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REVIEW OF METHODS FOR PREPARING HIGHLY PURIFIED WATER FOR INJECTIONS. ENVIRONMENTAL ASPECTS

The development of the pharmaceutical industry is important for humanity because it ensures a better standard of living. The development of new drugs makes it possible to overcome diseases that were previously considered incurable. One of the key aspects of ensuring the proper quality of medicines is the use of water of appropriate quality. According to the State Pharmacopoeia of Ukraine, water is classified as purified water, highly purified water, and water for injection. The latter is subject to the most stringent requirements, such as the complete absence of pyrogens, organic and inorganic impurities, and sterility. It is used to prepare injection solutions and other medicines that are administered directly into the bloodstream, so inadequate water quality can cause adverse reactions in the body or even pose a threat to the patient's life.

Water for injections is a key component in the production of sterile medicinal products for parenteral, ophthalmic, and inhalation use. It can also be used to prepare solutions for cell culture growth and to flush production equipment. The highest quality requirements are imposed on it, which in Ukraine are regulated by the provisions of the State Pharmacopoeia of Ukraine, harmonized with the relevant provisions of the European Pharmacopoeia. According to these documents, water for injections must not contain any impurities that could cause a negative reaction in the body or reduce the effectiveness of the drug. One of the main requirements is the complete absence of microorganisms and pyrogens, i.e., the water must not cause infection of the body or cause an increase in body temperature, increased heart rate, nausea, and other side effects when administered.

Historically, distillation was the only legally approved method of obtaining water for injections in various countries, as it ensured the effective removal of bacteria and endotoxins from water. However, the development of membrane water treatment technologies has changed the approach to the development of WTI systems. In 2017, the European Pharmacopoeia allowed the use of reverse osmosis in combination with electrodeionization or ultrafiltration as a method equivalent to distillation. In 2024, the Ministry of Health of Ukraine took into account the changes in the European Pharmacopoeia, and the use of membrane methods became possible at pharmaceutical enterprises in Ukraine.

Key words: *distillation process, multi-stage distillation, steam compression distillation, higher-temperature steam, evaporation column.*

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ОГЛЯД МЕТОДІВ ПІДГОТОВКИ ГЛИБОКОООЧИЩЕНОЇ ВОДИ ДЛЯ ІН'ЄКЦІЙ. ЕКОЛОГІЧНІ АСПЕКТИ

Розвиток фармацевтичної промисловості є важливим для людства, оскільки забезпечує кращий рівень життя. Розробка нових препаратів робить можливим подолання хвороб, що раніше вважались невиліковними. Одним із ключових аспектів забезпечення належної якості лікарських засобів є використання води відповідної якості. Згідно з Державною Фармакопеєю України, вода класифікується на воду очищену, воду високоочищену та воду для ін'єкцій. До останньої висуваються найсуворіші вимоги, такі як повна відсутність пірогенів, домішок органічного та неорганічного походження та стерильність. Вона використовується для приготування ін'єкційних розчинів та інших лікарських засобів, що вводяться безпосередньо у кров, тому невідповідна якість води може викликати побічні реакції організму або навіть становити загрозу життя пацієнта.

Вода для ін'єкцій є ключовим компонентом при виробництві стерильних лікарських засобів для парентерального, офтальмологічного та інгаляційного застосування. Також вона може використовуватись для приготування розчину для росту клітинних культур та промивання виробничого обладнання. До її якості висуваються найвищі вимоги, що в Україні регламентуються положеннями Державної Фармакопеї України, гармонізованими з відповідними настановами Європейської фармакопеї. Згідно з цими документами, вода для ін'єкцій не повинна

містити жодних домішок, які можуть викликати негативну реакцію організму або знизити ефективність лікарського засобу. Однією з основних вимог є повна відсутність мікроорганізмів та пірогенів, тобто вода не має призводити до зараження організму та не викликами підвищення температури тіла, почастішання пульсу, нудоту та інші побічні реакції при введені.

Історично дистиляція була єдиним законодавчо затвердженим методом отримання води для ін'єкцій у різних країнах, оскільки вона забезпечувала ефективне видалення бактерій та ендотоксинів з води. Однак, розвиток мембранних технологій водопідготовки дозволив змінити підхід до розробки систем підготовки ВДІ. Так, у 2017 році Європейська фармакопея дозволила використання зворотного осмосу у комбінації з електродеіонізацією або ультрафільтрацією, як метод, що еквівалентний дистиляції. У 2024 році Міністерство охорони здоров'я України врахувала зміни Європейської фармакопеї і використання мембранних методів стало можливим на фармацевтичних підприємствах України.

