance Liquid Chromatography (HPLC) for the assay of meloxicam in biological fluids and pharmaceutical preparations has also been reported [14-17, 20, 25, 26, 29, 31, 34-36, 39].

The HPLC is the most used method for meloxicam analysis because of its high precision and accuracy to separate meloxicam from its impurities, degradation products in pharmaceutical formulation. Most HPLC methods utilize reverse-phase columns with water, acetonitrile, methanol mixtures as mobile phases. Meloxicam detection is usually performed using UV detectors at a wavelength of 355 nm (λ max absorbance) [14, 20, 26, 27, 31, 40].

Gas Chromatography (GC): Used less commonly than HPLC, GC can be used for meloxicam analysis as well when coupled with mass spectrometry to increase sensitivity and specificity. Meloxicam needs to be derivatized for its adequate volatility, which can only take place in a GC column [35].

Absorption spectrophotometry in the UV-visible area (Spectrophotometry): This is a simple and relatively cheaper method for analysing the amount of meloxicam. This is a method that easily determines authenticate quality control can be developed and the absorbance of meloxicam can generally take place at specific wavelengths. Some common techniques for quantifying meloxicam by

spectrophotometry are presented below (Table 1.1) [15, 16, 17, 25, 29, 31, 34-36, 39].

Table 1.1

Methods of quantitative determination of meloxicam by spectrophotometry

Terms of definition (environment, pH, reagent)	λ_{max}, nm	Linearity range of the method, μg/ml
0.1 N NaOH solution	269	5-30
10% sodium citrate solution	269	5-30
1 M NaOH + MeOH (1:1, v/v)	341	1,0-14,0
Borate buffer (pH=8.5)	363	0,5-30
Phosphate buffer (pH=8) + methylene blue + chloroform	653,5	1,5
0.1 M NaOH solution + 5 % $FeCl_3$	476	50-250
3-methylbenzo-thiazolinone hydrazone + $Ce(NH_4)_2(SO_4)$	450	2-20
	360	1-10
2,3-dichloro-5,6-dicyano-p-benzocaine	455	40-160
Astrafloxin (pH=8-12) + DHE isooctane	541	0,7-20

In modern world pharmacopoeias, titrimetry methods are also used for quantitative determination of meloxicam in substances [27, 40, 42].

Conclusions to section I

1. A review of literature sources on the pharmacological properties, medical applications, physicochemical properties, and existing methods of quality control for meloxicam was conducted.

SECTION II
OBJECT AND METHODS OF RESEARCH, INFORMATION ABOUT DEVICES, EQUIPMENT AND REAGENTS

2.1 Analysis of the pharmaceutical market of medicinal products containing meloxicam

Pharmaceutical market analysis is a key stage in the research and assessment of the current state and development prospects of a particular group of medicinal products (MPs). It allows collecting and analysing data on the market situation, dynamics, trends, competitive environment, and consumer behaviour. The results of such analysis are an effective tool for identifying the main active pharmaceutical ingredients (API) used in the manufacture of finished MPs of this pharmacological group, available dosage forms, manufacturers, etc [1, 13].

To study the market of meloxicam-containing medicines, such information sources as the State Register of Medicines of Ukraine [4] and the Compendium Online Medicines Directory were used [5-12]. In the course of the research, methods of marketing analysis, study of the competitive environment and market structure were implemented [1, 13].

According to the results of the analysis, as of the third quarter of 2024, 70 names of MPs containing meloxicam were registered in Ukraine (Appendix A, Table 1). Given that 10 of them are APIs for the manufacture of finished MPs (Appendix A, Table 2), their number was not taken into account in further calculations [4, 5-12].

As a result of the studies, it was found out that according to the Anatomical Therapeutic Chemical Classification (ATC), these MPs belong to the group: ATC M01A C06 – Agents affecting the musculoskeletal system; Anti-inflammatory and anti-rheumatic agents, non-steroidal anti-inflammatory and anti-rheumatic agents; Oxycoms; Meloxicam [4, 5-12].

It was found that the most frequently used MP containing meloxicam are presented in the dosage forms ‘Tablets’ – 29 items (48.3 %) and “Solution for injections” – 28 items (46.7 %). A smaller share belongs to MPs in the dosage form “Suppositories” – 3 items (5.0 %) (Fig. 2.1) [4, 5-12].

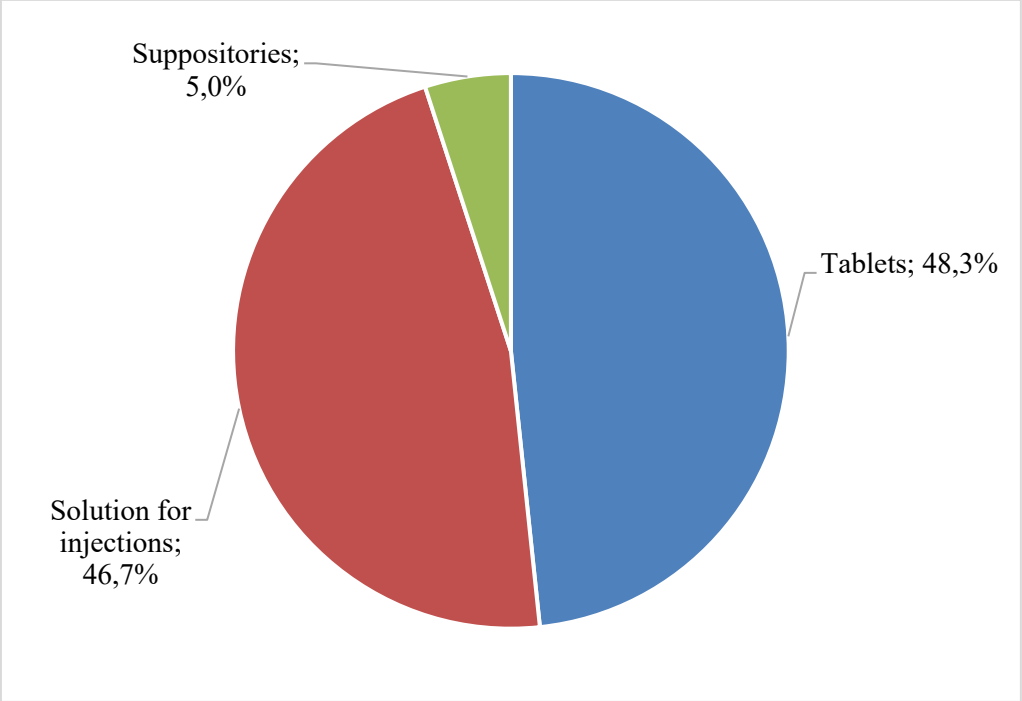

Fig. 2.1 Distribution of MPs of meloxicam by type of dosage form

According to the ATC classification, all of the above MPs are single-ingredient medicines – 60 items (100.0 %), while two- and combination medicines with meloxicam were not registered in Ukraine at the time of the study [4, 5-12].

The study of manufacturers of MPs with meloxicam found that the share of imported products and those manufactured in Ukraine is almost the same: 31 items (51.7 %), and 29 items (48.3 %), respectively. The largest importer is Greece – 8 items (13.3 %), Turkey has a smaller share in imports – 6 items (10.0 %); Spain, the Republic of Poland – 3 items (5.0 % each); Canada, Italy, India, Romania, Cyprus – 2 items (3.3 %); Slovenia – 1 item (1.7 %) (Fig. 2.2) [4, 5-12].

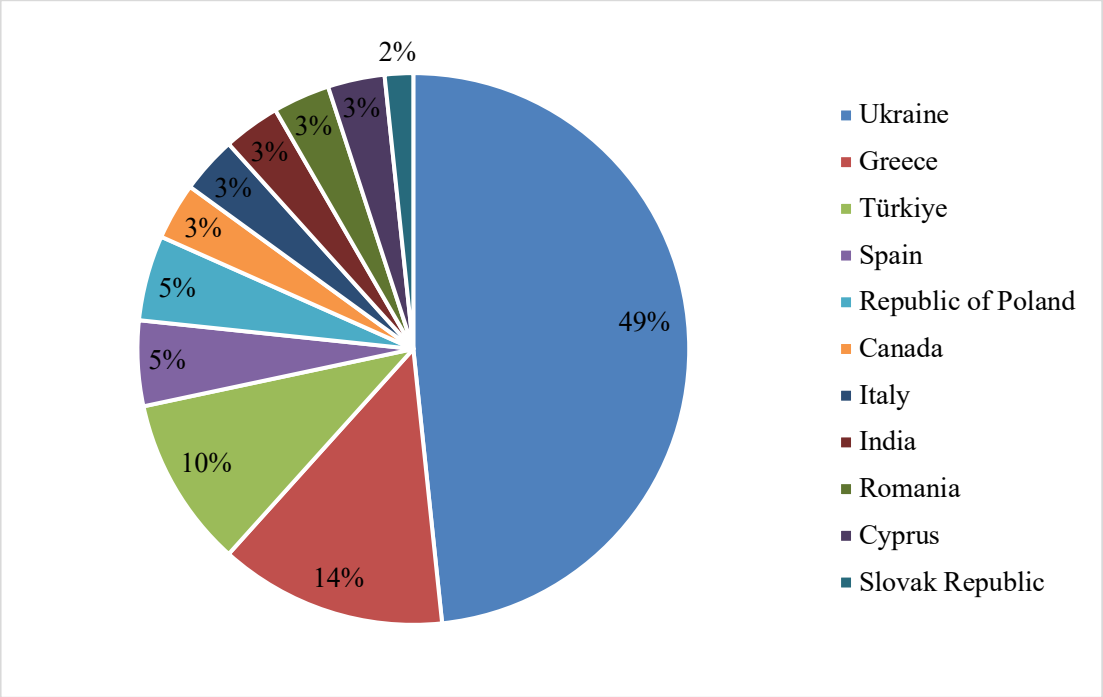

Fig. 2.2 Division of MPs by country of manufacture

The leading manufacturers of MPs with meloxicam in Ukraine, containing iron compounds, are Lekhim-Kharkiv JSC – 8 items (27.6 %*), Farmex Group LLC – 5 items (17.2 %*), Farmak JSC – 4 items (13.8 %*), and Novopharm-Biosynthesis LLC, MICROCHEM LLC – 3 items each (each 10.3 %*), ASTRAFARM LLC, Kyiv Vitamin Plant JSC – 2 items each (6.9 %*), Farmasel LLC, Research and Production Centre Borshchahivskiy Chemical and Pharmaceutical Plant JSC – 1 item each (3.4 %*) (Fig. 2.3). Note: * – in terms of the number of MPs manufactured by domestic manufacturers [5-12].

