Global Journal of Nanomedicine

Juniper Publishers key to the Researchers

Mini Review
Volume 3 Issue 5 - March 2018
DOI: 10.19080/GJN.2018.03.555624

Glob J Nanomed

A Review on the Applications of Nanofiltration in Virus Removal and Pharmaceutical Industries

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Submission: November 08, 2017; **Published:** March 19, 2018

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Abstract

Membrane filtration has traditionally been implemented in medical applications for size exclusion in high-throughput though relatively low-resolution requirements. These applications include microfiltration for clarification and sterile filtration and ultra filtration for protein concentration and buffer exchange. Membrane filtration has long been confined to plasma pool clarification, dialysis and concentration and bacterial filtration of products and buffers. To date, three main membrane filtration techniques (MF, UF and NF) are utilized for plasma fractionation. The first industrial applications of nanofiltration in the field of bio-pharmacy were in plasma-derived coagulation factor concentrates; where NF performs very effectively for virus removal. Viral safety is an important prerequisite for clinical immunoglobulin preparations. Nanofiltration is especially effective in the removal of non-enveloped viruses resistant to inactivation methods such as heat or solvent/detergent treatment.

keywords: Nanofiltration; Virus removal; Pharmaceutical industry; Membrane; Medicine

Abbreviations: MF: Microfiltration; UF: Ultrafiltration; NF: Nanofiltration; PPV: Porcine Parvovirus; PTC: Prothrombin Complex; FXI: Factor IX; RF: Reduction Factor; PDMS: Polydimethylsiloxane

Introduction

Membrane filtration has traditionally been implemented in medical applications for size exclusion in high-throughput though relatively low-resolution requirements. These applications include microfiltration for clarification and sterile filtration and ultra filtration for protein concentration and buffer exchange. Current research and development endeavors are directed toward significant improvements in selectivity while maintaining the inherent high-throughput characteristics [1]. However, membrane filtration has long been confined to plasma pool clarification, dialysis and concentration and bacterial filtration of products and buffers. To date, three main membrane filtration techniques (MF, UF and NF) are utilized for plasma fractionation [2]. Stringent viral reduction methods contribute greatly to virus safety and plasma manufacturers continue to introduce additional steps to enhance viral safety margins. Among these, filtration of plasma protein solutions via commercially available membranes is implemented to retain viruses based on sieving. As most of such membranes are characterized by a mean pore size of a few nanometers and also as they are specialized in virus removal, the technology is called "nanofiltration" to be distinguished from other filtration methods not designed for virus removal.

The first industrial applications of NF in the field of bio-pharmacy were in plasma-derived coagulation factor concentrates, where NF performs very effectively for virus removal in plasma manufacturing. The technique has now been added to other viral safety techniques being used for a wide range of bio-pharmaceutical products. Viral safety is an important prerequisite for clinical immunoglobulin preparations. The common manufacturing practice is to utilize several virus removal/inactivation process steps to ensure human intravenous immunoglobulin (IVIg) safety [3].

Engineering of NF membrane structures has allowed high-resolution protein–virus separation; thus their applicability to plasma and plasma-derived and to medicinal products prepared from human and animal cell lines was quickly recognized [2]. Nanofiltration of plasma products was actualized at industrial scales in the early 1990s as a complement to other viral reduction treatments, such as solvent– detergent and heat treatments, especially for the inactivation of human immunodeficiency virus, hepatitis B and hepatitis C. The main reason for the introduction of NF was the need to improve product safety against non-enveloped viruses and to provide a possible safeguard against new infectious agents potentially entering the human plasma pool.

Nanofiltration has gained quick acceptance as a relatively simple manufacturing step consisting of protein solution filtering through membranes of a very small pore size (typically

15-40nm) under conditions that retain viruses via size exclusion, combining efficient removal of>4-6 logs of a wide range of viruses without any denaturing effect on plasma proteins. In contrast to viral inactivation treatments that kill viruses but leave viral markers such as antigens and nucleic acids, NF may remove these markers which can be considered as an advantage. Recent studies indicate that NF may also remove prions opening new perspectives in the development of this technique and increasingly becoming a routine step in the manufacture of biopharmaceutical products [2], since it does not pose toxicity issues, while most viral inactivation treatments use toxic or mutagenic chemicals that require post-elimination from the protein solution.

Nanofiltration is especially effective in the removal of non-enveloped viruses resistant to inactivation methods such as heat or solvent/detergent treatment [4,5]. Yokoyama et al. [6] reported that such non-enveloped viruses such as human parvovirus B19 (B19), human encephalomyocarditis virus (EMC) or porcine parvovirus (PPV) aggregate in the presence of certain kinds of amino acids could be removed by NF. Glycine solution spiked with viruses was exposed to a 35nm pore-size filter, resulting in B19 reduction to 1:107•5 (7•5-log), whereas no reduction was observed in PBS. This was also confirmed with the other small non-enveloped viruses (EMC or PPV). When 5% globulin or albumin was added to the glycine solution, the removal rate was decreased. This can be attributed to the fact that viruses could aggregate in the presence of certain kinds of amino acids and effectively removed using a filter with a pore size larger than the size of the viruses [6].

