MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

***NICOLAE TESTEMIȚANU* STATE UNIVERSITY OF MEDICINE AND PHARMACY**

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DRUG SUBSTANCES FROM THE NITROFURAN GROUP

Methodical recommendation

SRL "Foxtrot"
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CONTENT

PREFACE

The use of 5-nitrofuran derivatives in the field of medicine dates back to 40s of the XX century and presents a series of advantages: it possesses activity against germs with resistance to other antimicrobials; increase the body's non-specific resistance; reduce the resistance of microorganisms to phagocytosis; inhibits the production of toxins by microorganisms; maintains its effectiveness in the presence of biological fluids (blood, serum, urine, etc.) and tissue destruction products; resistance develops slowly; they are comparatively cheap; rarely causes dysbacteriosis and candidiasis.

The methodological recommendation *Drug substances from the nitrofuran group* is designed as teaching material for students of the study program 0916. Pharmacy, residents of pharmaceutical specializations, master's students, PhD students, pharmacists, but it can also be used as a support for specialists in related fields or anyone interested in this theme.

ABBREVIATIONS

DAN – Normative Analytical Documents

DMFA – dimethylformamide

ed. – edition

etc. – etcetera

sec. – secol

UV-Vis – ultraviolet-visibile

INTRODUCTION

Currently, more than half of medicinal substances used in medicine belong to heterocyclic compounds, which include furan derivatives:

The goal of the theme. To be able to perform the quality analysis of medicinal substances, furan derivatives in correlation with the chemical structure, which determines their production, analysis methods, storage and use in medicine.

Recommended minimum duration

1 laboratory work (4 hours) is given for studying the theme.

Stages of the studying theme:

- The control and correction of the acquisition of the material according to the subjects for independent training.
- Students' practical work.
- Recapitulation of the topic material.

Theme objectives:

1. Based on the bibliographic data and the analytical documentation of the norm to analyze the medicinal substances from the studied group through the comparative assessment of the physical, physico-chemical and chemical properties.
2. To learn the appreciation of the quality of medicinal substances, derivatives of 5-nitrofuran in accordance

with the provisions of DAN.

3. To accumulate skills in performing general and particular reactions to identify the medicinal substances studied.
4. Based on the physical and chemical properties of medicinal preparations from the nitrofuran group, be able to determine impurities and argue their presence.
5. To be able to perform the dosing of medicinal substances from the nitrofuran group in accordance with DAN requirements.
6. To be able to establish the conditions of preservation of medicinal preparations depending on their chemical structure and properties.

SUBJECTS FOR INDIVIDUAL STUDENT PREPARATION BASED ON THEORETICAL MATERIAL

1. The general characteristic of heterocyclic compounds. Classification principles.
2. Historical and biochemical premises for the creation of medicinal substances, derivatives of heterocyclic compounds.
3. The methods of obtaining medicinal substances derived from 5-nitrofuran.
4. The physical and chemical properties (acid-base, oxidation-reduction, etc.) of 5-nitrofuran derivatives.
5. Methods of analysis of medicinal substances: nitrofural (furacilin), nitrofurantoin (furadoinin) and furazolidone.
6. The mechanism of action of 5-nitrofuran derivatives.
7. Storage and use conditions of medicinal substances, derivatives of 5-nitrofuran.

INFORMATIONAL MATERIAL

History of obtaining nitrofurans

5-nitrofurans are derivatives of furan, where the hydrogen atom is usually substituted in position 5 by the nitro group. In the 40s of the century XX it was established that the compounds containing the nitro group exhibited antimicrobial action. This was demonstrated for derivatives of nitrofurans, nitroimidazole and chloramphenicol.

The first representatives of the derivatives of the furan series were obtained in the first years of the development of organic chemistry: furancarbonic acid described by Scheele in 1780 and furfurol developed by Debereiner in 1832, but the effective medicinal substances of this series were discovered much later. The French chemist Marquis for the first time in 1901-1905 tried to introduce the nitro group into furan and its acidophobic derivatives. Although 5-nitrofuran derivatives were studied as antimicrobial remedies since the 18th century, it was only in 1944 that it was found that only the compounds containing the nitro group in position 5 of the furan ring show therapeutic activity.

For the first time in medical practice, nitrofuran drugs were used in military units in Normandy (1944). Medicinal substances from this group are still in demand due to the mechanism of action that differs from that of antibiotics and sulfanilamides. In connection with this, preparations from the 5-nitrofuran range have proven to be effective in treating

infectious processes, caused by strains of microorganisms resistant to the action of antibiotics and sulfanilamides. At the same time, it was demonstrated that the resistance of microorganisms to 5-nitrofuran compounds develops slowly.

