Ultrafiltration: Where Have We Been and Where Are We Going…

S. Mookie Sternberg, Baxter Healthcare Corporation

In this presentation the emphasis is on the inherent quality of the Ultrafiltration (UF) membrane. Ultrafiltration device design, flow engineering considerations, etc. are mentioned only in passing. We present the history of UF membrane development as it applies to the improvements in the inherent quality of the separation capabilities of the membrane itself, and its relative importance in different applications.

A perfect membrane will pass desired products only and retain contaminants only (or vice versa). Simple separations of large proteins from small molecules, like diafiltration of Cohn Fractions was a perfect use for the early UF membranes. It is when the membranes are required to remove an exceedingly small fraction of the solute that is a larger (than the product) contaminant, such as in virus removal from protein solutions, that the quality of the membrane itself may not be sufficient. We will demonstrate how the membrane improved over time and what we expect the next steps in improvements may be.

It is generally recognized that the age of Ultrafiltration started with Alan Sherman Michaels founding Amicon Corporation and introducing the UM family of Ultrafiltration membranes. It is interesting to note that those first UF membranes were not made of typical synthetic polymers; rather they were made of polyelectrolyte complexes. It was only later in the late 1960's that the XM series, based on a synthetic, noncellulosic polymer, and made according to Michaels' patent in 1971, arrived.

Membranes capable of discerning between species of molecular size have been produced before Michaels and Amicon: Bechhold (1906), Zsigismondi (1912) and Elford (1930) produced such membranes from Cellulose Nitrate.

Loeb and Sourirajan (1960) introduced Cellulose Acetate membrane which were highly asymmetric: The discerning layer, the 'skin', was dense and constituted an extremely small fraction of the total thickness of the membrane. The rest of the membrane was highly porous and offered virtually no resistance to hydraulic flow. The net result was a membrane exhibiting separation capabilities of a dense polymer with flux levels of a highly porous structure.

The early UF membranes possessed the advantages taught in all these early membranes. A highly asymmetric structure allowing for high fluxes, a dense skin capable of discerning between molecular size species, all on non-cellulosic, synthetic polymer matrix.

The characterization of UF membrane was originally done by passing solutions of protein of known molecular weight (thus size) through the membrane. By measuring the permeate and feed concentrations the membrane rejection level of the protein can be calculated. Obviously, the accuracy of results can be only as good as the accuracy of the detection levels. When no protein was detected in the permeate, the rejection was reported as >98%. This was sufficient for the users at the time, but will become insufficient when the membranes are used to remove trace quantities of say, a contaminant.

In the mid seventies, a new test for pyrogens (endotoxins, lypopolysacharides) was introduced. For the first time large molecular species were detectable to nanogram and picogram levels. Since the structure and size of the pyrogens was known, an excellent tool for UF membrane characterization became available. Testing of membranes that were to reject pyrogens completely proved that the membranes could remove only about two logs (99%), suggesting that there must be passage of larger species through micro voids, defects or just larger pores.

Since the discerning layer (skin) is exceedingly thin, and passage is assumed to take place through distinct pores in the skin, it follows that if two membranes are placed 'skin to skin', large holes or defects are not likely to align. Such structure should eliminate passage through few larger defects. DeWinter (1981) showed that when such structure was used, rejection of pyrogens was in excess of six logs. Henis and Tripodi (1980) showed that by spreading a thin layer of wetting fluid on the inside of a hollow fiber they could get rid of convective flow of gas through the membrane.

DiLeo and Allegrezza (1991) showed the first UF membrane exhibiting "…a monotonic increase in retention as test particle size is increased…" The reported membrane is made of two layers, cast independently of each other! In their papers the authors show that run of the mill UF membranes available to that point did not exhibit the same monotonic rise behavior, suggesting the presence of larger micro-defects that allow indiscriminant passage of all particles. However, even with this improved structure, the existence of larger pores is not eliminated: it is suggested that these larger pores are part of the natural pore size distribution of the membrane.

To test the effect of pore and defect diameter distribution on membrane rejection, Sternberg and Boggs (1999) showed a model of a membrane whose pore diameters are being distributed according to Gamma Distribution with a small number of larger pores having a normal distribution.

The analysis suggests that almost any large pore component of the distribution has a significant effect on rejection. Essentially, the analysis suggests that a pore size distribution devoid of pores as large or larger than the particle to be removed is needed. At the same time, there is a product particle that must pass through the pore if the membrane is to have any utility. Thus, a fine balance must be arrived at between the pore size required to pass the product and the pores size that may allow contaminant to pass. Obviously, a monodispersed pore size 'distribution' would be ideal.

Thermal Inversion Phase Separation (TIPS) in its initial instantaneous spinodal decomposition necessarily results in a liquid-liquid phase separation that is practically monodispersed. In simple terms, as spinodal decomposition takes place, phase separation takes place simultaneously everywhere, thus there is no reason for any of the phase boundaries in one location to be different from another. The distribution widens over time due to coarsening or 'ripening', as nascent individual phase boundaries combine to form larger volumes. The challenge is to keep this distribution from widening by coarsening or ripening. Interesting approaches taking advantage of this phenomenon (Lloyd et. al) show promise in reaching close to monodispersed distribution and will be described.

Another recent development is “High Performance Tangential Flow Filtration” – HPTFF (van Reis and Zydney 1999). While in typical UF membrane operation the selectivity is due to size only, in HPTFF a charge effect is superimposed on the size effect: The UF membrane surface is modified by charged species, and optimization of pH, solute charge and membrane charge, as well as flow and pressure conditions, result in superior performance.

References:

1. H. Bechhold, Biochem. Z., **6**, 379 (1907)
2. R. Zsigismondi, E. Wilke-Doerenfurt, and A. von Galecky, Chem. Ber. **45**, 570 (1912)
3. W. Elford, Proc. Roy. Soc. London, Ser., B **106,** 216 (1930)
4. S. Loeb and S. Sourirajan, UCLA Report 60 – 60 (1960)
5. D. deWinter, US Patent 4,261,834 (1981)
6. J. Henis et. al, US Patent 4,230,463 (1980)
7. A. DiLeo and A. Allegrezza, Nature 30 May 1991 issue
8. S. Sternberg and D. Boggs, Presented at NIST – ATP, San Jose, 1999
9. H. Matsuyama, S. Berghmans, and D.R. Lloyd, "Formation of Anisotropic Membrane Structures via TIPS." *Polymer*, 40, 2289–2301 (1999).
10. H. Matsuyama, S. Berghmans, M.T. Batarseh, and D.R. Lloyd, "Formation of Anisotropic and Asymmetric Membranes via Thermally Induced Phase Separation." ACS Symposium Series #744, 23–41 (2000).
11. P.M. Atkinson and D.R. Lloyd, "Anisotropic Flat Sheet Membrane Formation via TIPS. I. Thermal Effects." *J. Membr. Sci.*, **171**, 1–18 (2000).
12. P.M. Atkinson and D.R. Lloyd, "Anisotropic Flat Sheet Membrane Formation via TIPS. II. Forced Convection and Molecular Weight Effects." *J. Membr. Sci.*, **175**, 225–238 (2000).
13. H. Matsuyama, M. Yuasa, Y. Kitamura, M. Teramoto, and D.R. Lloyd, "Structure control of anisotropic and asymmetric polypropylene membrane prepared by thermally induced phase separation." *J. Membr. Sci.*, **179**, 91–100 (2000).
14. van Reis R, Zydney AL: “Protein Ultrafiltration” , Encyclopedia of Bioprocess Technology: Fermentation, Biocatalysis and Bioseparation. Edited by Flickinger MC, Drew SW. John Wiley & Sons; 1999:2197-2214