

# STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

## METHODS OF WATER PREPARATION AND CONDITIONING FOR PHARMACEUTICAL PURPOSES

A. E. Prikhod'ko<sup>1</sup> and S. A. Valevko<sup>1</sup>

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The quality of water used for pharmaceutical purposes is a key element ensuring the safety of manufactured preparations. All pharmaceutical plants and drugstores employ water of various quality grades. This liquid can be used as a raw material, auxiliary component, and/or energy-carrying medium in various stages of manufacturing technology [1 – 7].

Depending on the quality of initial water determined by the chemical composition and possible impurities (mechanical and colloidal particles, microorganisms, bacterial endotoxins, etc.), the technology of water conditioning for pharmaceutical purposes include important preliminary stages of purification such as filtration, ion exchange, reverse osmosis, etc. [8 – 11]. There are several grades of water differing with respect to purity characteristics. In Russia, the domestic normative documentation determining the quality of water for pharmaceutical purposes includes the pharmacopoeial articles "Purified Water," "Water for Injections," "Water for Injections in Ampules," and "Water for Injections in Bottles" [12 – 17].

In most countries, the main standards determining the quality of water for pharmaceutical purposes include, besides the national pharmacopoeias, restrictions formulated in the European Pharmacopoeia and in the United States Pharmacopoeia [2, 7, 18 – 21]. The most exhaustive classification of water for pharmaceutical purposes is provided by the 4th Edition of European Pharmacopoeia (Supplement 4.2, 2002) [22] and by the XXVth Edition (2002) of the US Pharmacopoeia [23].

The former document has introduced, in addition to the articles on "Purified Water," "Purified Bottled Water," "Water for Injections," and "Sterile Water for Injections" contained in the previous edition, a new article determining "Highly Purified Water" (HPW) [22]. The new grade was introduced after an international symposium in Strasbourg

(1999), which was devoted to the possibility of using reverse osmosis in preparing water for injections. The European Community has decided that reverse osmosis, albeit offering an effective method of water purification, is still not suited for the conditioning of "Water for Injections." According to the European Pharmacopoeia [22], the only means of obtaining "Water for Injections" is distillation.

Water of the HPW grade can be used for the preparation of all drugs requiring water of high biological quality, except for injection solutions. In the opinion of European specialists, the methods used for obtaining HPW are insufficiently reliable. One of these methods is double reverse osmosis in combination with, for example, ultrafiltration or ion exchange [22, 24].

Note that HPW meets the same requirements as "Water for Injections" with respect to physicochemical parameters, microbiological purity, and apyrogenicity [25]. Introduction of the new purity grade implies the possibility of using this water for the preparation of various drugs instead of "Water for Injections." At present, "Water for Injections" is frequently used in ophthalmologic preparations, compositions applied onto skin, and eye and otic drops because it is commonly believed that the quality of "Purified Water" is insufficient for such preparations. Thus, it is economically more efficient to use HPW possessing sufficiently high biological purity [22, 24].

The latest US Pharmacopoeia [23] retained the articles on "Water for Pharmaceutical Use," "Purified Water," "Water for Injections," "Sterile Purified Water," "Sterile Water for Injections," and "Sterile Water for Irrigation and Inhalation" from the preceding edition.

Selection of the methods and technological schemes of obtaining water for pharmaceutical purposes is determined by requirements and restrictions formulated in the pharmaco-

<sup>1</sup> Sechenov State Medical Academy, Moscow, Russia.

poetical articles and by the quality of the initial water [9 – 11, 26, 27].

Since water for pharmaceutical purposes is usually prepared from drinking water, which is obtained by conditioning natural water, an important task is to remove undesired impurities from the initial liquid [28, 29].

The primary preparation treatments most typically include the following [6, 9, 30 – 33]:

(i) rough filtration through sand or carbon filters, aimed at preventing colloidal blocking of subsequent filters;

(ii) chlorination preventing the growth and facilitating the removal of microorganisms;

(iii) acidification, adding antiscaling agents (sodium hexamethosphosphate), and softening to prevent scale deposition.

The resulting product must satisfy all requirements on the quality of drinking water stipulated by the Sanitary Norms and Rules (SNP 2.1.4.559–96 “Drinking Water. Hygienic Requirements to the Quality of Water in Central Water Supply Systems. Quality Control”) [33, 34]. This drinking water serves as the initial medium for obtaining purified water and water for injections. Before finally conditioning water so as to obtain water for pharmaceutical purposes, the initial liquid containing a large amount of undesired impurities is always subjected to the aforementioned preliminary treatments.