Synthesis of nitrofuran derivatives

The synthesis of medicinal substances from the nitrofuran group is made from furfural, which is usually obtained from economically accessible raw materials (corn cobs, sunflower seed husks and other agricultural residues). In all cases of synthesis of compounds of the 5-nitrofuran series, furfural is nitrated with nitric acid in the presence of acetic anhydride, which protects the aldehyde group from oxidation. At the same time, furan is unstable to the action of acids, it goes rancid, which is why nitration and sulfonation of furan under normal conditions is impossible.

The synthesis of 5-nitrofuran derivatives can be schematically represented as follows: furfural is nitrated in the medium of acetic anhydride and finally 5-nitro-2-furfuraldiacetate is obtained, and the hydrolysis of the latter leads to the formation of 5-nitro-2-furfurol, which it condenses with bases (carbazides, hydrazine derivatives, etc.) to obtain the corresponding derivatives (figure 1).

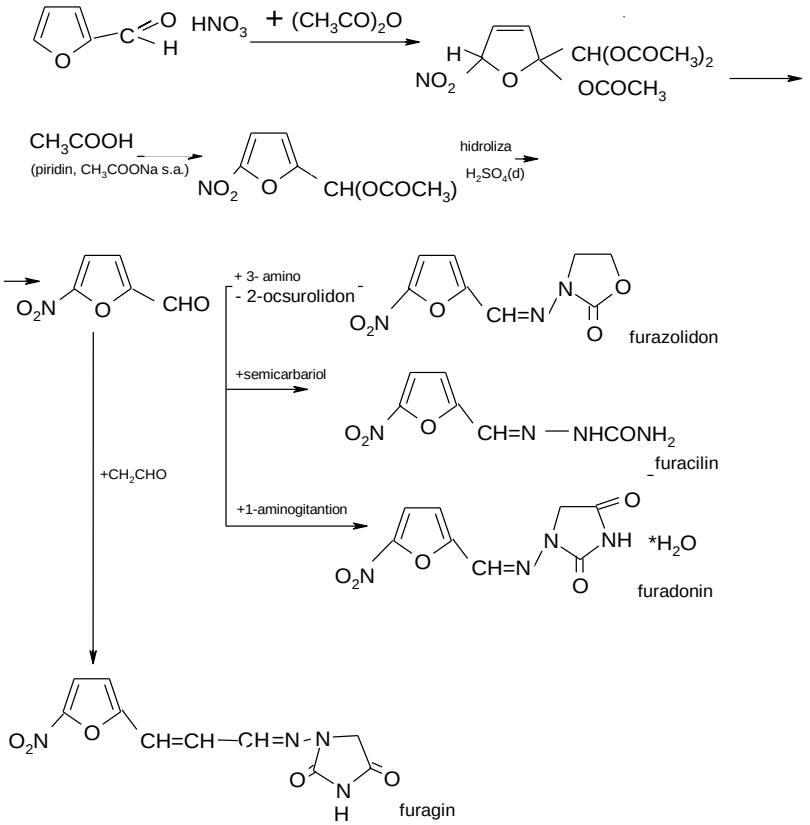


Figure l. General scheme for obtaining derivatives 5-nitrofuran

Physical-chemical properties

Most of the chemotherapeutic preparations of the 5-nitrofuran chain according to its structure are considered to be 5-nitro-2-furfurylidehydrazone substituents (figure 2):

- Furacilin, *N-(5-nitro-2-furfurylidene) semicarbazone*
- Furadonin, *N-(5-nitro-2-furfurylidene)-l-aminohydanione*

- Furagin, *N-(b-(5-nitro-2 furyl)acrylidene)-l -aminohydanione*
- Furazolidone, *N-(5-nitro-2 furfulidene)-3-amino-2-oxazolidone*

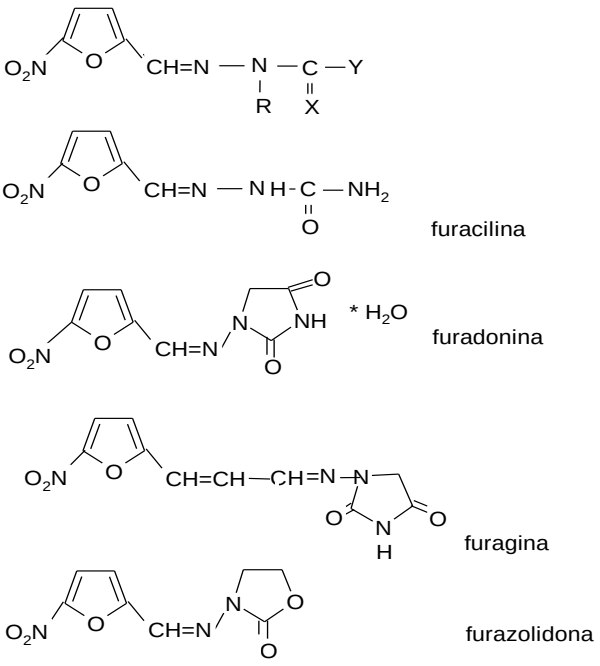
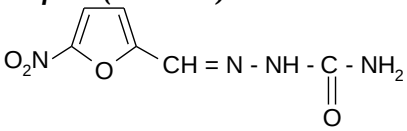
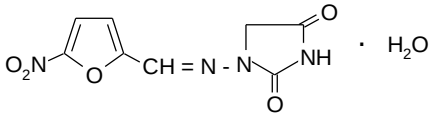


