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Short communication

Selection of filter for sterilization using process of membrane filtration based on potential adsorption of Benzalkonium chloride on filter membranes

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Introduction

Sterility is the absence of viable microorganisms and it is a critical quality attribute for a wide variety of human and veterinary preparations that are required to be sterile due to their route of administration, such as parenteral, ophthalmic, intrauterine and intramammary preparations, and some preparations intended for application on severely injured skin (Ph. Eur. 10.0). There are several types of methods of preparation of sterile products. The method chosen mainly depends on the physicochemical properties of the product to be sterilized. Membrane filtration is a widely used unit operation in the pharmaceutical industry for clarification purpose and/or sterilization using sterilizing grade filter membranes (0.2 µ or smaller pore size filters). Many factors contribute to the effectiveness of the filtration process like the shape, pore size, structure and the surface properties of the filter, interaction of the filter matrix with the product to be sterilized, as well as the applied pressure, flow and duration of the process (Ph. Eur. 10.0). One concern of using process of membrane filtration is that adsorption of solutes may occur and therefore their concentration in the final product may decrease.

Adsorption of solutes broadly depends upon type of the filter membrane (composition and chemical nature, electrostatic forces, surface area and mass of filter membrane) as well as formulation and process parameters (composition and chemical nature of ingredients, pH of formulation, ionic strength and temperature of process) (Sumitra et al., 2016). Pharmaceutical solutions often contain preservatives to destroy or impede the growth of microorganisms that inadvertently enter the product. It has been frequently noted that preservatives can be adsorbed by filters which may lead to a decrease or loss in preservative effectiveness (Tao et al., 1998).

An effective way of overcoming the reduction of preservative's concentration due to their adsorption on membrane filters during the sterilization process by using membrane filtration is presaturation of the filter membrane, before the process of filtration, by filtering a certain quantity of the solution containing the preservative, so the further process of membrane filtration can result with final sterile product with the proper preservative's concentration. The purpose of this study was determination of potential adsorption, as well as the required quantity of the test solution containing the preservative, in order to achieve fastest and complete saturation of the filter membrane so the concentration of the preservative in the final sterile product would not be below its predetermined specification limit.

Materials and methods

Materials

Laboratory trial, as test solution, of 250 mL solution for ophthalmic administration containing 50% aqueous solution of Benzalkonium chloride (Merck) as preservative was prepared. Two membrane filters Fluorodyne II DFL membrane, FTKDFL and N66 Nylon membrane, FTKNF (Pall Corp.) with pore size of 0.22 µm were used. Both membrane filters were mounted in 47-mm in-line holder. The effective filter area in the holder was 14.2 cm^2.

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Determination of preservative concentration

The adsorption profile of Benzalkonium chloride was determined using a flow-through technique. The test solution was pumped through the filter at flow rates controlled by a peristaltic pump (Watson-Marlow Bredel Pump). Ten consecutive samples of 5 mL were taken from the filtered test solution of total 50 mL solution passed through both of the membrane filters, respectively. The UV absorbance at 215 nm of all ten filtered samples, as well as a sample of the solution before the process of membrane filtration, was recorded using HPLC method.

Determination of preservative adsorption

The adsorption of Benzalkonium chloride on the membrane filters was determined as difference in the concentration of Benzalkonium chloride in the solution before the filtration and the concentration in the samples taken after the process of filtration through both of the membrane filters, respectively.

Results and discussion

The results obtained after determination of the concentration of Benzalkonium chloride of the ten filtered samples indicate that Fluorodyne II DFL membrane, FTKDFL is superior than Nylon 66 membrane, FTKNF. The specification acceptance criteria for assay of Benzalkonium chloride of 90-110% was achieved after third filtered sample, 15 mL, when filtered through Fluorodyne II DFL membrane, FTKDFL with surface area of 14.2 cm^2. Therefore, complete saturation of the Fluorodyne II DFL membrane, FTKDFL was achieved after filtration of 40-50 mL as the concentration of Benzalkonium chloride in the last two samples was higher, while the specification requirement of assay of the preservative when using Nylon 66 membrane, FTKNF was met after filtration of the fifth sample, 25 mL of the test solution and no complete saturation was achieved after filtration of 50 mL through Nylon 66 membrane, FTKNF with surface area of 14.2 cm^2.

Benzalkonium chloride is antimicrobial preservative widely used in pharmaceutical formulations in concentration of 0.01 and 0.02%. It is a quaternary ammonium compound with hydrophilic n-alkyl chain. Due to its cationic nature benzalkonium chloride induces antimicrobial action through attraction to the negatively charged microbial membranes.

Fluorodyne II DFL membrane, FTKDFL (Pall Corp.) is unique hydrophilic modified polyvinylidene fluoride membrane. It has some weak cation exchange capacity due to its acrylic acid resides (Tao et al., 1998). These membrane filters are recommended for sterilizing filtration of ophthalmic and other dilute preservative solutions.

Nylon 66 membrane, FTKNF (Pall Corp.) is polyamide type of membrane composed of adipic acid and hexamethylene diamine. It is hydrophobic polymer having a terminal amine group that is protonated below pH 10 (Tao at al., 1998). Nylon membranes are hydrophilic but they can be treated for hydrophobicity and may be used in both aqueous and organic solvent filtration applications.

Hydrophobic and/or electrostatic forces are chiefly responsible for adsorption mechanism of preservatives on membrane filters. Benzalkonium chloride shows lowest affinity of adsorption on hydrophilic and nonionic or hydrophilic and cationic membranes, while membranes that are hydrophobic or anionic exhibited significant Benzalkonium chloride adsorption. However, the positive charge of Nylon 66 membrane at pH conditions below pH 10 plays a very important role in reducing the adsorption of Benzalkonium chloride (Tao et al., 1998). Therefore, this study shows that Fluorodyne II DFL membrane, FTKDFL is superior in achieving faster and complete saturation and yet higher concentration of Benzalkonium chloride in the tested samples over Nylon 66 membrane, FTKNF.

Conclusion

The selection of filter for sterilization with process of membrane filtration is crucial during production of ophthalmic preparations, containing preservatives with adsorptive properties, on a bulk scale since the initial part of the filtrate is discarded by which time the filter surface get saturated.

This study demonstrated that faster and complete saturation is achieved while using membrane filter Fluorodyne II DFL membrane, FTKDFL over Nylon 66 membrane, FTKNF.

References

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