**Filtration.** Filtration technologies are of major importance in modern water conditioning systems. There is a large number of commercially available filtration devices for various purposes. The efficacy of separating foreign species significantly varies, beginning from rough filters (based on granulated anthracite [31], quartz or sand for large-scale systems, or bulk cartridges for small-scale setups) to membrane filters. The filter system design and configuration may also differ significantly, depending on the filtering medium and the technological process stage. Granulated filters or cartridges are used in systems of preliminary (rough) purification. These filters remove solid inclusions, thus protecting equipment of the subsequent stages from being blocked by these rough impurities (which leads to malfunction and decrease in the working life of equipment) [32, 35, 36]. There are features of the filter design that can influence the system functioning by leading to (i) conducting channels in the filtration medium, (ii) filter blocking by mud, (iii) bacterial growth, (iv) loss of filtration medium, etc. Therefore, it is necessary to provide for continuous monitoring of the flow pressure and rate in front of and behind the filters, backstream washing, sanitary treatment, and timely replacement of filters [23, 28, 37, 38]. It is very important to correctly determine the filter size so as to avoid channel formation and/or loss of filtration medium as a result of improper flow velocity [6, 9, 19].

Filters made of an activated charcoal are capable of absorbing organic materials possessing low molecular weight, oxidizing additives, and chlorine, so that these impurities can be effectively removed from water [19]. These filters ensure

obtaining certain qualitative characteristics (discoloration, taste improvement, etc.) and offer protection to equipment of the subsequent stages involving stainless steel surfaces, rubber parts, and membranes against the above aggressive components [35, 39]. However, it should be noted that, after the removal of active chlorine species, water is deprived of any bactericidal agent, and microorganisms exhibit accelerated growth. Charcoal filters provide for especially favorable conditions for the growth of microflora due to large and developed surface. The main difficulties in maintenance of the charcoal filters are related precisely to this contamination with microorganisms [40]. Other disadvantages are the ability to release bacteria, endotoxins, and fine carbon particles into the filtrate and to form hydraulic channels. In connection with this, it is very important to provide for a sufficiently high rate of water flow through such carbon filters. The major means of prophylaxis include periodic sanitary treatment with hot water and/or steam, backstream washing, absorption ability monitoring, and timely replacement. An alternative to activated charcoal filters is offered by some synthetic chemical reagents [6, 9, 23, 28, 39, 41].

**Chemical reagents.** Special chemical reagents are employed in water purification systems for reducing the level of microorganisms, pH control, more effective collection of suspended species, etc. However, additional treatment and neutralization stages are necessary in order to remove residual chemical reagents. The system design should provide a means of monitoring the content of chemical reagents in water and guarantee complete removal of these reagents as well as related reaction products from water [23, 28, 37 – 39, 41].

**Absorbing-collecting filters.** The main role of these filters consists in trapping organic components and mechanical particles which can be released from activated charcoal, ion-exchange resins, and various devices employed in the preliminary purification stage. In order to provide for the normal functioning of these filters, it is necessary to maintain continuous water recirculation through the system, to perform the necessary sanitary monitoring and cleaning, and to timely replace the working units [23, 27, 28].

**Ion exchange.** This process provides for effective removal of foreign anions and cations from water [36] and is one of the most important stages in water conditioning for pharmaceutical purposes [6, 9, 10, 29, 32, 42]. The ion exchange is conducted on special resins based on polymers crosslinked to various degrees, possessing a gel or microporous structure and containing covalently bound ionogenic groups. Dissociation of this system in water or in an aqueous solution yields an ion pair in the form of a polymer-bound ion and a mobile counterion. The latter ion can be involved in exchange with ions of the same sign (cations or anions) present in solution [42 – 44].

Ion exchange proceeds by migration of ions in the electrolyte solution toward the sorbent surface, diffusion of these ions inside the sorbent, displacement of the aforementioned mobile ions from the cation (or anion) complex of the

sorbent, and outdiffusion of the displaced mobile ions from the sorbent phase to the solution [6, 9].

As a rule, ion-exchange resins appear as spherical particles 0.5 – 1.2 mm in diameter, typically of dark-yellow color. The resins, especially of the anion-exchange type, possess a characteristic amine-like odor [29, 42].

By including various functional groups into the composition of resins, it is possible to obtain selective ion-exchange resins. In the chemical desalination process, reversible ion exchange takes place between solid and liquid phases. During this, no significant changes are observed in the resin structure, where one ion in the pair is always bound to the polymer network (and, hence, is insoluble and immobile in the solid phase) and the oppositely charged ion is mobile.

Ion-exchange resins are divided into anion- and cation-exchange types, in which the mobile particles are  $\text{OH}^-$  and  $\text{H}^+$  ions, respectively. Cation- and anion-exchange resins contain functional groups which can be replaced by other positive and negative ions, respectively [9].

