Membrane Processes

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Membrane processes have changed, from laboratory applications to industrial utilizations, through significant technical advances. This article discusses the fundamental principles of various membrane separation processes and conditions for their application in the pharmaceutical industry.

Separation, concentration and purification of chemical species existing in gas and liquid mixtures have always represented a relevant matter to chemical and pharmaceutical industries. In the last few years, a series of processes using semi-permeable membranes has been added to the conventional techniques used for separation, such as crystallization, extraction by solvents and distillation. Today, such processes are, in some cases, complementary to traditional techniques, while in other cases they are absolutely competitive. In fact, very often, membrane process techniques are quicker, more efficient and overall more economical. In addition, since they normally operate at ambient temperatures, they present relevant advantages in particular processes typical of chemical and pharmaceutical industries. For example, problems may arise during distillation if substances to be separated form azeotropes, or when feeding or if products obtained from distillation are thermally labile. In all those cases, special attention must be given (addition of a third component, vacuum distillations, etc.)

In case a gas mixture must be separated in its compounds, under ordinary conditions of temperature and pressure, it would be necessary, for example, to perform distillation at a temperature lower than ambient temperature. In this case distillation will require additional energy consumption.

The greater the difference between the requested temperatures and pressures versus ambiental conditions, the higher the energy consumption. Frequently, energy problems will arise in addition to crystallization processes when starting from very diluted solutions. These examples represent the same high number of potential applications of separation processes obtained by membrane.

In the pharmaceutical industry the greatest advantage of this process is the possibility of performing operations such as concentration and/or distillation without negatively affecting treated substances. Below are three examples of such industrial applications: Pectinase concentration, Amyloglycosidose purification, and Cefalosporins concentration. Industrial equipment for purification/concentration of substances contained in fermentation water has been operating for a few years; therefore, there are still limitations in the recovery of organic compounds from synthesis processes mainly due to the bad resistance of materials (membrane/module) in organic solvent processes. However, it safely can be said that membrane processes are out of the experimental phase, since they have shown to be effective, reliable and economical when dealing with watery solutions.

Main Principles of Membrane Processes

Membranes are defined as any barrier between two phases, which limits the transportation of various chemical species in a specific way. A membrane can be homogeneous or heterogeneous, porous or compact, symmetrical or asymmetrical, neutral or ionic. As a general rule, the force causing transportation of a chemical species through a membrane is the gradient of its chemical potential between the two faces of the same membrane. Such gradient includes various terms

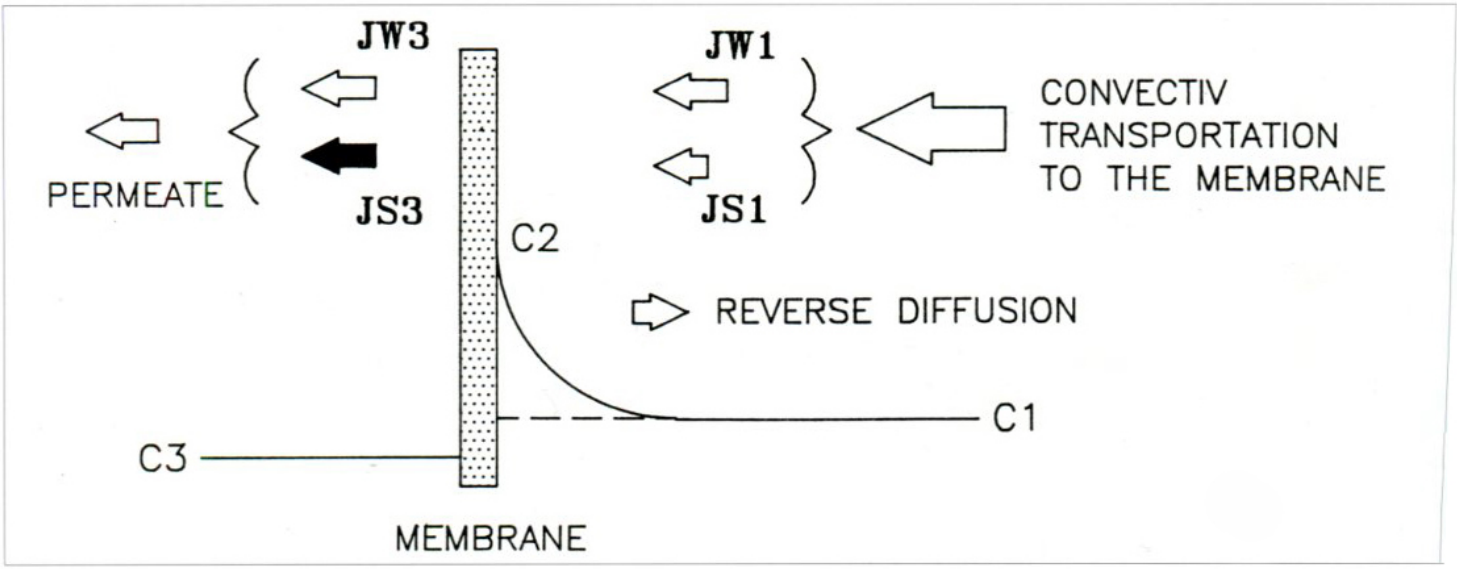


Figure 1. Concentration profiles. (JW1: solvent flow to the membrane; JS1: Solute flow to the membrane; JW3: Solvent flow through the membrane; JS3: Solute flow through the membrane.

Flow	Force	Relation	Constant of Proportionality
Mass (Jm)	Difference in Concentration (Δc)	Fick's Law $Jm = - D \Delta c$	Diffusivity (D)
Electrical Charge (I)	Difference in Electric Potential (ΔE)	Ohm's Law $I = \Delta E / R$	Resistance (R)
Heat (Q)	Difference in Temperature (ΔT)	Fourier's Law $Q = Kt\ \Delta T$	Thermal Conductivity (Kt)
Volume (V)	Difference in Pressure (ΔP)	Poiseuille-Hagen's Law $V = hd\ \Delta P$	Hydrodynamic Permeability (hd)

Table A. Phenomena relations between flows and corresponding forces.

Process	Motive Power	Membrane	Mechanical Transportation	Permeate
Micro-Filtration	Difference in Pressure (0.1/1 bar)	Porous (0.1/100µm)	Mechanical Filtration	Solvent
Ultra-Filtration	Difference in Pressure (1/5 bar)	Porous (1/10µm)	Mechanical Filtration	Solvent
Inverse Osmosis	Difference in Pressure (20/100 bar)	Asymmetrical Type Loeb-Sourirajan	Dissolution Diffusion	Solvent
Pervaporation	Difference in Concentration	Homogeneous	Dissolution Diffusion	Steam, Gases
Dialisis	Difference in Concentration	Porous (0.1/10µm)	Diffusion	Solvent+Salts and Micro-Solution
Gas Separation	Difference in Pressure	Homogeneous	Dissolution Diffusion	Gas
Electro-Dialisis	Difference in Electrical Potential	Ion-Exchange Membranes	Electrical Transportation	Ions

Table B. Membrane processes characteristics.

"One of the main problems relating to membrane processes is the polarization of the concentration phenomena..."

relative to gradients of pressure, concentration and electrical potential. In the most common cases, transportation induced by one of these terms prevails over the others. For this reason, the mass transfer phenomenon can be described with good approximation from a single relation of proportionality between the mass flow and the gradient of the motive-power prevailing in the process. Relations of phenomenon between flows and related forces are reported in Table A. The global factor of proportionality between flows through a membrane and process motive-posers are called permeability or permeation coefficients. Correlation between these values and the above mentioned coefficients depends on the global characteristics of the examined system, on the chemical and physical structures of the membrane and involved phases, on hydrodynamical factors and on the kind of mechanism by which transportation happens.

One of the main problems relating to membrane processes is the polarization of the concentration phenomena, which is the limit strata formation on membrane surfaces. Using selective transportation, the storage of the detained spores remains on one side of the membrane, while there is a depletion on the other side. Concentration profiles created are reported in Figure 1.

The following is obtained from the mass balance of Figure 1.

$$Jv = Kv \frac{C2 - C3}{C1 - C3}$$

where:

Kv = flow
C1 = solute concentration in feeding
C2 = solute concentration on membrane
C3 = solute concentration in the permeate
K = limit stratum thickness.

Definition of the membrane rejection:

$$R = 1 - C3/C2$$

Combining the equations we have:

$$C2/C1 = \frac{EXP\ (Jv/K)}{R + (1-R)\ EXP\ (Jv/K)}$$

where:

C2/C1 is the polarization of concentration module.

Area of Application	Micro-Filtration	Ultra-Filtration	Inverse Osmosis	Electro-Dialysis
Drinkable Industrial H_2O	Production of Ultrapure H_2O for the Electronic Industry	Production of Ultrapure H_2O for the Electronic Industry	Desalting of Sea H_2O	Desalting of Sea H_2O
			Hardness Removal for Boiler H_2O	Softening of Processed H_2O
	Particle Removal (Virus, Bacteria etc.) from Processed H_2O	Production of Sterile and Pyrogen Free H_2O	Sterilization and Deionization of H_2O for Chemical and Pharmaceutical Industry	
Separation in the Chemical and Pharmaceutical Industry	Sterile Filtration and Clarification	Sterile Filtration and Clarification	Concentration of Aminoacids, Alkaloids etc. in the Pharmaceutical Industry	Demineralization of Pharmaceutical Solutions
	Removal of Particular Virus, Bacteria	Concentration and Purification of Hormones, Enzymes, etc. from Pharmaceutical Solutions	Concentration of Components by Low Molecular Weight in the Chemical Industry	
	Sterile Filtration of Intra-venous Solutions			

Table C. Specific industrial applications of membrane processes.

The formation of this limit stratum negatively affects the separation process. Polarization of concentration can be controlled only by reducing the limit stratum thickness, or increasing the turbulence of the feeding solution.

In case of asymmetrical membranes, limit strata can be found inside the porous structure. These gradients of concentration can be controlled only acting on the porous stratum structure. There is no advantage to having modifications in the feeding hydrodynamics or in the permeate. Tables B and C are summaries of membrane processes' characteristics and specific industrial applications.

Classifications

A useful classification of the various processes is based on the kind of membrane used. A distinction can be made among processes using microporous membranes, homogeneous membranes, asymmetrical membranes and ionic exchange membranes.

Microporous Membranes

Microporous membranes consist of a solid matrix (counterfoil-plate) with some pores whose diameter varies between 20 and 50 µm. However, they are characterized more by the fact that the selective transportation of the mass happens with a simple mechanism of filtration and the dimensions of the particles to be separated than by the dimension of the pores. In the manufacturing of microporous membranes a large variety of materials is used, such as metallic ossides, metals, graphite, polymers, etc.

Microfiltration and ultrafiltration are the main processes using microporous membranes. The term microfiltration is referred to the case in which there is a separation of particles, whose diameter is between 0.1 and 10 µm, from the solvent or from other components with a low molecular weight; pressures vary between 0.1 and 2 bars. Ultrafiltration is when components to be separated are real molecules or particles whose diameter does not exceed 0.1 µm; pressures are around 1-5 bars.

The recent set-up of microporous membranes allows engineering to develop ultrafiltration processes to treat suspensions through filtration techniques with tangential flow. In this procedure, either the solid phase or the liquid phase are removed continuously from the membrane surface, avoiding accumulation phenomena that could stop the process. The

Type of Membrane	Hollow Fiber	Hollow Fiber	Flat	Spiral Wound	Spiral Wound	Hollow Fiber
Polimer Nature	Cellulose Triacetate	Aromatic Asymmetrical Polyamide	Cellulose Acetate Modified	Composite	Cellulose Acetate Modified	Cellulose Triacetate
Fiber Diameter (Micron)	250	85	100 (thickness)	-----	100 (thickness)	225
Membrane Permeability	High	Low	High	High	High	High
Salt Rejection	>90%	90%	96%	98.5%	97%	>90%
pH Field	4/7.5	4/11	4/7.5	2/11	4/7.5	3/7.5
Resistance to Free C12 (ppm)	1	0	1	0	1	1
Working Pressure (bar)	28	28	30	55	30	30
Module Production at Standard Conditions (lt/hrs)	3060	2200	756	600	760	3300
External Wrapper	Fiberglass & Epoxy Resin	Fiberglass & Epoxy Resin	Fiberglass & Epoxy Resin or Painted Steel	Stainless Steel or Fiberglass	Stainless Steel or Fiberglass	Fiberglass

Table D. Commercial membrane characteristics.

same process, if based on the use of membrane for ultrafiltration, will lead to the separation of the high molecular weight solutes from the low molecular weight solutes which are both in the permeate. The process is used more and more today in purification of antibiotics after fermentation. In the clarified and apirogenic permeate, the antibiotic free of any macromolecular species and insoluble species could be further clarified and concentrated.

Homogeneous Membranes

A homogeneous membrane is a dense film through which there is the passage of various chemical species caused by a gradient of pressure or concentration. The transportation mechanism is the so-called mechanism of dissolution-diffusion, for which there is a dissolution of a chemical species in the film, its following diffusion in the membrane and finally its de-absorption on the opposite side. The main processes using homogeneous membranes are: osmosis, inverse osmosis, pervaporation and gas separation. Presently the process of inverse osmosis is probably the most widely used amongst all membrane techniques. The introduction of asymmetrical membranes has optimized its results and extended its application to industrial waste-water treatment, to the food industry, to the production of extra pure water for the electronic and pharmaceutical industry, in addition to its traditional use which is to desalt water.