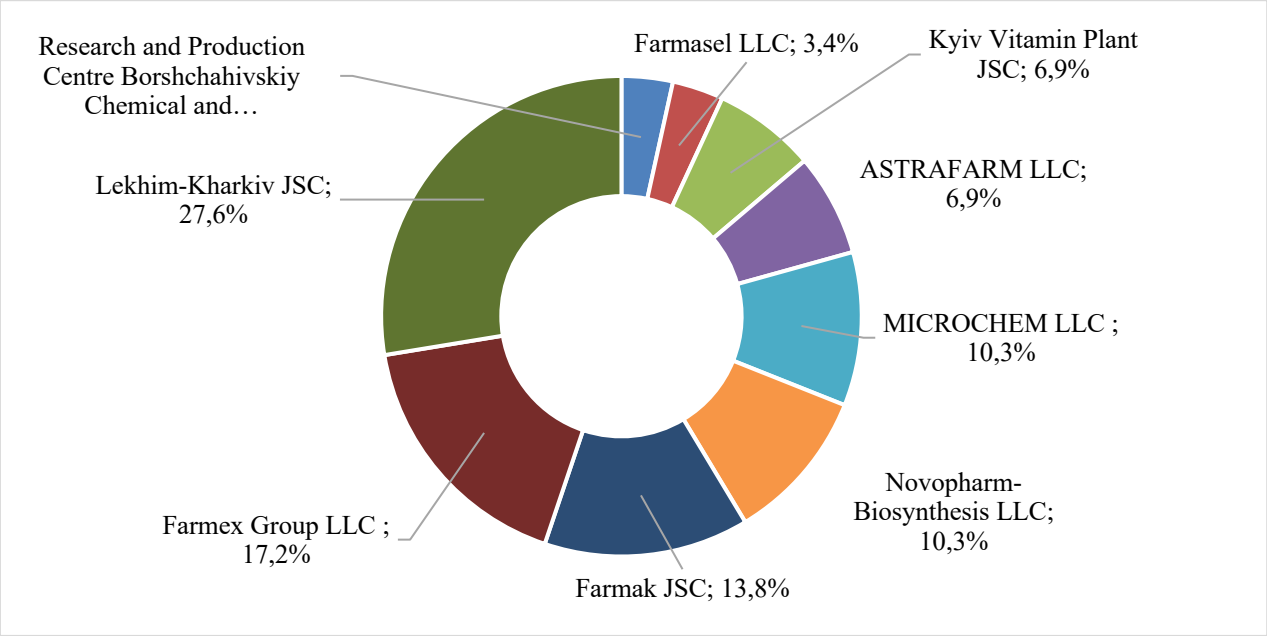

Fig. 2.3 Division of MPs produced by domestic manufacturers*

Thus, the analysis of the pharmaceutical market of Ukraine with MPs containing meloxicam revealed that they belong to the same ATC group (ATX M01A C06) and are represented by mono-preparations in tablet, suppository and injection solution dosage forms. The amount of MPs imported and produced in Ukraine is almost the same. The largest supplier is Greece. Ukrainian-made medicines are represented by 29 items manufactured by 9 pharmaceutical companies [4, 5-12].

2.2 The objects of the study

The object of the study was a new combined MP (series 01-03), the active substances of which are glucosamine sulfate sodium chloride (equivalent to 1.5 g of glucosamine sulfate and 0.384 g of sodium chloride) – 1.884 g and meloxicam – 0.015 g in the form of powder for oral solution, 4.0 g in a sachet.

2.3 Research methods and brief information on instruments, equipment and reagents

During the experimental part of the study, modern physical, physicochemical methods of analysis, statistical analysis of chemical experiment results and validation of analytical techniques and tests in accordance with the current edition of the State Pharmacopoeia of Ukraine (SPhU) [2, 3] and the European Pharmacopoeia (Ph.Eur.) [27] were used.

The research was carried out using analytical scales “Kern”, model “ABT 120-5DM” (Germany) and an ultrasonic bath “Sonorex, model “Super RK 103 H” (Germany).

Class A (first class) measuring utensils from “Simax” (Czech Republic) were also used for the analysis.

Working solutions were prepared in accordance with the methods given in section SPhU 2.0, “Reagents”; in some cases, working solutions were prepared according to the requirements of other pharmacopoeias, as indicated in the relevant methods. The solutions were used freshly prepared or within the shelf life specified in the relevant regulatory documents [2, 3].

2.3.1 Development of a technique for the quantitative determination of meloxicam by spectrophotometry

Absorption spectrophotometry in the UV-visible area (spectrophotometry) is a physicochemical method of analysis based on the determination of the absorption spectrum or measurement of light absorption at a specific wavelength. The method is characterised by simplicity of execution, accuracy of the results obtained and is used to identify compounds, study the composition, structure and quantitative analysis of individual substances and multicomponent systems [3, 15, 25, 27, 29, 40].

The determination was carried out by absorption spectrophotometry in the ultraviolet and visible regions in accordance with the requirements of the Ph.Eur./ SPhU, 2.2.25 [3, 27].

A Specord 200 double-beam spectrophotometer manufactured by AnalitykJena (Germany) was used for the research. The optical density of the test solutions and the standard solutions was measured in cuvettes with a layer thickness of 10 mm.

A standard sample of meloxicam (Sigma Aldrich, Cat. No. PHR1799, series LRAA8813) with a substance content of 100.0 % was used to prepare the comparison solutions.

2.3.2 Uniformity of mass of single-dose preparations

Sachet pouches are a popular form of dosage because they provide an exact amount of active ingredient for a single dose, are easy to use and protect the contents from external influences. However, even minor deviations from the nominal weight of the contents can affect the effectiveness of treatment, especially for MPs with a narrow therapeutic index. Therefore, determination of the indicator “Uniformity of mass of single-dose preparations” is an important component of quality control of powders in the form of sachet pouches [2, 3].

The determination was carried out in accordance with the requirements of the Ph.Eur/SPhU, 2.9.5. We randomly selected 20 pouches, weighed each pouch with its contents separately, emptied it of its contents and weighed it again. The difference was used to determine the weight of the pouch contents, and then the average weight was calculated [2, 3, 27].

In accordance with the requirements of the Ph.Eur/SPhU, if the average weight of the pouch contents is more than 300 mg, the permissible deviation should be ± 7.5 % [2, 3, 27]. For the batches of the analysed preparation (4,000 g), the average weight of the pouch contents should be between 3,700 g and 4,300 g.

Out of 20 test pouches, no more than 2 pouches with a deviation from the average weight of the pouch contents of more than ± 7.5 % are allowed, and no pouches with a deviation from the average weight of the pouch contents of more than ± 15 %. The determination was carried out for each batch of the medicine [2, 3, 27].

2.3.3. Validation of analytical techniques and statistical analysis of experimental results

The study of validation characteristics was carried out in accordance with the requirements of the general article of the SPhU, 5.3.N.2 “Validation of analytical techniques and tests” [3].

The statistical processing of the obtained results was carried out in accordance with the requirements of the general article of the SPhU, 5.3.N.1 “Statistical analysis of chemical experiment results N” using Microsoft Office 2019 software [3].

Conclusions to Section II

1. An analysis of the pharmaceutical market of Ukraine containing meloxicam was carried out. It has been established that according to the ATC classification, they belong to the same ATC group (ATX M01A C06) and are represented by mono-preparations in the dosage forms of tablets, suppositories and solution for injection. The amount of medicines imported and produced in Ukraine is almost the same. The largest supplier is Greece. Ukrainian-made MPs are represented by 29 items manufactured by 9 pharmaceutical companies.
2. The object of the study was chosen – a new combination MP (series 01-03), the active substances of which are glucosamine sulfate sodium chloride (equivalent to 1.5 g of glucosamine sulfate and 0.384 g of sodium chloride) – 1.884 g and meloxicam – 0.015 g in the form of powder for oral solution, 4.0 g in a sachet.
3. The methods, equipment and devices used in the research are described.

SECTION III
SELECTION OF CONDITIONS FOR THE QUANTITATIVE DETERMINATION OF MELOXICAM IN A COMBINED MEDICINAL PRODUCT AS A POWDER FOR ORAL SOLUTION PREPARATION

The development of a method for the quantitative determination of active pharmaceutical ingredients is a crucial step in ensuring the quality of medicines. In the case of MPs in powder form for the preparation of oral solutions, the accuracy of the dosage is essential to achieve the therapeutic effect and avoid side effects [2].

Before proceeding with the selection of conditions for the quantification of meloxicam in a combined MP, it is necessary to calculate the average weight of the package contents. This step is vital to ensure the accuracy of the analysis, as the uniformity of the active ingredient distribution in each dose directly affects the analysis results and the ability to achieve the required therapeutic concentration of meloxicam [2, 3, 27, 40].

3.1 Determination of the average weight of the sachet pouch contents

Determination of the average weight of the powder content in a sachet pouch is a necessary step in the calculation of the quantitative content of the active substance, as it allows for possible weight variations in individual product units. This indicator helps to ensure the accuracy and reliability of further analytical studies, as well as the compliance of the final results with the requirements of regulatory documents [2, 3, 27, 40].

The average weight and deviation from the average weight were calculated for all batches of the analysed MP (batches 01-03). The results of the study are presented in Table 3.1.

Table 3.1

Results of determination of the average weight and deviation from the average weight for the analysed oral powder in sachet pouches

	Batch 01	Batch 02	Batch 03
	3,8770	3,8584	3,8869
	3,8816	3,8701	3,8909
	3,8897	3,8804	3,8958
	3,9001	3,8904	3,9007
	3,9079	3,9007	3,9057
	3,9151	3,9106	3,9105
	3,9381	3,9208	3,9203
	3,9412	3,9503	3,9408
	3,9566	3,9607	3,9506
	3,9749	3,9812	3,9801
	3,9789	4,0007	4,0507
	3,9933	4,0405	4,0603
	4,0128	4,0508	4,0705
	4,0165	4,0713	4,1105
	4,0176	4,0812	4,1209
	4,0356	4,1003	4,1306
	4,0607	4,1103	4,1402
	4,0665	4,1206	4,1501
	4,1014	4,1312	4,1804
	4,1056	4,1412	4,1943
Average weight, g	3,9786	3,9986	4,0195
Deviation, %	-2,55% +3,19 %	-3,51% +3,57 %	-3,30% +4,35 %

According to the results of the study (Table 3.1), the average weight for batch 01 is 3.9786 g, for batch 02 – 3.9986 g, and for batch 03 – 4.0195 g.