Each type can be additionally subdivided into two: cation-exchange resins can be strongly or weakly acidic, while anion-exchange resins can be strongly or weakly basic [29, 42].

There are two main types of ion-exchange apparatus, which usually exhibit a column design: (i) with separate cation- and anion-exchange beds and (ii) with mixed bed. Apparatuses of the first type represent two serially connected columns, the first of which (in the process pathway direction) is filled with a cation-exchange resin and the second, with an anion-exchange one. Systems of the latter type appear as a single column filled with a mixture of resins of the two types. Water is passed through the column in ascending flow [28, 29, 42].

Separate (two-step) systems can be designed so as to make possible daily regeneration procedures. Mixed systems, which are subjected to a rather insignificant "salt load," are characterized by a longer working life and can operate without regeneration for several weeks. However, this may increase the risk of microbiological contamination. For this reason, the ion-exchange apparatus design must provide for a constant and continuous water flow through the column [10, 29, 42].

Ion-exchange resins possess a number of disadvantages which complicate and/or restrict their use in water purification systems:

(i) most ion-exchange resins are characterized by low hydrophilicity, which accounts for the relatively low rate of ion diffusion inside granules, as well as for the low rates of sorption and desorption.

(ii) granulated ion-exchange resins used in practice exhibit consolidation, which leads to the need for periodic loosening. This, in turn, causes mechanical damage of the granules and results in their accelerated degradation in the course of system operation.

(iii) ion-exchange resins require periodic regeneration to maintain the exchange capacity at a satisfactory level [10, 28, 29, 31, 32, 37, 38, 42, 43].

Ion-exchange resins are regenerated by treatment in hydrochloric acid solutions (for  $\text{H}^+$  form) or sodium hydroxide solutions (for  $\text{OH}^-$  form). This process is effected by a counterflow scheme (descending flow). The quality of regeneration depends on a number of factors, including (i) the selected treatment medium type, purity, and concentration, (ii) ion-exchange resin type, (iii) saturated resin layer composition, (iv) the solution flow rate and temperature, and the treatment duration (the time during which the treated resin contacts with a regenerating solution) [3, 9, 23, 28, 29, 31]. The regenerating solutions of hydrochloric acid and sodium hydroxide are prepared and stored in special vessels, with all the necessary measures taken for avoiding leaks and providing safety of personnel.

The regeneration process yields large amounts of strongly acidic and/or alkaline wash water, which has to be neutralized before discharge to the sewage system [28].

Additional difficulties in the operation of ion-exchange apparatuses can be related to air pollution (during the regeneration of mixed-bed systems), the formation of channels, the action of chemical additives, the silting of resin, etc. [29, 42]. The ion-exchange systems require preliminary flow purification (filtration) from solid (insoluble) particles, which can otherwise contaminate the resin and decrease its quality and the operation performance [28].

Ion-exchange systems provide for the classical desalination of water and offer an economic method of obtaining water for pharmaceutical purposes. For some other technological purposes, this method ensures obtaining water characterized by very low electric conductivity.

Prolonged use of ion-exchange resin may result in spontaneous growth of microorganisms. For this reason, timely regeneration and disinfection of the system upon exhaustion of the exchange capacity of a resin is of major importance [40]. The degree of microbiological contamination can be reduced by using UV lamps, ensuring constant water recirculation in the distribution loop, and minimizing (or eliminating) interruptions in the system operation (the flow rate must always be the same as that during the normal operation cycle) [28, 36 – 38, 42].

Evaluation of the safety and the efficiency of operation of an ion-exchange system requires constant physicochemical and microbiological monitoring of the process, including conductivity measurements in the flow. In the course of regeneration, the resin-charged columns (processed upon disassembly of the equipment) can be a source of contamination and has to be also thoroughly monitored [23, 41].

Despite all the advantages, the ion exchange process cannot provide microbiologically clean medium and, hence, the resulting water cannot be used in parenteral preparations.

**Softening.** This treatment is a partial case of ion exchange. Softeners remove cations such as magnesium and calcium, thus reducing the hardness of water. Softening significantly decreases the content of these ions in water entering the ion exchange stage or the reverse osmosis membranes [6, 9, 19, 28].

The softening process is usually conducted in automatically controlled columns filled with a cation exchanger (sodium chloride) [41]. Here, a necessary condition is a periodic regeneration of the resin by treatment in a sodium chloride solution. Common problems include increased growth of microorganisms, the formation of channels as a result of incorrectly set flow rates, organic contamination of the resin, mechanical cracking of the resin particles, and contamination from a regeneration solution.