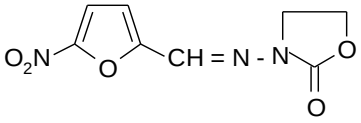
Figure 2. General formula and some derivatives of 5-nitro-2-furfurylidehydrazone

The 5-nitrofuran derivatives are crystalline compounds, colored depending on the length of the side chain from pale yellow to dark red or brown. All 5-nitrofurans, as a rule, are slightly soluble in water, well soluble in polyethylene glycol

and propylene glycol, very well dissolve in dimethylsulfoxide and dimethylformamide. In methyl alcohol and ethyl alcohol, 5-nitrofuran compounds dissolve much better than in water, and in ethyl ether and benzyl ether it is less soluble (table 1).

Table 1. ***Drug substances, derivatives of 5-nitrofuran***

The Romanian, Latin and chemical name. Structure formula	**Description, solubility**
Nitrofuralum ***Nitrofural (Furacilin)***  5-nitrofurfurol semicarbazone	Microcrystalline powder, yellow or yellow-green, odorless. Very slightly soluble in water, slightly soluble in alcohol 95%, soluble in alkalis. M_r=198,14.
Nitrofurantoinum ***Nitrofurantoin (Furadonin)***  N-(5-nitro-2-furfuralidene)-1 amino hydantoin	Microcrystalline powder, yellow or yellow-orange, odorless. Very slightly soluble in water, slightly soluble in alcohol 95%, slightly soluble in acetone. M_r =238,16.

The Romanian, Latin and chemical name. Structure formula	Description, solubility
Furazolidonum ***Furazolidone***  N-(5-nitro-2-furfuraliden)-3-aminooxazolidonă-2	Microcrystalline powder, yellow or greenish-yellow, odorless. Practically insoluble in water and ether, very slightly soluble in 95% alcohol. M_r =225,16.

Aqueous solutions of 5-nitrofuran derivatives are stable in weakly acidic, neutral and weakly basic environments. In the basic environment at pH 10.0, their decomposition takes place to 5-nitro-2-furfurol, which is unstable in the basic environment at pH 9.0. It is assumed that at the beginning the acid dissociation of the molecule takes place with the formation of the anion of the quinoid structure, then the furanic cycle opens and the compounds formed of the maleic semialdehyde type are prone to condensation, which leads to the formation of colored compounds.

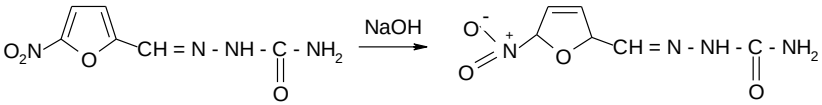
Chemical properties and methods of analysis

5-nitrofuran derivatives are acidic substances: nitrofural (furacilin) and nitrofurantoin (furadonin) are -NH-acids, and furazolidone -CH-acid. The nitro group, being a strong electron acceptor, increases the acidic properties. In nitrofural, the acidic properties are conditioned by the hydrogen atoms in the

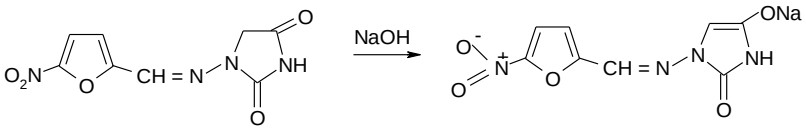
imide group, and in nitrofurantoin - by the keto-enolic and lactim-lactam tautomerism in the hydantoin nucleus.

The identity of medicinal substances derived from 5-nitrofuran is determined by the color reaction with the sodium hydroxide solution, upon the interaction of which, under normal conditions, salts are formed without destroying the furanic cycle.

