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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
faculty for foreign citizens' education
pharmaceutical chemistry department

QUALIFICATION WORK

on the topic: «**PHARMACEUTICAL ANALYSIS OF ACTIVE INGREDIENTS IN THE ANTICOLD DRUG**»

Prepared by: higher education graduate of group
Фм17(4,10д)англ-02
specialty 226 Pharmacy, industrial pharmacy
educational program Pharmacy
Hadi SAYEGH
Supervisor: assistant of department pharmaceutical chemistry, PhD
Nataliia SMIELOVA
Reviewer: professor of higher education institution of department medicinal chemistry, DSc, professor
Lina PEREKHODA

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ANNOTATION

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INTRODUCTION

Actuality of subject. It is obvious that the national policy in health care agreed with the concept of the WHO (Worth Health Organization), has the aim at providing government guaranteed quality, safe and effective drugs that are in circulation in the market of the country, equal access of all groups of the population to basic of vitally necessary drugs in their economic accessibility both for the state and the individual patient and rational use of drugs by doctors, pharmacists and patients, is to ensure wide access to quality treatment, creating conditions so that doctors prescribed, and patients used the drugs according to clinical advisability and economic affordability.

This is oriented on the patient extemporaneous preparations produced in pharmacy conditions prescribed by doctors and commissioned by health care institutions approved for use with active substances and excipients.

The analysis of the pharmaceutical market indicates that currently all regions of Ukraine, in contrast to the European Union countries, where there are pharmacies with extensive production functions, there is a tendency to reduce the number of pharmacies, which are engaged in production medicines in pharmacies conditions.

Noting the considerable development of industrial pharmacy, however, note that the current assortment of drugs in industrial production can not fully meet the needs of the doctor and patient individual approach to the treatment process. So extemporaneous compounding replacement deficiency of medicines, expanding the choice of doctor and patient in the methods and means of treatment. These drugs allow to avoid polypragmasy, optimize the use of drugs, as well as promote more effective treatment of certain diseases, industrial production of drugs which are not profitable, but they are vital for a group of patients. Assignment extemporal medicines consists in right assist certain citizens and society as a whole for the most optimal use of drugs.

Medical preparations that are prescribed for a specific patient and made by pharmacy always been and will be in demand. Indeed, thanks to such advantages as individual selection and combination of existing excipients according to age, weight, concomitant diseases, in the right dosage form, the patient receives necessary to him drug that the end result leads to better quality living standards.

Therefore, to improve of realization of state policy of medical drugs, creating the conditions for improved medical supply of institutions of health care, realization of the constitutional right of citizens for public health, ensuring accessibility of population to quality medicines for individual production, especially in rural areas, it is important expansion drugstores that can carry out economic activities for the production of medicines in pharmacies conditions.

Production and guaranteed providing an acceptable level quality control extemporaneous preparations, their compliance with regulatory and analytical documentation fully regulated requirements SPhU (State Pharmacopoeia of Ukraine) and numerous legal documents, harmonized, and close adapted to the provisions of the GPP (Good Pharmacy Practice) leadership.

In this context, an important task is to analyze the existing development of new rapid, accurate, highly sensitive, economically expedient analytical methods for identification and quantitative analysis, that are specially designed for the analysis of extemporaneous preparations.

Also this applies particularly to the manufacturing pharmaceutical powders for the symptomatic treatment of respiratory diseases containing acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride**.**

Purpose of work – development of methods for identification and assay of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride in powders produced in the pharmacy.

Tasks of work. For this objective the following tasks were supplied:

1. To study and summarize the literature data on obtaining, identification, assay and pharmacological activity of acetaminophen, ascorbic

acid, rutin, phenylephrine hydrochloride.

2. To develop methods of identification of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride.

3. To develop methods of quantitative determination of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride.

The object of the research is to develop methods for quality control of active pharmaceutical ingredients in powders produced in the pharmacy.

The subject of the research is powder which is made in the pharmacy, which contains acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride.

Methods of the research: titrimetric methods (iodometry, argentometry), spectral methods (spectrophotometry in the ultraviolet and visible spectrum), identification, quantitative determination.

The structure of the work. The work consists of an introduction, two chapters, general conclusions and list of references used, which is composed of 72 source. Contents of work posted on 60 typewritten pages and contains 8 tables, 9 figures and 2 schemas.

CHAPTER I
SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, IDENTIFICATION AND ASSAY OF ACTIVE PHARMACEUTICAL INGREDIENTS IN RESEARCH POWDERS (REVIEW OF THE LITERATURE)

1.1 Compounding: past and future

In the past the foundation of pharmacy was compounding pharmaceutical drugs. Throughout history pharmacists had to make drugs for patients who were assigned medicine by doctors. In the early 1900s, the pharmaceutical industry began manufacturing a lot of drugs and dosage forms for patients and the need for compounding diminished. Since the late 1900s, a lot has changed and the pharmaceutical industry supplies all the medications needed by patients [1].

Compounding is the technique of combining, mixing, or altering one or more ingredients to create a medication that is tailored to the needs of an individual patient. And that's why it is important for the following reasons:

- A patient has an allergy or needs a medication to be made without certain dyes or preservatives;
- An elderly patient or a child can't swallow a pill or needs a medicine in a liquid form that is not otherwise available;
- A drug has gone off the market or is on back order;
- A medication is not commercially available;
- A patient needs doses customized for his/her individual needs in a dosage form that fits his/her lifestyle;
- Intravenous admixtures in hospitals;
- New therapeutic approaches;
- Veterinary compounding;
- Clinical studies.

Compounding is a worldwide practice that has evolved over centuries. Compounding production of drugs developed in the world in different ways, but they all needs a common document which would describe the rules, standards of compounding practice and common monographs for preparations of preparation of drugs [2].

In 2011 the Committee of Ministers of the Council of Europe has adopted a Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. Aim of this resolution is to harmonize quality assurance and standards for pharmacy-made medicinal products among European countries and to pass the gap in quality assurance and standards between preparation in pharmacies and medicines prepared by the pharmaceutical industry [3].

Pharmaceutical compounding in modern Ukraine has a rich history and goes back to ancient times. Today in Ukraine, there is a revival of compounding practice, the opening of private compounding pharmacies, updating of the legislative framework and requirements of the State Pharmacopeia of Ukraine for compounding preparations, and the introduction of Good Pharmaceutical Practices [4-6].

Thus, all of the above contributed to the choice of our theme. Continuing research at the Department of Pharmaceutical Chemistry National University of pharmacy and for the tasks we have analyzed the assortment of extemporal dosage forms and selected recipe analysis:

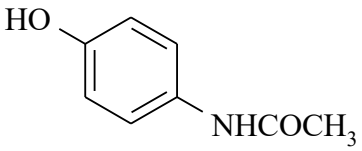
Rp.: Paracetamoli 0,5
Acidi ascorbinici 0,3
Rutini 0,05
Phenylephrini hydrochloridi 0,01
Glucosi ad 2,0

For the development of methods of identification and quantitative determination of active pharmaceutical ingredients in the recipe is necessary to consider the properties of each ingredient that is included in a recipe.

1.2 Synthesis, physicochemical properties, methods of identification and assay

1.2.1 Acetaminophen (Paracetamol)

Paracetamol, Acetaminophen (Paracetamolum)



$C_8H_9NO_2$ 151.16

Acetamide, N-(4-hydroxyphenyl)-4'-Hydroxyacetanilide

Action and use: Analgesic and Antipyretic, Miscellaneous

Brands: Acephen, Alagesic, Bupap, Butapap, Capacet, Cefecon, Efferalgan, Endocet, Excedrin, FeverAll, Fioricet, Goody's, Lortab, Midol, Norco, Ofirmev, Pamprin, Panadol, Percocet, Percogesic, Phrenilin, Premsyn, Primlev, Roxicet, Trezix, Tylenol, Tylenol PM, Ultracet, Vanquish, Vicodin.

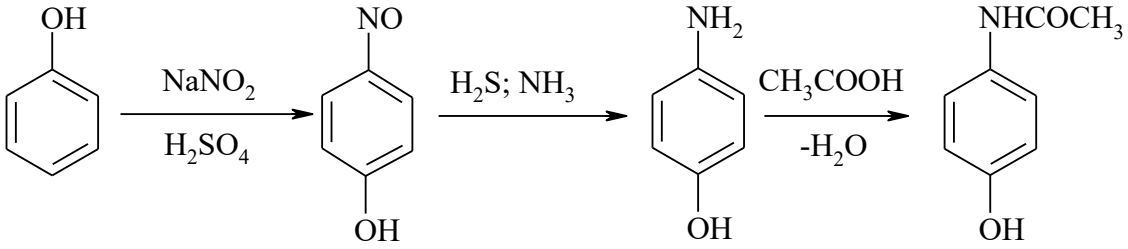
Acetaminophen, known as paracetamol, was introduced to medicine in 1893 in the United Kingdom. It had only limited use, however, until 1949, when it was identified as the active metabolite of 2 older antipyretic drugs, acetanilide and phenacetin. Its popularity as an analgesic and antipyretic gradually increased, but it was not marketed in the United States until 1955, by McNeil Laboratories, and it is now the best-selling analgesic under the trade name of Tylenol.

Acetaminophen is a coal tar derivative that acts by interfering with the synthesis of prostaglandins and other substances necessary for the transmission of

pain impulses. Although its action is similar to that of aspirin, it lacks aspirin's anti-inflammatory and blood-thinning effects, is less irritating to the stomach, and can be used by people who are allergic to aspirin [7-9].

Synthesis

The literature describes the stepwise obtaining of acetaminophen from phenol, which interacts with sodium nitrite in acidic medium. The obtained *p*-nitrosophenol is reduced with hydrogen sulphide in ammonium medium to *p*-aminophenol which is acetylated [10,11]:



Identification

A. Infrared Absorption spectrophotometry [12-14] (Fig. 1.1).

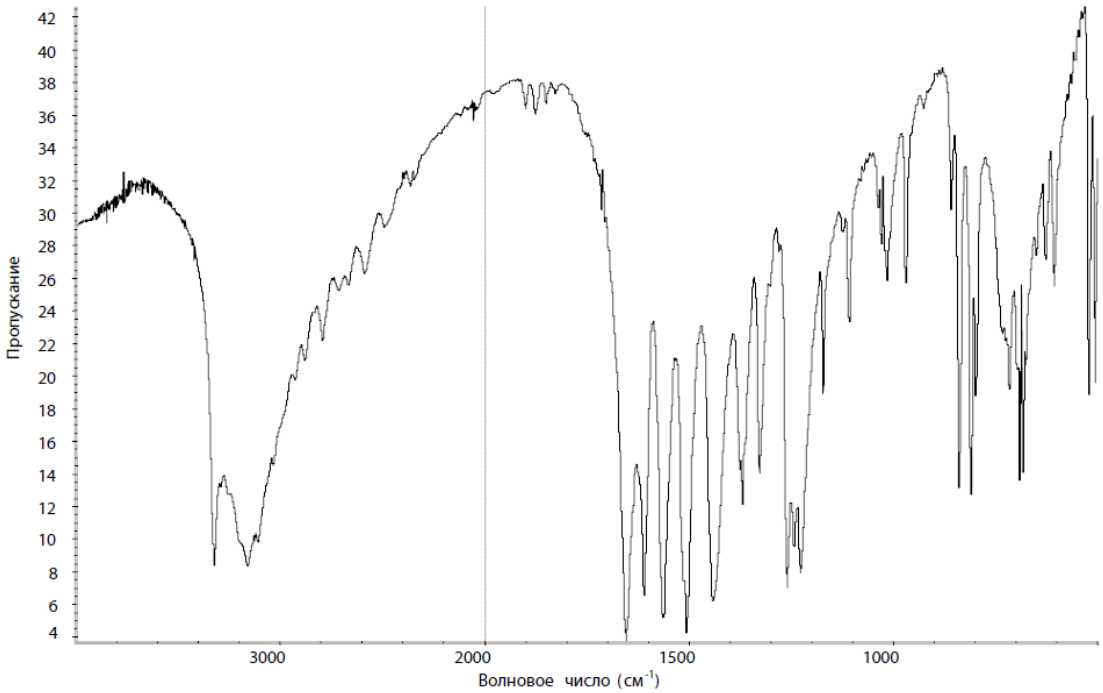


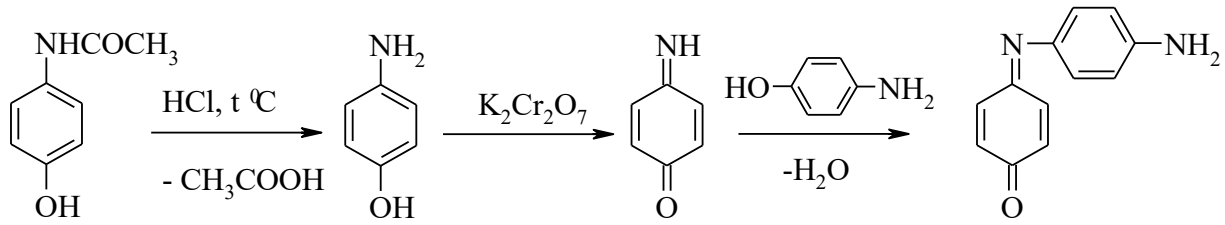
Fig. 1.1 Infrared transmission spectrum of pharmacopoeial standard sample of paracetamol in potassium bromide discs

B. Ultraviolet Absorption spectrophotometry in medium: 0.1 N hydrochloric acid in methanol (1 in 100); measure the absorbance at the absorption maximum at 249 nm. The specific absorbance at the maximum is 860 to 980 [12-14].

C. Thin-layer Chromatographic Identification Test. For this method used a test solution in methanol (1 mg per mL) and a solvent system consisting of a mixture of methylene chloride and methanol (4:1) being used [13].

D. Melting point 168 °C - 172 °C [12,14].

E. Reaction with potassium dichromate in the presence of hydrochloric acid. A violet colour develops which does not change to red [12,14].



F. It gives reaction of acetyl. Heat over a naked flame [12,14].

$La^{3+} + 3CH_3COO^- + 2H_2O \rightarrow La(OH)_2CH_3COO^- + 2CH_3COOH$

In addition, after boiling substances formed with mineral acids, acetic acid, which is determined:

- For the formation of red-brown color when interacting with a solution of iron (III) chloride:

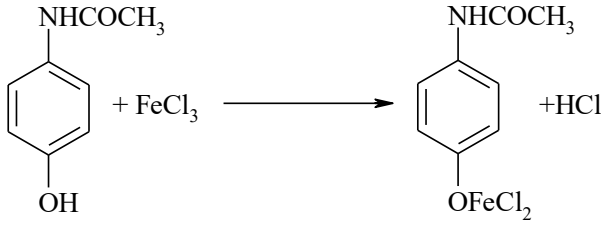
$$9CH_3COO^- + 3FeCl_3 + 2H_2O \rightarrow [Fe_3(OH)_2(CH_3COO)_6]\cdot CH_3COO^- + 9Cl^- + 2CH_3COOH$$

- - With the characteristic odor of ethyl acetate after heating to 96% ethanol in the presence of concentrated sulfuric acid:

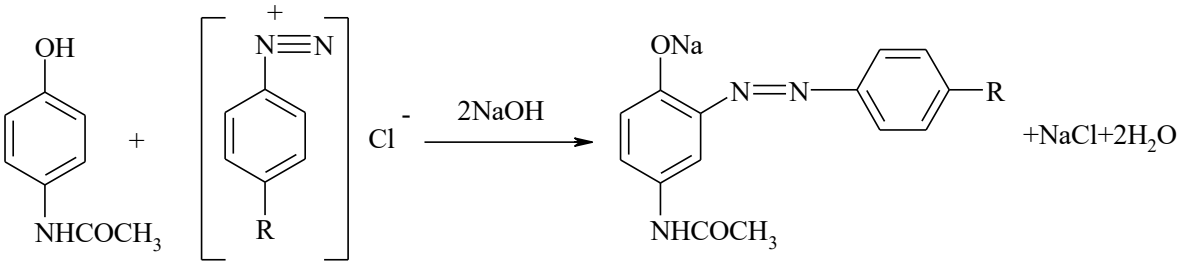
$$CH_3COOH + C_2H_5OH \xrightarrow{\text{к. } H_2SO_4,\, t0} H_3C-\overset{\overset{O}{\parallel}}{C}-OC_2H_5 + H_2O$$

Non-Pharmacopoeian reactions:

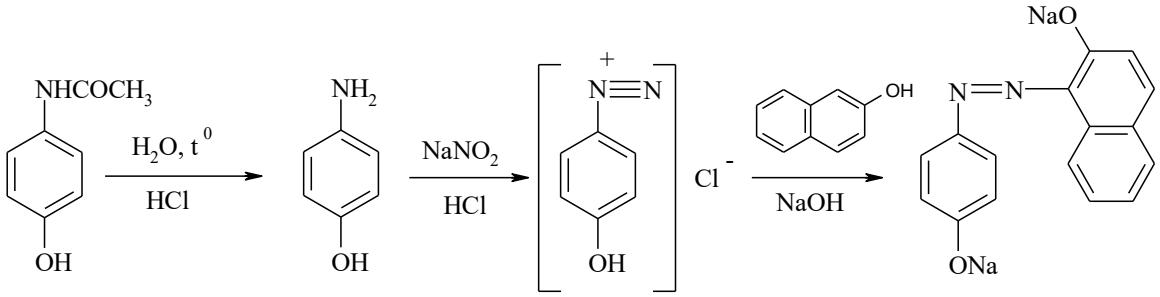
- Due to phenol hydroxyl with iron (III) chloride - a blue-violet color develops:



- Due to phenol hydroxyl in the structure of paracetamol the reaction with the diazotized salts is possible:



- After acidic hydrolysis the substance gives the reaction of primary aromatic amino-group:



For identification of acetaminophen also used his property under the influence of concentrated nitric acid to form the color yellow and brown. Paracetamol reacted with α-nitrozo-β-naphthol in the presence of nitric acid to form a red-brown color. It is proved that the reaction of a small amount of sodium nitrite accelerates the appearance of color [15].