Necessary conditions for the proper operation of a softening system are to provide for sufficiently intense water recirculation during low-consumption periods, determine the periodicity of the resin regeneration treatment, monitor water hardness, remove resin particles from the flow by filtration, periodic disinfection of resin and regenerating solution, and use of UV radiation [23, 28].

**Electrodeionization.** This treatment is also a kind of ion exchange. Electrodeionization is conducted in systems employing a combination of factors including ion-exchange resins, selective membranes, and electric charge so as to provide for continuous flows of both product and concentrated wastes, accompanied by continuous regeneration.

Here, supplied water is distributed between three flows. One part is passed through electrode channels, while the two other enter the channels of purification and concentration. The latter two represent layers of a resin confined between anionic and cationic membranes. The layers of mixed ion-exchange resins retain dissolved ions. The electric current drives cations through the cation-permeable membrane to a cathode, and through the anion-permeable membrane, to an anode. The ion-exchange resin on both sides of each membrane enhances the transfer of cations and anions through these membranes. The cation-permeable membrane eliminates the access of anions to the anode, while the anion-permeable membrane prevents cations from reaching the cathode. As a result, ions are concentrated inside this compartment and can be washed off to discharge into the sewage system. This method yields purified water of high quality. By separating water into hydrogen and hydroxyl ions in the purification channel (resin compartment) under the action of an applied electric potential, it is possible to provide for continuous regeneration of the resin.

Using the electrodeionization process, it is also possible to remove mineral impurities from water. The efficacy of this treatment depends on the initial level of contamination, the incoming water flow rate, and the character of the preceding purification stages. The electrodeionization process is expedient after the reverse osmosis stage. In this case, the total content of dissolved substances decreases by more than 99%, the electric conductivity decreases by a factor of more than 15, and the total organic carbon content can decrease by 50–90% (depending on the composition of organic matter in water and the character of preliminary purification stages. Dissolved carbon dioxide is converted into bicarbonate ion and eliminated with dissolved substances. The content of dis-

solved silicon dioxide decreases by 80–95% (depending on the operation conditions and regime).

The advantages of the electrodeionization technology are as follows [21, 23, 45–47]:

- (i) low energy consumption;
- (ii) possibility of continuous regeneration;
- (iii) no need to replace resin (the sorption capacity is retained);
- (iv) water purification process is never suspended as a result of the resin capacity exhaustion;
- (v) low system maintenance expenditures;
- (vi) no chemical reagents are necessary for regeneration.

On the other hand, the electrodeionization technology retains virtually all disadvantages inherent in the ion exchange process. Necessary conditions for the operation of such systems are a water temperature within 10–35°C and a level of free chlorine not exceeding 0.1 mg/liter. The probability of microbiological contamination of water after the electrodeionization stage can be reduced by using UV irradiation or by filtration through submicron filters [23, 48]. Electrodeionization units have to be periodically subjected to disinfection using peracetic acid, sodium hydroxide, etc. [28].

**Electrodialysis.** This separation process employs the phenomenon of directed ion motion in combination with selective membrane action under the conditions of current passage. In this process, water weight loss does not exceed 5%, electric power consumption for the dialysis amounts to 1.1 kW per 1000 liters of water, and the level of soluble salts decreases by 40–50%. No chemical additives are required to maintain the normal operation of equipment for a long time.

However, the method of electrodialysis (employing neither resins stimulating ion removal nor the flow of water) is less effective than electrodeionization. In order to maintain the system operation at a high level, it is necessary to perform periodic washing and change in the cell polarity. This technique can be employed either in a preliminary stage prior to ion exchange (which allows the necessary frequency of regeneration to be decreased) or in the stage of water preparation to the distillation stage [23, 27–29].

**Reverse osmosis.** This method employs the process of solvent (water) transfer from a solution through a semipermeable membrane under the action of an external pressure. The excess working pressure in a salt solution is much greater than the osmotic pressure, this difference being the driving force of the reverse osmosis process. In order to purify water using the reverse osmosis method, it is necessary to (i) apply an excess pressure exceeding the osmotic pressure and (ii) force molecules to diffuse through a semipermeable membrane in the direction opposite to that of direct osmosis (i.e., from the compartment of high-mineral water to that of demineralized water) so as to increase the volume of purified medium [9, 19, 27, 28, 32, 44, 49].

The reverse osmosis process ensures the finest level of filtration: such a membrane acts as a barrier for all soluble

salts, inorganic molecules, organic molecules with molecular weights above 100 amu, as well as for microorganisms and pyrogenic agents. On the average, the total concentration of dissolved substances after the reverse osmosis stage decreases to 1 – 9%, the content of organic matter drops to 5%, while colloidal species, microorganisms, and pyrogenic agents are completely removed. In addition, water purified by this method contains a minimum amount of total organic carbon [6, 32, 35, 50].