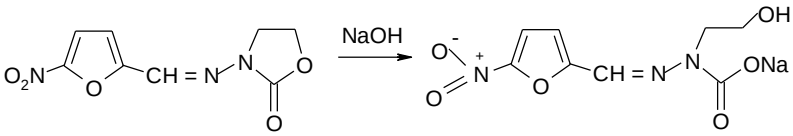
Thus, nitrofural (furacilin) in dilute solutions of bases at room temperature forms a red-orange coloration:



Nitrofurantoin (furadonin) in dilute solutions of bases at room temperature forms as a result of tautomeric transformations of the rest of hydantoin a salt, colored in dark red:



The furazolidone solution under the same conditions, but upon heating, will form a red-brown color due to the opening of the lactonic cycle and the formation of the salt:



Nirofuran derivatives can be distinguished from each other by the different coloring of the interaction products with

alcoholic solutions of alkalis in the medium of basic anhydrous solvents (dimethylformamide) (table 2 and table 3).

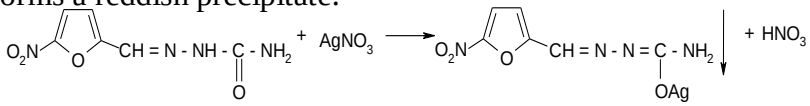
Table 2. ***Results of the reaction with the alcoholic solution of potassium hydroxide in anhydrous medium***

Drug substance	**Interaction results with:**	
	DMFA	**DMFA and alcoholic potassium hydroxide solution**
Nitrofural (Furacilin)	purple color	purple-reddish color on the walls of the test tube
Nitrofurantoin (Furadonin)	yellow color	yellow-brown color
Furazolidone	yellow color	purple color, but on the walls of the test tube-indigo

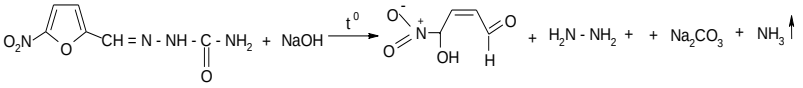
Table 3. ***Results of the interaction of 5-nitrofuran derivatives with aqueous sodium hydroxide solution and alcoholic potassium hydroxide solution in the presence of acetone***

Substanţa medicamtntoasă	**Interaction results with:**	
	Sodium hydroxide	**Alcoholic solution of potassium hydroxide in the presence of acetone**
Nitrofural (Furacilin)	brown color	dark red color
Nitrofurantoin (Furadonin)	red-orange color	yellow-green color that turns brown in the form of a precipitate
Furazolidone	dark red color	red colour, which appears over time and turns brown

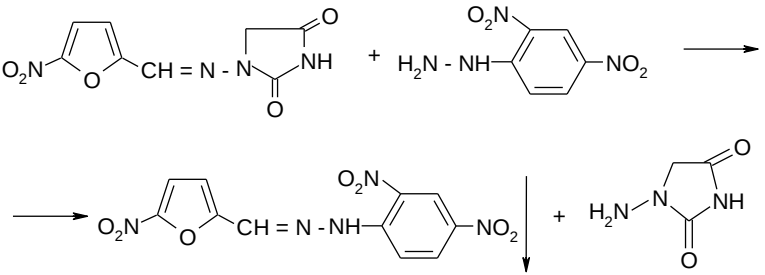
5-nitrofuran derivatives form colored compounds with heavy metal salts: silver nitrate, copper (II) sulfate, cobalt chloride. For example, nitrofural (furacilin) with silver ions forms a reddish precipitate:



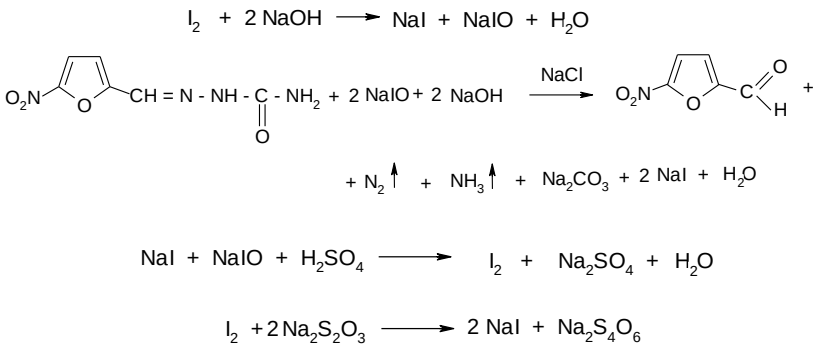
Hydrolytic decomposition. During the action with alkaline solutions upon heating, the opening of the furanic cycle takes place, other transformations being individual, depending on the character of the substituent. For example, when nitrofural (furacilin) is heated with alkaline solutions, hydrazine, sodium carbonate and ammonia are formed, which can be determined by the yellowing of red litmus paper:



Formation of hydrazones. All 5-nitrofuran derivatives upon interaction with phenylhydrazine or 2,4-nitrophenylhydrazine form hydrazones, which can be identified by the melting temperature. Thus, when boiling the solution of the medicinal substance from the group of furans with dimethylformamide, saturated solution of 2,4-dinitrophenylhydrazine and 2 mol/l hydrochloric acid solution, a precipitate with a melting temperature of 273^0C is formed:



The reducing properties of nitrofuran (furacilin) are used for quantitative determination by the iodometric method in a basic environment:



Nitrofurantoin and furazolidone, which have slightly acidic properties, can be dosed by the anhydrous neutralization method in an anhydrous environment (dimethylformamide). Titrate with sodium methoxide solution 0.1 mol/l (indicator – thymol blue).

The quantitative determination of 5-nitrofuran derivatives can also be carried out by the photocolorimeric method, based on the color reactions of medicinal substances with alkaline solutions.

Quantitative structure-activity relationship of 5-nitrofurans

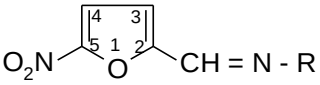
5-nitrofurans are active against microorganisms that may show resistance to other antibacterial preparations. The spectrum of action of nitrofurans includes:

- gram-positive bacteria: *Staphylococcus spp., Streptococcus spp. (S.pneumoniae, S. pyogenes, E. faecalis), Corynebacterium spp., Bacillus anthracis;*
- gram-negative bacteria: *Escherichia coli, Shigella spp.,*

Salmonella spp., Proteus spp., Klebsiella spp., Aerobacter faecalis, Aerobacter aerogenes, Vibrio cholerae, Haemophillus spp.;

- protozoa: *Trichomonas vaginalis, Lamblia intestinalis, Entamaeba hystolytica;*
- fungi: *Candida albicans, Microsporum spp., Trichophyton spp.*

Thus, to exert the therapeutic effect, 5-nitrofuran derivatives must contain the following structural elements:



1. the presence of the aromatic nitro group in position 5 gives an antibacterial effect; it manifests itself in connection with viruses, protozoa, gram-positive, gram-negative bacteria. Thus, according to the mechanism of action, 5-nitrofuran derivatives are similar to antibiotics, but have lower toxicity and are more stable during storage.
2. the transfer of the nitro group to another position leads to a decrease in activity;
3. the introduction of 2 nitro groups also leads to a decrease in activity;
4. an important role for the antibacterial action is played by the azomethine group - CH = N -;
5. the transfer of the radical from position 2 to any other position leads to the loss of activity;
6. lengthening of the side chain leads to an increase in the activity and a decrease in the toxicity of the drug substance.

Mechanism of action and use of derivatives of 5-nitrofuran

Although the mechanism of action of 5-nitrofuran derivatives is not fully elucidated, it has been established that 5-nitrofuran derivatives are reduced in sensitive bacterial cells by specific nitroreductases, which act in the presence of the cofactors NADH and NADPH to generate a hydroxylamine via a nitroso intermediate. Hydroxylamine can be further metabolized to form: a nitrenium ion, an amine form, or unsaturated and then saturated open-chain nitriles (figure 3).

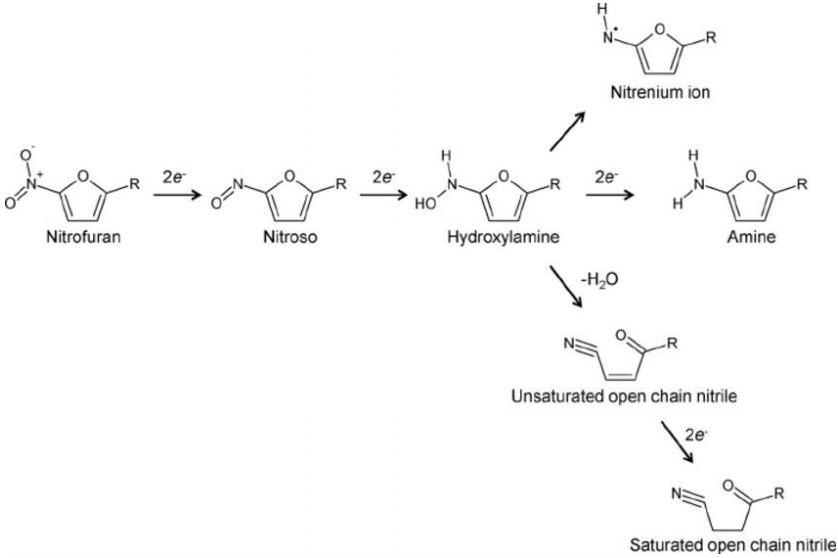


Figure 3. Metabolism of 5-nitrofuran derivatives

Following the reduction, a series of highly reactive intermediates are formed, which attack the bacterial enzymes with the dysregulation of the cytoplasmic membrane function and bactericidal effect. Nitrofurans, as well as their metabolites, can form complexes with nucleic acids, which leads to the inhibition of the synthesis of nucleic acids (mainly DNA), proteins and, respectively, to a bacteriostatic effect.

Nitrofurans, being oxygen acceptors, deregulate tissue respiration processes. It is also believed that they can inhibit a number of enzymes, including acetyl coenzyme A, glutathione reductase, pyruvate oxidase, aldehyde dehydrogenase.

Nitrofural (Furacilin) is an antibacterial substance that acts on various gram-positive and gram-negative bacteria (*staphylococci, streptococci, dysentery bacillus, Escherichia coli, Salmonella paratypha*, causative agent of gas gangrene, etc.).

Nitrofural (Furacilin) is indicated externally for the treatment and prevention of purulent-inflammatory processes and internally for the treatment of bacterial dysentery: purulent wounds, bedsores and ulcers, second and third degree burns, in osteomyelitis after surgery, in anaerobic infections, in chronic otitis, in conjunctivitis and blepharitis.

Nitrofural is used in the form of 0.02% aqueous solution (1:50,000), 0.066% alcoholic solution (1:1500) and 0.2% ointment.

Nitrofurantoin (Furadonin) is indicated in the treatment of uncomplicated acute urinary infections (cystitis,

pyelonephritis) and for the long-term prophylaxis of recurrent urinary infections caused by sensitive germs.

In case of association with gastric antacids, they will be administered 2 hours after nitrofurantoin. Nitrofurantoin does not associate with nalidixic acid and oxolinic acid, because it antagonizes their action.

Caution is recommended in patients with renal insufficiency. During the treatment it is recommended to avoid the consumption of alcoholic beverages. Nitrofurantoin can color the urine yellow-brown.

Furazolidone is an intestinal antiseptic active against numerous strains of pathogenic colibacilli, salmonella, shigella, enterococci, staphylococci, as well as against Trichomonas, Giardia and Entamoeba.

Furazolidone is indicated in food poisoning (salmonellosis), bacillary dysentery, infant infectious enteritis, giardiasis, amoebic dysentery.

Pharmaceutical presentation: Tablets of furazolidone 100mg or 25mg; suspension for pediatric use of furazolidone 0.5g/100g.

PRACTICAL WORK OF STUDENTS

Task 1. ***To assess the quality of medicinal substances according to the indications: "Description" and "Solubility".***

Note. Solvents are chosen according to the provisions of DAN.

Task 2. ***To appreciate the quality of medicinal substances***

1. Nitrofural (Furacilin)

1.1. Identification.

1.1.A. Reaction with sodium hydroxyde: 0.01 g of medicinal substance is dissolved in a mixture of 5 ml of water and 5 ml of 30% sodium hydroxide solution; a red-orange color appears. When the obtained solution is heated, ammonia is released, which is determined by the smell or by the yellowing of wet red litmus paper, introduced into the vapors of the boiling liquid.

1.2. Assay.

1.2.A. The iodometric method: about 0.1 g of drug substance (exact mass) is transferred to a volumetric flask with a volume of 500 ml, 4 g of sodium chloride, 300 ml of purified water are added and it is dissolved by heating on a water bath at 70-800C. The cooled solution is brought up to the level with purified water and mixed (solution A). To 5 ml of 0.01 mol/l iodine solution, taken in the 50 ml flask, add 0.1 ml of 0.1 mol/l sodium hydroxide solution and 5 ml of solution A. After 1-2 minutes, add 2 ml of dilute sulfuric acid solution and the

removed iodine is titrated with 0.01 mol/l sodium thiosulfate solution (starch indicator).

In parallel, the control test is performed.

1 ml of iodine solution 0.01 mol/l corresponds to 0.0004954 g $C_6H_6N_4O_4$, which in the preparation must be no less than 97.5% and no more than 102.0%.

1.2.B. Photocolorimetric method: about 0.02 g of drug substance (exact mass) is dissolved in 70-80 ml of purified water in a volumetric flask with a capacity of 100 ml, when heated on a water bath at 70-800C. After cooling, the volume is brought up to the mark with water. To 0.5 ml of the solution obtained, add 7.5 ml of water, 2 ml of 0.1 mol/l sodium hydroxide solution and mix. After 20 minutes, read the absorbance of the obtained solution with a photocolorimeter at a wavelength of about 450 nm in a vat with a layer thickness of 3 cm. Purified water is used as a reference solution. At the same time, the reaction is carried out with 0.5 ml of standard 0.02% furacilin solution and the absorbance is measured.

