Polymer Membranes in Medicine and Pharmaceutics

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Abstract

This review covers the main problems and basic principles of the use of various membranes in medicine and pharmacy. Developments in the field of sterilizing, bacteriostatic and bactericidal membranes and membranes for pyrogen-free water preparing are considered. An analysis of the scientific literature in this research area are identified. The main ways of development of this area, as well as an analysis of properties of membranes from different manufacturers for use in the medical and pharmaceutical industries are given. Their advantages and disadvantages are considered. It is shown that the main criterion for sterilizing membranes is the pore size, which should be no less than 0.1 microns. The most commonly used materials for sterilizing membranes are PTFE, polyamide and polysulfone.

Review of methods for bacteriostatic and bactericidal membranes showed that there are different prospective modification methods of widely used membranes. Examples of some membranes modifications with inorganic and organic substances are considered. It is shown that the most effective modifying agents are chitosan and silver compounds. The mechanism of action of the ions and silver nanoparticles on bacterial cells is shown. A comparison of the effectiveness of distillation and membrane filtration processes for the preparation of water for injection is given. The ultra- and nanofiltration membranes used for pyrogen-free water preparing are described. New data about the properties of charged membranes are given. It is shown that the use of positively charged membranes for pyrogen-free water preparing is perspective, because it works by sieve and adsorption mechanism.

Introduction

Polymer membranes are used in various fields of industry and human services. There are areas where membrane technologies do not have any competitors whatsoever, such as low-temperature sterilization of solutions, which removes not only bacteria, but also viruses, while preserving the valuable properties of thermally unstable substances. This is especially important in the production of biologically active substances, medicines, and ferments, and in the sterilization of blood and blood-based products.

The issues of biological safety have been and will remain important for all products that serve, to some extent, as nutrient media for microorganisms. Whereas the focus was on bacterial safety before the 1980 s, more attention is given now to viruses and prions. Nevertheless, new evidence that is now also available regarding bacteria calls for reconsideration of accepted views and standards [1].

Pharmaceutical enterprises and medical institutions are among the main consumers of high-quality water. Purified water, highly purified water, distilled water, and water for injections and hemodialysis are just some types of water produced by special multi-stage processes used in pharmaceutical and medical institutions.

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It should be pointed out that the use of polymer membranes in pharmaceutics and medicine is peculiar in several ways. The first peculiarity is that the filtrate being produced should be epidemically safe; all types of water used in medicine and pharmaceutical production should comply with requirements in terms of microbiological indicators. The second peculiarity is that water for injections, highly purified water, and water for hemodialysis should not cause pyrogenic reactions; it should comply with endotoxin content requirements.

Generally speaking, membranes for medical and pharmaceutical applications can be classified into three main types in terms of product purification and use requirements: sterilizing, bactericidal (bacteriostatic), and depyrogenating membranes.

Sterilizing Membranes

Sterilization (from the Latin *sterilis*, meaning "fruitless") means the removal of germs and disposal of all living matter.

Sterilizing membrane filtration of liquids and gases is successfully used in a broad range of various process applications, and it is considered the only available method of sterilization for many solutions of thermolabile substances.

The following types of filtration can be cited as examples of membrane sterilization:

- filtration of culture media for fermenters and bioreactors;
- filtration of auxiliary components of media for fermenters and bioreactors;
- filtration of sera for cell culture media;
- filtration of process water;
- filtration of chromatographic buffers;
- filtration of buffers for dialytic filtration;
- filtration of solvents;
- filtration of disinfectants;
- filtration of products intended for intermediate storage;
- filtration of non-sterile active pharmaceutical ingredients;
- filtration of sterile nutrient media for validation of aseptic metering;
- filtration of thermally sterilizable preparations for injections;
- filtration of aseptically metered sterile preparations for injections;
- filtration of aseptically metered sterile preparations for external use and medicines for applications in ophthalmology.

In the 1960 s, sterilization of liquids was carried out using 0.45-μm membranes. The membranes were qualified using the test culture Serratia marcescens, 0.6-1.0 μm in size. After Bowman discovered that Brevundimonas (Pseudomonas) diminuta penetrates through 0.45-μm membranes, a new standard was introduced for sterilizing membranes – 0.2/0.22 μm, and Brevundimonas diminuta at the minimum qualifying level of 10^7 colony-forming units (cfu)/cm^2 was adopted as a test culture for checking the sterilizing capacity of membranes, in accordance with recommendations of the main documents regulating the production of medicines in the USA: Food and Drug Administration and US Pharmacopeia [1].

