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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: **‘Justification of quality control methods and stability study of antimicrobial medicine used for intestinal infections’**

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ABSTRACT

In the qualification work, the indicators of quality control of the antimicrobial drug in the form of capsules, used in the therapy of intestinal infections, whose active substance is the active pharmaceutical ingredient nifuroxazid, are proposed and substantiated. The choice of the method of quantitative determination of nifuroxazid in capsules by the spectrophotometry method was justified, its validation characteristics were studied, and the degree of environmental friendliness was investigated. An analysis of the modern pharmaceutical market of products containing nifuroxazid was carried out.

The total volume of work is 49 pages. The work contains 8 figures, 6 tables, 47 literature sources, and 1 appendix.

Keywords: nifuroxazide; capsules; spectrophotometry; green chemistry; quality control of medicines.

АННОТАЦИЯ

В квалификационной работе предложены и обоснованы показатели контроля качества антимикробного лекарственного средства в форме капсул, применяемого в терапии кишечных инфекций, действующим веществом которого является активный ингредиент нифуроксазид. Обоснован выбор методики количественного определения нифуроксазида в капсулах методом спектрофотометрии, изучены ее валидационные характеристики и исследована степень экологичности. Проведен анализ современного фармацевтического рынка средств, содержащих нифуроксазид.

Общий объем работы 49 страниц.

Работа содержит рисунки – 8, таблицы – 6, источники литературы – 47, приложения – 1.

Ключевые слова: нифуроксазид; капсулы; спектрофотометрия; зеленая химия; контроль качества лекарственных средств

CONTENT

LIST OF TERMS, UNIT SYMBOLS, ABBREVIATIONS AND TERMS

MP – medicinal product;

DFM – dimethylformamide;

Spectrophotometry – Absorption spectrophotometry in the UV and visible regions;

INTRODUCTION

In the modern world, where the quality of medicinal products directly affects the health and well-being of people, the quality control of medicinal products becomes especially relevant. One of the drugs that requires careful monitoring is an antibacterial agent in the form of capsules, which is widely used for the treatment of intestinal infections, and the active substance of which is nifuroxazid. The importance of developing effective methods of quality control of nifuroxazid in medicinal forms is determined not only by the need to ensure the safety and effectiveness of treatment, but also by the requirements of modern standards of the pharmaceutical industry. In turn, when developing quality control methods, it is important to develop not only accurate and effective determination methods, but also those that will minimize the use of harmful reagents, reduce waste production and energy consumption, that is, comply with the principles of ‘green chemistry’.

The purpose of the qualification work is the development and substantiation of quality control methods of a medicinal product in the form of capsules for the treatment of intestinal infections, the active substance of which is the active pharmaceutical ingredient nifuroxazide.

To achieve the set goal, it was necessary to solve the following tasks:

– Conduct an analysis of literary sources regarding the causes of occurrenceacute intestinal infections and directions of modern pharmacotherapy; physico-chemical properties, extraction and existing methods of quality control of the active pharmaceutical ingredient nifuroxazid for the treatment of intestinal infections;

– Investigate the modern pharmaceutical market of Ukraine's medicinal products containing the substance nifuroxazide;

– Develop and substantiate the spectrophotometric method of quantitative determination of nifuroxazid in the composition of capsules, determine its validation characteristics; to investigate the environmental friendliness of the proposed method;

– To propose and substantiate the quality control indicators of nifuroxazid in the dosage form "hard capsules" for the treatment of intestinal infections.

Object of study is a drug in the form of capsules for the treatment of intestinal infections with nifuroxazide.

Subject of study is the development and substantiation of methods of quality control of nifuroxazid capsules.

Research methods is analysis of literary data, methods of marketing research, analysis of competitors and market structure, physical and physico-chemical research methods, methods of statistical processing of research results, validation of analytical methods.

Practical significance of the obtained results lies in the possibility of using approaches and methods for quality control of the dosage form with nifuroxazid.

*Scientific novelty*consists in the development of modern methods of quantitative determination of nifuroxazide by spectrophotometry in solid capsules and substantiation of indicators of quality control of the dosage form.

CHAPTER I
MODERN MEDICINAL PRODUCTS USED FOR THE TREATMENT OF INTESTINAL INFECTIONS. NIFUROXAZID: PHYSICO-CHEMICAL PROPERTIES, DIRECTIONS OF APPLICATION, EXISTING METHODS OF QUALITY CONTROL

1.1 Intestinal infections: causes and directions of modern pharmacotherapy

Intestinal infections are a group of diseases caused by viruses and bacteria that affect the mucous membrane of the stomach and intestines (less often the oropharynx). Getting into the digestive tract, they provoke nausea, gastritis with vomiting, acute diarrhea and, as a result, dehydration of the body. Characteristic symptoms also include general intoxication (poisoning), which can manifest itself in mild, moderate and severe forms [26, 29, 36].

Intestinal infections are among the most common diseases in the world, the frequency of which, according to WHO, is 1-1.2 billion cases per year. This problem is relevant for both adults and children [26]. So, for example, according to the literature, the morbidity rate among children of the younger age groups on intestinal infections is in second place, second only to acute respiratory viral infections, and in terms of the mortality rate from infections, these diseases occupy a leading position. Every year, about 5 million children die from intestinal infections and their complications worldwide [29, 36]. Adequate therapy prescribed in a timely manner allows to avoid complications and mortality from this disease [17, 26].

The main reasons for the occurrence of diseases at the intestinal infections are the use of drinking water and food products infected with pathogenic and opportunistic microorganisms, violation of the cooking technology, non-compliance with the temperature conditions for the storage of food products and food raw materials, their storage terms and the requirements of commodity proximity when they are stored in refrigeration equipment, neglecting the rules of personal hygiene, etc. [17, 29].

The most common types of intestinal infections among patients of all age categories are [26, 29, 36]:

– *Rotavirus infection*: The source of the disease is rotaviruses, which cause intestinal, stomach flu, enteritis. The ways of transmission are from a sick person to a healthy person, through a number of food products, unwashed hands [26, 29, 36].

– *Norovirus infection:*The disease is caused by a type of Caliciviridae enterovirus that provokes the development of the intestinal infections. The mechanism of transmission is through household items, food, liquids, orally and fecally [17, 29].

– *Dysentery (shigellosis):* The vector is pathogenic bacteria (dysenteric bacillus), which releases a toxin that affects digestion and general well-being. Ways of transmission are unboiled milk, unwashed fresh products, untreated water, dirty hands [36].

Prevention of the intestinal infections includes compliance with the rules of personal hygiene, careful consumption of food and water, as well as the use of certain types of medicinal products (MP). Modern pharmacotherapy of intestinal infections involves the use of medicinal zabos for rehydration, since it is important to restore lost fluid and electrolytes due to diarrhea and vomiting; antibiotics; antiviral drugs; antiseptics; antispasmodics, etc [3-7, 22, 34, 26, 29, 36].

1.2 Nifuroxazid is a modern drug for the pharmacotherapy of intestinal infections: pharmacological activity, therapeutic use

Nifuroxazide is one of the common antimicrobial MPs used for the treatment of gastrointestinal infections, especially diarrhea of infectious etiology. According to its chemical structure, it is a derivative of nitrofuran (4-hydroxy-N-[(E)-(5-nitrofuran-2-yl)methylidenamiino]benzamide) [3-7, 12, 21, 24, 27, 28, 38].

History of discovery. In 1961, nifuroxazide was first patented in France and since 1964 it has been sold under the trade name "Ercefuril". It has been on the US pharmaceutical market since 1966. After the expiration of patent protection, it became available in the form of generics [3-7, 12, 21, 24, 38].

Pharmacodynamics. The mechanism of action is not fully elucidated. It is assumed that nifuroxazide suppresses the activity of dehydrogenases and disrupts the synthesis of proteins in pathogenic bacteria. The antimicrobial and antiparasitic properties of nifuroxazid are probably due to the presence of an amino group. Local activity and lack of penetration into organs and tissues of the body determine the uniqueness of nifuroxazid compared to other nitrofuran derivatives, since there is no systemic effect of this antidiarrheal drug [3-7, 12, 21, 37, 38].

Due to the fact that nifuroxazide is poorly absorbed in the gastrointestinal tract, it is widely used as an intestinal antiseptic in the treatment of colitis, acute and chronic diarrhea, and gastroenteritis. Nifuroxazid has a complex mechanism of action, it disrupts a number of vital processes in the bacterial cell, including cellular respiration and protein synthesis, and also damages bacterial cell membranes. The active metabolite of the nifuroxazide molecule, 5-nitro-2-furyl, exhibits cytotoxic effects against bacterial cells with the formation of superoxide anions/radicals that damage macromolecules. As a result, lipid oxidation, cell membrane damage, enzyme inactivation, and, finally, DNA sequence fragmentation occur [3-7, 12, 21, 27, 28, 37, 38].

Nifuroxazide does not eliminate dehydration in patients with acute diarrhea and does not reduce its severity. Therefore, this drug should be used only as an additional therapy for oral rehydration [3-7, 12, 21, 24, 27, 28, 38].

Nifuroxazid is effective against most pathogens of intestinal infections (including mutant strains resistant to other antimicrobial agents). It has a local antibacterial effect in the lumen of the intestine against some types of gram-positive bacteria from the Staphylococcus family and some types of gram-negative bacteria from the Enterobacteriaceae family: *Yersinia spp., Escherichia spp., Citobacter spp., Enterobacter spp., Klebsiella spp., Salmonella spp.* [3-7, 12, 21, 37, 38].

In medium therapeutic doses, it exhibits bacteriostatic activity, and in higher doses, it acts bactericidally. In therapeutic doses, it practically does not disturb the balance of the saprophytic bacterial flora of the large intestine, does not cause the development of resistant strains of pathogenic microorganisms and cross-resistance of

bacteria to other antimicrobial agents, which allows for generalized infections to be prescribed in complex therapy with systemic antibacterial drugs. In intestinal infections of viral origin, it prevents the development of bacterial superinfection. The effectiveness of the drug does not depend on the pH in the lumen of the intestine. The therapeutic effect is achieved from the first hours of treatment [3-7, 12, 21, 24, 27, 28, 37, 38].

*Pharmacokinetics.*After oral administration, nifuroxazide is partially absorbed (10-20 %) from the gastrointestinal tract and is largely metabolized, with metabolites mainly circulating in the blood. Biotransformation of nifuroxazide occurs in the intestine, more than 20% is excreted unchanged. Nifuroxazide and its metabolites are excreted in feces. The rate of excretion depends on the amount of the drug taken and on the motility of the gastrointestinal tract. In general, the elimination of nifuroxazide is slow, it remains in the gastrointestinal tract for a long time [3-7, 24, 27, 28, 37, 38].

In preclinical safety studies, nifuroxazid shows mutagenic potential. The carcinogenic potential of nifuroxazide was evaluated in mice (50/sex/group) and rats (52/sex/group), which received nifuroxazide in the diet for 2 years at doses of 0, 200, 600 or 1800 mg/kg/day. Despite the mutagenic properties, the carcinogenicity of nifuroxazid was not proven either in mice or rats [3-7, 24, 27, 28].

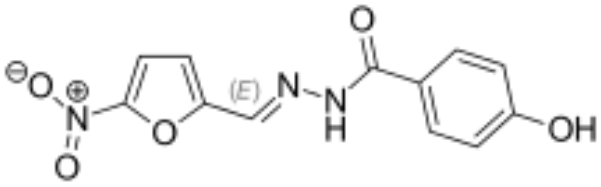
According to the results of 2-year studies on mice and rats (5400 mg/m2 and 10800 mg/m2, respectively), based on the comparison of the surface area with a factor of 11 and 22 times, the maximum dose for humans is 1800 mg (493 mg/m2 provided the patient weighs 60 kg) [3-7, 24, 27, 28].

*Indications for use.*Nifuroxazide is used for the treatment of acute diarrhea of infectious etiology and can be used for chronic diarrhea. It is not absorbed from the digestive tract and creates a high concentration in the intestines, which ensures effectiveness with minimal systemic side effects. Nifuroxazid is produced in the form of capsules, tablets, and suspensions [3-7, 12, 24, 27, 28, 37].

So, nifuroxazide–means in the treatment of infectious diseases of the gastrointestinal tract. Its history and pharmacological properties emphasize the importance of this drug in medical practice [3-7, 24, 27, 28, 37].

1.3 Physicochemical properties, extraction of the active pharmaceutical ingredient nifuroxazide, existing methods of quality control

Nifuroxazid is a synthetic antibiotic from the group of nitrofurans for oral use (5-nitrofuran derivative). The antimicrobial and antiparasitic properties of nifuroxazid are due to the presence of an amino group [3-7, 12, 21, 24, 27, 28, 38].



Nifuroxazide

4-Hydroxy-N'-[(5-nitrofuran-2-yl)methylene]benzohydrazide

$C_{12}H_9N_3O_5$ Mr 275.2

*Appearance.*Bright yellow crystalline powder [12, 21, 38].

*Solubility.*Practically insoluble in water, slightly soluble in ethanol (96 percent), practically insoluble in methylene chloride [12, 21, 38].

Extraction Since nifuroxazide is a compound of synthetic origin, there are several options for its extraction, one of which is given onFig. 1.1 [10, 25]:

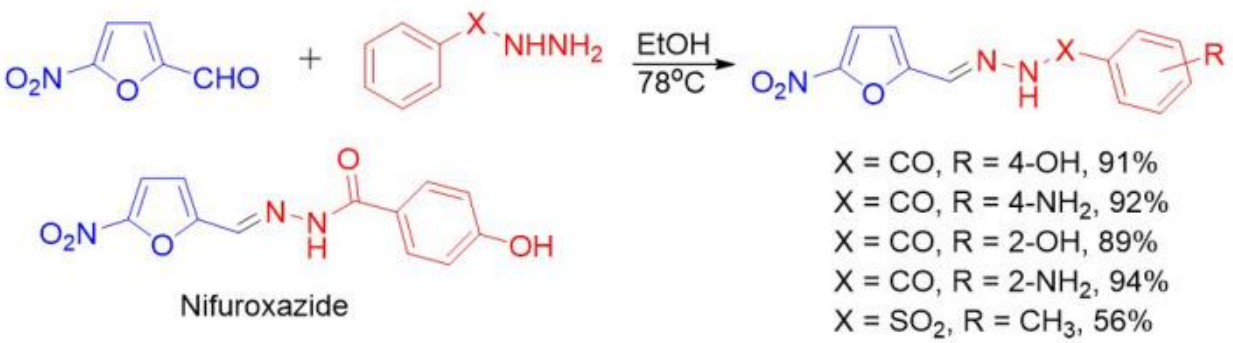


Fig. 1.1 Synthesis of nifuroxazide analog [10, 25]

According to literature data, physicochemical (instrumental) and chemical methods of analysis are used to control the quality of the active pharmaceutical ingredient nifuroxazid and its MPs [12, 21, 38].

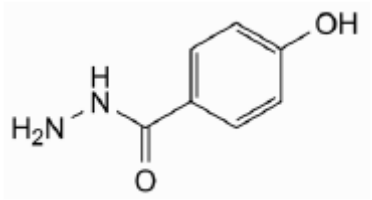
Quality control methods for the nifuroxazid substance are described in many pharmacopoeias, including the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BPh), the United States Pharmacopoeia (USP), etc. [12, 21, 38].

To identify the active substance, physicochemical methods of analysis are used, including absorption spectrophotometry in the IR region, where the IR spectrum of the tested solution is compared with the IR spectrum of the pharmacopoeial standard sample of nifuroxazid [12, 21, 30, 38, 41, 43].

To determine the purity of the substance, methods of absorption spectrophotometry in the UV and visible regions, high-performance liquid chromatography, etc. are used [12, 19, 21, 23, 31, 38, 40].

In the spectrophotometry method, the specific absorption index of the tested solution is calculated, which, according to the requirements of pharmacopoeias, should be in the range from 940 to 1000. The study is carried out after dissolving a portion of nifuroxazid API in ethylene glycol monomethyl ether, and the volume of the solution is adjusted with methanol. The same solvent is used for further dilution of the solution. The analysis is carried out at an analytical wavelength of 367 nm, where the maximum absorption is observed [12, 21, 38].

Also, the spectrophotometry method of the pharmacopoeia is recommended for determining impurity A, the content of which should not exceed 0.05%. This impurity is the starting point in the synthesis of nifuroxazid and is determined separately from other accompanying impurities (Fig. 1.2) [12, 21, 38, 40].



4-hydroxybenzohydrazide (p-hydroxybenzohydrazide)

Fig. 1.2 Chemical structure of impurity A

For its identification, a chemical reaction on secondary amines with a phosphoromolybdenum-tungsten reagent is used [12, 21, 38].

Determination of the limit content of impurity A is carried out by spectrophotometry at an analytical wavelength of 750 nm. The absorbance of the solution obtained with the test solution is not greater than that obtained with the reference solution (0.05%) [12, 21, 38, 40].

Among other impurities (Fig. 1.3), the main impurity of the degradation of the active pharmaceutical ingredient nifuroxazid is impurity E. Its content is regulated at a content level of no more than 0.3%. Other impurities (B, C, D) are specified according to the relative retention times specified in the EF monograph and are regulated at the level of 0.3%. But only one of them can be present in an amount greater than 0.1%. Impurities (B, C, D) are production impurities, they do not change during the storage of the MP. The amount of any other unspecified admixture is regulated at a level of no more than 0.1%. The sum of impurities, except for impurity E, is no more than 0.5% [12, 21, 38].

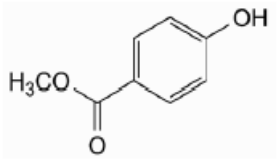
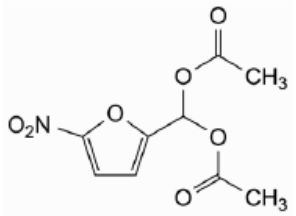
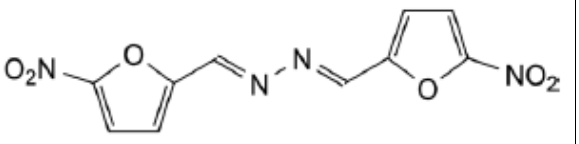
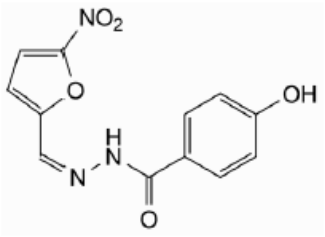
 Domishka V. *methyl 4-hydroxybenzoate (methyl parahydroxybenzoate)*	 Domishka S. *(5-nitrofuran-2-yl)methylidene diacetate*
 Impurity D. *(E,E)-N,N'-bis[(5-nitrofuran-2-yl)methylidene]hydrazine (5-nitrofurfural azine)*	 Domishka E. *(Z)-4-hydroxy-N'-[(5-nitrofuran-2-yl)methylidene]benzohydrazide*

Fig. 1.3 Identified impurities of nifuroxazid

Determination of other related substances of the pharmacopoeia is recommended to be carried out by the method of high-performance liquid chromatography. Research is conducted under the following conditions [12, 21, 38]:

- Column: size: 1 = 0.25 m, D = 4.6 mm; stationary phase: spherical octadecylsilyl silica gel for chromatography R (5 μm); temperature: 10 °C [12, 21, 38].
- Mobile phase: mobile phase A: tetrahydrofuran, water (5:95 V/V); mobile phase B: acetonitrile [12, 21, 38];
- Flow rate: 1.0 mL/min [12, 21, 38];
- Detection: spectrophotometer at 280 nm [12, 21, 38].

Pharmacopoeias recommend the use of a titrimetric method (alkalimetry) for the quantitative determination of API nifuroxazide. The substance is dissolved in dimethylformamide and brought up to the mark with water. 1 mL of 0.1M sodium hydroxide is equivalent to 27.52 mg of $C_{12}H_9N_3O_5$ [12, 21, 38].

In scientific articles, there are also methods of non-aqueous titration, high-performance liquid chromatography, spectrophotometry, etc. for the quantitative determination of nifuroxazid [12, 21, 38].

Conclusions to section I

1. Data from the scientific literature on the causes and directions of modern pharmacotherapy of intestinal infections are analyzed and summarized.

2. Data on physicochemical properties, methods of extracting the active pharmaceutical ingredient for the treatment of intestinal infections (nifuroxazide) and existing methods of its quality control are summarized.

SECTION II
THE MODERN PHARMACEUTICAL MARKET OF DRUGS IN UKRAINE CONTAINING NIFUROXAZID. RESEARCH OBJECTS AND METHODS

2.1 The modern pharmaceutical market of medicinal products in Ukraine containing the active pharmaceutical ingredient nifuroxazid

Studying the nomenclature, quantity and manufacturers of certain groups of drugs, as well as collecting data on market conditions, their changes, development trends, competition and consumer behavior is an important stage for assessing the current state and potential of the pharmaceutical market. By studying specific market segments, it is possible to determine the key active pharmaceutical ingredients used in the manufacture of finished medicines, as well as to establish different forms of their release and manufacturers [8, 9].

Today, on the world pharmaceutical market, nifuroxazid is found in many countries under the following trade names: Ambatrol, Antinal, Bacifurane, Diafuryl (Turkey), Benol (Pakistan), Pérabacticel (France), Antinal, Diax (Egypt), Nifrozid, Ercefuryl (Romania , Czech Republic, Russia), Erfuzide (Thailand), Endiex (Slovakia), Enterofuryl (Bosnia and Herzegovina), Pentofuryl (Germany), Nifuroksazyd Hasco, Nifuroksazyd Polpharma (Poland), Topron, Enterovid (Latin America), Eskapar (Mexico) , Enterocolin, Terracolin (Bolivia), Apazid (Morocco), Nifroxid (Tunisia), Nifural (Indonesia) and Septidiaryl. It is sold in capsule form and also as a suspension [2-7, 15].

To study the nomenclature of MPs containing the substance nifuroxazide, such information sources as the State Register of Medicinal Products of Ukraine [2] and "Compendium Online" [15] were used. The analysis was conducted among drugs whose registration certificate was valid as of the 1st quarter of 2024. Among the tools used for research were methods of marketing analysis, study of competitors and market share, as well as methods of statistical processing of results [8, 9].

According to the results of the analysis, 32 names of MPs are registered on the modern pharmaceutical market of Ukraine, the composition of which includes the substance nifuroxazide (Table Appendix A) [2-9, 15].

