MINISTRY OF HEALTH OF UKRAINE

ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty of Pharmacy

Department of Pharmaceutical Chemistry and Drug Technology

APPROVED by

Vice-rector for scientific and pedagogical work

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_____, 202_

METHODOLOGICAL DEVELOPMENT
TO THE LECTURES ON THE EDUCATIONAL DISCIPLINE

Faculty, course Pharmaceutical, III course

Educational discipline Pharmaceutical chemistry

(the name of the educational discipline)

Approved:

The meeting of the department Pharmaceutical chemistry

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Minutes № _ dated _____

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Lecture No. 1

Topic: Subject and tasks of pharmaceutical chemistry, history of development. The system of evaluation of the quality of medicinal products. The State Pharmacopoeia of Ukraine, its structure.

Actuality of theme: Pharmaceutical chemistry studies a wide range of issues related to medicinal products. in particular, sources and methods of their extraction, structure, physical and chemical properties; dependence of the physicochemical properties of medicinal products and their pharmacological action on the chemical structure; methods of quality control and changes occurring during storage and metabolism, as well as methods of obtaining and purifying medicinal products, biologically active compounds and their metabolites, etc. Pharmaceutical chemistry concentrates the achievements of medicine and biology, biochemistry, organic and analytical chemistry, as it is at the intersection of these sciences. Today, pharmaceutical chemistry is a science that develops at the fastest pace. Every year, more and more new drugs appear on the pharmaceutical market, new, more advanced methods of synthesis and analysis of already known drugs (so-called "generics") are being developed, so the study of the discipline is relevant.

Goal: to familiarize with the subject, content and history of the development of pharmaceutical chemistry, the concept of building the State Pharmacopoeia of Ukraine. Familiarize with the sources, means of extraction of medicinal substances, causes of contamination of medicinal products, as well as learn to determine the permissible limits of impurities in them.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. The subject, tasks and history of the development of pharmaceutical chemistry.
2. System for evaluating the quality of medicines.
3. Testing for purity and permissible limits of impurities.

4. Sources and causes of drug contamination.

Content of lecture material (lecture text):

1. The subject, tasks and history of the development of pharmaceutical chemistry.

Pharmaceutical chemistry is a science that studies the methods of preparation, structure, physical and chemical properties of medicinal products; the relationship between their chemical structure and effect on the body; methods of quality control of drugs and changes that occur during their storage, as well as their use in medicine.

The problems faced by pharmaceutical chemistry are solved with the help of physical, chemical and physicochemical methods used both for the synthesis and analysis of medicinal products.

Pharmaceutical chemistry is an applied science based on the theory and laws of such chemical sciences as inorganic, organic, analytical, physical, colloidal chemistry. In close connection with inorganic and organic chemistry, pharmaceutical chemistry is engaged in the study of methods of synthesis of medicinal products.

Since their effect on the body depends on both the chemical structure and the physicochemical properties, pharmaceutical chemistry uses the laws of physical chemistry.

Analytical chemistry methods are used in the development of methods of quality control of medicinal products and dosage forms in pharmaceutical chemistry. However, pharmaceutical analysis has its own specific features and includes three mandatory stages: establishing the validity of the medicinal product, controlling its benign quality (establishing acceptable limits of impurities) and quantitative determination.

The development of pharmaceutical chemistry is closely related to medical and biological (anatomy, physiology, biochemistry, pharmacology) and chemical (general and inorganic chemistry, organic, analytical chemistry) sciences. Pharmaceutical chemistry is at the same time the basis for the main profile

pharmaceutical disciplines: technology of dosage forms, toxicological chemistry and pharmacognosy.

The term "pharmaceutical chemistry" appeared in the middle of the 19th century. Pharmaceutical chemistry abroad. became an independent direction on the border of the 19th and 20th centuries. The history of the development of pharmaceutical chemistry can be divided into 3 eras: empirical, experimental and scientific, and the era of rational methods of directed synthesis based on innovative technologies (virtual screening, combinatorial chemistry, highly efficient screening, molecular modeling, etc.). Attempts at treatment have begun since the time when man appeared on Earth. Already the primitive man tried to ease the suffering of the sick, to prevent diseases, and, in fact, that's when the first medicines appeared. These were minerals and medicines that man discovered while looking for food. When she learned to hunt, she received medicine of animal origin (liver, fat, blood). Over time, people learned to provide primitive aid for injuries.

The main directions of modern pharmaceutical chemistry are: the purposeful search for new medicinal substances, the development and improvement of methods for assessing the quality of medicinal products in order to ensure their effectiveness, safety and storage. The main methods of researching medicinal substances in pharmaceutical chemistry are analysis and synthesis — dialectically closely related processes that complement each other.

Pharmaceutical chemistry considers the following problems: establishing the relationship between the structure of medicinal substances and their physicochemical and pharmacological properties; search for new ways of obtaining physiologically active substances by directed changes in their structure (subtle organic synthesis, chemical and biological modification) or by obtaining substances of a previously unknown structure; development of principles and requirements that determine the quality of medicinal substances, selection of methods for assessing the quality of pharmaceuticals, implementation of their control in accordance with the requirements of the SPhU and other AND.

2. System for evaluating the quality of medicines.

State Pharmacopoeia of Ukraine

STATE PHARMACOPEIA OF UKRAINE (SPhU) — this is a legal document containing general requirements for medicines, PhA (monographs), as well as methods of quality control (Law of Ukraine "On Medicines", Article 2). The SPhU has a legislative character. Its requirements for medicines are mandatory for all enterprises and institutions of Ukraine, regardless of their form of ownership, that manufacture, store, control and use pharmaceuticals.

Ukraine is the only one among the countries of the former USSR to have its own national Pharmacopoeia - SPhU 1st edition (SPhU 1), which was put into effect on October 1, 2001. The developer of the SPhU is the State Enterprise "Scientific Expert Pharmacopoeia Center". Leading specialists of higher schools, academic and industry institutes, regulatory bodies, pharmaceutical enterprises, and the pharmaceutical public took part in the development, review, and revision of general articles and monographs of SPhU.

In 1998, Ukraine received observer status in the European Pharmacopoeia. According to the Decision of the Council of Europe dated March 18, 2013, Ukraine became the 38th member of the European Pharmacopoeia. The SPhU is harmonized with the European Pharmacopoeia, which corresponds to Ukraine's course of integration into the EU. Therefore, the general articles and monographs of the SPhU consist of two interdependent parts — the European, identical to the corresponding article of the European Pharmacopoeia, and the national, which takes into account the specifics of the current state of pharmaceutical production in Ukraine. The national part does not contradict the European one, but contains additional requirements for medicine, which are not produced under the conditions of good manufacturing practice (GMP) established in the EU. The national part also includes additional informational materials and alternative methods. SPhU contains the following sections: "General remarks", "Methods of analysis", "Reagents", "General texts", "General articles on dosage forms", "General monographs", "Monographs", "Homeopathic medicines", etc. In order to maintain harmonization with the European Pharmacopoeia, which is updated annually, the SPhU is supplemented.

3. Testing for purity and permissible limits of impurities.

The quality of the medicinal product (suitability for medical use) is determined by the requirements of the pharmacopoeia or pharmacopoeial articles. In the private articles of the pharmacopoeia, various extraneous substances, called impurities, are allowed for individual medicinal products. The qualitative and quantitative composition of impurities for each drug is established experimentally and regulated by the pharmacopoeia. When performing an analysis for the benign quality of the drug, we determine whether the amount of one or another impurity does not exceed the limit established by the pharmacopoeia.

The state pharmacopoeia does not require an absolutely pure drug and allows impurities in it within strictly defined limits. This permissible limit is determined by the physiological effect of this impurity on the body and its effect on the properties of the medicinal product. Therefore, the same impurities are allowed in different amounts in different medicines.

Impurities in medicinal products are not random in nature, but are determined by completely natural sources.

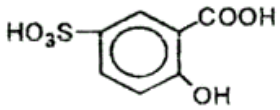
4. Sources and causes of drug contamination:

- ✓ As a result of receiving medicines. The main sources of impurities are equipment, raw materials, solvents and other substances used in the production of medicinal products. The material from which the equipment is made (metal, glass) can serve as a source of impurities of heavy metals and arsenic. In case of poor cleaning, impurities of solvents, fibers of fabrics or filter paper, sand, asbestos, etc., as well as residues of acids and alkalis may be contained in the preparations.
- ✓ Synthetic drugs usually contain impurities of starting and intermediate products of organic synthesis, and drugs obtained from plant and animal raw materials often have impurities of extraneous extractive substances.
- ✓ As a result of improper storage, when its properties were not taken into account or storage conditions were violated, as a result of which the medicinal product decomposes, often with the formation of products that are dangerous

for the body. Thus, storage conditions may become the cause of poor quality of medicines.

- ✓ The specific analysis of individual medicines always takes into account their individual characteristics and is, to a certain extent, relative, corresponding to the requirements of this pharmacopoeial article. Therefore, when choosing a reaction for a purity test, the general requirements are the following:
  - the sensitivity of the reaction in the conditions of experience;
  - specificity;
  - reproducibility.
- ✓ When determining impurities in medicinal products, the most sensitive reactions are usually used, because impurities, if they are allowed, are in very small quantities.

For example, iron (+3) can be opened with several reagents: ammonium rhodanide NH_4SCN, potassium ferrocyanide - $K_4[Fe(CN)_6]$ and sulfosalicylic acid.



But if iron (+3) is determined as an impurity, then sulfosalicylic acid is used, because with its help, the smallest amount of iron (+3) ion can be determined, that is, this reaction is the most sensitive.

Reference solutions are used to determine impurities and their approximate quantitative assessment in medicinal products. The standard is a sample containing a strictly defined amount of the impurity that opens.

When preparing standard solutions, they proceed from the sensitivity of the reaction to this ion. Reference solutions are prepared very accurately. For the preparation of reference solutions, chemically pure substances are usually taken that contain the ions whose standards need to be prepared.

The presence of impurities is determined by colorimetric or nephelometric methods, comparing the results of the reactions in the standard solution and in the drug solution after adding equal amounts of the corresponding reagents to them.

Because reference solutions are solutions with a strictly defined concentration of one or another ion, the qualitative tests on the impurity have a quantitative value. That is, we can say not only whether there is an impurity, but also what its approximate amount is. But it is worth remembering that standard solutions are used only when determining impurities allowed by the pharmacopoeia (allowable) (if the pharmacopoeial article states, for example, that chlorides should not be more than 0.02%). In the same case, when the corresponding article of the pharmacopoeia states that the medicinal product must not react to one or another impurity (impermissible impurity), it is not possible to compare the tested solution with the standard.

The state pharmacopoeia, when testing a drug for impurities, gives very detailed descriptions of the conditions for certain qualitative reactions. In those cases when the impurity is discovered and found in many medicines (chloride ion, sulfate ion, calcium ion, iron ion (+2), iron ion (+3), lead ion, ammonium ion, zinc ion, mouse ion 0-3), arsenic ion (+5)), the pharmacopoeia does not give a detailed method of determining this impurity in the private article of SPhU, but only indicates its permissible limit in the preparation. The methods of determining the most frequently occurring impurities are described in the general article "Test for purity and permissible limits of impurities" (p. 105, SPhU XI). The same article provides methods for preparing standard solutions for these impurities.

General remarks that must be observed when determining impurities:

- Water and reagents must be free of ions to be tested.
- Test tubes in which observations are made must be completely colorless and of the same diameter.
- Samples for preparation of reference solutions are taken with an accuracy of 0.001 g.
- Reference solutions B and C are prepared immediately before use.
- Turbidity and opalescence are observed in passing light on a dark background, and staining - in reflected light on a white background.

- Addition of reagents to the tested and reference solutions should be done simultaneously and in the same quantities.

In cases where it is stated in the relevant article of the GF that this or that impurity (inadmissible) should not be detected in a given concentration of the solution, they are received in the following way. The reagents used for each reaction are added to the tested solution, in addition to the main, opening given impurity (for example, when determining chlorides, nitric acid is added.). The resulting solution is divided into two equal parts, the main, opening reagent (silver nitrate) is added to one of them, and none is added to the other. And then both solutions are compared with each other. There should be no noticeable differences between them.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Subject, problems of pharmaceutical chemistry.
2. Sources and causes of contamination of medicines.
3. To characterize the general remarks that must be observed when determining impurities in medicinal preparations.

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Basic:

1. Handbook of pharmaceutical chemictry Vol. 117 / L. Ohannesian, Antony J. Streeter. 2016. – 582 p.
2. Pharmaceutical Chemistry I – Laboratory Experiments and Commentary / Attila Almási, Zsuzsanna Rozmer, Pál Perjési. 2014. – 179 p.
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8. Europian Pharmacopoeia 10th. 2019. – 4255 p.

Additional:

1. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
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4. Фармацевтична хімія / П.О. Безуглий, В.А. Георгіянц, І.С. Гриценко, І.В. та ін.: за ред. П.О. Безуглого. – Вінниця: Нова книга, 2017. – 456 с.
5. Фармацевтична хімія. Загальна та спеціальна фармацевтична хімія. Лікарські засоби неорганічної природи: лабораторно-практичні заняття. Навчальний посібник / Л.Г. Мішина. – Вінниця: ПП «ТД «Едельвейс і К»», 2010. – 384 с.

Lecture No. 2

Topic: Physico-chemical methods of analysis in the identification of medicinal products.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities

and the quantitative content of medicinal products in individual and multi-component medicinal preparations. Therefore, in order to deepen theoretical knowledge and improve practical skills in specific sections of pharmaceutical analysis, this program provides for a more detailed study of the methods of drug analysis based on the pharmacopoeial articles of the State Pharmacopoeia of Ukraine and other regulatory documentation. In order to consolidate theoretical knowledge and practical skills, a more in-depth study of the analysis of drugs by analytical-functional groups based on DFU is provided, which is necessary for mastering the methods of express analysis of drugs. Along with titrometric methods of quantitative analysis of medicinal products, the program provides a deeper study of instrumental methods of analysis, which are increasingly used in the practice of quality control of medicinal products.

Goal: familiarize with instrumental (physical and physico-chemical) methods of analysis.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis, chemical method of analysis, physical method of analysis, physicochemical method of analysis, microanalysis, microanalysis, semimicroanalysis, ultramicroanalysis.

Plan and organizational structure of the lecture:

1. Physico-chemical methods of quantitative analysis.
2. Methods of molecular absorption analysis.
3. Methods based on the phenomenon of polarization of molecules under the influence of light radiation.
4. Types of luminescent analysis. Quantitative and qualitative analysis.
5. Extraction-luminescence quantitative analysis.

Content of lecture material (lecture text):

1. Physico-chemical methods of quantitative analysis.

The most common physicochemical methods include optical ones.

Optical methods are based on measuring the optical properties of solutions:

- ✓ polarimetric - measurement of the angle of rotation of the plane of polarization in a solution of a substance;
- ✓ refractometric - measurement of the angle of refraction of light in a solution;
- ✓ photometric - measurement of the beam of light that passed through the solution;
- ✓ spectrophotometric - measurement of the intensity of a beam of light of a certain wavelength that passed through the solution.

Optical methods of analysis are classified into:

I. Absorption methods: based on measuring the absorption of light radiation by a substance:
   1) colorimetry;
   2) photocolorimetry;
   3) spectrophotometry.

II. Emission methods: based on measuring the intensity of light emitted by a substance:
   1) emission spectral analysis;
   2) flame photometry.

III. Methods based on measuring the intensity of light after its interaction with suspended particles in a solution (emulsions, suspensions):
   1) fluorimetry;
   2) turbidimetry;
   3) nephelometry.

IV. Methods based on the phenomenon of polarization of molecules under the influence of light radiation:
   1) refractometry;
   2) polarimetry.

2. Methods of molecular absorption analysis.

The analysis is based on measuring the absorption of electromagnetic radiation by molecules or ions in the visible, UV or IR region of the spectrum:

1) colorimetry - the method is based on a visual comparison of the color intensity of solutions of different concentrations.

The light is non-monochromatic.

Not subject to the law of light absorption.

Spectral region: 400-700 nm. Accuracy of measurements ±5-10%. Colorimetric test tubes are used for measurement;

2) photocolorimetry – the method is based on measuring the degree of absorption of non-monochromatic or partially monochromatic radiation by the substance to be determined in the visible region of the spectrum.

Subject to the law of light absorption.

Spectral range: 300-700 nm. The device is a photoelectric colorimeter. Measurement accuracy ±3%;

3) spectroscopy in the visible, UV, and IR regions of the spectrum - methods based on measuring the absorption of monochromatic radiation by a substance in the visible (360-760 nm), UV (180-360 nm), and IR regions (760-1100 nm) of the spectrum. The optical density of solutions is subject to the law of light absorption:

- spectral range – 180-760 nm. The device is a UV spectrophotometer. Measurement accuracy ±2%;

- spectral range – 7-1100 nm. The device is an IR spectrophotometer. Accuracy of measurements ± 2 %.

3. Methods based on the phenomenon of polarization of molecules under the influence of light radiation.

1) refractometry: the method is based on measuring the relative index of light reflection (n) by the test substance:

$$n = \frac{V_1}{V_2} = \frac{\sin\alpha}{\sin\beta},$$

where: n is the ratio of the speed of light propagation in air (V1), or the sine of the angle of incidence (sin α) to the speed of light in the analyzed solution (V2) or the sine of the angle of reflection (sin β) in the analyzed solution.

It is customary to indicate the value of n under the specified conditions: t° = 20°C; λ = 589.3 nm (yellow sodium line).

The measuring device is a refractometer.

Measurement accuracy ± 2 · 10^{-4}.

At the same time, the reflection index is indicated.

2) polarimetry: the method is based on measuring the angle of rotation of the plane of polarization (α) of a polarized light beam that has passed through an optically active medium:

$$[\alpha]_D^{20} = \frac{\alpha \cdot 100}{1 \cdot C},$$

where: - specific rotation value (const);

α – the measured rotation angle in degrees;

l – layer thickness, in dm;

C – concentration of the solution, in g/100 ml.

α depends on:

- the nature of the solvent;
- concentration of optically active substance (C);
- the thickness of the optically active substance layer (l).

Conditions: t° = 20°C; λ = 589.3 nm.

The device for measuring α is a polarimeter.

Measurement accuracy ± 0,02°.

4. Types of luminescent analysis. Quantitative and qualitative analysis.

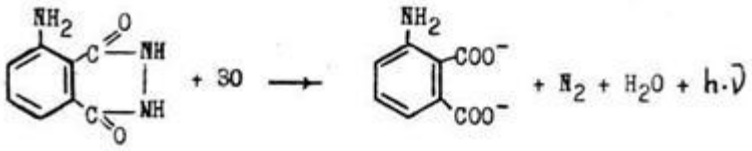
Quantitative luminescence analysis is based on the linear relationship between the luminescence intensity and the concentration of the luminescent substance I = KC.

It should be noted that the linear dependence is observed only at low concentrations of mol/l, that is, the luminescent method of analysis is used to determine microquantities of substances.

To determine the concentration of a substance, the calibration graph method is used, which is built in I - C coordinates.

The chemiluminescent method of analysis, which is based on the release of light during the course of chemical reactions, is currently widely used in analytical practice. The most commonly used chemiluminescent indicator (luminophore) is hydrazide-3-amivophthalic acid, which was named luminol for its bright chemiluminescence. When luminol is oxidized by hydrogen peroxide and other oxidants in an alkaline environment, a weak chemiluminescence is observed, the intensity of which increases sharply in the presence of trace amounts of metals - catalysts for the decomposition of hydrogen peroxide in an alkaline environment.

The luminol oxidation reaction proceeds according to the equation:



Currently, many methods of chemiluminescent determination of trace amounts (impurities) of metals in various materials of high purity have been developed. All of them are based on the linear relationship between the intensity of chemiluminescence and the concentration of the catalyst in the solution.

Luminescent indicators, for example, luminol, are also used to establish the equivalence point in titrometric analysis. The application is based on the dependence of the intensity of chemiluminescence on the pH of the solution.

The chemiluminescent method is also used for the analysis of small amounts of organic substances - aromatic amines, phenols, carbohydrates, etc. Recently, there is a possibility of using the luminescent method of analysis to determine fructose and sucrose in honey, carbohydrates.

The luminescence spectrum of any substance depends on its nature. Qualitative luminescence analysis is based on this dependence. Its essence is that when the same objects are viewed from the outside in white light, they do not differ from each other, but after illuminating them with ultraviolet light, they can glow in different ways. For example, fresh grain and perishable grain glow differently, which can be used to determine its quality. Sort analysis is used to sort different types of glass, different types of fuel, to detect forged documents, in medicine.

The so-called luminescence microscopy is widely used to detect various defects on the surface of metal products. The luminescent mineral oil applied to the examined surface, in the presence of a continuous crack, seeps through to the unlubricated surface of the part. The luminescent liquid remains in small cracks after it is removed from the surface of the part. Places of defects usually stand out against a dark background due to their bright luminescence.

A type of qualitative luminescent analysis is grade analysis, which allows you to detect differences in the object under investigation that are invisible under normal lighting and is used to detect the grade and quality of glass, seeds, agricultural products, to detect minerals in rocks, surface and through-hole defects, and detect fakes in criminology.

Fluorescent analysis is based on the formation of luminescent complex compounds of elements with organic substances, for example, flavone derivatives, such as morin, quercetin, trihydroxyfluorone derivatives, and hydroxyanthraquinone, 8-oxychnoline, rhodamines, etc. This method is not very selective, most of the reagents are group reagents, only lumogallion is specific for the detection of gallium and lumomagnesone - to detect magnesium, to increase selectivity, extraction-fluorescence analysis is used - preliminary separation of the analyzed mixture by the extraction method, as well as precipitation of solutions and cooling of solutions to liquid nitrogen temperatures and helium. In the latter case, phosphorescence may also occur.

Phosphorescence analysis is an analysis method with high selectivity, since only some cations form phosphorescent complexes with organic reagents, while the reagents themselves do not phosphoresce. A phosphoroscope is used to record spectra and intensity of phosphorescence, while fluorescence is not registered.

Chemiluminescence analysis is based on the glow that occurs as a result of redox reactions of organic substances (luminol, lucigenin) with cations of transition metals -. The concentration of metals is determined by the change in radiation intensity. The detection limit of metals is.

Luminescence analysis of organic compounds is difficult because their luminescence spectra are usually not specific. However, methods of quantitative detection of porphyrins, vitamins, antibiotics and chlorophyll in solutions are proposed. When using lasers, the limit of detection of these substances is. Aromatic compounds in frozen solutions of hydrocarbons at a temperature of 77 K give characteristic luminescence spectra for each compound (the Polsky effect). Therefore, this method is used to detect and quantify polycyclic aromatic compounds in extracts of plants, soils, and food products. The detection limit is.

The advantage of luminescent chemical analysis in comparison with other physical and chemical methods is its high sensitivity. With the help of luminescence analysis, it is possible to determine the percentage of a substance up to a millionth.

5. Extraction-luminescence quantitative analysis.

Extraction-luminescence quantitative analysis is used in the analysis of substances that contain impurities that interfere with the determination.

The test substance is extracted with an organic solution and determined by the method described above.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Classification of physical methods of analysis.
2. Optical methods of analysis, their classification.
3. Molecular absorption spectroscopy.
4. Refractometry. Optical methods of analysis.
5. Luminescent analysis.

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Basic:

1. Handbook of pharmaceutical chemictry Vol. 117 / L. Ohannesian, Antony J. Streeter. 2016. – 582 p.
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Lecture No. 3

Topic: Methods of identification of medicinal products.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component medicinal preparations. Therefore, in order to deepen theoretical knowledge and improve practical skills in specific sections of pharmaceutical analysis, this program provides for a more detailed study of the methods of drug analysis based on the pharmacopoeial articles of the State Pharmacopoeia of Ukraine and other regulatory documentation. In order to consolidate theoretical knowledge and practical skills, a more in-depth study of the analysis of drugs by analytical-functional groups based on SPhU is provided, which is necessary for mastering the methods of express analysis of drugs. Along with titrometric methods of quantitative analysis of medicinal products, the program provides a deeper study of instrumental methods of analysis, which are increasingly used in the practice of quality control of medicinal products.

Goal: to familiarize with the subject, content and history of the development of pharmaceutical chemistry, the concept of building the State Pharmacopoeia of Ukraine. Familiarize with the sources, means of extraction of medicinal substances, causes of contamination of medicinal products, as well as learn to determine the permissible limits of impurities in them.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Pharmaceutical analysis, depending on the tasks, includes various aspects of drug quality control.
2. Pharmaceutical analysis criteria.
3. Methods of identification of medicinal substances.
4. Physico-chemical methods of determining authenticity.
5. Chemical methods of establishing authenticity.

Content of lecture material (lecture text):

1. **Pharmaceutical analysis, depending on the tasks, includes various aspects of drug quality control.**

1) Pharmacopoeial analysis;
2) Step-by-step control of the production of medicinal products;
3) Analysis of individually manufactured medicinal products.

The main and most essential is the pharmacopoeial analysis, that is, the analysis of medicinal products for compliance with the standard - a pharmacopoeial article or another RD and, thus, confirmation of its suitability. Hence the requirements for high specificity, selectivity, accuracy and reliability of the analysis.

A conclusion about the quality of the medicinal product can be made only on the basis of the analysis of the sample (statistically reliable sample). The order of sample selection is specified either in a private article or in a general article of SPh X1 edition. (Issue 2) p. 15. In order to test medicinal products for compliance with the requirements of regulatory and technical documentation, a multi-stage selection of samples (samples) is carried out. In multi-stage sampling, the sample (sample) is formed by steps and the products in each stage are randomly selected in proportional quantities from the units selected in the previous stage. The number of steps is determined by the type of packaging.

1) degree: selection of packaging units (boxes, boxes, etc.);
2) degree: selection of packaging units in the packaging container (boxes, vials, cans, etc.);
3) degree: selection of products in primary packaging (ampoules, vials, contour packages, etc.).

A formula is used to calculate the selection of the number of products at each stage:

$$0{,}4\sqrt{n}$$

where n is the number of packaging units of this step.

2. Pharmaceutical analysis criteria.

For various purposes of the analysis, such criteria as selectivity of the analysis, sensitivity, accuracy, analysis time, amount of the tested substance are important.

The selectivity of the analysis is of significant importance in the analysis of complex drugs consisting of several active components. In this case, the selectivity of the analysis for the quantitative determination of each of the substances is very important.

Requirements for accuracy and sensitivity depend on the object and purpose of the study. When testing for purity or impurities, highly sensitive methods are used. For step-by-step production control, the time spent on analysis is an important factor.

An important parameter of the analysis method is the sensitivity limit of the method. This limit means the lowest content at which this substance can be reliably detected. The least sensitive are chemical methods of analysis and qualitative reactions. The most sensitive enzymatic and biological methods that allow detecting individual macromolecules of substances. Of the actually used, the most sensitive are radiochemical, catalytic and fluorescent methods, which allow to determine up to 10^{-9}%; sensitivity of spectrophotometric methods 10^{-3}-10^{-6}%; potentiometric 10^{-2}%.

The term "analysis accuracy" includes two concepts at the same time:

- ✓ reproducibility and correctness of the obtained results.
- ✓ reproducibility - characterizes the dispersion of the analysis results in comparison with the average value.
- ✓ correctness - reflects the difference between the actual and found content of the substance.

The accuracy of the analysis depends on the quality of the devices, the experience of the analyst, etc. The accuracy of the analysis cannot be higher than the

accuracy of the least accurate measurement. This means that if during titration, the accuracy is ± 0.2 ml plus the error from leakage is also ± 0.2 ml, i.e. a total of ± 0.4 ml, then when 20 ml of titrant is consumed, the error is 0.2%. The accuracy decreases with a decrease in the suspension and the amount of titrant. Thus, the titrimetric analysis allows determination with a relative error of ± (0.2-0.3)%. Each method has its own accuracy. When analyzing, it is important to have an idea of the following concepts:

Gross errors are a miscalculation by the observer or a violation of the analysis methodology. Such results are rejected as unreliable.

Systematic errors - reflect the correctness of the analysis results. They distort the measurement results, as a rule, in one direction by some constant value. Systematic errors can be partially eliminated by introducing corrections, calibrating the device, etc.

Random errors - reflect the reproducibility of the results of the analysis. They are caused by uncontrolled variables. The arithmetic mean of random errors tends to zero. Therefore, for calculations, it is necessary to use not the results of single measurements, but the average of several parallel determinations.

Absolute error - there is a difference between the obtained result and the true value. This error is expressed in the same units as the determined value.

The relative error value is equal to the ratio of the absolute error to the true value determined by the quantity. It is usually expressed in percentages or shares.

The values of the relative errors depend on the method by which the analysis is performed and what the analyzed substance is - an individual substance and a mixture of many components.

The relative error in the study of individual substances by the spectrophotometric method is 2-3%, IR-spectrophotometer - 5-12%; liquid chromatography 3-4%; Potentiometer 0.3-1%. Combined methods, as a rule, reduce the accuracy of the analysis. The least accurate are biological methods - their relative error reaches 50%.

3. Methods of identification of medicinal substances.

The most important indicator when testing medicinal substances is their identification or, as it is accepted in pharmacopoeial articles, authenticity. Numerous methods are used to determine the authenticity of medicinal substances. All the main and general ones are described in the SPhU. Historically, the main emphasis was on chemical, incl. qualitative color reactions characterizing the presence of certain ions or functional groups in organic compounds, at the same time physical methods were widely used. In modern pharmacopoeias, emphasis is placed on physicochemical methods.

Let's dwell on the main physical methods.

A fairly stable constant that characterizes a substance, its purity and authenticity is the melting point. This indicator is widely used for standardization of substances of medicinal substances. Methods for determining the melting temperature are described in detail in the SPhU, you were able to test it yourself in laboratory classes. A pure substance has a constant melting point, but when impurities are added to it, the melting point usually decreases very significantly. This effect is called a mixture test, and it is the mixture test that allows you to establish the authenticity of the drug in the presence of a standard sample or a clear sample. There are, however, exceptions, for example, racemic sulfocamphoric acid melts at a higher temperature, and different crystalline forms of indomethacin differ in melting point. That is, for some drugs, such an indicator as the hardening temperature is used. Another indicator that characterizes a substance is the boiling point or temperature limits of distillation. This indicator characterizes liquid substances, for example, ethyl alcohol. The boiling point is a less typical indicator, it strongly depends on the atmospheric pressure, the possibility of formation of mixtures or azeotropes and is used quite rarely.

Among other physical methods, it should be noted the definition of density, viscosity. Standard methods of analysis are described in the SPhU. The method that characterizes the authenticity of the drug is also the determination of its solubility in various solvents. This method is characterized as a property that can serve as an indicative characteristic of the tested drug. Along with the melting point, the

solubility of a substance is one of the parameters by which the authenticity and purity of almost all medicinal substances are determined. In the pharmacopoeia, an approximate gradation of substances in terms of solubility is established, from very easily soluble to practically insoluble. At the same time, a substance is considered to be dissolved in the solution of which no particles of the substance can be observed in the light.

4. Physico-chemical methods of determining authenticity.

The most informative from the point of view of determining the authenticity of substances are physicochemical methods based on the properties of molecules of substances together with any physical factors. Physico-chemical methods should include:

1) Spectral methods:

UV spectroscopy, Spectroscopy in visible light, IR spectroscopy, Fluorescence spectroscopy, Atomic absorption spectroscopy, X-ray methods of analysis, Nuclear magnetic resonance, X-ray structural analysis.

2) Sorption methods of analysis:

Thin-layer chromatography, Gas-liquid chromatography, High-performance liquid chromatography, Electrophoresis, Iontophoresis, Gel chromatography.

3) Mass methods of analysis:

Mass spectrometry, Chromatomass spectrometry.

4) Electrochemical methods of analysis:

Polarography, Electronic paramagnetic resonance.

5) Use of standard samples.

Let's briefly consider the methods of analysis applicable in pharmacy. All these methods of analysis will be read to you in detail at the end of December by Professor V. I. Myagkikh. Some spectral methods are used to determine the authenticity of medicinal substances. The most reliable is the use of the low-frequency region of IR spectroscopy, where the absorption bands most reliably reflect the given substance. I also call this area the fingerprint area. As a rule, to confirm the authenticity, a comparison of the IR spectra taken under standard

conditions of the standard sample and the tested sample is used. The coincidence of all absorption bands confirms the authenticity of the drug. The use of UV and visible spectroscopy is less reliable, because the nature of the spectrum is not individual and reflects only a certain chromophore in the structure of the organic compound. Atomic absorption spectroscopy and X-ray spectroscopy are used to analyze inorganic compounds and to identify chemical elements. Nuclear magnetic resonance makes it possible to establish the structure of organic compounds and is a reliable method of confirming authenticity, however, due to the complexity of the devices and the high cost, it is used very rarely and, as a rule, only for research purposes. Fluorescence spectroscopy is used only for a certain class of substances that fluoresce under the influence of UV radiation. At the same time, the fluorescence spectrum and fluorescence excitation spectrum are quite individual, but strongly depend on the medium in which this substance is dissolved. This method is more often used for quantification, especially of small quantities, because it is one of the most sensitive.

X-ray structural analysis is the most reliable method of confirming the structure of a substance, it allows you to establish the exact chemical structure of a substance, however, it is simply not suitable for the current analysis of authenticity and is used exclusively for scientific purposes.

Sorption methods of analysis are widely used in pharmaceutical analysis. They are used to determine authenticity, presence of impurities and quantification. You will be given a lecture in detail about these methods and the equipment used by Professor V. I. Myagkih - a regional representative of the Shimazu company - one of the main manufacturers of chromatographic equipment. These methods are based on the principle of sorption-desorption of substances on certain carriers in the carrier flow. Depending on the carrier and sorbent, they are divided into thin-layer chromatography, liquid column chromatography (analytical and preparative, including HPLC), gas-liquid chromatography, gel filtration, iontophoresis. The last two methods are used for the analysis of complex protein objects. A significant drawback of the methods is their relativity, that is, chromatography can characterize

a substance and its amount only when compared with a standard substance. However, it should be noted as a significant advantage - the high probability of the method and accuracy, because in chromatography any mixture must be divided into individual substances and the result of the analysis is exactly the individual substance.