3.2 Substantiation of conditions for the quantitative determination of meloxicam in a combination MP by spectrophotometry

Due to the fact that the analysed MP is a combination one, with glucosamine sodium chloride and meloxicam as active ingredients, the physicochemical properties of the components, their solubility, etc. should be taken into account to select the optimal conditions for the determination of meloxicam.

After analysing the literature sources, it was found out that glucosamine sulfate sodium chloride is a complex compound containing glucosamine (aminomonosaccharide), sodium, chloride and a sulfate group (Fig. 3.1) [41].

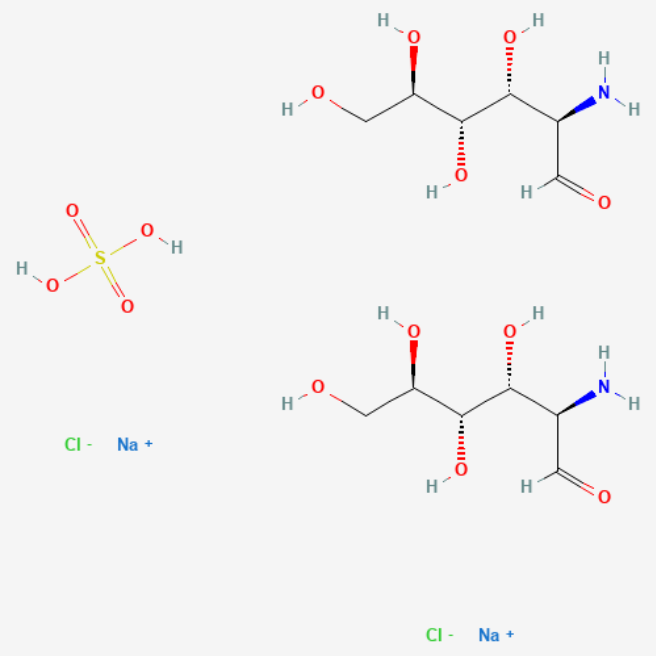

Fig. 3.1 Chemical structure of glucosamine sulfate sodium chloride

It is a highly water-soluble powder that is insoluble or practically insoluble in organic solvents (e.g. ethanol, acetone). In alkaline environments, chemical changes of the substance are possible, in particular, destruction of the amino group (deamination) or hydrolysis of glycosidic bonds [41].

At the same time, meloxicam is a water-insoluble, poorly soluble in alcohol, and highly soluble in strong alkalis and dimethylformamide powder. It is an amphoteric compound because it contains an acid (hydroxyl) and a basic (amino) group, and depending on the pH of the medium, it can be found in different forms - cationic (in an acidic environment), neutral and anionic (in an alkaline environment); the acid dissociation constant (pKa) is 4.08 [28, 35, 37]. It has chromophore groups, so currently, there are several approaches to the determination of meloxicam by spectrophotometry in the scientific literature, including the analysis in acidic and alkaline environments, by the reaction of complex formation with chromophore agents, etc [15, 16, 17, 25, 29, 34-36, 39].

In addition, the analysed MP is a combination one, other active and auxiliary substances may change the physicochemical properties of the solution, for example, ionic interactions between sodium, chlorine and buffer components may occur, which will complicate the spectrophotometric determination of meloxicam; glucosamine may form complex compounds or change the pH of the medium, which may affect the spectrum of meloxicam (shift in the maximum absorbance λ_{max} or decrease in signal intensity) [17, 25, 29].

Another option for the determination of meloxicam is the formation of complexes with chromophore reagents [15, 17, 25, 29, 31, 36, 39]. However, glucosamine sulfate sodium chloride is a polar ionic compound and also contains amino groups, which can lead to reactions with reagents that form chromophore complexes [41]. This may lead to changes in the optical properties of meloxicam complexes with chromophore reagents, which in general will reduce the selectivity and accuracy of the determination. In addition, other components of the MP, e.g. excipients, stabilisers, may also react with chromophore reagents, making the results difficult to interpret. Reactions to form chromophore complexes also require strict control of conditions, such as pH of the medium, concentrations of reagents, reaction time, temperature, etc. In combination preparations, these conditions can be difficult to reproduce due to the influence of other components of the medicine [20, 26].

Analysing the literature data, the most appropriate approach for the analysis of meloxicam in the investigational MP was chosen, which consists in its determination in an acidic environment. This is due to the fact that at pH < 7, meloxicam is converted to the cationic form, which is more stable, less sensitive to hydrolysis and better determined spectrophotometrically. As for glucosamine sodium chloride, in an acidic environment, protonation of its amino group occurs, which increases its ionisation and hydrophilicity (solubility increases) [16, 25, 28, 29, 31, 37].

The next stage of the study was to substantiate the solvent for the test solution. Glucosamine sulfate sodium chloride and meloxicam have different solubility properties: glucosamine is easily soluble in water, while meloxicam is a poorly

soluble in aqueous medium compound, but is well soluble in polar aprotic solvents, such as dimethylformamide (DMF). DMF can dissolve many organic and inorganic compounds due to its high polarity and ability to form hydrogen bonds. That is why DMF was chosen to dissolve the ingredients of the analysed MP [2, 27, 40].

3.3 Development of a technique for the quantitative determination of meloxicam in a combined MP by spectrophotometry

To accelerate the process of dissolution of the MP components, it is proposed to use ultrasonic treatment of the solution, as it promotes faster and more efficient dissolution of the medicine components, and eliminates possible aggregations that may affect the analysis results [25, 29].

After dissolving the medicine sample, the solution was filtered through a "blue ribbon" paper filter, an aliquot was taken and mixed with 0.1 M hydrochloric acid solution (to convert meloxicam to the cationic form). The optical density of the test solution was measured using a spectrophotometer using a 0.1 M hydrochloric acid solution as a compensation solution. A comparison solution of meloxicam was also prepared and its optical density was determined under the same conditions [15, 16, 17, 25, 29].

As a result of the conducted research, it was found out that in the wavelength range from 280 nm to 420 nm, the spectrum of the test solution has a maximum that coincides with the maximum of the reference solution at a wavelength of (345 ± 2) nm (Figs. 3.2, 3.3).

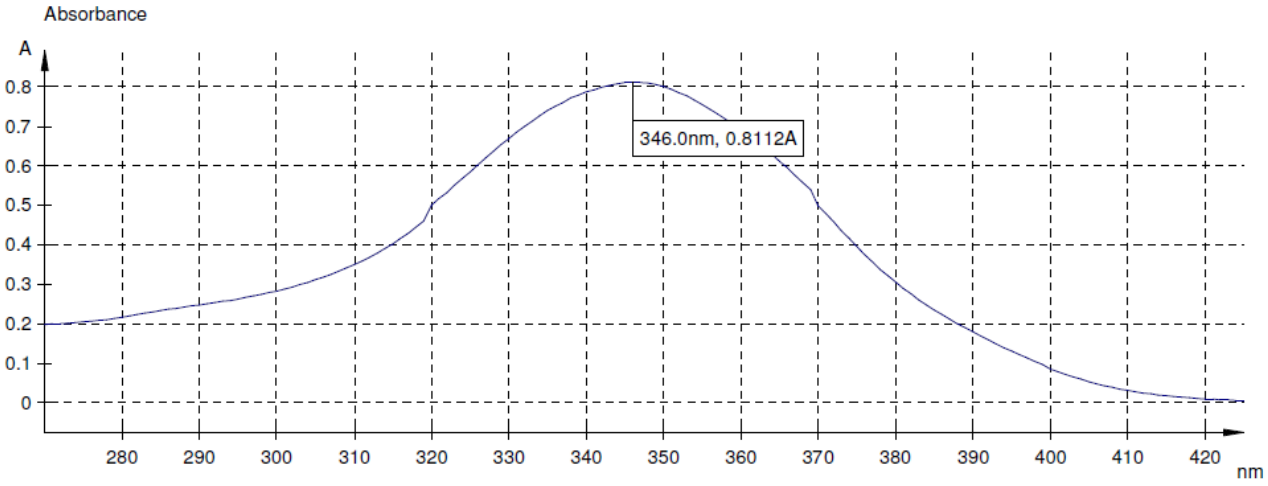

Fig. 3.2 Absorption spectrum of the standard sample of meloxicam (reference solution)

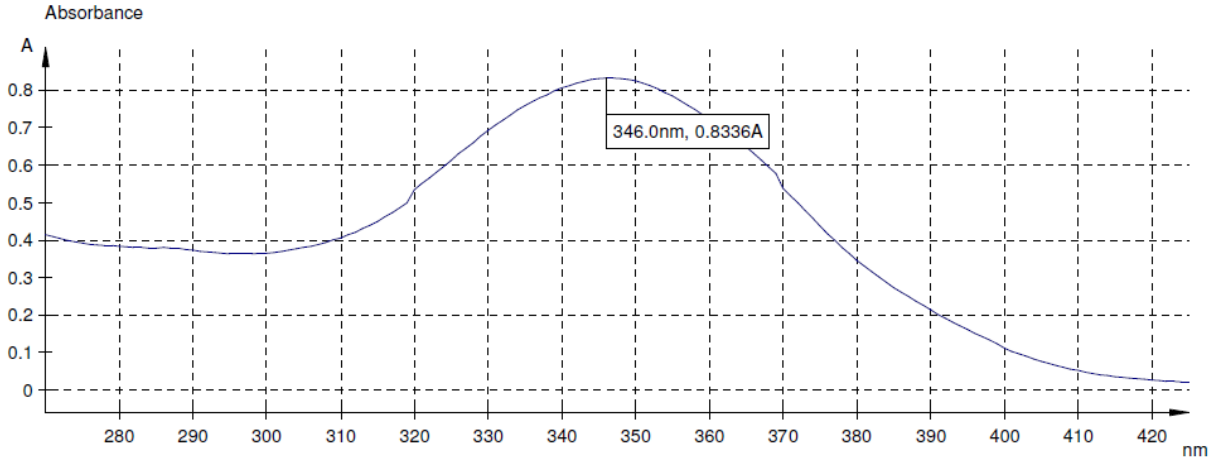

Fig. 3.3 Absorption spectrum of the analysed MP

The proposed *technique for the quantitative determination of meloxicam in a combined MP in the form of an oral powder* is presented below.