Menconi et al. [7] evaluated NF efficacy in removing B19V and TTV from three plasma-derived products: albumin solution, prothromb in complex (PTC) and factor IX (FIX). Virus removal was investigated with down-scale experiments performed with following steps of 35nm and 15nm NF of products spiked with virus DNA-positive sera. The 15nm NF removed more than 4.0 B19V log from all products, TTV was reduced from more than 3.0log from albumin solution and FIX by 35nm and 15nm NFs, respectively. Traces of TTV were still found in PTC after the 15nm NF [7]. Caballero et al. [8] assessed the virus-removal capacity of NF on a wide range of viruses (pseudo-rabies virus; human immunodeficiency virus; bovine viral diarrhea virus; West Nile virus; hepatitis A virus; murine encephalomyocarditis virus; and porcine parvovirus) with sizes in the 18-200nm size range. Reduction Factor (RF) was calculated by comparing the virus load before and after NF under each product purification condition. In all experiments, the RFs were close to or greater than 4 log10 (>99.99% of virus elimination). RF values were not significantly affected by process conditions within the limits assayed (pH, ionic strength, temperature, filtration ratio, and protein concentration). The virus-removal capacity of NF was just correlated with the size of the removed agent [8].

Zhao et al. [9] provided a fundamental understanding of separation behavior of a positively charged NF membrane for antibiotic removal at various pH values. Such membranes were prepared by cross-linking of P84 co-polyimide precursor membranes using polyethylenimine (PEI) with various MWs. Finally, the removal efficiency of two antibiotics, cefadroxil and enrofloxacin at various pH values were investigated. These antibiotics were selected since they were representatives of cephalosporin and fluoroquinolone, widely used as human and veterinary medicine. The results show that, PEI-25k NF exhibits positive charge in the 2-10pH range with strong charge intensity, moderate and weak in the pH ranges of <4, 4-7 and 8-10, respectively. For antibiotics removing, electrostatic interaction between antibiotics dissociation species and membrane surface controls the separation efficiency at different pH values. The antibiotics dipole moment might influence the retention by affecting molecular orientation approaching the membrane pores [9].

NF membranes fall into two major groups based on materials (Ceramic and Polymer).Although NF has benefits compared with other removal techniques but hybrid NF membranes have also attracted attention due to their ability to work at harsh conditions. Various polymers such as polyethersulfone(PES) [10], polydimethylsiloxane (PDMS) [11], polyvinylidene fluoride (PVDF) [12] and polysulfone (PS) [13] are used as the top-layer in hybrid membranes. Using polymers to prepare hybrid NF membranes provides this possibility to modify the pore size and chemical and charge properties of membrane surfaces. Some polymers such as PDMS with characteristics like non-toxicity, flexibility, thermal and chemical stability, antibacterial characteristics can be a good alternative as the thin selective layer. Shokri Doodeji et al. [14], fabricated alumina-PDMS hybrid NF membranes to investigate the effect of Mw of PDMS on rejection. Based on the results, increasing polymer Mw can lead to the reduction of pore size, which is promising for the fabrication of engineered membranes applicable with the desired pore size for special applications such as virus removal.

NF membranes have also been implemented in purification applications. Faneer et al. [15], Obtained high purity xylitol which is a stone corner in medicine industries. Many conventional techniques (crystallization and adsorption) were used for xylitol purification from fermentation media. Membrane technology has received a great attention in xylitol purification due to high performance. Among renowned co-polymers for polymer blending to produce membranes, pluronic is receiving much attention due to its strong hydrophilic character being used as both pore former and surface modifier [15].

Conclusion

Membrane filtration is very much developed in recent decades, due to simple use and safety for removing high fractions of enveloped and non-enveloped viruses that resilient

How to cite this article: M Shokri Doodeji, MM Zerafat. A Review on the Applications of Nanofiltration in Virus Removal and Pharmaceutical Industries. Glob J Nano. 2018; 3(5): 555624. DOI: 10.19080/GJN.2018.03.555624

to inactivation through heat or solvent/detergent treatment, filtration of plasma protein solutions, manufacture of plasma products and also the capacity to use for a wide range of bio-pharmaceutical products. The main reason for the introduction of NF was the need to improve product safety against non-enveloped viruses and to provide a possible safeguard against new infectious agents potentially entering the human plasma pool. The technology has major advantages due to flexibility combining efficient and largely predictable removal of more than 4 to 6 logs of a wide range of viruses without any denaturing effect on plasma proteins. Compared with other viral reduction means, NF may be the only method permitting efficient removal of enveloped and non-enveloped viruses under conditions where 90-95% of protein activity is recovered. NF is increasingly becoming a routine step in the manufacture of bio-pharmaceutical products since it does not pose toxicity issues, while most viral inactivation treatments use toxic or mutagenic chemicals that need to be eliminated from the protein solution upon implementation.

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DOI:10.19080/GJN.2018.03.555624