Ключові слова: *дистиляція, багатоступенева дистиляція, дистиляція з компресією пари, високотемпературна пара, випарна колона.*

Statement of the problem

Water for injections is a key component in the production of sterile medicinal products for parenteral, ophthalmic, and inhalation use. It can also be used to prepare solutions for cell culture growth and to flush production equipment. The highest quality requirements are imposed on it, which in Ukraine are regulated by the provisions of the State Pharmacopoeia of Ukraine, harmonized with the relevant provisions of the European Pharmacopoeia. According to these documents, water for injections must not contain any impurities that could cause a negative reaction in the body or reduce the effectiveness of the drug. One of the main requirements is the complete absence of microorganisms and pyrogens, i.e., the water must not cause infection of the body or cause an increase in body temperature, increased heart rate, nausea, and other side effects when administered [1–3].

Historically, distillation was the only legally approved method of obtaining water for injections in various countries, as it ensured the effective removal of bacteria and endotoxins from water. However, the development of membrane water treatment technologies has changed the approach to the development of WTI preparation systems. In 2017, the European Pharmacopoeia allowed the use of reverse osmosis in combination with electrodeionization or ultrafiltration as a method equivalent to distillation. In 2024, the Ministry of Health of Ukraine took into account the changes in the European Pharmacopoeia, and the use of membrane methods became possible at pharmaceutical enterprises in Ukraine [4].

Analysis of recent research and publications

The distillation process involves the transition of water from a liquid phase to a vapor phase, followed by condensation. This removes all non-volatile impurities, and the high operating temperatures ensure the microbiological purity of the finished distillate. Distillation apparatus of various designs can be used in the pharmaceutical industry. The multi-stage distillation method has become the most popular in European countries, while steam compression distillation has become the common method in US pharmaceutical companies [5,6].

The multi-stage distillation method involves the use of several columns connected in series, the main function of which is the repeated use of thermal energy. A distinctive feature of this design is that water evaporation using superheated technical steam occurs only in the first column [7].

When using the steam compression distillation method, the condensation of the formed steam occurs at higher temperatures than atmospheric pressure, since the steam pressure increases [8].

Purpose of the study

The purpose of this article is to critically analyze existing modern technologies for the preparation of deeply purified water for use in pharmaceutical production, namely for injections.

Presentation of the main research material

The multi-stage distillation method involves the use of several columns connected in series, the main function of which is the repeated use of thermal energy. A distinctive feature of this design is that water evaporation using superheated technical steam occurs only in the first column. First, water is sprayed by nozzles onto the surface of the heater and evaporates. The resulting pure steam passes through a pipeline to the second column, where heat exchange occurs between it and the water sprayed onto the outer surface of the pipes. The steam from the first stage is cooled, forming a distillate that is removed from the evaporator, and the water supplied to the second column turns into steam and passes through a pipeline to the next column. This process takes place in each column of the apparatus, the number of which varies depending on the production needs for distillate [9–11].

In this system, a condenser is installed at the outlet of the last column to cool the steam. For greater energy efficiency of this method, the outlet water can be used as a source of cold water, which, passing through the heat exchanger pipe, is additionally heated by the heat of the steam from the last section, cooling it. An example of a multi-stage distiller with three columns is shown in Fig. 1 [12].

To ensure that the distillate meets the requirements of the State Pharmacopoeia of Ukraine and to prevent salt deposits on the internal surfaces of the equipment, the feed water must undergo preliminary treatment: degassing, purification from organic contaminants, mechanical impurities, and partial removal of salts [13].