The determination is carried out by absorption spectrophotometry in the ultraviolet and visible regions in accordance with the requirements of Ph.Eur/SPhU, 2.2.25 [2, 3, 27].

The solutions are prepared shortly before use.

Test solution. Approx. 4,000 g (exact weight) of the substance powder is placed in a 50 mL volumetric flask, 30 mL of dimethylformamide is added, sonicated, made up to the volume with the same solvent and stirred. The resulting

solution is filtered through a "blue ribbon" paper filter [2, 3, 27].

2 ml of the obtained solution is placed into a 50 ml volumetric flask, the volume of the solution is brought to the mark with 0.1 M hydrochloric acid solution and stirred [2, 3, 27].

Comparison solution. About 30 mg (exact weight) of the meloxicam standard sample is placed into a 50 ml volumetric flask, dissolved in 30 ml dimethylformamide, sonicated, made up to the volume with the same solvent and stirred. The obtained solution is filtered through a "blue ribbon" paper filter [2, 3, 27].

2 ml of the obtained solution is placed in a 100 ml volumetric flask, the volume of the solution is brought to the mark with 0.1 M hydrochloric acid solution and stirred [2, 3, 27].

The optical density of the test solution and the reference solution is measured using a spectrophotometer at 345 ± 2 nm in a cuvette with a layer thickness of 10 mm, using 0.1 M hydrochloric acid as a compensation solution [2, 3, 27].

The content of meloxicam (X) in one sachet, in milligrams, is calculated by the formula:

$$X = \frac{A_i \cdot m_0 \cdot 50 \cdot 50 \cdot 2 \cdot b \cdot P \cdot 1000}{A_0 \cdot m \cdot 2 \cdot 50 \cdot 100 \cdot 100} = \frac{A_i \cdot m_0 \cdot b \cdot P \cdot 5}{A_0 \cdot m}$$

A is the optical density of the test solution at a maximum at a wavelength of 345 ± 2 nm;

A_0 is the optical density of the reference solution at a maximum at a wavelength of 345 ± 2 nm;

m is the weight of the medicine powder, in grams;

m_0 is the weight of meloxicam powder, in grams;

P is the content of the main substance in meloxicam, in a percentage;

b is the average weight of the sachet contents, in grams.

The content of meloxicam in one sachet should be from 13.88 mg to 16.13 mg (15 mg ± 7.5 %).

The metrological characteristics of the developed technique are given in Table 3.2.

Table 3.2

Metrological characteristics of the technique for the quantitative determination of meloxicam in a combined MP in the form of a powder for oral solution (batch 01)

X_i	X_{batch}	S^2	S_{batch}	P	t(P,ν)	Confidence interval	ε, %
0,8202	0,8201	0,000000167	0,0002	0,95	2,78	0,8201±0,0005	0,06
0,8201							
0,8205							
0,8194							
0,8202							

The results of the quantitative determination of meloxicam in a combination MP in the form of powder for oral solution (batches 01-03) are presented in Table 3.3.

Table 3.3

The results of the quantitative determination of meloxicam in a combination MP in the form of a powder for oral solution (batches 01-03)

	Standard meloxicam sample (P=100,0 %)	Batch 01	Batch 02	Batch 03
A_1	0,8143	0,8202	0,7865	0,8039
A_2	0,8142	0,8201	0,7871	0,8020
A_3	0,8142	0,8205	0,7876	0,8018
A_4	0,8139	0,8194	0,7876	0,8020
A_5	0,8134	0,8201	0,7866	0,8020
A_{batch}	0,8140	0,8201	0,7871	0,8023
$m_н$	0,0304	3,9867	3,9786	4,0323
b, g		3,9786	3,9986	4,0195
X, mg		**15,28**	**14,77**	**14,93**

As can be seen from the study results, the quantitative content of meloxicam in the combined MP in the form of powder for oral solution for batches 01-03 is

15.28 mg, 14.77 mg and 14.93 mg, respectively. The obtained values meet the requirements of regulatory documents.

Conclusions to Section III

1. The average weight and deviation from the average weight for the analysed batches of the medicine were determined: batch 01 – 3.9786 g (deviation: -2.55 %, +3.19 %), batch 02 – 3.9986 g (deviation: -3.51 %, +3.57 %), batch 03 - 4.0195 g (deviation: -3.30 %, +4.35 %).
2. Taking into account the physicochemical properties and solubility of glucosamine sodium chloride and meloxicam, the conditions for the quantitative determination of meloxicam in a combined MP were theoretically substantiated, which consist in dissolving a medicine sample in DMF using an ultrasonic bath and subsequent determination in an acidic environment (in a 0.1 M hydrochloric acid solution).
3. It was found out that in the wavelength range from 280 nm to 420 nm, the spectrum of the test solution has a maximum that coincides with the maximum of the reference solution at a wavelength of (345 ± 2) nm.
4. The quantitative content of meloxicam for batches 01-03 was calculated, which is 15.28 mg, 14.77 mg and 14.93 mg, respectively.

SECTION IV
VALIDATION OF THE TECHNIQUE FOR THE QUANTITATIVE DETERMINATION OF MELOXICAM IN THE ANALYSED DOSAGE FORM BY SPECTROPHOTOMETRY

The main purpose of validation of analytical techniques is to prove, on the basis of experimental data, that the technique is suitable or unsuitable for solving the intended problems. The validation of a technique necessarily involves the evaluation of the obtained validation characteristics in relation to the acceptance criteria [3, 27].

The method for the quantitative determination of meloxicam (active ingredient) by absorption spectrophotometry in the ultraviolet and visible regions requires full validation in terms of specificity, linearity, accuracy, precision and robustness [3, 27].

Therefore, we calculated the acceptance criteria taking into account the regulatory tolerances of the contents and the features of the spectrophotometric method in the standard method variant [3, 27].

1.1 The requirements for the technique uncertainty

The maximum permissible total uncertainty of the analysis method is related to the limits of the substance content in the preparation. The content of meloxicam in a sachet packet is standardised within the range of 13.88-16.13 mg, thus the half-difference of content tolerances is ± 7.5 % [3, 27].

The maximum permissible total uncertainty of the analysis technique:

$$\max\Delta_{AS}, \% \leq 0.32 \times 7.5 \% = 2.4 \%.$$

The criterion of insignificance was compared to the maximum permissible uncertainty of the analysis results (Δ_{AS}, insig) [3, 27]:

$$\Delta_{AS},\text{insig} \% \leq \max\Delta_{AS}, \% \times 0.32 = 2.4 \% \times 0.32 = 0.77 \%.$$

The calculation of the uncertainty of sample solution (Δ_{sr}), the uncertainty of the final analytical operation (Δ_{FAO}) and the total uncertainty of the analysis technique (Δ_{AS}%) is given in Table 4.1 [3, 27].

Table *4.1*

The calculation of the uncertainty Δ_{sp}, Δ_{FAO} i Δ_{AS}%

Sample solution operation	Value	Uncertainty, (Δ),%
Sample solution		
The weight of the preparation	4000 mg	0,01
Uncertainty of weighing	0,2 mg	
Bringing to volume	50 ml	0,17
Aliquot	2 ml	0,61
Bringing to volume	50 мл	0,17
Comparison solution		
The weight (m)	30 mg	0,5
Uncertainty of weighing	0,2 mg	
Bringing to volume	50 ml	0,17
Bringing to volume	2 ml	0,61
Bringing to volume	100 ml	0,12
Complete uncertainty of sample preparation Δsp%		1,1357
*The uncertainty of the final analytical operation Δ_{FAO} (spectrometry)**		0,7
Complete uncertainty othe analysis technique Δ_{AS}% $\Delta_{AS}\% = \sqrt{(\Delta sp\%)^2+(\Delta_{FAO}\%)^2}$		1,33

The total uncertainty of the analysis technique ΔAS% was calculated less than max Δ_{AS} (1.33 % < max Δ_{AS} = 2.4 %), which meets the requirements for this parameter [3, 27].

Thus, the total predicted uncertainty of the analytical technique for the determination of meloxicam in the analysed medicine does not exceed the maximum permissible uncertainty of the results.

1.1 Specificity

To study the specificity, the following solutions were prepared: placebo solution, comparison solution (meloxicam standard solution), and test solution [3].

Specificity (placebo effect). To determine the specificity of the technique, the average optical density of the placebo solution (A_{blank}) was calculated, which is conditioned by the absorption of excipients [3, 27]:

$$A_{blank} = 0{,}0053;\ A_{st} = 0{,}8140.$$

The contribution of placebo to the total absorption of the medicine should not exceed the value [3, 27]:

$$\frac{A_{blank}}{A_{st}} \cdot 100 \le 0{,}77\%$$

According to the experimental data, the placebo contribution was:

$$\delta_{exc} = \frac{A_{blank}}{A_{st}} \cdot 100\% = \frac{0{,}0053}{0{,}8140} \cdot 100\% = 0{,}65\%$$