The reverse osmosis separation process can be performed using membranes of two types:

(i) porous membranes (pore size from  $10^{-4}$  to  $10^{-3}$   $\mu\text{m}$ ), the selective permeability of which is related to the adsorption of water molecules on the surface of the membrane and in pores. Adsorbed molecules migrate from one adsorption site to another, not allowing salts to pass through the membrane;

(ii) nonporous diffusion membranes capable of forming hydrogen bonds with water molecules on the contact surface. Under the action of excess external pressure, the bonds break and the molecules diffuse toward opposite membrane sides, while the vacancies are occupied by the next candidates. Thus, water effectively dissolves on the surface and diffuses inward the membrane, while salts and almost all other chemical compounds (except for gases) cannot penetrate through such a layer.

Reverse osmosis membranes for pharmaceutical purposes can be fabricated from cellulose acetate, polyamides (aromatic and aliphatic), and composites in which the active layer is made of polyamides, polyesters, or polysulfone [28, 29, 50].

A typical reverse osmosis setup usually comprises a high-pressure pump, a permeator, and a control unit maintaining the optimum working regime. An important working characteristic of such a setup is the turnover coefficient determining the fractions of permeate and concentrate [6, 9, 28, 50].

The advantages of the reverse osmosis technology are (i) relative simplicity; (ii) the process is independent of the salt content in the initial water; (iii) relatively low energy consumption; (iv) low service and maintenance expenditures; (v) easy washing, disinfection, and cleaning; (vi) no need to use silyl reagents (requiring subsequent neutralization) [9, 35, 48, 51, 52].

A certain problem in realization of the reverse osmosis process is related to the choice and preparation of homogeneous membranes with pore dimensions within a narrow interval from  $3.5 \times 10^{-4}$  to  $5 \times 10^{-4}$   $\mu\text{m}$ . At the same time, the membranes must provide for a sufficiently high water flow rate. The membrane selection must take into account the requirements on water characteristics, working conditions and parameters, sanitary norms, safety, and water source type.

The reverse osmosis process is usually employed in systems of water conditioning for pharmaceutical purposes in the following cases [28, 47, 48]:

(i) in the stage before ion exchange, in order to reduce the consumption of acid and alkali for the resin regeneration purposes;

(ii) in the stage of "Purified Water" production and/or as a preliminary stage before distillation in the production of "Water for Injections";

(iii) in the final stage of "Water for Injections" production by a two-stage reverse osmosis technology.

The latter technology is now frequently employed for the conditioning of water for pharmaceutical purposes. According to this method, initial water enters the first stage of reverse osmosis, after which the concentrate is rejected and the permeate fed to the second stage. After repeated reverse osmosis, the concentrate (characterized by a lower salt content as compared to that in the initial water) can be returned to the system (to dilute the initial medium) [29, 35, 36, 47].

When the reverse osmosis is used for preliminary purification purposes, it is possible to use a single-stage setup. However, such a setup will not provide pharmacopoeial-quality water in cases of high salt load and/or high content of chlorides [10, 47].

The method of reverse osmosis is not free of disadvantages. Not all impurities can be completely removed by this process: in particular, the efficacy of separating dissolved organic substances with very low molecular weights is rather low. In comparison with ion-exchange systems, the method of reverse osmosis is not as effective in reducing conductivity, in particular, for water with a high content of carbon dioxide. Indeed, carbon dioxide readily passes through the membranes in reverse osmosis systems and is retained in the permeate virtually in the same amounts as in the initial water. To improve the situation, it is recommended to use anion-exchange resins prior to the reverse osmosis stage [32, 47, 48].

The material of membranes for reverse osmosis is rather brittle and can be readily damaged, which leads to failure of the entire setup. For this reason, the selection of membrane materials is a very important step in the system design for the successful use of cellulose acetate membranes, the concentration of free chlorine in the initial water must not exceed 0.5 – 1.0 mg/liter, whereas initial water in the systems employing polyamide and composite membranes must be completely free of chlorine (see Table 1) [28]. In order to use membranes not resistant to free chlorine, it is possible to introduce the stage of preliminary filtration through a carbon filter or a medium containing sodium sulfite [27, 28, 32, 37, 38].

The reverse osmosis membranes lose stability under the action of high temperatures. Therefore, heated water has to be cooled prior to purification by reverse osmosis.