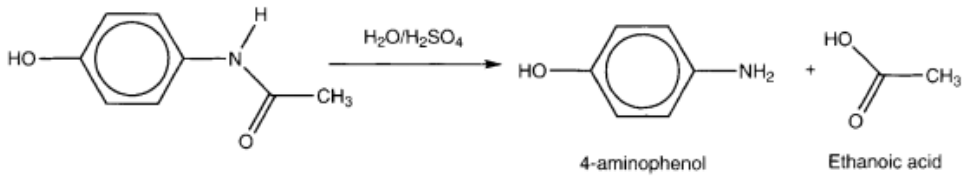
Assay

1. US Pharmacopoeia [13] recommends for the quantitative determination of paracetamol use spectrophotometry method. Used for this purpose the solution of the substance dissolved in methanol. Concomitantly determine the absorbances of this solution and of a Standard solution of acetaminophen, in the same medium, at

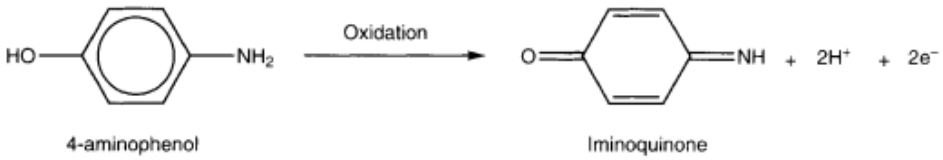
the wavelength of maximum absorbance at about 244 nm, with a suitable spectrophotometer, using water as the blank.

2. The British Pharmacopoeia and SPhU [12,14] recommended method of cerimetry for the analysis of paracetamol after acid hydrolysis. Titrate with 0.1 M cerium sulfate with ferroin as indicator until a greenish-yellow color is obtained. Carry out a blank titration.

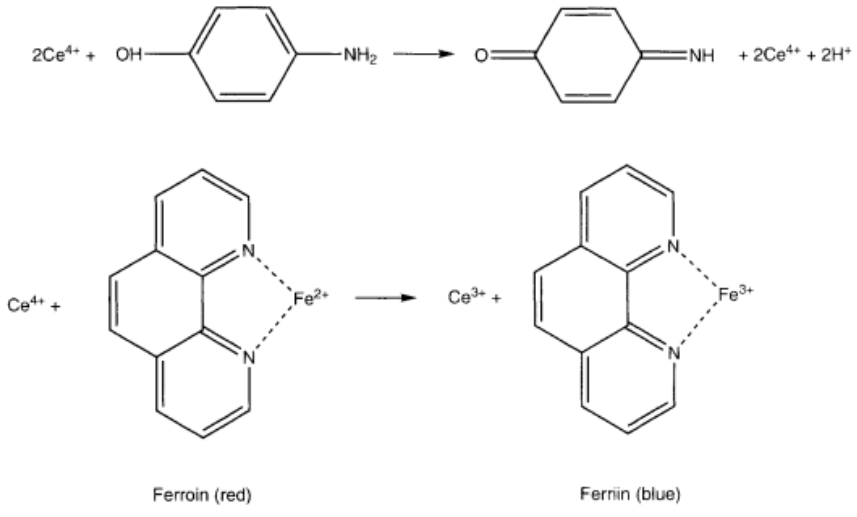
The first reaction is as follows:



4-Aminophenol can easily be oxidised as follows:

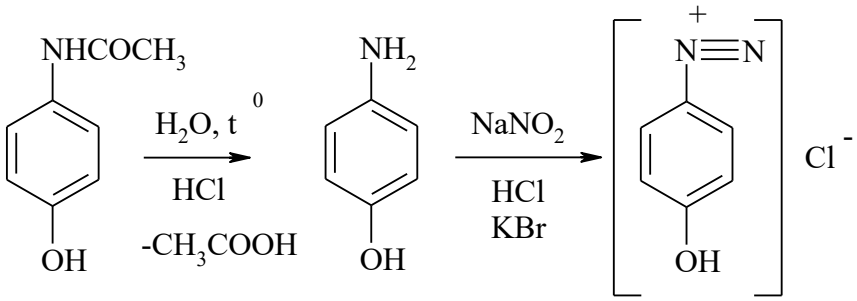


The role of the ammonium cerium (lV) sulfate is to oxidise the 4-aminophenol to the iminoquinone. Only after all the 4-aminophenol has been oxidised will the cerium (IV) reagent oxidise the ferroin indicator from Fe^{2+} to Fe^{3+} (ferriin).



Non-Pharmacopoeian methods

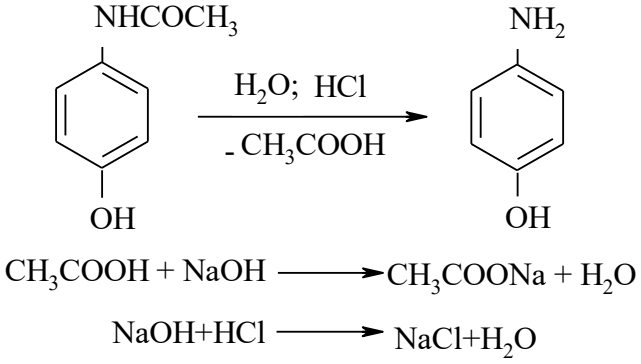
3. Nitritometry after hydrolysis. Indicator – starch-iodide paper.



The excess drop of titrant interacts with starch-iodide paper (it becomes blue):

$$2KIO_3 + 5\ NaNO_2 + 2HCl \rightarrow I_2 + 5NaNO_3 + 2KCl + H_2O$$

4. Alkalimetry after hydrolysis. Back titration with indicator phenolphthalein. Carry out a blank titration.



Acetaminophen is an active ingredient in hundreds of over-the-counter (OTC) and prescription medicines. Acetaminophen is a nonsteroidal anti-inflammatory drug with potent antipyretic and analgesic actions, but with very weak anti-inflammatory activity. And, it is also combined with other active ingredients in medicines that treat allergy, cough, colds, flu, and sleeplessness. In prescription medicines, acetaminophen is found with other active ingredients to treat moderate to severe pain [16-18].

The following table shows the most commonly used Compounding with acetaminophen according to the journal “International Journal of Pharmaceutical Compounding” [19-26] (Table 1.1).

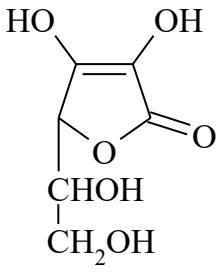
Table 1.1

Compounding with acetaminophen

Compounding	Dosage form
1	2
Tramadol Hydrochloride 7.5-mg/mL Acetaminophen 65-mg/mL	Oral Liquid
Oxycodone Hydrochloride 5-mg Acetaminophen 325-mg per 5-mL	Oral Solution
Acetaminophen 500-mg Diphenhydramine Hydrochloride 25-mg	Hot Therapy Packs
Acetaminophen, Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate	Powder Packets
Acetaminophen 400-mg, Aspirin 250-mg, Codeine Phosphate 30-mg	Antacids Capsules
Acetaminophen 325-mg, Codeine Phosphate 32.5-mg, Phenyltoloxamine Citrate 30-mg	Capsules
Promethazine 20-mg Acetaminophen 325-mg	Suppositories
Transdermal acetaminophen	Pluronic lecithin organogel

1.2.2 Ascorbic acid

Ascorbic acid (Vitamin C)



$C_6H_8O_6$ 176.12

L-ascorbic acid, L-(+)-ascorbic acid, vitamin C, 3-oxo-L-gulofuranolactone

Action and use. Vitamin C.

Brand: Ascorbin, Ascorbit, Ascorvit, Cantan, Cantaxin, Cebione, Cecon, Celin, Ceneton, Cevalin, Cevex, Laroscorbine, Redoxon, Scorbumine, Vicin, Vitascorbol.

Vitamin C is a water-soluble vitamin. It is needed for normal growth and development.

Function. Vitamin C is needed for the growth and repair of tissues in all parts of your body. It is used to:

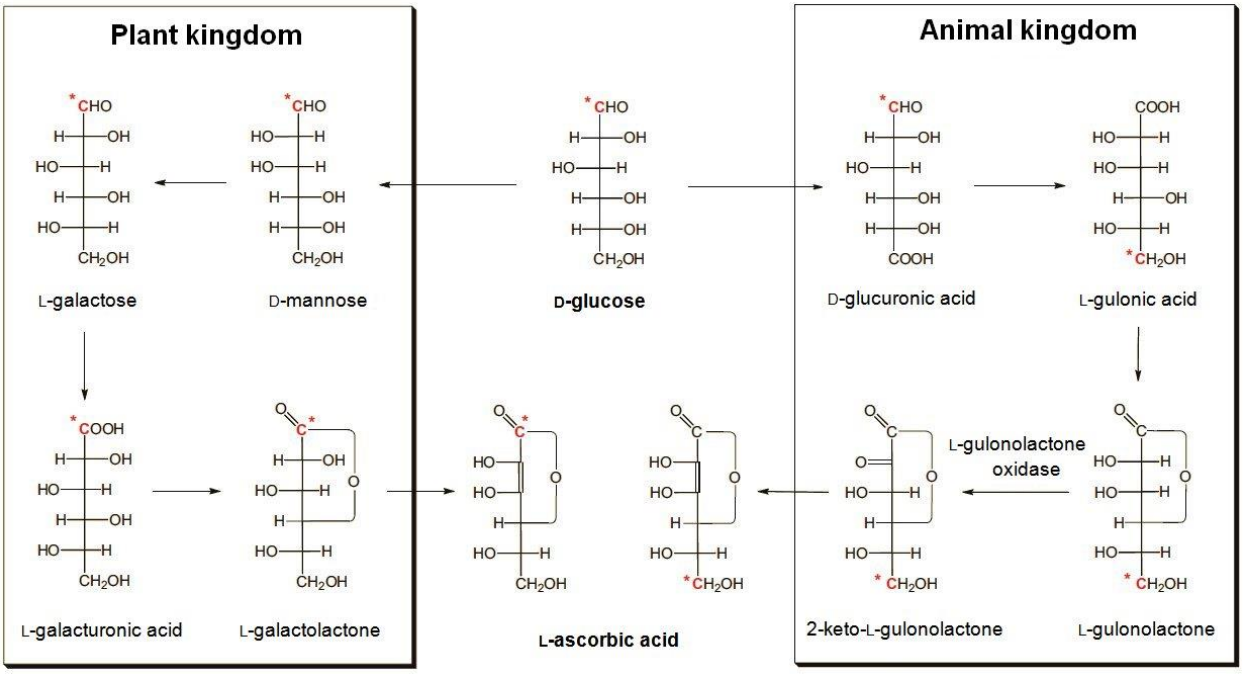
- Form an important protein used to make skin, tendons, ligaments, and blood vessels
- Heal wounds and form scar tissue
- Repair and maintain cartilage, bones, and teeth
- Aid in the absorption of iron

Vitamin C is one of many antioxidants.

The body is not able to make vitamin C on its own, and it does not store vitamin C. It is therefore important to include plenty of vitamin C-containing foods in your daily diet.

For many years, vitamin C has been a popular remedy for the common cold [27-31].

The *biosynthesis* of ascorbic acid in both plants and animals start from glucose (Scheme 1.1), and proceeds through multi step processes to the target L-ascorbic acid.



Scheme 1.1 The biosynthesis of ascorbic acid

Interestingly, as noted above, the synthesis of ascorbic acid begins, for both plants and animals alike with glucose, but from there it proceeds in entirely different ways. Animals carry out the required chain inversion analogously to that in the Reichstein synthesis, whereas plants have elected instead to invert the configurations at two specific stereogenic carbon atoms (C2 and C5) [32,33].

L-ascorbic acid is conventionally synthesized by hydrogenating D-glucose to D-sorbitol. The latter is made to yields L-sorbitol by oxidation with Acetobacter suboxydan, this followed by introducing carboxyl group at C1 while the L-sorbose is in the form of its diacetone derivative. The resulting diacetone-2-keto-L-gluconic acid is then heated with hydrochloric acid to give ascorbic acid [34,35].

Identification

1. Infrared absorption spectrum [12,13,36] study substance must meet the range of pharmacopoeial standard sample of ascorbic acid (Fig. 1.2).

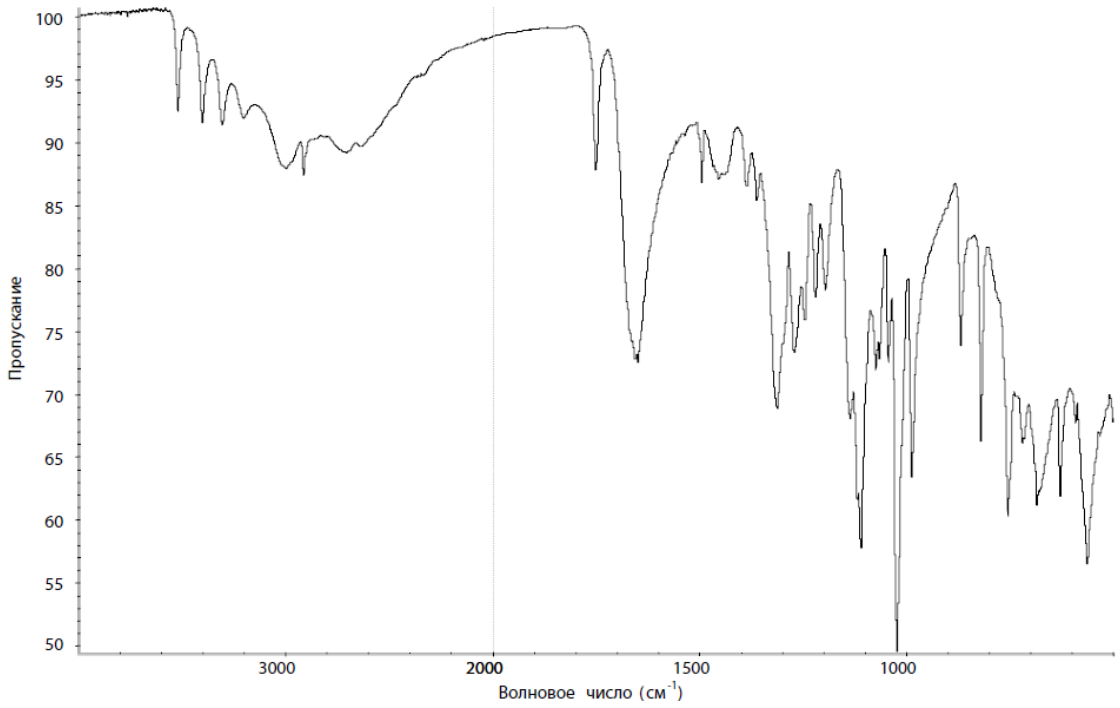


Fig. 1.2 Infrared transmission spectrum of pharmacopoeial standard sample of ascorbic acid

2. Research ultraviolet absorption spectrum of a 0.1 M solution of hydrochloric acid at wavelength 243 nm. Specific absorption rate at maximum must be between 545 to 585 [12,36].

The light absorption of the resulting solution exhibits a maximum only at 244 nm; A (1 %, 1 cm) at 244 nm, about 560.