Later, a bacterium was discovered at a microbiological laboratory of Pall Corporation (USA) that called for a change in the criteria used to assess sterilizing membranes, because the bacterium steadily penetrated through 0.2-μm membranes. The small bacterium has not been completely classified, but it was found that it belongs to the species Pseudomonas (Ps. sp) [2]. However, the bacterium is completely retained by 0.1 μm membranes, a fact that has also been noted by other researchers. It has been found that in some cases, medicines force microorganisms to "shrink" (their linear dimensions can decrease 40%). After a prolonged stay in a preparation in the absence of a nutrient medium, the microorganisms can also get much "slimmer."

The phenomenon of sprouting through the membrane has been given one more rational explanation: the bacterial cell is divided into two parts in the course of reproduction. After the division, the halved bacterial cell can probably penetrate through the membrane that is impermeable to it the rest of the time [3].

In connection with the aforesaid, new filter elements incorporating 0.1-μm membranes have emerged on the market. These elements are used in production processes, especially in processes involving the use of sera or media containing tissue cultures, where it is necessary to remove deformable bacteria (without rigid shells) and mycoplasmas, which have been shown to penetrate through-0.2 μm membranes [4].

At present, sterilizing membranes are mainly made of nylon, fluoroplastics, polysulfone, and cellulose ethers (esters). Each of the materials has its own advantages and disadvantages. In terms of chemical stability, fluoroplastics (hydrophobic materials indispensable for sterile filtration of air

and gases), as well as nylon and polysulfone, are the market leaders. Membranes made of cellulose ethers (esters) are not as strong and are unstable to flushing with alkali solution, which is an accessible, cheap, and efficient regenerating agent. The membrane material should be readily compatible with the product being filtered; ie, the product should not change the filtering properties of the membrane. In turn, the membrane should not shed any significant amount of extractables into the filtrate and should not sorb any substances from the filtrate onto itself. The rate of sorption is especially important in cases where highly diluted solutions are filtered with the content of the substance being filtered, comprising several fractions of microgram per milliliter or less.

The choice of membrane filtration as a preferable separation method is dictated by high medicine purity and safety requirements.

Microfiltration

The most suitable filters for filtration of injection solutions are microporous membrane filters, which use a sieving mechanism for the retention of microbial cells. The pore size of these filters is unvaried. The membrane filters are produced from polymer materials in the form of thin plates (films), with thickness ranging from 100 to 150 μm.

Microfiltration membranes should have a set of properties, such as high flux and selectivity, hydrophilicity or hydrophobicity, ion selectivity, hemocompatibility, bactericidal action, sterilizing capacity, and high thermal and chemical stability.

To sterilize solutions with pHs in the 1.0–10.00 range, the Vladipor membrane filter, produced from cellulose acetate, is widely used in Russia and the former Soviet republics. To sterilize solutions of pharmaceutical substances, MFA-3 filters, with 0.25–0.35-μm pore sizes, and MFA-4 filters, with 0.35–0.45-μm pore sizes, are used.

Membranes on the basis of polyvinylidene fluoride and polyethersulfone, 0.1 μm in size, produced by Millipore Corporation (USA), are recommended for use as final filters in sterilizing filtration of biological preparations [4].

Nanofiltration

For the removal of viruses at the final stage, Sartorius recommends using the Virosart CPV membrane, which retains more than 10^4 PFU/cm^2 parvoviruses and 10^6 PFU/cm^2 retroviruses (the analog is Viresolve NFP). The data on retention of the PP7 bacteriophage are provided in accordance with the results of the diffusion test. Various authors point out that virus removal efficiency using nanofiltration is significantly dependent on the parameters of the filtration process.

Ultrafiltration and Reverse Osmosis

Ultrafiltration is the process of separation of solutions carried out through a partition wall with the characteristic pore size of 0.001–0.1 μm, which is why no bacteria, viruses, cysts, endotoxins, or pyrogens are found in the filtrate of ultrafiltration elements. For this reason, the use of ultrafiltration at the final stage of high-quality water production is considered very promising in medicine and pharmaceutics.

