Lesson 5

**Analysis of purine derivatives: caffeine, caffeine-sodium-benzoate, theophylline, theobromine, pentocillin,**

**xenthol-quintol and euphylline pharmaceutical forms.**

The purine nucleus is formed from imidazole and pyrimidine rings. It has two isomers - 9H-purine and 7H-purine:

7

H

N

N

N

N

H

9

8

7

6

5

4

3

2

1

N

N

N

N

9H purine 7H-purine

CONTAINING XANTHINE (2,6-DIOXYPURINE) DERIVATIVES

MEDICATIONS

Purine alkaloids are derivatives of xanthine (2,6-dioxypurine). Xanthine exists in two forms - enol (1) and ketone (II):

O

H

N

O

H

N

N

N

O

N

H

O

N

N

N

H

H

H

I

I

I

Xanthine (2,6-dioxypurine)

Caffeine, theobromine and theophylline belong to the purine alkaloids.

Based on the concept of antimetallots of nucleic acids with purine bases in the molecule, powerful antiviral agents with guanine derivatives have been created in recent years:



6, 9-substituted purine derivatives have different pharmacological effects and have the following general structure:



The 9H purine isostere is a heterocyclic system consisting of 4H-pyrazolo-[3,4-d]pyrimidine:



The study of these derivatives has led to the creation of means that ensure the excretion of urate concretions.

Xanthine (2,6-dioxypurine) derivatives include caffeine, theobromine, theophylline alkaloids, as well as their synthetic analogues diprophylline, ethophylline, pentoxifylline and their salts caffeine sodium benzoate, aminophylline, xanthinol-nicotinate.

The general structure of substances belonging to this group can be shown as follows:



Caffeine is 1,3,7-trimethylxanthine, theobromine is 3,7-dimethylxanthine, and theophylline is 1,3-dimethylxanthine. All three substances have a stimulating effect on the central nervous system and cardiac activity. In this regard, caffeine is more active; while theobromine and theophylline have stronger vasodilator and diuretic effects.

Caffeine was first obtained by Runge in 1819, theophylline was first obtained by Kossel in 1889, and theobromine was obtained from coffee seeds and tea leaves in 1889.

These alkaloids are contained in the leaves of tea (Thea chinensis L.), coffee (Coffea arabica L.) and cola seeds, as well as in cocoa beans. Tea leaves and coffee beans contain up to 1-3% caffeine, and cocoa beans contain up to 30% theobromine.

In addition to caffeine, tea leaves also contain a small amount of theobromine, theophylline, and xanthine. It should be noted that caffeine is obtained from tea dust and scraps, which are formed as waste from tea production.

There are several ways to obtain caffeine from natural raw materials. One of the methods is countercurrent extraction. Water extraction is cleaned of impurities, ballast substances are precipitated with the help of lead, calcium and magnesium salts. The filtrate is evaporated. Caffeine is obtained by recrystallization from cooled aqueous solutions. In a similar way, theobromine is obtained from cocoa beans.

At present, methods of full synthesis and semi-synthesis are used to obtain these alkaloids. Because these methods are economically efficient.

1) Complete chemical synthesis was proposed by the German scientist Traube in 1900.

N

H

3

C

C

N

H

3

H

C

O

+

C

C

H

2

C

N

O

O

H

-

H

2

O

C

O

N

3

H

C

O

N

H

C

H

3

C

N

H

dimetil sidik sianasetat sian-asetildimetil

cövhəri turşusu sidik cövhəri

C

O

N

3

H

C

O

N

C

H

3

C

H

2

N

H

N

O

H

O

-

H

2

O

1,3-dimetil-4-imin-urasil

C

O

N

3

H

C

O

N

C

H

3

N

H

N

O

H

[

H

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C

O

N

3

H

C

O

N

C

H

3

N

H

2

N

H

2

 1,3-dimetil-4-imin- 1,3-dimetil-4,5-

 -5-izonitrozourasil diaminurasil

H

C

O

O

H

-

H

2

O

C

O

N

3

H

C

O

N

C

H

3

N

H

2

N

H

C

O

H

N

a

O

H

-

H

2

O

1-3-dimetil-4-amin-

-5-formil aminurasil

C

O

N

3

H

C

O

N

C

H

3

N

N

H

(

C

H

3

)

2

S

O

4

C

O

N

3

H

C

O

N

C

H

3

N

N

C

H

3

 teofillin kofein

If urea is given for condensation at the first stage, xanthine is obtained as the final product. Methylation of xanthine with dimethylsulfate at pH 8-9 gives caffeine, and methylation at pH 4-7 gives theobromine.

2) Semi-synthetic method.

Uric acid, used here as a raw material, is obtained by synthesis of urea (NH2CONH2) and acetal (СН3–СН(ОС2Н5)2) at a temperature of 1100 С or from bird droppings (guano). Its quantity in the bird's bell reaches 25%.

When uric acid is treated with formamide, xanthine is obtained, which is methylated under certain conditions for the synthesis of caffeine and theobromine. The process of methylation in the production of caffeine is carried out at pH 8-9, and in theobromine at a temperature of 60-700 C with the participation of KOH and methanol:

H

N

H

O

N

H

N

H

O

N

H

N

H

O

N

H

N

O

N

O

H

C

O

N

H

2

formamid

 sidik turşusu ksantin



**Caffeine — Caffeine**

**(Teinum)**

C

H

3

O

N

C

O

N

C

H

3

N

N

H

2

O

.

H

3

M.k. 212.21; 194.19 (anhydrous)

1,3,7-trimethylxanthine

Caffeine is white shiny needle crystals or white crystalline powder with a bitter taste. It gradually loses its water of crystallization in the air. Evolves when heated. Dissolve gradually (1:60) in water, slightly soluble in hot water and chloroform, moderately soluble in alcohol, very slightly soluble in ether. Melting temperature 235-2380 С.

Definition of personality

Oxidation, precipitation and complexation reactions are used to determine the identity of xanthine derivatives.

1) General recommendations for determining the authenticity of xanthine derivatives

a typical reaction is a test with murexide.

The essence of the murexide reaction is that when xanthine derivatives are heated with oxidants (hydrogen peroxide, bromine water, nitric acid, etc.), the purine molecule is split; Alloxanic and dialuronic acids are formed. As a result of the interaction of alloxan and dialuronic acid, alloxanthin derivatives are obtained, which give a cherry-red color when they interact with ammonia. The acquisition of color is caused by the formation of the ammonium salt of tetramethylpurpuric acid.

Place 0.1 g of the preparation in a porcelain dish, add 10 drops of concentrated hydrochloric acid, 10 drops of perhydrol and evaporate in a water bath until a dry residue is obtained. The residue is impregnated with 1-2 drops of NH3 solution; raspberry color is formed. The resulting color is lost under the action of several drops of an alkaline solution:

C

H

3

O

N

3

H

C

O

N

C

H

3

N

N

H

2

O

2

C

O

N

2

H

N

H

C

H

3

+

metilsidik cövhəri

O

O

O

O

N

N

3

H

C

C

H

3

+

O

C

H

3

O

O

N

N

3

H

C

O

H

H

C

l

 1-3-dimetilalloksan 1,3-dimetildialur

 turşusu

O

C

H

3

O

O

N

N

3

H

C

O

H

O

C

H

3

O

O

N

N

C

H

3

O

N

H

3

tetrametilalloksantin

O

C

H

3

O

O

N

N

3

H

C

N

O

C

H

3

O

C

H

3

N

N

O

4

H

N

tetramethylmuroxide

(ammonium salt of tetramethylpurpuric acid)

According to some authors (A.P. Arzamastsev), obtaining a cherry-red color is related to the formation of a mesomeric stabilized anion:



2) 0.01 g of the drug is dissolved in 10 ml of water. 0.1% tannin solution is added drop by drop to 5 ml of the obtained solution; a white precipitate is obtained which dissolves in the excess of the reagent.

3) dissolve 0.05 g of the drug in 5 ml of hot water, cool the solution, add 10 drops of 0.05 M iodine solution; sediment and turbidity should not be obtained. A brown precipitate is obtained by adding a few drops of dilute hydrochloric acid; the precipitate dissolves in an excess of alkaline solution:



caffeine

4) The melting temperature of caffeine should be 234-2370 C (after drying to a constant mass at 800 C).

5) UV-spectrophotometry: a solution of caffeine in 0.1 M hydrochloric acid gives maximum absorption at a wavelength of 273 nm.

6) Caffeine is determined with the help of precipitation reagents, specific for alkaloids, such as many derivatives of xanthine.

7) When caffeine is treated with mercury 2-chloride, a white complex compound (C8H10N4O2∙HgCl2) is formed, consisting of a mixture of both substances in equimolecular proportions.

8) It is determined by the IR-spectroscopy method.

Definition of cleanliness

Check the presence of extraneous alkaloids: 10 ml of the drug solution (1:100) should not be cloudy from the action of several drops of Mayer's reagent.

Impurities of foreign alkaloids are also tested with NTX. Additions of theobromine and theophylline to the preparation should not exceed 0.5%.

Quantitative assessment

Anhydrous titration method.

Since caffeine by its chemical nature is a weak base, its solutions have a neutral reaction. Caffeine does not form salts with mineral acids, as they are immediately hydrolyzed. Therefore, determination of caffeine by neutralization method in aqueous medium is impossible. In an anhydrous medium (chloroform, acetic acid, benzene), caffeine shows its basic properties and it can be titrated with acids.

About 0.15 g of the preparation, dried to a constant weight at a temperature of 800 C, dissolve in 10 ml of acetic anhydride while heating in a water bath, add 20 ml of benzene, 5 drops of a solution of violet crystals and titrate with 0.1 M of hydrochloric acid until it turns yellow.

A control experiment (T=0.01942 g/ml) is conducted in parallel.

C

H

3

O

N

3

H

C

O

N

C

H

3

N

N

C

l

O

4

.

+

K

o

f

e

i

n

+

H

C

l

O

4

H

2) Spectrophotometric method (see the 5th definition of identity).

3) Complexonometry method.

Caffeine, theobromine, and theophylline give a white precipitate-complex in a 1:1 ratio with Hg2+ ions (for example, caffeine forms a C8H10N4O2 HgCl2 compound). Therefore, using this reaction, they indirectly determine the amount of indicated drugs.

4) Serimetry method. Caffeine, theobromine and theophylline are oxidized by Ce(SO4)2. The excess of Ce(SO4)2 is determined by iodometry. For this, 10% KI solution and chloroform are added to the solution and titrated with 0.1 M Na2S2O3.

Kofein + 4Ce(SO4)2 + H2O → NH2–CO–NHCH3+ 2Ce2(SO4)3 + 2H2SO4 +

 (metil karbamid)

O

O

O

O

N

N

3

H

C

C

H

3

+

1,3-dimetilalloksan

2Ce(SO4)2 + 2KI → Ce2(SO4)3 + I2 + 2K2SO4

I2 + 2Na2S2O3→ 2NaI + Na2S4O6

5) Iodometry method (see caffeine sodium benzoate).

Caffeine is used as a CNS stimulant and cardiotonic agent. 0.05-0.1 g is given 2-3 times a day. It is released in the form of powder and combined preparations (cofetamin, pentalgin, citramon, etc.).

The drug is stored in tightly closed containers.

**Caffeine Sodium Benzoate**

**Caffeine benzoate Sodium**

C8H10N4O2⋅ C6H5COONa və ya Kofein $∙$ C6H5COONa

It is a white powder, odorless and slightly bitter taste. Easily soluble in water, moderately soluble in alcohol.

Acquisition

To get the preparation, they mix aqueous solutions of caffeine (40%) and sodium benzoate (60%) and evaporate to a dry residue.

Determination of identity

1) 0.5 g of the drug is dissolved in 3 ml of water, 1 ml of NaOH solution and 10 ml of chloroform are added and kept for 1-2 minutes. The chloroform solution is filtered from Na2SO4 into a porcelain dish and evaporated to a dry residue. The dry residue is divided into 3 parts, and the first and second reactions are carried out to determine the identity of caffeine in its two parts.

2) A part of the obtained residue is dried at a temperature of 800 C to a constant weight and the melting temperature is determined. The melting temperature of the dry residue should be between 232-2340 C.

3) 0.2 ml of iron 3-chloride solution is added to 2 ml of the drug solution (1:100), a pink-yellow precipitate is formed (benzoate ion).

6C6H5COONa + 2FeCl3 + 10H2O→ 6NaCl + 3C6H5COOH +

+ (C6H5COO)3Fe ⋅ Fe(OH)3⋅ 7H2O↓

1) The preparation turns the colorless flame yellow.

Determination of cleanliness

Solutions of the preparation should be colorless and transparent; If the 20% aqueous solution is heated in a boiling water bath for 30 minutes, nausea or sediment should be obtained.

Quantification

1) determined by UV-spectrophotometry. The optical density of the drug solution in water is determined at 272 nm d.u.

2) Caffeine is determined by iodometry. About 0.3 g (d.c.) of the drug is dissolved in 30 ml of water in a volumetric flask with a volume of 100 ml, 10 ml of clear H2SO4, 50 ml of 0.05 M iodine solution are added, the volume of the flask is brought to volume with water and mixed thoroughly. After keeping the solution for 15 minutes, they carefully filter it through cotton into a dry flask. They discard the first 10-15 ml of the filtrate, the excess of iodine in 50 ml of the filtrate

They titrate with 0.1 M sodium thiosulfate solution, add starch at the end of the titration.

In parallel, a control experiment is carried out.

1 ml of 0.05 M iodine solution corresponds to 0.00485 g of caffeine; its content should not be less than 38.0% and more than 40% based on dry matter.

3) Determination of sodium benzoate by neutralization (acidimetry): about 1.5 g (d.c.) of the drug is dissolved in 20 ml of water in a polished flask with a volume of 250 ml, 45 ml of ether, 3-4 drops of mixed indicator (1 ml of methyl orange and 1 ml of methylene blue mixture) are added and titrated with 0.5 M hydrochloric acid in the aqueous layer until lilac color.

1 ml of 0.5 M hydrochloric acid corresponds to 0.07205 g of sodium benzoate; its content should not be less than 58% and more than 62% based on dry matter.

C6H5COONa + HCl  C6H5COOH + NaCl

In tablets of 0.1 and 0.2 g, 10 and 20% solutions are released for injection in the amount of 1 and 2 ml. Caffeine is prescribed for the purposes indicated.

The drug is stored in tightly closed containers.

**Theophylline – Theophylline**

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O

N

3

H

C

O

N

C

H

3

N

N

H

2

O

H

**1,3-dimethylxanthine monohydrate**

**M.k. 198.18**

It is a white crystalline powder, odorless. It is slightly soluble in water, 95% alcohol, ether and chloroform, easily soluble in hot water and 95% hot alcohol, soluble in acids and alkalis.

Determination of identity

1) Gives Murexid test.

Unlike caffeine, theophylline and theobromine show acidic properties due to the hydrogen of the imide group in the 1st or 7th position. That is why they form salts with various cations (cobalt, mercury, copper, silver), which is also used to determine the identity of drugs. So, the sodium salt of theophylline is obtained by first reacting with alkali; cobalt-chloride solution is used to distinguish caffeine, theophylline and theobromine from each other. Under such conditions, theophylline gives a pinkish-white precipitate, and theobromine gives a grayish-blue precipitate.

2) 0.5 g of the preparation is shaken with 2 ml of 0.1 M NaOH solution for 2 minutes and filtered. 3 drops of 2% cobalt-chloride or cobalt-nitrate solution are added to the filtrate and mixed; a pinkish**-white precipitate (cobalt-theophylline) is obtained.**

O

N

3

H

C

O

N

C

H

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3

O

N

3

H

C

O

N

C

H

3

N

N

C

o

2

2+

3) Theophylline is heated and cooled in a boiling water bath with 30-40% NaOH solution and neutralized with 50% acetic acid. At this time, theophylline turns into theophyllide, which, when reacted with diazonium salts, turns into a red colored azo dye (pentoxifylline also gives this reaction). The processed azo dye gives a red-purple complex compound with Hg2+ ions.

0

H

N

3

H

C

+

N

H

3

H

C

H

N

N

T

e

o

f

i

l

l

i

n

N

a

O

H

t

C

N

R

N

C

l

O

teofillidin

N

N

N

H

3

H

C

H

N

H

3

H

C

O

N

N

R

teofillidin azoboyası

N

N

N

H

H

N

3

H

C

N

N

R

O

H

H

g

2

+

H3C



**of theophyllide azo dye**

**mercury complex (red-violet)**

4) The melting temperature of theophylline should be between 271-2740 C.

5) Unlike other purine alkaloids, theophylline gives a green color with a solution of sodium nitroprusside in alkali. It loses its color due to the excess of acid.

6) Theophylline at pH 8.5 (borate buffer solution) gives intense blue staining with 2,6-dichloroquinonechlorimide (indophenol dye):

-

H

C

l

N

l

C

+

n

i

l

l

i

f

o

e

T

C

l

O

C

l

O

N

3

H

C

O

N

C

H

3

N

N

H

C

l

O

C

l

N

7) Theophylline sodium salt with silver salts characteristic semi-transparent precipitate; when heated, the precipitate solidifies, and when cooled, it solidifies again:



8) UV-spectrophotometry: a solution of theophylline in 0.1 M hydrochloric acid gives maximum absorption at 272 nm d.u.

9) It is carried out by IR-spectroscopy in the fields of 4000-400 cm-1.

Determination of cleanliness

1) Other purine bases are checked: the solution of 0.2 g of the drug in 5 ml of ammonia should be transparent and colorless.

2) Organic compounds are checked: the solution of 0.1 g of the drug in 2 ml of concentrated sulfuric acid should be transparent and colorless.

Quantification

1. It is based on the formation of silver-theophylline and the neutralization of excreted nitric acid (alkalimetry):

O

N

3

H

C

O

N

C

H

3

N

N

H

+

A

g

N

O

3

O

N

3

H

C

O

N

C

H

3

N

N

+

H

N

O

3

A

g

HNO3 + NaOH → NaNO3 + H2O

 About 0.08 g of pre-dried drug is dissolved in 20 ml of boiled water for 5 minutes, 25 ml of 0.02 M silver nitrate, 1-1.5 ml of phenol red solutions are added, and 0.02 M NaOH solution is added. they titrate to violet-red color (T=0.0036 g/ml).

 2) Spectrophotometry method: based on the maximum absorption of theophylline solution in 0.1 M sodium hydroxide at a wavelength of 272 nm.

 3) It is carried out by serimetry method (see caffeine).

 Theophylline has a spasmolytic (vases, bronchial dilation), diuretic, CNS stimulating effect. Increases myocardial contractile activity. Theophylline is more widely used as a long-acting drug, rather than in the "usual" short-acting form, mainly as a bronchodilator. Such drugs include theophedrine N (Theophedrinum N), Theo-Asthalin (Theo-Asthalin), Theopek (Theopecum), Theobilong (Theobiolongum), Spofylline retard (Spophylline retard), Theodur (Theodur), Teotard (Theotard), Retafil (Retaphyl), Ventax (Ventax) and others. belongs to.

 The drug is stored in tightly closed containers, protected from light.

O

N

C

H

3

O

N

C

H

3

N

N

H

M.k. 180.17

3,7-dimethylxanthine

It is a white crystalline powder, odorless and bitter in taste. It is very slightly soluble in water, 95% alcohol, ether, chloroform, slightly soluble in hot water, and easily soluble in strong acid and alkaline solutions.

Determination of identity

1) The drug passes the Mureksid test.

2) they carry out the second reaction, which determines the identity

of theophylline; a dark-purple color that quickly disappears, and then a grayish-blue precipitate (cobalt-theobrominate) is obtained.

The reaction takes place in the imide group in the first position:

ONa

N

a

N

O

N

C

H

3

N

N

T

e

o

b

r

o

m

i

n

N

a

O

H

-

H

2

O

C

H

3



3) 0.05 g of the drug is dissolved in a mixture consisting of 3 ml of water and 6 ml of NaOH solution, 1 ml of NH3 and 2 ml of 5% AgNO3 solutions are added. When the mixture is shaken, a solid mass similar to gelatin (silver-theobrominate) is obtained; when mixed at a temperature of 800 C, it becomes a paste, when it cools, it solidifies again:



2) determined by UV-spectrophotometry. Theobromine 0.1 M sodium-

based on the maximum absorption at 272 nm d.u. of its solution in hydroxide.

3) determined by IR-spectroscopy.

Determination of cleanliness

3-methylxanthine is examd. Place 0.5 g of the preparation in a test bottle, add 2 ml of 0.1 M NaOH solution, shake for 2 minutes and filter. Add 3 drops of 2% solution of cobalt chloride (or cobalt nitrate) to the filtrate and mix quickly. The acquired purple color should disappear no later than 2 minutes.

Quantification

1) It is carried out in the same way as in theophylline. To buy silver-theobrominate and

based on the neutralization of the excreted HNO3 (T=0.0036 g/ml):

C

H

3

OAg

N

N

C

H

3

N

O

N

T

e

o

b

r

o

m

i

n

+

A

g

N

O

3

-

H

N

O

3

HNO3 + NaOH → NaNO3 + H2O

2) It is carried out by serimetry method (see caffeine).

3) It is carried out by UV-spectrophotometry method.

Theobromine as a spasmolytic (vases and bronchial dilator) and diuretic agent is released in powder, tablet (0.25 g) and tablets in case of combination with other drugs: Theodibaverine (Theodibaverine), Tepaphylline (Thepaphylline).

**Aminophylline - Aminophylline**

**(Euphyllinum)**

O

N

3

H

C

O

N

C

H

3

N

N

H

C

H

2

C

H

2

N

H

2

N

H

2

.

**Theophylline with 1,2-ethylenediamine**

It contains 80% theophylline and 20% ethylenediamine. It is a white or slightly yellow crystalline powder with a weak ammonia smell. It absorbs carbon dioxide from the air, as a result of which its solubility decreases. Soluble in water. The solution of the preparation in water has an alkaline reaction.

Determination of identity

1) As a result of the murexid test, a crimson color is obtained;

2) dissolve 0.1 g of the drug in 3 ml of water and add 5 drops of copper 2-sulfate solution; purple color - a complex compound is obtained.

C

H

2

C

H

2

N

H

2

N

H

2

3

+

C

u

S

O

4

C

H

2

N

H

2

C

H

2

N

H

2

C

u

3

S

O

4

3) 1 g of the drug is dissolved in 10 ml of water and neutralized with dilute hydrochloric acid until the pH is 4-5 according to the universal indicator. The obtained white precipitate is separated by filtering, washed with water and dried at a temperature of 100-1050 C. The melting temperature of the dried precipitate (theophylline) should be 269-2740 C. When the filtrate is treated with benzoyl chloride in an alkaline medium, dibenzoylethylenediamine precipitates. It is separated, crystallized from ethanol, washed and dried. Melting temperature should be 250-2510 C.

C

H

2

C

H

2

N

H

2

N

H

2

+

2

C

6

H

5

C

O

C

l

-2

H

C

l

C

H

2

C

H

2

N

H

C

O

C

6

H

5

N

H

C

O

C

6

H

5

dibenzoylethylenediamine

Quantification

1. Determination of ethylenediamine by neutralization (acidimetry):

C

H

2

C

H

2

N

H

2

N

H

2

+

2

H

C

l

N

H

2

H

C

l

C

H

2

C

H

2

N

H

2

H

C

l

.

.

About 0.3 g (exact weight) of the drug is dissolved in 25 ml of freshly boiled and cooled water and titrated with 0.1 M hydrochloric acid until orange-pink coloration (indicator - methyl orange; T=0.003005 g/ml).

The amount of ethylenediamine should be 14.0-18.0%.

1. Determination of theophylline by the formation of silver-theophylline:

about 0.08 g (d.k.) of the preparation is placed in a wide-mouth flask with a volume of 250 ml and kept in a drying cabinet at a temperature of 125-130°С. C in the course of 2.5 hours until the complete disappearance of the smell of amines. The dried sample is dissolved in 20 ml of freshly boiled hot water and boiled for 1 min. Add 25 ml of 0.02 M AgNO3 solution to the cooled solution and titrate with 0.02 M NaOH solution until red-violet coloration (indicator – phenol red; T=0.0036 g/ml). The amount of theophylline should be 80.0-85%.

3) Determination of theophylline in aminophylline by express method.

Aminophylline is dissolved in a mixture of dimethylformamide and water and titrated with a 0.1 M solution of NaOH in water (indicator - thymol blue).

It is used in bronchial asthma, spasms of the bronchi, as a diuretic, in ischemic stroke, chronic insufficiency of cerebral circulation and hypertensive disease. In tablets of 0.015 g, a 2.4% solution for intramuscular administration is produced in the amount of 5 and 10 ml, and a 24% solution for injections in the amount of 1 ml.

The drug is stored until the end in a completely filled container, protecting it from light and moisture.

**Pentoxifylline - pentoxifylline**

**(Trental, Agapurin, Radomin)**

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**3,7-dimethyl-1-(5-oxohexyl)-xanthine or**

**1-(5-oxohexyl)**

These preparations are a white crystalline powder, easily soluble in water and slightly soluble in alcohol.

Both drugs are used as myotropic antispasmodics in peripheral and brain vascular pathology, diabetic angiopathy (vessel tone disorder), and functional hearing disorders.

Xanthinol-nicotinate combines the effects of drugs of theophylline group and nicotinic acid. Pentoxifylline blocks adenosine receptors and slows down the action of the phosphodiesterase enzyme.

Xanthinol-nicotinate in tablets of 0.15 g, solution 15% in ampoules of 2 and 10 ml, pentoxifylline 0.1; 0.2; 2% solution for injections in the amount of 5 ml is available in tablets (drags) of 0.4 g.

Definition of personality

1) The melting temperature of nicotinate xanthine should be 180-1860 С, and the melting temperature of pentoxifylline should be 103-1060 С.

2) 0.001% solution of xanthine-nicotinate in water gives maximum absorption at a wavelength of 272±2 nm, and a maximum at a wavelength of 245±2 nm (pentoxifylline also gives these indicators).

A solution of xanthine-nicotinate in 0.1 M hydrochloric acid gives maximum absorption at a wavelength of 267 nm.

3) Chromatography is performed on a thin layer (silufol UF-254) on xanthine-nicotinate. For this, they use solutions of the drug in 5% water-alcohol (2:3), 1.4% solutions of nicotinic acid in water-alcohol (2:3) as a standard sample, n-butanol-methanol-25% ammonia as a standard sample. the solvent solution is taken - chloroform (8:9:6:14). The chromatogram is illuminated with UV rays. Along with the spots of the standard sample of xanthine base and nicotinic acid, one more spot should be present on the chromatogram, the Rf of which is at the same level as the Rf of the standard sample of nicotinic acid.

4) Both drugs are tested for murexide as a derivative of xanthine.

5) Pentoxifylline forms a yellow precipitate with Dragendorff's reagent.

6) IR-spectroscopy: the IR-spectra of the test sample and the standard must

be identical.

Definition of cleanliness

They also check pentoxifylline for extraneous impurities (not more than 1%), theophylline in xanthine-nicotinate (not more than 0.5%), NTX.

Quantitative assessment

It is carried out by the method of anhydrous titration. The classification is based on the formation of perchlorates due to the triplet nitrogen atoms of nicotinic acid in the 9th and 3'-positions of the purine nucleus:

The sample mass of the preparation is dissolved in a mixture of glacial acetic acid and acetic anhydride (2:10) and titrated with 0.1 M perchloric acid until it turns yellow (indicator – violet crystal; E=M.k./3; T=0.01448 g/ml).

Determination of the amount of pentoxifylline is carried out by anhydrous titration, as with caffeine.

The drug is stored in tightly closed containers.