According to the ATC classification (Anatomical Therapeutic Chemical), these drugs belong to group A07A Antimicrobial agents used in case of intestinal infections. By type of dosage form, the drugs are presented in the form of hard capsules and suspensions - 13 names each (40.6 % each), tablets covered with a shell - 5 names (15.6%), in powder form - 1 name (3.1 %) (Fig. 2.4) [2-9, 15].

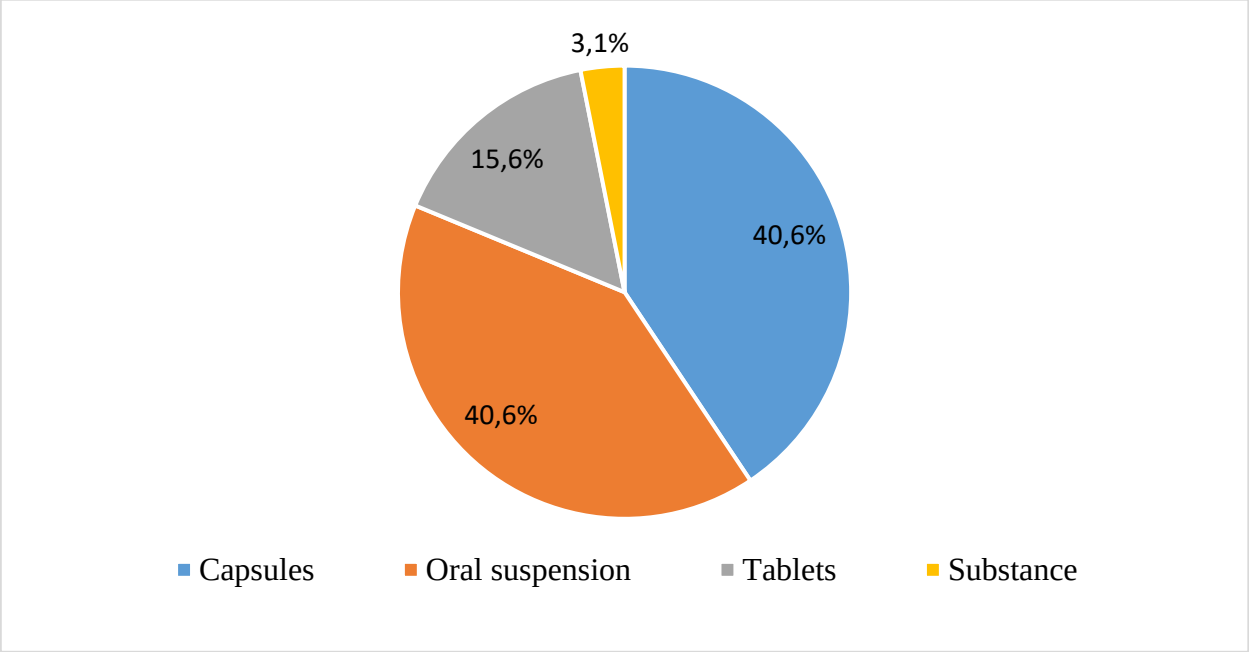


Fig. 2.4 Distribution of medicines with nifuroxazid by type of dosage form

According to the ATC classification, all the listed medicines with nifuroxazid have only one active substance, combinations of nifuroxazid with other active pharmaceutical ingredients are not presented on the pharmaceutical market [2-9, 15].

Among the means containing nifuroxazid substance, the largest number is produced by enterprises in Ukraine - 23 names (71.8 %). Among other countries, importers are the Republic of North Macedonia, Hungary, Bosnia and Herzegovina - 3 names each (9.4 % each) [2-9, 15].

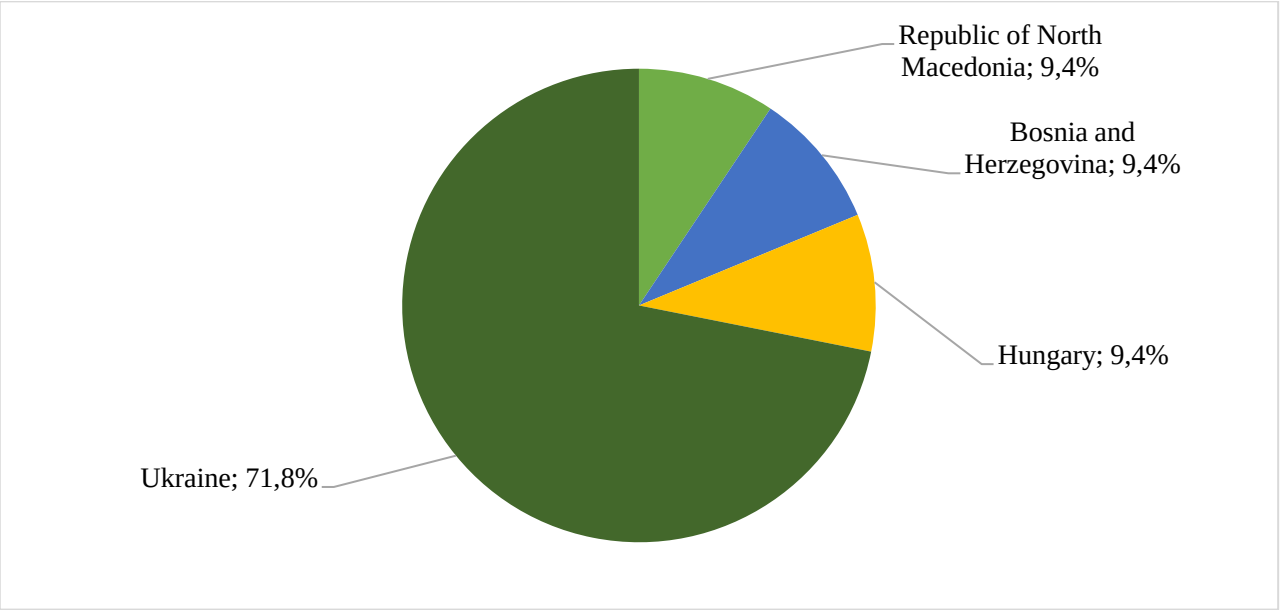


Fig. 2.5 Distribution of drugs with nifuroxazide by producing countries

LLC "ROCKET-PHARM", "Ternofarm" LLC are the leading producers of Ukrainian drugs containing nifuroxazid - 4 names each (17.4% each); "Health Corporation" LLC, LLC "Pharmaceutical Company "Zdorovya" - 3 names each (13.0% each); PJSC "Kyivmedpreparat", DKP "Pharmaceutical Factory" LLC, Joint Ukrainian-Spanish enterprise "Sperko Ukraine" - 2 names each (8.7% each); the remaining manufacturers - LLC "Unipharma", PJSC "Scientific and Production Center "Borshchagiv Chemical and Pharmaceutical Plant", PJSC "Halychpharm" - 1 name each (4.3% each) from the share on the Ukrainian market [2-9, 15].

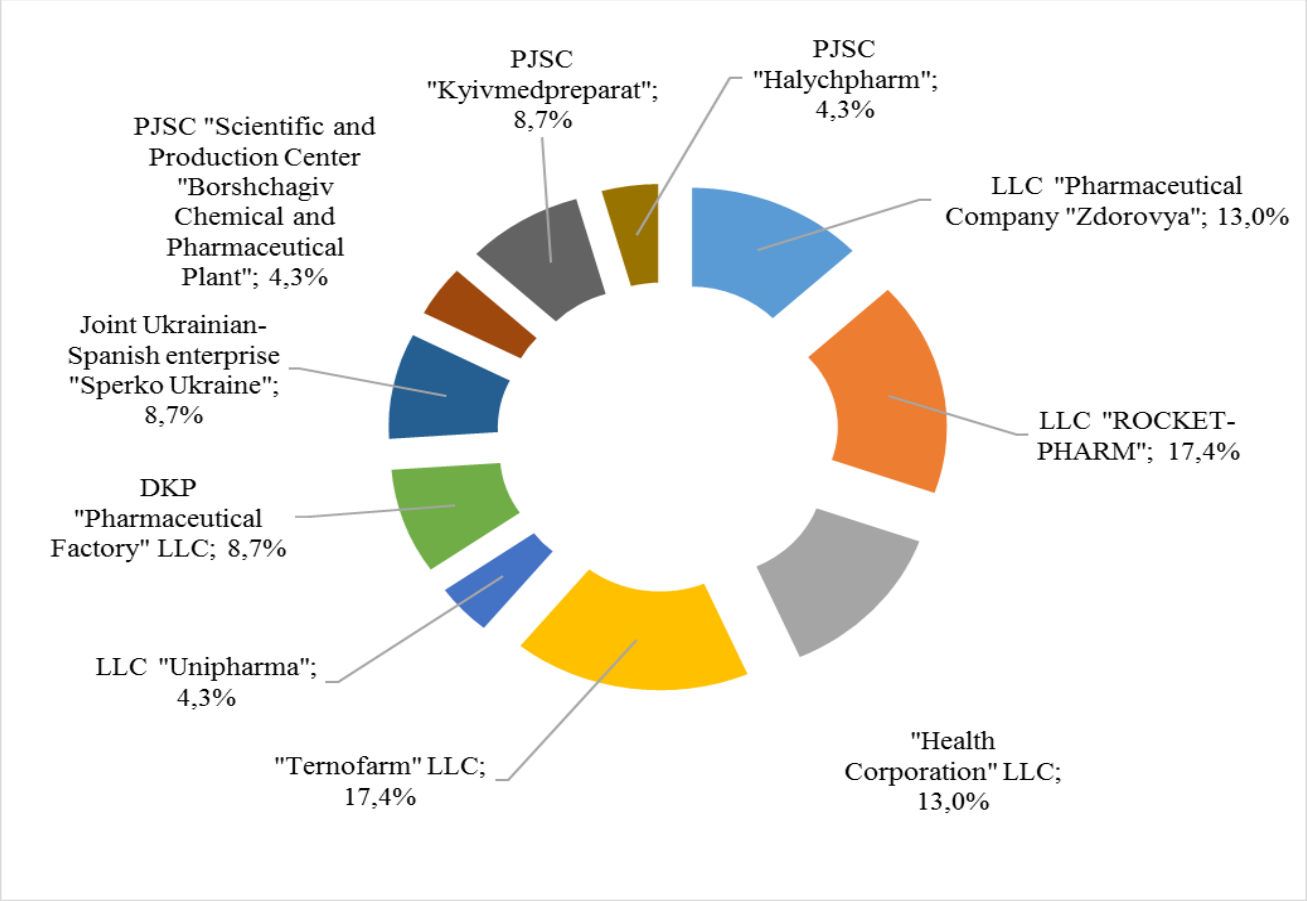


Fig. 2.6 Distribution of medicines with nifuroxazid produced by Ukrainian manufacturers

Therefore, as a result of the analysis of the pharmaceutical market of Ukraine, drugs containing the active pharmaceutical ingredient nifuroxazid, it was established that they belong to group A07A Antimicrobial agents used in case of intestinal infections. According to the type of dosage form, most of the drugs are presented in the form of solid capsules and suspensions, they are monopreparations. The largest amount is produced by enterprises in Ukraine, among other importers are the Republic of North Macedonia, Hungary, Bosnia and Herzegovina.