In addition, the use of ultrafiltration for the preliminary preparation of water upstream of reverse osmosis is already recognized worldwide as one of the best solutions (especially in cases where the flux is above 10 m^3/hour). Strict observance of required operating conditions, avoidance of prolonged downtimes for reverse osmosis systems, and compliance with all requirements for sanitization of reverse osmosis systems after downtime can ensure microbiological purity and apyrogenic condition of the filtrate. However, it is known, from the operating experience of reverse osmosis systems, that penetration of bacteria and bacterial endotoxins through the membrane, as well as sprouting of microbes through the membrane, are possible.

For this reason, the high microorganism retention capacity of ultrafiltration systems can significantly reduce the risks of microbiological contamination of reverse osmosis membranes, efficiently precluding the penetration of endotoxins and bacteria into the filtrate of reverse osmosis systems.

Another important aspect of using ultrafiltration for water conditioning in medicine and the pharmaceutical industry is the possibility of sterilizing the ultrafiltration membranes, not only with chemical agents, but also with pure steam (reverse osmosis membranes cannot be sterilized with pure steam; only some models can withstand short-term treatment with hot water at 80°C, such as HSR 0390-FF and HSR 04040-FF, produced by DOW Chemical).

In addition, ultrafiltration equipment is rapidly becoming even more automated, compact, simple, and easy to use.

Membranes having Bactericidal (Bacteriostatic) Properties

Colloidal, crystalline, and, especially, biological contamination of membranes results in drastic deterioration of their characteristics. One of the effective methods for counteracting the latter factor could be the development of membranes having bactericidal or bacteriostatic properties.

Bactericidal substances (from *bacterium* and the Latin *caedo,* meaning, "I kill") are substances that are capable of killing bacteria and other microorganisms.

The production of bactericidal membranes is based on the use of the following process techniques:

- the use of high MW bactericidal additives;
- the use of polymer complexes;
- the use of metal-containing bactericidal substances.

There are a large number of bactericidal polymers; however, at present, chitosan, a biodegradable and biocompatible polysaccharide, is increasingly used for that purpose. Due to the combination of specific properties (biological activity, biocompatibility, formation of chelate complexes, capacity for biodegradation, and flocculation), chitosan is widely used as a polyfunctional polymer in industry, agriculture, medicine, and pharmaceuticals [5-8].

Chitosan is also known to be a pH-sensitive polymer. At low pH values, amine groups of chitosan are protonated and positively charged, making it a water-soluble cation-active polyelectrolyte. At high pH values, amines are deprotonated, and the polymer loses its charge and becomes insoluble in water.

Dissolved chitosan has a positive charge resulting from the presence of NH^{3+} groups, which facilitate the localization of chitosan molecules near negatively charged surfaces, aggregation with polyanionic compounds, and the formation of chelates with ions of heavy metals. The mechanism of chitosan's antimicrobic action can be described in the following way:

1) the cationic nature of chitosan forces it to form bonds with the acid of phospholipins in microorganisms, which disrupts the exchange of intracellular substances with the external environment; and
2) the oligomer of chitosan penetrates into the cells of microorganisms and inhibits their growth.

The authors of ref. [9] investigated bactericidal and bacteriostatic properties of chitosan-modified cellulose membranes. For the process of membrane modification, which is based on activation (oxidation) of cellulose membranes with periodate and their interaction with chitosan, Nadir C010F, C030FM, and C100F porous cellulose membranes (Germany), with cut-offs of 10,000, 30,000, and 100,000 DA, respectively, were used as the initial material. To enhance the antimicrobial properties of chitosan, it was additionally modified by keeping it in solutions of well-known inorganic bactericidal agents ($AgNO_3$, $CuCl_2$, J_2), whereupon their bactericidal and bacteriostatic action was investigated for 56 days.

It has become known that the highest antimicrobial activity is manifested by fine-pored membranes modified with chitosan that has a higher molecular weight. At the same time, chitosan-modified membranes that were additionally treated with silver nitrate solution demonstrated 100% bactericidal activity, which was retained for 56 days. Membranes additionally treated with copper and iodine chloride solutions manifested bacteriostatic properties and retained them for 56 days as well.