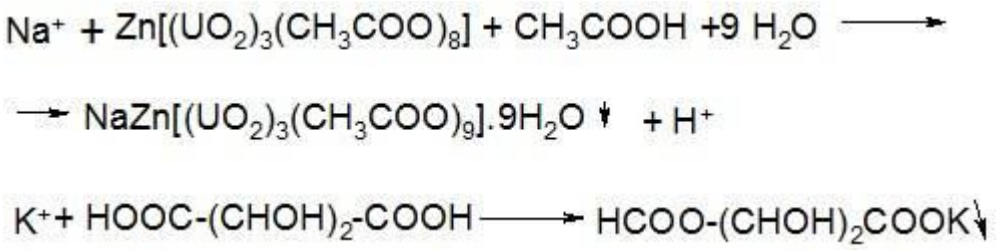
Mass spectrometric and electrochemical methods are rarely used to confirm authenticity.

A special place is occupied by methods of determining authenticity in comparison with a standard sample. This method is used quite widely in foreign pharmacopoeias to determine the authenticity of complex macromolecules, complex antibiotics, some vitamins, and other substances containing particularly chiral carbon atoms, since it is difficult or impossible to determine the authenticity of an optically active substance by other methods. The standard sample should be developed and produced on the basis of the developed and approved pharmacopoeial article.

5. Chemical methods of establishing authenticity.

Establishing the validity of medicinal substances by chemical methods is used mainly for inorganic medicinal substances, because other methods are often unavailable or require complex and expensive equipment. As already mentioned, inorganic elements are easily identified by the methods of atomic absorption or X-ray spectroscopy. Our pharmacopoeial articles generally use chemical authentication methods. These methods are usually divided into the following:

Reactions of deposition of anions and cations. Typical examples are the precipitation reactions of sodium and potassium ions with (cincuranyl acetate and tartaric acid), respectively:



A large number of such reactions are used and they will be discussed in detail in a special section of pharmaceutical chemistry in the section on inorganic substances.

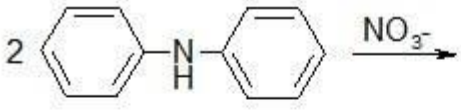
Redox reactions.

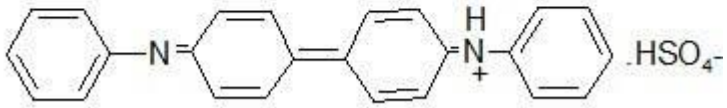
Redox reactions are used to recover metals from oxides. For example, silver from its formalin oxide (silver mirror reaction):

$$Ag_2O + HCOH \longrightarrow 2Ag\downarrow + HCOOH$$

$$CuSO_4 + Fe \longrightarrow Cu + FeSO_4$$

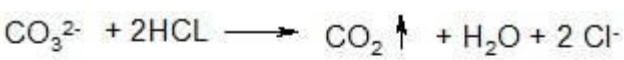
the oxidation reaction of diphenylamine is the basis of tests for the authenticity of nitrates and nitrites:



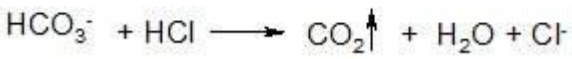


Reactions of neutralization and decomposition of anions.

Carbonates and hydrocarbons under the action of mineral acids form carbonic acid, which decomposes to carbon dioxide:



$$CO_3^{2-} + 2HCL \longrightarrow CO_2\uparrow + H_2O + 2\,Cl^-$$



$$HCO_3^- + HCl \longrightarrow CO_2\uparrow + H_2O + Cl^-$$

Similarly, nitrites, thiosulfates, and ammonium salts decompose.

Colorless flame changes. Sodium salts color the flame yellow, copper green, potassium purple, calcium brick-red. This principle is used in atomic absorption spectroscopy.

Decomposition of substances during pyrolysis. The method is used for preparations of iodine, arsenic, and mercury. Of the currently used, the most

characteristic reaction is the basic bismuth nitrate, which decomposes with the formation of nitrogen oxides when heated:

Identification of elemental-organic medicinal substances.

Qualitative elemental analysis is used to identify compounds containing arsenic, sulfur, bismuth, mercury, phosphorus, halogens in an organic molecule. Since the atoms of these elements are not ionized, preliminary mineralization, or pyrolysis, or pyrolysis with sulfuric acid is used for their identification. Sulfur is determined by hydrogen sulfide reaction with potassium nitroprusside or lead salts. Iodine is also determined by pyrolysis by the release of elemental iodine. Of all these reactions, the identification of arsenic is of interest, not so much as a medicinal drug - they are practically not used, but as a method of controlling impurities, but more on that later.

Testing the authenticity of organic medicinal substances.

Chemical reactions used to test the authenticity of organic medicinal substances can be divided into three main groups:

1) General chemical reactions of organic compounds;
2) Reactions of the formation of salts and complex compounds;
3) Reactions used to identify organic bases and their salts.

All these reactions are ultimately based on the principles of functional analysis, that is, the reactive center of the molecule, which reacts and gives the appropriate response. Most often, this is a change in any properties of a substance: color, solubility, aggregate state, etc.

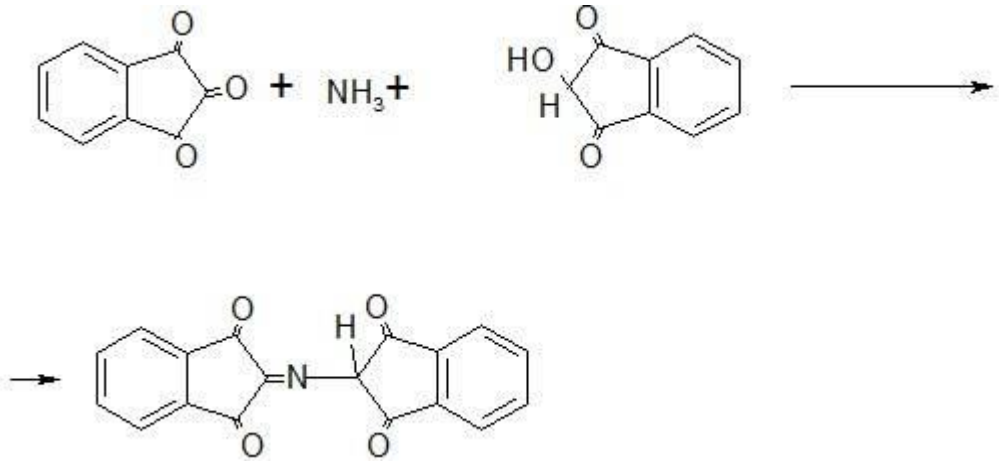
Let's consider some examples of the use of chemical reactions for the identification of medicinal substances.

1) **Nitration and nitrosation reactions.** They are used quite rarely, for example, to identify phenobarbital, phenacetin, dicain, although these drugs are almost never used in medical practice.
2) **Diazotization and azo-compound reactions**. These reactions are used to open primary amines. Diazotized amine combines with beta-naphthol, giving a characteristic red or orange color.

3) **Halogenation reactions**. They are used to open aliphatic double bonds - when bromine water is added, bromine is added to the double bond and the solution becomes discolored. A characteristic reaction of aniline and phenol - when they are treated with bromine water, a tribromine derivative is formed, which precipitates.
4) **Condensation reactions of carbonyl compounds**. The reaction consists in the condensation of aldehydes and ketones with primary amines, hydroxylamine, hydrazines and semicarbazide:

The formed azomethines (or Schiff bases) have a characteristic yellow color. The reaction is used to identify, for example, sulfonamides. As an aldehyde, 4-dimethylaminobenzaldehyde is used.

5) **Oxidative condensation reactions**. The process of oxidative splitting and formation of azomethine dye is the basis of the Ninhydrin reaction. This reaction is widely used for the discovery and photocolorimetric determination of α- and β-amino acids, in the presence of which an intense dark blue color appears. It is due to the formation of a substituted salt of diketohydrindylidenediketohydramine - a product of condensation of excess ninhydrin and reduced ninhydrin with ammonia released during the oxidation of the tested amino acid:



For the discovery of phenols, the reaction of the formation of dyes with triarylmethane is used. Thus, phenols interact with formaldehyde to form dyes. Similar reactions include the interaction of resorcinol with phthalic anhydride, which leads to the formation of a fluorescent dye - fluorescein.

Many other reactions are also used.

Reactions with the formation of salts and complexes are of particular interest. Inorganic salts of iron (III), copper (II), silver, cobalt, mercury (II) and others for testing the authenticity of organic compounds: carboxylic acids, including amino acids, barbituric acid derivatives, phenols, sulfonamides, some alkaloids. The formation of salts and complex compounds follows a general scheme:

$$R\text{-}COOH + MX \rightarrow R\text{-}COOM + HX$$

Complex formation of amines proceeds similarly:

$$R\text{-}NH_2 + X \rightarrow R\text{-}NH_2 \cdot X$$

One of the most common reagents in pharmaceutical analysis is a solution of iron (III) chloride. When interacting with phenols, it forms a colored solution of phenoxide, they are colored blue or purple. This reaction is used to discover phenol or resorcinol. However, meta-substituted phenols do not form colored compounds (thymol).

Copper salts form complex compounds with sulfonamides, cobalt salts with barbiturates. Many of these reactions are also used for quantitative determination.

General requirements for purity tests.

Another equally important indicator of the quality of a medicinal product is purity. All medicines, regardless of the method of obtaining them, feel clean. At the same time, the content of impurities in the drug is determined. Conventionally, impurities can be divided into two groups: the first, impurities that have a pharmacological effect on the body; the second, impurities that indicate the degree of purification of the substance. The latter do not affect the quality of the drug, but in larger quantities reduce its dose and, accordingly, reduce the activity of the drug. Therefore, all pharmacopoeias set certain limits for these impurities in medicinal preparations. Thus, the main criterion for the good quality of the drug is the absence

of impurities, which is impossible by its nature. The concept of absence of impurities is related to the limit of detection of certain methods.

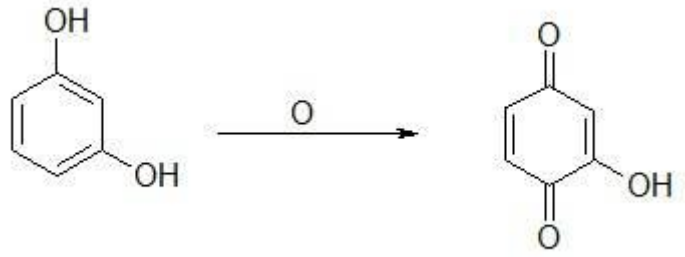
The physical and chemical properties of substances and their solutions give a general idea of the presence of impurities in medicinal preparations and regulate their suitability for use. Therefore, in order to assess the quality, along with establishing the authenticity and determining the quantitative content, a series of physical and chemical tests are conducted that confirm the degree of its purity:

Transparency and degree of turbidity. It is carried out by comparison with a turbidity standard, and transparency is determined by comparison with a solvent.

Color. A change in the degree of color may be due to:

a) the presence of an extraneous colored admixture;

b) chemical change of the substance itself (oxidation, interaction with Me^{+3} and $^{+2}$ or other chemical processes that occur with the formation of colored products. For example:



Resorcinol turns yellow during storage due to oxidation under the influence of air oxygen with the formation of quinones. In the presence of, for example, iron salts, salicylic acid acquires a purple color due to the formation of iron salicylates.

The chroma is evaluated based on the results of the comparison of the main experience with the chroma standards, and the colorlessness is determined by comparison with the solvent.

Very often, a test based on their interaction with concentrated sulfuric acid, which can act as an oxidizing or dehydrating agent, is used to detect impurities of organic substances. As a result of such reactions, colored products are formed. The intensity of the obtained color should not exceed the corresponding standard of color.

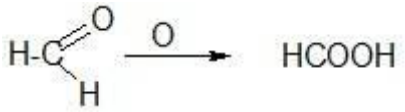
Determining the degree of whiteness of powdered medicinal products - a physical method. The degree of whiteness (hue) of solid medicinal substances can be estimated by various instrumental methods based on the spectral characteristics of the light reflected from the sample. For this, reflection coefficients are used when the sample is illuminated with white light obtained from a special source, with a spectral distribution or passed through light filters (with a transmission wavelength of 614 nm (red) or 439 nm (blue)). It is also possible to measure the reflectance of light transmitted through a green light filter.

A more accurate assessment of the whiteness of medicinal substances can be carried out using reflection spectrophotometers. The value of the degree of whiteness and the degree of brightness are characteristics of the quality of whites and whites with shades of medicinal substances. Their permissible limits are regulated in private articles.

Determination of acidity, alkalinity, pH.

The change of these indicators is conditioned:

a) by changing the chemical structure of the medicinal substance itself:



b) the interaction of the drug with the container, for example, exceeding the permissible limits of alkalinity in the cocaine solution due to glass leaching;

c) absorption of gaseous products (CO_2, NH_3) from the atmosphere.

Determination of the quality of medicinal products based on these indicators is carried out in several ways:

a) by changing the color of the indicator, for example, the admixture of mineral acids in boric acid is determined by methyl red, which does not change its color under the action of weak boric acid, but turns pink in the presence of mineral acid admixtures.

b) titrimetric method - for example, to establish the permissible level of the content of hydroiodic acid, which is formed when storing a 10% alcoholic solution of I_2, carry out titration with alkali (no more than 0.3 ml of 0.1 mol / l of NaOH by

volume of titrant). (Formaldehyde solution - titrate with alkali in the presence of phenolphthalein).

In some cases, SPh sets the volume of titrant to determine acidity or alkalinity.

Sometimes two titrated solutions are sequentially added: first the acid and then the alkali.

c) by determining the value of the pH - for a number of medicinal products (and necessarily for all injection solutions) according to the ARD, it is supposed to determine the pH values.

Techniques for preparation of substances in the study of acidity, alkalinity, pH.

1. Preparation of a solution of a certain concentration specified in the ARD (for substances soluble in water).
2. For those insoluble in water - prepare a suspension of a certain concentration and determine the acid-base properties of the filtrate.
3. For liquid preparations that do not mix with water, shaking with water is carried out, then the aqueous layer is separated and its acid-base properties are determined.
4. For insoluble solid and liquid substances, the determination can be carried out directly in suspension (ZnO).

The approximate pH value (up to 0.3 units) can be determined using indicator paper or a universal indicator.

The colorimetric method is based on the property of indicators to change their color at certain intervals of medium pH values. To carry out the tests, buffer solutions with a constant concentration of hydrogen ions are used, which differ from each other by a pH equal to 0.2. The same amount (2-3 drops) of indicator is added to a series of such solutions and to the tested solution. The pH value of the medium of the tested solution is judged by the coincidence of the color with one of the buffer solutions.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;

- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Subject, problems of pharmaceutical chemistry.
2. Sources and causes of contamination of medicines.
3. To characterize the general remarks that must be followed when determining impurities in medicinal preparations.
4. Give reactions for the determination of chlorides, sulfates, calcium, aluminum, ammonium, iron (II), zinc, and arsenic ions in medicinal products according to SPhU.

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Basic:

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Additional:

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Lecture No. 4

Topic: Methods of quantitative analysis of medicinal products.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component medicinal preparations. Therefore, in order to deepen theoretical knowledge and improve practical skills in specific sections of pharmaceutical analysis, this program provides for a more detailed study of the methods of drug analysis based on the pharmacopoeial articles of the State Pharmacopoeia of Ukraine and other regulatory documentation. In order to consolidate theoretical knowledge and practical skills, a more in-depth study of the analysis of drugs by analytical-functional groups based on SPhU is provided, which is necessary for mastering the methods of express analysis of drugs. Along with titrimetric methods of quantitative analysis of medicinal products, the program provides a deeper study of instrumental

methods of analysis, which are increasingly used in the practice of quality control of medicinal products.

Goal: to familiarize with the subject, content and history of the development of pharmaceutical chemistry, the concept of building the State Pharmacopoeia of Ukraine. Familiarize with the sources, means of extraction of medicinal substances, causes of contamination of medicinal products, as well as learn to determine the permissible limits of impurities in them.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Pharmaceutical analysis.
2. Gravimetric (weight) method.
3. Titrimetric methods.
4. Concentration of solutions.
5. Acid-base and redox titration.

Content of lecture material (lecture text):

1. **Pharmaceutical analysis, depending on the tasks, includes various aspects of drug quality control.**
   1) Pharmacopoeial analysis;
   2) Step-by-step control of the production of medicinal products;
   3) Analysis of individually manufactured medicinal products.

The main and most essential is the pharmacopoeial analysis, that is, the analysis of medicinal products for compliance with the standard - a pharmacopoeial article or another ND and, thus, confirmation of its suitability. Hence the requirements for high specificity, selectivity, accuracy and reliability of the analysis.

A conclusion about the quality of the medicinal product can be made only on the basis of the analysis of the sample (statistically reliable sample). The order of sample selection is specified either in a private article or in a general article of GF X1 edition. (Issue 2) p. 15. In order to test medicinal products for compliance with

the requirements of regulatory and technical documentation, a multi-stage selection of samples (samples) is carried out. In multi-stage sampling, the sample (sample) is formed by steps and the products in each stage are randomly selected in proportional quantities from the units selected in the previous stage. The number of steps is determined by the type of packaging.

1) degree: selection of packaging units (boxes, boxes, etc.);
2) degree: selection of packaging units in a packaging container (boxes, vials, cans, etc.);
3) degree: selection of products in primary packaging (ampoules, vials, contour packages, etc.).

A formula is used to calculate the selection of the number of products at each stage:

$$0{,}4\sqrt{n}$$

where n is the number of packaging units of this step.

2. Gravimetric (weight) method.

The method is used mainly for inorganic compounds, rarely for the quantitative determination of some alkaloids in the form of picrates or silicon tungstates and vitamins (for example, thiamine bromide and chloride).

3. Titrimetric methods.

Titrimetric (volumetric) methods of analysis are based on the exact measurement of the amount of reagent (titrant) spent on a reaction with a certain substance. During titration, the titrant is added in small portions to a solution that contains a precisely known mass (suspension) of the substance to be determined. After adding each new portion of the titrant in the system described by the chemical reaction equation, equilibrium is established:

$$nA + mB \rightarrow AnBm$$

where A is the analyzed substance;

B-titrant

n, m - stoichiometric coefficients.

As the reaction proceeds, the equilibrium concentrations of the determined substance and titrant decrease, and the equilibrium concentrations of the reaction products increase. When the amount of titrant equivalent to the amount of titrant substance is consumed, the reaction will end. This point is called the equivalence point. In practice, the end point of the titration (reaction) is fixed. Which with a certain shade of approximation corresponds to the point of equivalence. In titrimetric methods of analysis, it is fixed visually by a noticeable analytical effect (changes in the color of the solution, precipitation), which is caused by any of the starting compounds, reaction products or specially added substances - indicators. In physicochemical methods of analysis, the end point of the titration, as we have already said. Determined by some factor.

Reactions used in titrimetric must meet the following basic requirements: - the reaction must proceed quantitatively, that is, the equilibrium constant of the reaction must be sufficiently high; - the reaction must proceed at a high speed; - the reaction should not be complicated by side processes; - there must be a way to determine the end point of the titration.

If the reaction does not satisfy at least one of these requirements, it cannot be used in the titrimetric analysis.

In titrimetric, three methods of titration are distinguished: direct, reverse and indirect (substitute).

In direct titration, the determined substance A directly reacts with the titrant B:

$$A + B \rightarrow C$$

If such a reaction is impossible for any reason (there is no chemical interaction between the determined substance and the titrant, the reaction proceeds at an insufficiently high speed, there is no reliable way to determine the end of the titration, etc.), then the reverse or indirect method is used.

In reverse titration, an excess of titrant B is added to the analyte, the unreacted residue of which is titrated with titrant D:

$$A + B \rightarrow C$$

excess

$$B + D \rightarrow E$$

In INDIRECT (substitutive) titration with titrant B, the product of the intermediate reaction G reacts, the substance A is determined with the auxiliary reagent F:

$$A + F \rightarrow G$$

$$G + B \rightarrow K$$

For titration in titrimetric methods, solutions with a precisely known concentration are used, called titrants or titrate solution. The concentration of the solution to be titrated is denoted by the term's molar, NORMAL, TITR or TITR PO determined by the substance.

4. Concentration of solutions.

Molar concentration - is the number of moles of solute contained in one liter of solution. It is calculated as the ratio of the amount of dissolved substance to the volume of the solution in liters (dimension mol/l). A mole is the amount of a substance containing as many specified structural units as there are atoms in 0.012 kg (12 g) of the carbon-12 isotope.

Elementary particles, as well as ions, atoms, molecules or their particles can be selected as specified structural units. In analytical chemistry, the size of these particles is chosen so that each of them is responsible for the transfer of one electron in a redox reaction or is equivalent to one hydrogen ion in an acid-base reaction. The term "conditional fraction" is used to denote such a fraction of an ion, atom, or molecule. The conditional share is otherwise called the equivalent. The molar concentration of the titrated solutions is adopted by the SPh X1 edition in accordance with the IUPAC recommendation.

In analytical practice, along with the molar concentration of solutions, the normal concentration of the solution is also used.

NORMAL CONCENTRATION of the solution - is the number of moles of solute equivalent contained in one liter of solution. A solution containing 1 mole of equivalents of substances A in 1 liter is called a normal solution of this substance and is denoted - 1 n.

TITR it is the mass of solute contained in 1 milliliter of solution, expressed in grams. The titer is calculated as the ratio of the mass of the dissolved substance to the volume of the solution (dimension g / ml).

Titer of the titrant for the determined substance - it is expressed in grams, the mass of the substance is determined, equivalent to one milliliter of this titrant (dimension g / ml). The titer of the determined substance (TV / A) is calculated according to the formula:

$$T \rightarrow N \cdot E / 1000,$$

Where N is the normal (molar) titrant concentration; E-molar mass of the equivalent is determined by the substance.

The molar mass of the substance equivalent denotes the mass of one mole of the equivalent of this substance, which is equal to the product of the equivalence factor (*f*eq) by the molar mass of the substance.

Equivalence factor - this is a number indicating what fraction of a molecule of a substance is equivalent to one hydrogen ion in a given acid-base reaction or one electron in a given oxidation-reduction reaction.

For example, during the titration of sodium carbonate with a titrated solution of hydrochloric acid, it follows from the chemical reaction equation that feq (Na_2CO_3) = 1/2

$$Na_2CO_3 + 2HCl \rightarrow 2NaCl + CO_2 + H_2O$$

Calculation of the quantitative content of the analyzed individual substance in % (X) is carried out according to the formulas:

1. Direct and indirect (substitute titration):

$$X = \frac{V \cdot K \cdot T \cdot 100 \cdot W}{a \cdot V_a}$$

where V is the volume of titrant used for titration, ml;

K-correction coefficient to titrate the solution (titrant);

T-titre of the titrant for which the substance is determined

a-mass is determined by the medicinal substance taken for analysis (hanging), g;

W-volume of the measuring flask, ml;

Va - the volume of the solution taken for titration (volume of the pipette), ml.

2. REVERSE titration

$$X = \frac{(V_1 \cdot K_1 - V_2 \cdot K_2) \cdot T \cdot 100 \cdot W}{a \cdot V_a}$$

where V1 is the volume of titrant taken in excess, ml;

V2 - volume of titrant used for titration of the excess of the first titrant, ml;

K1, K2 - correction coefficients of titrated solutions.

If a control experiment (for the titrant and for the indicator) is carried out during the quantitative determination, then formulas 2 and 3 take the form:

1. Direct and indirect titration

$$X = \frac{(V_o - V_k) \cdot K \cdot T \cdot 100 \cdot W}{a \cdot V_a} \quad (4)$$

2. Back titration

$$X = \frac{(V_k - V_o) \cdot K \cdot T \cdot 100 \cdot W}{a \cdot V_a} \quad (5)$$

where Vo is the volume of titrant used for titration in the main experiment, ml;

Vk is the volume of titrant used for titration in the control experiment, ml.

5. Acid-base and redox titration.

Acidimetry.

In an aqueous environment, the reaction between an acid and a base can be represented by the equation:

$$H_3O^+ + OH^- \rightarrow 2H_2O$$

Strong acids (hydrochloric acid, sulfuric acid) are used as titrants - Acidimetry; or strong bases (caustic sodium, caustic alkali) - alkalimetry.

Alkalimetry is used for the quantitative determination of medicinal substances, which are:

- inorganic and organic acids; - salts of organic bases (hydrochlorides, nitrates, hydrogen phosphate, lactates, hydrotartrate, etc.).

Acidimetry is used for determination: - organic bases that exhibit basic properties in aqueous or alcoholic media; - sodium salts of weak inorganic and organic acids.

One of the used variants of acid-base titration is the combination of a neutralization reaction with preliminary esterification or hydrolysis. And some medicinal substances, derivatives of alcohols or phenols are acetylated with acetic anhydride (a complex ester is formed). Excess acetic anhydride is converted into acetic acid and titrated with alkali. The possibility of using the acid-base titration method for the analysis of medicinal substances is determined by the dissociation constant of the titrated substance and its concentration in the solution.

The magnitude of the titration jump on the titration curve depends significantly on the dissociation constant. When determining medicinal substances by the method of neutralization, Ka and Kv of acids and bases should be at least 10-7. Thus, when titrating 0.1 mol/l solutions of strong acids and alkalis, the titration jump is about 6 pH units; if Ka (Kv) = 10-3, then 3-4 pH units; at Ka (Kv) = 10^{-5}, 2-2.5 pH units; at Ka (Kv) = 10^{-9}-10^{-10} there is no titration jump and determination of the end point of the titration becomes practically impossible.

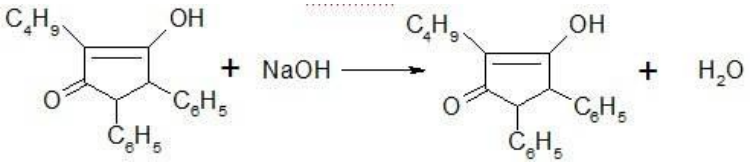
When titrating a 0.1 mol/l solution of a strong acid with an alkali solution and vice versa, the titration jump is about 6 pH units, at a concentration of 0.01 mol/l - 3.4 pH units, respectively; at 0.001 mol/l - 1.4 pH units; at 0.0001 mol/l there is no titration jump.

Mixed solvents are used to enhance the acid-base properties of certain substances and when the medicinal substance is poorly soluble in water (for example, titration of sulfonamide preparations with a dissociation constant of 10-7-10-8 (norsulfasol).

Alkalimetry (direct titration):

butadione

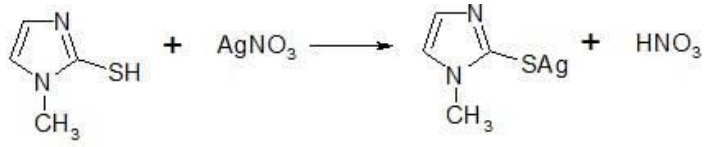
Phenolphthalein indicator. Titrant 0.1 M; 0.05 M; 0.02 M solutions of sodium hydroxide



The pH of the color transition of phenolphthalein is 8.2-10. Alkalimetry (substitute titration)

Mercazolil

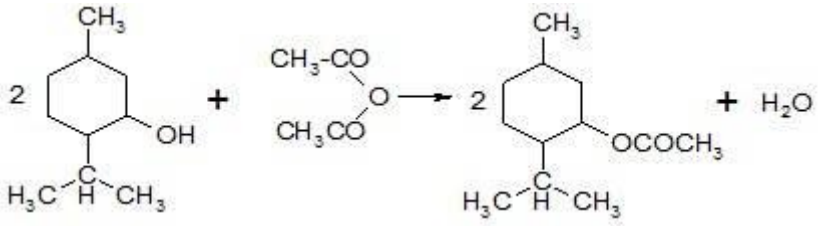
Bromothymol blue indicator. Titrant 0.1m sodium hydroxide solution

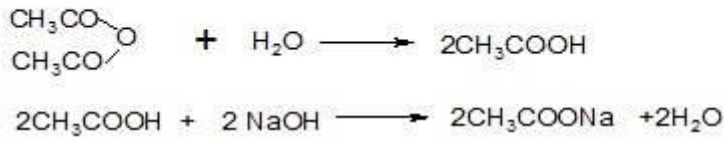


The pH of the transition of the color of the indicator bromothymol blue from yellow to blue is 6.0-7.6. Alkalimetry (back titration)

Menthol

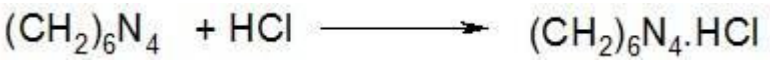
Phenolphthalein indicator. Titrant 0.5 M sodium hydroxide solution.





Acidimetry (direct titration)

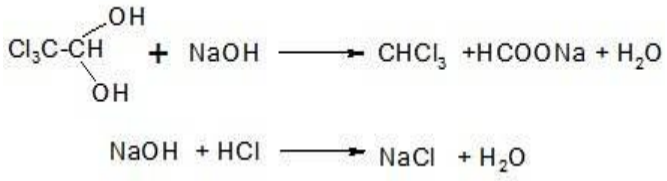
Hexamethylenetetramine. Indicator mixed methyl red and methylene blue. Titrant 0.5 M hydrochloric acid solution



The pH of the transition of methyl red color from red to orange is 4.2-6.2

Acidimetry (back titration)

Chloral hydrate. Indicator phenolphthalein. Titrant 0.1 M solution of hydrochloric acid



Titration in non-aqueous solvents.

The method of acid-base titration in non-aqueous solvents is used for quantitative determination of weak acids (barbiturates, sulfonamides), weak bases (caffeine, reserpine). Salts of organic bases. This method makes it possible to determine many medicinal substances that, when titrated in aqueous solutions, do not have a clearly defined end point of the titration. Under the influence of these solvents, the acid-base properties of various substances change. Depending on the solvent, the same substance can become an acid, a base, an amphoteric or neutral compound, a strong or weak electrolyte. The strength or weakness of an acid or base is determined by the nature of its interaction with the solvent. In the acid-base process, all solvents are divided into two large groups: aprotic and protolytic.

Aprotic solvents - these are chemical compounds of a neutral nature, the molecules of which are not ionized and are not able to either give or add a proton. Aprotic solvents do not interact with the substance dissolved in them. Such solvents include hydrocarbons (benzene, toluene, hexane) and their halogen derivatives. Aprotic solvents are often added to the solution to be titrated to suppress the process of solvolysis of neutralization products, which contributes to a clearer establishment of the end point of the titration. **Protolytic solvents -** these are chemical compounds whose molecules are capable of donating or attaching protons. They participate in the acid-base process. Proto-lytic solvents, in turn, can be divided into three groups:

Amphiprotonic - amphoteric, capable of both giving and attaching a proton. Water, alcohol.

Protogenome or acidic solvents. Substances in which the ability to give up a proton significantly exceeds the ability to attach it. Acetic acid, formic acid. Protogenic solvents enhance the main properties of chemical compounds.

Protophilic or basic solvents. Liquid ammonia, pyridine, DMF, etc. Protophilic solvents enhance the acidic properties of weak acids and amphoteric compounds.

A typical example is the titration of potassium acetate in anhydrous acetic acid with perchloric acid.

Titration in a protophilic solvent is carried out with potassium or sodium methylate in pyridine.

Methods of redox titration.

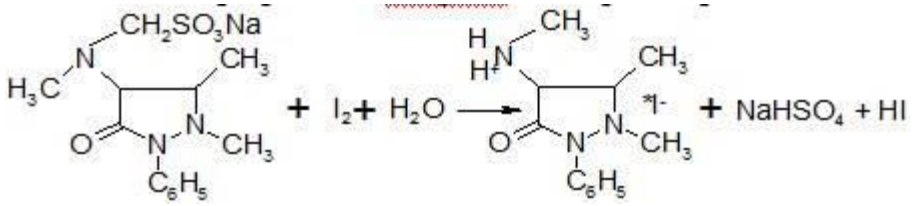
The basis of these methods is the use of oxidation-reduction reactions. In the process of titration, there is a change in the redox potentials of systems interacting with each other. If the potential difference is large enough (0.3-0.4 V), then the oxidation-reduction process proceeds to the end (so it is possible to use direct titration). The end points of the titration are set using special indicators (ferroin, diphenylamine), dissolved starch - when titrated with iodine, the indicators irreversibly lose their color in an excess of oxidant (methyl orange), by the indicator-free method in permanganatometry and the electrochemical method.

The following methods are used in pharmaceutical chemistry:

1. Iodimetry
2. Iodometry.
3. Iodine chlorometry.
4. Bromatometry.
5. Permanganatometry.
6. Cerimetry direct titration.

ANALGIN

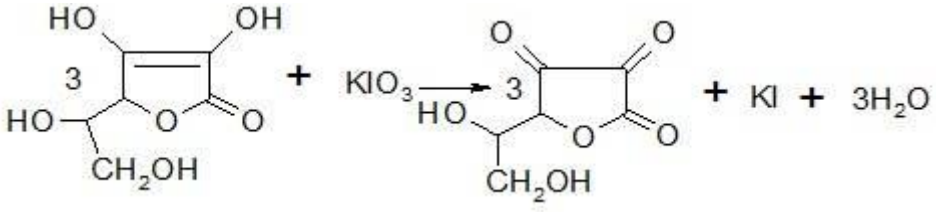
Starch indicator. Titrant 0.1 M iodine solution



Iodometry. The method is based on the use of a potassium iodate solution as a titrant, which is a strong oxidizer in an acidic environment. The method is based on a chemical reaction:

$$IO_3^- + 6H^+ + 6e \rightarrow I^- + 3H_2O$$

It follows from this equation that when preparing a titration solution of potassium iodate, the value of the molar mass of the equivalent, equal to 1/6 of the molar mass of potassium iodate, is taken into account. The iodatometric method is recommended for the quantitative determination of ascorbic acid:



At the end of the titration point, an excess titrate of the potassium iodate solution leads to the oxidation of the iodide ion in an acidic medium, and the formed iodine turns the starch blue.

Iodine chlorometry. A solution of iodine monochloride obtained from iodine and potassium iodate in an acidic environment is used.

Bromatometry. A solution of potassium bromate is used as a titrant.

Permanganatometry. The method is based on the oxygenation of substances determined by permanganate ions. Titration is carried out in a strongly acidic environment.

Cerimetry. Cerium sulfate (IV) is used as a titrant.

Precipitation titration. Argentometric titration.

Argentometric titration is based on precipitation reactions of halides with silver nitrate solution (titrant). The end point of the titration is set using INDICATORS:

1. Image of painted precipitation;

2. Image colored complexes;

3. Adsorption indicators;

4. Potentiometric

Inorganic substances containing halogens are determined by this method. As indicators, for example, potassium chromate is used, which forms a brick-red precipitate of silver chromate at the end of the titration. The solubility constant of silver chromate is significantly higher. Then chloride, therefore, an insoluble precipitate of silver chloride is first formed.

Complexometric titration.