The recalculated $C_6H_6N_4O_4$ content in the dry matter must be not less than 98% and not more than 102.0%.

1.2.C. UV-Vis spectrophotometric method: about 0.75 g of drug substance (exact mass) is transferred into a volumetric flask with a volume of 250 ml, dissolved in 30 ml of dimethylformamide. Bring the volume of the solution up to the level with purified water and mix. Take 5 ml of the solution obtained in the graduated flask with a volume of 250 ml, bring the volume of the solution up to the level with purified water

and mix. The absorbance of the obtained solution is read on a spectrophotometer at a wavelength of 375 nm in a vessel with a layer thickness of 1 cm. Purified water is used as a reference solution.

In parallel, the absorbance of the nitrofural standard sample is determined.

The recalculated $C_6H_6N_4O_4$ content in the dry matter must be not less than 98% and not more than 102.0%.

2. Nitrofurantoin (Furadonin)

2.1. Identification.

2.1.A. The UV-Vis spectrum of drug substance solution, prepared for quantitative determination, in the 220 nm and 400 nm regions has two absorption maxima, at 266 nm and 367 nm.

$Raportul = \frac{A_{la367nm}}{A_{la266nm}}$ must be from 1.36 to 1.42.

2.1.B. Reaction with sodium hydroxide: 0.01 g of drug substance is dissolved in a mixture consisting of 5 ml of purified water and 5 ml of 30% sodium hydroxide solution; dark red color appears.

2.1.C. Reaction with dimethylformamide: 0.01 g of drug substance is dissolved in 3 ml of dimethylformamide; a yellow color appears, which after adding two drops of sodium hydroxide solution 1 mol/l in 50% alcohol turns brown-yellow.

2.2. Assay.

2.2.A. Photocolorimetric method: about 0.1 g of medicinal substance (exact mass) is transferred to a volumetric flask with

a volume of 100 ml, 50 ml of purified water and 2.5 ml of sodium hydroxide solution 1 mol/l are added, it is dissolved by mixing, the volume is brought to of the solution up to the level with the purified water and mix well. 0.6 ml of the obtained solution are placed in a volumetric flask with a capacity of 100 ml and brought up to the level with purified water. More than 20 minutes after the addition of the 1 mol/l sodium hydroxide solution, the absorbance of the obtained solution is determined with a photocolorimeter in a vat with a layer thickness of 1 cm and at a wavelength of 360 nm. Purified water is used as a reference solution.

The content of $C_8H_6N_4O_4 \cdot H_2O$ upon recalculation in the dry matter must be not less than 98% and not more than 102.0%.

2.2.B. Neutralization method in anhydrous medium. About 0.4 g of medicinal substance (exact mass) is dissolved in a mixture consisting of 10 ml of dimethylformamide and 10 ml of dioxane. Add 0.1 ml indicator: thymol blue solution in dimethylformamide and titrate with 0.1 mol/l sodium methoxide solution until a violet coloration.

1 ml of sodium methoxide solution 0.1 mol/l corresponds to 0.02382 g $C_8H_6N_4O_5$, which in the preparation must be no less than 99.0% and no more than 101.0%.

2.2.B. UV-Vis spectrophotometric determination. About 0.12 g of medicinal substance (exact mass) is transferred to a volumetric flask with a volume of 1000 ml, dissolved in 50 ml of dimethylformamide and made up to volume with purified

water. Place 5 ml of the obtained solution in a graduated flask with a volume of 100 ml and bring it up to the mark with a solution containing sodium acetate 1.8% and acetic acid 0.14%. The absorbance of the obtained solution is determined at a wavelength of 367 nm.

The solution of sodium acetate 1.8% and acetic acid 0.14% is used as a reference solution.

The content of $C_8H_6N_4O_5$ when recalculated in the dry matter must be not less than 98.0% and not more than 102.0%.

3. Furazolidon

3.1. Identification.

3.1.A. The reaction with sodium hydroxide: 0.05 g of drug substance is mixed with 20 ml of purified water and 5 ml of 30% sodium hydroxide solution and heated; brown color appears.

3.1.B. The reaction with dimethylformamide: 0.01 g of drug substance is dissolved in 3 ml of dimethylformamide; yellow color appears. Add 2 drops of 1 mol/l sodium hydroxide solution in 50% ethyl alcohol. A purple color appears, and when the walls of the test tube are moistened with this solution, the color turns blue. 1 ml of solution is diluted with water up to 10 ml; yellow color appears. After adding a few drops of 1 mol/l sodium hydroxide solution in 50% ethyl alcohol, the color of the solution does not change.