To bond the modifying polymers with the surface of the polyethylene terephthalate (PETP) membrane, a method of treatment is used that involves the use of a bifunctional bonding agent that is capable of chemical interaction with both the surface of a track-etched membrane (TEM) and modifying polymers, such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyvinyl alcohol (PVA), and heparin. The role of the bifunctional agent is performed by polyethylenimine, a water-soluble polymer whose amino groups can form a polyelectrolyte complex, with carboxyl groups on the surface of track-etched PETP membranes and functional groups of modifying polymers.

It has been found that by selecting the modifying polymer, electric surface properties (the sign and size of the charge) and adsorptive properties of membranes can be modified in a controlled way. Lower adsorption of model adsorbates (proteins and the coloring agent) observed in the case of modified membranes can be explained by shielding adsorptive active sites on the surface of membranes by modifying polymers having an electrostatic and hydrophobic nature.

Modification of the surface of ultrafiltration track-etched PETP membranes with complex-

forming, water-soluble polymers, such as PEG, PVP, and PVA, makes it possible to reduce protein adsorption on their surface significantly, by a factor of 2 to 50.

The main function of antimicrobial additives used for the modification of membranes is to reduce the number of microbes or destroy microbes completely on their surfaces.

In terms of the mechanism of action, antimicrobial additives can be classified into two groups:

- Microbiostatic additives that slow down the process of reproduction of microorganisms. However, the cells do not die; their growth is only slowed down.
- Microbiocidal additives that destroy microorganisms completely, significantly reducing their number immediately after contact.

In most cases, gram-negative bacteria are less sensitive to antimicrobial additives compared to gram-positive ones, because they have an additional membrane that slows down penetration of the antimicrobial additive inside the cell.

Interaction of microorganisms with polymer membranes can manifest itself in the following way:

- Emergence of spots or discoloration due to the effect of intracellular pigments (mainly mold – penicillin and aspergill) or extracellular colorants (products of metabolism of bacteria).
- A change in mechanical properties as a result of the main polymer, e.g. cellulose and its derivatives or various additives, such as plasticizers and stabilizers, being consumed by bacteria. This is the most serious manifestation of biodegradation of polymer films and membranes.
- Contamination of the surface as a result of the formation of colonies of microorganisms, building up rough microscopic areas on which contaminations are retained.
- Emergence of a smell that results from release of the products of metabolism of microorganisms, such as amines, ammonia, and hydrogen sulfide.

As inorganic antimicrobial systems, compounds of silver, zinc, and copper are mainly used at present. Antimicrobial filter materials are used for the decontamination of fresh water contaminated with pathogenic flora. The most currently popular filters, including those intended for home use, have bactericidal action; i.e., they are able to suppress the activity of microorganisms or restrain their development.

The main requirements for bactericidal coatings based on silver and copper ions include strength and stability of the bond with the membrane in the course of the service life of the membrane. Therefore, the antibacterial substances should be chemically bonded to the surface of the membrane (by a coordinational, ionic, or covalent bond); ie, the membrane should contain active groups capable of entering into reactions of polymer-analogous transformations. The most common way of immobilizing metal ions on the membrane is through the introduction of carboxyl or hydroxyl groups. To this end, membranes can be modified with grafted polyacrylic or polymethacrylic acids, making it possible to fasten silver ions chemically to the membrane, thereby imparting bactericidal (bacteriostatic) properties to it [6].

Silver is most frequently used as a biocide, as it is one of the strongest natural antibiotics among those found on Earth. It has been established that silver can destroy more than 650 species of bacteria, which is why it has been used by man for the destruction of various microorganisms for thousands of years, proving its stable antibiotic effect.

The action of silver is specific, not in terms of infection (as in the case of antibiotics), but in terms of cellular structure. Any cell that has no chemically stable walls (such cellular structure is typical of bacteria and other organisms having no cellular walls, such as extracellular viruses) is subject to the action of silver. Because the cells of mammals have a membrane of a completely different type (containing no peptidoglycans), silver does not affect them in any way.

The mechanism of action of silver consists of three stages:

Stage 1: Silver penetrates into the cover of microorganisms and destroys cellular partitions before penetration into the cell.