As can be seen, the inequalities are satisfied, that means the background absorption is insignificant, and the technique is characterised by acceptable specificity [3, 27]:

$$0{,}64\% \le 0{,}77\ \%.$$

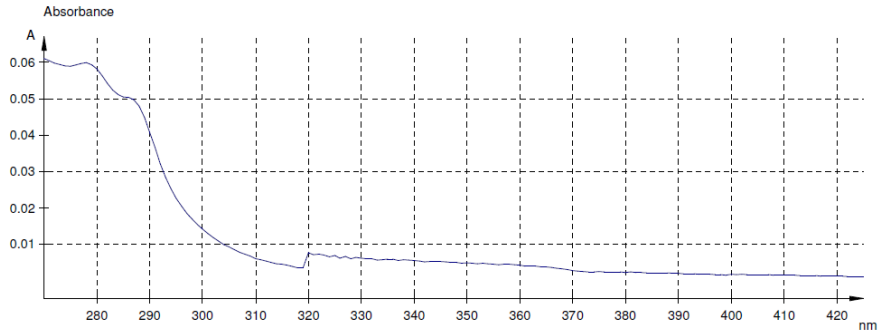

Fig. 4.1 Absorption spectrum of the placebo solution

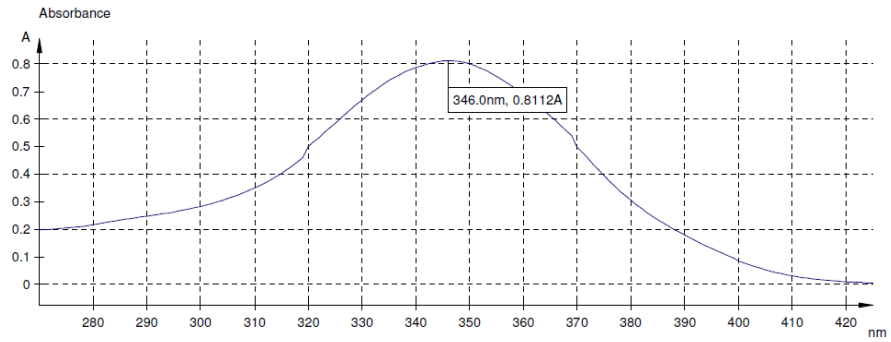

Fig. 4.2 Absorption spectrum of the comparison solution

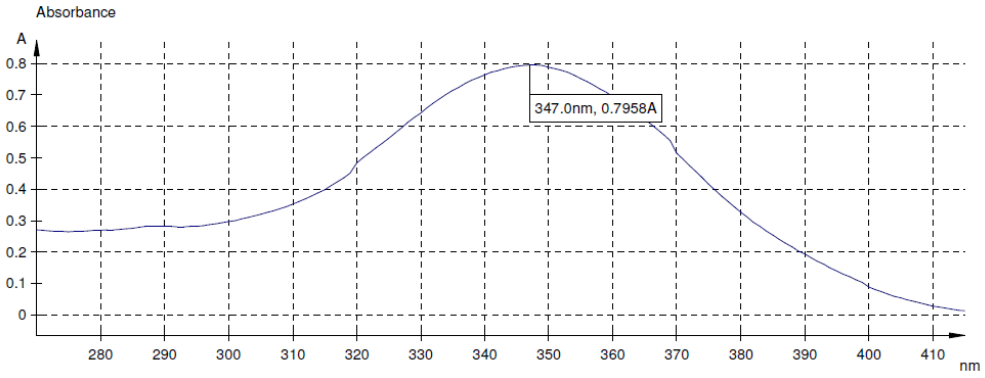

Fig. 4.3 Absorption spectrum of the test solution

1.2 Linearity

The quantification method should be linear within the range of application, which should cover the possible concentrations of the active substance. The Ph.Eur/SPhU establishes the range of application of quantification techniques as 80-120 % [3, 27].

To confirm the linearity of the technique, 9 model solutions of the analysed substance were prepared, the concentration of which varies uniformly within the range of application (step – 5 %) [3, 27].

Calculations and criteria are given for normalised values (Table 4.2):

$$X_i = C_i/C_{st} \cdot 100 \text{ та } Y_i = S_i/S_{st} \cdot 100$$

Table 4.2

Calculation of the linearity parameters of the technique for the quantitative determination of meloxicam

	C of the model solution, mg/ml (calc.)	B % of the standard solution $X_i = C_i/C_{st} \cdot 100$	The value of the optical density at the maximum (375 nm)	The average value of the optical density at the maximum	B % of the standard solution $Y_i = S_i/S_{st} \cdot 100$
80%	0,0096	80,00	0,6355	0,6357	80,24
			0,6359		
			0,6357		
85%	0,0102	85,00	0,6756	0,6755	85,26
			0,6758		
			0,6751		

	C of the model solution, mg/ml (calc.)	B % of the standard solution $X_i = C_i/C_{st} \cdot 100$	The value of the optical density at the maximum (375 nm)	The average value of the optical density at the maximum	B % of the standard solution $Y_i = S_i/S_{st} \cdot 100$
90%	0,0108	90,00	0,7156 0,7159 0,7161	0,7159	90,36
95%	0,0077	95,00	0,756 0,7565 0,7566	0,7564	95,47
100%	0,0114	100,00	0,7958 0,7951 0,7955	0,7955	100,40
105%	0,0120	105,00	0,8345 0,8348 0,8352	0,8348	105,37
110%	0,0126	110,00	0,8712 0,8708 0,8711	0,8710	109,94
115%	0,0132	115,00	0,9165 0,9166 0,9160	0,9164	115,66
120%	0,0138	120,00	0,9552 0,9550 0,9551	0,9551	120,55
Comparison solution	0,0120	100,0	0,7925 0,7923 0,7920	0,7923	100,0

Fig. 4.4 shows a graph of the linear dependence of the analytical signal on the actual concentration of the solution, built in normalised coordinates, based on the data given in the table (Table 4.2) [3, 27].

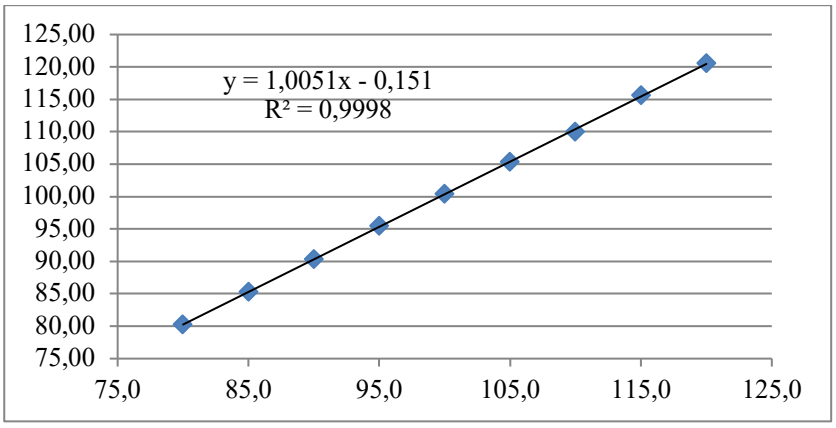

Fig. 4.4 Graph of the linear dependence Yi = b*Xi + a for meloxicam in sachet pouches

For the model solutions, the parameters of the linear dependence were calculated using the least squares method: the free component a, the residual standard deviation, and the correlation coefficient. The acceptance criteria are given in Table 4.3 [3, 27].

Table 4.3

Linearity test data for the quantification technique

Parameter	Requirements	The received value	Meeting the criterion
$\lvert a \rvert$	$\leq 3,8$	0,1510	Met
S_0	$\leq 1,27$	0,5879	Met
r	$> 0,9957$	0,9998	Met

Thus, the obtained results confirm that the technique for the quantitative determination of meloxicam in the analysed MP in the concentration range from 80 % to 120 % is linear.

1.3 Correctness

The correctness is studied using the placebo method by determining the response factor of a substance in model mixtures of placebo components.

To determine the correctness within the range of the analytical method, 9 test solutions were prepared, following all the steps of the analytical technique [3, 27].

The concentration of meloxicam in the solutions ranged from 80% to 120%.

The accuracy is characterised by two criteria [3, 27]:

- The criterion of statistical insignificance: $\delta\% = \left|Z - \bar{100}\right| \le \frac{\Delta z}{\sqrt{9}}$

δ% – the criterion of practical insignificance - if the above ratio is not met, the criterion of insignificance of this systematic error compared to the maximum permissible uncertainty of the analysis is used $\left|\bar{Z} - 100\right| \le \Delta_{AS,in\sin g} = 0{,}77\%$ [3, 27].

The determination of the parameters of correctness and the calculation of the acceptance criteria for meloxicam in sachet pouches are presented in Table 4.4.

Table 4.4

The calculation of meloxicam correctness parameters in sachet pouches

	Component concentration		
	Added in % to the concentration of the comparison solution $(C_i/C_{st})*100\%$	Found in % to the concentration of the comparison solution $(A_i/A_{st})*100\%$	Found in % to the added $Z_i = (A_i/A_{st})*100/(C_i/C_{st})$
1 solution	80,00	80,24	100,30
2 solution	85,00	85,26	100,31
3 solution	90,00	90,36	100,40
4 solution	95,00	95,47	100,49
5 solution	100,00	100,40	100,40
6 solution	105,00	105,37	100,36
7 solution	110,00	109,94	99,95
8 solution	115,00	115,66	100,58
9 solution	120,00	120,55	100,46
		***Z**aver.*	100,36
		***Relative standard deviation,** $s_z\%$*	0,178
		Відносний довірчий інтервал $\Delta Z = t(90\%,8)*s_z = 1.85950*s_z =$	0,33
		Critical value for the convergence of results $\Delta\% \le$	2,4
		Systematic error $\delta = \left\|Z_{cep} - 100\right\|$	0,36
		1) ***The criterion of statistical insignificance*** $\delta \le \Delta Z/3 = 0{,}33/3 = 0{,}11$ (0,36>0,11)*;* 2) If not met, then the criterion of practical insignificance, $\delta \le 0{,}77$ (0,36 < 0,77)	Unmet Met
		General conclusion about the technique	Correct

Fulfilment of the accuracy criteria for the determination of meloxicam in sachet pouches by spectrophotometry is shown in Table 4.5.

Table 4.5

The results of the correctness assessment by two criteria

Parameter	Value	Requirements for statistical insignificance	Requirements for practical insignificance	Meeting the criterion
$\lvert\bar{Z} - 100\rvert$	0,36	≤ 0,11	≤ 0,77	Met the second criterion

Thus, the technique for the determination of meloxicam in the analysed medicine meets the acceptance criteria for the validation indicator “Correctness”.

1.4 Precision

Convergence. Precision was studied on test solutions prepared to determine the criterion "Correctness". The fulfillment of the precision criteria of the technique for the quantitative determination of meloxicam in sachet pouches is given in Table 4.6 [3, 27].

Table 4.6

The results of the precision assessment of meloxicam in sachet pouches

Parameter	Value	Criterion	Meeting the criterion
ΔZ	0,36	≤ 2,4 %	Met

Therefore, the method is characterized by sufficient convergence, since the found value of the relative confidence interval is 0.36 %, which is less than the critical value for the convergence of the results (2.4 %) and satisfies the acceptability criteria of the validation indicator "Precision" [3, 27].

Intra-laboratory precision. For determination, the results of the study of test solutions of one sample were obtained by two analysts on different days during one working week using different measuring vessels.

The determination of the parameters of intra-laboratory precision and the calculation of its criteria are presented in Table. 4.7 [3, 27].

Table *4.7*

Determination of intra-laboratory precision parameters

№	Analyst №1	Analyst №2	
1	101,46	101,45	
2	101,45	101,49	
3	101,49	101,49	
4	101,50	101,45	
5	101,49	101,45	
Average	101,48	101,47	
Dispersion, s^2	0,0010	0,0010	
General average			101,47
Relative standard deviation, RSD%			0,02
Confidence interval, (Δ_{intra} = t(95%, m*n-1)* RSD,%=2,1318 *RSD,%			0,05

Meeting the intralaboratory precision criteria for the determination of meloxicam in sachet pouchers by spectrophotometry is given in the Table 4.8 [3, 27].