As is known, ultrafiltration membranes can accumulate contaminations. For this reason, such membranes should be employed in crossed flows, whereby a flow directed along the membrane surface carries away the separated material. Thus, the system yields both filtrate (permeate) and concentrate. As a rule, such systems include a back filtration cycle in which the filtrate is passed back through the membrane in

order to separate the deposited material and allow it to be removed with the concentrate [9, 28, 48].

Some compounds, such as barium and strontium sulfates, calcium carbonate, silicic acid, etc., are capable of blocking the pores of membranes. For this reason, a reverse osmosis system has to be characterized by the colloid index prior to use. The blocking can be avoided by adding agents preventing deposit formation or by using preliminary purification stages. Another detrimental contamination factor for reverse osmosis systems is the presence of iron salts. Conditioning drinking water with a high content of iron salts must be preceded by an iron deposition stage followed by filtration [10].

The above considerations show that effective operation of reverse osmosis systems is ensured by taking into account the quality of the initial water and correctly selecting the methods of pretreatment and the whole system design [11, 39].

The membranes are subject to chemical cleaning, which is a simple procedure consisting in recirculation of an acid solution, alkaline solution with detergent, and disinfection medium (containing active chlorine, formalin, or sodium bisulfite, depending on the membrane type) [28].

Theoretically, membranes must separate microorganisms and pyrogenic agents of all kinds. However, the results obtained in practice are rather contradictory. This situation is explained by the lack of reliable methods for checking the integrity of reverse osmosis systems, detecting small holes in membranes, cracks in filaments, and defects in seals. The membranes are also subject to chemical and microbiological changes that are rather difficult to reveal by methods of static monitoring. For this reason, the possibility of using water purified by the reverse osmosis method for preparing parenteral solutions in many countries is still under discussion [25, 53].

Membranes in reverse osmosis systems have to be replaced 3 – 4 times per year or even more frequently, which is not convenient. Water obtained from reverse osmosis setups is cold (most systems use initial water at temperatures within 5 – 28°C), which increases the risk of microbiological contamination [6, 8, 37, 38].

Another important circumstance, which can also be considered as a disadvantage of the reverse osmosis technology,

is the rather high requirements on the initial water quality, since this implies the need for high-cost preliminary treatments.

Reverse osmosis systems are tested by checking for the integrity of membranes. Another important point is monitoring of the microbiological contamination and the content of total organic carbon [40, 41, 54]. It is also necessary to monitor the working pressure difference, electric conductivity, and volume of the concentrate fraction [23, 28].

**Nanofiltration.** This method of preliminary purification is used to remove organic substances with molecular weights in the 250 – 1000 amu range and some ions (mostly bivalent). This filtration process is more economical (from the standpoint of water consumption and applied pressures) as compared to reverse osmosis.

The main disadvantages of nanofiltration, as well as of the other filtration techniques, are the need for periodical replacement, silting, risk of mechanical damage, and microbiological contamination [21, 23, 27].

**Ultrafiltration.** This is another technology employing semipermeable membranes, but these devices operate (unlike reverse osmosis systems) mostly by mechanical separation. The ultrafiltration is usually employed to remove pyrogenic agents and other dissolved organic substances with molecular weights exceeding 10,000 amu [19]. The filtration capacity of such membranes is also sufficient to significantly reduce the level of macromolecular and microbiological contaminations such as bacterial endotoxins. This technology can be useful at an intermediate or final stage of the purification process. Similar to the case of reverse osmosis, effective operation of an ultrafiltration system requires certain pretreatment of the initial water.

The main difficulties in realization of the ultrafiltration process are related to ensuring compatibility of the membrane material with disinfection agents, silting with organic particles and microorganisms, mechanical damage, deposition of contaminations in the cartridge, and breakage of sealing spacers. These problems can be solved by correctly selecting membrane materials, disinfection agents, and system design (easy washing of the membrane surface) and by

**TABLE 1.** Conditions for Effective Operation of Reverse Osmosis Membranes

Membrane material	Cellulose acetate	Polyamide composite	Polysulfone composite
pH	4 – 7	2 – 11	2 – 12
Limiting content of free chlorine, mg/liter	1.0	0.05*	5.0
Protection against microorganisms	Poor	Good	Good
Working temperature range, °C	15 – 28	5 – 50	15 – 50
Degree of purification, %	90 – 98	97 – 99	95 – 98
Maximum disinfection temperature, °C	30	50 – 80	70
Maximum possible initial content of dissolve impurities, mg/liter	30 – 1000	30 – 1000	30 – 1000
Colloid index	5	5	5

\* Best operation requires the absence of free chlorine.

timely replacement of cartridges. It is necessary to eliminate stagnant water sites (bacterial growth in reserve and standby compartments), especially in systems of parallel and serial configurations.