Stage 2: Silver interacts with enzymes and deactivates viable molecules.

Stage 3: At the final stage, silver interacts with DNA cells, precluding their reproduction.

Silver ions stop the progress of most chemical reactions inside bacteria, which is why many bacteria do not breed in the presence of silver nanoparticles.

Numerous investigations carried out over the past 30 years have shown that surface properties of membranes, including their electric surface

properties, determine their operating characteristics to a great extent, such as adsorption of various substances. Retention efficiency of several contaminants, including biological ones, can be increased by using the so-called "charged membranes."

The "charged membranes" are those with a surface electric charge (zeta-potential).

Surface properties of membranes have a significant and sometimes decisive effect on their operating characteristics. The size and sign of charge on the surface of membranes and particles being retained (colloids, high MW compounds, ions, etc) that are present in the mixture being filtered determine the intensity of electrostatic interaction between them, which initiates the adsorption process that can result in either the increase in retention efficiency or the plugging of pores and reduction of membrane flux. It is known that aliphatic polyamides used for the production of membranes, unlike other membrane-forming polymers (cellulose acetate, fluoroplastics, acrylonitrile, etc) have the isoelectric point in which positive and negative charges compensate each other. The isoelectric points of polyhexamethylene diamine (PA 66) and polycaproamide (PA 6) are located in the 7.6-8.6 pH range, depending on the ratio of amino and carboxyl groups. If the pH is above the isoelectric point, the membrane has a negative charge; if not, it has a positive charge.

Technofilter Research-and-Manufacturing Enterprise Ltd has carried out investigations that made it possible to develop two techniques for modifying microfiltration polyamide membranes [11, 12]:

- the introduction of modifying additives into the molding material (bulk modification)
- the application of modifying agents on the surface of the membrane

Properties of samples of the modified membranes have been investigated, and it has been shown that surface-modified polyamide membranes containing silver nanoparticles in amounts of 16 mg/g to 2.22 mg/g possess bactericidal properties for seven days.

Specialized markets in the USA and Europe are saturated with silver-based biocidal preparations. The annual consumption of these biocides is expected to grow by more than 20% in Europe, by 25% in the USA, and by almost 15% in China. European sales of biocidal preparations are expected to grow.

Depyrogenating Membranes

Endotoxins, lipopolysaccharides present in the cellular membrane of gram-positive bacteria, are pyrogens that should be removed from pharmaceutical preparations, solutions for injections of parenteral preparations, and some media for tissue cultures.

Endotoxins are modified proteins capable of converting other proteins into the prionic form, which are perceived by the human immune system as foreign substances and subsequently converted by it into an insoluble, idle form. These proteins accumulate in a nerve cell and kill it, ultimately resulting in the degeneration of the central nervous system [1, 13].

Hence, the removal of microorganisms from water significantly complicates the medicine production process, because achieving sterility of the injection preparation is only one aspect of the task to be solved. It is also very important to ensure depyrogenation of sterile medical preparations in the course of their production, because bidistillation, a traditional technique used for the production of water for injection at major pharmaceutical enterprises in the Russian Federation, is too expensive for small municipal and clinical drugstores, whereas monodistillation, a more resource-saving technique, does not ensure proper quality of water in terms of endotoxin content.

If endotoxins have penetrated into liquids being used in the course of preparation of a parenteral medicine (water, buffers, nutrient media, etc), the patient to whom the medicine has been administered develops a fever. This is primarily relevant for preparations that are administered in large amounts, such as blood substitutes, disinfectants, and extremely toxic cytostatics. For this reason, the content of pyrogens in these preparations should be strictly monitored (eg, their content in water for injections should be lower than 0.025 ng/ml). The label on the package of the preparation should contain the notice "apyrogenic" in addition to "sterile." The amount of endotoxin administered to a human capable of producing a pyrogenic reaction is 5 EU/kg of body weight per hour, where EU is the standard endotoxin unit. This level of the threshold pyrogenic dose was first approved by US Pharmacopeia in 1987 and is now an international norm [14].

Bidistillation, a traditional technique used to produce water for injections at large-scale

pharmaceutical enterprises, is too expensive for small municipal and clinical drugstores, whereas monodistillation, being a more energy- and resource-saving technique, does not make it possible to achieve water quality in compliance with Farmstatya FS 42-2620-97, Amendment No. 1, "Water for injections." Reverse osmosis and nanofiltration also do not guarantee the production of apyrogenic water, because penetration of bacteria and bacterial endotoxins are quite possible and take place quite frequently.

When developing the design of the system for depyrogenation of solutions containing proteins and peptides, many factors have to be taken into account, such as the composition of the compound being purified; concentration of electrolytes; pH of the solution; presence of other proteins or peptides in the solution and their concentrations; molecular weight of the proteins and their isoelectric point; and the character of intermolecular interaction. The combination of these factors determines the choice of the most effective technique for the removal of pyrogens.

The technique of one-stage or two-stage treatment of solutions by ultrafiltration at neutral pH using membranes having cut-offs of 10,000 to 20,000 Da was considered to be the most effective one. The first stage is intended to produce the first filtrate, the product is subjected to repeated ultrafiltration, and the secondary filtrate is used as the end product. However, it should be taken into account that if the solution being depyrogenated contains low MW compounds (a buffer, a solution of amino acids, nucleotides, short peptides), endotoxins can be separated by ultrafiltration, using filters with cut-offs of 10 to 20 kDa; however, if the protein has a molecular weight similar to that of the endotoxin, ultrafiltration is unsuitable for separation of the endotoxin [15-17].

To achieve complete removal of endotoxins, Millipore (USA) and Sartorius (Germany) propose that uncharged nanofiltration membranes with cut-off threshold of 10 kDa should be used in the form of plate-and-frame and spiral-wound filter elements. However, even using this approach, the same molecular weight restrictions are in effect as in the cases of virus removal – the separation is possible if the MW of the useful product is less than 10 kDa.

It has been stated already, in the previous section, that charged membranes can be regarded and used as sorbents. The concept of the membrane sorbent, i.e., a membrane whose surface has sorptive properties, was introduced into the practice of biotechnology about 15 years ago. It is known that membranes produced from polymer solutions by the phase-inversion technique feature a structure of interconnected voids chaotically arranged in the space (interstructural spaces) in a certain size range, characteristic of that type of membrane, and functionally constituting a multi-layered sieve. The sieving retention mechanism involves the use of one layer consisting of separate porous elements, whereas the sorptive mechanism involves the use of all layers of the microfilter – more precisely, of the whole membrane surface [18].

The sorptive mechanism, therefore, is preferable to the sieving mechanism in terms of filtration rates. If the sieving mechanism is used, the pores should be smaller than the particles being retained, whereas in the case of the sorptive mechanism, they can be larger. This ensures a significant advantage in terms of the filtration rate. The latter fact makes it possible to use a stack of in-series membranes instead of a single membrane in order to increase the sorptive capacity.

Membrane sorbents, therefore, are surface- or bulk-modified microfilters offering improved sorptive properties [19-21].

Sartorius has developed a strategy for removing endotoxins from protein solutions based on membrane adsorption that can have two implementations:

- The use of a strong, basic ion-exchanger with pH of the buffer lower than the isoelectric point of the protein. In this case, the endotoxin is bound, whereas the protein easily penetrates through the membrane.
- The use of a strong acidic ion-exchanger with pH lower than the isoelectric point of the protein. In this case, the protein is bound, whereas the endotoxin penetrates through the membrane.

Some properties of resins used in chromatography restrict the possibilities of their use. These include low flow rates, prolonged recovery periods, and limited chemical stability. The use of membrane adsorbers makes it possible to avoid these problems. Highly effective and easy-to-use depyrogenating ion exchange membranes can be used in both laboratory and industrial applications.

Adsorptive matrices produced by Sartorius are membranes made of modified cellulose with large pore sizes (3–5 μm). The pore surfaces of Sartobind membrane adsorbers contain covalently bound

ionic functional groups. The adsorbers demonstrate high bonding dynamics and chemical stability. These properties of membrane adsorbers make it possible to remove undesirable contaminants (endotoxins, DNA, proteins) from various solutions rapidly and effectively. High density, uniform distribution, and accessibility of functional groups ensure high efficiency of the adsorption process during the passage of the liquid through the pores.

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