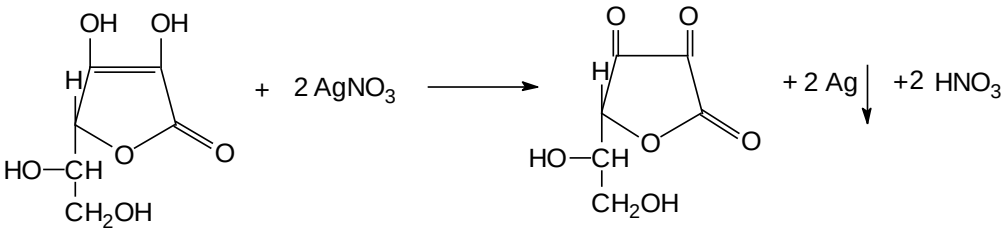
3. pH of the prepared solution must be from 2.1 to 2.6 [12,36].

4. A solution (1 in 50) reduces alkaline cupric tartrate slowly at room temperature but more readily upon heating [13].

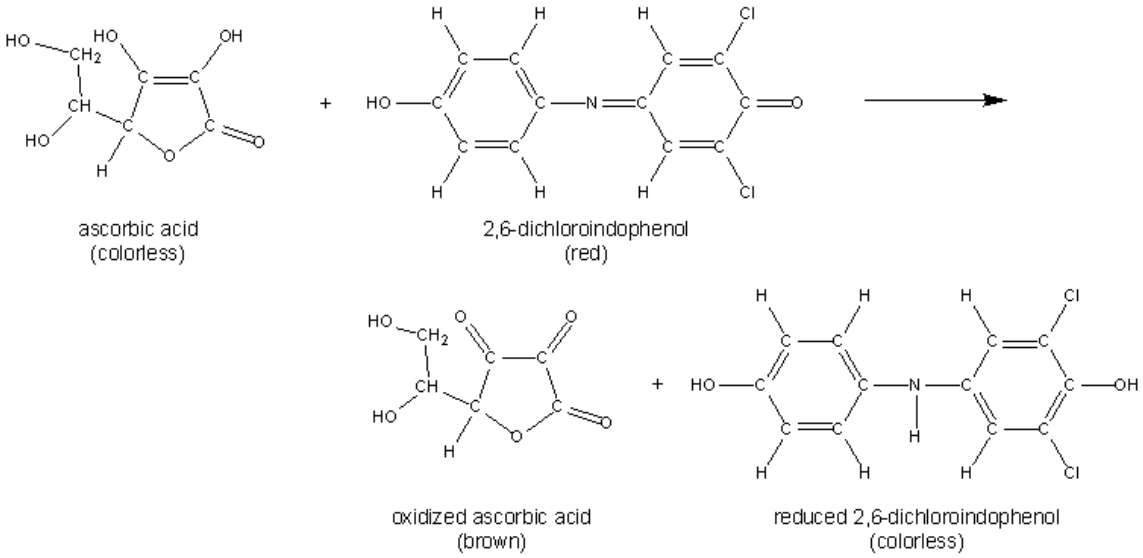
5. Specific rotation: between $+20.5^0$ to $+21.5^O$, the optical rotation being measured immediately, following the preparation of the solution [13].

The peculiarities chemical structure specifies the possibility of using oxidation reactions of ascorbic acid to dehydroascorbic using these reagents:

6. To a solution of ascorbic acid adds nitric acid and silver nitrate; a gray precipitate is formed [13,36]:



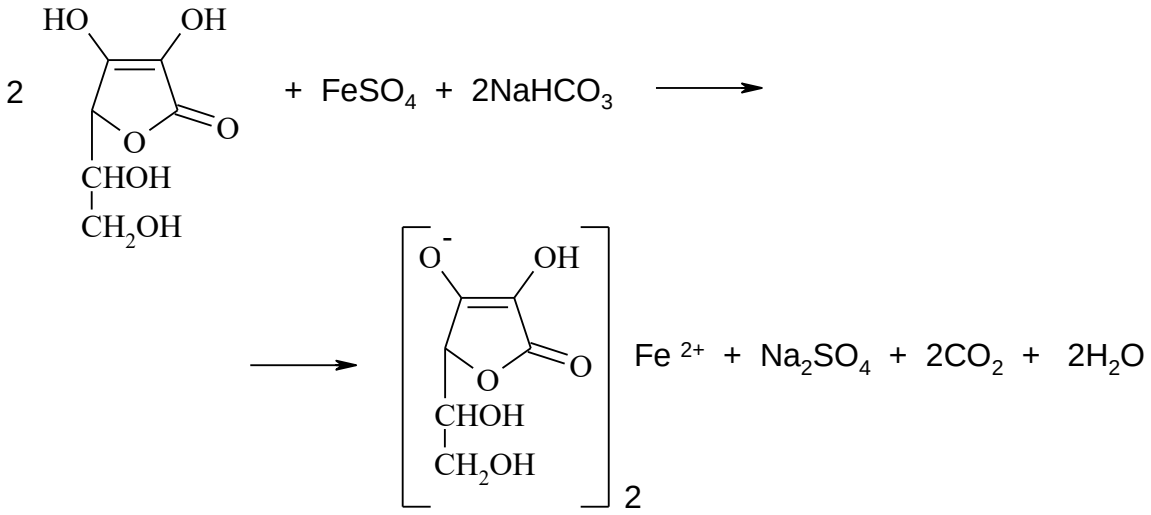
7. Solution of ascorbic acid decolorizes 2,6-dicholorophenolindophenol solution [15]:



8. To solution of ascorbic acid add drops of methylene blue and after heating the deep blue color becomes appreciably lighter or is completely discharged within 3 minutes [37].

9. In rapid analysis use reaction of formation "Prussian blue" [15].

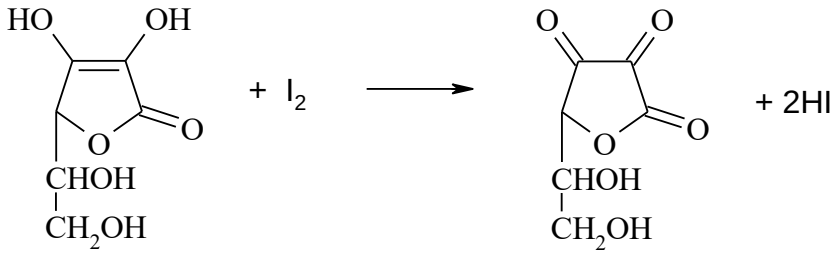
10. The acidic properties of the compound confirmed the decomposition reaction of sodium bicarbonate and color askorbinazu reaction of iron (II) purple influence of solution of iron (II) sulfate [15,37]:



Assay

USP, BP and SPhU recommended for quantities analysis of ascorbic acid used method of iodometry [12-14].

This method determines the vitamin C concentration in a solution by a redox titration using iodine. As the iodine is added during the titration, the ascorbic acid is oxidised to dehydroascorbic acid, while the iodine is reduced to iodide ions.



Due to this reaction, the iodine formed is immediately reduced to iodide as long as there is any ascorbic acid present. Once all the ascorbic acid has been oxidised, the excess iodine is free to react with the starch indicator, forming the blue-black starch-iodine complex. This is the endpoint of the titration.

Also, this method is suitable for use with vitamin C tablets, fresh or packaged fruit juices and solid fruits and vegetables [38].

The endol group present in the molecule allows ascorbic acid to be determined alkalimetric and redox methods. The sensitivity to oxidising agents has

been used in iodometric, cerimetric, polarographic titration of 2,6-dichloroindophenol and in the colorimetric method of determination of ascorbic acid [39].

Another methods:

- Spectrophotometric Methods (Colorimetric, Ultraviolet Spectrofluorimetric) [37].
- Chromatographic Methods (Paper Chromatography, Gas-Liquid Chromatography, High Pressure Liquid Chromatography) [37].

Historically, vitamin C was used for preventing and treating scurvy. These days, vitamin C helps in the formation of a protein that makes up the tissues of the body, like the tendons, ligaments, skin and blood vessels. As a powerful antioxidant, vitamin C helps to defend the cells of the body against free radicals that can damage them and lead to illness, while also boosting the immune system. Daily intake of vitamin C can help lower your risk for developing certain cancers as well as heart disease and inflammatory conditions, including arthritis, by promoting collagen production. While vitamin C hasn't been proven to directly prevent a common cold, it can help shorten the length of a cold and reduce the severity of symptoms. Vitamin C is now a common ingredient in anti-aging creams, lotions and serums for preventing and improving the appearance of lines and wrinkles as well as dark spots. Vitamin C can help protect the venous tone of the arteries, prevent atherosclerosis (hardening of the arteries) and lower the risk for developing peripheral arterial disease in women [27,40-44].

The following table shows the most commonly used Compounding with ascorbic acid according to the journal “International Journal of Pharmaceutical Compounding” [45-47] (Table 1.2).

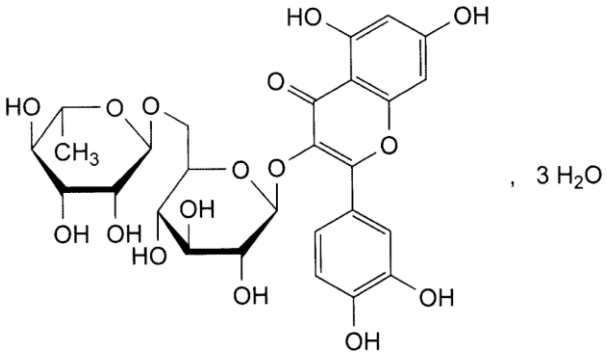
Table 1.2

Compounding with ascorbic acid

Compounding	Dosage form
Ascorbic Acid 250-mg/mL	Injection
Ascorbic Acid 10%	Ophthalmic Solution
L-Arginine Ascorbic Acid	Hydrating Ulcer Gel
L-arginine, ascorbic acid, zinc sulfate, methylcellulose, propylene glycol, methylparaben, purified water, poloxamers, lecithin and isopropyl palmitate	PLO

1.2.3 Rutin (Rutoside trihydrate)

Rutin (Rutoside trihydrate, Quercetin-3-rutinoside trihydrate, Rutin trihydrate, Vitamin P trihydrate)



$C_{27}H_{30}O_{16},3H_2O$ M.M. 665

3-[[6-*O*-(6-Deoxy-a-L-mannopyranosyl)-b-D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one

Action and use: Bioflavinoid.

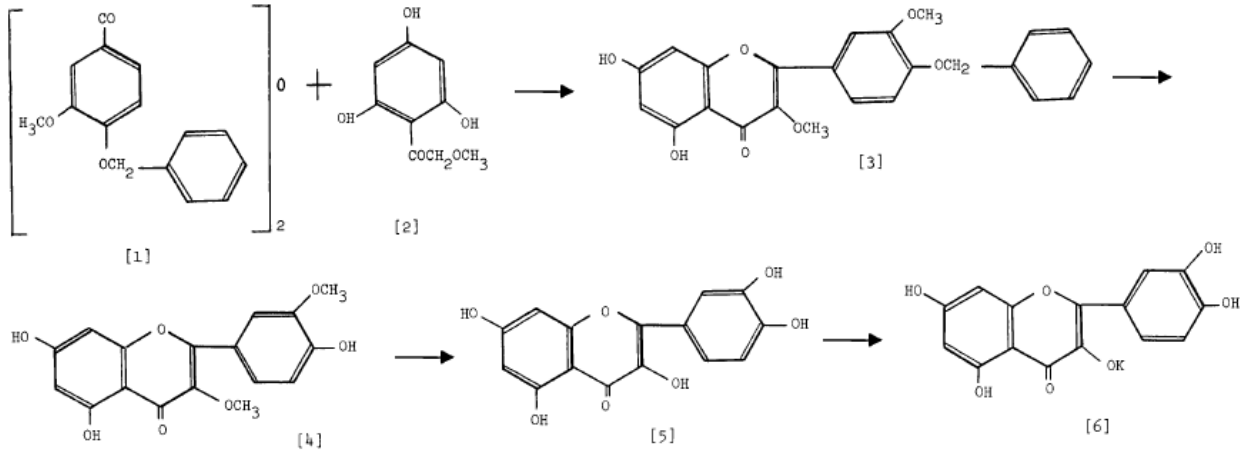
Brands: Ascorut (Rutoside and Ascorbic Acid), Ascorutin (Rutoside and Ascorbic Acid), Atofen, Cerutin (Rutoside and Ascorbic Acid), Meflavon, Nosirax,

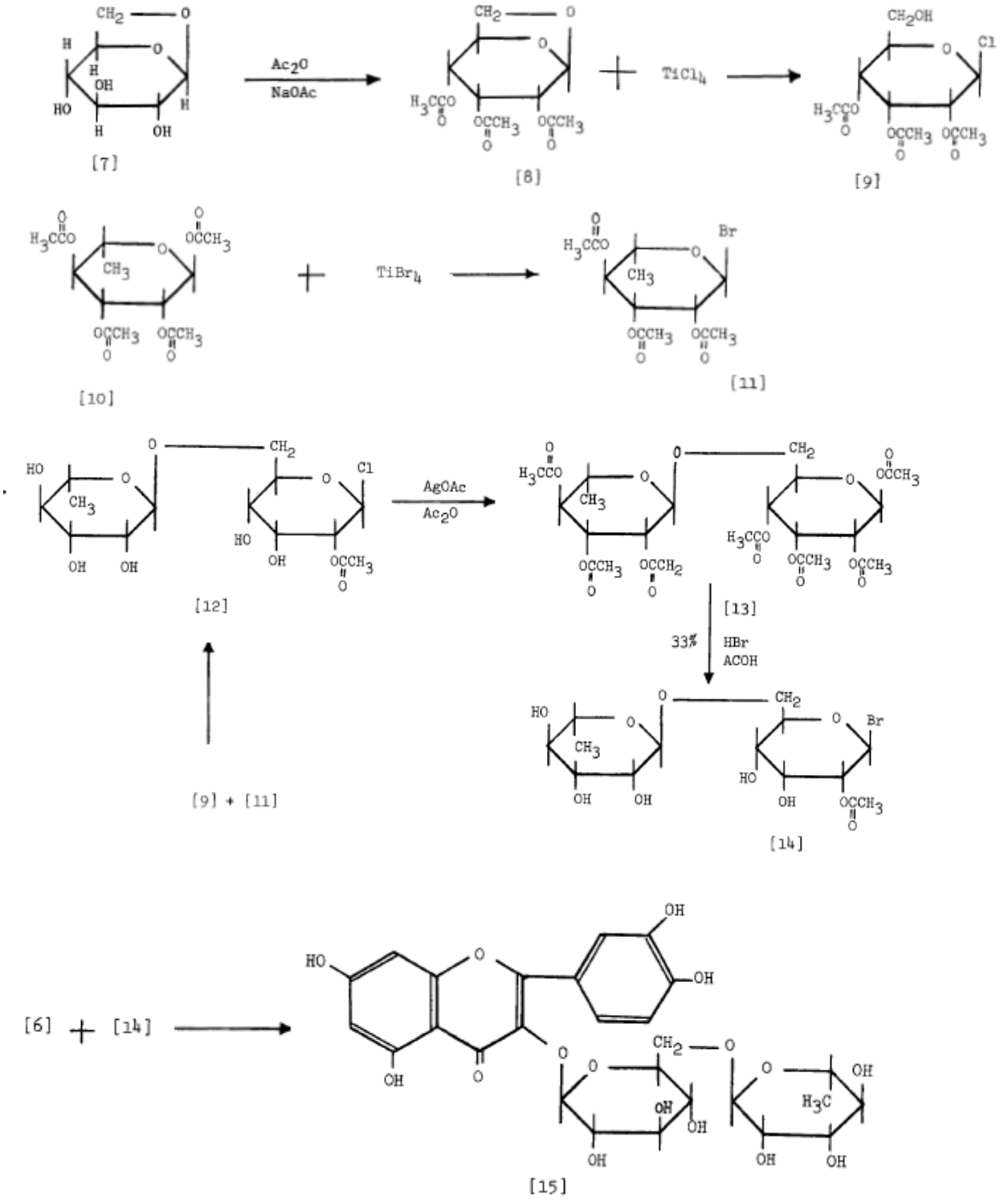
Poloris (Rutoside and Ascorbic Acid), Probien, Ruta C (Rutoside and Ascorbic Acid), Rutascorbin (Rutoside and Ascorbic Acid), Rutalex (Rutoside and Ascorbic Acid), Rutin, Rutin C (Rutoside and Ascorbic Acid), Rutinoscorbin (Rutoside and Ascorbic Acid), Rutin-Vitamin C, Veraldid (Rutoside and Ascorbic Acid), Venescin, Venoruton, Vincarutine (Rutoside and Vincamine), Vitarutine (Rutoside and Nicotinamide).

Contained in the leaves of fragrant rue (Ruta graveolens L.) and other plants. For medical use is extracted from Sophora flower green mass of buckwheat and kidney Japanese (Sophora japonica), the family. legumes (Leguminoseae).

Synthesis

According to the literature the synthesis of rutin can be achieved according to the schemes, which differ in the synthesis of quercetin (the aglycone moiety of rutin). Shakhova et al. had been discrebed complete synthesis of rutin (Scheme 1.2) [48].





Scheme 1.2 Synthesis of rutin

Identification

For identification a substance routine British and European Pharmacopoeia [12,49] recommends the use of:

A. Ultraviolet and visible absorption spectrophotometry. UV spectrum of 0.002% ethanol solution of substance in the range of 210 nm to 450 nm should be characterized by the presence of two absorption maxima at wavelengths of 257 nm and 358 nm. Examined between 210 nm and 450 nm, the solution shows 2 absorption maxima at 257 nm and 358 nm. The specific absorbance at the maximum at 358 nm is 305 to 330.

B. Infrared absorption spectrophotometry: compared to infrared absorption spectrum pharmacopoeial standard sample of rutin (Fig. 1.3).

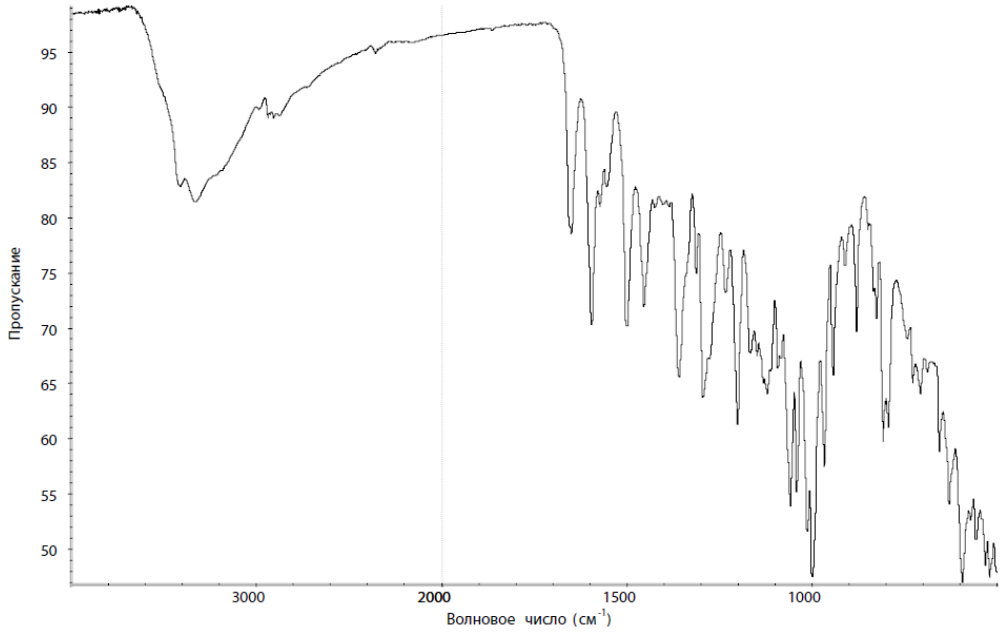
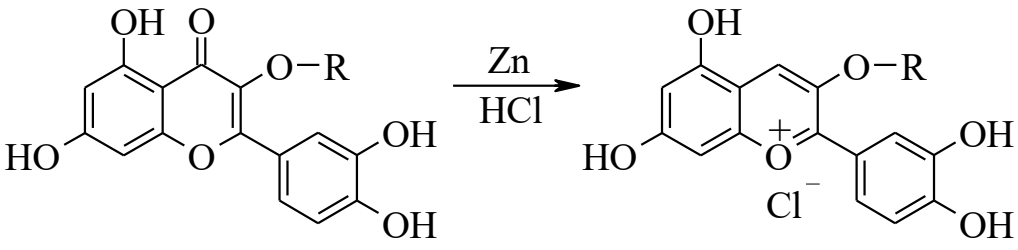


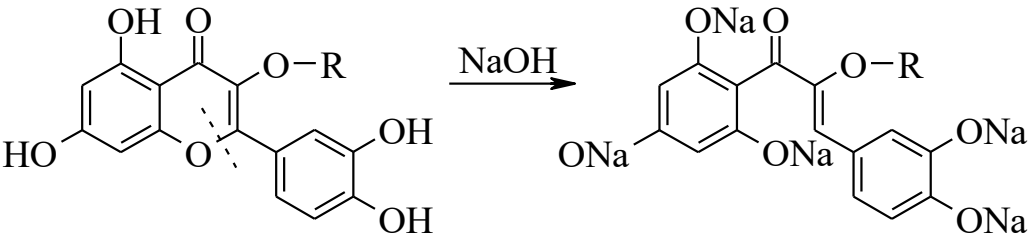
Fig. 1.3 Infrared transmission spectrum of pharmacopoeial standard sample of rutin

C. Thin-layer chromatography

D. “cianidynova” reaction - of formation of red colour when heated alcohol solution of substance with zinc in acidic medium:



When dissolved substances in sodium hydroxide solution appears yellow-orange colour due to the formation halkonu:



Due to the presence in the structure of phenolic hydroxyls, rutin solution of iron (III) chloride forms a green colour [48].

Another tests

1. Spot Appearance [48]:

Daylight : grenish yellow

UV : deep purple

UV / NH_3 : yellow

2. Microcrystal Tests [48].

Assay

British Pharmacopoeia for the quantitative determination rutin recommends alkalimetry method. For this first sample is dissolved in a solution of dimethylformamide. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically [12].

The patented method for the quantitative determination routine by TLC. For this preparation is dissolved in ethanol under heating, followed by chromatography on silica gel plates using the brand «Sorbfil», eluent - ethyl acetate-glacial acetic acid-water (7.5: 1.5: 1.5); developer - 5% solution of NaOH in alcohol [50].

Another methods [48]*:*

1. Colorimetry.

2. Polarography

3. Gravimetry

Rutin is prescribed for hypovitaminosis and avitaminosis P prevention and treatment; in diseases accompanied by increased capillary permeability; in the treatment of radiation sickness, bacterial endocarditis, rheumatism, glomerulonephrosis, hypertension, allergic diseases. And as for the prevention and treatment of capillary lesions when using anticoagulants, salicylates, arsenical drugs.

Rutin is a flavonoid which belongs to the Euflavonoid group. It diminishes capillary permeability and strengthens capillary resistance, increases strength of erythrocytes, lowers muscle tone and relieves spasm of smooth muscle

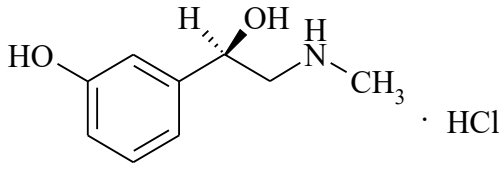
– Diminishing capillary permeability and strengthening capillary resistance.

– Treatment of haemorrhage, sclerosis, hypertension, purpura, varicose veins (edema, pain, heavy legs, haemorrhoid).

Rutin as well as its aglycone quercetin, have a direct constructor action on the capillary bed and decrease the permeability and fragility of the vessels [27].

1.2.4 Phenylephrine hydrochloride

Phenylephrine hydrochloride



$C_9H_{13}NO_2$,HCl 203.7

(1*R*)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol hydrochloride

Action and use. Alpha-adrenoceptor agonist.

Brands: Agrus (Phenylephrine, Chlorpheniramine Maleate, Dextromethorphan), C -Floxn (Phenylephrine, Ciprofloxacin), Coryna –CZ (Phenylephrine, Cetirizine), Mezatone, Mucobar Cold (Phenylephrine, Cetirizine, Paracetamol), Nazol Bebi, Terfed D (Phenylephrine, Terfenadine), Relif, Rhinall.

Phenylephrine hydrochloride has a vasoconstrictor, hypertensive effect, increasing the total vascular resistance (due to stimulation of α1-adrenergic receptors located on blood vessels).

Synthesis

Different methods for the synthesis of phenylephrine hydrochloride have been documented in the literature [51-53].

One of the modern methods of synthesis described by scientists from Thailand. They suggest using m-hydroxybenzaldehyde as starting material of racemic phenylephrine hydrochloride, two separate pathways - epoxidation and bromohydrin formation - are presented. A practical and alternative method for the synthesis of racemic phenylephrine hydrochloride has been performed using mild conditions with good overall yields [54].

Identification

British Pharmacopoeia and SPhU [12,55] for identification of phenylephrine hydrochloride recommends the use of:

A. Specific optical rotation.

B. Melting point : 171 °C to 176 °C.

C. Infrared absorption spectrophotometry: compared to IR-absorption spectrum pharmacopoeial standard sample of phenylephrine hydrochloride (Fig 1.4).

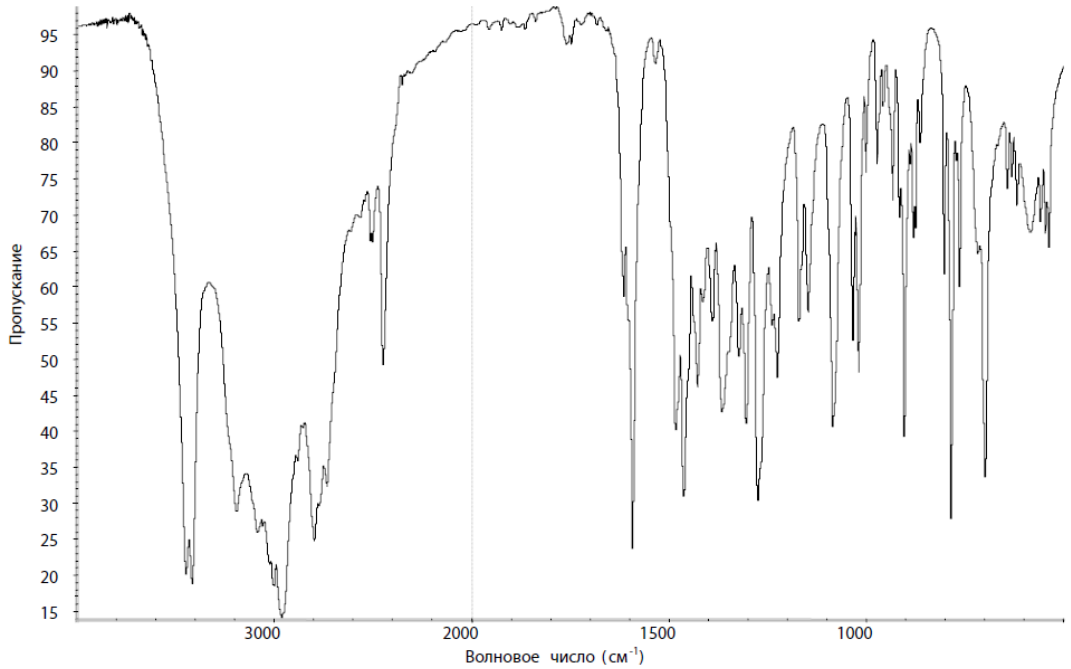
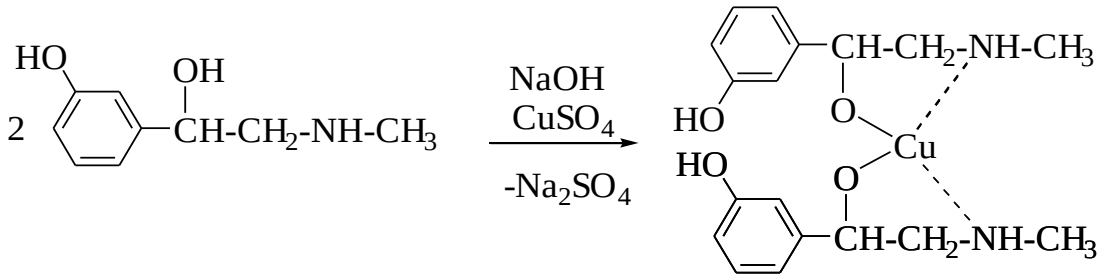


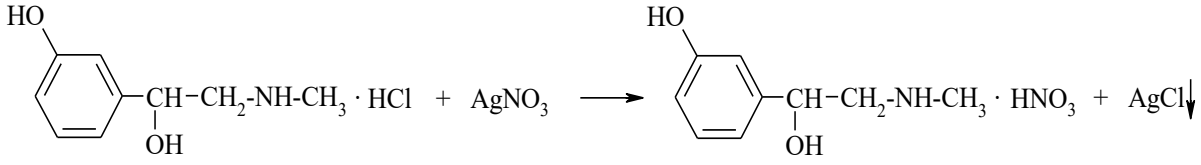
Fig. 1.4 Infrared transmission spectrum of pharmacopoeial standard sample of phenylephrine hydrochloride

D. To distinguish phenylephrine hydrochloride from other aminoalcohols, reacting complexation with a solution of copper (II) sulfate in an alkaline environment. Formed by a set of purple-blue color is not extracted with ether (the upper layer remains colourless).



E. It gives reaction (a) of chlorides.

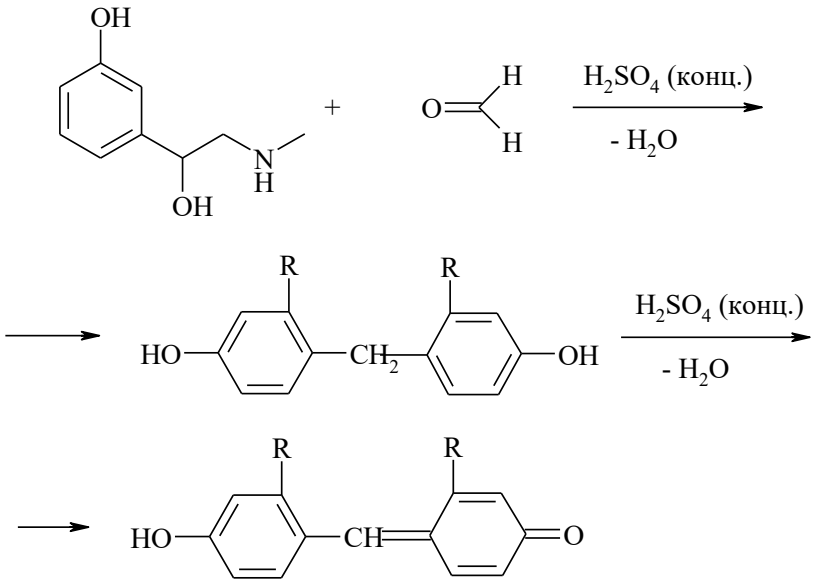
Researched compound is organic basis hydrochloride. So the remaining hydrochloric acid reaction can be confirmed with a solution of silver nitrate - a white cheesy precipitate soluble in ammonia solution.



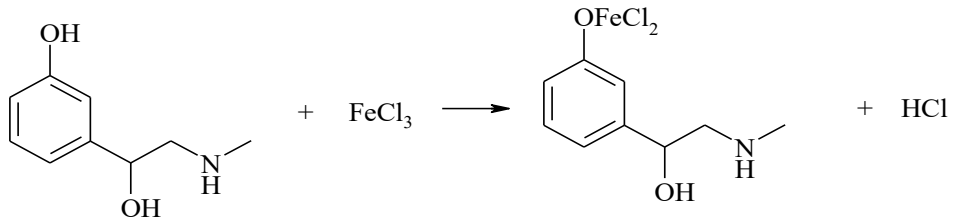
$$AgCl + 2NH_4OH \rightarrow [Ag(NH_3)_2]Cl + 2H_2O$$

Non-Pharmacopoeian reactions

1. Due to the presence of a phenolic hydroxyl phenylephrine hydrochloride dissolves in solutions of alkali metal hydroxide and capable of oxidation. Marki reagent oxidizing action, resulting in the observed dark red color [56]:



2. The presence of phenolic hydroxyl also prove by reaction with a solution of iron (III) chloride is formed violet [56]:

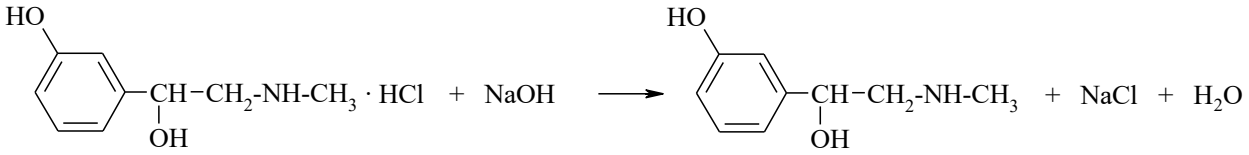


3. In the literature, in order to distinguish phenylephrine hydrochloride ephedrine use of phosphomolybdic acid; pink precipitate formed. With further addition of ammonia solution is painted in blue [56].
4. phenylephrine hydrochloride, like other phenols gives a color reaction with potassium iodate in acidic environment (cherry-red color) [57].

Assay

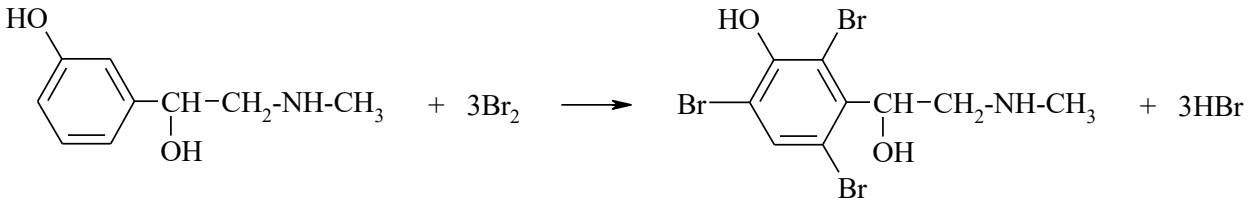
Pharmacopeia method of quantitative determination of phenylephrine hydrochloride is alkalimetry in a mixture of *hydrochloric acid* and *ethanol*. Carry out a potentiometric titration using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion [12,55].

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



Method bromatometry based on reaction bromination of phenols. To a solution of phenylephrine hydrochloride add a solution of potassium bromide, potassium bromate and hydrochloric acid. Provided bromide, which reacts electrophilic substitution. An excess bromine is determined iodometric - add potassium iodide and iodine, which separated, titrated sodium thiosulfate. The reverse titration, indicator - starch. Simultaneously hold control experiment [58].

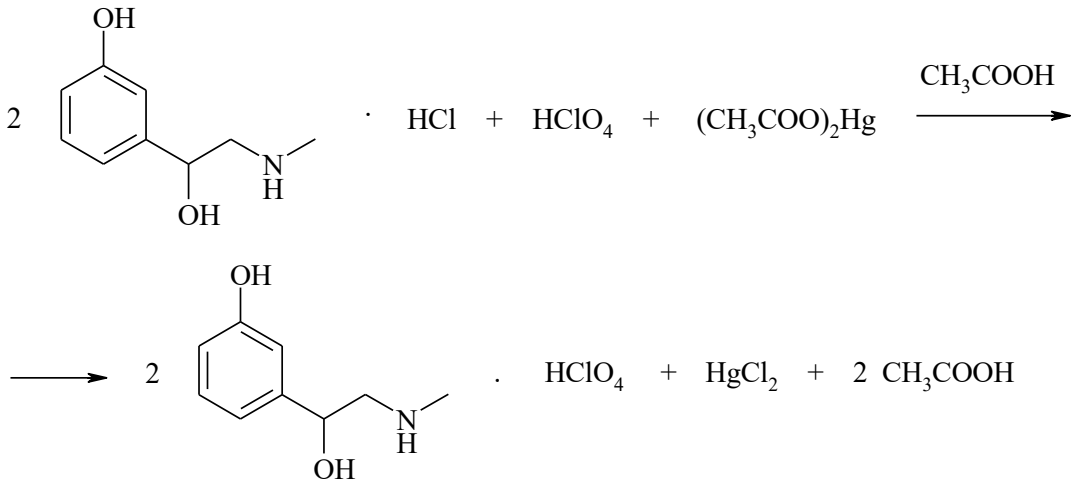
$$KBrO_3 + 5KBr + 6HCl \rightarrow 3Br_2 + 6KCl + 3H_2O$$



$$Br_2 + 2KI \rightarrow I_2 + 2KBr$$

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

The method of acidimetry in non-aqueous medium in the presence of mercury (II) acetate.



Phenylephrine hydrochloride (Mezaton) - adrenomimetic synthetic drug. It is a powerful stimulant and-adrenoceptor; little effect on cardiac P-receptors. It causes constriction of peripheral blood vessels and increased blood pressure, bronchodilation, inhibition of intestinal peristalsis, dilation of the pupils.

Phenylephrine hydrochloride contained in nasal and eye drops, pills and powders to treat the symptoms of colds, anti hemorrhoidal suppositories and others. Used in:

a) to increase blood pressure in the collapse and hypotension associated with a decrease in vascular tone, including in preparation for operations and during operations, with intoxication, infectious diseases, hypotension,

b) for narrowing vessels and reducing inflammation with vasomotor and hay fever, conjunctivitis and so on. etc.;

c) as a substitute for epinephrine in the anesthetic solution;

d) to improve pupil. [27,59,60].

The following table shows the most commonly used Compounding with phenylephrine hydrochloride according to the journal “International Journal of Pharmaceutical Compounding” [61-68] (Table 1.3).

Table 1.3

Compounding with phenylephrine hydrochloride

Compounding	Dosage form
cyclopentolate hydrochloride 0.51 mg/ml, phenylephrine hydrochloride 5.1 mg/ml, tropicamide 0.51 mg/ml lidocaine hydrochloride 2% gel	preoperative cataract surgery gel
phenylephrine hydrochloride (0.2 and 0.1 mg/ml) in 0.9% sodium chloride	injection stored in polyvinyl chloride bags
phenylephrine hydrochloride 10-mg/ml	injection
cyclopentolate hydrochloride 0.2% phenylephrine hydrochloride 1%	ophthalmic solution
cyclopentolate hydrochloride 0.5%, phenylephrine hydrochloride 2.5%, tropicamide 0.5%	ophthalmic solution
phenylephrine hydrochloride 2.5%	ophthalmic solution
phenylephrine 0.25%	ophthalmic solution, preservative free
lidocaine hydrochloride phenylephrine hydrochloride	spray

Conclusions

Thus, were studied possible methods for identification and quantitative determination of substances: acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride. Summarized information about the pharmacological activity and compounding with according substances used in pharmaceutical practice.

CHAPTER II
DEVELOPMENT OF METHODS FOR IDENTIFICATION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS IN THE RESEARCH POWDERS

Recently in Ukraine is growing number of medicines made in pharmacies, which in turn leads to the monitoring and implementation of internal control in pharmacy. As the improvement a medical care expands assortment of medicinal matters complicated composition and chemical analysis of drugs made in drug stores. Medicinal forms usually contain 3-4 or more substances with different chemical groups, for the separation, identification and of quantitative determination they need quickly performed and reliable methods of analysis.

In pharmacies used different types of control, including the most usable chemical method, less physical chemistry (refractometry, photocolorimetry et al.).

Internally pharmaceutical chemical control consists in identification of drugs by using precipitation reactions, colored and fluorescent, and determining the quantitative content in dosage forms using different titrimetric, refractometric, photocolorimetric, visual colorimetric and nephelometric method.

2.1 Identification of research substances

For identification of the research substances in powder extemporal production using the reaction of silver nitrate.

To do this, first 0.2 g of powder was dissolved in 10 ml of water. Parallel we prepare solutions:

1 mg of phenylephrine hydrochloride in 10 ml of water,

5 mg of rutin in 10 ml of water,

30 mg of ascorbic acid in 10 ml of water,

50 mg of paracetamol in 10 ml of water,

114 mg of glucose in 10 ml of water.

Then we take 1 ml of the obtained solutions in separate test glass and add 2 drops of silver nitrate. After this was added into each test glass solution of ammonia. The results obtained are shown in Table 2.1, Fig. 2.1 and 2.2.

Table 2.1

The results of the reaction of the identification with a solution of silver nitrate

Test tube with a solution	The result of the reaction	
	with a solution of silver nitrate	with a solution of ammonia
the studied powder	gray-white precipitate	gray precipitate and yellow solution
phenylephrine hydrochloride	white precipitate	colorless solution
rutin	pink solution	yellow solution
ascorbic acid	gray precipitate	gray precipitate
paracetamol	colorless solution	colorless solution
glucose	colorless solution	characteristic gray ring

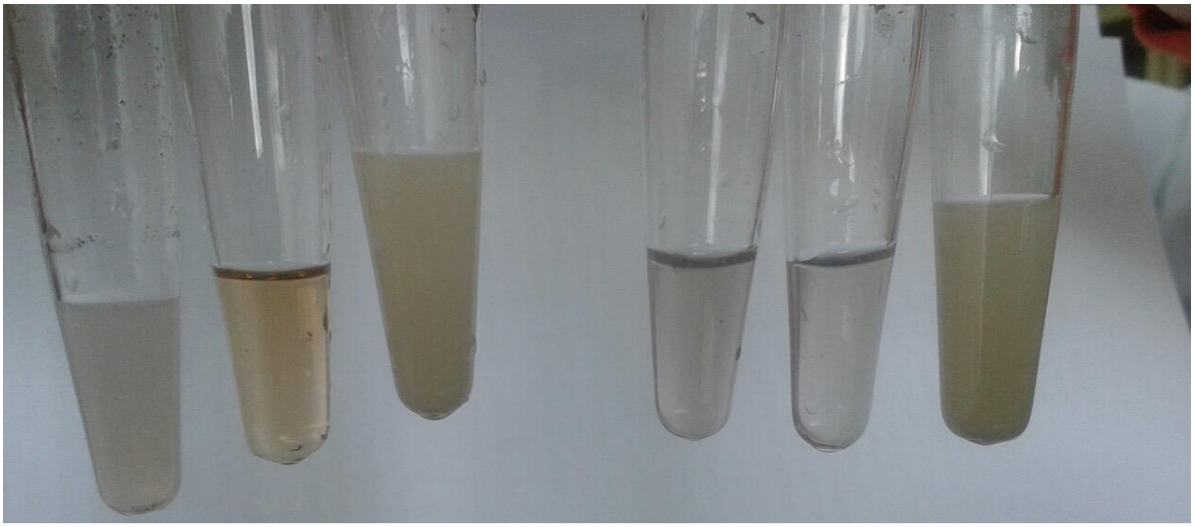


Fig. 2.1 Results of the reaction with silver nitrate: 1-phenylephrine hydrochloride; 2-rutin; 3-ascorbic acid; 4-paracetamol; 5- glucose ; 6-researched powder

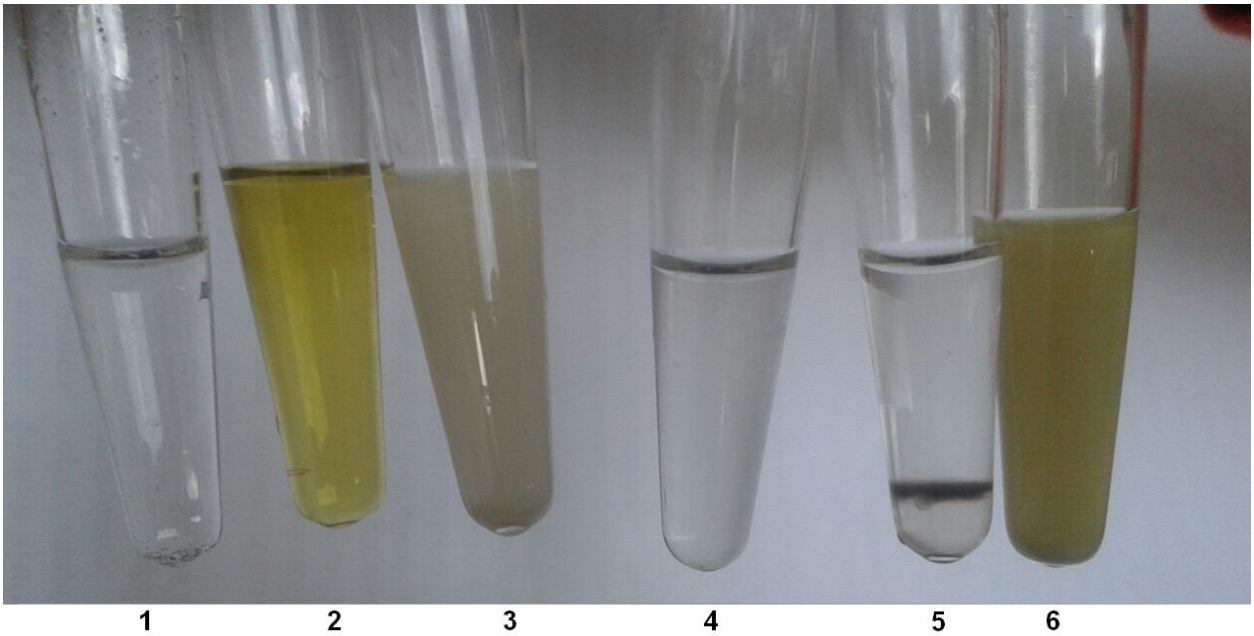
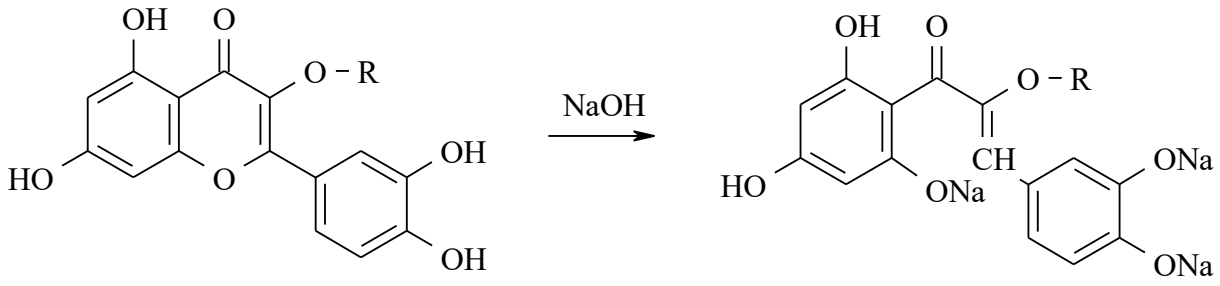


Fig. 2.2 Results of the reaction with silver nitrate after the addition of ammonia solution: 1-phenylephrine hydrochloride; 2-rutin; 3-ascorbic acid; 4-paracetamol; 5-glucose ; 6-researched powder

Rutin

Rutin in powders can be defined as in appearance - yellowish powder, and chemical reactions. Rutin is a glycoside and with acid hydrolysis gives aglicon quercetine and disaccharide - rutinose composed of glucose and rhamnose.

When a solution of sodium hydroxide added to solution of studied powder appears yellow-orange color. A result of reaction is that the flavonoid turns into chalconoid:



Due to the presence in the structure of phenolic hydroxyls, rutin with solution of iron (III) chloride forms a green colour.

Methods.

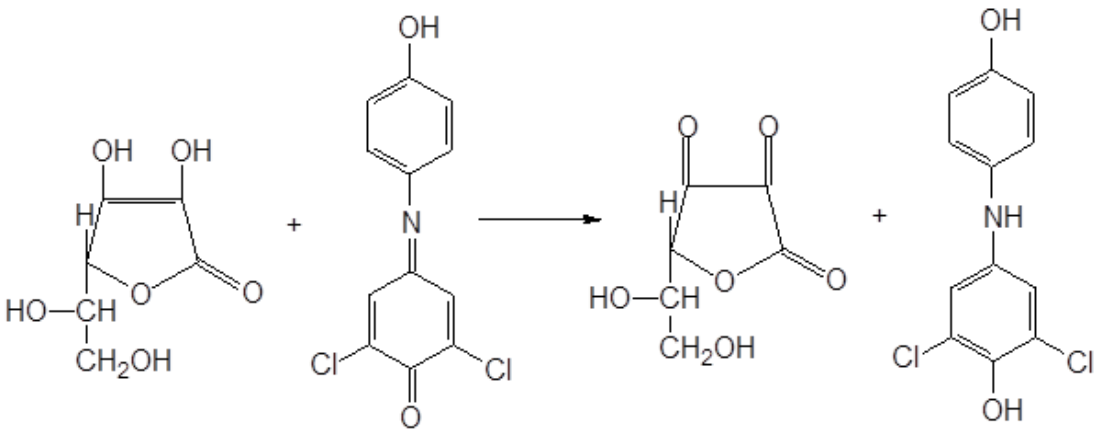
0.2 g of powder was dissolved in 5 ml of water and this solution is used for further identification.

To 1 ml of solution add 2-3 drops of sodium hydroxide. Appears a steady yellow-orange color.

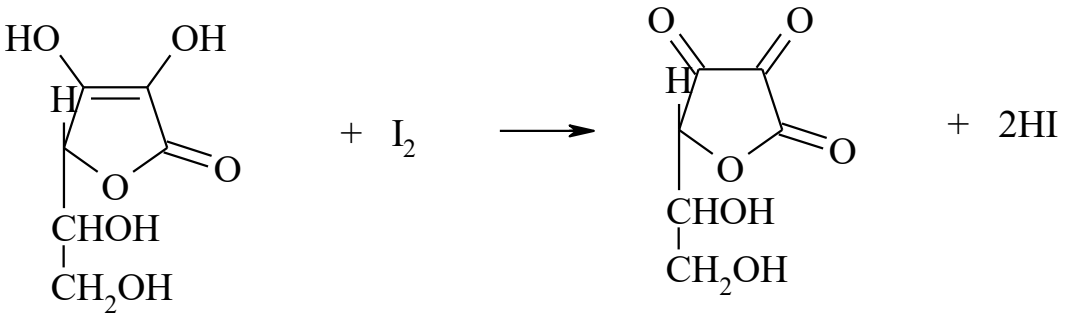
To 1 ml of solution, add 1-2 drops of water and a solution of iron (III) chloride. Gradually appears dark green color.

Ascorbic acid

When added to a solution of ascorbic acid to a solution of 2,6-dicholorophenolindophenol, its blue color disappears:



Iodine solution colorless after add water solution of research powder:



Methods.

To 1 ml of powder add dropwise a solution of 6- dicholorophenolindophenol to the disappearance of its blue coloring.

To 1 ml of powder add 3-5 drops of water and 1-2 drops of 0.05 M iodine solution. There is discoloration of the solution of iodine.

Conclusions

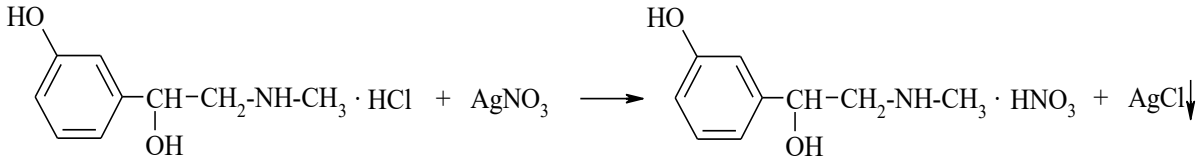
1. Methods of identification of active pharmaceutical components in the composition of a multicomponent anti-cold drug in the form of a sachet are proposed.
2. As a result, phenylephrine hydrochloride, acetaminophen, ascorbic acid and rutin in the anti-cold powders were identified.

CHAPTER III
DEVELOPMENT OF QUANTATIVE DETERMINATION METHODS FOR ASSAY OF THE ACTIVE PHARMACEUTICAL INGREDIENTS IN THE RESEARCH POWDERS

3.1. The choice of methods of quantitative determination of phenylephrine hydrochloride

For the quantitative determination of phenylephrine hydrochloride in the composition of the powders used the method of deposition, titrated by 0,1 M solution of silver nitrate - direct titration. A determination was performed in the acetic acid medium using as indicator bromphenol blue.

To the water solutions of standard sample phenylephrine hydrochloride and model solution of powder in equal concentrations added indicator - bromphenol blue. In the case of the solution of standard sample phenylephrine hydrochloride was formed purple color, and in the studied solution - yellow color. Purple color in the solution of the standard sample phenylephrine hydrochloride changed to yellow-green by adding drops of dilute acetic acid. Both solutions are titrated by 0.1 M solution of silver nitrate - in the case of standard sample phenylephrine hydrochloride solution formation of a purple color, and in the studied solution - to grayish color. Volume of 0.1 M solution of silver nitrate titration spent equal.



Methods: Dissolve 2.0 g of powder in 5 ml of water, add 2 drops of bromphenol blue and titrate with 0.1 M silver nitrate solution from yellow to gray color.

1 ml of 0.1 M silver nitrate solution corresponds to 0.02037 g of phenylephrine hydrochloride.

The contents of phenylephrine hydrochloride in milligrams (X) is calculated by the formula:

$$X, mg = \frac{V \cdot K \cdot T \cdot m_{prescr.} \cdot 1000}{m},$$

where:

V– volume of 0.1M solution of silver nitrate, ml;

T – titer of phenylephrine hydrochloride by 0.1 M solution of silver nitrate, g/ml;

$m_{prescr.}$ – mass of powder for the prescription, g;

m – mass of sample dosage form for the quantitative determination, g.

Results of quantitative determination of phenylephrine hydrochloride in powders by the method of argentometry and metrological characteristics of the results are shown in Table 3.1.

Table 3.1

The results of quantitative determination of phenylephrine hydrochloride by argentometry

№	T, g/ml	V_{AgNO_3}, ml	K	m_{powder}, g	Found, mg	Metrological characteristics
1	0,020367	0,52	0,9900	2,0001	10,48	$\bar{x}$ = 10,31
2		0,49		1,9999	9,88	S^2 = 0,1187
3		0,52		2,0001	10,48	S = 0,3444
4		0,49		1,9998	9,88	$S_{\bar{x}}$ = 0,1406
5		0,53		2,0002	10,68	Δx = 0,6941
6		0,52		2,0001	10,48	$\Delta\bar{x}$ = 0,2834 ε = 2,75%

The results of statistical analysis can be considered reliable only if the variants that it includes, not rough error.

To exclude such errors sample is verified on homogeneity.

The value scale variation R:

R = $\left|9,88\text{-}10,68\right|$ = 0,8

Control criteria for identifying of rough errors:

$$Q = \frac{\left|X_1 - X_2\right|}{R}$$

$$Q_1 = \frac{\left|9,88 - 9,88\right|}{0,8} = 0$$

$$Q_2 = \frac{\left|9,88 - 10,48\right|}{0,8} = 0,75$$

$$Q_3 = \frac{\left|10,48 - 10,48\right|}{0,8} = 0$$

$$Q_4 = \frac{\left|10,48 - 10,48\right|}{0,8} = 0$$

$$Q_5 = \frac{\left|10,48 - 10,68\right|}{0,8} = 0,25$$

A sample can be considered homogeneous with probability 95%, because Q (P,n) = Q (95%, 6) = 0,56 [69].

Then counting metrological characteristics of average results.

Average value

$$\bar{x} = \frac{\sum_i^n x_i}{n} = \frac{9,88 + 9,88 + 10,48 + 10,48 + 10,48 + 10,68}{6} = 10,31$$

Dispersion

$$S^2 = \frac{\sum_i^n x_i^2 - nx^2}{\nu} = \frac{9,88^2 + 9,88^2 + 10,48^2 + 10,48^2 + 10,48^2 + 10,68^2 - 6 \cdot 10,31^2}{5} = 0,1187$$

$;(\nu = n - 1)$

Standard deviation

$$S = \sqrt{S^2} = \sqrt{0{,}1187} = 0{,}3444$$

The relative (relative to the average results) standard deviation

$$S_{\bar{x}} = \frac{S}{\sqrt{n}} = \frac{0{,}3444}{\sqrt{6}} = 0{,}1406$$

Half-width of the confidence interval of a single determination:

$$x \pm \Delta x = x \pm t(P,\nu) \cdot S = 10{,}31 \pm 2{,}015 \cdot 0{,}3444 = 10{,}13 \pm 0{,}6941$$

Half-width confidence interval of the average results:

$$\bar{x} \pm \Delta\bar{x} = \bar{x} \pm \frac{t(P,\nu) \cdot S}{\sqrt{n}} = 10{,}13 \pm \frac{2{,}015 \cdot 0{,}3444}{\sqrt{6}} = 10{,}13 \pm 0{,}2834$$

The relative uncertainty of a separate determination:

$$\varepsilon = \frac{\Delta x}{x} \cdot 100\% = 6{,}73\%$$

The relative uncertainty of the average result:

$$\bar{\varepsilon} = \frac{\Delta\bar{x}}{\bar{x}} \cdot 100\% = 2{,}75\%$$

The results are shown in Table 2.2.

3.2 The choice of methods of quantitative determination of rutin

Absorption methods are based on the properties of substances absorb light in different spectral regions.

Depending on the equipment used distinguish spectrophotometric methods - analysis of substances absorption of monochromatic radiation; colorimetric and photocolorimetric - analysis of absorption substances nomonochromatic emission [14,58].

Objective selection of optimal conditions for quantitative spectrophotometric analysis can be done only previous study of ionization constants, influence the nature of solvents, pH and other factors, the nature of the absorption spectrum.

Atomic absorption spectrophotometry based on the use of ultraviolet or visible radiation resonant frequency. Absorption of radiation caused by the transition of electrons from outer orbitals of atoms in orbitals of higher energy.

Spectrophotometric measurements in the ultraviolet and visible regions are often carried out for solutions, although these measurements can be conducted for substances that are in the vapor, liquid and solid state.

Spectrophotometric analysis by direct measurement of the optical density can be conducted for substances that have only certain structural features (aromatics, compounds with conjugated multiple bonds, etc. [14,58,70].

Photocolorimetric method unlike UV-spectrophotometry carried out in the visible spectrum. Determined substance by using a reagent transferred to the colored compound, and then measure the intensity of the color on photocolorimeter. Accuracy of definitions depend on the choice of optimal conditions of chemical reactions [49].

Determination of measurement of absorption of electromagnetic radiation based on joint law Beer-Lambert law [71]:

$$A = \varepsilon \cdot C \cdot b,$$

where:

A – absorbance (optical density of the solution; this value is obtained from the spectrophotometer);

ε - constant known as the molar extinction coefficient (molar absorption rate);

C - the concentration of substances in solution, in moles L^{-1};

b - the path length of the sample cell, in cm.

Absorbance (A) is defined as the logarithm to base 10 of the reciprocal of the transmittance [12]:

$$\mathbf{A} = \lg(\frac{1}{\mathbf{T}}) = \lg(\frac{\mathbf{I_o}}{\mathbf{I}})$$

$$\mathbf{T} = \frac{\mathbf{I}}{\mathbf{I_o}},$$

where:

I_o - intensity of incident radiation;

I - intensity of transmitted radiation.

The value $A_{1см}^{1\%}$ is the specific physical constant for each substance and can be used for the purposes of identification.

This value is the specific absorption rate, to wit the optical density of the solution of a substance with a concentration of 10 g/l in cell layer with a thickness of 1 cm, to wit:

$$A_{1см}^{1\%} = \frac{10 \cdot \varepsilon}{М.м.}$$

The curve depending absorption (absorption function) of the wavelength or wave number is called the absorption spectrum is the specific characteristic of the substance.

Absorption spectrophotometry in the ultraviolet and visible regions of the spectrum is usually used to identify drugs in the following versions:

1. A comparison of the spectra of absorption of the test solution and the solution comparison; in this region of the spectrum must be match the provisions of highs, lows, shoulders and points inflection.

2. In this region of the spectrum at these wavelengths must be observed the highs, the lows, the shoulders, and points of inflection; It is possible to specify only some of these characteristics. The difference between the study and specified wavelengths should not exceed 2 mm.

3. In addition to option 2 also suggest specific indicators absorption at these wavelengths.

4. In addition to option 2 resulting relationship absorbance at these wavelengths [55].

One-component one wave analysis (or "ordinary spectrophotometry") - is a quantitative determination of a component of a medicinal product by measuring the absorbance of the solution at one test sample analytical wavelength.

Such analysis can be carried out using the method of indicator absorption and the method of standard.

When using methods absorption rate, quantitative determination of carried integrally by measuring absorbance (A) solution at wavelength of the optical density test sample and calculate the concentration (C) of the test component by the formula:

$$C = \frac{A}{A_{1см}^{1\%}},$$

where:

$A_{1см}^{1\%}$ - specific absorption rate of the test component at sample analytical wavelength;

C - the concentration of the analyzed substance in percent (weight / volume).

When using the Standard Method quantitative determination is carried out by using analytical measurements at the wavelength of the optical density of the solution test sample (A) and solution (A_o) with a concentration C_o and calculate the concentration (C) of the test component, based on the formula:

$$\frac{\mathbf{C}}{\mathbf{C}_0} = \frac{\mathbf{A}}{\mathbf{A}_0}$$

Measure the absorbance of the test solution and reference solution should be in the same conditions with a minimum interval of time.

In general, more reliable method is the standard. The possibility of using the method of absorption rate is necessary in each case to prove, based on tolerance quantitative content of the analyzed components, methods and metrological characteristics requirements spectrophotometer. Usually the method absorption

rate applicable at the test component tolerances content of not less than ± 10% of nominal content [55].

Therefore, absorption spectroscopy in the ultraviolet and visible region of the spectrum is the most simple and widely used in pharmacy analysis method, which is used to all stages of pharmaceutical analysis of drugs.

Rutin contains in its structure unsubstituted in *para*-position of the phenolic hydroxyls. Typical reactions to rutin is the reaction with concentrated sulfuric acid, salts of heavy metals from alkaline solutions, etc. [72].

In the literature [72] describes the methodology of identification and quantitative determination of the rutin in the presence of ascorbic acid and glucose by reaction with a solution of sodium hydroxide, which was applied in the analysis of the studied powders. When added to a small number of analyzed dosage form solution of sodium hydroxide appears yellow-orange coloring. or quantitative estimation we used alcohol solution dosage form, which added a 0.1 m solution of sodium hydroxide and the measured absorption spectrum of absorption of the resulting colored mortars in the area of wavelength from 350 nm to 500 nm. Parallel comparison solution was prepared, which includes besides the standard sample routine includes ascorbic acid, which can affect the pH and thus on the optical density (Fig. 3.1).

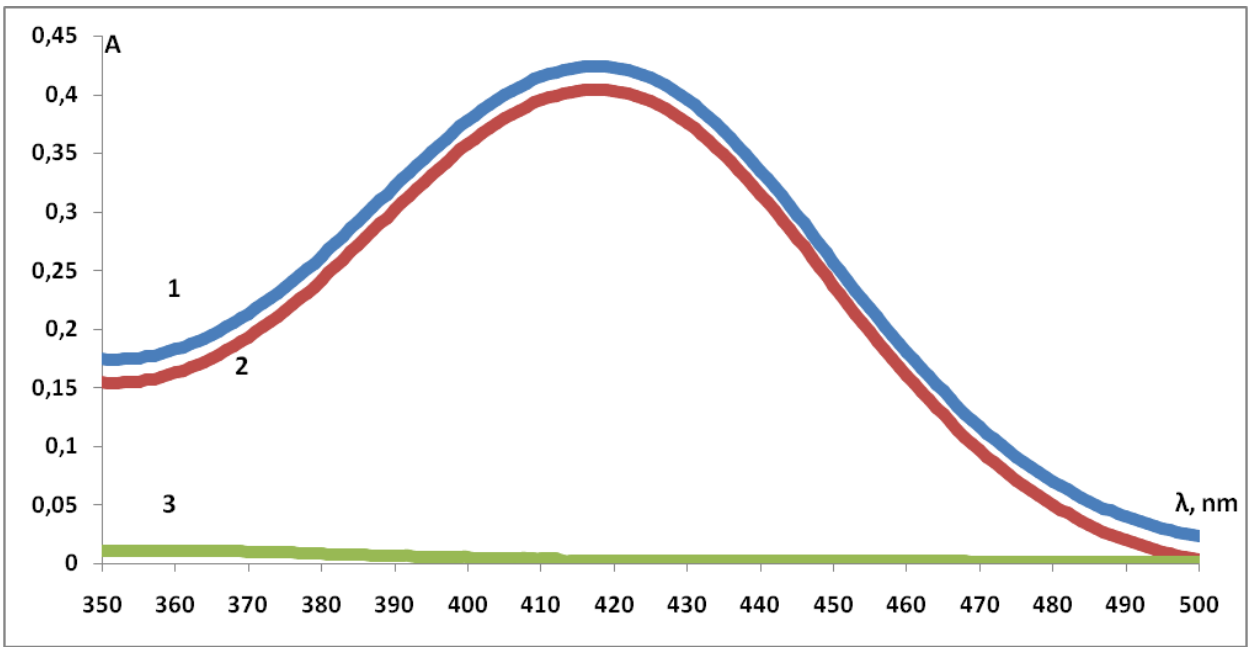
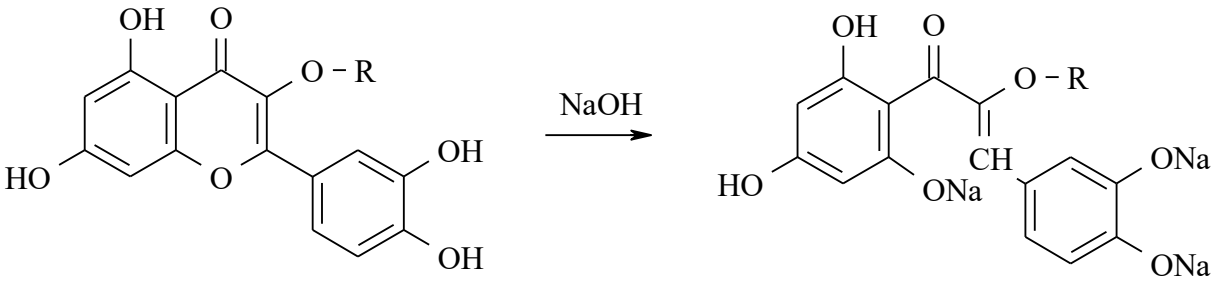


Fig. 3.1 Absorption spectra after reaction with sodium hydroxide 1 - the standard sample of rutin; 2 - researched model mix powders; 3 – placebo

So we decided the reaction of formation of chalconoid under the influence of a solution of sodium hydroxide used for the quantitative photocolorimetric determination of rutin:



Methods.

Test solution. Approximately 0.200 g of powder dissolved in 15 ml of 96% ethanol in a volumetric flask 25 ml by heating in a water bath. After cooling the solution volume adjusted 96% ethanol to the mark and mix.

0.5 ml of the obtained solution is placed in a volumetric flask 10.0 ml, add 4.5 ml of 96% ethanol, 0.5 ml of 0.1 M sodium hydroxide and dilute with distilled water to the mark.

Reference solution. 0.01 g of standard sample routine placed in a volumetric flask 50.0 ml, add 20 ml of 96% ethanol, dissolved by heating in a water bath and after cooling dilute 96% ethanol to the mark.

0.5 ml of the obtained solution is placed in a volumetric flask 10.0 ml, add 4.5 ml of 96% ethanol, 0.6 ml of 0.1% solution of ascorbic acid, 0.5 ml of 0.1 M sodium hydroxide and dilute with distilled water to the mark.

Compensation solution. A mixture of 96% ethanol and water (1: 1).

The content of rutin in powders, in milligrams (X) calculated by the formula:

$$X, mg = \frac{A \cdot m_{st.s} \cdot V_{v.f.(test)} \cdot V_{v.f.(test)} \cdot V_{pip(st.s)} \cdot m_{prescr} \cdot 1000}{A_{st.s} \cdot m \cdot V_{v.f.(st.s)} \cdot V_{v.f.(st.s)} \cdot V_{pip.(test)}}$$

where:

A – absorbance (optical density) of the test solution;

$A_{st.\,s.}$ – absorbance (optical density) of standard sample solution;

$m_{st.\,s.}$ –mass of standard sample, g;

m – mass of sample dosage form for the quantitative determination, g;

$m_{prescr.}$ – mass of powder for the prescription, g;

$V_{v.f.}$ – the volume of volumetric flask of the test solution and reference solution, ml;

$V_{pip.}$ – aliquot volume (pipette) of test and reference solution, respectively, ml.

Results photocolorimetric quantitative determination of rutin in powders and metrological characteristics of the results are shown in Table 3.2.

Table 3.2

The results of quantitative determination of rutin by method of photocolorimetry

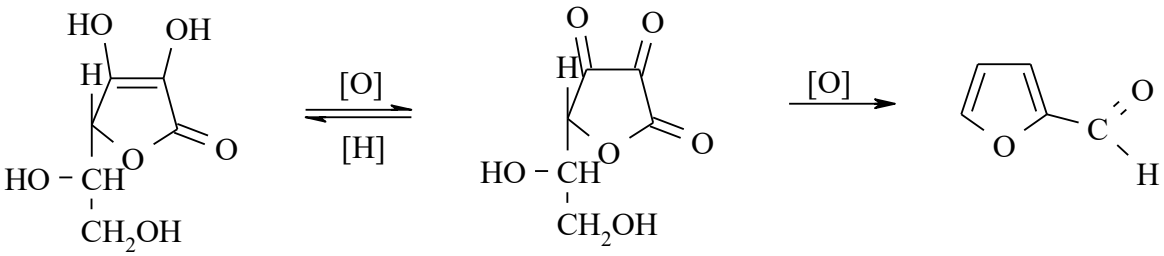
Powder sample, g	A	$A_{st.s}$	Found rutin, mg	Metrological characteristics
0,2	0,370 0,372 0,369 0,373 0,370 0,375	0,415	44,58 44,82 44,46 44,94 44,58 45,18	$\bar{x}$=44,75 S^2=0,0074 S=0,02721 $S_{\bar{x}}$=0,1111 $\Delta\bar{x}$=0,2855 $\bar{\varepsilon}$,%=0,6379

3.3. The choice of methods of quantitative determination of ascorbic acid

Ascorbic acid according to chemical properties showing acidic properties, due to the mobility of hydrogen of the hydroxyl group in position 3.

Reducing properties of ascorbic acid are caused by to its ability to oxidation in two stages:

1) reversible oxidation to dehydroascorbic acid (ketone form);
2) irreversible oxidation process, which eventually leads to the formation of furfural:



Thus, the quantitative determination of l-ascorbic acid can be done as a method of acid-base titration, and redox methods. The method of acid-base titration in this case the use is not advisable, as in the study mixture contains phenylephrine hydrochloride and rutin, which also interact with the alkali solution.

Pharmacopeia method of quantitative evaluation of ascorbic acid is a method iodometry, direct titration in the presence of starch as an indicator. Exactly this method was chosen for the definition of quantitative determination of Ascorbic acid.

Iodometry – method of quantitative determination of free iodine, or substances that quantify secrete it in the reactions of and of those compounds that bind iodine or iodine oxidized in metric quantities stehio.

Iodometric method of quantitative determination has a wide practical application; by its simplicity and precision, he is recognized as one of the best redox methods of quantitative determination.

The basis of the iodometric determination are reactions:

$$[I_3]^- + 2\bar{e} \rightleftharpoons 3I^-$$

$$3I^- - 2\bar{e} \rightleftharpoons [I_3]^-$$

The normal redox potential of the system is equal to 0.545 V. Those substances which have lower potential oxidation of iodine and substances with a high potential oxidation of iodide ions to iodine, which can then be titrated by reaction:

$$2S_2O_3^{2-} + [I_3]^- \rightarrow S_4O_6^{2-} + 3I^-$$

The normal redox potential of the system $S_4O_6^{2-}/2S_2O_3^{2-}$ is 0,17 В.

Iodine is able to enter into reactions that are used in analytical chemistry for determining the double bonds in unsaturated organic compounds, as well as substitution reaction of hydrogen atoms in aromatic and heterocyclic compounds

(phenols, aromatic amines, etc.) that are used to quantitative determination of these substances.

Endpoint titration in iodometry determines:

A) Without indicator - a solution of iodine in potassium iodide is colored in brown, so when you titration a excess drop gives the solution that titrated, in light yellow color; to increase the sensitivity of the determination of the endpoint titration to the solution titrated, add a small amount of organic solvent (methylene chloride, chloroform), which is colored in pink;

B) With indicator - 0.5% solution of starch. Starch with iodine in the presence of iodide ions forms the complex connection of an intense blue color, allows most clearly define the end point titration.

Starch is a specific indicator and in the presence of small quantities of iodine forms a adsorption complex, colored in blue, in the formation of which involved a soluble part of the starch - β-amìloza. The complex is easily destroyed, consequently, the solution becomes colorless when you restore I_2 to I. With a large concentration of I_2 starch is destroyed by the formation of the products that are irreversible indicators. Therefore, starch should be added to solutions containing a minor amount of iodine, which is indicated by a light yellow color solution.

By direct iodometric titration identify substances with strong reducing properties (sodium thiosulfate, ascorbic acid, pharmaceutical compounds arsenic (III), etc.) and are able to recover the iodine to iodide ions. Determination is carried out in acidic, neutral or slightly alkaline environment. Titrant is a solution of iodine in potassium iodide. During the titration reducing agents with iodine, starch is added immediately before the titration, and titrated colorless solution to the appearance of blue color.

Conditions of direct titration:

1. Titration performs during cooling because iodine - volatile substances, as well as heating decrease the sensitivity of starch as an indicator.

2. Environment of solution that titrated should be acidic or neutral, because in an alkaline environment runs the reaction dismutation iodine:

$$I_2 + 2OH^- \rightarrow IO^- + I^- + H_2O$$

The method of reverse iodometry identifies compounds that slowly oxidized iodine (isoniazid), which form with its complex compounds (caffeine), gives the reaction of the aromatic substitution (fenazon).

When using reverse Iodometry for the quantitative determination of aldehydes and some other compounds accuracy may decrease due to evaporation of a solution of iodine, iodide oxidation oxygen acid formed during the reaction:

$$4HI + O_2 \rightarrow 2I_2 + 2H_2O$$

or reversibility process of oxidation:

$$R–COH + I_2 + H_2O \rightarrow RCOOH + 2HI$$

$$RCOOH + 2HI \rightarrow R–COH + I_2 + H_2O$$

To prevent all these complications allows for determination in an alkaline environment. First there dismutation reaction of iodine:

$$[I_3]^- + 2OH^- \rightleftharpoons 2I^- + IO^- + H_2O$$

Further oxidants are hypo-iodide ion, which reacts according to the scheme:

$$IO^- + H_2O + 2\bar{e} \rightleftharpoons I^- + 2OH^-$$

The normal redox potential of the system is equal to 0.49 B.

After the oxidation reaction add excess acid and iodinAfter the oxidation reaction add excess acid and iodine that outshone, titrated sodium thiosulfatee that outshone, titrated sodium thiosulfate:

$$IO^- + 2I^- + 2H^+ \rightleftharpoons [I_3]^- + H_2O$$

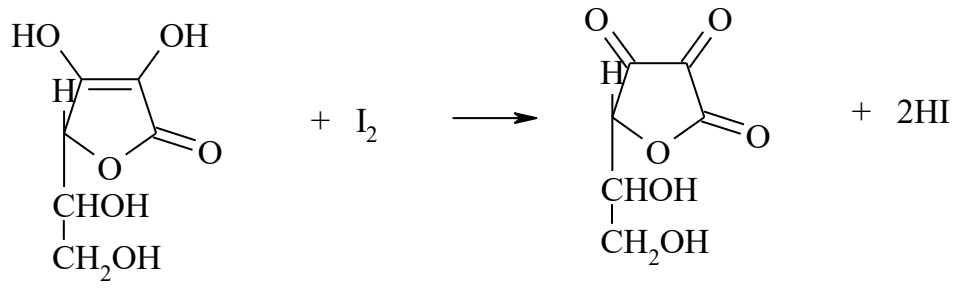
When conducting reverse iodometric determination of starch added at the end the titration, when the bulk of iodine titrated and the solution becomes pale yellow-appears intense blue coloring-and then titrated to bleaching. Add starch to the solutions with high concentration of iodine, can not, because in this case happens irreversible binding of iodine leads to obtaining inflated results.

Conditions reverse titration:

1. Titration perform during cooling.

2. Depending on the properties of oxidized substances, environment solution may be alkaline, close to neutral or slightly acidic [58,70].

For the quantitative determination of ascorbic acid, a sample of the powder was dissolved in water and titrated 0,05 M iodine solution to blue color by using as an indicator of starch solution that is added to at the end titration.



Methods.

Dissolve 0.05 g of powder in 2 ml of water and titrate with 0.05 M iodine solution to brownish-blue color (indicator - starch solution).

1 ml of 0,05 M iodine solution complies 0.0088 g ascorbic acid.

The content of ascorbic acid in g (X) calculated by the formula:

$$X = \frac{V \cdot K \cdot T \cdot m_{prescr.}}{m}$$

where:

V – the amount of 0,05 M iodine solution, ml;

T – titre acids Ascorbic by 0.05 m iodine solution, g/ml;

$m_{prescr.}$ – the mass of powder by the prescription, g;

m– mass of weighing the dosage form for quantitative determination, g.

The results of the quantitative determination of ascorbic acid in powder by the redox-method and metrological characteristics of the results are shown in Table 3.3.

Table 3.3

The results of the quantitative determination of ascorbic acid in powder by the redox-method

№	T g/ml	$V_{0,05M\ I_2}$, ml	K	m, g	Found g	Metrological characteristics
1	0,0088	0,89	0,9999	0,0502	0,312	$\bar{x}$ = 0,31100
2		0,88		0,0501	0,309	S^2 = 0,00001
3		0,91		0,0504	0,317	S = 0,00343
4		0,88		0,0500	0,309	$S_{\bar{x}}$ = 0,00140
5		0,88		0,0501	0,309	Δx = 0,00691
6		0,88		0,0501	0,309	$\Delta\bar{x}$ = 0,00282
						ε = 0,90609

3.4. Development of methods for the quantitative determination of paracetamol

Paracetamol (acetaminophen) - organic aromatic compound which absorbs in the ultraviolet. We decided to determine the quantitative content of paracetamol use the method of absorption spectrophotometry. As the solvent used 0.1 M solution of hydrochloric acid. To determine the influence of other active pharmaceutical ingredients (APIs), studied the UV absorption spectra of 0.001% solution of paracetamol, solution model mixture of powders in concentration paracetamol 0.001%, 0.0006% solution of ascorbic acid, 0.0001% solution rutin, 0.00002% solution of phenylephrine hydrochloride in the area from 220 nm to 300 nm (Fig. 3.2).

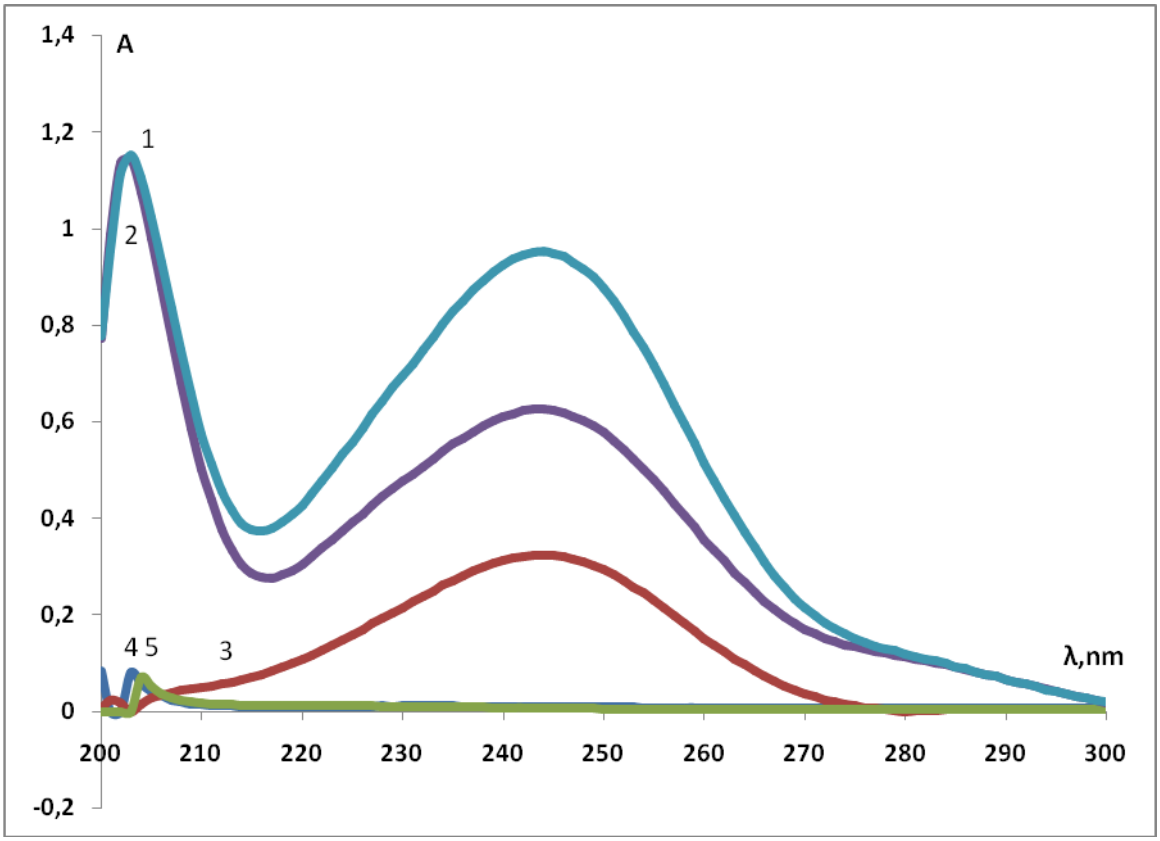


Fig. 3.2 Absorption spectra in 0.1 M solution of hydrochloric acid: 1-model mixtures of researched powders; 2-0.001% solution of paracetamol; 3-0.0006% solution of ascorbic acid; 4-0.0001% the solution of rutin; 5-0.00002% solution of phenylephrine hydrochloride

Established that the absorption spectrum of paracetamol in these conditions characterized by a peak a wavelength of 244 nm. On the character of the spectrum the absorption of paracetamol affects ascorbic acid, maximum absorption, which is observed at 243 nm. So, the solution mixture model is characterized by a peak wavelength of 244 nm, which is much more intense than most paracetamol solution in the same concentration.

Removing the effects of other active pharmaceutical ingredients on the character of the UV-spectrum of paracetamol, succeeded by adding ascorbic acid to a solution of standard sample of paracetamol in the an amount of prescription (Fig. 3.3).

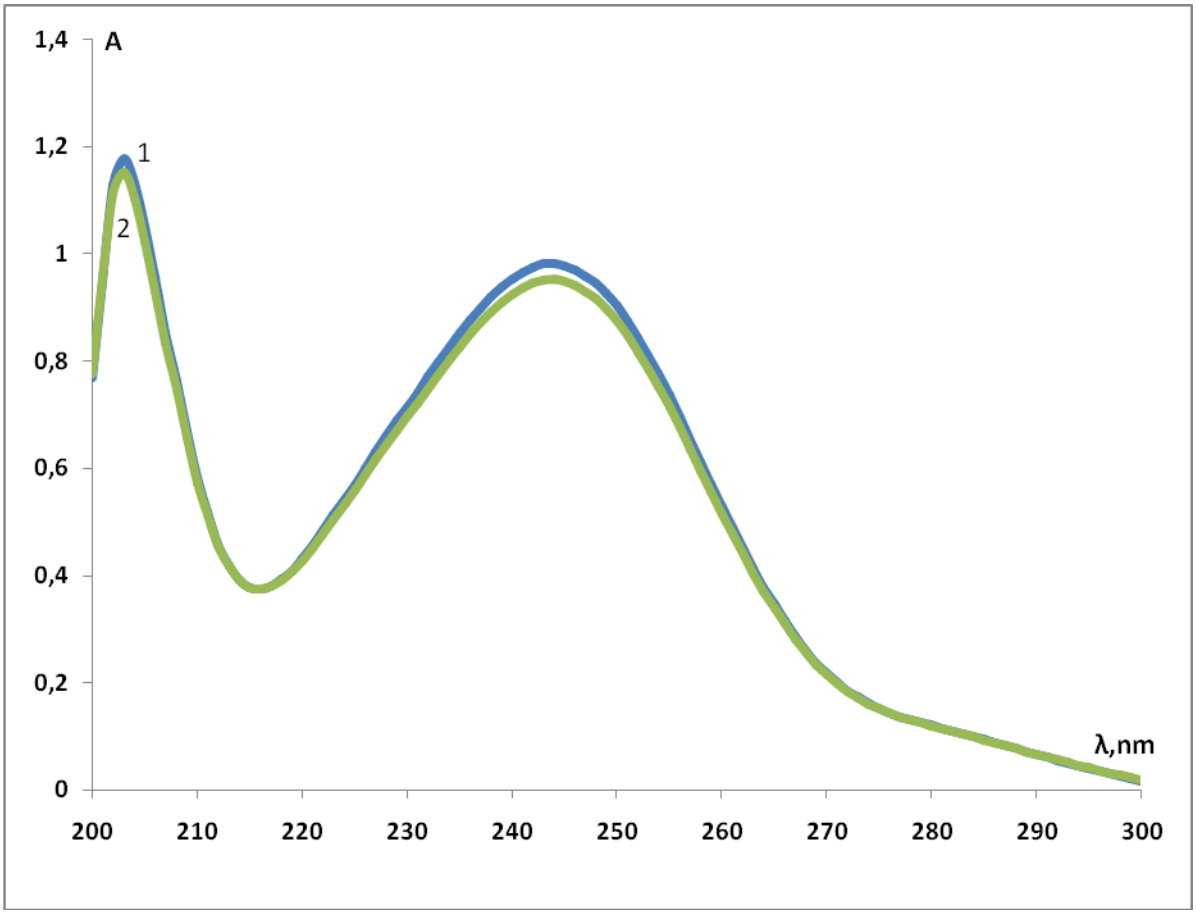


Fig. 3.3 Absorption spectra in 0.1 M solution of hydrochloric acid: 1 - solution of sample standard of paracetamol with added of ascorbic acid; 2 - studied model mix powders

Methods.

Test solution. About 0.200 g of powder shake for 10 min with 30 ml of a 0.1 M solution of hydrochloric acid in a volumetric flask 50.0 ml, dilute the same solvent to the mark and mix. The solution is filtered if necessary (rutin in these conditions, poorly soluble), discarding the first portion of the filtrate.

0.5 ml of the obtained solution is placed in a volumetric flask 100.0 ml, dilute 0.1 M solution of hydrochloric acid to the mark and mix.

Reference solution. 0.05 g of standard sample of paracetamol, placed in a volumetric flask 50.0 ml, dissolved in 30 ml of 0.1 M solution of hydrochloric acid, dilute the same solvent to the mark and mix.

0.5 ml of the obtained solution is placed in a volumetric flask 100.0 ml, add 0.3 ml of freshly made 0.1% solution of ascorbic acid and dilute 0.1 M solution of hydrochloric acid to the mark and mix.

Compensation solution. 0.1 M solution of hydrochloric acid.

The content of paracetamol in powders, in milligrams (X) calculated by the formula:

$$X, mg = \frac{A \cdot m_{st.s} \cdot V_{v.f.(test)} \cdot V_{v.f.(test)} \cdot V_{pip(st.s)} \cdot m_{prescr} \cdot 1000}{A_{st.s} \cdot m \cdot V_{v.f.(st.s)} \cdot V_{v.f.(st.s)} \cdot V_{pip.(test)}}$$

where:

A – absorbance (optical density) of the test solution;

$A_{st.\,s.}$ – absorbance (optical density) of standard sample solution;

$m_{st.\,s.}$ –mass of standard sample, g;

m – mass of sample dosage form for the quantitative determination, g;

$m_{prescr.}$ – mass of powder for the prescription, g;

$V_{v.f.}$ – the volume of volumetric flask of the test solution and reference solution, ml;

$V_{pip.}$ – aliquot volume (pipette) of test and reference solution, respectively, ml.

The results of the quantitative determination of paracetamol in powders by the spectrophotometric method and metrological characteristics of the results are shown in Table 3.4.

Table 3.4

The results of the quantitative determination of paracetamol by spectrophotometry

Powder sample, g	A	$A_{st.s}$	Found paracetamol, mg	Metrological characteristics
0,2	0,487 0,490 0,488 0,488 0,493 0,488	0,495	49,19 49,49 49,29 49,29 49,80 49,29	$\bar{x}$=49,39 $S^{2=}4,9\cdot10^{-7}$ S=0,0022 $S_{\bar{x}}$=0,0009 $\Delta\bar{x}$=0,0023 $\bar{\varepsilon}$,%=0,4702

Conclusions

1. Methods photocolorimetric quantitative determination routine, which is based on receiving the stained in yellow halkonìv, used and approved on research powders. The determination was carried in alcohol medium at a wavelength of 500 nm at a concentration of 0.1 mg rutin/ml by method standard.
2. The method of spectrophotometric quantitative determination of paracetamol in the studied dosage form based on the determination of absorbance 0.0005% solution of substance in 0.1 N hydrochloric acid solution at 244 nm wavelength. It is proved that on the character of the absorption spectrum in these conditions affects ascorbic acid, which proposed adding to a solution of paracetamol standard sample.
3. Quantitative determination of phenylephrine hydrochloride proposed conduct titrimetric method. With this purpose developed direct, method of

argentometry, which is recommended in acetic acid medium with indicator, bromphenol blue.

5. The quantitative content of ascorbic acid in the dosage form proposed to carry out redox method. Titration was carried out 0.05 m iodine solution as no indicator (weakly yellow coloring) and indicator-starch solution (to the blue coloring).
6. Developed methods of quantitative determination of active substances in the studied powders, pharmaceutical manufacturing different sufficient accuracy that proved when calculating the average relative errors result.

General conclusions

1. Studied literature data about methods of synthesis, methods of analysis and pharmacological activity of phenylephrine hydrochloride, acetaminophen, ascorbic acid and rutin.
2. Developed method of identification of active substances in the researched powder by chemical reaction.
3. The developed method of spectrophotometric quantitative determination of paracetamol and photometric - routine in the pharmaceutical manufacturing powders have enough degree of reliability.
4. Proposed quantitative determination of phenylephrine hydrochloride and ascorbic acid in composition powders carry out titrimetric methods argentometry and iodometric respectively.
5. It is established that the content of active ingredients in this dosage form meets the requirements of the State Pharmacopoeia of Ukraine.
6. Developed by us methods for quantitative determination of active pharmaceutical ingredients in powders extemporal production, can be included in the project of quality control methods on the analyzed dosage form.

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Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of pharmaceutical chemistry

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of pharmaceutical chemistry
_____
Victoriya GEORGIYANTS
"_29__" __June____ 2021

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Hadi SAYEGH

1. Topic of qualification work: «Pharmaceutical analysis of active ingredients in the anticold drug», supervisor of qualification work: Nataliia SMIELOVA, PhD,
approved by order of NUPh from "17th" of February 2022 № 76

2. Deadline for submission of qualification work by the applicant for higher education: april 2022.

3. Outgoing data for qualification work: Today in Ukraine, there is a revival of compounding practice, the opening of private compounding pharmacies, updating of the legislative framework and requirements of the State Pharmacopeia of Ukraine for compounding preparations, and the introduction of Good Pharmaceutical Practices. Also this applies particularly to the manufacturing pharmaceutical powders for the symptomatic treatment of respiratory diseases containing acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): To study and summarize the literature data on obtaining, identification, assay and pharmacological activity of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride; to develop methods of identification of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride; to develop methods of quantitative determination of acetaminophen, ascorbic acid, rutin, phenylephrine hydrochloride

5. List of graphic material (with exact indication of the required drawings):
8 tables, 9 figures and 2 schemas

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Nataliia SMIELOVA, assistant of department pharmaceutical chemistry	29.06.21	29.06.21
2	Nataliia SMIELOVA, assistant of department pharmaceutical chemistry	19.01.22	19.01.22
3	Nataliia SMIELOVA, assistant of department pharmaceutical chemistry	14.02.22	14.02.22

7. Date of issue of the assignment: «_29_» June 2021.

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Study and analysis of reference data on the use of expectorants. Writing 1 chapter.	Jun-Nov 2021	**done**
2	Study, processing and analysis of literature data on the use of acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride and their combination, methods of their synthesis, analysis and metabolism and physic-chemical properties. Writing 2 chapter.	Dec 2021 - Jan 2022	**done**
3	Development of the procedure for the determination of the active pharmaceutical compounds in the anti-cold drug.	Jan-Feb 2022	**done**
4	Statistical processing of experimental data. Writing 3 chapter.	March 2022	**done**
5	Summing up, preparation for defense	April 2022	**done**

An applicant of higher education _____ Hadi SAYEGH

Supervisor of qualification work _____ Nataliia SMIELOVA

ВИТЯГ З НАКАЗУ № 76

По Національному фармацевтичному університету
від 17 лютого 2022 року

1. Нижченаведеним студентам 5-го курсу 2021-2022 навчального року, навчання за освітньо-кваліфікаційним рівнем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація освітня програма – фармація, денна форма навчання (термін навчання 4 роки 10 місяців), які навчаються за контрактом, затвердити теми магістерських робіт:

№ з/п	Прізвище студента	Тема магістерської роботи	Посада, прізвище та ініціали керівника	Рецензент магістерської роботи
по кафедрі фармацевтичної хімії				
1.	Саєгх Хаді	Фармацевтичний аналіз активних інгредієнтів протизастудного препарату Pharmaceutical analysis of active ingredients in the anticold drug	ас. Смєлова Н.М.	проф. Перехода Л.О.

Підстава: подання декана, згода ректора.

Ректор
Вірно. Секретар

Національний фармацевтичний університет * УКРАЇНА * Факультет з підготовки іноземних громадян №02010936 місто Харків

Ф А 2.2.1-32-353

REVIEW

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

Hadi SAYEGH

on the topic: «Pharmaceutical analysis of active ingredients in the anticold drug»

Relevance of the topic. Analytical control of raw materials, intermediates and final products plays an important role in the quality assurance system of pharmaceutical products. Analytical methods begin to be used at the stage of development and research of drugs, production technologies and continue to be used during the serial production of pharmaceutical products both industrial production and produced in a pharmacy. The qualification work is devoted to the development of methods for the determination of acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride in the composition of the anti-cold drug in the joint presence.

Practical value of conclusions, recommendations and their validity. The results of the study can be applied in practice to develop regulatory and technical documentation for quality control of the anti-cold multicomponent drug, which consists of acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride.

Assessment of work. The work was done at a high scientific level; the applicant of high education independently reviewed the scientific literature in the field of pharmacological studies of anti-cold drugs. Under the guidance of the supervisor, the experimental part of the work and a review of the literature were completed.

General conclusion and recommendations on admission to defend. The qualification work meets the requirements for theses and can be recommended for defense to the Examination Commission of the NUPh.

Scientific supervisor _____ Nataliia SMIELOVA

« 14th» of April 2022

Ф А 2.2.1-32-356

REVIEW

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

Hadi SAYEGH

on the topic: «Pharmaceutical analysis of active ingredients in the anticold drug»

Relevance of the topic. The quality of drugs directly depends on the methods of their analysis, and therefore the development of new and improvement of existing methods for the analysis of drugs is an urgent task today. The qualification work is devoted to methods for the determination of acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride, which are simple, fast and economical, which is an advantage for quality control of the drug in laboratories of different equipment levels.

Theoretical level of work. The qualification work is performed at a high theoretical level with the use of modern theoretical approaches to the analysis of relevant scientific literature, legal framework and modern methods of analysis for quality control of the object of study.

Author's suggestions on the research topic. The author reviewed the literature and proposed identification reactions and methods of quantitative determination of acetaminophen, ascorbic acid, rutin and phenylephrine hydrochloride for quality control methods of the anti-cold multicomponent drug.

Practical value of conclusions, recommendations and their validity. The developed methods can be used to quantify active pharmaceutical compounds in

the anti-cold drug, and can be included in the regulatory and technical documentations.

Disadvantages of work. The work submitted for review does not have any significant shortcomings or disadvantages that affect compliance with the requirements of qualifying works.

General conclusion and assessment of the work. The work meets the requirements for qualification works of the master's level and can be recommended for defense in the Exam Commission of the NUPh.

Reviewer _____ prof. Lina PEREKHODA

« 22nd» of April 2022

Ф А2.2.1-38-287

ВИТЯГ З ПРОТОКОЛУ № 12

засідання кафедри фармацевтичної хімії

Національного фармацевтичного університету

від _26 квітня_ 2022 р.

ПРИСУТНІ:

проф. Георгіянц В.А., Власов С.В., Євтіфєєва О. А. Сидоренко Л.В.; доц.: Абу Шарк А.І., Бевз Н. Ю., Бур'ян Г.О., Гарна Н.В., Головченко О.С., Горохова О.В., Гриненко В.В., Грудько В.О., Колісник О.В., Петрушова Л.О., Северіна Г.І., ас. Григорів Г.В., Смєлова Н.М.

ПОРЯДОК ДЕННИЙ: заслухати звіт про стан виконання кваліфікаційних робіт.

СЛУХАЛИ: доповідь здобувача вищої освіти Хаді САЄГХ студента факультету з підготовки іноземних громадян на тему «Фармацевтичний аналіз активних інгредієнтів протизастудного препарату / Pharmaceutical analysis of active ingredients in the anticold drug», керівник асистент кафедри фармацевтичної хімії, к.ф.н. Наталія СМЄЛОВА.

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Хаді САЄГХ до офіційного захисту в ЕК.

Зав. кафедри фармацевтичної хімії,

професор **Вікторія ГЕОРГІЯНЦ**

Секретар кафедри фармацевтичної хімії,

доцент **Лідія ПЕТРУШОВА**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Хаді САЄГХ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Фармацевтичний аналіз активних інгредієнтів протизастудного препарату».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Хаді САЄГХ при проведенні експериментальних досліджень показав себе досить освідченим щодо хімічних фізико-хімічних методів. До написання роботи і підготовки до захисту ставився дуже відповідально. Робота цілком відповідає вимогам, що висуваються до кваліфікаційних робіт магістерського рівня і може бути рекомендована до захисту в Екзаменаційній комісії НФаУ.

Керівник кваліфікаційної роботи

_____ Наталія СМЄЛОВА

«14» квітня 2022 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри
фармацевтичної хімії

_____ Вікторія ГЕОРГІЯНЦ

«26» квітня 2022 року

Qualification work was defended

of Examination commission on

« ___ » _____ 2022

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /