Separation Science and Technology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713708471

Separation and Fractionation of Macromolecular Solutions by Ultrafiltration

M. Abdul Mazid[ab]
[a] INRAD INDUSTRIAL RESEARCH & DEVELOPMENT LTD. WINNIPEG, MANITOBA, CANADA [b] Chembiomed Ltd., Edmonton Research Park, Edmonton, Alberta, Canada

To cite this Article Mazid, M. Abdul(1988) 'Separation and Fractionation of Macromolecular Solutions by Ultrafiltration', Separation Science and Technology, 23: 14, 2191 — 2210
To link to this Article: DOI: 10.1080/01496398808058450
URL: http://dx.doi.org/10.1080/01496398808058450

SEPARATION SCIENCE AND TECHNOLOGY, 23(14 & 15), pp. 2191-2210, 1988

REVIEW

Separation and Fractionation of Macromolecular Solutions by Ultrafiltration

M. ABDUL MAZID*

INRAD INDUSTRIAL RESEARCH & DEVELOPMENT LTD.
WINNIPEG, MANITOBA, CANADA R3A 0W5

Abstract

The present state-of-the-art of membrane ultrafiltration with reference to macromolecular fractionations is reviewed. Ultrafiltration is now a widely used technique, both in the laboratory and industrial applications, which stems from the development of asymmetric membranes followed by the recognition of the importance of fluid mechanical and mass transfer processes and their management through equipment design and fluid-flow practices. However, large-scale fractionation of macromolecular mixtures or solutions such as proteins has not yet been feasible. This inability is attributable to a number of factors, viz., concentration polarization and fouling processes which may also be coupled with limitations imposed by nonuniform pore size as well as protein-protein (solute) interactions, the latter being determined by the solution chemistry. It is now well recognized that boundary-layer and interfacial effects, in general, are extremely important in membrane applications, as evidenced by a number of manifestations. Several models have been put forward to explain the effects of concentration polarization, whereas membrane-fouling owing to solute-membrane interactions and membrane pore-obstruction or secondary membrane formation via macrosolute deposition, thus causing major changes in effective pore size distribution and therefore effecting inevitable changes in membrane characteristics, have hardly been considered in detail in ultrafiltration transport modeling. Nevertheless, the recognition of the importance of surface and colloid chemical phenomena in governing membrane performance has focused attention upon techniques of membrane modification and feed solution properties control as the key to ultrafiltration applications. These are particularly important for macro-

*Present address: Chembiomed Ltd., Edmonton Research Park, P. O. Box 8050, Edmonton, Alberta, Canada T6H 4N9.

molecular fractionations which depend upon a reasonably clear understanding of the mechanisms of the various processes and which emerge from a good deal of basic or fundamental research.

INTRODUCTION

Ultrafiltration is a widely used technique that utilizes synthetic membranes for concentrating dilute protein solutions and separating proteins from low molecular weight solutes, such as salts, or from much larger particles, such as cells. The earliest applications of ultrafiltration were in the laboratory where small-scale separations and/or concentrations of biologicals were essential for research or clinical studies. A large number of laboratory-scale and industrial applications of ultrafiltration have now been examined, and it is estimated that the industry has grown to a worldwide market of $50 million/year of which about 75% is in industrial separations and the rest is in laboratory applications (*1*).

The important industrial applications of ultrafiltration have been in the areas of pollution control and in the recovery of valuable by-products. One of the most important applications to date is the recovery of paint in the electrophoretic painting process (*2*, *3*) and from the anionic electrocoat paint dispersions used in the automobile industry. Ultrafiltration is also used extensively to break oil–water emulsions common to machining and metal-finishing operations (*4–8*). It has been applied on a significant scale to the recovery of polymer latex wastes and sizing agents used in fabric finishing (*9*, *10*). Ultrafiltration has been examined as a pretreatment for reverse osmosis units, especially in seawater desalting operations (*11*), and for organic uses (*12*).

The state-of-the-art of membrane applications, including ultrafiltration, to the rapidly growing field of biotechnology, in general, has been reviewed and the opportunity areas for "fruitful union" of these two disciplines have been discussed by Michaels (*13*). These include macrosolute fractionation by ultrafiltration, removal of cells from fermentation broths, membrane-moderated immobilized enzyme/cell bioreactors, etc. A major emerging application for industrial ultrafiltration is in the separation and concentration of foods, pharmaceuticals, and biologicals (*14–16*). Here, ultrafiltration competes successfully with other separation and dewatering processes since it can be carried out at room temperature and without phase change such that sensitive biologicals like enzymes are not denatured.

Yet another area of large-scale application is the separation of proteins and enzymes from much larger particles such as cells. This is particularly

important during the production of intracellular materials such as bacterial enzymes which involves initial cell disruption followed by the removal of cell debris before further purification can be effected. Until recently, high-speed centrifugation was the only viable option available to the biochemical process engineer, but for a number of years cross-flow microfiltration has been used for the concentration of bacterial cells and particulate suspensions. However, attempts at the fractionation of macromolecular mixtures such as proteins by the use of membranes have met with repeated failure due to pore-fouling (*17*) and other reasons which we will discuss in this article.

VARIOUS MEMBRANE SEPARATION PROCESSES

In the membrane literature the terms microfiltration, ultrafiltration, and hyperfiltration are frequently used to describe various membrane processes. It is important to note that there is hardly anything unique about these terms which are coined by the different prefixes to -filtration and that the differences are trivial rather than essential. All of these processes utilize synthetic polymeric or nonbiological membranes which of course differ in their average pore size and pore size distribution, and operate under somewhat different process conditions. As a matter of fact, what we now call microfiltration, ultrafiltration, and reverse osmosis (sometimes termed hyperfiltration) were all known some 50 years ago by the generic name ultrafiltration, and even today the lines of demarcation are not clearly defined (*1*) or rather cannot be defined. Some workers proposed the molecular/particle size classification which, although arbitrary, seems to be generally accepted at present. Thus, according to Porter (*18*), the size of the smallest molecule or particle retained by reverse osmosis, ultrafiltration, and microfiltration membranes falls within the ranges of 1–10 Å, 10–200 Å, and 200–100,000 Å (0.02–10 μm), respectively. Correlations between the so-called molecular-weight-cut-off and the membrane pore size has been proposed (*19*); however, converting molecular size to molecular weight is not straightforward, particularly in the case of macromolecules for which, owing to their flexibility, molecular shape is a very important factor. As a rough guideline, it has been suggested that reverse osmosis membranes retain species with MWs generally greater than about 300 or less, ultrafiltration membranes retain species in the MW range of 300–300,000, and microfiltration membranes retain species larger than about 300,000, in each case the molecular-weight-cut-off being dependent on the particular membrane as well as the solution chemistry.

DEVELOPMENT OF ULTRAFILTRATION MEMBRANES

A good deal of research on ultrafiltration was carried out during the first half of this century, but the ultimate commercialization which began in the mid-1960s was an evolutionary consequence of the discovery of the asymmetric cellulose acetate reverse osmosis membrane by Loeb and Sourirajan (*20*) in the late 1950s. These membranes have the characteristic skinned structure, typically of the order of microns skin thickness, and are made by what is now generally known as the phase-inversion method. According to this technique, a casting solution prepared by dissolving a polymer in a good solvent, frequently with the addition of one or more cosolvents or nonsolvents, is used to draw a film on a clean surface under controlled conditions and is followed by quenching or gelling in a nonsolvent (usually water) bath and, optionally, annealing in water. The unannealed Loeb-Sourirajan-type membranes were found to be reasonably good for ultrafiltration, and the incorporation of additives into the casting solution gave much more porous structures which in essence made a range of molecular-weight-cut-off membranes commercially available. The early commercial ultrafiltration devices utilized these cellulose acetate membranes, but with the passage of time membranes have been developed that are increasingly resistant to solvents, pH and temperature extremes, and oxidizing cleaning agents such as chlorine. Ultrafiltration membranes have now been prepared from a number of other polymers such as polycarbonates, polyamides, polysulfones, polyvinyl chloride, polyvinylidene fluoride, copolymers of acrylonitrile and vinyl chloride, polyacetals, polyacrylates, polyelectrolyte complexes, and crosslinked polyvinyl alcohol.

Ultrafiltration membranes made from polymers other than cellulose acetate also have the characteristic skinned structure but they differ from common asymmetric cellulose acetate membranes in certain aspects, the most pronounced difference being the occurrence of so-called fingers within the porous matrix of the noncellulosic asymmetric membranes. These fingers are drop-shaped cavities possessing a porous or nonporous inner skin, and may disturb or at least weaken the active skin layer of the corresponding asymmetric membranes, especially if they extend into the active layer (*21*). Nevertheless, phase inversion membranes may act as depth filters which can become easily plugged by macromolecules trapped irreversibly in the membrane structure simply due to their tortuous pore morphology. In addition, these membranes are completely unfit for a fractionation of components, the molecular weight and concentration of which are in the same order of magnitude, especially if the pore size distribution of the membrane is large.

It is to be noted that neither ultrafiltration nor microfiltration membranes, in general, have pores of sharply defined size. In fact, with the single exception of Nucleopore microfiltration membranes, all polymeric membranes have a spectrum of pore size and therefore do not exhibit a sharply defined molecular-weight-cut-off, the latter being ordinarily used to characterize these membranes. This method of characterization has its limitations since it depends necessarily on the reference solute as well as the conditions under which it is used, and at times can be quite misleading. However, a very narrow distribution of pore size is considered highly desirable for molecular fractionations, and it has been stated that fractionation of species differing in molecular weight by less than about an order of magnitude is rarely, if at all, achieved in ultrafiltration (*1*).

BOUNDARY-LAYER AND INTERFACIAL EFFECTS

It is now well recognized that in membrane applications boundary-layer and interfacial effects are exceedingly important. Two phenomena occur that can override the inherent ability of the asymmetric membrane and alter the intrinsic rejection characteristics of the membrane, thereby modifying its filtration characteristics. There is invariably the tendency for rejected solutes to accumulate near the membrane surface and for certain solutes to interact with the membrane to some extent. The first of these phenomena is generally termed concentration polarization, which essentially means an increase in the concentration of rejected species with decreasing distance from the membrane, while the latter relates specifically to the so-called fouling.

Concentration polarization is to be reckoned with in all membrane separation processes and is particularly troublesome in ultrafiltration, although to a lesser extent than the fouling problem because of the nature of the solutions being processed. It occurs almost instantaneously on initiation of ultrafiltration, and arises due to the slower rate of diffusion of macromolecular solutes back into the bulk of the solution than the rate of their convective transport with the solvent permeating through the membrane, resulting into what is frequently referred to as the formation of a gel layer. The solute polarization at the upstream side manifests itself by a considerable reduction in membrane hydraulic permeability (sometimes tenfold or greater) relative to the measured pure water permeation rate, along with a very marked negative dependence of permeability on the concentration of solutes being retained in the upstream fluid. The gel layer, which is capable of providing mechanical

resistance to solvent flux, can also increase the rejection of a second partially rejected solute, whose size is much larger than that of the solvent molecule, depending, however, on the properties of the macromolecular solute, viz., protein, under a given set of conditions such as solution pH, temperature, ionic composition, etc.

The interaction of solute molecules with the membrane, arising out of the interplay of interfacial forces, results in a more serious and further problem of membrane-fouling. The macromolecular solutes may adhere to the walls of the membrane pores, and therefore reduce the average pore size and pore size distribution. This can affect the membrane permeability quite markedly, as expected from the fourth-power dependence of flux on pore radius in the Poiseuille expression, which was used in the early modeling of flow-through porous membranes. More importantly, macromolecules may be deposited on the surface of the membrane which, in many cases, forms a layer that becomes the dominant resistance to flow through the membrane. Adherence of macromolecular solutes either into the membrane pores or deposition onto the membrane surface is a very common phenomenon, although not always fully understood, in ultrafiltration of proteinaceous and other macromolecular solutions. This phenomenon is generally known as membrane-fouling and is responsible for the steady decline of ultrafiltration flux over a long period of time. It can cause as much as 90% irreversible loss of flux within a period of days or weeks under certain circumstances. The slow and continuous decline of permeation flux is substantially independent of feed-solute concentration and upstream hydrodynamic conditions. The fouling process is also very unpredictable at times, and varies markedly in severity depending on membrane composition, the nature of retentates, and such other variables as solution pH, ionic strength, electrolyte composition, temperature, and operating pressure.

EXTENT OF MACROMOLECULAR ADSORPTION

The underlying reason behind the major problems in ultrafiltration has been linked to the irreversible binding of macromolecules such as proteins to the membrane in varying degrees. A very important practical consideration in ultrafiltration is therefore the ease with which the membranes can be cleaned or, in some applications, sterilized subsequent to the inevitable fouling. Following ultrafiltration of whey proteins, Lee and Merson (*22*) and Cheryan and Merin (*23*) observed protein layers of 0.5–1.0 μm thickness by electron microscopy. Ingham et al. (*24*)

measured protein binding which they referred to as multilayer adsorption. They found that adsorbate protein bulk concentrations between 0.001 and 0.01 mg/mL produced sufficient adsorption to reduce the permeate flux by 37%. This led to the obvious conclusion that, in ultrafiltration, almost all the practical range of bulk concentrations is sufficient to cause adsorption on the membrane and consequently reduce the flux quite significantly. Fane and coworkers also described bound protein as multilayer adsorption in the ultrafiltration of proteins with retentive (*25*) and partially permeable membranes (*26*). The amount of protein found on a PM30 membrane (retentive to BSA) after 8 h of usage with only 0.1% BSA was 50–60 μg/cm^2 of membrane area with the adsorbed deposits up to 0.6 μm thick, which is equivalent to about 80 monolayers. As the authors discussed, this may be due to adsorption, which refers strictly to an equilibrium process with partitioning of solute between the solution and the surface, and also due to the additional influence of convection-induced deposition.

Likewise, in studies of the ultrafiltration of protein solutions, Howell et al. (*27*) found that 68–88 μg of papain were adsorbed per cm^2 of a PM30 membrane, and that the protein molecules apparently adsorbed directly onto the surface of the membrane. The amount of direct adsorption, however, depends on the pore size of the membrane relative to the protein being ultrafiltered. Thus, if the protein molecule is larger than the pore, it will not permeate through the membrane, but in the initial pore size distribution few pores are likely to be larger than the protein molecule, so that some protein will pass through, at least initially. These larger pores are gradually closed up by the adsorbed protein and therefore penetration declines and eventually ceases. For a larger ratio of average pore size to that of the protein, the decline may be relatively slower, and for the largest ratio with the smallest protein there may not be any discernible decline in protein permeation. It is, however, possible that because of the establishment of adsorption equilibrium, the amount of protein initially passing through the membrane can be quite negligible, regardless of the relative size of the pores.

The distribution of the adsorbed protein between internal (pore) and external (surface) adsorption was considered somewhat in more detail by Fane et al. (*26*). These workers inferred that the adsorption was largely on the surface, mainly from the fact that chemical cleaning by detergents was reasonably effective, which points to the removal of surface deposit. They made an approximate estimate of the potential for adsorption within the pores (internal) in the asymmetric layer of the membrane. Assuming a skin thickness in the range of 0.2–1.0 μm, approximately cylindrical pores, and typical surface porosities, calculations showed that

a monolayer within the pores was roughly equivalent to 0.1–0.5 μg/cm^2 of the top surface. These values were found to be two or three orders of magnitude lower than the measured values of the amount of protein adsorbed. Therefore, the amount of protein adsorbed within the pores can be a minor fraction of the total quantity adsorbed; however, it can have a profound effect on membrane performance, as mentioned previously. Thus, flux histories with the partially permeable membranes showed a much steeper initial decline than with the retentive membranes, presumably because of the fact that partially permeable membranes are more susceptible to rapid loss of pore flow area due to plugging and internal adsorption.

MANIFESTATIONS OF SOLUTE-MEMBRANE INTERACTIONS

The importance of interfacial effects at the membrane-solution boundary in influencing ultrafiltration have been evidenced by a number of experimental observations. Notable among these are the striking differences in membrane fouling tendency by cationic as contrasted with anionic electrocoat paint dispersions. It has been found that flux decline is far more rapid with cationic dispersions when ultrafiltered through polysulfone or polyacrylic membranes. Another common observation is that serum plasma proteins have a far more depressing effect upon the hydraulic permeability of the more hydrophobic polysulfone membranes than upon the relatively hydrophilic polyion complex or cellulosic membranes. These observations appear to indicate the importance of coulombic forces and hydrophobic molecular interactions in governing ultrafiltration dynamics, as noted by Michaels (*28*).

Apart from the adverse effects on membrane hydraulic permeability, the membrane-solute interactions are frequently responsible for marked effects upon solute rejection characterstics of the membrane, and perhaps the most undesirable consequence is the inability to make effective use of the macromolecular fractionation capabilities of ultrafiltration membranes for the large-scale resolution of macromolecular mixtures. An excellent example of the latter is provided by the ultrafiltration of human blood serum where, in principle, it should be possible to pass serum albumin through a membrane that retains the larger gamma globulin and thus effects a separation or fractionation of the two important macromolecules. It has also been observed that during unsteady-state permeation of serum albumin solutions through asymmetric ultrafiltration membranes, which are normally regarded as albumin-retentive, the membranes are quite permeable to the protein upon their initial exposure

to albumin solutions but the albumin transport drops to exceedingly low values within minutes. In reality, however, the presence of even a relatively low concentration of gamma globulin increases the rejection of albumin to the extent that separation is rendered completely ineffective. This loss in fractionation capability or the selectivity of the membrane is still poorly understood, although it is attributable to a number of factors related to concentration polarization and fouling processes, such as partial membrane pore-obstruction or secondary membrane formation via macrosolute deposition. As a consequence, the potentially exciting utilization of membrane ultrafiltration processes for large-scale resolution of complex macromolecular solutions or mixtures which are currently being carried out by such techniques as gel permeation, adsorption or ion-exchange chromatography, selective precipitation, electrophoresis, or high-speed centrifugation remain unaffordable (*28*).

It is notable that certain macromolecular mixtures such as dextran, polyvinylpyrrolidone (*29*), and hydroxyethyl cellulose are amenable to fractionation by ultrafiltration. These are generally polydisperse mixtures of predominantly linear macromolecules of quite high hydrophilicity, and are well solvated and chain extended in aqueous solutions, with the exception of dextran which is a branched molecule with a random-coil configuration. The hydraulic permeability of most asymmetric ultrafiltration membranes to solutions of these polymers is sometimes equal to that measured for pure water. This verifies the low adsorptivity of these polymers to the membranes studied as well as the highly hydrated nature of the polarization layers which may be formed during ultrafiltration of these macromolecules. Indeed, it has been suggested that the absence of pore obstruction via solute adsorption, and the structural openness of the polarization layers, may account for the ability of ultrafiltration to separate mixtures of this type (*28*).

Another manifestation of the influence of solute–membrane interactions is the frequently observed effect of the presence of membrane-retained polyelectrolytes upon the permeation of ionic microsolutes under normal ultrafiltration conditions. The presence of such polyelectrolytes is usually accompanied by the development of significant microion rejection by a membrane which would normally display no such retention capacity. Also, in hyperfiltration or ultrafiltration of ionic solutes, the presence of impermeable ions sometimes induces an increase in permeability of permeable ions of a like charge, as reported recently by Hayashita et al. (*30*). These phenomena have been attributed to Donnan ion-exclusion or Donnan membrane effect by the polyelectrolyte polarization-layer formed on the upstream membrane surface. It may be noted that the same result would be observed if the polyelectrolyte molecules

were to adsorb on the upstream membrane surface or the walls of the membrane pores (*28*). The phenomena of Donnan ion-exclusion by adsorbed or pore-obstructing polyelectrolytes applied to porous supports has long been utilized in the so-called "dynamic membrane" reverse osmosis desalination concept, which, coupled with the later development of high-flux asymmetric ultrafiltration membranes, now provides the basis for a new and improved, low-energy-demand, and high-capacity water desalting process.

MEMBRANE PERFORMANCE AND ULTRAFILTRATION SYSTEMS

It is obvious from the above discussions that membrane performance depends substantially on a number of factors, viz., membrane properties, solution properties, polarization, and fouling phenomena, as well as the operating conditions (*31*). The chemical nature of the base polymer is undoubtedly one of the most important factor in determining membrane characteristics such as its permeability, but the latter also depends on the morphological structure of the membrane which in turn is greatly related to its preparation conditions. The morphological structure of a membrane essentially refers to its thickness and porosity (size, number, and distribution of pore size) of the skin layer and the porous sublayer.

Next, the transport through the pores of a membrane can be affected by interfacial forces at the membrane–solution interface as well as by possible interactions between the solute and the membrane. These interactions may concern attractive van der Waals forces or the formation of chemical bonds (*32*), in the absence of which the transport through the pores would depend on the driving force, i.e., the differential pressure across the membrane, and the relative size of the solute and the pores. Thus, the transport is governed by the operating pressure, the diffusion coefficients of the solute and the solvent molecules, and the number and distribution of pores. In addition, the solute can affect the membrane performance owing to its chemical and conformational stability, the latter being dependent on the thermodynamic characteristics of the solvent.

Another important factor in the use of ultrafiltration, especially for fractionating proteins, is related to the role of protein–protein interactions. For example, in a complex mixture such as human plasma, reversible interactions between different proteins can interfere with attempts to separate them by any method (*24*). In ultrafiltration, such interactions may lower the effective sieving coefficients (separation

factors) of the constituent proteins, while in some cases it might be feasible to exploit them by appropriate manipulation of solution conditions such as pH, temperature, ionic composition, etc., which in turn would affect the gel polarization or the boundary-layer phenomena.

The polarization problem encountered in ultrafiltration has been mitigated to some extent by relatively simple operating procedures which are based on years of engineering experience in conventional continuous particle-filtration practice. For example, it has been well recognized that permeation rates can be maintained at considerable levels for reasonably long periods by operating ultrafiltration membrane modules at relatively high feed flow rates (with or without recirculation), thereby maintaining high hydraulic shear rates at the membrane surface, by deliberately adding particulate solids to the feed-side to provide scouring action, and by operating under the lowest practicable transmembrane driving pressures. The importance of intermittent and periodic flushing of the upstream feed-channels and membrane surface with suitable cleaning solutions, sometimes containing enzymes or surfactants, to restore the losses in permeability attendent upon fouling, has also been well recognized and practised.

It can be noted that an appreciation of the boundary-layer and interfacial phenomena has had substantial influence on ultrafiltration systems and module design. In fact, the recognition of the importance of such phenomena and their management through equipment design and fluid flow practices allowed ultrafiltration to become an industrial process in the late 1960s. The advent of thin-channel devices, flat-plate or narrow tubular configurations which allow laminar flow conditions, and cross-flow systems in which the feed solution is rapidly recirculated over the membrane surface, thus providing high shear-rates, has considerably reduced some problem. Furthermore, the introduction of hollow-fiber membrane modules which can withstand negative pressure differences across the fiber wall, and thus permit the module to be operated in a "back-wash" mode or in the so-called "blocked-permeate/reverse-feed-flow" mode, has been particularly intriguing. However, it is generally accepted that in order to have finite fluxes, even with these engineered systems, one must tolerate a finite amount of concentration polarization, let alone membrane fouling. There are other basic designs of ultrafiltration equipments such as the open-tubular and spiral-wound modules, but in any processing, particularly with tubular and laminar thin-channel devices, the recirculation pumping costs constitute a significant fraction of operating expenses.

MECHANISTIC AND ANALYTICAL MODELS IN ULTRAFILTRATION

Of all the factors affecting the performance of a ultrafiltration system, it is now well recognized that membrane fouling and polarization phenomena play a paramount role in practice. As we have already discussed, these phenomena can completely modify or change the transport properties, viz., the flux and separation characteristics of the membrane. In discussing the negative aspects associated with concentration polarization, Mathiasson and Sivik (*33*) noted that the transmembrane fluxes in commercial plants are only 2–10% of the transmembrane flux for pure water, and that it is not always possible to explain the flux behavior as a consequence of concentration polarization only. Fouling is said to occur as well, and it is regarded as an accumulation of material on the surface of the membrane, sometimes as a result of irreversible adsorption that decreases the permeate flux.

Strictly speaking, concentration polarization is a reversible phenominon which does not involve forces between the macromolecules in the gel layer formed as a consequence. It is generally affectd by the fluid mechanical and the mass transfer conditions under which the ultrafiltration process is carried out. The influence of fluidodynamic conditions was evaluated by means of several models. The first model proposed to explain the effects of polarization in ultrafiltration was the "gel polarization" model, originally put forward by Michaels (*34*) and later developed by Blatt et al. (*35*) and Porter (*36*). The fundamental assumption of this model is that beyond a certain value of applied pressure, the membrane permeation rate is limited by the presence of a gel layer deposited on the membrane. This increase the effective membrane thickness and therefore reduces the hydraulic permeability. The mass transfer occuring in the polarization layer is also decreased, which can be explained by the low diffusion coefficients of the macromolecular solutes.

Another assumption, implicit in the classical gel polarization model, is that the osmotic pressures of macromolecular solutions are negligible. As pointed out by Goldsmith (*37*), this assumption is not correct since concentrated solutions of macromolecules, as found in gel polarization layers, have osmotic pressures (*38*, *39*) which can be of the same order of magnitude as the applied pressures generally used in ultrafiltration. Therefore, the question arises as to what extent the limitation of the permeation rate in ultrafiltration can be explained by osmotic effects. Several authors have presented models with more or less wholly osmotic limitations to flux (*40–42*), while it is also evident that a certain degree of pore blocking is inevitable in ultrafiltration (*27*). The relationship

between ultrafiltration flux decline and protein adsorption has been examined by Suki et al. (*43*), whereas Ingham and Busby (*44*) were able to distinguish the permeate flux drop caused by protein adsorption (below 0.01 mg/mL) from that caused by gel formation (above 0.1 mg/mL) while continuously adding albumin to feed solution.

A great deal of experimental work on polarization in ultrafiltration has consisted of comparing overall permeate fluxes with the values given by model calculations. The acceptability of the gel polarization theory has been substantiated by the success with which it has been applied to the analysis of flux versus concentration data. Howell et al. (*27*) criticized that the effect of polarization on the sieving (separation) properties of the membrane should not be ignored and that predictions about the unsteady-state flux behavior have been speculative since they do not stem from the transient solution of the solute conservation equation at the membrane surface. These workers presented a model which differs from the gel polarization theory in that it ascribes the rapid flux drop over the first minute to convective gel deposition from a wall concentration while the concentration profile is still in the unsteady state (*27*). During this initial period all the gel is assumed to form, and the later slower flux decline is ascribed to hardening of the gel.

More recently, Clifton et al. (*45*) studied the growth of the polarization layer in ultrafiltration with hollow-fiber membranes by measuring the local permeation rates under conditions in which osmotic effects are likely to predominate. Synthetic polymeric solutes were chosen particularly because they are not easily denatured or precipitated, thus making it possible to avoid the time-dependent fluxes observed with membrane-fouling solutes. However, as the authors pointed out, the relevance of the work to industrial situations, in which some degree of fouling is inevitable, will have to be decided by further experimental work with model solutes similar to those actually found in the feed solutions treated industrially (*45*).

There is now a consistent body of experimental results from which some logical mechanistic deductions can be drawn, especially about polarization, but our present state of knowledge, particularly about the fouling phenomena, still remains quite rudimentary. The explanation of the instantaneous flux-loss on macrosolute ultrafiltration by classical fluid mechanical and mass transfer theory of the polarization process vis-á-vis gel-film polarization model has been valid only under limited conditions of sufficiently low permeation flux, sufficiently high mass transfer rates in the upstream fluid channel, and adequately low macrosolute concentration in the solution. According to Michaels (*28*), the inconsistencies of the classical polarization model can be reconciled,

in a qualitative sense, by postulating that membrane fouling is a hybrid process of particle filtration and classical polarization, the former mechanism dominating the events occurring in a zone very close to the upstream membrane surface while the latter dominates events taking place at a greater distance from the membrane. Thus, specific interactions between the ultrafiltered macromolecules and the surface of the underlying membrane, changes in macromolecular configuration or conformational change due to adsorption, or short-range forces of interaction between macromolecules can all have a marked effect upon the morphology of the "concentrated macromolecular cake" which accumulates on the membrane surface. These interactions, in turn, can have a major influence upon the hydraulic resistance to solvent flow through the membrane and, in addition, can cause major changes in the effective pore size and pore size distribution of the initial membrane, with inevitable alteration in the solute rejection properties of the membrane. Obviously, the surface chemistry and colloid chemical phenomena which markedly influence solute/membrane and solute/solute interactions may prove to be far more consequential in determining the dynamics of solute and solvent transport through ultrafiltration membranes than has heretofore been suggested (*28*).

The importance of surface and colloidal phenomena in influencing ultrafiltration has been evidenced earlier by several experimental observations. The essential link between flux decline and protein deposited (bound) onto the membrane during ultrafiltration has been examined by Suki et al. (*43*). A semiempirical relationship, including the deposition kinetics and the deposited layer resistance, was found to give reasonable prediction of the observed flux decline. However, the various interactions causing major changes in the effective pore size and pore size distribution of the initial membrane, with consequent changes in membrane characteristics, have hardly been treated in ultrafiltration transport modeling. So far the only treatment which deals with these aspects is that described by the generalized surface force-pore flow model developed by Matsuura and Sourirajan (*46*). In this approach the surface forces acting on the solute are expressed by an electrostatic or a Lennard-Jones type of potential function, and the solute and solvent transport through the membrane under the influence of such forces are expressed through appropriate mass transport equations for an individual cylindrical pore having an average radius and an average effective pore length. The analytical expressions were derived in detail, and it has been illustrated that the experimental reverse osmosis data are well predicted by the surface force-pore flow model which allows characterization and specification of a membrane precisely in terms of an average

pore size and its distribution along wtih a quantitative measure of surface forces. The same treatment applies equally well for transport through ultrafiltration membranes, as reviewed recently for reverse osmosis membranes *(47)*.

DIRECTIONS IN ULTRAFILTRATION RESEARCH

It is important to note that the establishment of the actual mechanism in ultrafiltration may be crucial to future developments, especially for macromolecular fractionations. Thus, as Michaels (*28*) points out with respect to the separation of a mixture of serum proteins by ultrafiltration, if the hypothesis is correct that polarization at the upstream membrane surface by a film of concentrated macromolecules such as globulin, whose pore structure is too fine to permit the passage of the smaller albumin molecule, then no obvious modification in either membrane properties or process operating conditions are likely to mitigate the problem. On the other hand, if the loss of albumin/globulin separative capacity is related to the preferential or strong adsorption of globulin and/or albumin molecule onto or within the pores of the membrane, thereby reducing the membrane hydraulic-permeability as well as blocking the passage of either the larger or the smaller solute molecule, then suitable surface treatment or chemical modification of the membrane to reduce or eliminate macrosolute adsorption should markedly increase the separation efficiency for macromolecular mixtures.

There is a great interest in membrane plasmapheresis, especially in blood purification, and significant progress has been made in this area. The mass transfer performance of a number of available plasma filters as well as some secondary filters used in cascade filtration has been evaluated recently (*48*). It has been noted that the filters for cascade filtration vary widely in performance and still require further development for optimal use. However, the recognition of the importance of surface chemical and colloidal phenomena in membrane fouling has focused attention upon techniques of membrane modification and feed solution properties-control as the key factors in improving ultrafiltration process performance and economics. There is evidence that techniques for altering the hydrophilicity and/or electrostatic charge of ultrafiltration membranes, either by preparing membranes from polymer blends or block copolymers having hydrophilic or ionogenic components, or by posttreatment of membranes by chemical means to introduce ionic groups, may provide the solution to irreversible membrane-fouling or at least produce membranes with improved resistance to macrosolute and colloidal fouling (*28*). Yet another approach to the solution of the fouling

problem is the pretreatment of membranes with selected water-soluble polymer solutions to form highly hydrated and high hydraulic permeability surface films which would prevent further adsorption or adhesion of fouling macromolecules or colloidal particles onto the membrane. Finally, there is the awareness of the importance of solution-composition variables such as pH, ionic strength, and the presence of such water-miscible organic solvents as alcohol in low concentrations upon the state of aggregation, conformation, and charge of macromolecules in solution. These could be effectively used in reducing membrane obstruction by adsorption and increasing the water and solute permeability of polarization layers by rendering such layers more open structured, larger pored, and less cohesive (*28*).

There is little or no doubt that macromolecular adsorption, internal and/or external, is the primary and the most important reason behind membrane fouling. Unfortunately, this problem has no unique solution and, unlike the concentration polarization phenomena, equipment design and fluid-flow practices are far from adequate for any significant improvement. It would certainly be desirable to have a membrane material available which has little affinity for the proteins or macromolecules concerned, and one that can also be fabricated into thin porous sheets capable of withstanding varying degrees of mechanical stress. Such a material should preferably be hydrophilic and bear very little or no net charge, but these are quite challenging criteria for the membrane chemists. Additionally, membranes are to be made with appropriate pores and as narrow a pore-size distribution as possible, which are particularly important for any fractionation applications.

An alternative approach to the problem as a whole, perhaps a compromise between the availability of an "ideal" polymer and the resulting membrane modification, would be to saturate the binding sites on suitable membranes with an appropriate reagent such as a protein and then evaluate the permeability and flow characteristics with respect to the desired application. It has been indicated by Le et al. (*17*) that since membrane fouling by most proteins is unavoidable, and that a limited fractionating capability could still be achieved by incorporating a membrane of suitable structure as allowance for the fouling layer. Thus, the polymeric membrane would effectively provide a support structure on which a secondary membrane of protein could be established. For instance, ovalbumin can form a secondary or dynamic membrane (*49*) which would almost completely cause the rejection of other ovalbumin molecules. Under ideal conditions, such a membrane should not attract further adsorption since it is composed of the same material as the solute being transmitted. In practice, however, the fouling process can prevail

indefinitely due to the random process of protein denaturation. Also, the formation of a secondary membrane on the surface would not necessarily prevent internal adsorption, which may cause even more severe fouling. Our recent work (*50*) along these lines has shown that these problems can be avoided to some extent provided the selected protein or macromolecule is appropriately immobilized onto the membrane in a controlled manner such that the resulting membrane performance is reproducible and predictable. Thus, it would appear that a marriage of membrane formation with suitably chosen or modified materials and protein or macromolecular immobilization by appropriate techniques to impart specific surface and pore characteristics may provide a practical solution to irreversible membrane-fouling in ultrafiltration, and therefore allow macromolecular fractionation. It is to be noted that, since the preparation and submission of this article, some papers have appeared (*51*, *52*) which indeed confirm and support ideas consistent with the above work (*50*).

CONCLUSIONS

Although the development of asymmetric membranes followed by the recognition of the importance of fluid mechanical and mass transfer processes and their management through equipment design and fluid-flow practices allowed ultrafiltration to become an industrial process in the late 1960s, the fractionation of macromolecular mixtures or solutions such as proteins by utilizing commercially available membranes and optimizing process operating conditions has not yet been satisfactory. It is now well recognized that ultrafiltration is not a mere sieving process, and that the existence of (solute) protein adsorption, solute–membrane interaction, and protein–protein interactions must be minimized or controlled to improve and maintain the protein yield. However, despite the recognition of various problems associated with large-scale ultrafiltration applications, progress in macromolecular fractionations by this technique remains frustrating. This is obviously a reflection of the nature of the problems involved, which must take cognizance of all the basic principles and cannot depend on experience in fluid-flow practices alone for any solution. It is the interdisciplinary nature of the problems which require not only a successful exploitation of fluid-mechanical and mass transfer processes but also of surface and colloidal phenomena.

A proper choice of the membrane characteristics, which include the material and pore morphology, would seem to be prerequisites to any practical application. A thorough understanding of the physicochemical

mechanisms by which polymeric networks and incipient pores are formed during membrane casting, membrane modification by post-treatment, together with a considerable degree of knowledge of the physical chemistry of macromolecular solutions, particularly biological, are essential for any meaningful development of fractionation processes. A rational attack and consequent solution(s) to the problems depend upon a reasonably clear understanding of the molecular events or microscopic features of the processes involved. These will emerge from a good deal of basic research which should eventually lead to the development of practical membranes made of appropriate materials and with appropriate pore sizes and distributions, and also with specific surface characteristics, whose performance will be predictable from an analysis of some basic experimental data.

REFERENCES

1. H. K. Lonsdale, "The Growth of Membrane Technology," *J. Membr. Sci., 10,* 81-181 (1982).
2. F. Forbes, "Ultrafine Filtration of Electrophoretic Painting," *Prod. Finish., 23,* 24-29 (1970).
3. J. Zahka and L. Mir, *Ultrafiltration of Cathodic Electrodeposition Paints—Seven Years of Field Experience,* Association for Finishing Processes of the Society of Manufacturing Engineers, Technical Paper FC79-684, 1979.
4. W. Eykamp, *Ultrafiltration of Aqueous Dispersions,* Paper Presented at the 79th National Meeting of the American Institute of Chemical Engineers, Houston, Texas, March 18, 1975.
5. L. Mir, W. Eykamp, and R. L. Goldsmith, "Current and Developing Applications for Ultrafiltration," *Ind. Water Eng.,* pp. 14-19 (May/June 1977).
6. S. D. Pinto, "Ultrafiltration for Dewatering of Waste Emulsified Oils," in *Lubrication Challenges in Metalworking and Processing, Proceedings of the First International Conference, June 7-9, 1978,* ITT Research Institute, Chicago, Illinois, pp. 1-4.
7. J. R. Wahl, T. C. Hayes, M. H. Kleper, and S. D. Pinto, "Ultrafiltration for Today's Oily Wastewaters: A Survey of Current Ultrafiltration Systems," in *Proceedings of the Industrial Waste Conference,* Ann Arbor Science Publishers, Ann Arbor, Michigan, 1979.
8. Product Bulletin, *Ultrafiltration for Oily Wastewater Treatment,* Abcor Inc., Wilmington, Massachusetts.
9. J. Zahka and L. Mir, "Ultrafiltration of Latex Emulsions," *Chem. Eng. Prog.,* pp. 53-55 (1977).
10. D. Kirjassoff, S. D. Pinto, and C. Hoffman, "Ultrafiltration of Waste Latex Solutions," *Ibid.,* pp. 58-61 (1980).
11. B. Kilcullen, *Evaluation of Hollow Fiber Ultrafiltration as a Pretreatment for Reverse Osmosis Desalination of Seawater,* Paper Presented at the Office of Water Research and Technology Membrane Symposium, Wrightsville Beach, North Carolina, November 17-19, 1980.

12. A. Iawama and Y. Kazuse, "New Polyimide Ultrafiltration Membranes for Organic Use," *J. Membr. Sci., 11,* 297–309 (1982).
13. A. S. Michaels, "Membrane Technology and Biotechnology," *Desalination, 35,* 329–351 (1980).
14. S. E. Charm and C. J. Lai, "Comparison of Ultrafiltration Systems for Concentration of Biologicals," *Biotechnol. Bioeng., 13,* 185–202 (1971).
15. M. C. Porter, "Applications of Membranes to Enzyme Isolation and Purification," *Biotechnol. Bioeng. Symp., 3,* 115–144 (1972).
16. M. C. Porter and L. Nelson, "Ultrafiltration in the Chemical, Food Processing, Pharmaceutical and Medical Industries," *Recent Dev. Sep. Sci., 2,* 227 (1972).
17. M. S. Le, L. B. Spark, and P. S. Ward, "The Separation of Aryl Acylamidase by Cross-Flow Microfiltration and the Significance of Enzyme/Cell Debris Interaction," *J. Membr. Sci., 21,* 219–232 (1984).
18. M. C. Porter, "Selecting the Right Membrane," *Chem. Eng. Prog., 71,* 55 (1975).
19. M. N. Sarbolouki, "A General Diagram for Estimating Pore Size of Ultrafiltration and Reverse Osmosis Membranes," *Sep. Sci. Technol., 17,* 381–386 (1982).
20. S. Loeb and S. Sourirajan, "Sea Water Demineralization by Means of an Osmotic Membrane," *Adv. Chem. Ser., 38,* 117 (1962).
21. W. Pusch and A. Walch, "Synthetic Membranes: State of the Art," *Desalination, 35,* 5–20 (1980).
22. D. N. Lee and R. L. Merson, "Examination of Cottage Cheese Whey by Scanning Electron Microscopy: Relationship to Membrane Fouling During Ultrafiltration," *J. Dairy Sci., 58,* 1423 (1975).
23. M. Cheryan and U. Merin, "A Study of the Fouling Phenomena during Ultrafiltration of Cottage Cheese Whey," in *Ultrafiltration Membranes and Applications* (A. R. Cooper, ed.), Plenum, New York, 1980, pp. 619–629.
24. K. C. Ingham, T. F. Busby, Y. Sahlestrom, and F. Castino, "Sepration of Macromolecules by Ultrafiltration: Influence of Protein Adsorption, Protein–Protein Interaction, and Concentration Polarization," in *Ultrafiltration Membranes and Applications* (A. R. Cooper, ed.), Plenum, New York, 1980, pp. 141–158.
25. A. G. Fane, C. J. D. Fell, and A. Suki, "The Effect of pH and Ionic Environment on the Ultrafiltration of Protein Solutions with Retentive Membranes," *J. Membr. Sci., 16,* 195–210 (1983).
26. A. G. Fane, C. J. D. Fell, and A. G. Waters, "Ultrafiltration of Protein Solutions through Permeable Membranes—The Effect of Adsorption and Solution Environment," *Ibid., 16,* 211–224 (1983).
27. J. A. Howell, O. Velicangil, M. S. Le, and A. L. H. Zeppelin, "Ultrafiltration of Protein Solutions," *Ann. N. Y. Acad. Sci., 369,* 355–366 (1981).
28. A. S. Michaels, "Fifteen Years of Ultrafiltration: Problems and Future Promises of an Adolescent Technology," in *Ultrafiltration Membranes and Applications* (A. R. Cooper, ed.), Plenum, New York, 1980, pp. 1–19.
29. R. W. Baker, "Methods of Fractionating Polymers by Ultrafiltration," *J. Appl. Polym. Sci., 13,* 369–376 (1969).
30. T. Hayashita, M. Takagi, and K. Ueno, "Donnan Membrane Effect-Aided Separation of Metal Cyanide Complexes by Hyperfiltration through Cellulose Acetate Membranes," *Sep. Sci. Technol., 19,* 375–388 (1984).
31. A. Bottino, G. Capannelli, A. Imperato, and S. Munari, "Ultrafiltration of Hydrosoluble Polymers: Effect of Operating Conditions on the Performance of the Membrane," *J. Membr. Sci., 21,* 247–267 (1984).
32. K. Chan, T. Matsuura, and S. Sourirajan, "Interfacial Forces, Average Pore Size and

Pore Size Distribution of Ultrafiltration Membranes," *Ind. Eng. Chem., Prod. Res. Dev., 21,* 605-612 (1982).
33. E. Mathiasson and B. Sivik, "Concentration Polarization and Fouling," *Desalination, 35,* 59-103 (1980).
34. A. S. Michaels, "New Separation Technique for the CPI," *Chem. Eng. Progr., 64,* 31 (1968).
35. W. F. Blatt, A. David, A. S. Michaels, and L. Nelson, "Solute Polarization and Cake Formation in Membrane Ultrafiltration: Causes, Consequences and Control Technique," in *Membrane Science and Technology* (J. Flinn, ed.), Plenum, New York, 1970, pp. 47-97.
36. M. C. Porter, "Concentration Polarization with Membrane Ultrafiltration," *Ind. Eng. Chem., Prod. Res. Dev., 11,* 234 (1972).
37. R. L. Goldsmith, "Macromolecular Ultrafiltration with Microporous Membranes," *Ind. Eng. Chem., Fundam., 10,* 113 (1971).
38. P. J. Flory, *Principles of Polymer Chemistry,* Cornell University Press, Ithaca, New York, 1953.
39. C. Tanford, *Physical Chemistry of Macromolecules,* Wiley, New York, 1961.
40. D. R. Trettin and M. R. Doshi, "Pressure-Independent Ultrafiltration—Is It Gel Limited or Osmotic-Pressure Limited," in *Synthetic Membranes, Vol. II, Hyper- and Ultrafiltration Uses* (A. F. Turbak, ed.), American Chemical Society, Washington, D.C., 1981, p. 373.
41. M. Wales, "Pressure Drop accross Polarization Layers in Ultrafiltration," in *Synthetic Membranes, Vol. I, Desalination* (A. F. Turbak, ed.), American Chemical Society, Washington, D.C., 1981, p. 159.
42. V. L. Vilker, C. K. Colton, and K. A. Smith, "Concentration Polarization in Protein Ultrafiltration," *AIChE J., 27,* 632 (1981).
43. A. Suki, A. G. Fane, and C. J. D. Fell, "Flux Decline in Protein Ultrafiltration," *J. Membr. Sci., 21,* 269-283 (1984).
44. T. F. Busby and K. C. Ingham, "Separation of Macromolecules by Ultrafiltration: Removal of Polyethylene Glycol from Human Albumin," *J. Biochem. Biophys. Methods, 2,* 191-206 (1980).
45. M. J. Clifton, N. Abidine, P. Aptel, and V. Sanchez, "Growth of the Polarization Layer in Ultrafiltration with Hollow-Fiber Membranes," *J. Membr. Sci., 21,* 233-246 (1984).
46. T. Matsuura and S. Sourirajan, "Reverse Osmosis Transport through Capillary Pores under the Influence of Surface Forces," *Ind. Eng. Chem., Process Des. Dev., 20,* 273-282 (1981).
47. M. A. Mazid, "Mechanisms of Transport through Reverse Osmosis Membranes," *Sep. Sci. Technol., 19,* 357-373 (1984).
48. H. J. Gurland, M. J. Lysaght, W. Samtleben, and B. Schmidt, "Comparative Evaluation of Filters Used in Membrane Plasmapheresis," *Nephron, 36,* 173-182 (1984).
49. S. Kimura, T. Ohtani, and A. Watanabe, "Nature of Dynamically Formed Ultrafiltration Membranes," *ACS Symp. Ser., 281,* 35-46 (1985).
50. M. A. Mazid, Unpublished Results (1985).
51. U. B. Sleytr and M. Sara, "Ultrafiltration Membranes with Uniform Pores from Crystalline Bacterial Cell Envelope Layers," *Appl. Microbiol. Biotechnol., 25,* 83-90 (1986).
52. M. Sara and U. B. Sleytr, "Production and Characteristics of Ultrafiltration Membranes with Uniform Pores from Two-Dimensional Arrays of Proteins," *J. Membr. Sci., 33,* 27-49 (1987).

Received by editor October 5, 1987