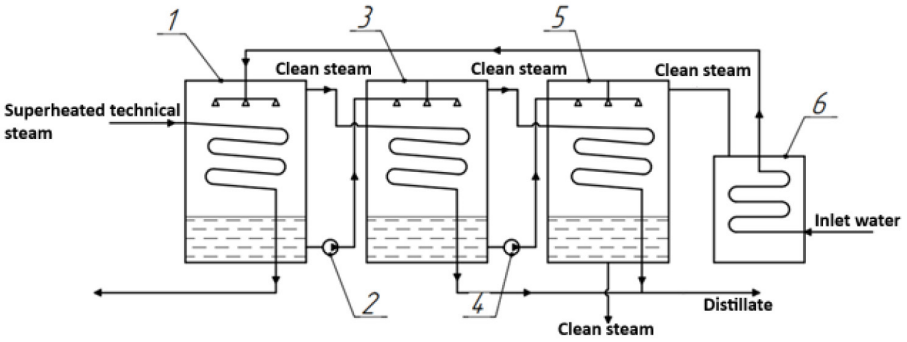

Fig. 1. Scheme of a multi-stage distiller

1,3,5 – evaporation columns; 2,4 – pumps; 6 – condenser

The main advantages of multi-stage distillation are the reliability of the process and the stability of the distillate quality. High operating temperatures ensure water disinfection, and the evaporation process effectively removes microorganisms, pyrogens, dissolved salts, and other non-volatile contaminants, ensuring that the water composition complies with VDI standards [14,15].

The reuse of thermal energy generated in the first evaporation column to heat water at other stages makes this process energy efficient. Such a system significantly reduces energy consumption, but its consumption remains quite high, which can lead to significant financial costs for the enterprise [16].

The use of complex equipment entails high costs for the enterprise to install this distillation system, and its large dimensions can be a problem for installation in enterprises with limited working space. In addition, a multi-stage distiller requires constant maintenance to clean the internal surfaces from scale, which can impair heat transfer in the columns [17].

When using the steam compression distillation method, the condensation of the formed steam occurs at higher temperatures than atmospheric pressure, since the steam pressure increases. First, water is fed to the evaporator and heated to 100 °C, after which a pump reduces the pressure in the evaporator, accompanied by the evaporation of water at lower temperatures. The steam formed is fed to the compressor, where it is compressed, resulting in an increase in the pressure and temperature of the gas phase. The resulting higher-temperature steam meets the heat exchanger, because of which the released heat is fed to the evaporator to heat the next portion of water, and the water vapor condenses and the resulting distillate is removed from the system. An example of a steam compression distiller is shown on Fig. 2 [18–20].

The main advantages of steam compression distillers are high energy efficiency, which is due to the use of steam heat to heat the feed water. Also, reducing the pressure in the evaporation column lowers the boiling point of water, which minimizes the risk of corrosion and scale formation. Another advantage is the compactness of the installation, which allows it to be installed in limited production space [21].

The disadvantages of this method are the high initial costs of purchasing and installing the equipment. The complexity of the design also increases the maintenance costs of the distillation unit. Despite the energy efficiency of the steam conversion distiller, energy costs can be significant, especially for large systems [22].

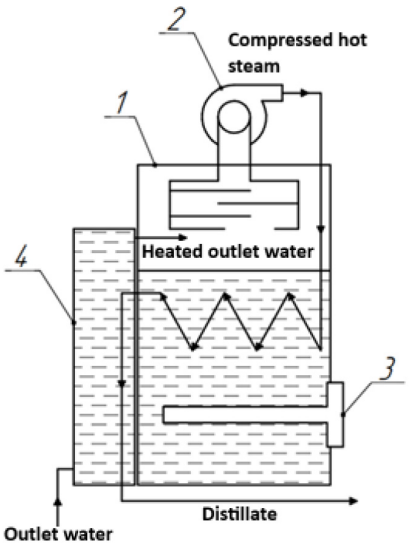

Fig. 2. Scheme of a steam compression distiller

1 – evaporation column; 2 – compressor; 3 – heater; 4 – heat exchanger

Conclusions

The distillation process involves the transition of water from a liquid phase to a vapor phase, followed by condensation. This removes all non-volatile impurities, and the high operating temperatures ensure the microbiological purity of the finished distillate.

The multi-stage distillation method involves the use of several columns connected in series, the main function of which is the repeated use of thermal energy. A distinctive feature of this design is that water evaporation using superheated technical steam occurs only in the first column.

The main advantages of steam compression distillers are high energy efficiency, which is due to the use of steam heat to heat the feed water. Also, reducing the pressure in the evaporation column lowers the boiling point of water, which minimizes the risk of corrosion and scale formation. Another advantage is the compactness of the installation, which allows it to be installed in limited production space.

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