Table 4.8

Results of intra-laboratory precision assessment

Parameter	Criterion requirements	The obtained value	Meeting the criterion
Δintra	≤ 2,4	0,05	Met

Therefore, the technique for quantitative determination of meloxicam meets the acceptance criteria of the “Intra-laboratory precision” test.

1.5 Robustness (stability over time of analytical solutions)

The stability of the comparison solutions (Table 4.9) and the test solutions (Table 4.10) was studied immediately after preparation, after 15 min, 30 min, 1 hour and after 2 hours [3, 27].

Table 4.9

Determination of stability of analytical solutions of meloxicam over time

No.	0 min	After 15 min	Changes parameter	After 30 min	Changes parameter,	After1 hour	Changes parameter	After 2 hours	Changes parameter параметру
1	0,7123	0,7117	0,01	0,7105	0,34	0,7122	0,01	0,7131	0,04
2	0,7124	0,7123	0,01	0,7099	0,35	0,7120	0,06	0,7128	0,01
3	0,7131	0,7115	0,08	0,7098	0,46	0,7118	0,18	0,712	0,15
Δ_{aver}			0,04		0,38		0,08		0,07

Acceptance criteria. The differences between the obtained values of the meloxicam content in sachet pouches should not exceed the criterion of non-significance compared to the maximum permissible uncertainty of the analysis results (Δ_{AS}, insig), that is 0.77 %. The criterion is met after 15 min, 30 min and 1 hour, however, the optical density of the tested solutions after 2 hours does not meet the criteria. According to the above data, it is advisable to use the solutions for quantitative determination within 2 hours.

Table 4.10

Determination of stability of analytical solutions of meloxicam in sachet pouchers over time

No.	0 min	After 15 min	Changes parameter	After 30 min	Changes parameter	After1 hour	Changes parameter	After 2 hours	Changes parameter
1	0,7781	0,7786	0,06	0,7771	0,13	0,7764	0,22	0,7700	1,04
2	0,778	0,7785	0,06	0,7772	0,10	0,7769	0,14	0,7698	1,05
3	0,7782	0,7782	0,00	0,7773	0,12	0,7773	0,12	0,7701	1,04
Δ_{aver}			0,04		0,12		0,16		1,05

Acceptance criteria. The differences between the obtained values of the meloxicam content in sachet pouches should not exceed the criterion of non-significance compared to the maximum permissible uncertainty of the analysis results (Δ_{AS}, insig), that is 0.77 %. The criterion is met after 15 min, 30 min and 1

hour, however, the optical density of the tested solutions after 2 hours does not meet the criteria. According to the above data, it is advisable to use the solutions for quantitative determination within 1 hour [3, 27].

The results of the test "Robustness (stability over time of analytical solutions)" (for 30 minutes and 1 hour) meet the acceptance criteria.

Therefore, all the calculated parameters meet the necessary validation criteria. The technique is considered validated and can be used for the quantitative determination of meloxicam in sachet pouches by absorption spectrophotometry in the ultraviolet and visible regions according to the draft methods for quality control of MPs.

Conclusions to Section IV

1. Validation of the technique of quantitative determination of meloxicam by spectrophotometry was carried out.
2. All the calculated parameters meet the necessary validation criteria.
3. The techniqueis correct and can be used for the quantitative determination of meloxicam in a MP in the form of a powder for the preparation of an oral solution by spectrophotometry.

GENERAL CONCLUSIONS

The qualification work is dedicated to solving the scientific task of substantiating and selecting optimal conditions for the quantitative determination of meloxicam in the composition of a combined medicinal product in the form of a powder for oral solution preparation:

1. A review of literature sources on the pharmacological properties, medical applications, physicochemical properties, and existing methods of quality control for meloxicam was conducted.

2. The current pharmaceutical market of Ukraine for meloxicam-containing products was analyzed. It was found that these products are predominantly single-component drugs in the form of tablets, suppositories, and injectable solutions, all belonging to the same ATC group (ATC M01A C06). The market share of imported and domestically produced medicines is almost equal, with Greece identified as the largest supplier.

3. The mean weight and deviations from the mean weight for the analyzed batches of the drug (batches 01-03) were determined: batch 01: 3.9786 g (deviation: -2.55 %, +3.19 %); batch 02: 3.9986 g (deviation: -3.51 %, +3.57 %); batch 03: 4.0195 g (deviation: -3.30 %, +4.35 %).

4. Taking into account the physicochemical properties and solubility of glucosamine sodium chloride and meloxicam, the conditions for the quantitative determination of meloxicam in a combined medicinal product were theoretically substantiated, which consist in dissolving a sample in DMF using an ultrasonic bath and subsequent determination in an acidic environment (in a 0.1 M hydrochloric acid solution). It was found out that in the wavelength range from 280 nm to 420 nm, the spectrum of the test solution has a maximum that coincides with the maximum of the reference solution at a wavelength of (345 ± 2) nm.

5. The quantitative content of meloxicam for batches 01-03 was calculated, which is 15.28 mg, 14.77 mg and 14.93 mg, respectively.

6. The developed method was validated. The method is accurate and suitable for the quantitative determination of meloxicam in the composition of a combined medicinal product in the form of a powder for oral solution preparation using spectrophotometry.

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APPENDIX

Appendix A

Table 1

Medicinal products on the pharmaceutical market of Ukraine containing meloxicam

No.	Name	Release form (medicinal form, potency (dosage), packaging	Composition of active substances	Producer
1.	MOVIKSIKAM® ODT	7.5 mg orodispersible tablets; 10 tablets in a blister; 2 blisters in a cardboard pack	1 tablet contains meloxicam 7.5 mg	Lamp San Prospero S.p.A., Italy
2.	MOVIKSIKAM® ODT	tablets dispersible in the oral cavity, 15 mg each, 10 tablets in a blister; 1 or 2 blisters in a cardboard pack	1 tablet contains meloxicam 15 mg	Lamp San Prospero S.p.A., Italy
3.	MELOXIKAM-KV	tablets of 15 mg, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam 15 mg	Kyiv Vitamin Plant JSC, Ukraine
4.	MELOXIKAM-KV	tablets of 7.5 mg, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam 7.5 mg	Kyiv Vitamin Plant JSC, Ukraine
5.	REVMOXIKAM®	solution for injections 1% of 1.5 ml in an ampoule; 3 or 5 ampoules in a blister; 1 blister in a pack; 1.5 ml in an ampoule; 5 ampoules in a pack	1 ml of the drug contains meloxicam in 100% substance 10 mg	Farmak JSC, Ukraine
6.	REVMOXIKAM®	15 mg rectal suppositories; 5 suppositories in a blister; 1 blister in a cardboard pack	1 suppository contains meloxicam 15 mg	Farmak JSC, Ukraine
7.	REVMOXIKAM®	tablets of 15 mg, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam - 15 mg	Farmak JSC, Ukraine

			(calculated as 100% anhydrous substance)	
8.	REVMOXIKAM®	tablets of 7.5 mg, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam - 7.5 mg (calculated as 100% anhydrous substance)	Farmak JSC, Ukraine
9.	AROXIKAM	tablets of 15 mg, 10 tablets in a blister; 1 blister in a cardboard pack	1 tablet contains 15 mg of meloxicam	Aurobindo Pharma Limited - Unit III, India
10.	AROXIKAM	tablets of 7.5 mg, 10 tablets in a blister; 1 blister in a cardboard pack	1 tablet contains 7.5 mg of meloxicam	Aurobindo Pharma Limited - Unit III, India
11.	MOVALIS®	solution for injection, 15 mg/1.5 ml; 1.5 ml in an ampoule; 5 ampoules in a cardboard box	1.5 ml of the drug contains 15 mg of meloxicam	Behringer Ingelheim Espana, Spain
12.	MOVALIS®	15 mg tablets; 10 tablets each; 1 or 2 blisters in a cardboard box	1 tablet contains meloxicam 15 mg	Behringer Ingelheim Espana, Spain
13.	MOVALIS®	7.5 mg tablets; 10 tablets each; 2 blisters in a cardboard box	1 tablet contains meloxicam 7.5 mg	Behringer Ingelheim Espana, Spain
14.	ASPIKA	tablets of 15 mg, 10 tablets in a blister; 1 or 2 or 3 blisters in a cardboard box	1 tablet contains meloxicam 15 mg	Biopharm Ltd., Republic of Poland
15.	ASPIKA	tablets of 7.5 mg, 10 tablets in a blister; 1 or 2 or 3 blisters in a cardboard box	1 tablet contains meloxicam 7.5 mg	Biopharm Ltd., Republic of Poland
16.	MELBEC®	solution for injection, 15 mg/1.5 ml; 1.5 ml each in ampoules with a volume of 2 ml; 3 ampoules in a cardboard package	1 ampoule (1.5 ml) of the drug contains 15 mg of meloxicam	Idol Ilac Dolum Sanai Ve Tijaret A.Sh., Turkey

17.	ELIPROB	solution for injections, 15 mg/1.5 ml, 1.5 ml in an ampoule, 3 or 5 ampoules in a contoured blister pack; 1 contour envelope in a cardboard pack	1.5 ml of solution contains 15 mg of meloxicam	K.T. Romfarm Company S.R.L., Romania
18.	ALGESIKAM®	tablets of 15 mg No. 10 (10x1), No. 20 (10x2) in blisters	1 tablet contains meloxicam 15 mg	CO "MAGISTRA S & S" T. AT. V., Romania
19.	MELOX	solution for injections, 15 mg/1.5 ml of 5 ampoules in a shaped blister; 1 or 2 blisters in a cardboard box	1.5 ml of solution (1 ampoule) contains meloxicam 15 mg	Medocemi Limited, Cyprus
20.	MELOX	15 mg tablets; 10 tablets in a blister; 1 blister in a cardboard box	1 tablet contains meloxicam 15 mg	Medocemi Limited, Cyprus
21.	MELBEC®	tablets, 15 mg each, 10 tablets in a blister; 1 or 3 blisters in a cardboard package, 4 tablets in a blister; 1 blister in a cardboard package	1 tablet contains meloxicam 15 mg	NOBEL ILAC SANAI VE TIJARET AS, Turkey
22.	MELBEC®	tablets, 7.5 mg each, 10 tablets in a blister; 1 or 3 blisters in a cardboard package	1 tablet contains meloxicam 7.5 mg	NOBEL ILAC SANAI VE TIJARET AS, Turkey
23.	SANAKOM	solution for injections 10 mg/ml; 1.5 ml in an ampoule; 5 ampoules in a blister, 1 blister in a pack	1.5 ml of the drug contains 15 mg of meloxicam; 1 ml of the drug contains 10 mg of meloxicam	Lekhim-Kharkiv JSC
24.	ALSOKAM	solution for injections, 10 mg/ml, 1.5 ml in an ampoule; 5 ampoules in a blister; 1 blister in a pack	1.5 ml of the drug contains 15 mg of meloxicam; 1 ml of the drug contains 10 mg of meloxicam	Lekhim-Kharkiv JSC