2.2 Research objects

Capsules, the active substance of which is the substance nifuroxazide in a dosage of 200 mg (Nifuroxazide, capsules) became the object of the study.

Microcrystalline cellulose, corn starch, sucrose, magnesium stearate became auxiliary substances of the capsules.

3 series of MP (01-03) were used for the analysis.

Indications for the use of the medicine: acute and chronic diarrhea of infectious origin [2-9, 15].

2.3 Research methods and brief information about devices, equipment and reagents

During the experimental part of the research, modern physical, physico-chemical methods of analysis, statistical processing of the results of the chemical experiment were used in accordance with the current edition of the State Pharmacopoeia of Ukraine and the European Pharmacopoeia [1, 21].

Class A (first class) measuring vessels from the company "Simax" (Czech Republic) were also used for the analysis. Solutions for analysis were used freshly prepared or used within the expiration date specified in the relevant regulatory documentation [1, 21].

Weighing was carried out on analytical balances "Mettler Toledo" model "AB-204/A" (Switzerland).

2.3.1 Development of a technique for quantitative determination of nifuroxazide by absorption spectrophotometry in the UV and visible regions

Absorption spectrophotometry in the UV and visible regions (spectrophotometry) is a physicochemical method of analysis based on the determination of the absorption spectrum or the measurement of light absorption at a certain wavelength. The method is characterized by ease of implementation, accuracy of the obtained results and is used for the identification of compounds, composition, structure and quantitative analysis of individual substances and multicomponent systems [14, 24, 27, 28, 47].

The development of the methodology for the quantitative determination of nifuroxazid in medicinal form was carried out on a double-beam spectrophotometer Specord 200 of the company "AnalitykJena" (Germany), measuring the optical density in cuvettes with a layer thickness of 10 mm. The research was conducted in accordance with the requirements of the SPhU/Ph.Eur., 2.2.25 [1, 21].

2.3.2 Assessment of ecological ("greenness") of analytical procedures

The scientific literature emphasizes the importance of environmental assessment in the development of quality control methods. This includes taking into account the impact of all key components of the research methodology on the environment [13, 16, 18, 20, 21, 32, 39, 44, 46].

However, environmental assessment requires special tools that provide easily interpretable and informative results, especially when comparing different analysis methods [13, 16, 18, 20, 21, 32, 35, 39, 42, 44, 46].

For these purposes, the analytical calculator GREEnness is used. Its evaluation criteria are based on twelve principles of "green chemistry" and transformed into a unified scale from 0 to 1. The final score is calculated based on principles of importance, where the importance of each principle is reflected by the width of the corresponding segment on the icon. This icon shows the final score and performance of the analytical procedure for each indicator [35, 42, 44].

A convenient software, Analytical GREEnness Metric Approach, is used to evaluate the results, which can be downloaded from the official website. This is an open resource that allows not only to evaluate the environmental friendliness of analytical procedures, but also to use the obtained icon for comparison with existing methods of analysis [35, 42, 44].

2.3.3 Homogeneity of dosage units

For capsules that contain 25 mg or more of the active substance, which is 25 % or more of the weight of the dosage unit or the content of the solid capsule, the uniformity of the dosage units is controlled by the calculation-weighing method. To determine the homogeneity of the dosage units in the analyzed drugs, the calculation-weight method (SPhU/Ph.Eur., Tabl. 2.9.40.-1) [1, 21].

For hard capsules, accurately weigh each of the 10 selected capsules, carefully monitoring their integrity. Extract the contents of each capsule in a suitable way. Weigh each of the emptied shells accurately and calculate the net mass of the contents for each capsule by subtracting the mass of the shell from the corresponding total mass. The content of the active substance in each capsule is calculated based on the individual mass extracted from the capsule and the result of quantitative determination [1, 21].

The calculation of the acceptance rate AV is carried out in accordance with the SPhU/Ph.Eur., Tabl. 2.9.40.-2, using case 1 as the reference value M [1, 21].

2.3.4 Disintegration

The determination is carried out in accordance with the requirements of the SPhU, 2.9.1 [1, 21].

Water P is used as a liquid medium, maintaining the temperature of the immersion liquid (37 ± 2) °C. Since the capsule floats to the surface of the water, a disc is used. Research is conducted within 30 minutes [1, 21].

During the specified time, all capsules should disintegrate completely. If 1 or 2 capsules have not disintegrated, the test is repeated on 12 additional capsules. The requirements of the test are considered fulfilled if at least 16 of the 18 tested capsules have disintegrated [1, 21].

Samples are considered to have completely disintegrated if there is no residue of the dosage unit on the grid of the device used in the test, except for fragments of the insoluble coating or shell of the capsules, or adhering to the lower surface of the discs, if they have been used, or a soft mass remains that is not a noticeably hard core [1, 21].

2.3.3 Statistical analysis of the results of experimental studies and study of validation characteristics

For the implementation of quality control methods for finished MPs, its validation procedure is mandatory, which is a guarantee that the given method within the selected range of determination meets the acceptance criteria and allows obtaining the correct results with the necessary precision and reproducibility. The methods presented in the pharmacopoeias do not require validation, when they are introduced into the regulatory documentation, depending on the tasks, they can be verified. However, when the conditions of experimental research are changed or a new analytical technique is developed, validation is mandatory [1, 19, 47].

Within the framework of the dissertation study, the validation characteristics of the methods were determined for the developed quality control methods in accordance with the requirements of the SPhU, 5.3.N.2. "Validation of analytical methods and tests", as well as in accordance with the recommendations of scientists in this field [1].

The statistical processing of the obtained results was carried out according to the requirements of the general article of the SPhU, 5.3.N.1 "Statistical analysis of the results of a chemical experiment N" [1, 47] using Microsoft Office 2021 software.

Conclusions to section II

1. An analysis of the pharmaceutical market of Ukraine, which contains API nifuroxazide in its composition, was carried out. It was established that according to the ATS classification they belong to group A07A Antimicrobial agents used in case of intestinal infections. According to the type of dosage form, most of the drugs are presented in the form of solid capsules and suspensions, they are monopreparations. The largest amount is produced by enterprises in Ukraine, among other importers are the Republic of North Macedonia, Hungary, Bosnia and Herzegovina.

2. The object of the research was chosen - hard capsules of nifuroxazid (series 01-03), which are indicated for use in acute and chronic diarrhea of infectious origin.

3. The methods, equipment and devices used in the research are described.

CHAPTER III
SELECTION OF CONDITIONS FORQUANTITATIVE DETERMINATION OF NIFUROXAZIDE IN CAPSULES FOR THE TREATMENT OF INTESTINAL INFECTIONS

3.1 Determination of the average weight of capsules

The primary task of the study was to determine the average weight of the contents of the capsules, as this is an important parameter in quantitative determination. This indicator directly reflects the stability of the dosage and ensures that each capsule has the same dose, which, in general, ensures the effectiveness of the drug [1, 21, 45].

For all 3 series of the analyzed drug Nifuroxazid, capsules, the average weight and deviations from the average weight were determined [1, 21].

According to the requirements of regulatory documentation, for the MP Nifuroxazid, the average weight of the capsule contents must be within ± 7.5%, that is, the requirements must be met: from 323.75 mg to 376.25 mg (350 mg ± 7.5%) [1, 21].

For all three batches of the MP, the average weight of the capsule contents and the deviation from the average weight were calculated. The results are presented in table. 3.1.

Table 3.1

The average weight of the contents of capsules and deviations from the average weight for the drug Nifuroxazid, capsules (series 01-03)

	A series of medicinal preparations		
	01	02	03
1	0.3343	0.3412	0.3378
2	0.3378	0.3459	0.3387
3	0.3387	0.3487	0.3397
4	0.3421	0.3488	0.3421
5	0.3443	0.3491	0.3443
6	0.3465	0.3495	0.3443
7	0.3476	0.3496	0.3467
8	0.3487	0.3499	0.3478
9	0.3492	0.3499	0.3499

10	0.3509	0.3499	0.3502
11	0.3518	0.3500	0.3521
12	0.3539	0.3500	0.3534
13	0.3543	0.3501	0.3543
14	0.3551	0.3501	0.3556
15	0.3567	0.3507	0.3567
16	0.3575	0.3507	0.3575
17	0.3580	0.3512	0.3589
18	0.3593	0.3517	0.3593
19	0.3602	0.3521	0.3600
20	0.3624	0.3536	0.3642
The average mass of the contents of the capsule, g	0.3505	0.3496	0.3507
Deviation from the average mass, %	-4.61% +3.41%	-2.41% +1.13%	-3.67% +3.86%

According to the results of the research, the average mass of the contents of capsules for the MP "Nifuroxazid, capsules" is: series 01 - 0.3505 g (deviation -4.61%; +3.41%); series 02 – 0.3496 g (deviation -2.41%; +1.13%); series 03 – 0.3507 g (deviation -3.67%; +3.86%), which meets the requirements of regulatory documentation.

3.2 Selection of conditions for the quantitative determination of nifuroxazide in capsules by the spectrophotometry method and study of the validation characteristics of the technique

For the quantitative determination of nifuroxazide in the MP, we proposed to use the spectrophotometry method, as it has high sensitivity and selectivity, gives accurate results, and the equipment used is affordable and convenient for conducting the study. In addition, according to literature data, the active pharmaceutical ingredient of the analyzed capsules is nifuroxazid, a bright yellow substance with an absorption maximum in the visible region in the wavelength range of 365-375 nm, depending on the selected solvent [1, 12, 21, 24, 27, 28, 38].

However, taking into account the physical properties of nifuroxazide (practically insoluble in water, slightly soluble in ethanol (96 percent), practically insoluble in methylene chloride), for the preparation of the tested solutions it was necessary to first dissolve the sample in a suitable solvent. The European Pharmacopoeia recommends that for the quantitative determination of nifuroxazide by titrimetry, the substance should first be dissolved in dimethylformamide (DMF) [21].

We investigated the nature of the spectrum of a standard sample of nifuroxazid after dissolving the sample in DMF and adjusting the volume of the solution with methanol and ethanol (96%). The concentration of the nifuroxazide solution for the test was selected in such a way that the optical density was in the range of 0.2-0.8. The preparation of the studied solution was carried out according to the method [21]:

110 mg (exact weight) of a standard sample of nifuroxazid was placed in a volumetric flask with a capacity of 25.0 ml, 5 ml of dimethylformamide was added, and vigorously shaken until the substance was completely dissolved. The volume of the solution was brought up to the mark with ethanol (96%) or methanol. The optical density of the solution was measured on a spectrophotometer in a cuvette with a layer thickness of 10 mm, using ethanol (96%) or methanol as a compensation solution. The corresponding spectra are presented in Fig. 3.1, 3.2 [31, 47].

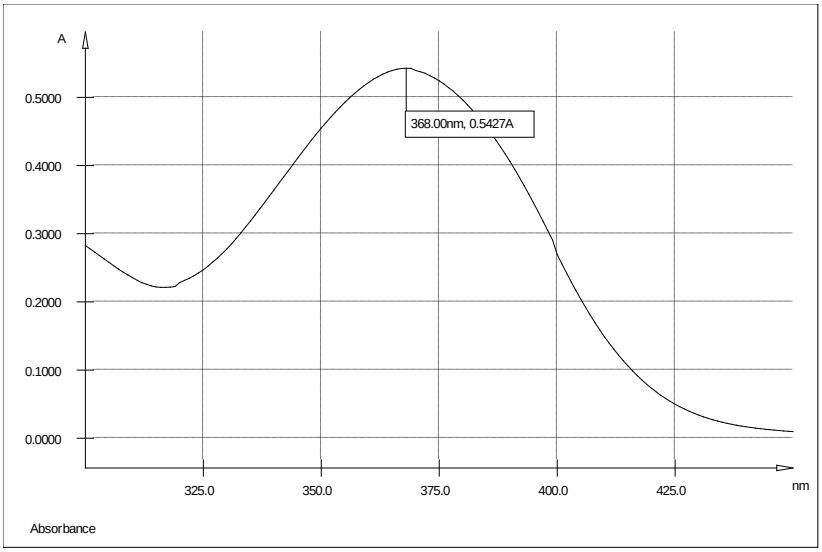


Fig. 3.1 Maximum absorption of nifuroxazide solution in ethanol (96%)

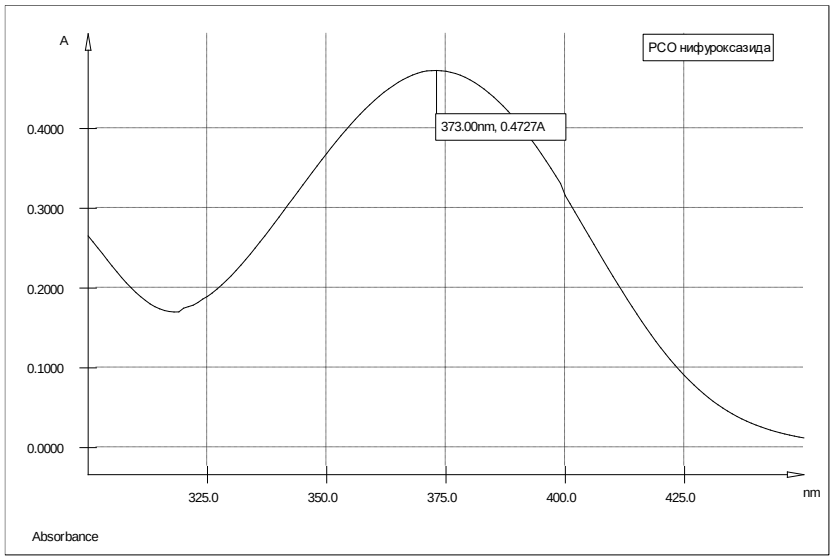


Fig. 3.2 Maximum absorption of a solution of a standard sample of nifuroxazide in methanol

As we can see from the research results, for the ethanol and methanol solutions of the standard sample of nifuroxazid, there are clear maxima at the wavelengths of 368 ± 2 nm and 373 ± 2 nm, respectively. Taking into account the less toxic effect of ethanol (96%) for the analyst, this solvent was chosen for the quantitative determination of nifuroxazide [1, 12, 21, 38].

For the quantitative determination of nifuroxazid in the analyzed capsules (series 01-03), the preparation of the test solution and comparison solutions was carried out as follows [1, 12, 21, 38]:

Test solution. 200 mg (exact weight) of the contents of the capsules were placed in a measuring flask with a capacity of 25.0 ml, 5 ml of dimethylformamide was added, and vigorously shaken until the substance was completely dissolved. The volume of the solution was brought up to the mark with ethanol (96%) [1, 12, 21, 38].

Comparison solution. 110 mg (exact weight) of a standard sample of nifuroxazid was placed in a volumetric flask with a capacity of 25.0 ml, 5 ml of dimethylformamide was added, and vigorously shaken until the substance was completely dissolved. The volume of the solution was brought up to the mark with ethanol (96%) [1, 12, 21, 38].

The optical density of the solution was measured on a spectrophotometer in a cuvette with a layer thickness of 10 mm, using ethanol (96%) or methanol as a compensation solution [1, 12, 21, 38].

The content of nifuroxazid in one capsule, in milligrams, based on the average weight of the capsule, was calculated according to the formula [1, 12, 21, 38]:

$$X = \frac{A \cdot 25 \cdot m_0 \cdot P \cdot b \cdot 1000}{A_0 \cdot m \cdot 25 \cdot 100} = \frac{A \cdot m_0 \cdot P \cdot b \cdot 10}{A_0 \cdot m}$$

where A is the optical density of the tested solution [1, 12, 21, 38];

A0 is the optical density of the comparison solution [1, 12, 21, 38];

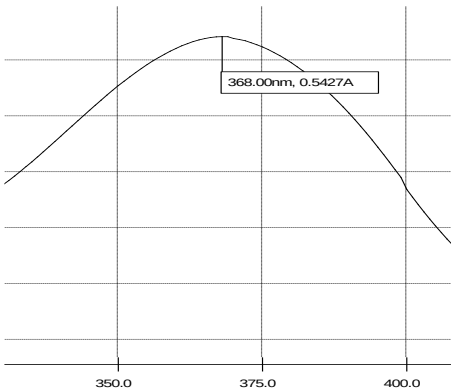
m0 – the weight of a standard sample of nifuroxazid, taken to prepare a comparison solution, in grams [1, 12, 21, 38];

m– the weight of the powder of the drug taken to prepare the tested solution in grams [1, 12, 21, 38];

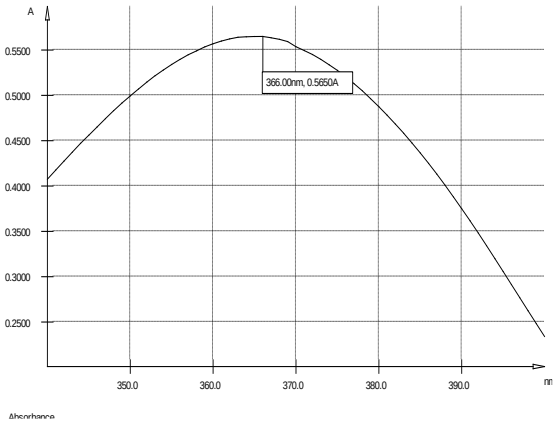
P is the content of the main substance in the standard sample of nifuroxazid, specified in the quality certificate, in percent [1, 12, 21, 38];

b –the average mass of the contents of the package in grams [1, 12, 21, 38].

The resulting spectrum of the tested solution and the comparison solution (for series 01) is shown in Fig. 3.3.



AND



IN

Fig. 3.3 Absorption spectra of the reference solution (A) and the tested solution (B)

Quantitative determination of nifuroxazide in the drug was carried out for all 3 series of the analyzed drug. Metrological characteristics of the method of quantitative determination are presented in the table. 3.2.

Table 3.2

Metrological characteristics of the method of quantitative determination of nifuroxazid in capsules

Series of the drug	Xi	Khsr	S2	Scp	P	t(P,ν)	Confidence interval	ε, %
01	201.1 200.5 199.8 202.9	200.6	2.3937	0.6919	0.95	2.78	200.6 ± 1.9235	0.96
02	198.8 202.3 211.2 198.1 199.8 200.3 201.5	202.3	26.7730	2.3140	0.95	2.78	202.3 ± 6.4329	3.18
03	199.6 199.9 207.9 200.5	201.9	11.8520	1.5396	0.95	2.78	201.9 ± 4.2801	2.12

As we can see from the research results, the systematic error of the method can be considered insignificant, the relative uncertainty of a single determination for a probability of 95 % is 0.96 %, 3.18 % and 2.12 %, respectively.

For the proposed method of quantitative determination, determination of validation characteristics was carried out according to such indicators as specificity, linearity, correctness, precision and robustness. The research was conducted on the 01 drug series [19, 47].

The maximum permissible total uncertainty (max ΔAS) of the analysis method is related to the limits of the content of the substance in the preparation. In the package, the content of nifuroxazid was normalized in the range from 0.190 g to 0.210 g, that is, the tolerances of the content were chosen to be ± 5.0 % [19, 47].

The maximum permissible total uncertainty of the analysis method [19, 47]:

$$max\ \Delta AS,\ \% \leq 0.32 \cdot 5.0\% = 1.6\%.$$

The criterion of insignificance of sample preparation against the maximum permissible uncertainty of the analysis results (ΔAS, insig %) [19, 47]:

$$\Delta AS,\ insig\ \% \leq \max \Delta AS,\ \% \cdot 0.32 = 1.6\ \% \cdot 0.32 = 0.51\ \%.$$

The results of calculating the total uncertainty for the developed technique are given in the table. 3.3 [19, 47].

Table 3.3

The results of the calculation of the uncertainty of the analysis method

Parameter	Result, %
Total uncertainty of sample preparation, Δ SP %	0.39
*Uncertainty of the final analytical operation, Δ FAO (spectrophotometry)**	0.70
Full uncertainty of the analysis method ΔAs % =√(Δsp %)²+(Δ FAO %)²	0.80

Therefore, the calculated total uncertainty of the analysis method ΔAS % is less than max ΔAS (0.80 % < max ΔAS = 1.6 %), which meets the requirements for this parameter [19, 47].

To study the specificity, a placebo solution, a comparison solution and a test solution were prepared [19, 47].

The average value of the optical density of the placebo solution (Ablank), due to the absorption of excipients, is: Ablank = 0.0013; Ast = 0.5427 [19, 47]:

$$\frac{A_{blank}}{A_{st}} \cdot 100 \leq 0{,}51\ \%$$

The inequality is satisfied, that is, the background absorption is insignificant, the method is characterized by an acceptable specificity: 0.24% ≤ 0.51%, because the contribution of the placebo to the total absorption of the drug does not exceed the normalization [19, 47].

When comparing the spectra of the reference solution and the tested capsules, we have a coincidence of absorption maxima (368 ± 2 nm) [19, 47].

The obtained results confirm that the method of quantitative determination of nifuroxazide is specific [19, 47].

The method of quantitative determination should also be linear within the range of application, which overlaps the possible values of concentrations of the active substance in the range of application of the method 80-120% [**Ошибка! Источник ссылки не найден.**]. To confirm the linearity of the method, 9 model solutions of nifuroxazid were prepared, the concentration of which varies uniformly within the application range (5% step) [19, 47].

In fig. 4.21 shows a graph of the linear dependence of the analytical signal on the actual concentration of the active substance [19, 47].

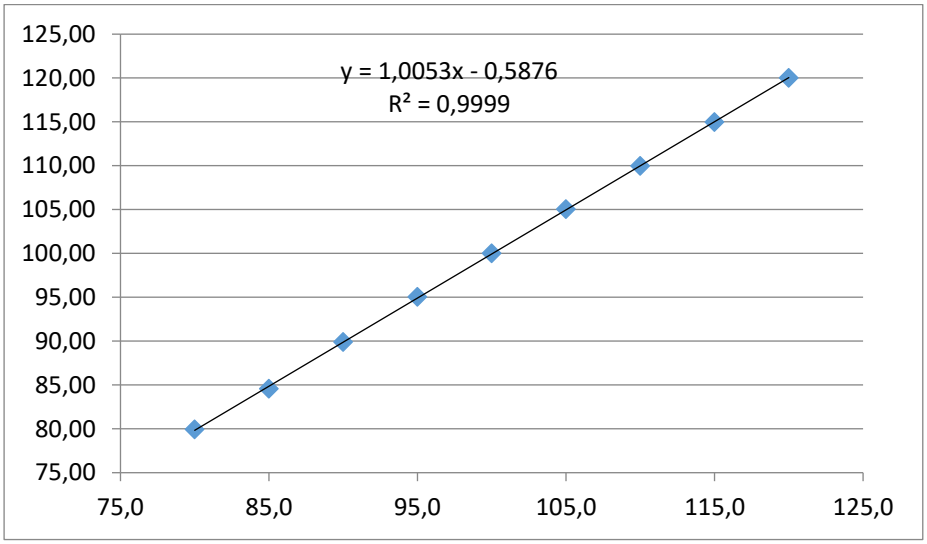


Fig. 4.21 Graph of linear dependence of nifuroxazide [19, 47]

For model solutions, parameters of linear dependence were calculated by the method of least squares: free term a, residual standard deviation S0, correlation coefficient r. Acceptability criteria are listed in table. 3.4.

Table 3.4

Data for checking the linearity of the quantification method

Parameter	Requirements	The resulting value	Performance of the criterion
$\lvert a \rvert$	≤ 3.8	0.5876	Executed
S_0	≤ 1.27	0.1517	Executed
r	> 0.9957	0.9999	Executed

The obtained results confirm that the method of quantitative determination of nifuroxazid in the range of concentrations from 80% to 120% is linear[19, 47].

The fulfillment of the criteria of correctness and precision for the determination of glycine in the preparation is given in the table. 3.5 [19, 47].

Table 3.5

The results of assessing the correctness and precision of the methodology

Parameter	Value	Criterion, %		Performance of the criterion
		Requirements for statistical insignificance	Requirements for practical insignificance	
$\lvert\bar{Z} - 100\rvert$	0.07	≤ 0.10	≤ 0.512	It is performed according to two criteria
ΔZ	0.31	≤ 1.6		Executed

The method of quantitative determination of glycine in the preparation satisfies the acceptance criteria of validation indicators "correctness" and "precision" [19, 47].

The fulfillment of the criterion of intralaboratory precision for determining glycine in the preparation by the developed method is shown in the table. 3.6 [19, 47].

Table 3.6

Results of intralaboratory precision assessment

Parameter	Criterion requirements, %	Obtained value, %	Performance of the criterion
Δ intra	≤ 1.6	0.99	Executed

The method of quantitative determination of glycine in the preparation meets the acceptance criteria of the "intra-laboratory precision" test [19, 47].

When studying robustness, the stability of solutions during analysis was checked. The stability of nifuroxazid solutions was studied immediately after preparation, after 15, 30, 45 minutes and after 1 hour. The differences between the obtained values of the nifuroxazid content should not exceed the criterion of

insignificance against the maximum permissible uncertainty of the analysis results (As, insig), i.e. 0.51%. The criterion is fulfilled after 15 minutes, 30 minutes, 45 minutes and 1 hour. According to the above data, for quantitative determination it is advisable to use solutions within 1 hour after preparation [19, 47].

Therefore, all validation parameters meet the necessary acceptance criteria. The results prove that the technique can be correctly reproduced and is suitable for further use.

3.3 Assessment of environmental friendliness of analytical methods

Environmental assessment of analytical methods is an important step in the development and implementation of new methods of analysis. This process helps identify possible negative impacts on the environment and human health. In general, environmental assessment helps ensure the safety and sustainability of the use of analytical methods [13, 16, 18, 20, 21, 32, 39, 44, 46].

To determine the environmental friendliness of the proposed method, we used the analytical calculator GREEnness, whose evaluation criteria are based on the twelve principles of "green chemistry" and transformed into a unified scale from 0 to 1 [35, 42].

For the proposed method of quantitative determination of nifuroxazide in capsules, environmental friendliness was calculated, the results of the study are shown in fig. 3.4.

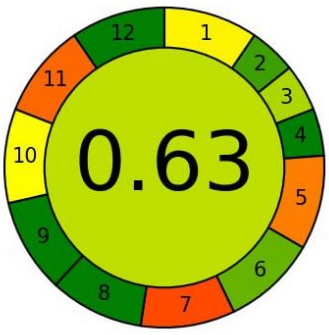


Fig. 3.4 Diagram of assessment of environmental friendliness of the method of quantitative determination of nifuroxazide by the spectrophotometry method

The most "non-ecological" stages were those that evaluated the impact of solvents (stages 10, 11), waste generation (7) and automation of the research process (1, 5). Ethanol (96%) is used as a solvent for the preparation of analyzed solutions, it has the highest degree of environmental friendliness (1.0). However, DMF was used to dissolve the sample, which has a rather strong irritating effect on mucous membranes and skin. Penetrating into the body, it has a resorptive effect: it damages the liver and kidneys, slightly depresses the central nervous system. To improve the technique, it would be advisable to choose a solvent that would allow the nifuroxazide substance to dissolve and would have less impact on the environment and the analyst [1, 12, 21, 38].

For comparison, the titrimetric technique proposed by pharmacopoeias for the quantitative determination of the substance was used. The method consists in dissolving 0.2 g (exact dosage of the dosage form) in 30 ml of DMF and 20 ml of purified water. Titration is carried out with a 0.1 M sodium hydroxide solution with potentiometric determination of the equivalence point [21, 38].

The amount of reagents that should be used for the titration of the dosage form was calculated theoretically, based on the weight of the MP and the theoretical volume of the titrant. A control experiment was also taken into account. The results are presented in fig. 3.5.

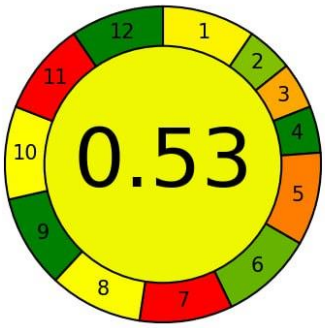


Fig. 3.5 Diagram of assessment of environmental friendliness of the method of quantitative determination of nifuroxazide by the method of titrimetry

As we can see from the results of the study, the most "critical" were the stages assessing the effect of solvents (stages 10, 11), waste generation (7) and automation of the research process (1, 3, 5, 8).

Therefore, the proposed method of quantitative determination of nifuroxazide in capsules is characterized by greater "greenness" and can be used to control the quality of the MP.

Conclusions to section III

1. The average weight of the contents of the capsules and the deviation from the average weight for the medicine "Nifuroxazid, capsules" were calculated, which is: series 01 - 0.3505 g (deviation -4.61%; +3.41%); series 02 – 0.3496 g (deviation -2.41%; +1.13%); series 03 – 0.3507 g (deviation -3.67%; +3.86%).

2. The conditions for the quantitative determination of nifuroxazid in capsule form by spectrophotometry at a wavelength of 368 ± 2 nm after dissolving a portion of the drug in DMF and adjusting the volume of the solution with ethanol (96%) were selected. Quantitative content in the analyzed capsules is: series 01 - 200.6 ± 1.9235 mg; series 02 - 202.3 ± 6.4329 mg; series 03 - 201.9 ± 4.2801 mg.

3. The validation characteristics of the method (specificity, linearity, correctness, precision and robustness) were determined, and its correctness was confirmed.

4. Using the GREEnness analytical calculator, the environmental friendliness of the method was determined, which is 0.63 (according to the system from 0 to 1). The criteria that affect the reduction of "greenness" and directions for improving the methodology are defined.

CHAPTER IV
JUSTIFICATION OF QUALITY CONTROL INDICATORS OF NIFUROXAZIDE CAPSULES AND RESEARCH OF THEIR CHEMICAL STABILITY

The key to the effective use of MP is their proper quality, which is established from the moment of receiving the active pharmaceutical ingredient to the final stage of the use of the medicine by the consumer. Establishing and ensuring high quality standards at all stages of production is a key element of obtaining high-quality and effective medicinal products [45].

Capsules are solid MPs with a hard or soft shell of various shapes and capacities, usually a capsule contains one dose of the active substance. The quality control of hard capsules in accordance with the current edition of the SPhU/Ph.Eur. is carried out according to such indicators as the description; identification; homogeneity of dosage units (homogeneity of mass; homogeneity of content); accompanying impurities; dissolution; disintegration; loss in mass during drying or water; microbiological purity; quantitative determination [1, 12, 21, 38].

4.1 Justification of capsule quality indicators

4.1.1 Description, identification

Description

The description of the MP is a detailed overview of its characteristics, properties and application. According to the requirements of SPhU/Ph.Eur., capsules must have a smooth surface without damage and visible air and mechanical inclusions [1, 21, 45].

The requirements for the "Description" indicator were selected based on the results of the analysis of 3 series of the drug nifuroxazid: "Hard gelatin capsules with

a yellow body and lid. The contents of the capsules are bright yellow powder. The presence of white inclusions and agglomerates of particles is acceptable."

Identification

Identification of medicinal substances in MPs is an important process that allows determining the presence of a specific substance and making sure that the MP contains exactly the active substance that it should contain [1, 21, 45].

As already stated in section I,chemical and physicochemical methods of analysis are used to identify nifuroxazid in dosage forms[1, 12, 21, 38, 45].

For the analyzed dosage form, it is proposed to use a chemical reaction with DMF in an alkaline environment for the qualitative determination of nifuroxazide. This reaction is typical for 5-nitrofuran compounds. In an alkaline environment, DMF can act as a nucleophilic reagent that attacks the carbonyl group of nifuroxazide, which is electrophilic due to the polarization of the bond between carbon and oxygen. This can lead to the formation of various products, depending on the specific reaction conditions [1, 12, 21, 38, 45].

The research was carried out according to the method: 10 ml of dimethylformamide was added to 100 mg of capsule contents in small portions over 10 minutes. The solution was filtered on a paper filter "blue tape". 0.1 ml of sodium hydroxide solution was added to 5 ml of filtrate [1, 12, 21, 38, 45].

In the course of the reaction for 3 series of the analyzed MP, the appearance of a purple-red color was observed, which, when an excess of the reagent was added, turned into dark blue, which confirms the presence of nifuroxazide in the analyzed series of the drug.

Another method that was used to identify the active substance is the spectrophotometry method. Research simultaneously with quantitative determination of the substance. The ultraviolet absorption spectrum of the tested solution in the range from 320 nm to 450 nm should have a maximum absorption at a wavelength of 368 ± 2 nm [1, 12, 21, 24, 27, 28, 38, 45].

For all tested solutions of 3 series of the analyzed drug nifuroxazid, the UV absorption spectrum in the region from 320 nm to 450 nm had a maximum absorption at wavelengths of 368 ± 2 nm.

4.1.2 Uniformity of dosage units

Capsules must pass the test for uniformity of dosage units (SPhU/Ph.Eur., 2.9.40) or, in justified and permitted cases, tests for the homogeneity of the content and/or the homogeneity of the mass of the active substance in a unit of the dosed MP. This test does not apply to MPs containing medicinal plant raw materials and herbal medicines [1, 21].

Homogeneity of dosage units

The "Uniformity of dosage units" test is performed to regulate the limits of the content of the active substance in each dosage unit in the series. This content should be within the accepted limits of the nominal content [1, 21].

The analyzed batches of the MP "Nifuroxazid" pass the test if the acceptance number AV for the first 10 units is less than or equal to L1=15, or the final acceptance number calculated from 30 units is less than or equal to L1=15 and no individual content in the dosage unit is less than 0.75M and not more than 1.25M [1, 21].

According to the results of the study, all analyzed series meet the requirements, the acceptance number is less than 15.

Homogeneity of content

Capsules with an active substance content of less than 2 mg or less than 2% by weight of the content must pass the test for the uniformity of the active substance content in a unit of the dosage medicine (test B), unless there are other indications or justifications and permits. If the MP contains more than one active substance, the

requirements apply only to those substances whose content meets the above conditions [1, 21].

Since the content of nifuroxazide in the analyzed MP is 200 mg, which significantly exceeds the specified requirements, the "Content homogeneity" test is not conducted [1, 21].

Homogeneity of mass

Capsules must pass tests for uniformity of mass for a unit of dosed medicine. The tests are carried out in accordance with the requirements of the SFU/EF, 2.9.5. The permissible deviation should not exceed 10% with an average weight of less than 300 mg [1, 21].

That is, the average weight of the contents of nifuroxazid capsules should be from 180 mg to 220 mg (200 mg ± 10.0%) [1, 21].

As we can see from the results given in section III, the requirements for this test are fulfilled for all analyzed batches of the drug.

4.1.3 Disintegration

This indicator is mandatory for hard capsules. The analysis was carried out according to the methodology given in section II [1, 21].

When conducting experimental studies of 3 series of the drug "Nifuroxazid, capsules", the requirements of the "Disintegration" test are fulfilled.

4.1.4 Accompanying impurities

Domishka A

As already mentioned in section I, impurity A is a starting substance in the synthesis of nifuroxazid and is determined by a separate method from other

accompanying impurities. For its qualitative determination, a reaction to secondary amines with a phosphoromolybdenum-tungsten reagent is used, and the quantitative content is regulated at the level of no more than 0.05% [1, 21].

Determination is carried out by the method of absorption spectrophotometry in the ultraviolet and visible regions (SPhU/Ph.Eur., 2.2.25) [1, 21].

All analyzed series of capsules meet the requirements of this test.

Accompanying impurities

The determination is carried out by the HPLC method in accordance with the requirements of the SPhU/Ph.Eur., 2.2.29 [1, 21].

Determination of impurities in the drug Nifuroxazide is carried out according to the method of determination of accompanying impurities in the substance Nifuroxazide, which is given in the EF monograph on Nifuroxazide. The main impurity of API degradation of the drug is impurity E. The content of impurity E at the time of release of the finished MP is regulated at the level of content in the substance (0.3%), during the storage period - no more than 2.0% [1, 12, 21, 38, 40].

Other impurities (B, C, D) are specified according to the relative retention times specified in the EF monograph on the API nifuroxazid and are regulated at the level of 0.3%. But only one of them can be present in an amount greater than 0.1%. Impurities (B, C, D) are production impurities, they do not change during the storage of pharmaceuticals. The amount of any other unspecified admixture is regulated: no more than 0.1%. The sum of impurities, except for impurity E, is no more than 0.5% [1, 12, 21, 38, 40].

4.1.5 Quantification

Quantification of a MP is the process of determining the concentration or amount of an active substance (API) in a specific MP. This is an important aspect of quality control in pharmaceutical and industry [1, 21].

The study of the quantitative content of nifuroxazid in the analyzed capsules was carried out according to the proposed methodology, given in section III.

The content of nifuroxazid ($C_{12}H_9N_3O_5$) in 1 capsule, based on the average weight of the contents of the capsule, should be from 190 mg to 210 mg.

As we can see from the research results (Chapter III), all analyzed series of nifuroxazid meet the requirements.

4.1.7 Packaging, labeling, storage

Capsules must be produced in tightly closed packaging that protects against moisture. The surface of the capsule can be marked. The MP should be stored in the original packaging at a temperature not higher than 25 °C [3-7].

4.2 Study of the chemical stability of the medicinal product

In the modern world of pharmaceutical science and practice, the issue of ensuring the stability of medicines is becoming particularly relevant. The stability of drugs is a key factor affecting their safety, efficacy and quality. Studying the stability of medicines allows determining the optimal conditions of storage, transportation and use, as well as establishing the shelf life of products [45].

As part of the qualification work, the stability of the analyzed MP was investigated for 6 months.

Indicators subject to control during extract stability tests included: description; identification; average weight of capsule contents; homogeneity of mass; disintegration; impurity A (4-hydroxybenzhydrazide); quantitative determination [45].

Indicators subject to control when conducting extract stability tests according to the abbreviated program B: description; average weight of capsule contents; homogeneity of mass; disintegration; impurity A (4-hydroxybenzhydrazide); quantitative determination [45].

The stability testing program includes drug control indicators that may change during storage and may affect the quality, safety and efficacy of the drug, namely: "Description", "Average mass of capsule contents", "Mass uniformity", "Disintegration", " Accompanying impurities", "Quantitative determination" [45].

The results of the stability study are presented in the table. 4.1.

According to the results of the study, all analyzed series of the drug "Nifuroxazid, capsules" are stable for 6 months.

Table

The results of the study of the chemical stability of the drug "Nifuroxazid, capsules" (series 01-03)

Series and date of study	Description	Identification		Average weight of capsule contents	Homogeneity masses	Disintegration	Impurity A (4-hydroxybenzhydrazide)	Quantitative determination
		2.1.	2.2.					
	Hard gelatin capsules with yellow body and cap. The contents of the capsules are bright yellow powder. The presence of white inclusions and agglomerates of particles is allowed.	Reaction with dimethylformamide in an alkaline environment; a purple-red color appears, which changes to dark blue when an excess of the reagent is added.	The ultraviolet absorption spectrum of the tested solution in the region from 320 nm to 450 nm should have an absorption maximum at a wavelength of 368 ± 2 nm.	From 323.75 mg to 376.25 mg	The acceptance number is less than or equal to 15.0	No more than 30 minutes (with discs)	Not more than 0.2%	The content of nifuroxazide in 1 capsule should be from 190 mg to 210 mg (from 95% to 105% of the amount indicated in the "Composition" section), calculated on the average weight of the contents of the capsule
01 series - 0 months	Corresponds	Corresponds	Corresponds	350.5	Corresponds	Corresponds	Corresponds	200.6 ± 1.9235
Series 01 – 3 months	Corresponds	—	—	349.1	Corresponds	Corresponds	Corresponds	196.9 ± 3.1218
Series 01 – 6 months	Corresponds	Corresponds	Corresponds	351.8	Corresponds	Corresponds	Corresponds	199.7 ± 2.7182
Series 02 - 0 months	Corresponds	Corresponds	Corresponds	349.6	Corresponds	Corresponds	Corresponds	202.3 ± 6.4329
Series 02 – 3 months	Corresponds	—	—	339.8	Corresponds	Corresponds	Corresponds	203.0 ± 3.1298
Series 02 – 6 months	Corresponds	Corresponds	Corresponds	345.5	Corresponds	Corresponds	Corresponds	199.2 ± 3.2627
Series 03 – 0 months	Corresponds	Corresponds	Corresponds	350.7	Corresponds	Corresponds	Corresponds	201.9 ± 4.2801
Series 03 – 3 months	Corresponds	—	—	352.4	Corresponds	Corresponds	Corresponds	197.6 ± 3.8272
Series 03 – 6 months	Corresponds	Corresponds	Corresponds	355.0	Corresponds	Corresponds	Corresponds	198.9 ± 2.1617

Conclusions to section IV

1. Quality control indicators for the MP "Nifuroxazid, capsules" are proposed and substantiated according to such indicators as description; identification; homogeneity of dosage units and homogeneity of mass; accompanying impurities; dissolution; disintegration; quantitative definition.

2. The chemical stability of the drug "Nifuroxazid, capsules" has been confirmed for 6 months.

CONCLUSIONS

The qualification work is devoted to the solution of issues related to the development and substantiation of quality control methods of a medicinal product in the form of capsules for the treatment of intestinal infections, the active substance of which is the active pharmaceutical ingredient nifuroxazide:

3. An analysis of literary sources regarding the causes of occurrence was carried outacute intestinal infections and directions of modern pharmacotherapy; physicochemical properties, extraction and existing methods of quality control of the active pharmaceutical ingredient nifuroxazid for the treatment of intestinal infections.

4. The modern pharmaceutical market of medicinal products of Ukraine containing the substance nifuroxazide was studied.It was established that according to the ATS classification they belong to group A07A Antimicrobial agents used in case of intestinal infections. According to the type of dosage form, most of the drugs are presented in the form of solid capsules and suspensions, they are monopreparations. The largest amount is produced by enterprises in Ukraine, among other importers are the Republic of North Macedonia, Hungary, Bosnia and Herzegovina.

5. The object of the research was chosen - hard capsules of nifuroxazid (series 01-03), which are indicated for use in acute and chronic diarrhea of infectious origin.

6. The average weight of the contents of the capsules and the deviation from the average weight for the medicinal product "Nifuroxazid, capsules" were calculated, which is: series 01 - 0.3505 g (deviation -4.61%; +3.41%); series 02 – 0.3496 g (deviation -2.41%; +1.13%); series 03 – 0.3507 g (deviation -3.67%; +3.86%).

7. The conditions for the quantitative determination of nifuroxazid in capsule form by spectrophotometry at a wavelength of 368 ± 2 nm after dissolving a portion of the drug in dimethylformamide and adjusting the volume of the solution with ethanol (96%) were selected. Quantitative content in the analyzed capsules is: series 01 - 200.6 ± 1.9235 mg; series 02 - 202.3 ± 6.4329 mg; series 03 - 201.9 ± 4.2801 mg. The validation characteristics of the method (specificity, linearity, correctness, precision and robustness) were determined, and its correctness was confirmed.

8. Using the GREEnness analytical calculator, the environmental friendliness of the method was determined, which is 0.63 (according to the system from 0 to 1). The criteria that affect the reduction of "greenness" and directions for improving the methodology are defined.

9. Quality control indicators for the medicinal product "Nifuroxazid, capsules" are proposed and substantiated according to such indicators as description; identification; homogeneity of dosage units and homogeneity of mass; accompanying impurities; dissolution; disintegration; quantitative definition.

10. The chemical stability of the drug "Nifuroxazid, capsules" has been confirmed for 6 months.

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APPLICATIONS

APPENDIX A

Medicinal products containing AFI nifuroxazid and registered on the pharmaceutical market of Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
1.	Nifuroxazide Alkaloid	Hard capsules, 100 mg, blister, No. 30	Active substance: nifuroxazid; 1 capsule contains nifuroxazide 100 mg; auxiliary substances: microcrystalline cellulose, corn starch, povidone, colloidal anhydrous silicon dioxide, sodium lauryl sulfate, magnesium stearate; capsule composition: titanium dioxide (E 171), quinoline yellow (E 104), yellow sunset FCF (E 110), gelatin	ALKALOID AD Skopje, Republic of North Macedonia
2.	Nifuroxazide Alkaloid	Hard capsules, 200 mg, blister, number 20	Active substance: nifuroxazid; 1 capsule contains nifuroxazide 200 mg; auxiliary substances: microcrystalline cellulose, corn starch, povidone, colloidal anhydrous silicon dioxide, sodium lauryl sulfate, magnesium stearate; capsule composition: titanium dioxide (E 171), quinoline yellow (E 104), FCF sunset yellow (E 110), gelatin.	ALKALOID AD Skopje, Republic of North Macedonia
3.	Nifuroxazide Alkaloid	Oral suspension, 200 mg/5 ml, bottle, 90 ml, with measuring cup, with measuring cup. with a glass, No. 1	Active substance: nifuroxazid; 5 ml of oral suspension contain nifuroxazide 200 mg; excipients: non-crystallizing sorbitol solution, glycerin, carbomer 940, polysorbate 80, disodium edetate, sodium benzoate, sodium citrate dihydrate, sodium saccharin, banana flavoring, flavoring agent, simethicone emulsion, purified water	ALKALOID AD Skopje, Republic of North Macedonia
4.	ENTEROFURIL®	hard capsules of 100 mg each, 10 capsules in a	1 hard capsule contains nifuroxazide 100 mg	Bosnalek d.d., Bosnia and Herzegovina

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
		blister; 3 blisters in a cardboard box		
5.	ENTEROFURIL®	hard capsules of 200 mg, 8 capsules in a blister, 1 or 2 blisters in a cardboard box	1 hard capsule contains nifuroxazide 200 mg	Bosnalek d.d., Bosnia and Herzegovina
6.	ENTEROFURIL®	oral suspension, 200 mg/5 ml of 90 ml in a bottle; 1 bottle with a plastic dosing spoon in a cardboard box	5 ml of suspension contain nifuroxazide 200 mg	Bosnalek d.d., Bosnia and Herzegovina
7.	STOPDIAR	hard capsules of 200 mg each, 12 capsules in a blister; 1 blister in a cardboard package	1 hard capsule contains nifuroxazide 200 mg	JSC "Gedeon Richter", Hungary
8.	Nifuroxazide Richter	Oral suspension, 220 mg/5 ml, bottle, 90 ml, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain 220 mg of nifuroxazide (220 mg/5 ml); auxiliary substances: carbomer, sucrose, sodium hydroxide (E 524), citric acid monohydrate (E 330), simethicone, methylparaben (E 218), banana essence, purified water.	JSC "Gedeon Richter", Hungary
9.	Nifuroxazide Richter	Film-coated tablets, 100 mg, No. 24	Active substance: nifuroxazid; 1 tablet contains nifuroxazide 100 mg; auxiliary substances: colloidal anhydrous silicon dioxide, potato starch, gelatin, talc, magnesium stearate; shell: hypromellose (E 464), polyethylene glycol, quinoline yellow (E 104), titanium dioxide (E 171), talc.	JSC "Gedeon Richter", Hungary
10.	Nifuroxazide	Oral suspension, 220 mg/5 ml, bottle, 100 ml, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain nifuroxazide 220 mg; excipients: carbomer; saccharose; sodium hydroxide (E 524); citric acid, monohydrate (E	PJSC "Halychpharm", Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
			330); simethicone; methyl parahydroxybenzoate (E 218); banana flavoring; the water is purified.	
11.	Nifuroxazide	Film-coated tablets, 200 mg, blister pack, No. 10	Active substance: nifuroxazid; 1 tablet contains 200 mg of nifuroxazid in 100% substance; excipients: microcrystalline cellulose; povidone; lactose, monohydrate; calcium stearate; coating mixture "Opadry II Yellow" 33G22623, containing: hypromellose; lactose, monohydrate; titanium dioxide (E 171); polyethylene glycol 3000 (macrogol); triacetin; quinoline yellow (E 104); FCF yellow west (E 110); iron oxide yellow (E 172); indigo carmine (E 132).	PJSC "Kyivmedpreparat", Ukraine
12.	Nifuroxazide	Film-coated tablets, 200 mg, blister pack, No. 20	Active substance: nifuroxazid; 1 tablet contains 200 mg of nifuroxazid in 100% substance; excipients: microcrystalline cellulose; povidone; lactose, monohydrate; calcium stearate; coating mixture "Opadry II Yellow" 33G22623, containing: hypromellose; lactose, monohydrate; titanium dioxide (E 171); polyethylene glycol 3000 (macrogol); triacetin; quinoline yellow (E 104); FCF yellow west (E 110); iron oxide yellow (E 172); indigo carmine (E 132).	PJSC "Kyivmedpreparat", Ukraine
13.	Nifuroxazide	Oral suspension, 220 mg/5 ml, polymer bottle, 100 ml, with a measuring spoon, in a pack, with a measuring cup. spoon, in a pack, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain 220 mg of nifuroxazide (220 mg/5 ml); auxiliary substances: carbomer, sucrose, sodium hydroxide, citric acid monohydrate, simethicone emulsion, methyl parahydroxybenzoate (E 218), food flavoring "Banana", purified water.	PJSC "Scientific and Production Center "Borshchagiv Chemical and Pharmaceutical Plant", Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
14.	Nifuroxazid-Sperko	Capsules, 200 mg, container, in a pack, in a pack, No. 12	Active substance: nifuroxazid; 1 capsule contains nifuroxazide 200 mg; excipients: sucrose, anhydrous lactose, corn starch, talc, magnesium stearate. The capsule shell includes: gelatin, titanium dioxide (E 171), quinoline yellow (E 104), FCF yellow (E 110).	Joint Ukrainian-Spanish enterprise "Sperko Ukraine", Ukraine
15.	Nifuroxazid-Sperko	Oral suspension, 200 mg/5 ml, container, 100 ml, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain nifuroxazide 200 mg; auxiliary substances: methylparaben (methylparahydroxybenzoate) (E 218), sugar, carbomer, citric acid, monohydrate, simethicone emulsion, food flavoring "banana" (contains propylene glycol), sodium hydroxide, purified water.	Joint Ukrainian-Spanish enterprise "Sperko Ukraine", Ukraine
16.	NIFUROXAZIDE	200 mg capsules; 10 capsules in a blister; 1 or 2 blisters in a pack	1 capsule contains nifuroxazide 200 mg	DKP "Pharmaceutical Factory" LLC, Ukraine
17.	NIFUROXAZIDE	oral suspension, 220 mg/5 ml in 90 ml bottles or jars; 1 bottle or jar with a measuring cup in a pack	5 ml of suspension contain nifuroxazide 220 mg	DKP "Pharmaceutical Factory" LLC, Ukraine
18.	NIFUROXAZIDE	powder (substance) in double polyethylene bags for the production of non-sterile dosage forms	nifuroxazid not less than 98.5% and not more than 101.5% in terms of dry matter	"Unipharma" LLC, Ukraine
19.	Nifuroxazide	Oral suspension, 200 mg/5 ml, bottle, 90 ml, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain nifuroxazide 200 mg; auxiliary substances: sucrose, carbomer, citric acid monohydrate, sodium hydroxide,	Ternofarm LLC, Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
			methylparaben (E 218), flavoring "Banana" (contains propylene glycol), ethanol 96%, purified water.	
20.	Nifuroxazide	Oral suspension, 200 mg/5 ml, bottle, 90 ml, TM Ilan Pharm, TM Ilan Pharm, No. 1	Active substance: nifuroxazid; 5 ml of suspension contain nifuroxazide 200 mg; auxiliary substances: sucrose, carbomer, citric acid monohydrate, sodium hydroxide, methylparaben (E 218), flavoring "Banana" (contains propylene glycol), ethanol 96%, purified water.	Ternofarm LLC, Ukraine
21.	Nifuroxazide	Film-coated tablets, 0.1 g, blister, No. 30	Active substance: nifuroxazid; 1 tablet contains nifuroxazide 0.1 g; auxiliary substances: potato starch, povidone, colloidal anhydrous silicon dioxide, talc, magnesium stearate; shell: hypromellose (hydroxypropylmethylcellulose), titanium dioxide (E 171), polyethylene glycol (macrogol), quinoline yellow (E 104).	Ternofarm LLC, Ukraine
22.	Nifuroxazide	Film-coated tablets, 0.1 g, blister, TM Ilan Pharm, TM Ilan Pharm, No. 30	Active substance: nifuroxazid; 1 tablet contains nifuroxazide 0.1 g; auxiliary substances: potato starch, povidone, colloidal anhydrous silicon dioxide, talc, magnesium stearate; shell: hypromellose (hydroxypropylmethylcellulose), titanium dioxide (E 171), polyethylene glycol (macrogol), quinoline yellow (E 104).	Ternofarm LLC, Ukraine
23.	NIFUROZID-HEALTH	100 mg capsules, 10 capsules in a blister; 1 or 2 blisters in a cardboard box	1 capsule contains nifuroxazide 100 mg	ZDOROVYA CORPORATION LIMITED LIABILITY COMPANY, Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
24.	NIFUROZID-HEALTH	200 mg capsules, 10 capsules in a blister; 1 or 2 blisters in a cardboard box	1 capsule contains nifuroxazide 200 mg	ZDOROVYA CORPORATION LIMITED LIABILITY COMPANY, Ukraine
25.	NIFUROZID-HEALTH	oral suspension, 200 mg/5 ml, 50 ml in a polymer bottle, 1 bottle with a measuring spoon in a cardboard box; 100 ml each in a polymer or glass bottle; 1 bottle with a measuring spoon in a cardboard box	5 ml of the drug contain 200 mg of nifuroxazide	ZDOROVYA CORPORATION LIMITED LIABILITY COMPANY, Ukraine
26.	MIROFURYL	capsules of 200 mg, 5 capsules in a blister; 2 or 3 blisters in a cardboard box	1 capsule contains nifuroxazide 200 mg	"ROCKET-PHARM" Limited Liability Company, Ukraine
27.	MIROFURYL	200 mg capsules, 5 capsules in a blister; 2 or 3 blisters in a cardboard box	1 capsule contains nifuroxazide 200 mg	"ROCKET-PHARM" Limited Liability Company, Ukraine
28.	MIROFURYL	oral suspension, 200 mg/5 ml per 90 ml of oral	5 ml of suspension contain nifuroxazide 200 mg	"ROCKET-PHARM"

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
		suspension in a bottle; 1 bottle with a measuring cup in a cardboard box		Limited Liability Company, Ukraine
29.	MIROFURYL	oral suspension, 200 mg/5 ml, 90 ml of oral suspension in a bottle; 1 bottle with a measuring cup in a cardboard box	5 ml of suspension contain nifuroxazide 200 mg	"ROCKET-PHARM" Limited Liability Company, Ukraine
30.	NIFUROZID-HEALTH	100 mg capsules, 10 capsules in a blister; 1 or 2 blisters in a cardboard box	1 capsule contains nifuroxazide 100 mg	Limited liability company "Pharmaceutical company "Zdorovya", Ukraine
31.	NIFUROZID-HEALTH	200 mg capsules, 10 capsules in a blister; 1 or 2 blisters in a cardboard box	1 capsule contains nifuroxazide 200 mg	Limited liability company "Pharmaceutical company "Zdorovya", Ukraine
32.	NIFUROZID-HEALTH	oral suspension, 200 mg/5 ml, 50 ml in a polymer bottle, 1 bottle with a measuring spoon in a cardboard box; 100 ml each in a polymer or glass bottle; 1 bottle with a	5 ml of the drug contain 200 mg of nifuroxazide	Limited liability company "Pharmaceutical company "Zdorovya", Ukraine

No. z/p	Title/form of release	Pharmaceutical form, packaging	Composition of active substances	Producer
		measuring spoon in a cardboard box		