3.2. Assay.

3.2.A. Photocolorimetric method. About 0.1 g of drug substance (exact mass) is transferred to a volumetric flask with

a volume of 50 ml, 30 ml of dimethylformamide is added and mixed. After dissolving the medicinal substance, add 0.05 mol/l alcoholic sodium hydroxide solution, mix, cool and make up to volume with dimethylformamide. Place 0.6 ml of the obtained solution in a volumetric flask with a volume of 100 ml, bring it up to volume with purified water. More than 20 minutes after the addition of the 0.05 mol/l alcoholic sodium hydroxide solution, the absorbance of the solution is read on the photocolorimeter in the vat with a layer thickness of 0.5 cm at a wavelength of 360 nm.

The content of $C_8H_7N_3O_5$ when recalculated in the dry matter must be not less than 98.0% and not more than 102.0%.

Note. The results obtained when performing tasks 1-2 to be presented in table 4.

Table 4. ***The results obtained when performing the tasks***

The name of medicinal substances in Latin, Romanian; rational name; structure formula; description (for analyzed substances)	**Identification of drug substances:** work technique (conditions, analytical effect); reaction chemistry (for analyzed substances)	**Quantitative determination:** working method, reaction chemistry for chemical methods of analysis or postulates for physico-chemical methods; calculation formula for determining the content of the active substance; the conclusion about the quality of the analyzed substance based on the results obtained.

Task 3. ***To carry out the interaction reaction of 5-nitrofuran derivatives with heavy metal salts***

Working technique: 0.05 g of drug substance is dissolved in 8 ml of 0.1% sodium hydroxide solution and the obtained solution is divided into 3 test tubes, to which 2-3 drops of copper sulfate solution are added (in the 1st test tube) , cobalt chloride solution (in the II test tube) and silver nitrate solution (in the III test tube). I enter the obtained results in table 5.

Table 5. ***Results obtained when performing task 2***

Drug substance	**The reagents and the obtained results**		
	Solution of copper sulfate	**Solution of cobalt chloride**	**Solution of silver nitrate**

Recapitulation control

1. Control of theoretical knowledge.
2. Control of the practical work performed within the laboratory work.

TASKS FOR INDIVIDUAL WORK

1. Compilation and formation of the report for the practical tasks performed in the laboratory work.
2. Questions for individual solution:

2.1. Explain what chemical properties 5-nitrofuran derivatives have and indicate the functional groups that provide these properties.

2.2. Can furacilin be differentiated from other 5-nitrofuran derivatives? Argue.

2.3. Explain the essence of the method for obtaining 5-nitrofuran derivatives. Write the chemistry of the chemical reactions to obtain nitrofural (furacillin), nitrofurantoin (furadonin) and furazolidone.

2.4. Explain how the identification of nitrofural (furacillin) by reaction with sodium hydroxide under ordinary conditions differs from the reaction with sodium hydroxide on heating. Write the chemistry of chemical reactions.

2.5. Write the chemistry of the chemical reactions used to detect the specific semicarbazide impurity in nitrofural (furacilin). Explain the source of this impurity in the drug substance.

3. Solving calculation problems:

3.1. Write the chemistry of the nitrofuran dosage reaction by the iodometric method.

Calculate the titer, the equivalent molar mass of nitrofuran, the theoretical volume of the 0.01 mol/l sodium thiosulfate

solution, which was consumed when titrating the excess of the 0.01 mol/l iodine solution for the quantitative determination of nitrofuran, if the mass of the sample taken for the analysis of was 0.1081 g. The percentage content of the preparation according to DAN must be no less than 99.8 %.

3.2. Explain the essence of UV-Vis spectrophotometric physico-chemical method.

Calculate the concentration of nitrofural (furacillin), if 0.041 g of sample was dissolved in 200 ml of purified water. Sodium hydroxide solution was added to 2 ml of the obtained solution and brought up to 50 ml. The absorbance of the obtained solution was determined, being 0.491, on a photocolorimeter in a vat with a layer thickness of 10 mm (specific absorbance is 499.71).

3.3. Explain the main essence of the quantitative determination of furadonin by the photocolorimetric method (write the chemistry of the reaction).

Calculate the concentration of nitrofurantoin in sodium hydroxide 0.01 mol/l, if 0.1001 g of the medicinal substance was dissolved in 200 ml of purified water. 0.01 mol/l sodium hydroxide solution and purified water up to 50 ml were added to 1.5 ml of the obtained solution, and the absorbance of the obtained solution was determined, being 0.520, with a photocolorimeter in a 10 mm layer thickness vessel (specific absorbance is 519.67).

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