Asymmetrical Membranes

An important step toward the industrial application of membrane techniques is the introduction of asymmetrical membranes, which combine the characteristics of homogeneous and microporous membranes. The membranes are made of a

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very thin polymer stratum (0.1 ≠ 2 μm) supported by a thick, very porous stratum (100 ≠ 200 μm). As flows through a membrane are inversely proportional to the non-porous stratum thickness, the results are much higher than those which can be obtained with thick homogeneous membranes without causing excessive losses of selectivity. The porous stratum in addition has not only the function of a mechanical support but it also allows a reduction of problems relating to membranes obstruction, which are typical of ultrafiltration and inverse osmosis processes. Membranes of this kind can be composite membranes or membranes made for phase inversion.

Ion-Exchange Membranes

Ion-exchange membranes have microporous structures in which the pore walls have fixed positive or negative charges. The selective properties of these membranes are the result of the nature of the existing fixed charges, to their specific concentration and to concentrations of ionic species existing in the surrounding solutions. A fixed positive charge membrane is called an ion-exchange membrane while a fixed negative charge membrane is called a cation-exchange membrane. The main application of ion-exchange membranes is electrodialysis, more specifically in desalting water. Such a process takes advantage of the gradient of electrical potentialities to separate ions of water solutions. Although electrodialysis is historically derived from dialysis, the two techniques have major differences. While dialysis takes advantage of a gradient of concentration, the direct reason the flow always goes towards the most diluted solution, in electrodialysis the transportation direction depends on the electrical field applied.

Membrane Modules

A fundamental requisite in membrane technology development is the construction of proper modules, able to satisfy needs (technical and economical) which are very often in direct contrast. As the various processes differ greatly from each other in principles, conditions and applications, so do the results differ from case to case. In general; however, a distinction can be made between at-stratum, tubular, spiral and hollow fiber modules.

In Table D the characteristics of commercial membranes are reported. Hollow fiber membrane modules can accumulate the maximum of active surface at equal volume. In such a case, the loss of concentrated load is very low. On the contrary, the fluodynamics of the concentrate seems to be causal, one reason for which fouling is very difficult to control and the washing is more difficult.

"...tubular membrane modules are usually placed inside a duct made of plastic."

Modules made of flat membranes (spiral wound) are the most manufactured, especially when using polymers. They are surely most suitable to the mathematical definition, as far as the concentrate fluodynamics is concerned; but at the same time they are the most difficult to manufacture. The active surface that can be obtained in a module is certainly inferior per unit of the module volume than that which can be obtained in the hollow fiber modules; the loss of load (even though it can be mathematically defined) is higher. However, the membrane washing is more difficult and the possibility of having points in which the concentrate stagnates is extremely reduced.

Finally, tubular membrane modules are usually placed inside a duct made of plastic. The permeate which goes through a membrane spreads on the supporting material and flows outside the duct made of plastic through the holes. Although this is the most used configuration, there are few cases in which the membrane is laid externally to the tube which gives mechanical support. In either case, the tubes are assembled by seven or eight in one module. The length of the tubular elements can be different: the longer the modules, the cheaper they are. The same goes for heat exchangers. It is easily understood that in cases where the solution flows internally to the tube, the flow dynamics are easier to control.

In fact, acting on the flow speed, the fooling can be affected and this type of module also can be used for cloudy solutions or with suspensions. The situation is continuously moving. In spiral wound modules, as in the tubular ones, mechanical modifications are being made to improve their reliability and to minimize the possibility of breaking between modules inter-connections and possibility of telescopic deformation, the last as far as spiral wound modules are concerned.

Conclusions

When preparing an industrial equipment project with membranes, technical and economical aspects must be considered. For every process, the system design is as important as the availability of proper membranes and modules. Low investments are required, as well as high specific surfaces of exchange, high flows and long lasting equipment. Moreover, in most cases prior treatments of the feeding fluid are necessary, such as pre-filtrations, flocculations, pH control, etc., so that in the overall system only a small fraction of the total cost can be attributed to the membranes. Therefore, even though having proper membranes necessary to solve a given separation problem, several engineering aspects must be considered, since they can considerably affect the convenience and efficiency of the same process.