25.	INFLAMINE	rectal suppositories of 0.015 g, 5 suppositories in a blister; 2 blisters in a cardboard pack; rectal suppositories of 0.015 g, in bulk No. 1250: 5 suppositories in a blister; 250 blisters in a box	1 suppository contains meloxicam 15 mg	Lekhim-Kharkiv JSC
26.	MELOXIKAM	solution for injections, 15 mg/1.5 ml of 1.5 ml solution in an ampoule; 5 ampoules in a blister; 1 blister in a cardboard pack	1 ml of solution contains meloxicam 10 mg	Lekhim-Kharkiv JSC
27.	ALGESIKAM®	solution for injections, 10 mg/ml, 1.5 ml in an ampoule, 5 ampoules in a blister, 1 blister in a pack	1.5 ml of the drug contains 15 mg of meloxicam; 1 ml of the drug contains 10 mg of meloxicam	Lekhim-Kharkiv JSC
28.	MELOXIKAM	tablets of 0.0075 g in bulk: 5000 tablets in plastic containers; tablets of 0.0075 g, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam 7.5 mg	Lekhim-Kharkiv JSC
29.	MELOXIKAM	tablets of 0.015 g in bulk: 5000 tablets in plastic containers; tablets of 0.015 g; 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam 15 mg	Lekhim-Kharkiv JSC
30.	INFLAMINE	solution for injections 10 mg/ml, 1.5 ml in an ampoule, 100 ampoules in a pack; 1.5 ml in an ampoule; 5 ampoules in a pack; 1.5 ml in an	1 ml of solution contains 10 mg of meloxicam	Lekhim-Kharkiv JSC

		ampoule; 5 ampoules in a blister; 1 blister in a pack		
31.	MELOXIKAM	solution for injections, 15 mg/1.5 ml in ampoules of 1.5 ml; 5 ampoules in a cassette; 1 cassette in a pack	1.5 ml of the drug contains 15 mg of meloxicam;	Research and Production Centre Borshchahivskiy Chemical and Pharmaceutical Plant JSC, Ukraine
32.	MELOXA-XANTHIS	15 mg tablets; 10 tablets in a blister, 1 or 2, or 3, or 5, or 6, or 10 blisters in a cardboard pack	1 tablet contains 15 mg of meloxicam	Saneka Pharmaceuticals AT, Slovak Republic
33.	EXISTEN-SANOVEL	tablets of 15 mg, 10 tablets in a blister; 1 or 3 blisters in a cardboard box	1 tablet contains 15 mg of meloxicam	Sanovel Ilyach Sanai ve Tijaret A.Sh., Turkey
34.	MELSI	tablets of 15 mg, 10 tablets in a blister; 2 blisters in a box	1 tablet contains meloxicam 15 mg	ASTRAFARM LLC, Ukraine
35.	MELSI	tablets of 7.5 mg, 10 tablets in a blister; 2 blisters in a box	1 tablet contains meloxicam 7.5 mg	ASTRAFARM LLC, Ukraine
36.	RHEUMATOP	solution for injections, 10 mg/ml, 1.5 ml in an ampoule; 5 ampoules in a cardboard pack	1 ml of solution contains meloxicam 10 mg	Farmasel LLC, Ukraine
37.	MELOXIKAM-PHARMAX	solution for injection, 10 mg/ml; 1.5 ml in a bottle; 5 bottles each in contoured packaging; 1 contour envelope in a pack; 1.5 ml in an ampoule; 5 ampoules in a blister; 1 blister in a pack; 1.5 ml in an ampoule; 5 ampoules in a pack	1 ml of solution contains meloxicam 10 mg	Farmex Group LLC

38.	REVMALGIN	rectal suppositories of 15 mg, 5 suppositories in a strip; 1 or 2 strips in a cardboard pack	1 suppository contains meloxicam in 100% dry substance 15 mg	Farmex Group LLC
39.	REVMALGIN	tablets of 15 mg, 10 tablets in a blister; 1 or 2 blisters in a pack	1 tablet contains meloxicam 15 mg	Farmex Group LLC
40.	REVMALGIN	tablets of 7.5 mg, 10 tablets in a blister; 2 blisters in a cardboard pack	1 tablet contains meloxicam 7.5 mg	Farmex Group LLC
41.	REVMALGIN	solution for injection, 10 mg/ml; 1.5 ml in a bottle; 5 bottles each in contoured packaging; 1 contour envelope in a pack; 1.5 ml in an ampoule; 5 ampoules in a blister; 1 blister in a pack; 1.5 ml in an ampoule; 5 ampoules in a pack	1 ml of solution contains meloxicam 10 mg	Farmex Group LLC
42.	MELOSSO	solution for injection, 15 mg/1.5 ml; 1.5 ml in an ampoule; 5 ampoules in a blister pack in a cardboard pack	1.5 ml of solution for injection contains 15 mg of meloxicam	MICROCHEM LLC, Ukraine
43.	MELOSSO	7.5 mg tablets; 10 tablets in a blister; 2 blisters in a cardboard pack; 20 tablets in a jar; 1 can in a cardboard pack	1 tablet contains 7.5 mg of meloxicam	MICROCHEM LLC, Ukraine
44.	MELOSSO	15 mg tablets; 10 tablets in a blister; 2 blisters in a cardboard pack; 20 tablets in a jar; 1 can in a cardboard pack	1 tablet contains 15 mg of meloxicam	MICROCHEM LLC, Ukraine
45.	PHARMACISTS	solution for injection, 10 mg/ml, 1.5 ml in a vial, 5 vials in a contour	1 ml of solution contains meloxicam 10 mg; 1 vial	Novopharm-Biosynthesis LLC, Ukraine

		blister pack, 1 contour blister pack in a cardboard pack	(1.5 ml) contains meloxicam 15 mg	
46.	NOVOXIKAM	solution for injections, 10 mg/ml, 1.5 ml in a vial; 5 bottles each in contoured packaging; 1 contour envelope in a cardboard pack	1.5 ml of solution contain meloxicam 15 mg	Novopharm-Biosynthesis LLC, Ukraine
47.	MELSI	solution for injection, 10 mg/ml; 1.5 ml in a bottle; 5 bottles each in contoured packaging; 1 contour envelope in a cardboard pack	1 ml of solution contains meloxicam 10 mg	Novopharm-Biosynthesis LLC, Ukraine
48.	LOXIDOL	tablets of 15 mg, 10 tablets in a blister; 1 or 2 blisters in a cardboard box	1 tablet contains meloxicam 15 mg	WORLD MEDICINE ILACH SAN. VE TIJ. A.Sh., Turkey
49.	LOXIDOL	solution for injection 15 mg/1.5 ml, 1.5 ml in an ampoule, 3 ampoules in a cardboard box	1.5 ml of solution for injection contains 15 mg of meloxicam	PharmaVision San. in Tij. A.Sh., Turkey
50.	MOVALGIN	tablets of 15 mg, 10 tablets in blisters; 1 blister in a cardboard box	1 tablet contains 15 mg of meloxicam	Pharmascience Inc., Canada
51.	MOVALGIN	tablets of 7.5 mg, 10 tablets in blisters; 1 blister in a cardboard box	1 tablet contains 7.5 mg of meloxicam	Pharmascience Inc., Canada
52.	MELOXIK	solution for injection, 15 mg/1.5 ml; 1.5 ml in an ampoule; 3 or 5 ampoules in a contoured blister pack; 1 contoured envelope in a cardboard pack	1.5 ml of the drug contains 15 mg of meloxicam	Pharmaceutical Plant "Polpharma" S. A., Poland

53.	MELOXIKAM-VISTA	solution for injection, 15 mg/1.5 ml of 1.5 ml (15 mg) in an ampoule, 5 ampoules in a cassette in a pack	1 ampoule (1.5 ml) contains meloxicam 15 mg;	HELP SA, Greece
54.	MELOLGAN	solution for injection, 15 mg/1.5 ml of 1.5 ml (15 mg) in an ampoule, 5 ampoules in a cassette in a pack	1 ampoule (1.5 ml) contains meloxicam 15 mg	Help SA, Greece
55.	RECLINE	solution for injection, 15 mg/1.5 ml of 1.5 ml in an ampoule, 5 ampoules in a pack	1.5 ml of the drug contains 15 mg of meloxicam	HELP SA, Greece
56.	MELOKTAM	solution for injection, 15 mg/1.5 ml, 1.5 ml (15 mg) in ampoules, 5 ampoules in a cassette in a pack	1 ampoule (1.5 ml) contains meloxicam 15 mg	HELP SA, Greece
57.	MILIXOL	solution for injections, 15 mg/1.5 ml of 1.5 ml in ampoules, 5 ampoules in a cardboard pack	1.5 ml of solution contains 15 mg of meloxicam	HELP SA, Greece
58.	MELODEV	solution for injections, 15 mg/1.5 ml, 1.5 ml in an ampoule; 5 ampoules in a cardboard pack	1 ampoule contains meloxicam 15 mg	HELP SA, Greece
59.	MELOXIKAM-TEVA	solution for injections, 15 mg/1.5 ml, 1.5 ml in an ampoule; 5 ampoules in a plastic container in a cardboard box	1 ampoule (1.5 ml) contains meloxicam 15 mg	Help SA, Greece
60.	MOVIKSIKAM®	solution for injections, 15 mg/1.5 ml, 1.5 ml in an ampoule; 5 ampoules in a plastic container in a cardboard box	1 ampoule (1.5 ml) contains meloxicam 15 mg	Help SA, Greece

Table 2

Active pharmaceutical ingredients of meloxicam registered in Ukraine

No.	Name	Release form (medicinal form, potency (dosage), packaging	Composition of active substances	Producer
1.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0%, in terms of dry substance	Swati Spentoz Pvt. Ltd., India
2.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry substance	Sun Pharmaceutical Industries Ltd., India
3.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry substance	Zhejiang Excel Pharmaceutical Co., Ltd., China
4.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% (in terms of dry substance)	Swati Spentoz Pvt. Ltd., India
5.	Meloxicam	powder (substance) in double plastic bags for pharmaceutical use	meloxicam from 99.0% to 101.0% on a dry matter basis	Derivados Cuimicos, S.A.U., Spain
6.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry substance	Swati Spentos Private Limited, India

7.	Meloxicam	powder (substance) in polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry substance	Micro Labs Limited, India
8.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% (in terms of dry substance)	Swati Spentoz Pvt. Ltd., India
9.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry substance	UNIMARK REMEDIES LTD., India
10.	Meloxicam	powder (substance) in double polyethylene bags for pharmaceutical use	of meloxicam not less than 99.0% and not more than 101.0% in terms of dry matter	Derivados Cuimicos s.a.u., Spain

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department pharmaceutical chemistry
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department of pharmaceutical chemistry

_____
Victoriya GEORGIYANTS
"_06_" ____May___ 2024 year

ASSIGNMENT
FOR QUALIFICATION WORK OF
AN APPLICANT FOR HIGHER EDUCATION

Nissrine DRAIDRY

1. Topic of qualification work: «Selection of conditions for the quantitative determination of meloxicam in a combined medicine», supervisor of qualification work: Nataliia SMIELOVA, PhD in pharmacy, assistant of the pharmaceutical chemistry department

approved by order of NUPh from "06th" of February 2024 № 34

2. Deadline for submission of qualification work by the applicant for higher education: November 2024

3. Outgoing data for qualification work: study of approaches to quantitative determination of meloxicam. in substances and medicines

4. Contents of the settlement and explanatory note (list of questions that need to be developed): To review and summarize scientific literature data on the pharmacological properties and medical applications of meloxicam; to investigate the physicochemical properties of meloxicam and existing methods for its quality control; to theoretically substantiate and select the conditions for the quantitative determination of meloxicam in the composition of a combined medicinal product in the form of a powder for the preparation of an oral solution; and to validate the developed methodology

5. List of graphic material (with exact indication of the required drawings):
tables 14, figures 11

6. Consultants of chapters of qualification work

Chapter	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Nataliia SMIELOVA, assistant of higher education institution of the Department of pharmaceutical chemistry	08.05.2024	08.05.2024
2	Nataliia SMIELOVA, assistant of higher education institution of the Department of pharmaceutical chemistry	29.05.2024	29.05.2024
3	Nataliia SMIELOVA, assistant of higher education institution of the Department of pharmaceutical chemistry	17.06.2024	17.06.2024
4	Nataliia SMIELOVA, assistant of higher education institution of the Department of pharmaceutical chemistry	02.09.2024	02.09.2024

7. Date of issue of the assignment: "06th_" of May 2024

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Review of scientific literature data	**May 2024**	**done**
2.	Selection of conditions for the quantitative determination	**May–June 2024**	**done**
3.	Validation of the method of quantitative determination	**June–September 2024**	**done**
4.	Preparation of qualification work and submission to the Examination Commission	**October 2024**	**done**

An applicant of higher education _____ Nissrine DRAIDRY

Supervisor of qualification work _____ Nataliia SMIELOVA

ВИТЯГ З НАКАЗУ № 34
По Національному фармацевтичному університету
від 06 лютого 2024 року

1. Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу 2 циклу Фм20*(4,10д) 2024-2025 навчального року, ступінь вищої освіти «магістр», галузь знань 22 Охорона здоров'я, спеціальність 226 – Фармація, промислова фармація, освітньо-професійна програма – Фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців). Мова навчання англійська

№ з/п	Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармацевтичної хімії**					
23.	Драйдрі Ніссрін	Підбір умов для кількісного визначення мелоксикаму у комбінованому лікарському засобі	Selection of conditions for the quantitative determination of meloxicam in a combined medicine	Ас. Смєлова Н.М.	Проф. Колісник С.В.

Ректор

Вірно. Секретар

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«26» листопада 2024 р. № 329753124

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Драйдрі Ніссрін, Фм20*(4,10д)-англ-01, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Підбір умов для кількісного визначення мелоксикаму у комбінованому лікарському засобі / Selection of conditions for the quantitative determination of meloxicam in a combined medicine», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Nissrine DRAIDRY

on the topic: «Selection of conditions for the quantitative determination of meloxicam in a combined medicine».

Relevance of the topic. In connection with the growing range of drugs on the pharmaceutical market, including combined drugs with meloxicam, identifying optimal methods for their quality control has become a pressing task.

Practical value of conclusions, recommendations, and their validity. The conditions for the quantitative determination of meloxicam in the composition of a combination drug in the form of a powder for the preparation of an oral solution have been theoretically substantiated and selected, and the developed methodology has been validated.

Assessment of the work. The qualification work follows a classical structure: an introduction, four chapters (a literature review and three chapters of experimental research), conclusions, and a list of references. The work convincingly substantiates the relevance of the topic, thoroughly describes the materials and research methods, presents the results systematically, provides an in-depth analysis of the findings, and logically formulates the conclusions. The research is conducted at a modern and high level, and the conclusions are well-founded.

General conclusion and recommendations on admission to defend. The qualification work of Nissrine Draidry meets the requirements for qualification works in terms of the relevance and scope of the performed research, the novelty of the obtained results, their theoretical and practical significance and can be recommended for defense at the Examination Commission.

Scientific supervisor _____ Nataliia SMIELOVA

«17» October 2024 year

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Nissrine DRAIDRY

on the topic: «Selection of conditions for the quantitative determination of meloxicam in a combined medicine».

Relevance of the topic. Medicinal products containing meloxicam are widely used for the short-term symptomatic treatment of acute attacks of rheumatoid arthritis and occupy a significant segment of the modern pharmaceutical market. The successful use of such products in medicine requires guaranteed quality, which is established during pharmaceutical development. In this context, selecting conditions for the quantitative determination of mediciness, particularly in the composition of combined medical products, is an urgent task.

Theoretical level of work. Qualification work is performed at a high theoretical level with the application of modern theoretical approaches to the analysis of scientific literature and methods of analysis to conduct experimental studies for the studied object.

Author's proposals on the research topic. The researcher has theoretically substantiated and selected an approach for the quantitative determination of meloxicam in the composition of a combined medicinal product in the form of a powder for the preparation of an oral solution. Additionally, validation of the developed methodology was carried out.

Practical value of the findings, recommendations and their validity. The spectrophotometric method of quantitative determination of meloxicam can be used in the quality control of combined medicines with meloxicam in the form of a powder for the preparation of an oral solution.

Shortcomings of the work. The master's thesis contains some spelling and punctuation errors. However, there are no substantial or fundamental comments on the content of the work.

General conclusion and assessment of the work. The qualification work of Nissrine Draidry meets the requirements of the *Regulation on the Procedure for the Preparation and Defense of Qualification Works* at the National University of Pharmacy in terms of the scientific novelty of the obtained results, relevance, methodological level, theoretical and practical significance, and the scope of the conducted research. It is recommended for defense before the Examination Commission.

Reviewer _____ prof. Sergiy KOLISNYK

«21» October 2024 year

Ф А2.2.1-38-287

ВИТЯГ

з протоколу засідання кафедри фармацевтичної хімії

№ 04 від 31 жовтня 2024 р.

ПРИСУТНІ: проф. Георгіянц В. А., проф. Перехода Л. О., проф. Баюрка С.В., проф. Сидоренко Л. В., проф. Северіна Г. І.; доц.: Абу Шарк А. І., доц. Бевз Н. Ю., доц. Віслоус О. О., доц. Головченко О. С., доц. Гриненко С. Г., доц. Кобзар Н. П., доц. Петрушова Л.О., доц. Рахімова М. В., доц. Яременко В.Д., доц. Михайленко О.О., ас. Смєлова Н. М.; аспіранти: Гуріна В. О., Асмолов В. Є., Коптєлов А. С., Мураль Д. В., Гуд В. А., Сайфудінова Р. П., Куцанян А. А., Сулейман Р. М.

ПОРЯДОК ДЕННИЙ:
Звіт про стан виконання кваліфікаційної роботи здобувача вищої освіти факультету з підготовки іноземних громадян, Фм20*(4,10д)англ-01 групи, спеціальності «226 Фармація, промислова фармація», освітньої програми «Фармація» Драйдрі Ніссрін на тему: «Selection of conditions for the quantitative determination of meloxicam in a combined medicine / Підбір умов для кількісного визначення мелоксикаму у комбінованому лікарському засобі».

СЛУХАЛИ:
доповідь здобувача вищої освіти факультету з підготовки іноземних громадян, Фм20*(4,10д)англ-01 групи, спеціальності «226 Фармація, промислова фармація», освітньої програми «Фармація» Драйдрі Ніссрін на тему: «Selection of conditions for the quantitative determination of meloxicam in a combined medicine / Підбір умов для кількісного визначення мелоксикаму у комбінованому лікарському засобі», керівник асистент закладу вищої освіти кафедри фармацевтичної хімії, к. фарм. н. Наталія СМЄЛОВА.

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Драйдрі Ніссрін до офіційного захисту в ЕК.

Голова
Завідувачка кафедри
фармацевтичної хімії,
доктор фарм. наук, проф. _____ Вікторія ГЕОРГІЯНЦ
(підпис)

Секретар
канд. фарм. наук, доц. _____ Марина РАХІМОВА
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Драйдрі Ніссрін до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Підбір умов для кількісного визначення мелоксикаму у комбінованому лікарському засобі»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Драйдрі Ніссрін виконала роботу на сучасному рівні. За період виконання кваліфікаційної роботи здобувач проявив високий рівень теоретичної підготовки. Кваліфікаційна робота викладена послідовно, грамотно, висновки коректні та логічні, витікають зі змісту роботи. Кваліфікаційна робота Драйдрі Ніссрін може бути рекомендована до захисту в Екзаменаційній комісії.

Керівник кваліфікаційної роботи

_____ Наталія СМЄЛОВА

«17» жовтня 2024 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Драйдрі Ніссрін допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
фармацевтичної хімії

_____ Вікторія ГЕОРГІЯНЦ

«31» жовтня 2024 р.

Qualification work was defended

of Examination commission on

«28 » of November 2024

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /