Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

QUALITY DETERMINATION "PURIFIED WATER"

Lesson 5

V term

Volgograd, 2022

QUESTIONS FOR THE LESSON

1. Water in pharmaceutical practice.
2. Purified water analysis.
3. Testing of water for injection. Pyrogenicity.
4. Sterility.
5. Microbiological purity.

WATER IN PHARMACEUTICAL PRACTICE

Water is an essential part of plant and animal organisms. It makes up 65% of the total human mass.

Water is a product which is widely used in pharmacy for various purposes:

- ✓ an auxiliary substance in the composition of medicinal products
- ✓ solvent for preparation of preparations for use
- ✓ solvent in drug synthesis and production of drugs,
- ✓ a cleaning agent for flushing and cleaning equipment, primary packaging materials, etc.

The term 'water' is used to describe drinking water, freshly drawn directly from a public water supply and suitable for drinking.

Water used in the pharmaceutical industry and related industries is divided into the following types:

1. drinking water (fit for drinking),
2. purified water, (aqua purificata)
3. sterile purified water (water purified for injections)
4. water for injections, (water for injections)
5. sterilised water for injections (sterilised water for injections)
6. bacteriostatic water for injections,
7. sterile water for irrigation and sterile water for inhalation.

For all systems for the above types of water, except drinking water, a validation process is required.

Water quality requirements for various applications in the pharmaceutical industry are regulated in the pharmacopoeia of the Russian Federation.

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Pharmacopoeial monographs in force in Russia:

2.2.0020.18 'Purified water';

2.2.0019.18 "Water for Injection";

2.2.0020.15 "Purified Water";

2.2.0019.15 "Water for Injection";

42-213-96 "Water for Injection in ampoules;

2998-99 "Water for injection in vials".

Producers in most countries of the world, and Russia in particular, at the same time as the national pharmacopoeia for assessing water quality for pharmaceutical purposes also take into account the requirements of the USP and European Pharmacopoeia as they contain more stringent requirements for water quality.

There are monographs in the European Pharmacope:

"Purified water";

"Water for injection";

"Highly purified water";

"Purified water, packaged";

"Sterile water for injection, packed".

PURIFIED WATER

Purified water is used for

- ✓ preparation:
    a. mixtures and solutions for internal use,
    b. eye drops and ophthalmic solutions,
    c. nasal drops,
    d. certain solutions for external use,
    e. semi-finished products and other non-sterile preparations,
- ✓ steam production,
- ✓ sanitising,
- ✓ washing of containers and closures (except for final rinsing in the production and/or manufacture of sterile medicines),
- ✓ in laboratory practice.

Purified water can be obtained from drinking water by distillation (distilled water), ion exchange, reverse osmosis or electrodialysis. Experts consider ion exchange or reverse osmosis to be the preferred and most economical methods of obtaining purified water.

Purified water can be stored for a maximum of three days under aseptic conditions. Storage tanks must be tightly sealed to prevent contamination by impurities and micro-organisms.

Purified water is monitored daily from each cylinder or pipeline for pH, chloride and sulphate ions and Ca^{2+} ions.

HIGHLY PURIFIED WATER

Highly purified water (Aqua valde purificata) is intended for the preparation of medicines where higher biological quality water is required, except where only water for injection is needed. It can be used mainly for cleaning containers and surfaces in contact with parenteral products, provided the containers and surfaces are depyrogenated.

The production method used is moveable reverse osmosis, ultrafiltration and deionisation.

WATER FOR INJECTION

Water for injection is used for the production and/or manufacture of sterile medicinal products, finish rinsing of containers and closures, treatment of preparation, storage and distribution systems that are in direct contact with the end product.

Use freshly prepared or store at 5°C - 10°C or 80°C - 95°C in closed containers made of materials that do not change the properties of water, protecting the water from mechanical impurities and microbiological contamination, but not longer than 24 hours.

WATER FOR INJECTION IN AMPOULES

Water for injection in ampoules is used as a solvent for the preparation of dosage forms for injection. Available in ampoules or vials.

Store at a temperature not exceeding 25 °C for 4 years.

PURIFIED WATER ANALYSIS

To control the quality of treated water, the State Pharmacopoeia recommends that a series of tests to determine the absence or the permissible limit of of various impurities.

1. Acidity or alkalinity

Determined by using a phenol red indicator.

Technique: *To 20 ml of purified water add 0.05 ml of 0.1% phenol solution purified water is added with 0.05 ml of 0.1 % phenol red solution. When yellow colouring appears it should When the yellow colouring changes to red with the addition of max. 0.1 ml of 0.01 M sodium hydroxide solution on the addition of 0.01 mL. If the colour red appears should change to yellow with the addition of up to 0.15 mL 0.01 M sodium hydroxide solution mL of 0.01 M hydrochloric acid solution should be added.*

2. Dry residue

To test for salt impurities, 100 ml of water are evaporated, then dried at 100 - 105 °C, weighed and the mass fraction of the dry residue calculated. The State Pharmacopoeia allows a dry residue of max. The State Pharmacopoeia allows a dry residue of not more than 1mg (0.001%).

3. Carbon dioxide impurity

Water absorbs carbon dioxide easily. The State Pharmacopoeia does not allow the presence of carbon dioxide. If it is present, it can be detected by the turbidity of the lime water (saturated calcium hydroxide solution) taken in equal volume with water, in a topped up and tightly closed vessel for and kept tightly closed for 1 hour.

Technique: *Place 50 ml of test water and 50 ml of lime water in a 100 ml flask, cork well and mix thoroughly: after 1 hour there should be no clouding of the solution.*

4. Chloride impurities

The chloride impurity is determined by reacting with silver nitrate:

No opalescence should be observed

Technique: *To 10 mL of test water add 0.5 mL of diluted nitric acid diluted and 0.5 ml silver nitrate solution are added, stirred and allowed to stand for 5 minutes. The mixture is stirred and allowed to stand for 5 minutes. There should be no opalescence.*

5. Sulphate impurities

Sulphates are detected by reacting with barium chloride:

No turbidity should be observed.

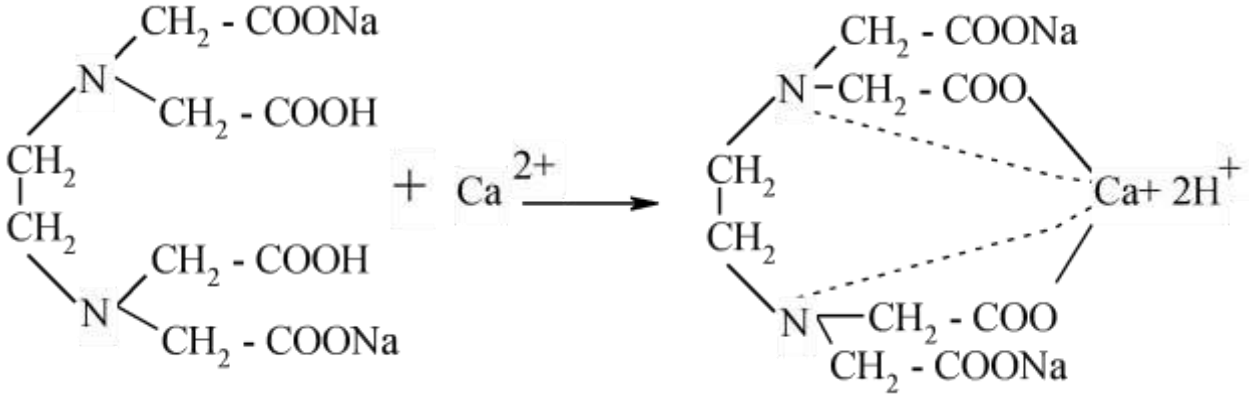
Technique: *To 10 ml of test water add 0.5 ml of diluted hydrochloric acid and 1 ml of barium chloride, stir and leave for 10 minutes. There should be no turbidity.*

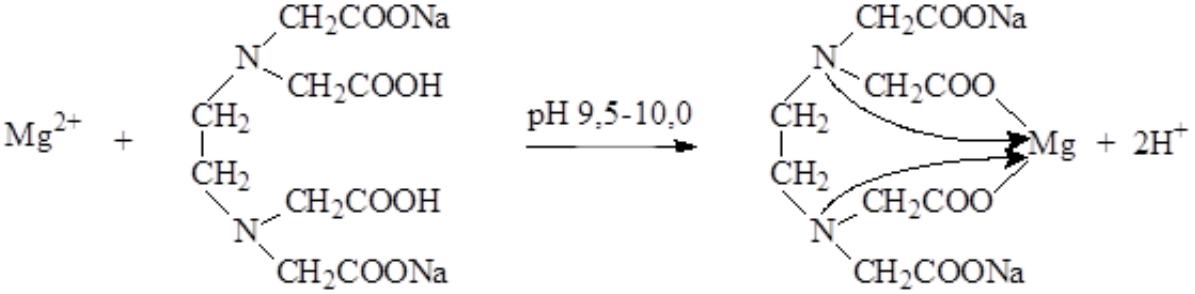
6. Calcium and magnesium salt impurities

The presence of magnesium and calcium salts is determined with sodium edetate and the indicator eriochrome black T. The determination is carried out at pH 10.

If there are no impurities, a clear blue colouring of the indicator will be observed.

If calcium or magnesium salts are present, the following reactions take place:

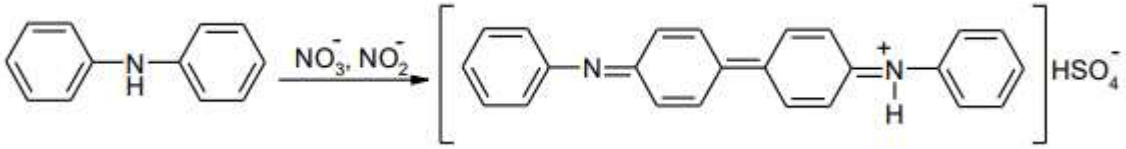




Technique: *To 100 ml purified water add 2 ml ammonium chloride buffer solution, pH 10.0, 50 mg eriochrome black T indicator and 0.5 ml sodium edetate 0.01 M solution. The solution should show a clear blue colouring (without a violet tint).*

7. Nitrate and nitrite impurities

Impurities of nitric and nitric acid salts are determined by reacting with a solution of diphenylamine:

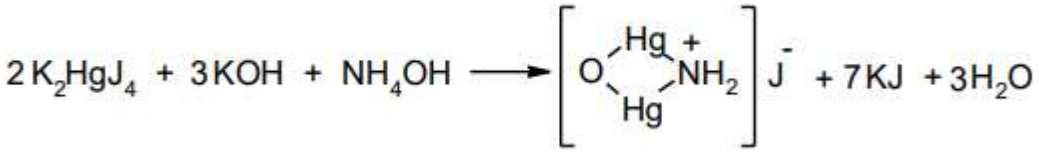


Must not appear blue colouring.

Technique: *Carefully add 1 ml of freshly prepared diphenylamine solution to 5 ml of purified water. diphenylamine solution freshly prepared; no blue staining should appear No blue staining should appear.*

8. Ammonia impurity

Purified water shall have a permitted Ammonium ion impurity content of not more than 0,00002%. For comparison, it is necessary to use a reference solution containing 0.00002% ammonia. Reaction with Nessler's reagent (K2HgJ4 solution in KOH) is carried out in parallel in the test water and in the reference solution:



The colouring (brown or yellow) in the test water must not be more intense than in the reference solution.

Technique: *20 ml of the test purified water is placed in a test tube and 1 ml of Nessler's reagent is added. A reference solution is prepared in parallel by adding 1 mL of Nessler's reagent to 4 mL of standard ammonium solution and 16 mL of ammonia-free water. After 5 minutes the solutions are compared. The colour intensity of the test solution must not exceed the colour intensity of the reference solution.*

9. Heavy metal impurities

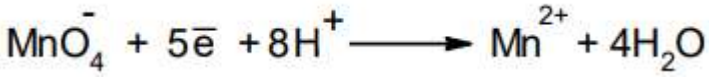
Determination of impurities of heavy metals in medicinal products is based on the formation of coloured sulphides. For example, the iron (II) salts give a black precipitate with the sulphide ion:

Technique: *In a test tube 10 ml of purified test water, add 1 ml of acetic acid diluted 30%, 2 A drop of 2% sodium sulphide solution is added and the mixture is stirred. After 1 minute observe the colour change of the solution. There should be no colouration.*

10. Reducing substance

The reducing (organic) impurities in the water create conditions for the development of various moulds, fungi, bacteria, saprophytes etc.

The reducing agents are determined by adding a solution of potassium permanganate and sulphuric acid.



The pink colouring of the solution must be retained.

Technique: *To 100 ml test water, add 1 ml 0.02 M potassium permanganate solution acidified with diluted sulphuric acid (2 ml 16%), bring the water to the boil and boil for 10 min. The pink colouring of the water should be retained.*

11. Microbiological purity

Purified water must also be monitored for microbiological purity. Total number of aerobic micro-organisms (bacteria and fungi) max. 100 CFU in 1 ml. The presence of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* in 100 ml is not allowed. The determination is carried out by membrane filtration under aseptic conditions.

TESTING OF WATER FOR INJECTIONS

Water for injection must pass the "water purified" test and be apyrogenic, free of antimicrobial substances and other additives.

Pyrogenicity is the ability of chemical agents or of any other substance to cause the organism into which it has entered, a response in the form of fever.

Pyrogenic substances are determined biologically. Water is considered apyrogenic if, when injected into the ear vein of three rabbits, their temperature does not rise by more than 0.6° by compared to the initial temperature (before the experiment).

LAL reagent is also used to determine the pyrogenicity of water for injection. The LAL test is based on the ability of Amebocyte Lysate (blood cells) of Mechebotail (Lysate of Amebocyte Limulus: LAL-reactive) to react specifically with bacterial endotoxins. The reaction between endotoxins and the LAL test gives clouding of the reaction mixture and an increase in its viscosity to the point of to the formation of a solid gel.