Effective operation of an ultrafiltration setup requires constant monitoring of the initial water temperature, total organic carbon, working pressure difference, filter integrity, and microbiological contamination levels [21, 27, 28, 50, 55].

**Microfiltration.** Using this kind of filters, it is possible to purify water from small particles and microorganisms. At present, most frequently used are filters of the following types: deep-bed filters (ceramic, porcelain, fluoroplastic) with a pore size of 3 – 4  $\mu\text{m}$ , glass filters with a pore size of about 2  $\mu\text{m}$ , and paper – asbestos filters with pore dimensions below 0.3  $\mu\text{m}$ .

Filters with a pore diameter of 2 – 3  $\mu\text{m}$  are usually employed for preparing water for passing through reverse osmosis and ultrafiltration membranes, while filters with 0.22  $\mu\text{m}$  pores are used in the final stage of conditioning water for injections and in water delivery systems (in order to prevent high-purity water from mechanical and microbiological contaminations). Such filters are also employed in the final stage of manufacturing parenteral drug preparations not subject to thermal sterilization [19, 27, 28].

**Distillation.** This is a traditional, effective, and reliable method ensuring a high degree of purification and offering the possibility of obtaining hot water and steam treatment [6, 9, 19, 32, 49], which is very important for drug preparation according to GMP rules [56].

The general principle of water purification by distillation is as follows. Drinking water having passed a preliminary conditioning stage enters a distiller comprising three main units: evaporator, condenser, and collector. The evaporator with water is heated to boiling. Water vapor enters the condenser and condenses into distillate which is discharged into the collector. All nonvolatile impurities present in the initial water are retained in the distiller [9, 43, 44, 49].

Water for pharmaceutical purposes can be obtained using distillers with different means of heating, productivity, and design features [57]. The method of single distillation is unprofitable, since 1 liter of distillate is obtained from 11 liters of initial water. More effective and economic systems are based on multicolumn distillation schemes [9, 28, 49].

Multicolumn schemes are less expensive, both from the standpoint of explicit cost and with respect to the ratio of the initial water and condensate volumes. The main principle of multicolumn distiller design is that the temperature difference required for the heat transfer (equivalent to a pressure difference) is provided by heating the first column using high-temperature vapor. The vapor formed in the first column condenses into distillate, which heats the second column operating at a lower temperature and pressure. The vapor formed in the second column, in turn, heats the third column operating at atmospheric pressure. The number of sequential columns can vary, but only vapor in the last col-

umn is condensed to distillate by the usual heat exchanger with cold-water jacket. Thus, the energy is spent only for heating the first column, and cold water is supplied only for cooling vapor in the last column. By increasing the number of columns, it is possible to reduce the specific consumption of both vapor and water, since the amount of evaporated water and condensed vapor decreases in each next column. According to estimates for foreign distillers, the most effective from the standpoint of energy consumption are four- and five-column distillation plants [28, 49].

Another economically efficient method of distillation is that based on thermal compression. Operation of a compressor distiller setup is based on the principle of natural gas laws, whereby the gas temperature increases upon an increase in the gas pressure (i.e., with a decrease in volume). When water in the boiling tank and the apparatus are heated to 100°C by energy supplied from outside, water begins to boil at atmospheric pressure. At this instant, a pump is switched on and the pressure in the tank decreases. Thus, the boiling point of water at the input decreases. At the same time, as the vapor density at the output grows, the temperature and pressure in this region tend to increase. The resulting vapor at elevated pressure and temperature is passed through a spiral to heat the boiling tank. This vapor cools and the distillate is discharged. This apparatus does not contain the usual heat exchanger and requires no cooling water. If the distillate is used cool, the heat evolved in the distiller is almost completely transferred to a feeding heat exchanger. With the thermal compressor switched on and the distiller operating in a stabilized regime, the system does not consume additional energy [9].

The disadvantages of this scheme are the possibility of foreign particles appearing in the distillate, a relatively high hose level, and the need for constant technical maintenance. For these reasons, the method of thermal compression is virtually not employed for obtaining water for pharmaceutical purposes.

According to the opinion of many specialists in Russia and abroad, distillation should be used in the final stage of conditioning water for injections because this method is more reliable in providing for the required quality of water [6, 43, 57].

The advantages of the distillation method are a high degree of purification and the possibility of obtaining hot water and providing vapor treatment [9, 37, 38].

The disadvantages of the distillation process are its comparatively high cost and relative large energy consumption. The possibility of scale formation on the distiller surfaces and the inability to remove gaseous substances (e.g., ammonia) require appropriate preliminary conditioning treatments [5, 9, 43].

Effective operation of a distillation plant requires monitoring of the physicochemical parameters (conductivity, etc.), microbiological contamination level, and apyrogenic state [41, 54, 58]. Another important factor is timely disinfection of the equipment [23, 28].

One of the most important problems encountered in the preparation of water for pharmaceutical properties, both Russia and abroad, is the need to ensure microbiological purity of "Purified Water" and "Water for Injections." This topic is usually the main subject for discussions in most international meetings and conferences.

In various stage of water conditioning, as well as in the systems of storage and delivery, the required microbiological purity of water for pharmaceutical purposes is usually achieved through UV irradiation and ozonation.

**UV irradiation.** The radiation sources are provided by low-pressure mercury lamps made of uviol or a quartz glass transmitting in the shortwave UV range. As is known, the photochemical oxidation of water under the action of UV radiation with a wavelength of 185 or 245 nm eliminates traces of organic compounds and kills microorganisms [19, 59]. Quartz glass can transmit 95% and uviol glass, about 75% of the incident UV radiation (in contrast to Teflon, which absorbs up to 30 – 40% of the incident UV radiation). The latter wavelength (254 nm) is used to prevent bacterial growth in drinking water reservoirs.

The UV radiation striking bacteria, viruses, mold, yeast fungi, and algae passes through the external membrane and produces photochemical damage of the enzyme system, acts upon protoplasm with the formation of toxic peroxides, and leads to photodimerization of thiamines. Efficacy of the UV treatment depends on a number of factors, including the irradiation dose, the type of microorganisms, etc. Vegetative cells are more sensitive to UV radiation than the spore cells, the latter requiring on the average a tenfold greater irradiation dose for a comparable cell loss.

The UV treatment of water is produced using apparatuses with immersed or nonimmersed radiation sources. In the former case, a lamp placed inside a tube is streamlined by water. In the latter case, a lamp is situated above the surface of water. The system may involve obstacles in the form of plates, which render the flow turbulent to increase the irradiation effect. When water flows around guiding quartz plates, microorganisms are exposed to radiation for a longer period of time.

The best effect of UV irradiation is achieved when the water flow is permanently irradiated. Periodic switching on and off is detrimental to the efficacy of treatment and reduces the working life of the lamps. A constant water flow can be provided by using a recirculation loop [43].

Control of the effective operation of a UV lamp includes measurement of the radiation intensity, monitoring of the working temperature (overheating causes premature failures), and evaluation of the microbiological contamination level.

UV lamps have to be replaced upon losing 40% of the initial irradiation effect. It should be noted that such lamps do not merely fail as common incandescent lamps do. After a 8000-h operation of a lamp, the quartz glass becomes opaque and loses transparency for UV radiation, which makes the UV treatment insufficiently effective. The lamps have to be

periodically cleaned at an interval depending on the quality of water processed [28, 41]. Additional problem with UV lamps is presented by the storage and utilization of used devices, which requires a special service [23, 28].

**Ozonation.** Ozone is known to be a strong oxidizer. Ozonation can be used for providing microbiological purity of water, especially in delivery systems. Since ozone is characterized by a short half-decay time in water, this agent has to be continuously introduced into the system.

The main requirement to systems employing ozone for water conditioning purposes is that this agent should be completely removed from the final product, which is provided by UV irradiation converting ozone into oxygen. An advantage of using ozone for the treatment of water is, besides the high oxidizing activity, the fact that this treatment cannot contaminate water with foreign ions [27, 28, 36, 45].

In the conditioning of water for pharmaceutical purposes, the quality of the initial water can be improved using electrochemical techniques (reducing the content of ions), filtration through a positively charged medium (decreasing the level of bacterial endotoxins), and other methods [23, 52, 60, 61].

**Conclusion.** Thus, the preparation and conditioning of water for pharmaceutical purposes is a complicated multi-stage process, which has to be conducted taking into account a number of factors:

(1) The quality of initial (drinking) water and the presence of specific impurities (hard salts, colloidal iron, free chlorine, etc.)

(2) Purposeful, justified selection of the scheme of water treatment, ensuring that the obtained water for pharmaceutical purposes would possess stable characteristics meeting all requirements of the normative documentation, with an allowance for the seasonal variations of the quality of drinking water.

(3) Since the general quality characteristics of "Purified Water" and "Water for Injections" are the same (except for the requirement of apyrogenicity and the absence of bacterial endotoxins in the latter case), the schemes of water treatment for these purposes possess many common features (except for the last stage).

(4) A distinctive feature of the systems of conditioning water for pharmaceutical purposes is that the final treatment in the preparation of "Water for Injections" can be provided only by distillation (multicolumn schemes are preferred) or reverse osmosis (two-stage) with more rigid control and continuous monitoring of the microbiological characteristics.

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