The method of complexometric titration is based on the reaction of the formation of intracomplex compounds of metal ions with special complex-forming reagents called complexons.

Nitritometry. Method of quantitative determination of primary aromatic amines. It is based on the diazotization reaction. The end point of the titration in nitritometry is set:

With the help of internal indicators: tropeolin 00, neutral red. With the help of external indicators - iodine-starch paper.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Describe the methods of quantitative analysis of drugs.
2. The essence of the gravimetry method in the quantitative analysis of drugs.
3. Method of quantitative determination of analgin?
4. Which method according to SPhU can be used for the quantitative determination of drugs with a primary aromatic amino group?

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8. Europian Pharmacopoeia 10th. 2019. – 4255 p.

Additional:

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5. Фармацевтична хімія. Загальна та спеціальна фармацевтична хімія. Лікарські засоби неорганічної природи: лабораторно-практичні заняття. Навчальний посібник / Л.Г. Мішина. – Вінниця: ПП «ТД «Едельвейс і К»», 2010. – 384 с.

Lecture No. 5

Topic: Express analysis of medicines. Modern trends in the development of pharmaceutical analysis.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component medicinal preparations. Therefore, in order to deepen theoretical knowledge and improve practical skills in specific sections of pharmaceutical analysis, this program provides for a more detailed study of the methods of drug analysis based on the pharmacopoeial articles of the State Pharmacopoeia of Ukraine and other regulatory documentation.

Goal: to familiarize with modern trends in the development of pharmaceutical analysis, the concept of building the State Pharmacopoeia of Ukraine.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Internal pharmacy control of medicines.
2. Express analysis.

Content of lecture material (lecture text):

1. Internal pharmacy control of medicinal products.

Quality control. Medicines manufactured in pharmacies are currently controlled in accordance with the requirements regulated by the State Pharmacopoeia and current regulatory documents. These requirements apply to all pharmacies, including homeopathic ones, regardless of ownership and departmental affiliation. The production of pharmaceuticals according to individual prescriptions,

in the form of an in-house preparation, as well as concentrates and semi-finished products, is considered completed only after assessing the quality of their production and the correctness of the design.

Regardless of the source of receipt, medicinal products are subject to acceptance control. Medicinal products manufactured in pharmacies according to individual prescriptions or requirements of medical institutions are subject to internal pharmacy control: written, organoleptic and control during vacation - mandatory; survey and physical - selective, as well as chemical control.

The pharmacist-analyst is required to have all types of internal pharmacy control. Appointed to the position for the first time, the pharmacist-analyst undergoes a mandatory internship in the territorial control and analytical laboratory. A pharmacist-analyst, appointed to the position to perform quality control of homeopathic medicinal products manufactured in a pharmacy, undergoes an internship at faculties of advanced training of pharmacists who have an educational license.

A specially equipped workplace is set aside for chemical quality control of drugs manufactured in the pharmacy. Typical equipment, devices and reagents are placed on it. The pharmacist-analyst is provided with regulatory documents and reference literature.

The results obtained during the quality control of medicinal products are recorded in journals that are kept in the pharmacy throughout the year. Once a year, a report on the work on the quality control of drugs manufactured in the pharmacy is sent to the territorial control and analytical laboratory or the drug quality control center.

Let's consider all types of internal pharmacy control in more detail.

Acceptance control. Such control is carried out in order to prevent the entry of low-quality medicines into the pharmacy. Acceptance control consists in checking incoming drugs for compliance with the requirements according to the indicators "Description", "Packaging", "Marking"; in checking the correctness of settlement documents (invoices), as well as the presence of quality certificates (passports) of

the manufacturer and other documents confirming the quality of drugs, in accordance with current orders and instructions.

Control of the "Description" indicator includes checking the appearance and smell of drugs. In case of doubt as to the quality of drugs, the samples are sent to the territorial control and analytical laboratory.

When checking according to the "Packaging" indicator, special attention is paid to its integrity and compliance with the physical and chemical properties of the drug.

When monitoring the "Marking" indicator, it is necessary to check whether the name of the manufacturing enterprise or the enterprise that carried out the packaging is on the labels. The name of the drug, its mass (volume), concentration or composition, batch number, analysis number, expiration date and packaging date are also checked. For cardiac glycosides, the number of units of action in 1 g of medicinal plant material or in 1 ml of liquid medicinal product should be indicated.

In accordance with this Agreement, "Suitable for injections" on the packaging labels of drugs intended for the manufacture of injection or infusion solutions. Packages with poisonous and narcotic drugs must be designed in accordance with the requirements of current orders and instructions.

Written control. When producing medicine form according to the prescriptions and requirements of medical institutions, passports of written control are filled out. The passport must contain; date of manufacture, number of the prescription (hospital number, name of the department), name of the medicines taken and their quantity, number of doses, signatures produced, packaged and checked the medicines. In the case of production of medicines, the intern puts the signature of the person responsible for production practice. Keeping passports of written control, if medicines are produced and issued by the same person, is also mandatory. In this case, the passport is filled in during the production of the medicines.

All calculations must be made before the production of the medicines and recorded on the back of the passport. The passport is filled out immediately after the production of the medicines by memory in the Latin language in accordance with

the sequence of technological operations. When filling out a passport for homeopathic medicines, the homeopathic names of consecutively taken medicines are indicated.

In the case of using semi-finished products and concentrates, their composition, concentration, taken volume or weight are indicated in the passport. When manufacturing powders, suppositories, and pills, the total weight, quantity, and weight of individual doses are indicated. The total mass of pills or suppositories, the concentration and volume (or mass) of isotonic and stabilizing substances added to eye drops, solutions for injections and infusions must be indicated not only in passports, but also on prescriptions.

The passport should indicate the calculation formulas and the water absorption coefficients used for medicinal plant raw materials, the coefficients of the increase in the volume of solutions when dissolving the drug, and the substitution coefficients in the manufacture of suppositories.

Passports of written control are kept in the pharmacy for two months.

Manufactured medicines, prescriptions and completed passports are submitted for verification to the pharmacist, who performs control functions during the manufacture and dispensing of medicines - the pharmacist-technologist. The control consists in checking the correspondence of the entries in the passport to the written control of the prescription, the correctness of the calculations. If the pharmacist-analyst has carried out a full chemical quality control of the medicine, then the analysis number and the signature of the pharmacist-analyst are affixed to the passport.

During the production of concentrates, semi-finished products, internal pharmacy preparation and packaging of medicines, all records are made in the accounting books of laboratory and packaging work.

Questionnaire control. This type of control is applied selectively. It is carried out after the production of no more than five dosage forms by a pharmacist.

When conducting a survey control, the pharmacist-technologist names the substance included in the MF first, and in the MF with a complex composition, its

quantity is also indicated. After that, the pharmacist names all the drugs taken and their quantities. When using semi-finished products (concentrates), the pharmacist also names their composition and concentration.

Organoleptic control. MF is checked according to the following indicators: appearance ("Description"), smell, uniformity, absence of mechanical inclusions (in liquid MF). LFs intended for children are selectively tested for taste.

The homogeneity of powders, homeopathic triturations, ointments, pills, suppositories is checked before dividing the mass into doses in accordance with the requirements of the current MF. The check is carried out selectively at each pharmacist during the working day, taking into account the types of MF.

The results of organoleptic control are recorded in a journal using a special form.

Physical control. Physical control consists in checking the total mass or volume of the MF, the number and mass of individual doses (at least three doses) included in this MF. When checking the MF, the quality of clogging is also controlled.

When conducting physical control, the following are subject to inspection: each series of packaging and internal pharmacy preparations in the amount of at least three packages (including packaging of industrial products and homeopathic medicines);

MF, manufactured according to individual recipes (requirements), selectively during the working day, taking into account all types of MF, but not less than 3% of the number of MF produced per day;

Each series of MF requiring sterilization, after packaging before their sterilization, in the amount of at least five vials (bottles);

The number of homeopathic granules in a certain mass of the sample in accordance with the requirements of current regulatory documents.

The results of physical control are registered in the journal using a special form.

Chemical control. Chemical control consists in the assessment of the quality of the manufacture of medicinal products according to the indicators "Authenticity", "Testing for purity and permissible limits of impurities" (qualitative analysis) and "Quantitative determination" (quantitative analysis) of medicinal products included in its composition.

They must undergo qualitative analysis:

- purified water (it is necessary to send it quarterly to the territorial control and analytical laboratory for a complete chemical analysis);
- water for injections every day (from each cylinder, and when water is supplied through the pipeline at each workplace) for the absence of chlorides, sulfates and calcium salts;
- water intended for the production of sterile solutions, in addition to the above-mentioned tests, must be tested for the absence of reducing substances, ammonium salts and carbon dioxide in accordance with the requirements of the current HF.

All medicinal products, concentrates and semi-finished products (including homeopathic tinctures, solutions, dilutions) coming from the storage rooms to the assistant's room are subject to chemical control.

Concentrates, semi-finished products and liquid pharmaceuticals in burette units and in dipsticks with pipettes are subject to chemical control in the assistant room when filling.

A selective high-quality chemical analysis is carried out for LFs manufactured according to individual prescriptions and requirements of medical institutions (for each pharmacist during the working day, but not less than 10% of the total number of MFs produced). The examiner should be exposed to various types of MF. Special attention is paid to MF:

- for children;
- used in intramural practice;
- contain narcotic and poisonous substances;

- homeopathic dilutions of the fourth decimal dilution containing poisonous and potent biologically active substances or poisonous and potent inorganic and organic compounds.

The results of the qualitative analysis are recorded in journals using special forms.

All solutions for injections and infusions are subject to mandatory full chemical control (qualitative and quantitative analysis) before sterilization, including determination of the pH value, isotonizing and stabilizing substances. Solutions for injections and infusions are checked for pH value, identity and quantitative content of active substances after sterilization. Stabilizers in these solutions are checked after sterilization in the cases stipulated by current regulations. One bottle of the solution of each series is selected for full chemical control after sterilization. Sterile solutions for external use (ophthalmic solutions for irrigation, solutions for the treatment of burn surfaces and open wounds, for intravaginal administration, etc.) are subject to control.

Eye drops and ointments containing narcotic and poisonous substances are subject to control. Stabilizing substances and substances that ensure the physiological value of osmotic pressure (isotonizing substances) in eye drops are determined before sterilization.

All dosage forms for newborn children are subject to mandatory full chemical control. In the absence of methods of quantitative analysis of MF for newborn children, these MF are analyzed qualitatively.

As an exception, MF for newborns with complex composition, which do not have methods of qualitative and quantitative analysis, are made under the supervision of a pharmacist-analyst or a pharmacist-technologist.

Atropine sulfate and hydrochloric acid solutions (for internal use), silver nitrate solutions, all concentrates, semi-finished products, triturations, including liquid homeopathic dilutions of inorganic and organic drugs and their triturations up to the third decimal dilution, are subjected to quantitative and qualitative analysis. As an exception, the production of homeopathic medicinal products that do not have

methods of qualitative and quantitative analysis is carried out under the supervision of a pharmacist-analyst or a pharmacist-technologist.

Full chemical control is carried out for each series of intra-pharmacy drug preparations; stabilizers used in the manufacture of solutions for injections; buffer solutions used in the manufacture of eye drops.

Ethyl alcohol is subjected to mandatory chemical control, determining its concentration when diluted in a pharmacy or when taken from a warehouse, as well as in water-alcohol homeopathic solutions and drops. Homeopathic granules are checked for disintegration (each batch).

Selective qualitative and quantitative analysis (full chemical control) of MF, manufactured in a pharmacy according to individual prescriptions or requirements of medical institutions in the amount of at least three during work in one shift, taking into account all types of MF, are subjected. Special attention is paid to MF for children; means used in ophthalmic practice, as well as containing narcotic and poisonous substances; solutions for therapeutic enemas.

The results of full chemical control are recorded in the journal using a special form.

Special requirements for quality control of sterile solutions. Production and quality control of sterile solutions in pharmacies is carried out in accordance with the requirements of the current GF, "Methodical instructions for the production of sterile solutions in pharmacies", current regulatory documents, orders and instructions.

Sterile solutions of pharmacy production include: solutions for injections and infusions, eye drops, ophthalmic solutions for irrigation, all solutions for newborn children, separate solutions for external use.

The manufacture of sterile solutions is prohibited in the absence of data on the chemical compatibility of medicinal substances included in them, technology and mode of sterilization, as well as in the absence of analysis methods for their complete chemical control.

The preparation of auxiliary, sealing materials, dishes, means of small mechanization must be carried out in accordance with the requirements of current regulatory documents, orders and instructions.

Purified water, water for injections, medicinal substances and auxiliary materials used in the manufacture of sterile solutions must meet the requirements of the current GF and other regulatory documents.

The simultaneous production of several sterile solutions containing drugs with different names or the same name, but in different concentrations, at the same workplace is strictly prohibited.

Sterilization of solutions must be carried out no later than three hours after the start of production, under the supervision of a pharmacist or pharmacist.

Microbiological control of solutions for sterility and testing for pyrogenicity of solutions for injections and infusions is carried out in accordance with the requirements of the current SPhU.

Sterile solutions must be stored in conditions that take into account the physical and chemical properties of the substances included in them, and no longer than the established expiration date. After the expiration date, sterile solutions must be removed. Repeated sterilization of solutions is not allowed. Sterile solutions are considered rejected if they do not meet the requirements of regulatory documents in terms of appearance; pH value; authenticity and quantitative content of included substances; the presence of visible mechanical inclusions; with unacceptable deviations from the nominal volume of the solution; violations fixed ™ clogging; violations of the current requirements for the registration of medical records intended for vacation.

Control at release. All drugs produced in pharmacies (including homeopathic ones) are subject to this type of control.

At the same time, compliance is checked:

- pharmaceutical packaging by the physical and chemical properties of the drugs included in them; the patient's age of the doses of poisonous, narcotic or potent drugs specified in the prescription;

- number on the prescription number on the label;
- correspondence of the patient's last name on the receipt, label and prescription or its copy;
- copies of prescriptions with prescriptions; registration of medical devices according to current requirements.

Preventive measures of internal pharmacy quality control of drugs. During the manufacture of pharmaceuticals in the pharmacy, sanitary norms and rules must be strictly observed, the anti-epidemic regime in accordance with the current regulatory documents, instructions and orders.

It is also mandatory to observe the rules for obtaining, collecting and storing purified water, water for injections; timely sanitation of the pipeline; control over the timely removal of sterile solutions, purified water, water for injections, for sterility tests in accordance with current requirements. Containers for purified water, water for injections must have a clear inscription: "Purified water", "Water for injections". A tag indicating the date of receipt, analysis numbers and signatures of examiners must be attached here. When using several reservoirs at the same time, they must be numbered.

In the pharmacy, the conditions and terms of storage of pharmaceuticals must be provided in accordance with their physico-chemical properties and the requirements of the current SPhU, current orders and instructions. In the storage facilities of the pharmacy, the following must be indicated on all drug vials: serial number of the manufacturing plant, analysis number of the control and analytical laboratory (drug quality control center), expiration date, date of filling, and signature of the person who filled the vials.

The number of units of action in 1 g of medicinal plant raw materials or in 1 ml of the drug must be indicated on the drug sticks containing cardiac glycosides. In the assistant's rooms, all barbells with medicines must be marked with: the date of completion, the signature of the person who filled out the barbell and checked the authenticity of the medicines. Higher single and daily doses should be indicated on barbells with poisonous and potent drugs. The warning inscription "For sterile

dosage forms" must be on the barbells with medicines intended for the manufacture of sterile MF.

Glass bottles with solutions, tinctures and liquid semi-finished products should be equipped with droppers. The number of drops in the specified volume should be determined by weighing and marked on the dipsticks. Filling of flasks, burettes in a burette unit, pipettes with a dropper or pipette should be carried out only after complete use of the drug and appropriate processing of pipettes (burettes).

The nomenclature of concentrates, semi-finished products, and intra-pharmacy preparations of drugs manufactured in pharmacies can only include prescriptions that contain compatible drugs, for which there are methods of analysis for chemical control and established expiration dates.

Production of in-house pharmacy preparations, the analysis of which cannot be carried out in the conditions of a pharmacy, must be carried out under the control of a pharmacist-analyst or a pharmacist-technologist. Such preparations include, in particular, drugs for external use containing tar, ichthyol, sulfur, naphthalene oil, collodion, as well as aromatic waters and homeopathic dilutions.

Peculiarities of express analysis of dosage forms in a pharmacy. The express method of chemical in-house pharmacy control provides for quick analysis of drugs and minimal consumption of research objects and reagents.

For the accelerated determination of the authenticity of substances in medicines, droplet reactions are usually used, which are performed in test tubes, on object or time glasses, in porcelain cups, on filter paper impregnated with appropriate reagents. 1 - 5 drops of liquid MF, 0.01 - 0.03 g of powders, 0.05 - 0.1 g of ointments and suppositories are used for reactions.

Quantitative express analysis in the conditions of a pharmacy involves determining the content of ingredients in pharmaceuticals using methods of volumetric titration and refractometry. When titrating, use such an amount of solvent that 2-3 ml of titrant is used. Liquid of medicines is taken with 1-, 2- or 5-ml pipettes. The mass of powders - 0.05, 0.1 or 0.2 g - is determined on manual pharmacy scales. The accuracy of mass determination is 0.01 g. The mass of ointments or

suppositories placed on pre-weighed parchment paper is determined on pharmacy scales and placed together with the paper in a test tube, flask or glass for analysis. Add water or an organic solvent, an indicator and titrate from a microburette with a division value of 0.02 ml.

2. Express analysis.

In the general unified system of state control over the quality of drugs in our country, a large role belongs to internal pharmacy quality control of drugs, which is carried out directly in pharmacies.

The percentage of ready-made medicinal forms in pharmacies is currently 85%, the remaining 15% are extemporaneous formulations that must be analyzed.

Up to 15% of drugs included in ready-made dosage forms are internal pharmacy preparations, which must also be analyzed.

Eye drops make up 20-25% of extemporaneous formulations.

A large percentage (70-80%) are injection solutions, which must be subject to not only qualitative, but also quantitative analysis.

Thus, the volume of work of analytical offices of pharmacies is extremely large and, if we take into account that in our country, all drugs manufactured in a pharmacy must be subject to various types of control, it is natural that a necessary condition for the analysis of drugs in pharmacies is the speed of analysis, in therefore, analysis methods should be simple, do not require complex equipment, the consumption of drugs and reagents should be minimal (0.5-2 ml of liquid dosage form or 0.05-0.1 g of powder), so that there is no need for repeated preparation laziness medicine These requirements are met by chemical express analysis, which takes a leading place among other types of internal pharmacy control.

Qualitative express analysis is carried out by the drop method in a small porcelain cup, on a glass slide or filter paper. The filter paper is placed on the glass, a solution of the test substance is collected in the capillary and, applying it to the filter paper, the liquid is released from it. From another, larger capillary, a corresponding reagent is released into the center of the formed stain of the substance

under investigation, as a result, a color appears on the filter paper (the product of the interaction of the substance under investigation with the reagent).

When using strong acids and alkalis, it is recommended to carry out the reactions on a glass slide, as strong acids and alkalis destroy the paper. Often, for qualitative reactions, reactive papers soaked in appropriate reagents and dried are used. For example, reactive papers impregnated with a solution of copper sulfate are used to identify sulfonamide drugs, carboxylic acids, and barbiturates.

Quantitative express analysis is performed using volumetric research methods that differ in the necessary accuracy, simplicity and speed of execution.

When analyzing powders, 0.05-0.1 g of the prepared powder mass (it is possible to divide it into doses) is weighed on manual scales with such a calculation that 1-2 ml of titration solution is used for titration.

When analyzing liquids, add 1-2 drops of the indicator to 1-2 ml of the tested solution and titrate to 0.1 or 0.05 n. appropriate titrant.

When analyzing concentrated solutions for titration of 1 ml, a relatively large amount of the solution to be titrated must be spent, therefore, concentrated solutions are pre-diluted. Mixtures in which the concentration of the tested ingredient does not exceed 4% are usually not diluted.

To quantify the ingredients in the ointment, samples are taken on parchment paper and placed in a flask, where. add 3-5 liters of alcohol or ether. After dissolving the ointment form, the resulting solution is titrated.

Processing of the analysis results depending on the problem to be solved is carried out according to several calculation formulas. For the main designations of the names of the quantities entered into the formula, the designations recommended by the I3pГ are taken, namely: V - volume in milliliters (ml); a - weight of the drug in grams (g); K-correction coefficient to the standard (titrate) solution; T - concentration of the standard solution for the given substance in g/ml; c-concentration of solutions in percent, grams or milligrams in 1 milliliter. m If it is necessary to enter some more notations into the calculation formula, then, as a rule, capital, but not capital, letters are used.

Thus, the following calculation formulas are most commonly used:

1) the content of the substance in percent (X) in the powder or ointment is calculated according to the formula:

where V is the volume of a standard (titrated) solution of a certain normality, ml; T - titer, g / ml; To - correction factor; a - mass of the drug, g;

2) the content of the substance in percent (X) in the solution is calculated according to the same formula

3) if in the process of analysis, a dilution of a part of the drug to the exact volume is used and an aliquot (exact) part of such a dilution is taken for determination, then the content of the substance in percent is calculated according to the formula:

where *V, K, T* and a have the same designations; V 1 - volume of the drug solution of the first dilution, ml; V 2 - the volume of the aliquot part of the dilution taken for determination, ml;

4) the content of the substance in grams (X) in powders, tablets or mixture is calculated according to the formula:

where a is the mass of one powder or one tablet, g; or the total volume of the mixture, ml;

5) if the reverse titration option is used in the analysis process, then the content of the substance is calculated according to the same basic formulas, but instead of indicating the standard solution through V, the difference in the form of (Vo - Ko - Vk) is introduced into the calculation formula, where: Vo - volume of the main standard solution that reacts with the specified substance, ml; V - the volume of the auxiliary standard solution, with which the excess of the main standard solution is titrated, ml; To - correction coefficient of the main standard solution; To is the correction factor of the auxiliary standard solution.

Microburette device. Microburettes (Fig. 1) proposed by the All-Union Research Institute of Pharmacy (AURIPh) are used for titration by the express method.

Work order. 1) Filling the microburette with a titrated solution and the bottom of a bent pipette with a rubber nozzle. With the faucet closed, squeeze the rubber canister with the middle finger and thumb of the left hand in such a way that the index finger closes the air hole in it and, gradually releasing the canister, fill the titration solution into the burette (about 2 / of its part). Close the faucet and turn the rubber nozzle upwards (according to the type of connected vessels), press the bead and fill the pipette with the titrated solution. There should be no air in the dropper.

If the solution is not well received in the capillary, it is advisable to squeeze the rubber can and the bead at the same time and fill the curved pipette under pressure.

2. Filling the microburette with a titrated solution and setting it to the zero mark. Bring the pipette to its initial position, open the tap and, using a rubber spray bottle, as in the first case, fill the burette with the titration solution. Close the tap, lower the titrating solution to zero with its help, and the microburette is ready for work.

For the convenience and speed of filling the burette, the following rules must be followed:

a) the rubber canister must have a small opening for air entry and exit;

b) It is NOT recommended to squeeze and release the rubber can sharply and forcefully, otherwise the liquid will get into the can;

c) do not allow the titration solution to fall into the rubber can, otherwise during titration the solution will fall into the burette and accurate titration will be impossible; when the titration solution gets into the spray bottle, it is necessary to remove the burette from the glass and by frequent compressions, should be freed from the liquid.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Organoleptic control.
2. Physical control.
3. Chemical control.
4. Special requirements for quality control of sterile solutions.

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Lecture No. 6

Topic: Principles of classification of medicinal products, their nomenclature. Structure-activity relationship in the creation and analysis of medicinal products. Creation of innovative medicines. The main ways of metabolism of medicines. Chemical reactions that underlie metabolic transformations. Phases of metabolism. Factors affecting metabolic processes. Prodrugs.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component medicinal preparations. Therefore, in order to deepen theoretical knowledge and improve practical skills in specific sections of pharmaceutical analysis, this program provides for a more detailed study of the methods of drug analysis based on the pharmacopoeial articles of the State Pharmacopoeia of Ukraine and other regulatory documentation.

Goal: familiarize with the principles of classification of medicines, their nomenclature. Must know the main ways of drug metabolism. Chemical reactions that underlie metabolic transformations. Phases of metabolism. Factors affecting metabolic processes. Structure-activity relationship in the creation and analysis of medicinal products.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Medicines.
2. The principle of combinatorial chemistry methodology.
3. Biological activity of the substance.
4. Metabolism.

Content of lecture material (lecture text):

1. Medicines.

Medicinal products (medicinal preparations, drugs, medicines) — substances or mixtures of substances used for prevention, diagnosis, treatment of diseases, prevention of pregnancy, elimination of pain; obtained from blood, blood plasma, human or animal organs and tissues, plants, minerals, chemical synthesis (pharmaceuticals, drugs or medicines) or with the use of biotechnology (vaccines).

Medicinal products are studied by pharmacology and pharmacy. Pharmaceutics is a part of pharmacy directly related to the production of drugs. Medicinal products obtained from raw materials of plant or animal origin, studied by Pharmacognosy, are divided into the following groups:

1. medicinal raw materials, which are released to the patient from the pharmacy in the form of:

- powder;
- tea;
- collection

2. galenic and newly galenic preparations — alcohol extracts in the form of:

- tincture;
- extracts.

3. products of primary processing of plants:

- essential and fatty oils;
- macerates;

- resins;

- gum.

4. individual active substances:

- alkaloids;

- glycosides;

- components of essential oils;

- and other.

There are several classifications based on different characteristics of medicinal products.

- by chemical structure (for example, compounds — derivatives of furfural, imidazoles, pyrimidines, etc.);
- by origin — natural, synthetic, mineral;
- by pharmacological group — the most common classification based on the drug's effect on the human body;
- nosological — classification by diseases for the treatment of which a medicinal product is used;
- anatomical-therapeutic-chemical (ATC) — an international classification that takes into account the pharmacological group of the drug, its chemical nature and the nosological unit of the disease for which the drug is prescribed.

It is used as a raw material for the production of medicinal products:

- ✓ plants (leaves, herbs, flowers, seeds, berries, bark, roots) and their processing products (fatty and essential oils, juices, gums, resins);
- ✓ animal raw materials - animal glands and organs, lard, wax, cod liver, sheep wool fat, etc.;
- ✓ Fossil organic raw materials — oil and products of its distillation, products of coal distillation;
- ✓ inorganic minerals — mineral rocks and products of their processing by the chemical industry and metallurgy (metals);
- ✓ all kinds of organic compounds are products of the large chemical industry:

- ✓ aliphatic - alkanes and their halogen derivatives; alcohols; aldehydes; carboxylic acids, hydroxy- and amino acids; ethers and esters.
- ✓ alicyclic - terpenoids; derivatives of cyclopropane, adamantane.
- ✓ aromatic - phenols; aromatic amines and their acyl derivatives; hydroxy- and amino acids of the aromatic series; derivatives of aromatic sulfonic acids.
- ✓ heterocyclic — classified by the nature of the heterocycle included in the molecule.
- ✓ biologically active natural compounds — alkaloids; carbohydrates and glycosides; hormones; vitamins; antibiotics.

The number of factors that determine the biological activity of substances is so large and diverse that trying to take them all into account is an impossible task. At the same time, there are various approaches that allow building model schemes for the directed search of biologically active substances and on this basis - the search for new effective drugs. At the same time, it must be taken into account that the search for only high activity is not enough to achieve this goal; low toxicity of the proposed compounds, optimal pharmaco-kinetic parameters, directions of their biotransformation, and possible side effects are no less important problems. In general, it should be noted that the most important task of synthetics is to create a structure that would be able to interact with those parts of the biological system that are responsible for certain physiological effects. The very idea of a connection between the chemical structure of organic compounds and their biological activity was first expressed by scientists in the middle of the 19th century. However, despite more than a century and a half of work by many generations of researchers, until now it has been possible to establish only certain certain regularities.

Every year, chemists synthesize, isolate and characterize from 300 to 400 thousand new substances. By the beginning of the new millennium, scientists had obtained more than 18 million individual substances. About 80% of them are compounds of Carbon with such elements as Hydrogen, Oxygen, Nitrogen, Sulfur, Phosphorus, halogens. A significant part of these substances undergoes initial tests

to detect one or another biological activity. This stage of searching for the biological activity of an organic substance is called screening. This principle was first developed during the search for antisyphilitic agents among organic arsenic compounds in biological laboratories on living cells, microorganisms or pieces of living tissue (in vitro), on healthy or specially infected animals (in vivo): on mice, rats, guinea pigs, dogs, monkeys. At the same time, a few of the most active drugs are selected from hundreds and thousands of substances, which are then submitted for in-depth testing. If the high activity of the substance is confirmed, then it passes all stages of biological study, which culminate in clinical trials on humans. After that, the drug begins to be produced on an industrial scale and used in medical practice.

Certain strict requirements are imposed on medicinal products. First of all, Medicines should have high activity, selectivity and duration of medicinal action. Also, it should be harmless and not cause unwanted side effects. Medicines must contain highly pure components and be sufficiently stable during storage. In addition, there are some economic requirements - the drug should be affordable, and the ratio of cost price and possible price should ensure a sufficiently high profit from the sale of drugs to the pharmaceutical market. All these factors determine the life expectancy of this drug among other drugs that have a similar effect and are used in international medical practice.

It is considered necessary that all new synthesized substances pass primary tests. However, until now 12, about 20 million substances have been synthesized, at the same time, there are more than 10 thousand types of biological activity and diseases. Obviously, the possibility of testing all new compounds for all the required types of activity is still unrealistic. Computer technology comes to the aid of chemists and biologists, allowing to determine the potential of synthesized substances, their possible biological activity by means of machine analysis. This approach is based on the cluster analysis of a large array of already known medicinal substances grouped by their structures or by the types of bioactivities they exhibit. Another type of machine analysis can be computer modeling of the mechanism of

interaction of a medicinal substance with a bioreceptor or its other empirical connections with biotargets. Both a chemist and a biologist do not need to have a substance in their hands, but it is enough to enter information about its structure into the computer. Upon completion of the machine analysis, the operator receives recommendations on the expediency or impracticality of testing this substance for one or another type of activity. Such machine screening (screening) saves time, materials and effort in the process of searching for medicinal substances. However, the discovery of fundamentally new types of activity or new types of pharmacophore groups will for a long time be based on the experiment and intuition of the researcher.

2. The principle of combinatorial chemistry methodology.

The principle of combinatorial chemistry methodology - the combination of chemistry and biology arose and began to develop very quickly in the 90s of the 20th centuries. as part of the overall strategy for the discovery of new medicinal substances. The strategy is based on the method of parallel synthesis and testing of a large number of compounds. A technique for miniaturization of syntheses and biological testing of the obtained compounds was created, which made it possible to obtain from a hundred to several thousand new (related) compounds in a very short time and to significantly speed up their testing in the form of mixtures or individual substances. In combination with automation, the process of synthesis of entire classes (or "libraries") of substances requires significantly lower costs of reagents with a significant increase in productivity. Principles of creating new medicinal products Today, the strategy and tactics of creating modern medicinal substances are based on the following principles: Copying known physiologically active substances. An example of the use of such a method can be the synthesis of the antibiotic chloramphenicol. Initially, chloramphenicol (chloramphenicol) was isolated from the culture fluid of Streptomyces Venezuela, and then it was produced synthetically. Currently, this drug is obtained in industry by a 10-stage synthesis from styrene. The principle of chemical modification of the structure of known synthetic and natural medicinal substances. This technique is intuitive, speculative.

With its help, based on the analogy of two chemically similar structures, the activity of an already known substance is transferred to a new compound, trying to make the bioactivity of the latter appear greater. A typical example of the application of the principle of chemical modification can be the modification according to the indicated arrows of penicillins (Oxacillin, Ampicillin, Ampioks) and cephalosporins (Cefazolin (Kefzol), Cefatoxime, Cephalexin). This made it possible to obtain a number of new drugs with improved antibacterial properties. Another vivid example was a similar chemical modification of sulfonamides (Furosemide, Bufenox, Clopamid), which, in addition to the main antibacterial effect, also had a side diuretic effect. As a result, a new class of sulfonamide diuretics was created. This technique is widely and successfully used nowadays for the synthesis of derivatives of almost all classes of medicinal substances. The principle of introducing the pharmacophore group of a known medicinal substance into the molecule of a new compound. A structural element or fragment of a molecule that provides pharmacological activity is called a pharmacophore. Thus, a number of anticancer drugs were obtained on the basis of nitrogen mustard by introducing N, N-dichlorodiethylamine or aziridine fragments into various substances (for example, Sarcolysin). The principle of molecular modeling. This approach, combined with X-ray structural analysis, allows us to establish the stereochemical features of the drug molecule and the bioreceptor, the configuration of their chiral centers, and measure the distance between individual atoms, groups of atoms, or between charges in the case of zwitterionic structures of the drug in the bioreceptor site of its capture. The data obtained in this way make it possible to carry out the synthesis of bioactive molecules with parameters set at the molecular level in a more targeted manner. This method was successfully used in the synthesis of highly effective analgesics - morphine analogues, as well as for obtaining a number of medicinal substances that act on the central nervous system analogously to the natural neurotransmitter - aminobutyric acid. Creation of combined drugs. The simultaneous action of the components of different drugs in one drug, for example, biseptol, which is a combination of trimethoprim and sulfamethoxazole, is characterized by synergism (strengthening of the action) when

they are combined. This allows the use of medicinal substances in lower doses, thereby reducing their toxic effect.

The simultaneous use of these medicinal substances provides high bactericidal activity against gram-positive and gram-negative microorganisms, including bacteria resistant to sulfonamide drugs, and is used for the treatment of bacterial dysentery, bronchitis, and infectious diseases of the urinary tract. Another example of a combined drug is sulfathon, which simultaneously includes sulfamonomethoxine in comparison with sulfamethoxazole. Strategy of prodrugs. Many compounds with potent effects are tested for low activity, which may be the result of many factors, including poor absorption, rapid metabolism or elimination, slow penetration to the site of action, etc. Another serious drawback is often high toxicity. All this forces us to search for structures that would not have the above negative qualities. In such a case, it may be useful to create prodrugs - inactive compounds that, as a result of biotransformation in the body, turn into an active form, penetrate to the site of action and provide the desired pharmacological result. Prodrugs have such structural groupings that allow them to easily overcome protective barriers in the body and precisely reach the diseased organ. After reaching the biotarget, these compounds are metabolized, turning into real drugs. This strategy is very common nowadays. The concept of antimetabolites is based on the creation of a synthetic medicinal substance structurally close to the natural metabolite of the human body. The task of such a synthetic substance, which is called an antimetabolite, is to replace the metabolite in the body's natural reactions. Antimetabolites should only partially perform the functions of metabolites in the body. Being chemical imitators of metabolites, medicinal substances of this kind "fool" the controlling enzyme systems, are integrated into the metabolic scheme and change the real metabolite. A similar technique was successfully used in the synthesis of anticancer drugs, as well as to inhibit the growth and development of pathogenic viruses in the creation of acyclovir, a highly effective antiherpes drug. An interesting fact was established by scientists when studying the metabolism of the well-known red streptocide drug (prontozil), which showed high activity against

hemolytic streptococcus. It turned out that in a living organism it was transformed into an active medicinal substance - sulfanilamide, namely streptocide. Further tests showed that sulfonamides are structural analogues of para-aminobenzene acid and disrupt the synthesis of folic acid. The enzyme responsible for the synthesis of the latter does not use aminobenzene acid itself, but its imitator - sulfonamide. Folic acid is needed by the body for the synthesis of purine bases and subsequent synthesis of nucleic acids. The appearance of sulfanilic acid derivatives in the environment leads to the cessation of bacterial cell growth.

3. Biological activity of the substance.

The biological activity of a substance is determined by its chemical and spatial structure. However, the level of such activity (effectiveness of action) may depend significantly on other factors. Thus, an important factor for many LRs is good solubility in water, because they are carried in the body, mainly by the blood flow, which contributes to the creation of a concentration sufficient to detect a pharmacological effect. Also, medicinal substances must have good lipophilicity and have the ability to penetrate through cell semipermeable membranes in order to influence the biochemical processes of metabolism. Drugs that act on the central nervous system must freely pass from the blood to the cerebrospinal fluid and the brain, that is, overcome the blood-brain barrier that protects the brain from the penetration of foreign substances dissolved in the blood. Another barrier for the penetration of a medicinal substance from the blood to the tissues of the organ - the target is the walls of the capillaries. For most medicinal substances with a small molecular weight, this barrier is insurmountable. There is another barrier - the placental barrier, which separates the mother's body from the fetus. Usually, it is easily permeable to medicinal substances, so the choice of drugs for pregnant women is extremely careful. In general, the drug molecule, in addition to the main pharmacophore group, which is directly responsible for the therapeutic effect, must also contain hydrophilic and (or) lipophilic fragments (be balanced by them) in order to carry out its normal transfer to the corresponding body system. In the process of designing a medicinal product, they try to take into account the above factors when

introducing appropriate chemical groups into a potential medicinal substance. Thus, the introduction of phenolic groups, carboxyl or sulfo groups, a basic or amine nitrogen atom (a quaternary salt) into the structure improves the water solubility of an organic molecule of a medicinal substance, changes its basicity or acidity, as well as enhances its bioactivity. The presence of n-alkyl chains, their lengthening, and the introduction of halogens, on the contrary, increase the lipophilicity of drugs (solubility in fatty tissues, which can act as a drug depot) and facilitate their passage through biomembranes. The presence of branched alkyl substituents and halogen atoms complicates the metabolism (in particular, biooxidation) of medicinal substances. Cycloalkyl groups improve binding to the bioreceptor due to van der Waals forces. The use of drugs with alcohol or carboxyl groups (in the form of their complex or simple esters) changes the polarity of the drug molecule and inhibits biodecarboxylation. Biological systems, when synthetic medicinal substances act on them, do not feel the difference between substances in the molecules of which the benzene ring is replaced by a pyridine ring, or a furan ring by a pyrrole or thiophene ring. That is, replacing one flat ring with another does not significantly affect the beneficial bioactivity. At this time, a number of pharmacophore groups have been identified, the introduction of which into the molecule of a potential medicinal substance gives it the necessary bioactivity. For example, the presence of a phenolic group can give the substance antiseptic properties.

4. Metabolism.

Metabolism. Most medicines undergo metabolic changes in the body. This process is called biotransformation. The essence of metabolic transformations is that a foreign, dangerous agent for the body turns into a highly water-soluble compound that can be easily excreted with urine, bile or sweat. Such polar metabolites are poorly soluble in lipids and have a low ability to interact with blood plasma and tissue proteins. Metabolites, as a rule, do not penetrate biological membranes well and are not reabsorbed in the kidneys and intestines. Biotransformation of drugs occurs mainly in the microsomal apparatus of the liver. Some metabolic transformations of certain drugs can

occur in the intestines, lungs, skin, and blood plasma. Only some drugs are excreted unchanged from the body.

There are two main types of drug metabolism:

- metabolic transformation;
- conjugation.

Metabolic transformation is a chemical transformation of a substance by oxidation, reduction or hydrolysis.

Oxidation is one of the most common ways of drug inactivation. Oxidation of drugs occurs in the liver with the participation of microsomal oxidase enzymes (the main representative of cytochrome P-450). The essence of oxidation is the separation of hydrogen ions from the side chains of drug molecules. NADH and oxygen take part in the reaction.

Recovery is a rarer route of drug metabolism. Reduction reactions are catalyzed by such enzyme systems as nitro- and azoreductases, etc. Metabolism by recovery is characteristic of steroid hormones and their analogs.

Hydrolysis is a way of inactivating esters and amides. In the process of hydrolysis, the ether or amide bond is destroyed. The reaction takes place with the participation of water. Enzymes that catalyze hydrolysis (esterases) exhibit substrate specificity.

Conjugation is the reaction of joining a certain hydrophilic endogenous metabolite to a drug molecule. These metabolites are pre-activated, forming a macroergic connection due to ATP. Typical conjugation reactions are the addition of residues of acetic or glucuronic acids, glutathione, sulfates, glycine, methyl residues, etc. to drug molecules. Conjugation may be the only way of transformation of medicinal substances in the body, or it may occur after previous metabolic transformation. In the process of metabolic transformation and conjugation, drugs, as a rule, lose their biological activity. Drug detoxification processes are significantly slowed down in patients with liver pathology (cirrhosis, acute and chronic hepatitis, etc.). This leads to an increase in the duration of action of drugs, the development of overdose phenomena.

During the use of some medicines, a change in the activity of liver enzyme systems can be observed. Some drugs cause induction of microsomal enzymes. As a result, when other drugs are used with inducers of microsomal enzymes, their metabolism is accelerated, which leads to a decrease in their concentration in blood plasma and body tissues, and, accordingly, to a decrease in their biological activity. Induction of microsomal enzymes is observed when using barbiturates (most often phenobarbital), non-steroidal anti-inflammatory drugs (phenylbutazone), anticonvulsants (carbamazepine, difenin), rifampicin, griseofulvin, cordiamine, antihistamines (diphenhydramine, chloropyramine), oral hypoglycemic drugs (glutethimide), meprobamate.

When using some drugs, there is a decrease in the activity of microsomal enzymes, which leads to an increase in the concentration in the blood plasma and body tissues of other drugs that are used simultaneously with inhibitors of microsomal enzymes. As a result of the increase in the concentration of drugs in the blood and tissues, both the biological activity of drugs and the probability of toxic effects of drugs used simultaneously with inhibitors of microsomal enzymes increase. Inhibition of microsomal enzymes is observed when using cimetidine, chloramphenicol, ketoconazole, imipramine, morphine, codeine, tetracycline antibiotics and macrolides (erythromycin, oleandomycin), metronidazole, allopurinol. Inhibition of microsomal enzymes is also observed when consuming grapefruit juice and ethanol, as well as when salts of heavy metals (cadmium, lead, mercury) enter the body.

A change in the rate of biotransformation of drugs is also observed in the case when two or more drugs compete for the same binding site on the enzyme, which leads to the inhibition of the metabolism of a part of the drugs that have a lower affinity for these enzymes. Inhibition of the metabolism of certain drugs leads to an increase in their half-life, and also leads to an increase in the frequency of side effects and an increase in the toxicity of drugs. In particular, the toxicity of paracetamol increases with simultaneous use of the drug with ethanol or isoniazid. When using rifampicin or glucocorticoids together with cyclosporine, the rate of

biotransformation of cyclosporine increases, which leads to a decrease in its concentration in the blood. When using cyclosporine together with erythromycin or ketoconazole, the rate of metabolism of cyclosporine decreases, which leads to an increase in its concentration in the blood. When using omeprazole, there is an induction of one of the lysoforms of cytochrome P-450 — P450-I-A, which is involved in the metabolism of many procarcinogens, carcinogens and many drugs, which can cause a change in their concentration in the blood.

The activity of enzymes that metabolize drugs also depends on the patient's gender, age, and body condition (nutrition, state of enzyme systems, state of pregnancy, presence of concomitant diseases). Drug metabolism is also affected by stress, ionizing radiation, environmental pollution and other external factors. In particular, men have a higher activity of microsomal enzymes, which leads to an increase in the rate of metabolism of drugs and a reduction in the time of action of drugs in men. In babies of the first month of life, the activity of most microsomal enzymes is reduced, which leads to a significant decrease in the rate of biotransformation of some drugs (in particular, chloramphenicol), which can lead to an increase in the toxicity of these drugs. A decrease in the activity of microsomal enzymes is also observed in old age, which requires correction of the dose of medicines in the elderly. Debilitated persons and persons with overfatigue also have a decrease in the activity of enzyme systems. In liver diseases (in particular, in liver cirrhosis), there is a decrease in the activity of enzyme systems, as well as a decrease in intrahepatic blood flow, which leads both to an increase in the half-life of drugs, and to a decrease in the rate of their detoxification and removal from the body, which leads to an increase in the toxicity of drugs and an increase in the frequency of their side effects. A change in the rate of biotransformation of drugs can also be caused by congenital pathology of enzyme systems, which can lead to both an increase in the rate of drug metabolism and a decrease in it. In particular, with a deficiency of the enzyme glucose-6-phosphate dehydrogenase of erythrocytes, when using quinine, quinidine, acetylsalicylic acid, chloramphenicol or sulfonamides, hemolytic anemia can be observed. With a deficiency of the plasma pseudocholinesterase

enzyme, there is a significant increase in the duration of action of the muscle relaxant succinylcholine (up to 6-8 hours instead of the normal 5-7 minutes), which is associated with a decrease in the rate of biotransformation of the drug. With liver N-acetyltransferase deficiency, there is an increase in the frequency of adverse reactions when using isoniazid, novocainamide, and sulfonamide drugs due to the slowing down of the metabolism of these drugs. In case of catalase deficiency, there is no effect when applying hydrogen peroxide due to the slow formation of atomic oxygen. In addition, genetic differences in the activity of enzymes that catalyze the reactions of the metabolism of drugs can contribute to the emergence of idiosyncrasy to these drugs.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Principles of classification of medicinal products, their nomenclature.
2. Structure-activity relationship in the creation and analysis of medicinal products. Creation of innovative medicines.
3. The main ways of drug metabolism. Chemical reactions that underlie metabolic transformations. Phases of metabolism.
4. Factors affecting metabolic processes. Prodrugs.

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Additional:

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Lecture No. 7

Topic: Nonsteroidal anti-inflammatory drugs, narcotic analgesics and their analogues Characteristics, classification, relationship between structure and

pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, studying the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component NSAIDs.

Goal: familiarize yourself with the group of drugs that exhibit anti-inflammatory and analgesic activity and belong to NSAIDs and narcotic analgesics. Must know the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Nonsteroidal anti-inflammatory drugs (NSAIDs).
2. Classifications of NSAIDs.
3. Classification by the mechanism of inhibition of cyclooxygenase activity.
4. Pharmaceutical analysis of the main representatives of NSAIDs.

Content of lecture material (lecture text):

1. Nonsteroidal anti-inflammatory drugs (NSAIDs).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs that have analgesic, antipyretic, and anti-inflammatory effects, reduce pain, fever, and inflammation. For the first time, the term was proposed by J. Flower, which emphasized their fundamental differences from glucocorticoids, which have not only anti-inflammatory, but also other, sometimes undesirable, properties. The first natural analogue of NSAIDs, sodium salicylate, contained in willow bark extract, entered clinical practice more than 200 years ago (E. Stone, 1829) and for a long time remained almost the only one against pain and fever. The first synthetic NSAID acetylsalicylic acid appeared at the turn of the 19th and 20th centuries and for 50

years, before the discovery of glucocorticoids, was also the only agent that suppresses inflammation. Not so much the lack of effectiveness as the toxicity of high (anti-inflammatory) doses of acetylsalicylic acid became an incentive for the development of new, non-salicylate NSAIDs. The first of them, phenylbutazone, and then indomethacin began to be widely used in clinical practice in the 50s and 60s of the last century. Derivatives of propionic (ibuprofen, ketoprofen), phenylacetic (diclofenac) and enolic (piroxicam) acids soon appeared. Since that time, NSAIDs have steadily taken their place in the treatment of diseases manifested by pain or inflammation.

2. Classifications of NSAIDs.

ATC classification:

M: MEASURES AFFECTING THE SUSTAINABLE MOVEMENT APPARATUS

M01 Anti-inflammatory and anti-rheumatic agents

M01A Non-steroidal anti-inflammatory and anti-rheumatic drugs

M01AA Butylpyrazolidines

M01AB Acetic acid derivatives and related compounds

M01AB01 Indomethacin

M01AB05 Diclofenac

M01AB08 Etodolac

M01AV15 Ketorolac

M01AB55 Diclofenac, combinations 364

M01AC Oxykyam

M01AC01 Piroxicam

M01AC02 Tenoxicam

M01AC06 Meloxicam

M01AE Propionic acid derivatives

M01AE01 Ibuprofen

M01AE02 Naproxen

M01AE03 Ketoprofen

M01AE11 Tiaprofenic acid

M01AE51 Ibuprofen, combinations

M01AG Fenamaty

M01AG01 Mefenamic acid

M01AH Coxby

M01AH01 Celecoxib

M01AЧ Other non-steroidal anti-inflammatory and anti-rheumatic agents

M01AX01 Nabumeton

M01AX02 Niflumic acid

M01AX04 Azapropazone

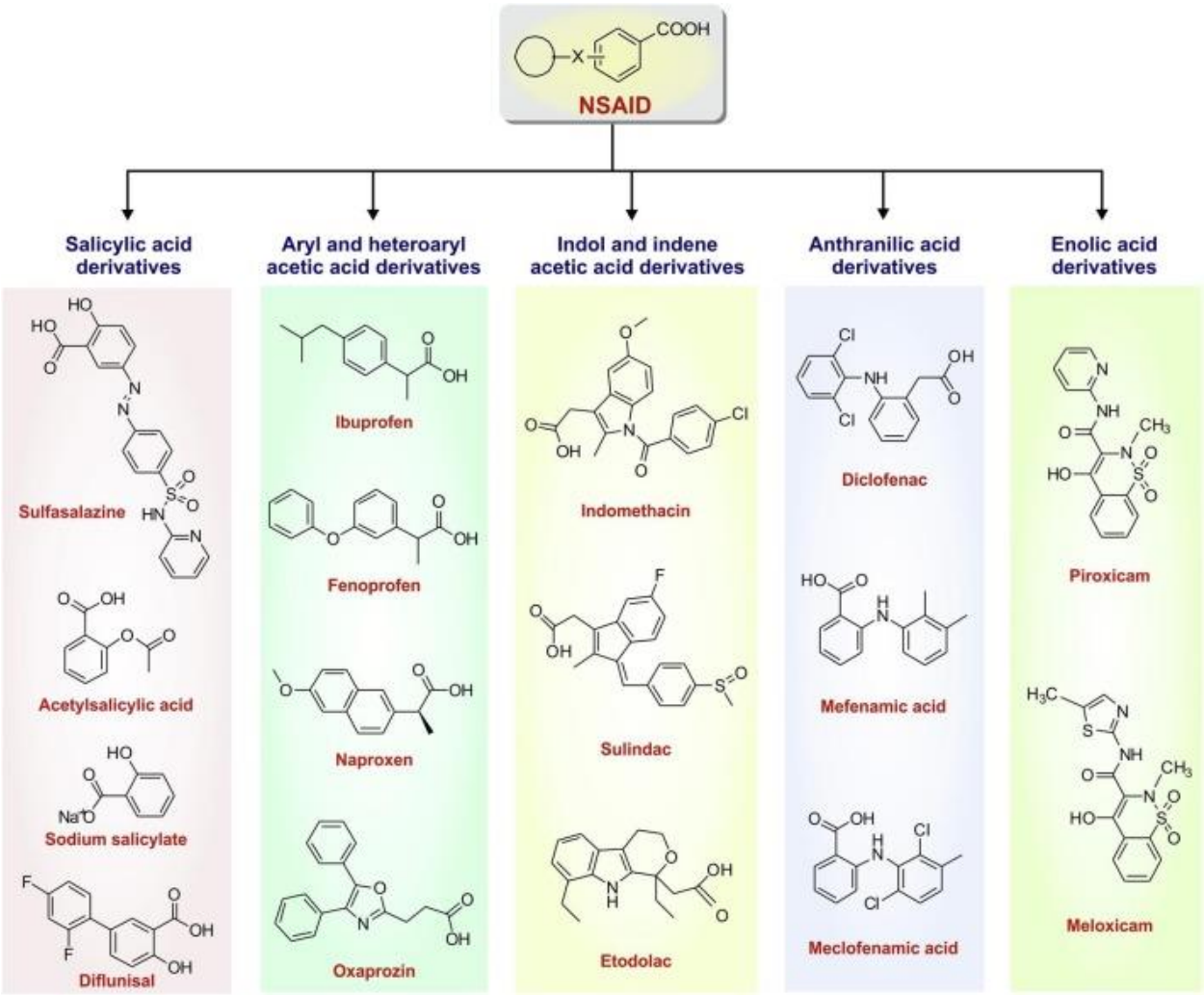
M01AX17 Nimesulide

M01AX22 Morniflumate

NSAIDs are classified into groups depending on their chemical structure, severity of activity, and mechanism of inhibition of cyclooxygenase (COX) activity.

Classification by chemical structure

The classification of NSAIDs by chemical structure is presented in table.



Classification by anti-inflammatory activity NSAIDs are also classified depending on the degree of anti-inflammatory activity (table).

NSAID
Non steroidal anti-inflammatory Drugs

*Classification- KD Tripathi

Non-Selective COX Inhibitor	Preferential COX_2 Inhibitor	Selective COX_2 Inhibitor	Analgesic-Antipyretic with poor Anti-inflammatory Action
	Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac	Celecoxib, Etoricoxib, Parecoxib	

Category	Example
Salicylates	Aspirin
Acetic acid derivative	Indomethacin, Nabumetone, Ketorolac,
Pyrazolone derivative	Oxyphenbutazone, Phenylbutazone
Propionic acid derivative	Ketoprofen, Flurbiprofen, Ibuproprofen, Naproxen,
Fenamate	Mephenmic acid
Enolic acid derivative	Piroxicam, Tenoxicam

Example
Paracetamol (Acetaminophen)
Metamizol, Propiphenazone
Nefopam

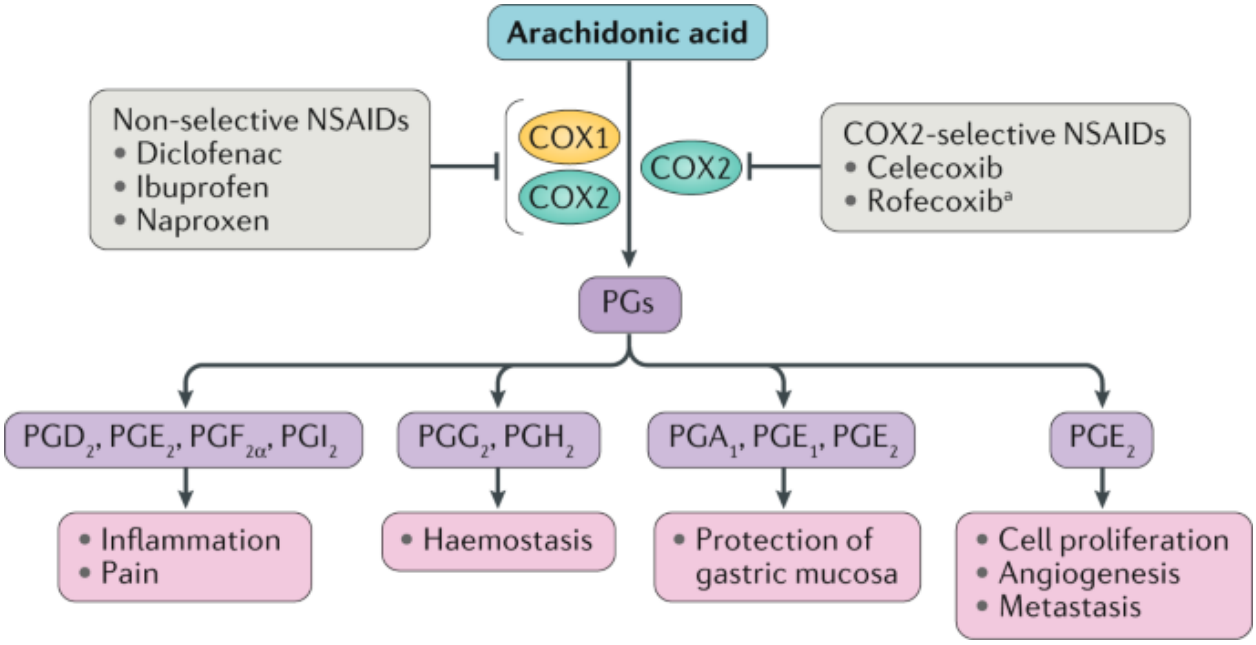
*Constitutive = Constant Production

Key Point (Solution) - As name Indicate NSAIDs are those agents which are used to get relief from pain, inflammation and fever. And as per the COX pathway we understand that **COX-1** and **COX-2** ultimately form prostaglandin which initiates perception of pain and inflammation. So anyhow if we block or inhibit the synthesis of PG we may reduce pain and inflammation. Although COX-1 is constitutive in nature thus it always get secreted without induction of injury and called as a house keeper so it's better to inhibit COX-2 rather than COX-1.

The first group includes drugs with a high anti-inflammatory effect. NSAIDs of the second group have a weak anti-inflammatory effect and are often labeled as "non-narcotic analgesics" or "antipyretic analgesics". From a practical point of view, it is important that drugs even of the same group and similar in chemical structure differ somewhat both in terms of the strength of the effect and the frequency of development and nature of undesirable reactions. The clinical effectiveness of the drug may depend on the appearance and characteristics of the course of the disease, as well as the individual reaction of the patient to it).

3. Classification by the mechanism of inhibition of cyclooxygenase activity.

The classification of NSAIDs according to the mechanism of inhibition of cyclooxygenase activity is presented in table.



The most important mechanism that determines the effectiveness and toxicity of NSAIDs is related to inhibition of COX activity, an enzyme that regulates the biotransformation of arachidonic acid into prostaglandin (PG), prostacyclin, and thromboxane, which in turn is released from phospholipids of the cell wall due to the enzyme phospholipase A2. Prostaglandins are mediators and regulators in the development of inflammation. Although according to in vitro studies, NSAIDs inhibit PG synthesis to varying degrees (some strongly, others weakly), a direct relationship between the degree of PG inhibition, on the one hand, and the anti-

inflammatory and analgesic activity of NSAIDs, on the other hand, has not been proven. Of particular importance is the nature of the effect of NSAIDs on the newly discovered isoforms of COX - COX-1 and COX-2 (Table 2.82). For the discovery, John Wayne later received the Nobel Prize. COX-1 is constantly present in most tissues (albeit in varying amounts), belongs to the category of constitutive (structural) enzymes that regulate the physiological effects of PG, COX-2 is not detected in most tissues in healthy people, but its level increases significantly against the background of inflammation. However, in some tissues (brain, kidneys, bones and, probably, in the reproductive system in women) COX-2 plays the role of a structural enzyme. One of the characteristic features of COX-2 is that its expression, unlike COX-1, is also inhibited by glucocorticoids. Inhibition of COX-2 is considered as one of the important mechanisms of anti-inflammatory activity of NSAIDs, and COX-1 development of side effects. Therefore, the effectiveness and toxicity of standard NSAIDs are associated with their low selectivity, that is, the ability to equally inhibit the activity of both COX isoforms. All these data served as the basis for the creation of a new group of NSAIDs with positive properties of standard NSAIDs, but less toxic. They are defined as specific COX-2 inhibitors or COX-1 sparing drugs (or coxibs).

Main clinical effects

1. ***Anti-inflammatory effect*** – NSAIDs mainly inhibit the exudation phase. The most effective are indomethacin, diclofenac, and phenylbutazone, which also act on the proliferation phase (reducing collagen synthesis and associated tissue sclerosing), but weaker than on the exudative phase. NSAIDs practically do not affect the alteration phase. In terms of anti-inflammatory activity, all NSAIDs are inferior to glucocorticoids, which inhibit the metabolism of phospholipids and disrupt the formation of both prostaglandins and leukotrienes, one of the most important mediators of inflammation.

2. ***Analgesic effect*** – to a greater extent, it is manifested in pains of weak and medium intensity, which are localized in muscles, joints, tendons, nerve trunks, as well as in headaches or toothaches. For severe visceral pain, most NSAIDs are

inferior to drugs of the morphine group (narcotic analgesics). At the same time, a number of clinical studies have shown sufficiently high analgesic activity of diclofenac, ketorolac, ketoprofen, metamizole, perecoxib for colic and postoperative pain.

3. ***Antipyretic effect*** – NSAIDs act only in case of fever and do not affect normal body temperature, which is how they differ from "hypothermic" agents (chlorpromazine and others).

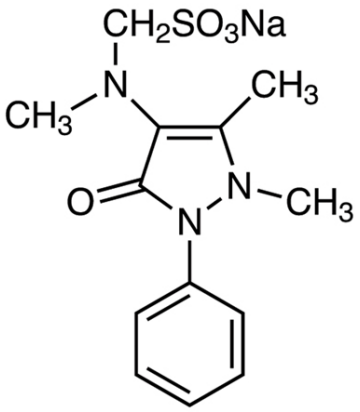
4. ***Antiaggregating effect*** – as a result of inhibition of COX-1 in platelets, the synthesis of the endogenous proaggregant thromboxane is inhibited. Acetylsalicylic acid has the strongest and longest-lasting antiaggregating activity, which irreversibly suppresses the platelet's ability to aggregate for the entire duration of its life (7 days). The antiaggregating effect of other NSAIDs is weaker and reversible. Selective COX-2 inhibitors do not affect platelet aggregation.

5. ***Immunosuppressive effect*** – it is expressed moderately, it is detected with long-term use and has a "secondary" character: by reducing the permeability of capillaries, NSAIDs make it difficult for immunocompetent cells to contact antigen and for antibodies to contact the substrate.

4. Pharmaceutical analysis of the main representatives of NSAIDs.

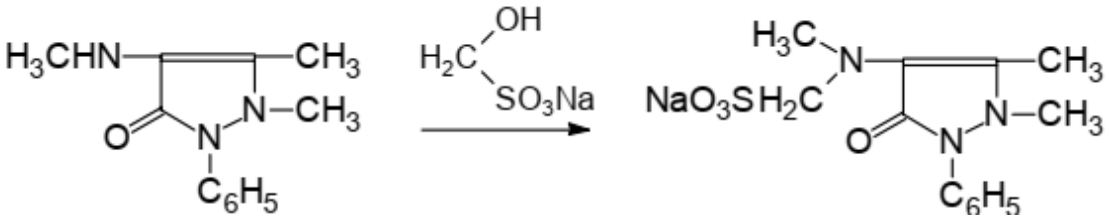
NSAIDs, which belong to pyrazole and paraaminophenol derivatives, are widely used in everyday medical practice. These are antipyrine, aminopyrine, and analgin drugs. Usually, these drugs provide not only an analgesic, but also an antipyretic (antipyretic) effect. It has also been established that with long-term use of drugs of this group, a number of undesirable side effects occur, which led to the limitation of their use. The action of analgin develops very quickly, but unlike amidopyrine, it does not cause convulsive effects, it can be used orally, intramuscularly, and intravenously. However, it has been established that analgin suppresses hematopoiesis. Therefore, at present, paracetamol in combination with acetylsalicylic acid is more often used as antipyretic drugs.

Metamizole Sodium Salt



Sodium (1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) (methylamino)methanesulfonate

Synthesis. It is carried out according to the following scheme:



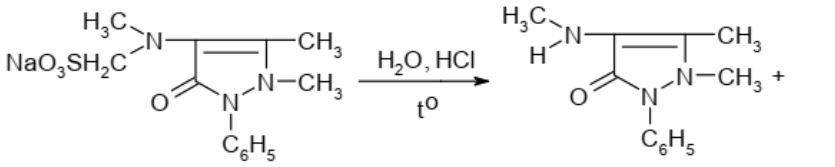
Properties. Crystalline powder of white or almost white color. Decomposes in the presence of moisture. Aqueous solutions turn yellow on standing. Very easily soluble in water, soluble in 96% alcohol.

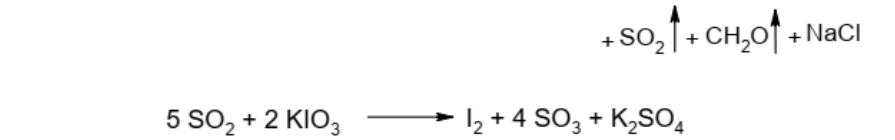
Identification:

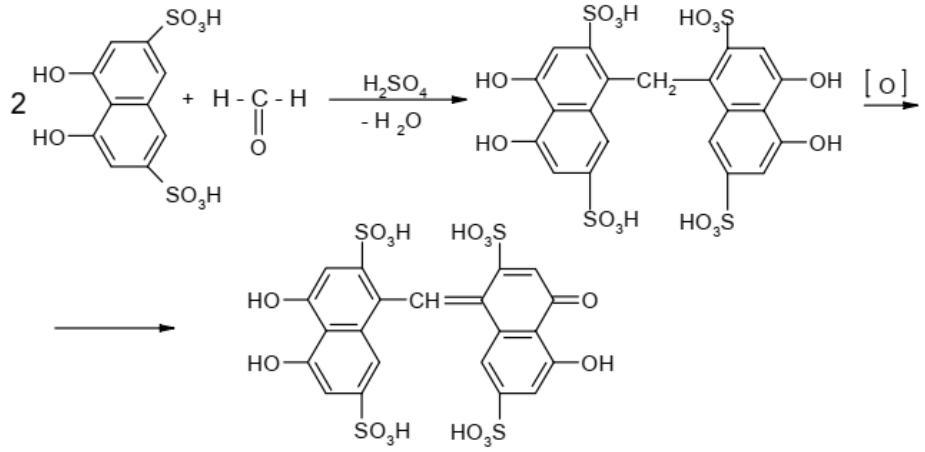
1. IR spectroscopy.

2. The substance with a solution of concentrated hydrogen peroxide gives a blue color, which quickly disappears and turns into intense red after a few minutes. With other oxidants ($FeCl_3$, perchloric lime, HNO_3 conc.) analgin also forms colored oxidation products.

3. The acidified solution of the substance is carefully heated. The test tube is covered with filter paper soaked in potassium iodate solution and starch solution. The sulfur (IV) oxide vapors released turn the filter paper blue. Released formaldehyde with a solution of the sodium salt of chromotropic acid in sulfuric acid gives a blue-violet color:





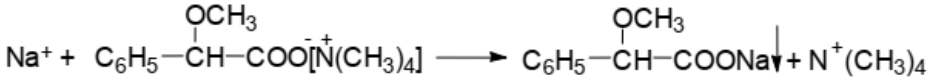


4. The substance reacts to sodium ions.

а) with a solution of potassium pyroantimonate (potassium hexahydroxostibiate (V)) - a white precipitate is formed:

$$Na^+ + K[Sb(OH)_6] \rightarrow Na[Sb(OH)_6]\downarrow + K^+$$

б) with a solution of the methoxyphenylacetic acid reagent - a bulky white crystalline precipitate is formed:

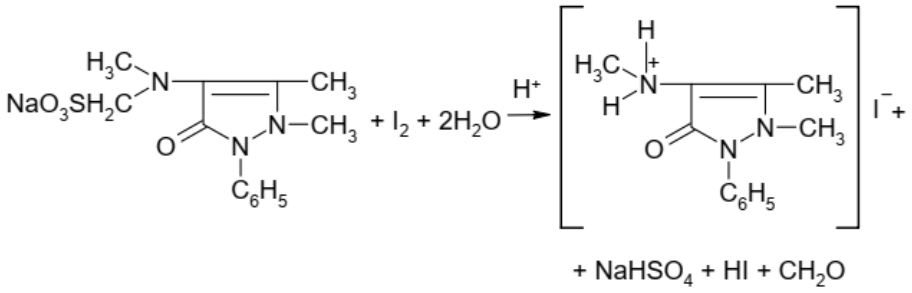


The precipitate dissolves when a diluted ammonia solution is added and does not fall out again when the ammonium carbonate solution is added.

в) sodium salt, moistened with dilute hydrochloric acid and introduced into a colorless flame, turns it yellow.

5. non-pharmacopoeial reaction. An acidified alcoholic solution of the substance, when potassium iodate solution is added, turns crimson (oxidation intermediates), and upon further addition of the reagent, the color intensifies and a brown precipitate of iodine is released.

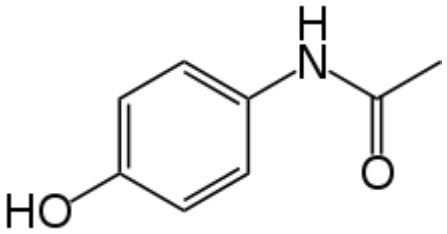
Quantitative definition. Iodometry (SPhU), direct titration, indicator - starch, s=1. The acidified solution of the substance is titrated with iodine solution until a blue color appears, which does not disappear within 2 minutes. The temperature of the solution during titration should not exceed 10 °C:



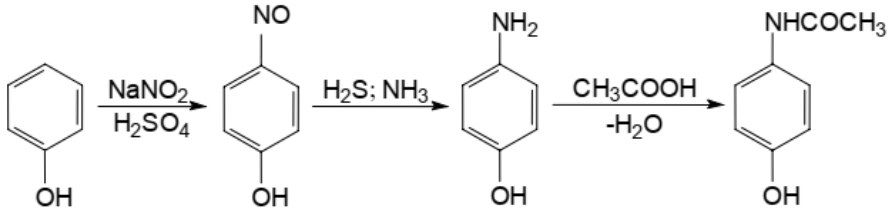
Storage. In well-stoppered glasses made of dark glass, in a place protected from light.

Application. In terms of activity and speed of action, analgin is superior to antipyrine. Its solubility promotes rapid absorption, and also facilitates elimination from the body. It is especially convenient in those cases when it is necessary to urgently create a high concentration of a medicinal substance in the blood.

Paracetamol / acetaminophen



Synthesis. Phenol is nitrosated with sodium nitrite in an acidic environment. The formed p-nitrosophenol is reduced with hydrogen sulfide in an ammonia medium to p-aminophenol, which is acetylated:

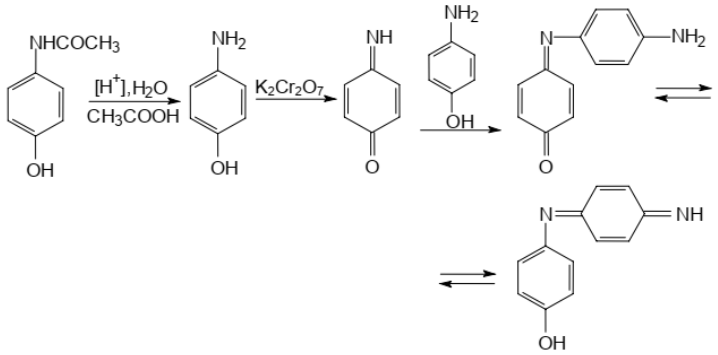


Properties. White crystalline powder. Moderately soluble in water, slightly soluble in 96% alcohol, very slightly soluble in methylene chloride. Due to phenolic hydroxyl, it dissolves in alkalis.

Identification:

1. Physico-chemical methods: melting point, UV and IR spectroscopy.

2. During acid hydrolysis, n-aminophenol is formed, which is oxidized by potassium dichromate to indophenol of violet color, which does not turn red:



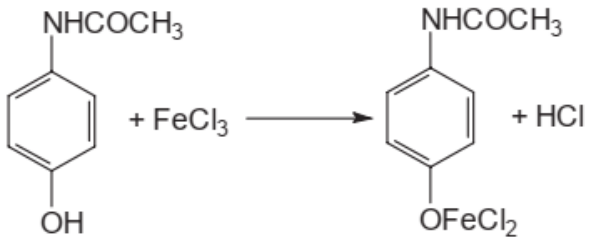
3. The substance reacts with acetyl. Heating is carried out over an open flame.

With a solution of lanthanum (III) nitrate in the presence of iodine and an ammonia solution, a blue color or a blue precipitate is formed when heated:

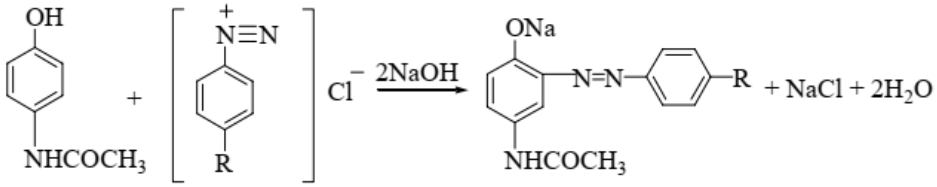
$$La^{3+} + 3CH_3COO^- + 2H_2O \xrightarrow{I_2} La(OH)_2(CH_3COO) + 2CH_3COOH$$

4. non-pharmacopoeial reactions:

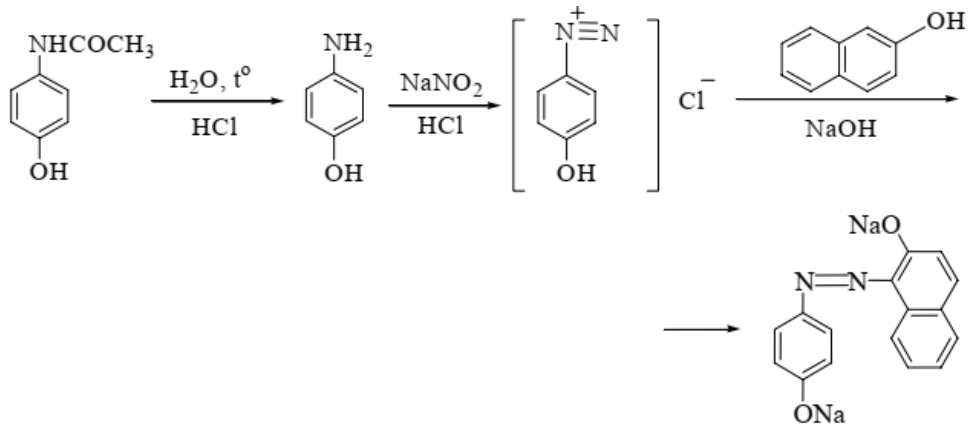
a) with a solution of ferrum (III) chloride, a blue-violet color is formed:



б) the presence of phenolic hydroxyl in the molecule causes the reaction of paracetamol with diazonium salts - a red azo dye is formed:

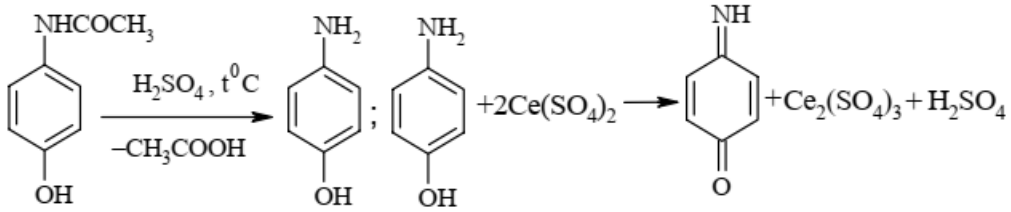


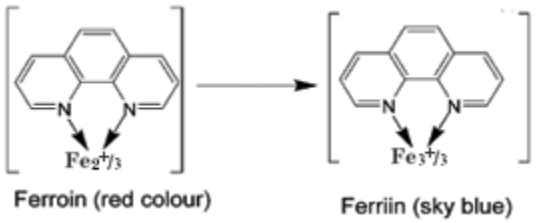
в) after acid hydrolysis, during which the primary aromatic amino group is formed, the medicinal substance gives a diazotization reaction followed by azo coupling:



Quantitative definition:

Cerimetry (SPhU) after preliminary hydrolysis of the substance with dilute sulfuric acid. The formed n-aminophenol is titrated with a solution of cerium (IV) sulfate, the indicator is. In parallel, a control experiment is conducted, s = 1/2:

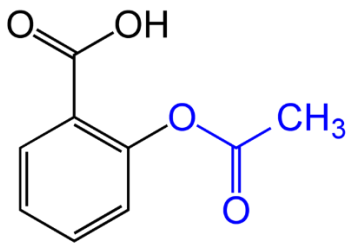




Storage. In a sealed container that protects against light.

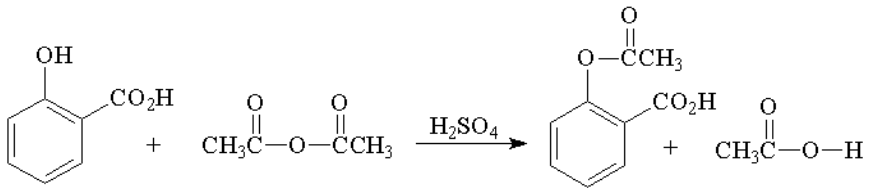
Application. Antipyretic and pain reliever.

Acetylsalicylic acid

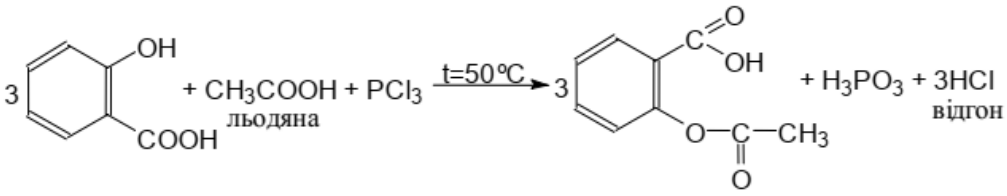


Synthesis.

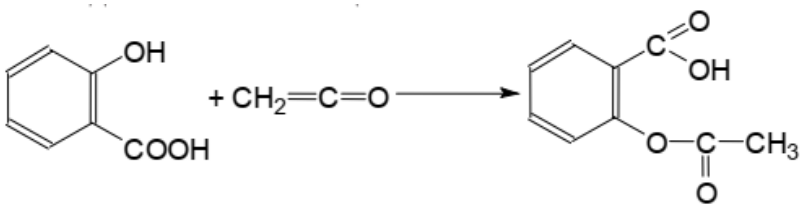
1. Acetylation of salicylic acid with acetic anhydride:



2. Acetylation of salicylic acid with acetic acid in the presence of phosphorus trichloride:



3. The interaction of salicylic acid with ketene:

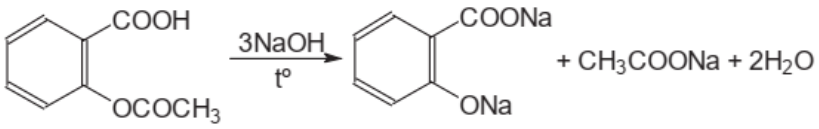


Properties. White crystalline powder or colorless crystals. The drug is stable in dry air, in moist air it is gradually hydrolyzed with the formation of acetic and salicylic acids. Sparingly soluble in water, easily soluble in 96% alcohol, soluble in ether, solutions of alkali metal hydroxides and carbonates.

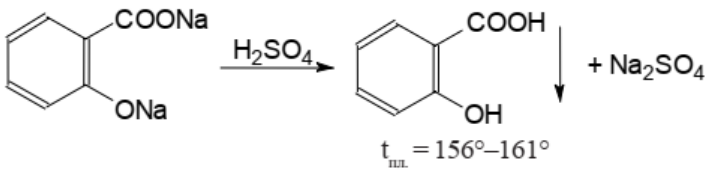
Identification:

1. IR spectroscopy.

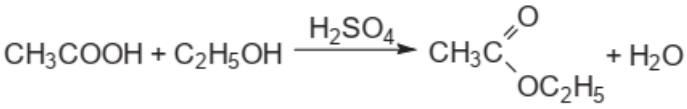
2. The drug is subjected to alkaline hydrolysis:



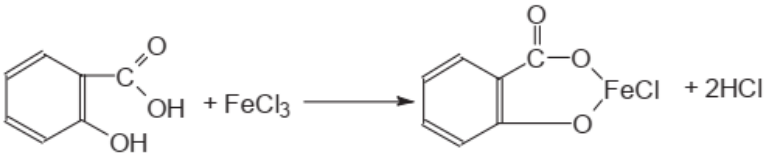
Then it is acidified with dilute sulfuric acid - the formation of a white crystalline precipitate of salicylic acid is observed, which is identified by its melting point (MP):



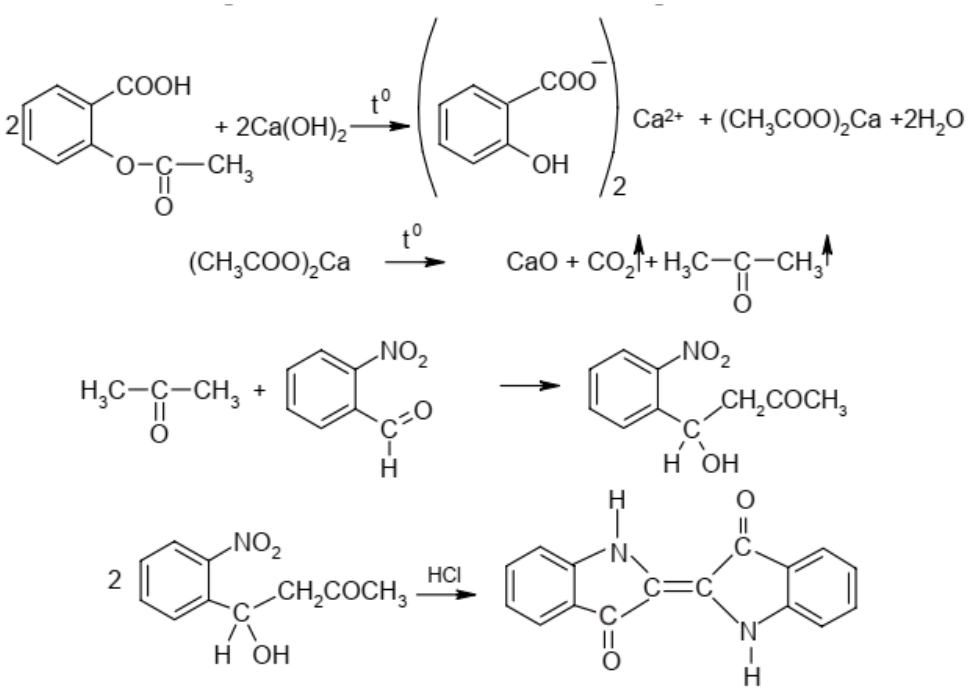
The reaction mixture is filtered, alcohol and concentrated sulfuric acid are added to the filtrate: acetic ethyl ester is formed, which has a characteristic smell (non-pharmacopoeial reaction):



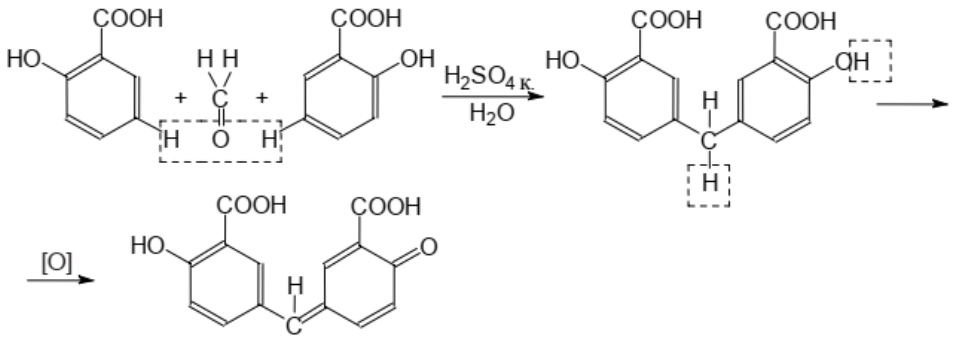
Salicylic acid contained in the precipitate is identified with a solution of ferrum (III) chloride by the appearance of a purple color (SPhU).



3. When calcined with calcium hydroxide, acetone is formed, the vapors of which color the filter paper moistened with o-nitrobenzaldehyde yellow-green, blue-green, and when moistened with a solution of hydrochloric acid - blue (SPhU):

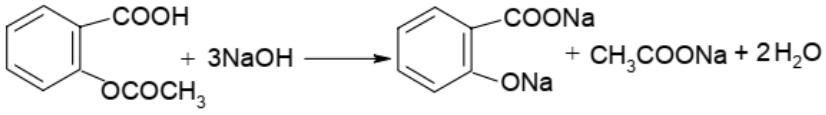


4. Non-pharmacopoeial reaction: acid hydrolysis. When concentrated sulfuric acid is added, the smell of acetic acid appears. If you then add a formaldehyde solution to the mixture, a pink color appears (salicylic acid).

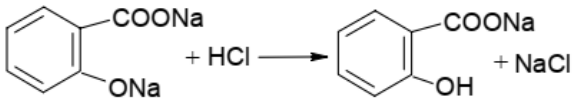


Quantitative definition:

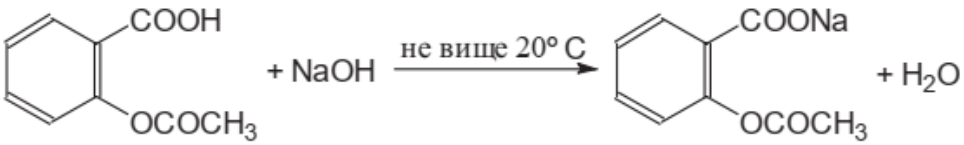
1. Alkalimetry, reverse titration (SPhU). The method is based on the saponification of the substance with a solution of sodium hydroxide, the excess of which is titrated with hydrochloric acid (the indicator is phenolphthalein); s = 1/2. In parallel, a control experiment is conducted:



надл. $NaOH + HCl \rightarrow NaCl + H_2O$



2. Alkalimetry, direct titration in phenolphthalein-neutralized alcohol, s = 1:

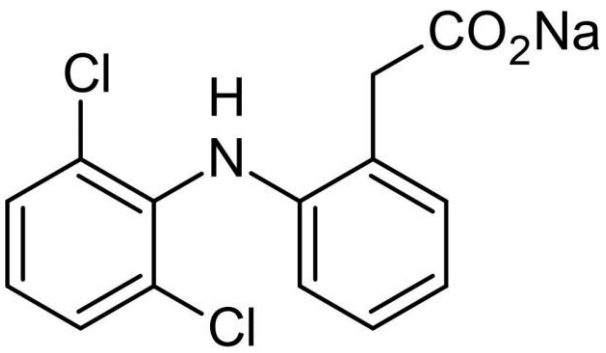


At a temperature above 20 °C, the medicinal substance can be partially hydrolyzed.

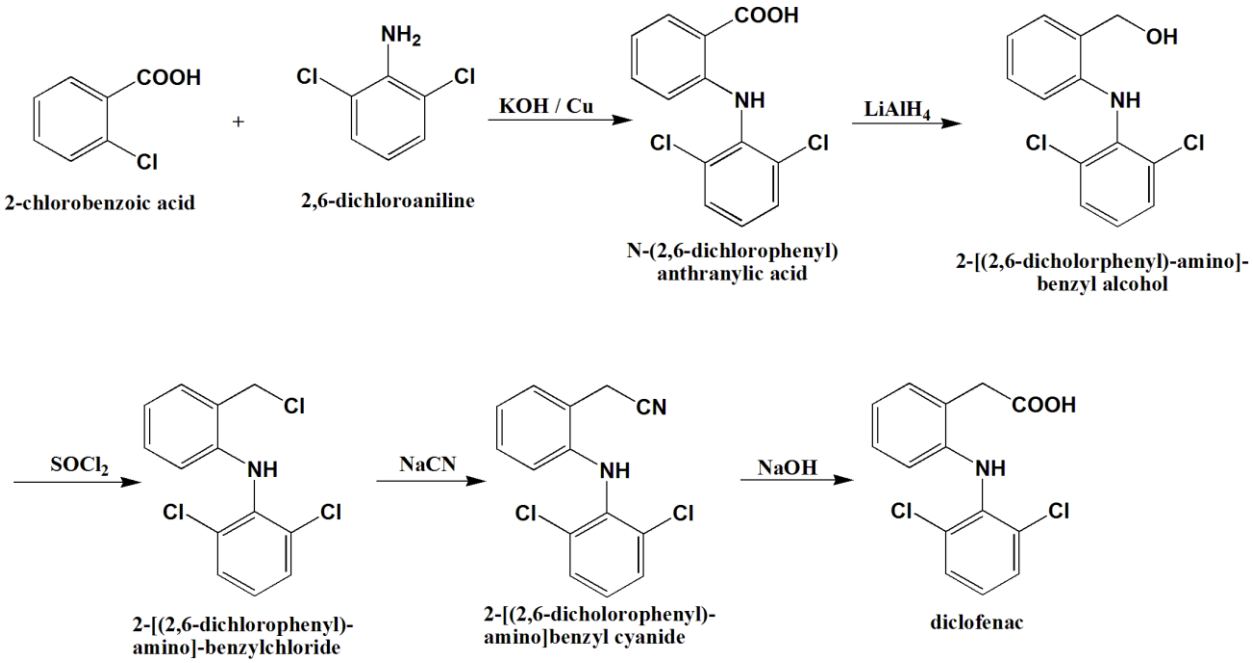
Storage. In a sealed container.

Application. Antirheumatic, anti-inflammatory, antipyretic, pain reliever, as well as to prevent the formation of blood clots, in case of thrombosis of retinal vessels, impaired cerebral blood circulation, to prevent complications and reduce angina attacks in coronary heart disease.

Sodium diclofenac



Synthesis. It is carried out according to the following scheme:



Properties. Crystalline powder of white or white with a yellowish tinge in color, low hygroscopic. Moderately soluble in water, slightly soluble in methanol, soluble in 96% alcohol, sparingly soluble in acetone, practically insoluble in ether. Melts at a temperature of about 280 °C with decomposition.

Identification:

1. Physico-chemical methods: IR spectroscopy, thin-layer chromatography.
2. With a solution of potassium ferricyanide and a solution of ferric (III) chloride in the presence of hydrochloric acid, a blue color gradually appears and a blue precipitate is formed.
3. The substance reacts to sodium.

а) with a solution of potassium pyroantimonate (potassium hexahydroxostibiate (V)) - a white precipitate is formed:

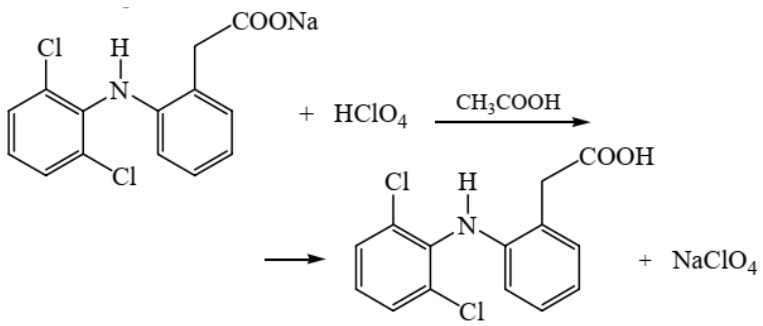
$$Na^+ + K[Sb(OH)_6] \rightarrow Na[Sb(OH)_6]\downarrow + K^+$$

б) with a solution of the methoxyphenylacetic acid reagent - a bulky white crystalline precipitate is formed:

The precipitate dissolves when a dilute ammonia solution is added and falls out again when the ammonium carbonate solution is added.

в) sodium salt, moistened with dilute hydrochloric acid and introduced into a colorless flame, turns it yellow.

Quantitative definition. Acidimetry in a non-aqueous medium is potentiometric, s = 1:



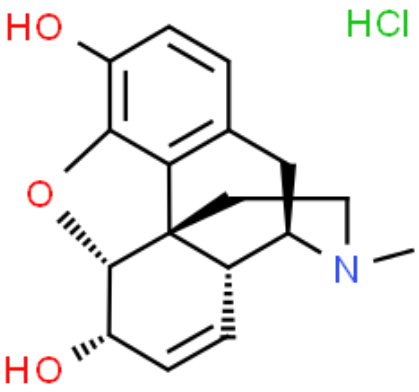
Storage. In a dry place protected from light.

Application. Analgesic, has pronounced anti-rheumatic, anti-inflammatory and antipyretic effect.

Narcotic analgesics - morphine and alkaloids close to it (opiates) and synthetic compounds that have similar properties (opioids). Narcotic analgesics are characterized by a strong analgesic effect. Drugs of this group are used in extraordinary cases, when there is an urgent need for quick and effective pain relief (surgical intervention, wounds, severe injuries, malignant neoplasms, which are accompanied by a pain syndrome). Another characteristic of compounds of this type is the effect on the central nervous system, which is expressed in manifestations of euphoria, as well as in the effect of addiction, which leads to physical and psychological dependence (drug addiction), which limits their long-term use. The

most famous representative of analgesics is morphine. In insufficient (for sleep) dosages, morphine causes a feeling of euphoria, relief from anxiety, and relief from pain. The morphine molecule was modified many times - while it was possible to obtain compounds with significantly greater analgesic activity, but, unfortunately, with higher toxicity.

Morphine hydrochloride



Properties. White needle crystals or white crystalline powder that turns slightly yellow on storage. Slowly soluble in water, hardly soluble in alcohol, very slightly soluble in chloroform and ether.

Identification:

1. The substance reacts to chlorides.

а) with a solution of argentum nitrate in the presence of dilute nitric acid, a white cheesy precipitate is formed, soluble in ammonia solution:

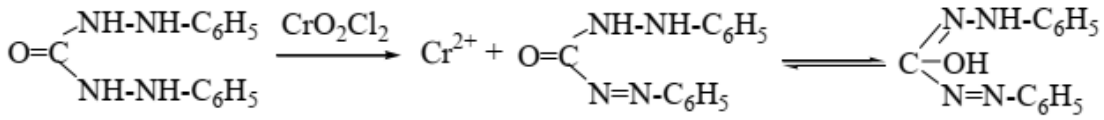
$$Cl^- + AgNO_3 \rightarrow AgCl\downarrow + NO_3^-$$

$$AgCl + 2NH_4OH \rightarrow [Ag(NH_3)_2]Cl + 2H_2O$$

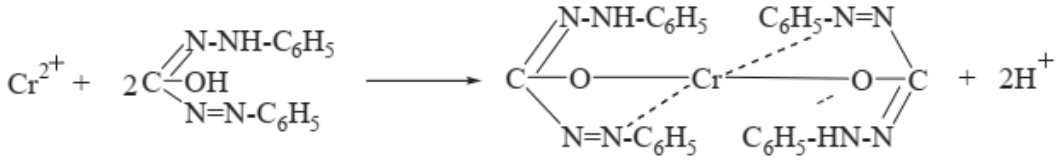
б) by the reaction of the dry substance with potassium dichromate and sulfuric acid, paper impregnated with a solution of diphenylcarbazide turns purple-red. Chlorides interact with potassium dichromate in the presence of sulfuric acid with the formation of a volatile compound - chromyl chloride:

$$4Cl^- + K_2Cr_2O_7 + 3H_2SO_4 \rightarrow 2CrO_2Cl_2\uparrow + K_2SO_4 + 3H_2O + 2SO_4^{2-}$$

Chromyl chloride oxidizes diphenylcarbazide to colorless diphenylcarbazone:



Next, an internally complex violet-red compound is formed:



2. With Frede's reagent, the color is purple, turning blue, and turning green upon standing.

3. When ammonia is added to the solution, a white crystalline precipitate is released, which dissolves in sodium hydroxide solution (as a result of the formation of a sodium salt from phenolic hydroxyl).

4. With Markey's reagent - a purple color that quickly turns blue-violet (different from codeine).

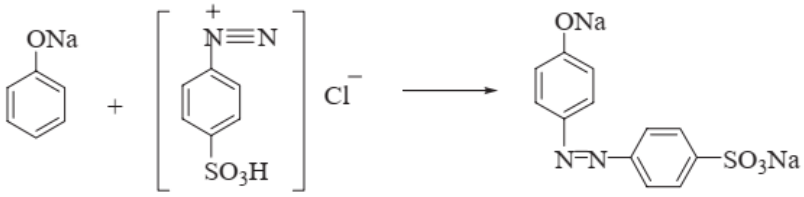
5. Specific rotation from –97° to –99° (2% aqueous solution).

6. With a solution of ferric (III) chloride - blue color (reaction to phenolic hydroxyl).

A phenol solution gives a purple color with a solution of ferrum (III) chloride, which disappears when 2-propanol is added (reaction to phenolic hydroxyl):

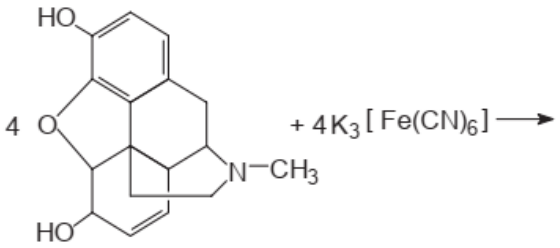
7. An azo dye form with diazonium salts.

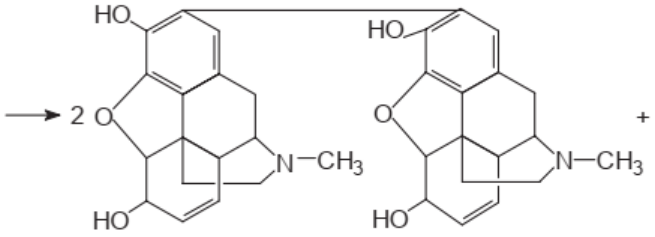
An alkaline solution of phenol forms cherry-red or orange-red colored azo dyes with diazonium salts, for example:



8. The reaction of potassium hexacyanoferrate (III) oxidation in an acidic environment with the formation of oxydimorphine. Upon further addition to the

reaction mixture of a solution of ferrum (III) chloride, "Berlin blue" (blue color) is formed:





$$+ 3\ K_4[Fe(CN)_6] + H_4[Fe(CN)_6]$$

$$3K_4[Fe(CN)_6] + 4FeCl_3 \longrightarrow Fe_4[Fe(CN)_6]_3 + 12KCl$$

9. When interacting with concentrated sulfuric or hydrochloric acids, apomorphine is formed, which acquires an intense red color from the addition of concentrated nitric acid.

Quantitative definition:

1. Acidimetry in a non-aqueous environment in the presence of mercury (II) acetate, the indicator is crystal violet, s = 1.

2. Argentometry according to the Folgard method, s = 1.

Storage. In well-closed jars of dark glass, in a place protected from light.

Application. Analgesic (narcotic) agent. A prolonged morphine preparation is morphilong - a 0.5% solution of morphine hydrochloride in a 30% aqueous solution of polyvinylpyrrolidone.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Principles of classification of NSAIDs, narcotic analgesics and their analogues.
2. Characteristics, classification, relationship between the structure and pharmacological action of NSAIDs, narcotic analgesics and their analogues.
3. Methods of obtaining, methods of analysis of NSAIDs, narcotic analgesics and their analogues.
4. Use of NSAIDs, narcotic analgesics and their analogues in medicine.

References:

Basic:

1. Handbook of pharmaceutical chemictry Vol. 117 / L. Ohannesian, Antony J. Streeter. 2016. – 582 p.
2. Pharmaceutical Chemistry I – Laboratory Experiments and Commentary / Attila Almási, Zsuzsanna Rozmer, Pál Perjési. 2014. – 179 p.
3. Introduction to Pharmaceutical Chemical Analysis / S. Hansen, S. Pederson-Bjergaard, K. Rasmussen. 2012. – 496 p.
4. Chemical Analysis Modern Instrumentation Methods and Techniques 2nd Edition / F. Rouessac, A. Rouessac. 2007. – 599 p.
5. Pharmaceutical drug analysis / Addis Ababa. 2005. – 554 p.
6. Analytical Chemistry Series / John M., Chalmers, Alan J. Handley. 2003. – 384 p.
7. HANDBOOK OF MODERN PHARMACEUTICAL ANALYSIS Vol. 3 / Satinder Ahuja, Stephen Scypinski. 2001. – 587 p.
8. Europian Pharmacopoeia 10th. 2019. – 4255 p.

Additional:

1. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
2. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. :

Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 2. – 724 с.

3. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 3. – 732 с.
4. Фармацевтична хімія / П.О. Безуглий, В.А. Георгіянц, І.С. Гриценко, І.В. та ін.: за ред. П.О. Безуглого. – Вінниця: Нова книга, 2017. – 456 с.
5. Фармацевтична хімія. Загальна та спеціальна фармацевтична хімія. Лікарські засоби неорганічної природи: лабораторно-практичні заняття. Навчальний посібник / Л.Г. Мішина. – Вінниця: ПП «ТД «Едельвейс і К»», 2010. – 384 с.

Lecture No. 8

Topic: Means for anesthesia. Psychotropic and hypnotic drugs. Characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, studying the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component anesthetics, psychotropic drugs and hypnotics.

Goal: familiarize with the group of drugs used as anesthetics and with the group of drugs that exhibit psychotropic and hypnotic effects. Must know the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Central nervous system (CNS).
2. Pharmaceutical analysis of the main representatives of anesthetic agents.

Content of lecture material (lecture text):

1. Central nervous system (CNS).

The functioning of a complex multicellular organism requires coordinated activity of its parts. In the body, the functions that control the activity of its individual parts (cells, tissues or organs), regulate the transmission of information from one part to another, are performed by two closely related systems - endocrine and nervous. However, there is a fundamental difference between the operation of these systems. The endocrine system controls processes that occur relatively slowly, and the nervous system controls rapid reactions, the duration of which is measured in fractions of a second. The nervous system of the body reacts sensitively to changes occurring both in the external environment and in all organs. Therefore, it directly participates in all processes related to the occurrence and development of body diseases.

The central nervous system (CNS) is the main part of the nervous system of animals and humans. It consists of neurons and their processes (axons). In invertebrates, the central nervous system is represented by a system of closely interconnected nerve nodes (ganglia), in vertebrates - animals (including humans) - by the spinal cord and brain.

The main and specific function of the central nervous system is the implementation of simple and complex highly differentiated appropriate reactions, which are called reflexes. The peripheral nervous system connects the central nervous system with organs and limbs. Medicines that act mainly on the central nervous system include substances that change its functions, directly affecting different parts of the brain. The transmission of nerve impulses in the synapses of the central nervous system, as well as in the synapses of the peripheral nervous system, is carried out with the help of mediators. Acetylcholine, norepinephrine, dopamine, serotonin, γ-aminobutyric acid (GABA), some other amino acids (glutamic, aspartic acid) play the role of mediators in CNS synapses. Medicinal

substances affecting the central nervous system stimulate or inhibit the transmission of nerve impulses in synapses. Mechanisms of action of substances on CNS synapses are different. Substances can affect the synthesis, release of mediators or their inactivation, disrupt or block receptors on which mediators act. Medicinal substances acting on the CNS are represented by the following groups: anesthetics, hypnotics, antiepileptics, antiparkinsonian agents, analgesics, analeptics, psychotropic agents.

Means for anesthesia in therapeutic doses cause the reverse suppression of spinal reflexes, loss of consciousness, all kinds of sensitivity, decrease in the tone of skeletal muscles while preserving the activity of the respiratory and vascular centers. The basis of the action of narcotic drugs are processes that lead to disruption of interneuron synaptic transmission. Depending on the depth, there are four levels of surgical anesthesia. Depending on the physico-chemical properties of narcotics and methods of their use, anesthetics are divided into inhalation and non-inhalation.

Anesthesiologists use various drugs for general anesthesia (narcosis or general anesthesia). Means for inhalation anesthesia include a number of liquids that evaporate easily: flurothane, methoxyflurane, diethyl ether and some other gaseous substances (for example, nitrous oxide). Drugs of this group are introduced into the body by inhalation. Inhalation narcotics are quickly absorbed and also quickly removed from the body through the respiratory tract. Diethyl ether, ethyl chloride and chloroform were widely used for anesthesia from the first years of its emergence. For a long time, these compounds were the dominant inhalation anesthetics, however, nowadays they have been replaced by less toxic compounds: flurothane (galathane), teflurane and other halogen-containing compounds. One of the important properties of inhalation anesthetics is their lipophilicity. The lipophilicity of a substance is defined as the ratio of the concentration of this substance in adipose tissue to its concentration in the aqueous phase (when the substance is distributed between phases). The mechanism of action of narcotic substances (general anesthetics) has not yet been clarified, but it can be said that there is a relationship

between the minimum concentration that causes anesthesia and the lipophilicity of general anesthetics**.**

2. Pharmaceutical analysis of the main representatives of anesthetic agents.

CF_3-CHBrCl

Fluoroethane

This compound has a strong narcotic effect, quickly (after 1-2 minutes) causes narcosis, acts for another 3-5 minutes after stopping the administration.

Synthesis. Bromination of 1,1,1-trifluoro-2-chloroethane:

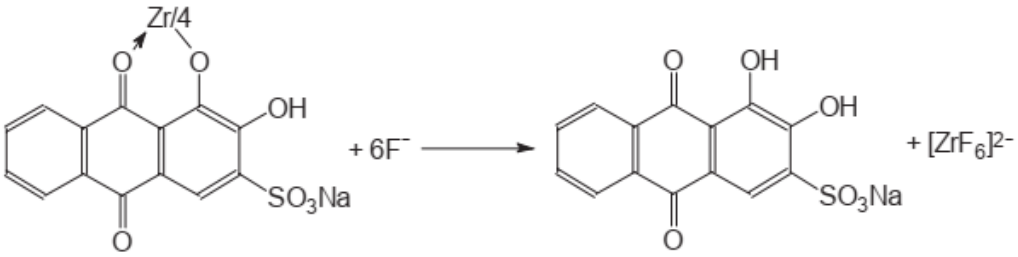
$$CF_3\text{-}CH_2Cl + Br_2 \rightarrow CF_3\text{-}CHClBr + HBr$$

Properties. A transparent, colorless, heavy, volatile liquid with an odor reminiscent of chloroform, sweet and burning to the taste, does not act. Contains 0.01% thymol added as a stabilizer. Slightly soluble in water, miscible with anhydrous alcohol, ether, chloroform, trichlorethylene, essential and fatty oils.

Identification:

1. By physical constants (density, boiling point, refractive index). Having a high density (1.865–1.870), fluoroethane, unlike chloroform and trichlorethylene, when concentrated sulfuric acid is added, is in the lower layer.

2. To determine fluorine, the drug is fused with metallic sodium. Fluoride ions are detected with a mixture of zirconium nitrate and alizarin red - the red color of the solution changes to bright yellow:

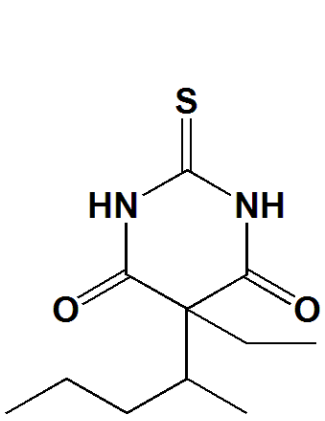


3. The IR spectrum is compared with the spectrum of a standard sample. Thymol content is determined colorimetrically by reaction with titanium (IV) oxide, comparing with a standard solution.

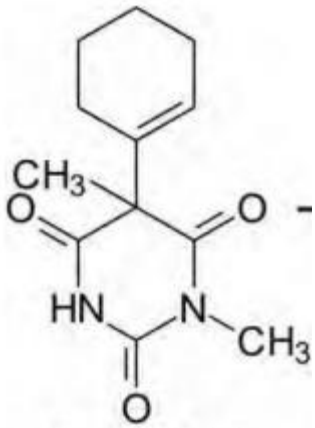
Storage. In well-stoppered glasses of dark glass, in a dry, cool place, protected from light. After the end of every 6 months of storage, the medicinal product is retested.

Application. Means for inhalation anesthesia. Can be used with oxygen and ether. Not explosive.

According to the modern classification, drugs for non-inhalation (injection) anesthesia are divided into barbiturates (hexenal and sodium thiopental) and non-barbiturate drugs (droperidol, ketamine, sodium oxybutyrate, predion, sombrevin). Thiopental and hexenal depress the higher parts of the brain (at high concentrations, they can block the centers of the medulla oblongata and stop breathing). It should be noted that thiopental is used to induce the anesthetic effect of fluorotane - after an intravenous injection, the patient falls asleep in 15 seconds. It should be noted that injectable anesthesia agents are often combined with inhalation agents, this is due to the use of lower doses of both components.

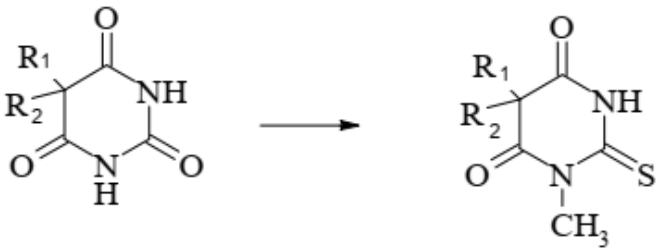


Thiopental



Hexobarbital

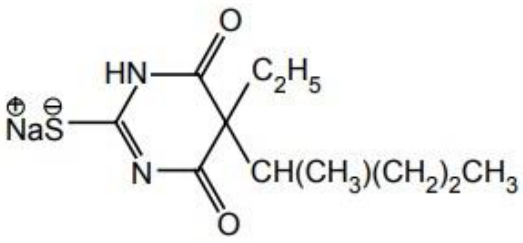
Thanks to the systematic study of the relationship between structure and biological activity, a number of barbiturates (derivatives of barbituric acid) have been obtained with ultra-short-acting drugs that are quickly eliminated from the body. Such means can cause loss of consciousness. An increase in the narcotic activity of barbiturates is observed when the oxygen atom in position 2 of the barbituric acid system is replaced by a sulfur atom (such compounds are called thiobarbiturates) and N-methylation of barbiturates:



The strengthening of narcotic activity with such modifications of barbiturates is explained by an increase in the lipophilicity of their molecules. It should be noted that barbiturates are weak acids. After administration, they decompose into a large number of non-ionized forms with high lipophilicity, and accordingly, with a high ability to penetrate through various membranes and the blood-brain barrier.

As injectable anesthetics, barbiturates have a number of advantages: at the first stage of the development of narcosis, they have a calming effect, relieve patients of fear and reduce the possibility of narcosis shock. A significant disadvantage of injectable anesthetics is the difficulty of controlling the depth and duration of anesthesia.

Thiopental sodium

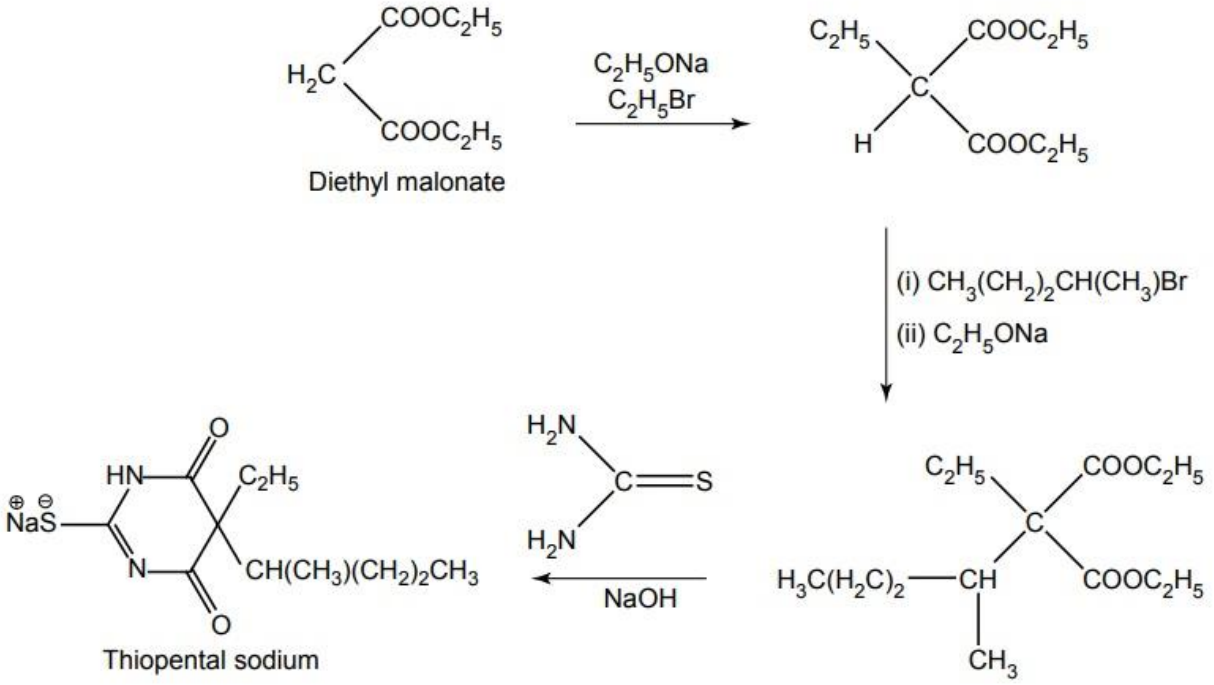


Sodium salt of 5-ethyl-5(1-methyl butyl)-2-thio barbiturate

Synthesis. The synthesis of barbituric acid derivatives consists of two stages:

1) obtaining the corresponding ester of malonic acid;

2) condensation of the ester with urea in the presence of sodium alcoholate in a solution of absolute alcohol.



Identification:

1. Physico-chemical methods: determination of the melting point, IR spectroscopy, thin-layer chromatography.

2. Formation of complex salts with cations of heavy metals:

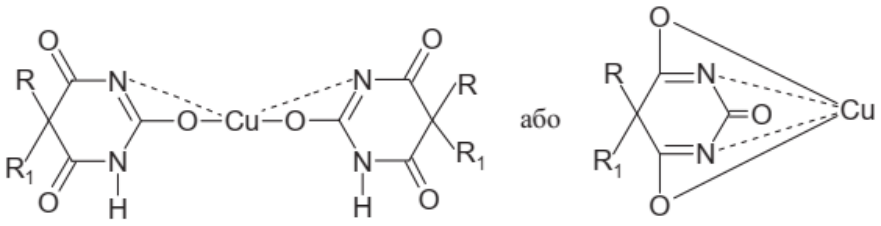
with argentum nitrate - a white precipitate;

with cobalt (II) nitrate in the presence of calcium chloride - blue-violet color and precipitate (group reaction to barbiturates, except for N-substituted ones) (SPhU);

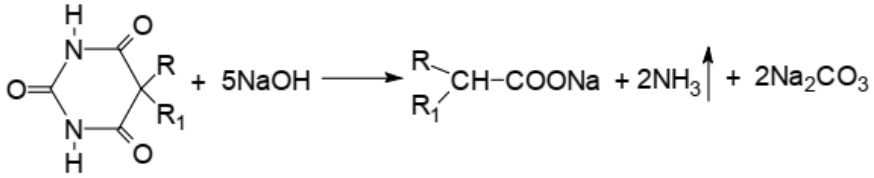
from copper (II) sulfate in the presence of potassium bicarbonate and potassium carbonate (specific reaction):

hexanal – a blue color that turns into bright blue, after which a white precipitate falls out;

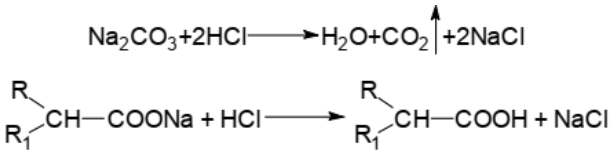
The reactions must be carried out in a neutral environment (to prevent the formation of precipitates of metal hydroxides). Acidic forms are first neutralized with sodium hydroxide solution. It is assumed that the composition of the complexes can be as follows:



3. Fusion reaction with sodium hydroxide with the formation of salts of disubstituted derivatives of acetic acid, ammonia and sodium carbonate:



During further acidification, gas bubbles (CO_2) are released and the characteristic smell of acetic acid derivatives is felt:

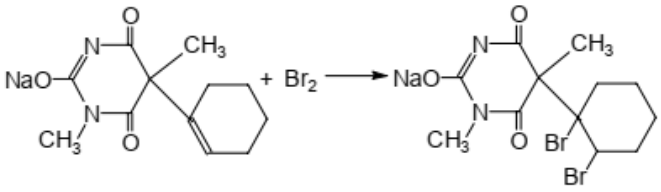


4. Reactions of the formation of colored products during condensation:

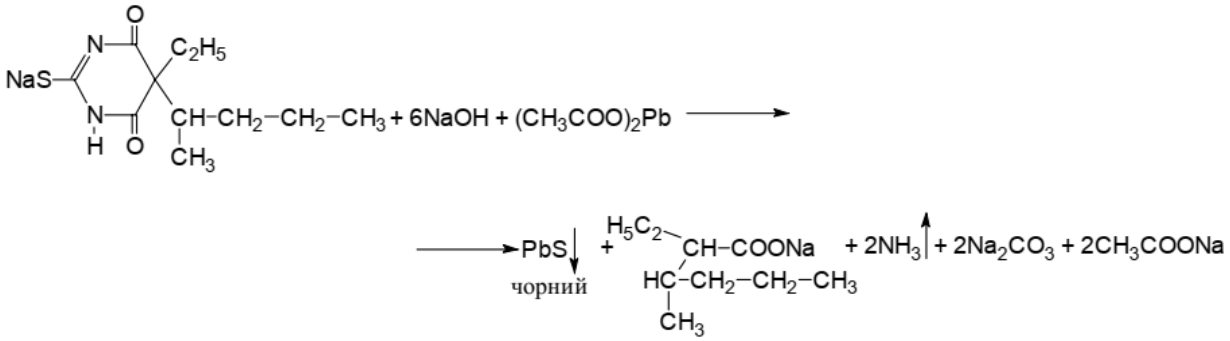
with formaldehyde and concentrated sulfuric acid:

hexenal - dark red with green fluorescence;

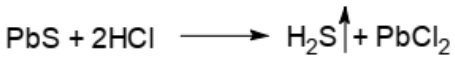
5. Hexenal decolorizes potassium permanganate solution and bromine water (due to the presence of a double bond):



6. Sulfur in sodium thiopental is detected: a) when heated with solutions of lead (II) acetate and sodium hydroxide:



After acidification, hydrogen sulfide is released:

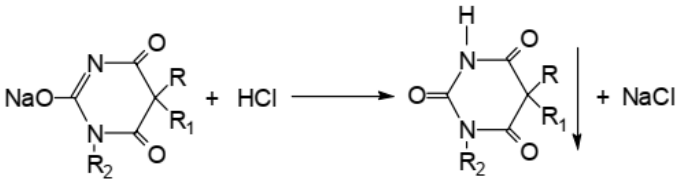


б) reaction to sulfate ions after dry mineralization with a mixture of sodium carbonate and potassium nitrate.

7. Sodium salts of barbiturates are also identified as:

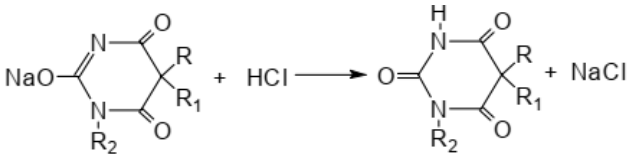
a) corresponding reactions to sodium;

b) by the melting point of the acidic form after adding hydrochloric acid:

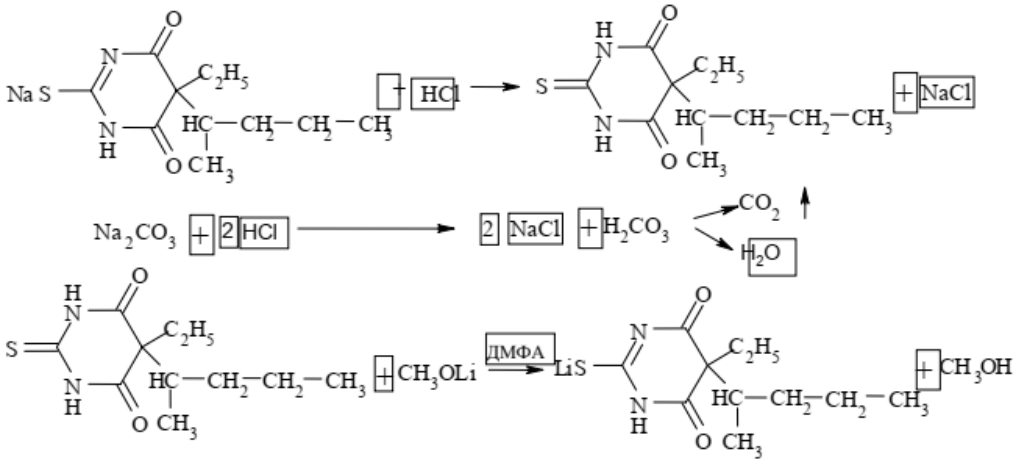


Quantitative definition:

1. Acidimetry in an aqueous environment for sodium salts of barbiturates, indicator – methyl orange, s = 1:



2. Sodium thiopental is converted into an acid form and titrated with a solution of lithium methylate, s = 1:



Storage. In well-stoppered glasses. Phenobarbital and benzonal - in glasses made of dark glass in a place protected from light. Hexenal and sodium thiopental - in glass vials of 0.5–1.0 g each, hermetically closed with rubber stoppers, crimped with aluminum caps, in a dry, cool, light-protected place. 0.05–0.25% sodium

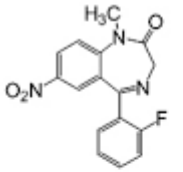
hydroxide is added to hexenal as a stabilizer; sodium thiopental - 5–6% of sodium carbonate. Aqueous solutions of sodium salts of barbiturates are easily hydrolyzed, so their solutions are prepared ex tempore.

Medicines that make it possible to regulate sleep are called hypnotics. Sedatives also contribute to normal sleep. They cause sedation by suppressing the increased excitability of the central nervous system. A common feature of hypnotics and sedative compounds is the ability to cause depression of the central nervous system, normalizing the processes of analysis and synthesis in it. In small doses, hypnotics can have a sedative effect, induce drowsiness, in turn, sedatives can correct sleep. According to M.D. According to Mashkovsky, hypnotics should have the following properties:

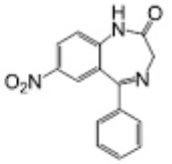
1. Restore normal (physiological) sleep.
2. To be effective and safe for different groups of patients.
3. Give a quick effect.
4. To ensure the optimal duration of sleep.
5. Do not cause respiratory depression, memory impairment, etc
side effects.
6. Not to cause addiction, physical and physiological dependence.

Currently, such "ideal" sleeping pills have not yet been found. The first drugs that had a hypnotic effect were derivatives of barbituric acid - barbiturates. The first of this group of drugs that showed high hypnotic activity was veronal (barbital), synthesized in 1903 in the laboratory of E. Fisher. Of the 2,500 compounds of this class synthesized so far, more than 50 are used in clinical practice.

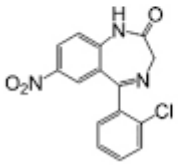
Of the relatively new drugs, hypnotics should be noted, which have a benzodiazepine ring in their composition, among which the most active are 7-nitro derivatives of benzodiazepines: nitrazepam, flunitrazepam, triazolam, clonazepam:



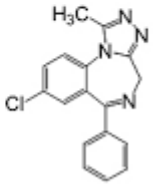
Flunitrazepam



Nitrazepam

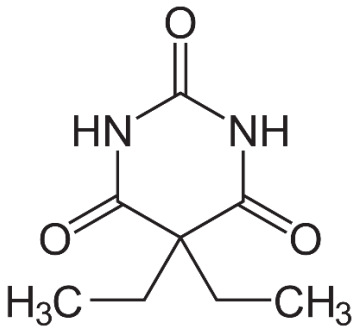


Clonazepam



Alprazolam

Barbital



5,5-diethylbarbituric acid

Identification:

1. Physico-chemical methods: determination of the melting point, IR spectroscopy, thin-layer chromatography.

2. Formation of complex salts with cations of heavy metals:

with argentum nitrate - a white precipitate;

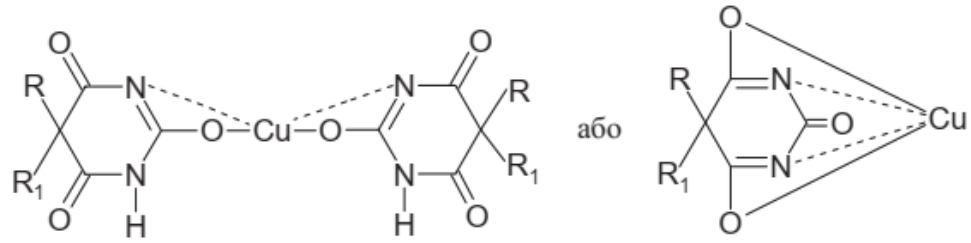
with cobalt (II) nitrate in the presence of calcium chloride - blue-violet color and sediment (group reaction to barbiturates, except for N-substituted ones) (DFU);

with copper (II) sulfate in the presence of potassium bicarbonate and potassium carbonate (specific reaction):

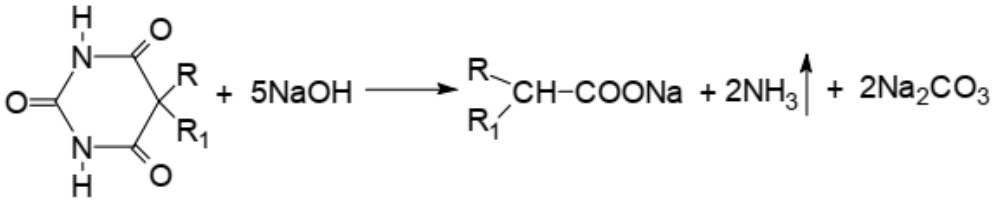
barbital - blue color and red-lilac precipitate;

The reactions must be carried out in a neutral environment (to prevent the formation of precipitates of metal hydroxides). Acidic forms are first neutralized with sodium hydroxide solution.

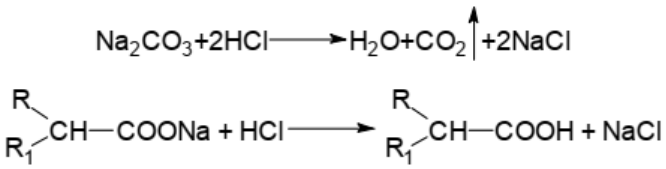
It is assumed that the composition of the complexes can be as follows:



3. Fusion reaction with sodium hydroxide with the formation of salts of disubstituted derivatives of acetic acid, ammonia and sodium carbonate:



During further acidification, gas bubbles (CO2) are released and the characteristic smell of acetic acid derivatives is felt:



4. Reactions of the formation of colored products during condensation:

a) with formaldehyde and concentrated sulfuric acid: phenobarbital, benzonal - pink color;

hexenal – dark red with green fluorescence;

b) with p-dimethylaminobezaldehyde and concentrated sulfuric acid:

etaminal-sodium – cherry-red color;

barbital - yellow.

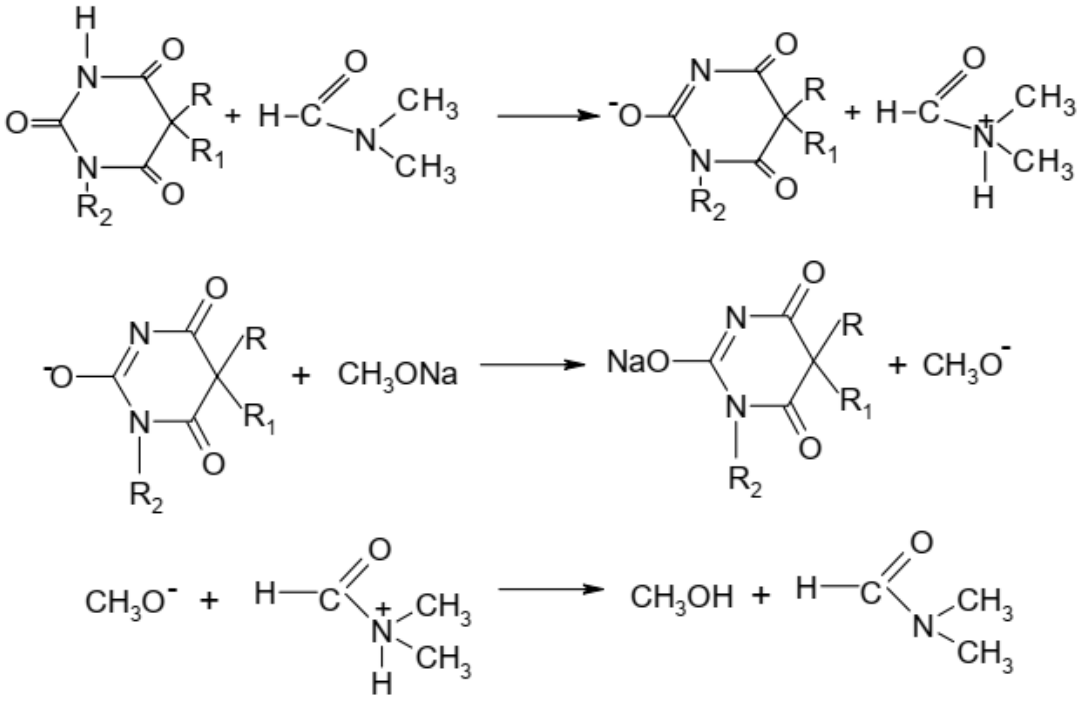
Purity test. n barbital and phenobarbital, in addition to general impurities, an admixture of 5-ethyl- or 5-phenylbarbituric acid, respectively, is determined by acidic properties. Since these acids are stronger than the corresponding barbiturates, when methyl red is added, the solution should be red-orange (but not red). In salt forms of barbiturates, allowable impurities are determined:

a) free alkali (by titration with hydrochloric acid, indicator – thymolphthalein);

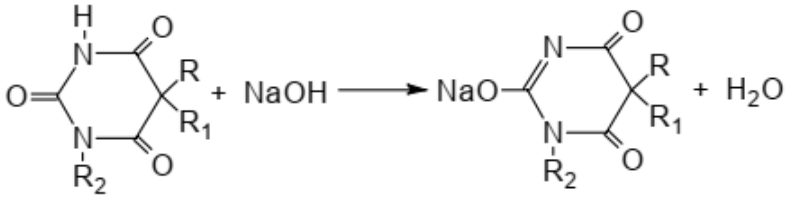
b) methyl alcohol by reaction with chromotropic acid.

Quantitative definition: Acid-base titration:

a) alkalimetry in a non-aqueous medium for acid forms of barbiturates. The weight of the substance is dissolved in dimethylformamide (DMF) or a mixture of dimethylformamide and benzene, neutralized by thymol blue (strengthens the acidic properties of barbiturate) and titrated with a solution of sodium methylate or a solution of sodium hydroxide in a mixture of methanol and benzene, the indicator is thymol blue, s = 1:



б) alkalimetry in a water-alcohol environment for acid forms of barbiturates. The sample is dissolved in thymolphthalein-neutralized alcohol to improve the solubility of barbiturates and reduce the hydrolysis of their salts, s = 1:



General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Principles of classification of anesthetics, psychotropic drugs and hypnotic drugs.
2. Characteristics, classification, relationship between the structure and pharmacological action of psychotropic drugs.
3. Methods of obtaining, methods of analysis of sleeping pills, narcotic analgesics and their analogues.
4. Use of psychotropic drugs, narcotic analgesics and their analogues in medicine.

References:

Basic:

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2. Pharmaceutical Chemistry I – Laboratory Experiments and Commentary / Attila Almási, Zsuzsanna Rozmer, Pál Perjési. 2014. – 179 p.
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4. Chemical Analysis Modern Instrumentation Methods and Techniques 2nd Edition / F. Rouessac, A. Rouessac. 2007. – 599 p.
5. Pharmaceutical drug analysis / Addis Ababa. 2005. – 554 p.
6. Analytical Chemistry Series / John M., Chalmers, Alan J. Handley. 2003. – 384 p.
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8. Europian Pharmacopoeia 10th. 2019. – 4255 p.

Additional:

1. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.

2. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 2. – 724 с.
3. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 3. – 732 с.
4. Фармацевтична хімія / П.О. Безуглий, В.А. Георгіянц, І.С. Гриценко, І.В. та ін.: за ред. П.О. Безуглого. – Вінниця: Нова книга, 2017. – 456 с.
5. Фармацевтична хімія. Загальна та спеціальна фармацевтична хімія. Лікарські засоби неорганічної природи: лабораторно-практичні заняття. Навчальний посібник / Л.Г. Мішина. – Вінниця: ПП «ТД «Едельвейс і К»», 2010. – 384 с.

Lecture No. 9

Topic: Anticonvulsant and antiepileptic drugs. Means for the treatment of parkinsonism. Characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, examining the purity and permissible limits of impurities and the quantitative content of drugs in individual and multicomponent anticonvulsant and antiepileptic drugs.

Goal: get acquainted with the group of drugs that have anticonvulsant and antiepileptic effects. Must know the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

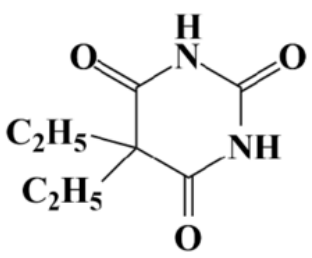
Plan and organizational structure of the lecture:

1. Pharmaceutical analysis of the main representatives of drugs with anticonvulsant and antiepileptic effects.
2. Pharmaceutical analysis of antiparkinsonian drugs.

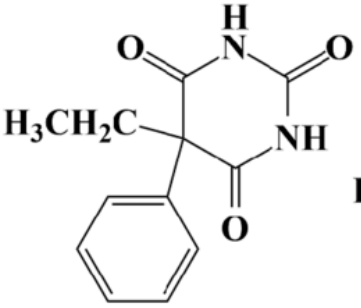
Content of lecture material (lecture text):

1. Pharmaceutical analysis of the main representatives of drugs with anticonvulsant and antiepileptic effects.

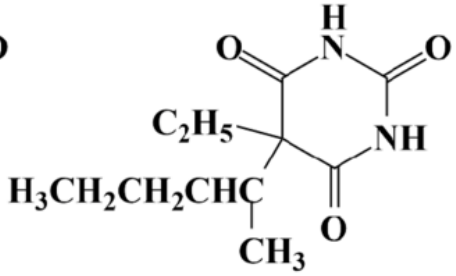
Among known anticonvulsant (antiepileptic) drugs, drugs that have structural similarities are used. The first group of antiepileptic drugs is barbiturates and related compounds (for example, hexamidine, which is a deoxybarbiturate by chemical structure and differs from phenobarbital in the absence of a carbonyl group in position 2):



Barbital



Phenobarbital



Pentobarbital

Phenobarbital is still one of the most effective anti-epileptic drugs (although it was first used at the beginning of the 20th century). It specifically suppresses the high-voltage, high-frequency discharges that occur in the brain during a severe epileptic seizure. Benzonal is easily converted to phenobarbital by 1-debenzoylation, which takes place in the input media. This process easily takes place in the human body, thus, benzonal is a prodrug.

Properties. White crystalline substances, white foamy mass (hexenal) or dry porous mass of yellowish color with a peculiar smell (thiopental sodium), bitter in

taste. Acid barbiturates are practically insoluble or very slightly soluble in water, soluble or hardly soluble in alcohol and other organic solvents, easily soluble in alkali solutions. Barbiturate salts are hygroscopic, soluble or easily soluble in water and alcohol, practically insoluble in ether.

Identification:

1. Physico-chemical methods: determination of the melting point, IR spectroscopy, thin-layer chromatography.

2. Formation of complex salts with cations of heavy metals:

with argentum nitrate - white precipitate;

with cobalt (II) nitrate in the presence of calcium chloride - blue-violet color and sediment (group reaction to barbiturates, except for N-substituted ones) (SPhU);

from copper (II) sulfate in the presence of potassium bicarbonate and potassium carbonate (specific reaction):

barbital - blue color and red-lilac precipitate;

phenobarbital - a light lilac-colored precipitate that does not change upon standing;

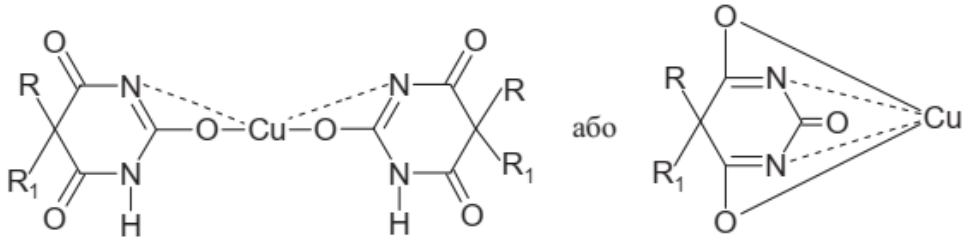
benzonal - a gray-blue color that turns into bright blue, after which a white precipitate falls out;

sodium ethaminal - a blue precipitate;

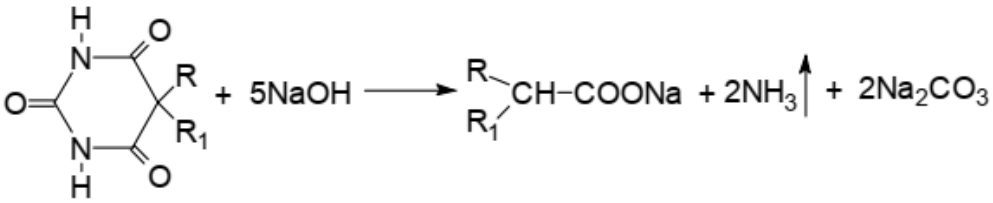
hexenal - a blue color that changes to bright blue, after which a white precipitate falls out; **sodium thiopental** - yellow-green color with suspension.

The reactions must be carried out in a neutral environment (to prevent the formation of precipitates of metal hydroxides). Acidic forms are first neutralized with sodium hydroxide solution.

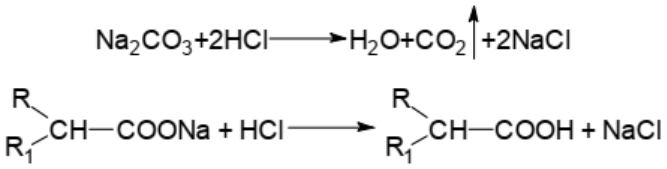
It is assumed that the composition of the complexes can be as follows:



3. Fusion reaction with sodium hydroxide with the formation of salts of disubstituted derivatives of acetic acid, ammonia and sodium carbonate:



During further acidification, gas bubbles (CO_2) are released and the characteristic smell of acetic acid derivatives is felt:



4. Reactions of the formation of colored products during condensation:

a) with formaldehyde and concentrated sulfuric acid: phenobarbital, benzonal - pink color;

hexenal – dark red with green fluorescence;

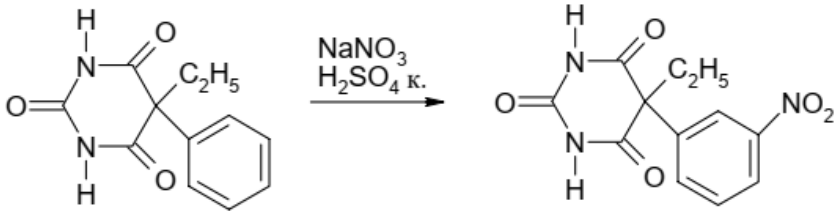
b) with p-dimethylaminobezaldehyde and concentrated sulfuric acid:

etaminal-sodium – cherry-red color;

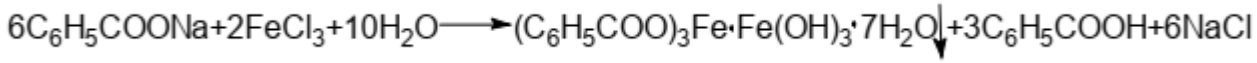
barbital - yellow.

Specific reactions are due to the presence of substituents in positions 1 and 5.

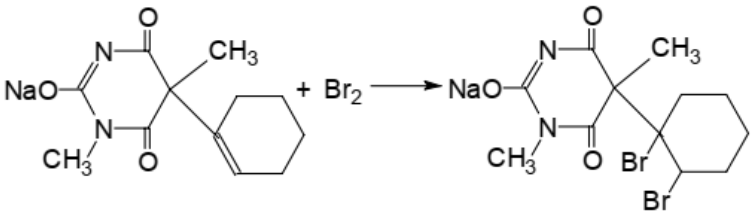
5. When phenobarbital interacts with sodium nitrate and concentrated sulfuric acid, a yellow color appears (reaction to the phenyl radical):



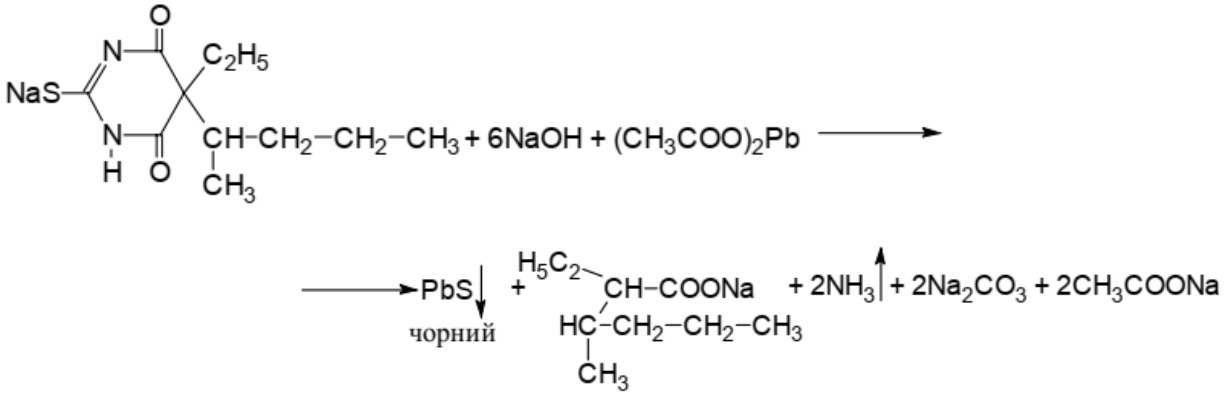
6. Benzonal after alkaline hydrolysis gives a reaction to the benzoate ion (with ferrum (III) chloride - a pinkish-yellow precipitate).



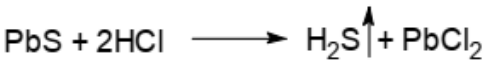
7. Hexenal decolorizes potassium permanganate solution and bromine water (due to the presence of a double bond):



8. Sulfur in sodium thiopental is detected: a) when heated with solutions of lead (II) acetate and sodium hydroxide:



After acidification, hydrogen sulfide is released:



б) reaction to sulfate ions after dry mineralization with a mixture of sodium carbonate and potassium nitrate.

Purity test. In barbital and phenobarbital, in addition to general impurities, an admixture of 5-ethyl- or 5-phenylbarbituric acid, respectively, is determined by acidic properties. Since these acids are stronger than the corresponding barbiturates, when methyl red is added, the solution should be red-orange (but not red). In salt forms of barbiturates, allowable impurities are determined:

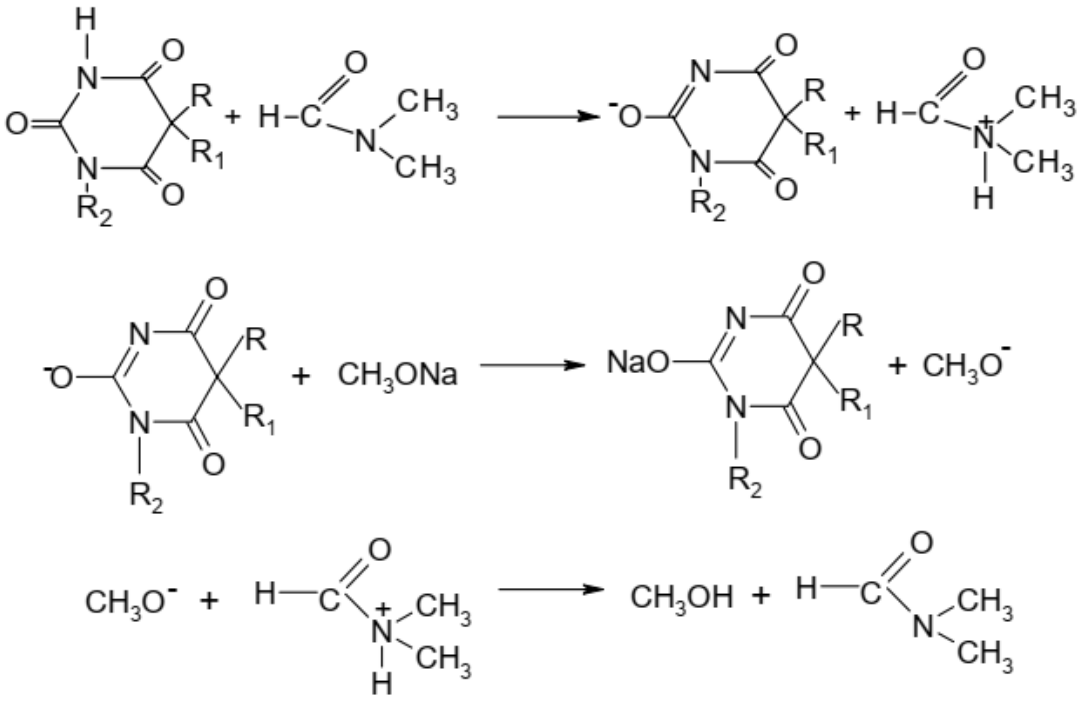
a) free alkali (by titration with hydrochloric acid, indicator – thymolphthalein);

b) methyl alcohol by reaction with chromotropic acid.

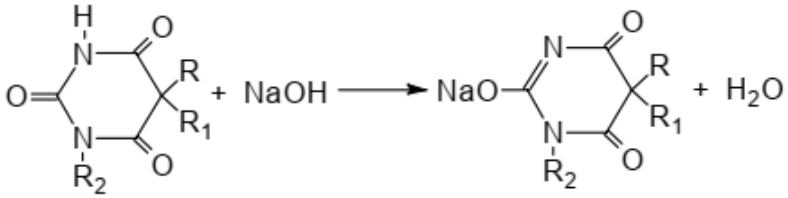
Quantitative definition: Acid-base titration:

a) alkalimetry in a non-aqueous medium for acid forms of barbiturates. The weight of the substance is dissolved in dimethylformamide (DMF) or a mixture of dimethylformamide and benzene, neutralized by thymol blue (strengthens the acidic properties of barbiturate) and titrated with a solution of sodium methylate or a

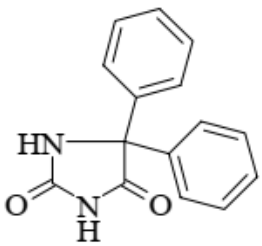
solution of sodium hydroxide in a mixture of methanol and benzene, the indicator is thymol blue, s = 1:



б) alkalimetry in a water-alcohol environment for acid forms of barbiturates. The sample is dissolved in thymolphthalein-neutralized alcohol to improve the solubility of barbiturates and reduce the hydrolysis of their salts, s = 1:



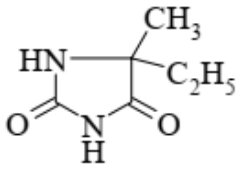
A highly active anticonvulsant compound is the drug diphenyl, which belongs to hydantoin derivatives. It has structural similarities with barbiturates:



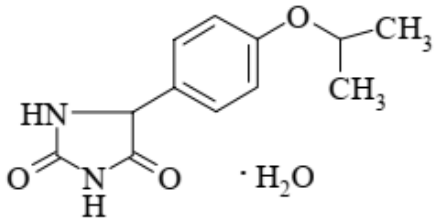
Дифеніл

Diphenyl specifically inhibits changes in the permeability of sodium ions in the central nervous system, which leads to a decrease in the spread of convulsive

activity. Ethoxymid and pufemid depress the motor centers of the cerebral cortex and increase the seizure threshold:

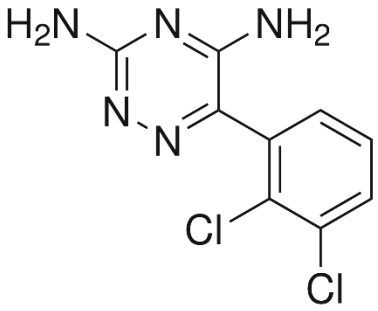


Етоксимід



Пуфемід

A significant anticonvulsant effect is characteristic of carbamazepine (finlepsin), which also has an analgesic effect, is used as a psychotropic drug for some types of depression, for the treatment of manic-depressive syndrome. It should be noted that there are two approaches to the creation of anticonvulsants. On the one hand, it is the stimulation of inhibitory central GABA synergistic processes, which should lead to a decrease in the excitation of postsynaptic membranes. Thus, it is necessary to search for GABA receptor agonists or GABA transferase blockers. On the other hand, another approach is possible, based on the blockade of excitatory neurotransmitters - aspartic and glutamic acids, which are released. At present, the anticonvulsant drug lamotrigine is widely used, which stabilizes presynaptic neuronal membranes, blocks Na+ channels, thereby preventing the release of excitatory neurotransmitter amino acids.



Lamotrigine

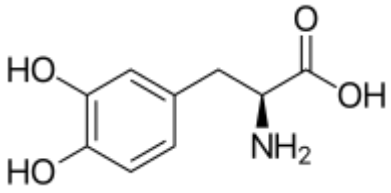
It should be noted that none of the anticonvulsants do not cure, they only prevent an epileptic attack or reduce the likelihood of its occurrence. Therefore, it is important that anticonvulsants do not have harmful side effects. In practice, this is partly achieved by using a combination of two drugs, because it allows to reduce the therapeutic dose of each of them**.**

2. Pharmaceutical analysis of antiparkinsonian drugs.

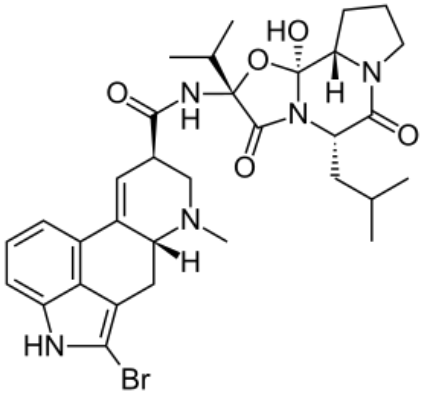
Antiparkinsonian drugs — a group of drugs that are used to treat Parkinson's disease and parkinsonism of various origins.

In this disease, the content of dopamine decreases in the basal nuclei of the brain, as well as in the substantia nigra, which mainly exerts an inhibitory effect on the neostriatum. The latter is involved in the regulation of spinal cord functions. According to modern ideas, a decrease in the level of dopamine is the most likely cause of motor and mental disorders that characterize parkinsonism syndrome. In the development of parkinsonism, an imbalance between the dopaminergic and glutamatergic systems of the brain occupies a leading place. Against this background, the stimulating effect of glutamatergic neurons prevails. This leads to violations of motor and mental functions. Akinesia, tremor, rigidity occur. Thus, the therapy of Parkinson's disease is aimed at restoring the dynamic balance between the various mediator systems that regulate the functions of the basal nuclei. One of the main ways of pharmacotherapy of parkinsonism is to eliminate dopamine deficiency in the corresponding nuclei.

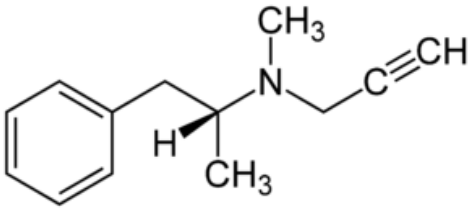
Drugs for the treatment of parkinsonism are classified according to the mechanism of action on drugs that activate dopaminergic effects - dopamine precursor levodopa, drugs that stimulate dopamine receptors - bromocriptine, selegiline; drugs that inhibit glutamatergic effects — amantadine, glutanthan; drugs that inhibit cholinergic effects - trihexyphenidyl, diphenyltropine hydrochloride, triperidine, dietazine. The main pharmacological effect of antiparkinsonian drugs is the elimination of parkinsonism symptoms: reduction of rigidity and stiffness of skeletal muscles (trihexyphenidyl, triperiden, levodopa, amantadine, glutantane, bromocriptine); elimination of tremors (levodopa, glutantan); drooling (levodopa, triperidine, trihexyphenidyl); sweating and oiliness of the skin (diphenyltropine, dietazine). Amantadine and glutantane have an antiviral effect.



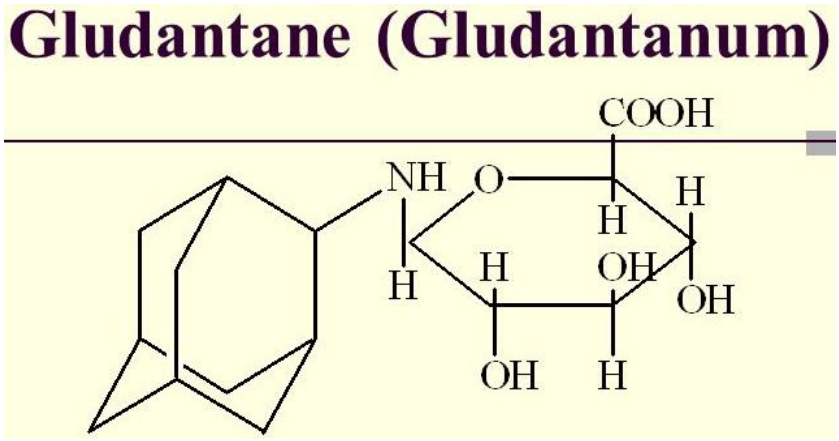
Levodopa



Bromocriptine



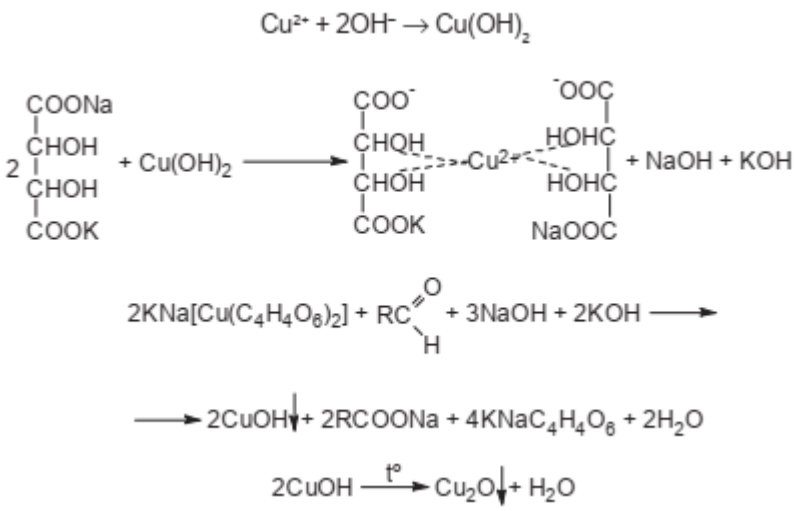
Selegiline



Properties. White, sometimes with a slight yellowish tinge, odorless crystalline powder. Hardly soluble in water, slightly soluble in alcohol.

Identification:

1. Interaction with copper-tartrate reagent (Fehling's reagent) (reductive properties of glucuronic acid).



2. A green color is formed from sodium nitroprusside in the presence of acetone and sodium carbonate.

Quantitative definition. Acidimetry in a non-aqueous medium, direct titration, indicator – crystal violet, s = 1.

Storage. In a dry place protected from light.

Application. Antiparkinsonian agent.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Principles of classification of anticonvulsant and antiepileptic drugs, drugs for the treatment of parkinsonism.
2. Characterization, classification, relationship between the structure and pharmacological action of anticonvulsant and antiepileptic drugs, drugs for the treatment of parkinsonism.
3. Methods of obtaining, methods of analysis of anticonvulsant and antiepileptic drugs, drugs for the treatment of parkinsonism.
4. Medical use of anticonvulsant and antiepileptic drugs, drugs for the treatment of parkinsonism.

References:

Basic:

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2. Pharmaceutical Chemistry I – Laboratory Experiments and Commentary / Attila Almási, Zsuzsanna Rozmer, Pál Perjési. 2014. – 179 p.
3. Introduction to Pharmaceutical Chemical Analysis / S. Hansen, S. Pederson-Bjergaard, K. Rasmussen. 2012. – 496 p.
4. Chemical Analysis Modern Instrumentation Methods and Techniques 2nd Edition / F. Rouessac, A. Rouessac. 2007. – 599 p.
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7. HANDBOOK OF MODERN PHARMACEUTICAL ANALYSIS Vol. 3 / Satinder Ahuja, Stephen Scypinski. 2001. – 587 p.
8. Europian Pharmacopoeia 10th. 2019. – 4255 p.

Additional:

1. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
2. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 2. – 724 с.
3. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». – 2-е вид. – Х. : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. – Т. 3. – 732 с.

4. Фармацевтична хімія / П.О. Безуглий, В.А. Георгіянц, І.С. Гриценко, І.В. та ін.: за ред. П.О. Безуглого. – Вінниця: Нова книга, 2017. – 456 с.
5. Фармацевтична хімія. Загальна та спеціальна фармацевтична хімія. Лікарські засоби неорганічної природи: лабораторно-практичні заняття. Навчальний посібник / Л.Г. Мішина. – Вінниця: ПП «ТД «Едельвейс і К»», 2010. – 384 с.

Lecture No. 10

Topic: Antitussives. Nootropic drugs. Antihistamines. Emetics and antiemetics. Characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Actuality of theme: Chemical and physico-chemical quality control involves determining the identity, investigating the purity and permissible limits of impurities and the quantitative content of medicinal products in individual and multi-component antitussive, nootropic, antihistamine drugs.

Goal: familiarize with the group of drugs that have an antitussive, emetic and antiemetic effect, nootropic, antihistamine drugs. Must know the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of preparation, methods of analysis, application in medicine.

Basic concepts: pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1. Pharmaceutical analysis of expectorant medicines.
2. Pharmaceutical analysis of nootropic drugs.
3. Pharmaceutical analysis of antihistamine drugs.
4. Pharmaceutical analysis of emetic and antiemetic drugs.

Content of lecture material (lecture text):

1. Pharmaceutical analysis of antitussive drugs.

ANTI-COUGH DRUGS (Latin *antitussive*) — drugs that have an antitussive effect in diseases of the lungs and upper respiratory tract.

Antitussives reduce the excitability of the cough center and suppress cough. The process of cleaning the respiratory tract occurs as a result of a reflex increase in the secretion of the bronchial glands, the activity of the ciliated epithelium and the peristaltic movements of the bronchioles. Irritation of cough reflexogenic zones, especially in the area of bifurcation of the trachea and below the larynx, causes coughing. Coughing is a reflex act coordinated by the cough center, which is located in the medulla oblongata next to the respiratory center. Cough is a protective reaction that helps to eliminate the irritant from the respiratory tract. In cases of their filling, the secret becomes viscous due to an increase in the concentration of proteins, glycosaminoglycans, and leukocytes and is difficult to separate. The cough becomes long-lasting and exhausts the patient. A coughing attack causes an increase in the tone of the bronchial muscles, distension of the lungs, a decrease in pulmonary ventilation, impaired heart function and blood circulation in the small and large circles. When using antitussives, you should not completely suppress the cough, as this impairs the self-cleaning of the bronchi and delays the recovery process.

Medicines that suppress cough (antitussives) and drugs that facilitate the release of sputum (expectorants) are used against cough..

Classification. Antitussives are divided into two groups: 1. Means of central action that suppress the cough center: a) narcotic analgesics (codeine phosphate, morphine hydrochloride); b) non-narcotic antitussives (glaucin, oxeladin). 2. Means of peripheral action that block sensitive nerve endings of cough reflexogenic zones (libexin).

Drugs of central action include narcotic analgesics (codeine phosphate, morphine hydrochloride) and non-narcotic antitussives (glaucine hydrochloride, oxeladin, butamirate citrate), which are used in cases where the cough is not productive. The main indication for their use is a long dry cough with chronic inflammatory processes of the respiratory tract.

In cases of long-term use of codeine phosphate, together with weakening of cough, pulmonary ventilation decreases due to suppression of the respiratory center and the possibility of addiction arises. Codeine phosphate is contraindicated for children under 6 months. In connection with the possibility of the development of addiction, it is prescribed with restrictions, like other narcotic analgesics. Codeine phosphate is part of the combined tablets used against cough "Kodterpin", "Cough tablets", etc.

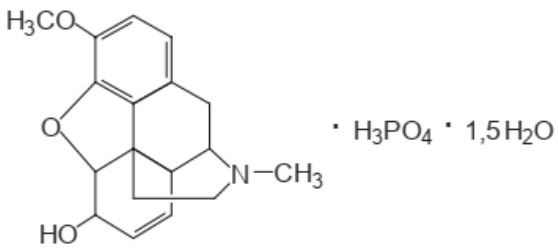
Glaucine hydrochloride is an alkaloid of yellow poppy family. Unlike opiates, it acts on the cough center selectively, without suppressing breathing and without delaying the release of sputum. Does not cause constipation and drug addiction, is not contraindicated for children. The drug has adrenoblocking properties, so it is not recommended in case of low blood pressure.

Oxeladin (Paxeladine, Tusuprex) selectively suppresses the cough center. Does not cause drowsiness, does not suppress breathing, does not affect bowel motility. Side effects: nausea, vomiting, epigastric pain.

Butamirate citrate (intusin, stoptusin, synecod) has bronchodilator, expectorant, anti-inflammatory effects in addition to antitussive.

Libexin is a synthetic drug of mainly peripheral action with local anesthetic and antispasmodic properties. Its antitussive effect is not inferior to codeine hydrochloride, but it does not suppress breathing and does not cause addiction. Indications: acute respiratory viral infection, bronchitis, bronchial asthma, etc. Cough suppressants are combined with expectorants.

Кодеїну фосфат (Codeini phosphas)



Properties. White crystalline powder, odorless, bitter in taste. It weathers in the air. Easily soluble in water, slightly soluble in alcohol, very slightly soluble in ether and chloroform.

Identification:

1. The substance gives the same reactions as codeine:

a) Physico-chemical methods: melting point, UV and IR spectroscopy.

b) When heated with concentrated sulfuric acid and a solution of ferrum (III) chloride, a blue color appears, which changes to red when one drop of dilute nitric acid is added.

c) Non-pharmacopoeial reactions:

- with Marki's reagent - a blue-violet color that intensifies when standing;
- with concentrated nitric acid - orange color.

2. Codeine phosphate is also identified as:

a) by the reaction of phosphates with a solution of argentum nitrate after the precipitation of a yellow precipitate.

With argentum nitrate solution; a yellow precipitate is formed, the color of which does not change during boiling and which dissolves when ammonia solution is added:

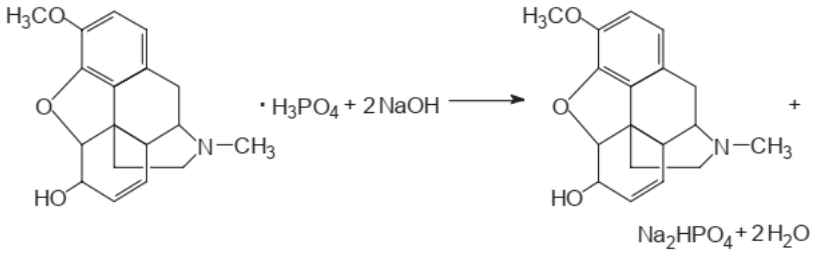
$$PO_4^{3-} + 3AgNO_3 \rightarrow Ag_3PO_4\downarrow + 3NO_3^-$$

b) by the melting temperature of the codeine base isolated under the action of sodium hydroxide solution (154–157 °C).

Quantitative definition.

1. Acidimetry in a non-aqueous environment, s = 1.

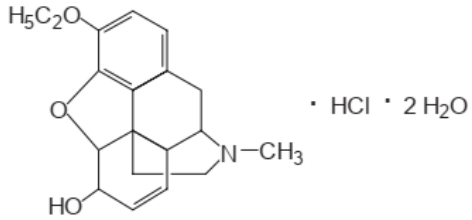
2. Alkalimetry in the presence of an alcohol-chloroform mixture, the indicator is phenolphthalein, s = 1/2:



Storage. In a sealed container that protects against light.

Application. Analgesics (narcotics) and antitussives.

Етилморфіну гідрохлорид
(Aethylmorphini hydrochloridum) (ДФУ)
Діонін (Dioninum)



Properties. Crystalline powder of white or almost white color. Soluble in water and 96% alcohol, practically insoluble in ether.

Identification:

1. Physico-chemical methods: IR spectroscopy.

2. According to the melting temperature of the base of ethylmorphine, selected under

by the action of sodium hydroxide solution.

3. When heating the substance with concentrated sulfuric acid and a solution of ferrum (III) chloride, a blue color appears, which changes to red after the addition of concentrated nitric acid.

4. The substance reacts to chlorides.

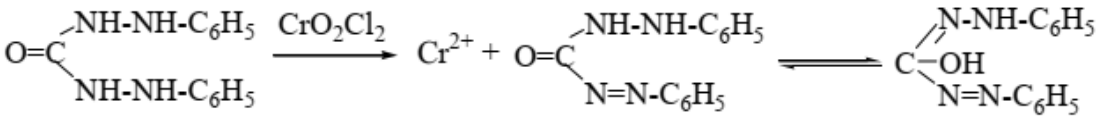
a) with a solution of argentum nitrate in the presence of dilute nitric acid, a white cheesy precipitate is formed, soluble in an ammonia solution:

$$Cl^- + AgNO_3 \rightarrow AgCl\downarrow + NO_3^-$$
$$AgCl + 2NH_4OH \rightarrow [Ag(NH_3)_2]Cl + 2H_2O$$

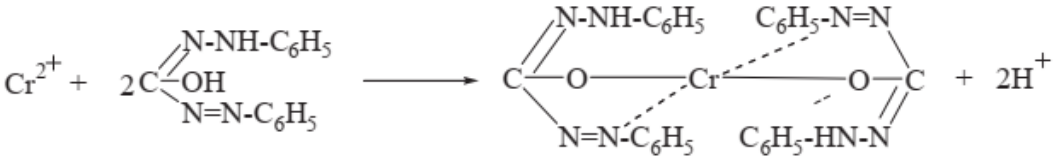
b) the reaction of a dry substance with potassium dichromate and sulfuric acid - paper impregnated with a solution of diphenylcarbazide turns purple-red. Chlorides interact with potassium dichromate in the presence of sulfuric acid with the formation of a volatile compound - chromyl chloride:

$$4Cl^- + K_2Cr_2O_7 + 3H_2SO_4 \rightarrow 2CrO_2Cl_2\uparrow + K_2SO_4 + 3H_2O + 2SO_4^{2-}$$

Chromyl chloride oxidizes diphenylcarbazide to colorless diphenylcarbazone:



Next, an internally complex violet-red compound is formed:



5. non-pharmacopoeial reactions.

a) iodoform test. When the mixture of the substance, crystalline iodine and sodium hydroxide solution is heated to boiling, the characteristic smell of iodoform appears:

$$R\text{-}OC_2H_5 + NaOH \rightarrow R\text{-}ONa + C_2H_5OH$$

$$C_2H_5OH + 4I_2 + 6NaOH \rightarrow CHI_3\downarrow + 5NaI + HCOONa + 5H_2O$$

b) with concentrated nitric acid - orange color;

c) UV spectrophotometry.

Quantitative definition.

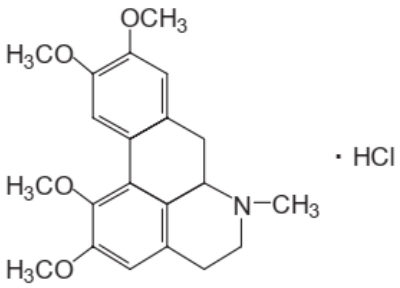
1. Acidimetry in a non-aqueous environment in the presence of mercury (II) acetate, the end of the titration is determined potentiometrically, s = 1.

2. Alkalimetry in a water-alcohol medium with the addition of chloroform, s = 1

Storage. In well-stoppered dark glass jars.

Application. Analgesic (narcotic) and antitussive. For the treatment of eyes as an anti-inflammatory agent.

Глауцину гідрохлорид (Glaucini hydrochloridum)



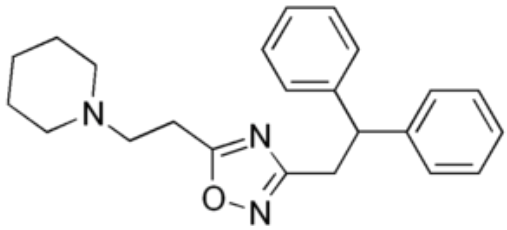
Alkaloid from the grass of the yellow cat.

Properties. White or light cream fine crystalline powder. Soluble in water, hardly soluble in alcohol.

Storage. In a dry place protected from light.

Application. Antitussive; unlike codeine, it does not suppress breathing, does not cause addiction and addiction, has a moderate hypotensive effect.

Libexin (Prenoxdiazin hydrochloridum)



3-(β, β-Diphenylethyl)-5-(β-1'-piperidylethyl)-1,2,4-oxadiazole hydrochloride

White crystalline powder, soluble in water. Its antitussive activity corresponds to codeine, but unlike it, it does not suppress breathing and does not cause addiction. In chronic bronchitis, it has an anti-inflammatory effect.

It is used as an antitussive agent for catarrh of the upper respiratory tract, acute and chronic bronchitis, bronchopneumonia, bronchial asthma and other diseases.

2. Pharmaceutical analysis of nootropic drugs.

Nootropic drugs (lat. *nootropa* < Greek. *noos* — mind, thinking + *tropos* — direction) — drugs that have a specific effect on the highest integrative functions of the brain, stimulate the learning process, improve memory and mental activity, increase the resistance of the brain to aggressive influences, strengthen the cortico-subcortical connection. The group of nootropic drugs has been known since 1972. Drugs that fully meet these requirements do not exist today, and it is hardly possible to expect the creation of drugs with such a multifaceted, complex, positive effect on the most complex functions of the body. However, the term "nootropics" entered medical practice, and drugs that correspond to one degree or another to the properties listed above began to be included in the group of nootropic drugs.

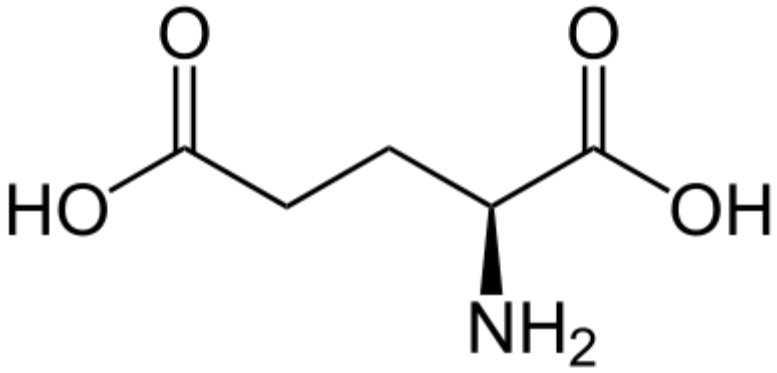
Generally accepted classification There is no generally accepted classification of nootropic drugs yet. According to modern beliefs, nootropic drugs include: pyrrolidone derivatives — piracetam, etiracetam, aniracetam, oxiracetam, pramiracetam, nefiracetam, etc.; dimethylaminoethanol derivatives — deanol aceglumate, meclofenoxat, centrophenoxine; pyridoxine derivatives — pyrithinol;

neuroamino acid preparations — GABA, GABA derivatives — phenibut, nicotinoyl GABA, hopanthenic acid, glycine, glutamic acid, sodium oxybutyrate; drugs that increase cerebral blood circulation, microcirculation and metabolism - nicergoline, vinpocetine, vincamine, cinnarizine, flunarizine, nimodipine; xanthine derivatives — penoxyphyllin, carnitine, phosphatidylserine; vitamins and their derivatives — pyridoxine, pantothenic acid, folic acid, vitamin E; cholinomimetics of central action — choline alfoscerate; Ginkgo biloba preparations — Bilobil, Memoplant, Revital ginkgo, Tanakan, etc.; intermediate products of cell metabolism — orotic and succinic acids; substrates providing energy: inosine, ATP, RNA, glucose-1- and glucose-6-phosphate; combined drugs — Instenon. Despite the difference in the spectrum of effects, all the listed drugs have a positive effect on memory (nootropic effect). Nootropic drugs differ from other psychotropic drugs by their main pharmacological properties. They do not have a pronounced psychostimulant or sedative effect, do not cause specific changes in the bioelectric activity of the brain, depletion of the body's functional capabilities, addiction and addiction. At the same time, they in one way or another stimulate the transmission of excitation in central neurons, facilitate the transmission of information between the cerebral hemispheres, improve energy processes and blood supply to the brain, and increase its resistance to hypoxia. The most important manifestation of their action is the activation of intellectual and memory functions, antihypoxic activity. Nootropic drugs can enhance the effects of GABA, synthesis of dopamine, increase the level of norepinephrine in the brain. Under the influence of piracetam and meclofenoxat, the content of acetylcholine at the level of synapses and the density of cholinergic receptors increases. Some drugs are able to increase the content of serotonin in the brain. Along with nootropic activity, the drugs of this group also show other pharmacological properties. For example, pantothenic acid and nicotinyl GABA exhibit anticonvulsant activity, and phenibut has a tranquilizing effect, and nicotinyl GABA and phenibut have antioxidant properties. does not exist yet. According to modern beliefs, nootropic drugs include: pyrrolidone derivatives — piracetam, etiracetam, aniracetam, oxiracetam, pramiracetam, nefiracetam, etc.;

dimethylaminoethanol derivatives — deanol aceglumate, meclofenoxat, centrophenoxine; pyridoxine derivatives — pyrithinol; neuroamino acid preparations — GABA, GABA derivatives — phenibut, nicotinoyl GABA, hopanthenic acid, glycine, glutamic acid, sodium oxybutyrate; drugs that increase cerebral blood circulation, microcirculation and metabolism - nicergoline, vinpocetine, vincamine, cinnarizine, flunarizine, nimodipine; xanthine derivatives — penoxyphyllin, carnitine, phosphatidylserine; vitamins and their derivatives — pyridoxine, pantothenic acid, folic acid, vitamin E; cholinomimetics of central action — choline alfoscerate; Ginkgo biloba preparations — Bilobil, Memoplant, Revital ginkgo, Tanakan, etc.; intermediate products of cell metabolism — orotic and succinic acids; substrates providing energy: inosine, ATP, RNA, glucose-1- and glucose-6-phosphate; combined drugs — Instenon. Despite the difference in the spectrum of effects, all the listed drugs have a positive effect on memory (nootropic effect). Nootropic drugs differ from other psychotropic drugs by their main pharmacological properties. They do not have a pronounced psychostimulant or sedative effect, do not cause specific changes in the bioelectric activity of the brain, depletion of the body's functional capabilities, addiction and addiction. At the same time, they in one way or another stimulate the transmission of excitation in central neurons, facilitate the transmission of information between the cerebral hemispheres, improve energy processes and blood supply to the brain, and increase its resistance to hypoxia. The most important manifestation of their action is the activation of intellectual and memory functions, antihypoxic activity. Nootropic drugs can enhance the effects of GABA, synthesis of dopamine, increase the level of norepinephrine in the brain. Under the influence of piracetam and meclofenoxat, the content of acetylcholine at the level of synapses and the density of cholinergic receptors increases. Some drugs are able to increase the content of serotonin in the brain. Along with nootropic activity, the drugs of this group also show other pharmacological properties. For example, pantothenic acid and nicotinyl GABA exhibit anticonvulsant activity, and phenibut has a tranquilizing effect, nicotinyl GABA and phenibut have antioxidant properties.

Mechanisms of action. It has been established that their stimulating effect on memory, thinking and learning is caused mainly by the effect of nootropic drugs on metabolic processes in nervous tissue. It is known that there are several mechanisms underlying the therapeutic effect of nootropic drugs: improving the energy state of neurons (increasing ATP synthesis, antihypoxic and antioxidant action); activation of plastic processes in the central nervous system due to increased synthesis of RNA and proteins; strengthening of synaptic transmission processes in the central nervous system; improvement of glucose utilization; membrane stabilizing action.

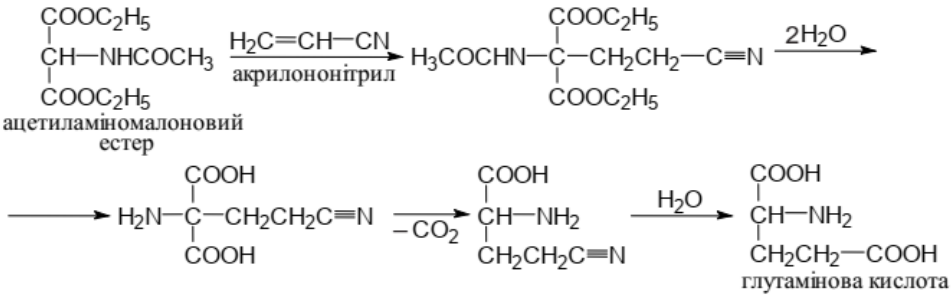
Glutamic acid



1-aminopropane-1,3-dicarboxylic acid; or 2-aminopentanedioic acid; or L-2-aminoglutaric acid

Glutamic acid is part of a number of protein substances: myosin, casein, α-lactoglobulin, etc., it is found in large quantities in brain proteins, cereals.

Synthesis. Glutamic acid is obtained by hydrolysis of protein substances or synthetically. The starting materials for the synthesis are acrylonitrile and acetylaminomalon ester:

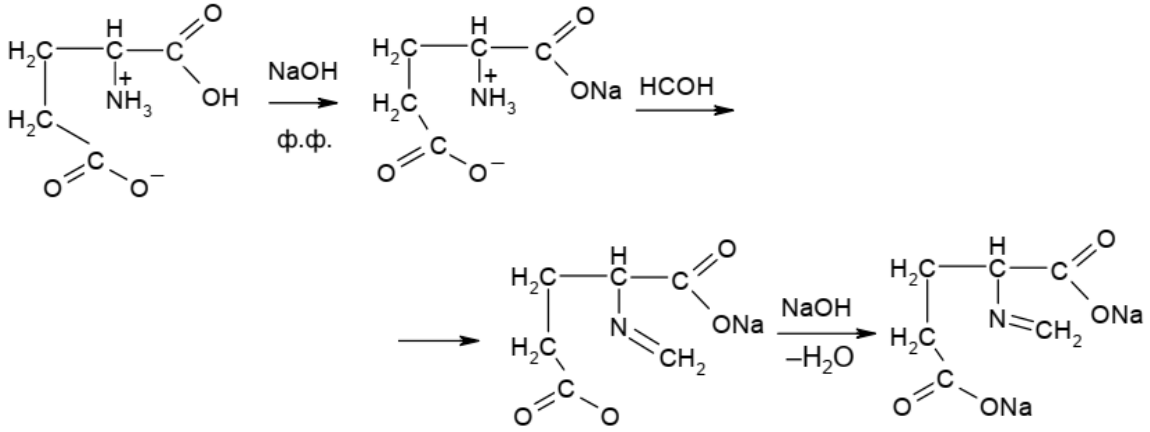


Properties. White crystalline powder or colorless crystals. Easily soluble in boiling water, slightly soluble in cold water, practically insoluble in acetic acid, acetone, 96% alcohol and ether.

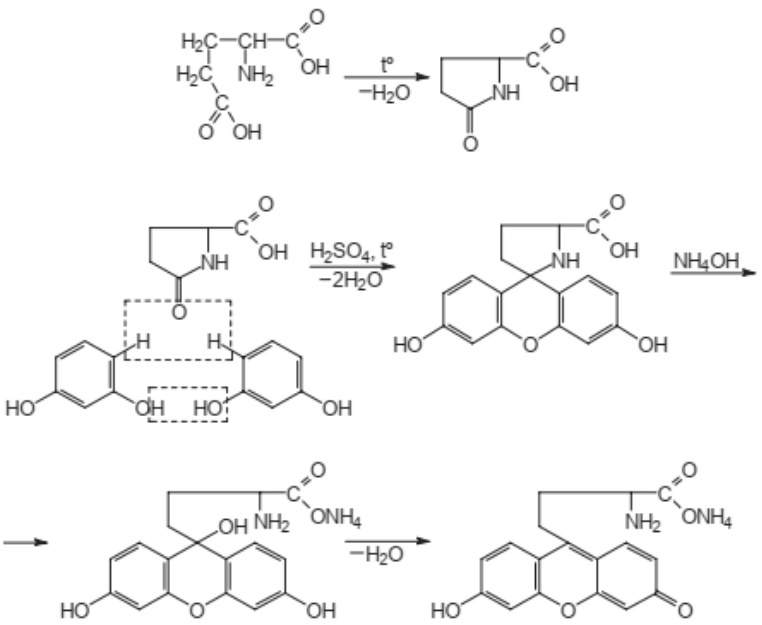
Identification:

1. According to physical constants: specific rotation; by physical and chemical methods: IR spectroscopy and thin-layer chromatography.

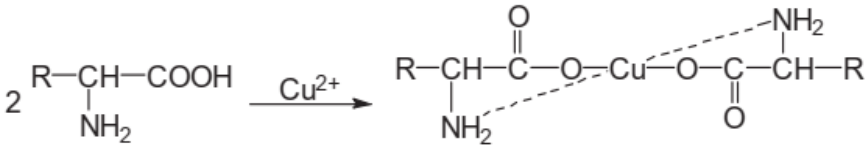
2. Reaction with sodium hydroxide in the presence of a solution of formaldehyde and phenolphthalein. Add phenolphthalein to the glutamic acid solution and neutralize with 1 M sodium hydroxide solution until a red color appears. Then a solution of formaldehyde is added; discoloration is observed. 1 M sodium hydroxide solution is added to the reaction mixture until a red color appears. The total volume of spent 1M sodium hydroxide solution should be from 4.0 ml to 4.7 ml:



3. non-pharmacopoeial reaction: during fusion with resorcinol in the presence of concentrated sulfuric acid, a red melt is formed; when water and ammonia solution are added, a red-violet color with green fluorescence appears:

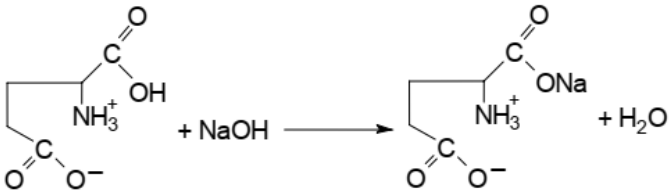


4. non-pharmacopoeial reaction: with $CuSO_4$ in an alkaline environment, a complex salt, colored in dark blue, is formed.



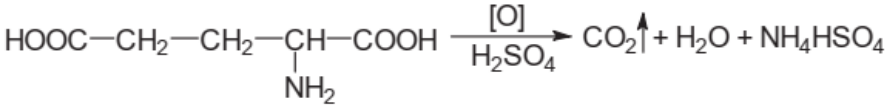
Quantitative definition.

1. Alkalimetry, direct titration, indicator – bromothymol blue, s = 1:

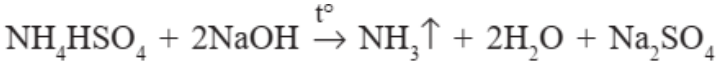


2. Determination of nitrogen after mineralization with sulfuric acid.

The method includes two stages: mineralization of organic matter (boiling in a special device in the presence of K_2SO_4, $CuSO_4$, concentrated H_2SO_4 and selenium) and acid-base titration:



Then add concentrated NaOH solution:



The released ammonia is distilled into a receiving flask containing a 0.01 M solution of hydrochloric acid:

$$NH_3 + HCl \rightarrow NH_4Cl$$

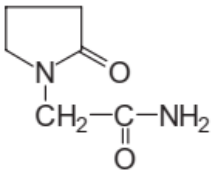
The excess of hydrochloric acid is titrated with a 0.01 M solution of sodium hydroxide, using a mixed solution of methyl red as an indicator:

$$HCl + NaOH \rightarrow NaCl + H_2O$$

Storage. In a sealed container that protects against light.

Application. In medical practice, glutamic acid is used mainly for the treatment of CNS diseases, epilepsy, psychoses, and reactive states. In pediatrics, the drug is used for retardation of mental development of various etiologies, cerebral palsy, Down's disease.

Пірацетам (Pyracetamum)
Ноотропіл

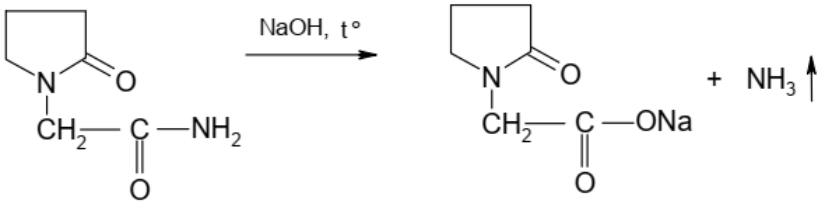


2-(2-Оксопіролідин-1-іл)ацетамід

Properties. White crystalline powder, easily soluble in water and ethanol, slightly soluble in chloroform.

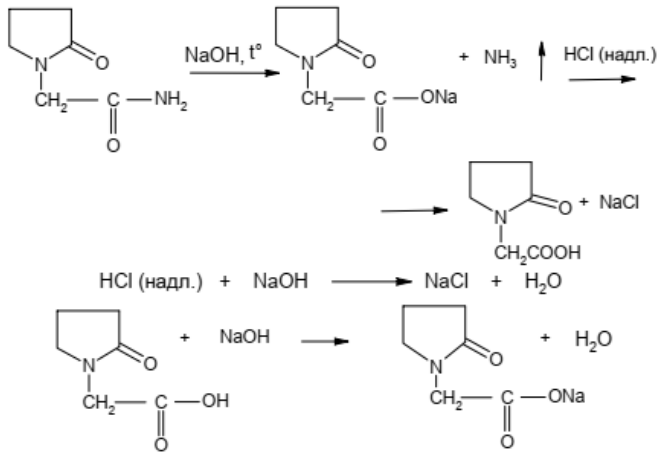
Identification:

1. IR spectroscopy.
2. Absence of pronounced absorption maxima in the UV spectrum of a 1% aqueous solution in the range of 230–350 nm.
3. Release of ammonia when heated with sodium hydroxide solution:



Quantitative definition:

1. According to Ph. Eur. alkaline hydrolysis of the substance is carried out beforehand, after which an excess of a titrated solution of hydrochloric acid is added, followed by titration of the reaction mixture with a solution of sodium hydroxide, the indicator is phenolphthalein, s = 1:



2. Determination of nitrogen in organic compounds.

Storage. In a dry place protected from light.

Application. Psychotropic (nootropic) agent.

3. Pharmaceutical analysis of antihistamine drugs.

ANTIHISTAMINIC DRUGS (Greek anti- — against + histos — tissue + Latin aminum — amine) — a specific group of antiallergic drugs, the pharmacological effect of which is the blockade of H-receptors (H comes from Histamine). There are several types of histamine receptors: H1, H2 and H3.

H1-receptors are located in non-striated (smooth) muscles of the bronchi, intestines, arteries, veins, capillaries, and heart in neurons of the central nervous system. H2-receptors are located in the parietal cells of the mucous membrane of the stomach, non-striated muscles of arteries, in neurons of the central nervous system, heart, myometrium, mast cells, basophilic and neutrophilic leukocytes, T-lymphocytes, and in adipose tissue. H3 receptors are located in the neurons of the central nervous system, the cardiovascular system, the gastrointestinal tract, and the upper respiratory tract.

Antihistamine drugs that block H1-receptors (H1-histamine blockers), thereby eliminating or reducing such types of histamine action (see Histamine), such

as increasing the tone of non-striated muscles of the bronchi, intestines, uterus; decrease in blood pressure (partially); increased permeability of capillaries with the development of edema; hyperemia and itching during intradermal administration of histamine or when endogenous histamine is released in the skin. The indicated effects are caused mainly by allergic reactions of the immediate type, which are accompanied by the phenomena of acute exudation: allergic rhinitis, urticaria, angioedema, insect bites, allergic reactions to LP, food allergy, serum sickness, dermatoses, para(pseudo)allergic reactions .

Today, there are three generations of LPs of this group on the market. and the generation of antihistamine drugs (40s of XX century) — non-selective blockers of histamine receptors, the action lasts for 4–8 hours (diphenhydramine (diphenhydramine), promethazine (diprazine, pipolfen), chloropyramine (suprastin), mebhydrolin (diazolin), clemastine (tavegil), sequifenadine (fencarol), cyprofentadine (peritol), ketotifen (zaditen); dimetinden and clemastine - up to 12 hours, mebhydrolin - up to 24 hours). They block m-cholinoreceptors in peripheral tissues, which leads to a decrease in the secretion of exocrine glands, an increase in the viscosity of the secretion, including bronchial, dryness of the mucous membranes of the oral cavity, decreased motility of the gastrointestinal tract and tone of the urinary tract, impaired accommodation, increased intraocular pressure and heart rate. The development of antiemetic and antiparkinsonian effects is possible, and some antihistamines have antidopamine, antitussive, and anxiolytic effects. Undesirable effects from the gastrointestinal tract can be manifested by nausea, vomiting, diarrhea, decreased or increased appetite. The frequency of adverse reactions decreases when taking antihistamines with food. They penetrate through the blood-brain barrier and block H1-receptors of the central nervous system, which is manifested by a sedative effect, drowsiness, decreased psychomotor activity, increased appetite, a feeling of lethargy, impaired coordination of movements, decreased ability to learn and concentrate. Most often, sedation is caused by drugs of the diphenhydramine group (diphenhydramine). The sedative effect increases under the influence of alcohol and other substances that depress the central nervous

system: tranquilizers, neuroleptics, sedatives and some other drugs. Dizziness, ringing in the ears, apathy, fatigue, decreased visual acuity, diplopia, nervousness, insomnia, tremors are often possible. With long-term use of antihistamines, their effectiveness decreases (addiction). A.p. and generation is not recommended to be prescribed in the first 3 months of pregnancy, to patients with glaucoma, benign prostatic hyperplasia, bronchial asthma, as well as to elderly patients. A significant drawback is the appointment of these drugs several times a day.

Antihistamines of the II generation (80s of the 20th century) — terfenadine (Trexyl), astemizole (Hismanol), loratadine (Cloritin), astemizole, acrivastine, cetirizine, ebastine — differ in the absence of a sedative effect, an effect on choline and serotonin receptors, interactions with alcohol and psychotropic drugs, addiction with long-term use, as well as high affinity for H1 receptors. Binding to receptors is long-lasting and non-competitive. These drugs are prescribed 1-2 times a day. However, terfenadine and astemizole have a significant side effect — an effect on the cardiovascular system (ventricular arrhythmias with prolongation of the Q–T interval on the ECG, tachycardia that develops due to the blocking of potassium channels that control the repolarization of myocardial membranes). All AP The II generation (with the exception of cetirizine and acrivastine) are prodrugs, the action of which is determined by active metabolites formed in the liver with the help of the CYP 3A4 isoenzyme of the cytochrome P450 system. They should not be used with drugs that are metabolized by the same enzyme systems: macrolide antibiotics (erythromycin, clarithromycin, oleandomycin, azithromycin), antifungal drugs (ketoconazole, itraconazole), H2-receptor blocker cimetidine, some antiarrhythmic drugs (quinidine, procainamide, disopyramide), antidepressants (fluoxetine, sertraline and paroxetine), as well as in case of impaired liver function, which can lead to the appearance of a cardiotoxic effect (for terfenadine and astemizole).

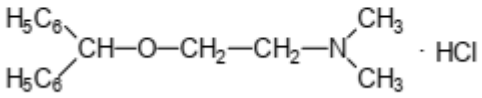
Antihistamines of the III generation are active metabolites of drugs of the II generation (fexofenadine - active metabolite of terfenadine, norastemizole - astemizole, desloratadine - loratadine), provide an increased level of safety profile. They inhibit mediators of systemic allergic inflammation, including cytokines and

chemokines, and reduce the expression of adhesion molecules, inhibit chemotaxis, activation of eosinophilic granulocytes, and superoxide radical formation; reduce bronchial hyperreactivity. Application of AP the III generation is the most rational for long-term treatment of allergic diseases (year-round allergic rhinitis, seasonal allergic rhinitis or rhinoconjunctivitis with exacerbations lasting more than 2 weeks, chronic urticaria, atopic and allergic contact dermatitis). H2-receptor blockers (cimetidine, ranitidine, famotidine, nizatidine) are competitive antagonists of histamine. From a chemical point of view, they can be considered as histamine derivatives. H2 receptors are bound to adenylate cyclase. This is manifested in the fact that when H2 receptors are stimulated by histamine, there is an increase in intracellular cAMP, while the secretory activity of the parietal cells of the gastric mucosa increases. In addition, when H2-receptors are stimulated by histamine, heart rate increases, a positive inotropic effect is noted in the heart; in non-striated muscles of arterial vessels there is a decrease in tone; in mast cells and basophilic leukocytes — inhibition of degranulation; in neutrophilic leukocytes — a decrease in chemotaxis, suppression of the release of lysosomal enzymes; in T-lymphocytes — a decrease in cytotoxic activity, production of a factor that inhibits macrophage migration; in adipose tissue - increased release of fatty acids. Acting on H2-receptors of parietal cells, they reduce the secretion of hydrochloric acid. To a lesser extent, they suppress the secretion of pepsin and gastromucoproteid (Kasl's intrinsic factor). These drugs have low lipophilicity, so they do not cross the blood-brain barrier. H2-receptor blockers are used as antisecretory drugs for duodenal and gastric ulcers, hypergastrinemia, peptic (reflux) esophagitis, erosive gastritis, duodenitis. Unlike ranitidine, famotidine and nizatidine are more active, act longer (prescribed once a day) and have fewer side effects.

H3 receptors were originally found on histaminergic neurons of the CNS as presynaptic receptors that regulate the formation and release of histamine. H3-receptors as a target of pharmacological influence are less important today. Histamine-containing neurons are mainly localized in the posterior hypothalamus. In addition to the inhibitory effect on the release of histamine, presynaptic H3

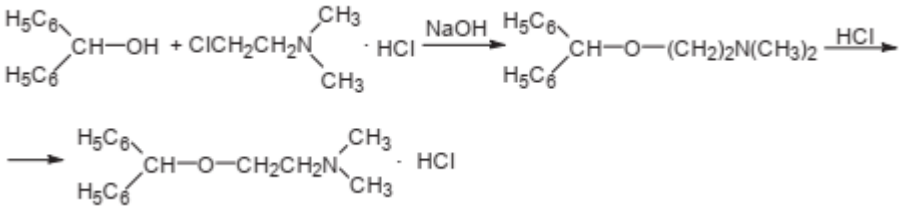
receptors are involved in the regulation of the production of some other mediators/modulators (acetylcholine, GABA, dopamine, glutamine, serotonin, norepinephrine), thus, they also function as heteroreceptors. In addition to the central nervous system, H3-receptors are present in the gastrointestinal tract (their stimulation suppresses the secretion of hydrochloric acid in the stomach; they are involved in gastroprotective action), in the cardiovascular system (activation of presynaptic H3-receptors suppresses the adrenergic effect), in the upper respiratory tract (anti-inflammatory effect). Blockers of H3 receptors include ciproxifan, clobenpropit, thioperamide, clozapine.

Дифенгідраміну гідрохлорид
(Diphenhydramini hydrochloridum) (ДФУ)
Димедрол (Dimedrolum)



2-(дифенілметокси)-*N*,*N*-диметилетанаміну гідрохлорид

Synthesis. By the interaction of benzhydrol and β-dimethylaminoethyl chloride hydrochloride in the presence of sodium hydroxide:

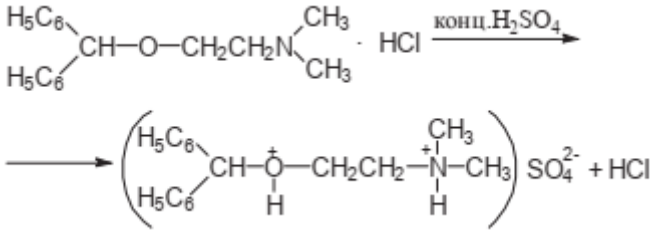


Properties. Crystalline powder of white or almost white color. Very easily soluble in water, easily soluble in 96% alcohol.

Identification:

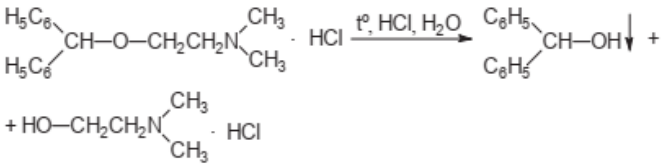
1. Physicochemical methods: melting point, IR spectroscopy, UV spectroscopy.

2. The reaction of the formation of an oxonium salt when interacting with concentrated sulfuric acid - an intense yellow color appears, which turns red when concentrated nitric acid is added. The resulting solution is diluted with water, cooled and chloroform is added; the chloroform layer turns intense purple:



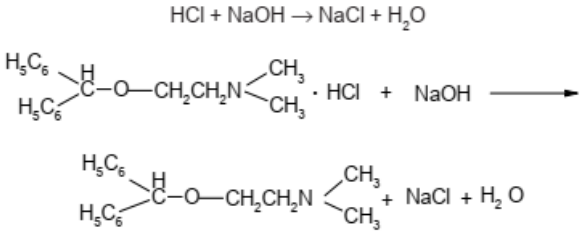
3. The substance reacts to chlorides.

4. Acid hydrolysis reaction:



The melting point of the formed benzhydrol is checked (62–67 °C).

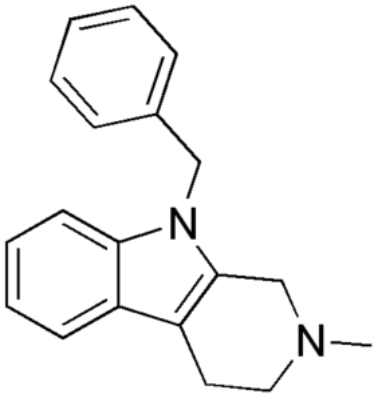
Quantitative definition. 1. Alkalimetry in a mixture of alcohol and a 0.01 M solution of hydrochloric acid, direct titration, potentiometric, s = 1. The volume of the titrant between two potential jumps on the titration curve (SPhU) is taken into account:



Storage. In a sealed container that protects against light and moisture, as the drug is hygroscopic and can gradually hydrolyze.

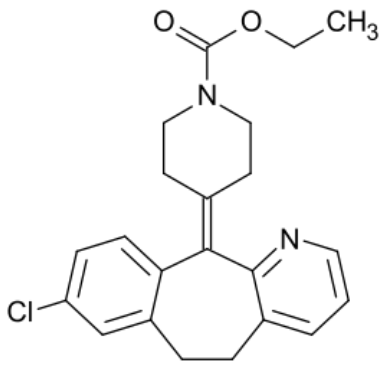
Application. Antihistamine (antiallergic) agent.

Mebhydrolin



9-benzyl-2-methyl-2,3,4,9-tetrahydro-1H-β-carboline

Loratadine / Claritin



11-(1'-Carbethoxy-4'-piperidinylidene)-8-chloro-5,6-dihydrobenzocycloheptapyridine

4. 4. Pharmaceutical analysis of emetic and antiemetic drugs.

VOMITING DRUGS — drugs that have the ability to selectively excite the vomiting center. In some cases, there is an acute need to vomit, which helps to empty the stomach and remove from it substances that irritate and damage its mucous membrane. This complex reflex act is carried out with the help of B.p. Introduction of B.p. causes antiperistalsis of the small intestine, as a result of which its contents can be partially thrown into the stomach, increasing its volume. Then there is a spasm of the pyloric part of the stomach and relaxation of the body of the stomach and its cardiac opening. The cardiac part of the stomach is pulled up, the esophagus expands and becomes shorter. Favorable conditions are created for reverse ejection of stomach contents. This is facilitated by intensive contractions of the diaphragm and muscles of the abdominal wall. A sharp increase in intra-abdominal and intra-gastric pressure creates conditions for emptying the stomach. Vomiting is usually preceded by a period of nausea. Paleness, cold sweat appear, increased secretion of salivary, gastric and bronchial glands, lacrimation, breathing becomes arrhythmic, blood pressure decreases, general weakness, suppression of voluntary movements, severe subjective sensations are noted. Soon after vomiting, the phenomena disappear.

The central link of the act of vomiting is the vomiting center, which coordinates this complex reflex process. A special chemoreceptor zone is connected to the center, which is called the starting (trigger) zone. Excitation of the vomiting center by chemicals can be carried out by direct exposure or reflexively. In this regard, B.p. is distinguished. central (direct) and reflex (peripheral) action.

The mechanism of action of B.p. central action consists in the fact that they are agonists of dopamine receptors and cause excitation of receptors of the chemoreceptor zone. To B.p. central action belongs to apomorphine hydrochloride, which is obtained as a result of the action of hydrochloric acid on morphine. The direct effect of apomorphine is evidenced by the appearance of vomiting after applying it directly to the trigger zone of the vomiting center. To B.p. of reflex action include preparations of emetic root, anise grass, copper sulfate, zinc sulfate, emetine, etc. The reflex nature of the emetic effect of emetine was first established in the laboratory of I.P. Pavlov was his student N.N. Tokarev He proved that this alkaloid induces vomiting in dogs only when administered into the stomach. When crossing the vagus nerves, lubricating the gastric mucosa with local anesthetic drugs, as well as when emetine is administered parenterally or into the rectum, the vomiting effect does not occur. Drugs of this group, including copper and zinc sulfate, are used very rarely due to their irritating effect on the gastric mucosa and general toxic effect.

Copper sulfate pentahydrate (Copper (II) sulfate pentahydrate)

(Cupri sulfas pentahydricus) (ДФУ)

$CuSO_4 \cdot 5H_2O$

Synthesis. Dissolving pure copper in concentrated sulfuric acid in the presence of concentrated nitric acid:

$$3Cu + 3H_2SO_4 + 2HNO_3 \rightarrow 3CuSO_4 + 4H_2O + 2NO\uparrow$$

The solution is evaporated (H_2SO_4, HNO_3, NO are removed), the residue is dissolved in water - $CuSO_4 \cdot 5H_2O$ crystallizes from it.

Properties. Blue crystalline powder or transparent blue crystals. Easily soluble in water, soluble in methanol, practically insoluble in 96% alcohol. Aqueous solutions have an acidic reaction of the medium due to hydrolysis:

$$Cu^{2+} + H_2O \rightleftharpoons CuOH^+ + H^+$$

Identification:

1. A blue precipitate of the basic salt is formed with a dilute ammonia solution:

$$2CuSO_4 + 2NH_4OH \longrightarrow (NH_4)_2SO_4 + Cu_2(OH)_2SO_4\downarrow$$

The precipitate dissolves in an excess of the reagent with the formation of a dark blue complex salt:

$$Cu_2(OH)_2SO_4 + 6NH_4OH + (NH_4)_2SO_4 \rightarrow 2[Cu(NH_3)_4]SO_4 + 8H_2O$$

2. The substance reacts to sulfates.

3. Non-pharmacopoeial reactions:

a) an aqueous solution (1:20) of copper (II) sulfate when immersing iron covers it with a red coating of metallic copper:

$$CuSO_4 + Fe \rightarrow FeSO_4 + Cu$$

b) With a solution of sodium sulfide, it forms a black precipitate of copper (II) sulfide, soluble in nitric acid with the release of a yellow precipitate of sulfur:

$$CuSO_4 + Na_2S \rightarrow \underset{\text{чорний}}{CuS\downarrow} + Na_2SO_4$$

$$3CuS + 8HNO_3 \rightarrow 3Cu(NO_3)_2 + \underset{\text{жовтий}}{3S\downarrow} + 2NO\uparrow + 4H_2O$$

c) upon the action of potassium ferrocyanide on a copper (II) solution, a red-brown precipitate is formed, soluble in an ammonia solution:

$$2CuSO_4 + K_4[Fe(CN)_6] \rightarrow Cu_2[Fe(CN)_6]\downarrow + 2K_2SO_4$$

d) a characteristic reaction to copper (II) ions is the interaction with polyatomic alcohols, amino and hydroxy acids (glycerol, gluconic acid, etc.) with the formation of complex compounds of intense blue color.

Quantitative definition. Iodometry by substitute. Potassium iodide is added to the mass of the substance in the presence of sulfuric acid and titrated with sodium thiosulfate solution, the indicator is starch, s = 1:

$$2CuSO_4 + 4KI \rightarrow 2CuI_2\downarrow + 2K_2SO_4$$

$$2CuI_2 \rightarrow Cu_2I_2 + I_2$$

$$I_2 + 2Na_2S_2O_3 \rightarrow 2NaI + Na_2S_4O_6$$

Storage. In a sealed container.

Application. Externally – antiseptic, astringent, caustic, internally – emetic.

ANTI-EMITIC DRUGS (lat. antiemetica) are drugs that stop and prevent vomiting. Substances that affect various links of nervous regulation can have an antiemetic effect. So, for example, if vomiting is caused by local irritation of the stomach, then reducing the stimulation of stomach receptors and suppressing nausea and vomiting can be achieved by taking local anesthetics (benzocaine, novocaine), if necessary, astringent and enveloping drugs can be prescribed. Sedatives and hypnotics were mainly used to eliminate the excitation of the vomiting center. Important successes in obtaining more specific, highly effective antiemetic drugs of central action are associated with the study of cholinolytic, antihistamine, neuroleptic drugs. The antiemetic effect of various neurotropic drugs is largely related to their effect on the neurotransmitter systems of the vomiting center and the chemoreceptor trigger zone. The chemoreceptor zone contains dopamine receptors, cholinergic (muscarinic), histamine (H1) and serotonin (5-HT3) receptors are contained in various nuclei of the vomiting center. Cholinolytic drugs are widely used for the prevention and treatment of sea and air sickness, Meniere's disease. Antihistamines are widely used for this purpose. An example of the first can be dimenhydrinate, the second - diphenhydramine, promethazine. Effective antiemetic drugs are neuroleptic drugs of the phenothiazine group (perphenazine, prochlorperazine, trifluoperazine) and butyrophenone (haloperidol). The phenothiazine derivatives, which have a strong antiemetic effect and act more selectively than other neuroleptics, do not cause side effects associated with general neuroleptic activity, include the drug thiethylperazine. Ondasetron, tropisetron, and granisetron belong to drugs whose antiemetic action is mainly associated with the blockade of central peripheral serotonin (5-HT3) receptors. Metoclopramide, bromopril, domperidone block serotonin (5-HT3) and dopamine (D2) receptors. All antiemetic drugs have a selective antiemetic effect, bromopril and metoclopramide have an anti-itching effect. Metoclopramide, bromopril, domperidone increase the tone and motor activity of the stomach and intestines.

General material and educational and methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Principles of classification of antitussives, nootropic drugs, antihistamines, emetics and antiemetics.
2. Characterization, classification, relationship between the structure and pharmacological action of antitussives, nootropic drugs, antihistamines, emetics and antiemetics.
3. Methods of obtaining, methods of analysis of antitussives, nootropic drugs, antihistamines, emetics and antiemetics.
4. Medical use of antitussives, nootropic drugs, antihistamines, emetics and antiemetics.

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Basic:

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Additional:

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