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MEMBRANE SYSTEMS FOR PHARMACEUTICAL APPLICATIONS

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16.1 INTRODUCTION

Membrane separation technologies are being rapidly incorporated in a number of industries. There are a number of reasons: they are often cheaper, modular, athermal, and can achieve separations difficult to achieve otherwise. In specific industries, for example, desalination/water treatment they are becoming the dominant technology. In biopharmaceutical industry, the processes of dialysis for buffer adjustment, microfiltration for clarification, ultrafiltration, and membrane chromatography are widely used. An earlier brief review of applications of membrane technologies in pharmaceutical industry is available in Sirkar [1]. There have been, however, limited applications of membrane technologies in the pharmaceutical industry during active pharmaceutical ingredient (API) processing in the presence of organic solvents. The membrane technologies that are being used and/or explored in a more than cursory fashion in pharmaceutical processing are pervaporation and organic solvent nanofiltration. To that extent our focus in this chapter will be on pervaporation first and then on organic solvent nanofiltration. At the end, we will briefly focus on membrane solvent extraction.

16.2 PERVAPORATION IN THE PHARMACEUTICAL INDUSTRY

16.2.1 Introduction

Pervaporation is a process in which a feed liquid mixture at atmospheric or higher pressure is brought into contact with a membrane, which allows the selective removal of one or more components of the feed stream into a gaseous/vapor stream on the other side of the membrane (permeate side). Separation is achieved by maintaining a difference between the species partial pressure in equilibrium with the feed liquid and the permeate side partial pressure of the species in the feed to be removed. The partial pressure differential is commonly established by applying vacuum at the permeate side, flowing an inert gas or a combination of the above techniques. When the feed is a vapor stream the process is called vapor permeation. Some researchers treat the two processes as different. However, the operating principles and the membranes used in pervaporation or vapor permeation are similar and the two processes will be treated here as variations of the same technique.

The term pervaporation is a composite of the words permeation and evaporation. The evaporation heat required

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to transfer the permeating component(s) from the liquid phase in the feed to the vapor phase in the permeate side is supplied by the sensible heat of the feed stream. Separation in pervaporation processes is the outcome of a sequence of three steps [2]:

- Preferential sorption of one or more components into the feed side of the membrane.
- Selective diffusion through the membrane.
- Desorption to the vapor phase at the permeate side.

It is apparent that complex mass and heat transfer phenomena occur during pervaporation. The membrane acts in two ways: first, as a physical barrier between the liquid and vapor phases and second as an additional component in the system, which alters its thermodynamics and allows the separation of its components. The last point is significant in understanding why pervaporation has been successfully used to break azeotropes (i.e., ethanol–water), for which conventional distillation is unsuccessful. Separation efficiency in distillation is governed by the vapor–liquid equilibria (VLE) of the system, which for an azeotrope cannot change. In pervaporation, separation is driven by differences in solubility and diffusivity of the components in the feed stream through the membrane used.

Pervaporation has found industrial applications in various fields including the dehydration of organic solvents [3, 4], the separation of organic–organic mixtures [5–7], the concentration/extraction of aroma compounds from water solutions in the food industry [8], the removal of VOCs from aqueous waste streams [9], and the enhancement of reaction conversion/rate by removal of water during condensation or esterification reactions [10]. In the above applications, pervaporation is applied either as a standalone technique or in a hybrid process combined with distillation. When the feed stream contains chemicals harmful to the membrane or solids, which would foul the membrane and reduce performance, vapor permeation can be applied. In this case, the stream is evaporated via distillation and while at the vapor state is passed through the pervaporation module. Vapor permeation has found extensive application in distillation–pervaporation hybrid units [11].

16.2.2 Process Description and Theory

A schematic of the process is shown in Figure 16.1. A liquid feed containing components 1 and 2 is entering the membrane device at a temperature $T_{\mathrm{f,in}}$ and pressure $P_{\mathrm{f,in}}$. A reduced pressure P_{p} is applied at the permeate side of the membrane. The membrane preferentially permeates component 1 over 2. Under these conditions, component 1 permeates through the membrane and appears in the vapor phase on the permeate side. The net outcome is the removal of component 1 from the feed stream. The heat of evaporation for the permeating component(s) is supplied by the sensible heat of the feed. The latter is, therefore, cooled to a temperature $T_{\mathrm{f,out}}$ at the outlet of the membrane.

Figure 16.2 shows a schematic of the two operating configurations most commonly used in pervaporation applications. Both of them utilize a pump to circulate the feed solution through the membrane module and optionally a heat exchanger to preheat the feed stream to the appropriate temperature, although an effort is always made to use heat available from upstream processing to minimize operating costs. At the permeate side a condenser is available to collect the permeating species. The two configurations shown differ only in the way the driving force across the membrane is established: in Figure 16.2a a vacuum pump is used, while in Figure 16.2b a carrier gas is used to reduce the mole fraction y_i of the permeating species and hence its partial pressure.

The quality of the separation is commonly expressed in terms of the separation factor, α, which for a binary system of species 1 and 2 is given by

$$\alpha = \frac{y_1}{x_1}\frac{x_2}{y_2} \tag{16.1}$$

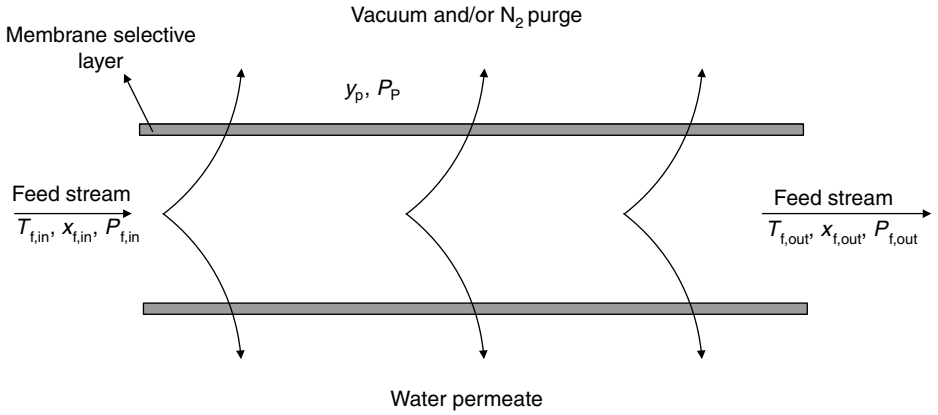

FIGURE 16.1 Operating principle of pervaporation.

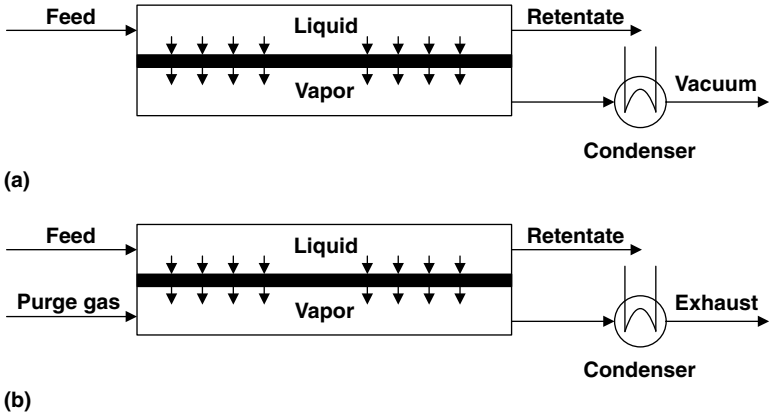

FIGURE 16.2 Schematic of different pervaporation operating schemes. (a) Vacuum on the permeate side and (b) inert carrier gas on the permeate side.

where y_i is the mole fraction of component i in the permeate, x_i is the mole fraction of component i in the feed stream.

The flux of component i through the membrane is given by the following expression:

$$J_i = \frac{Q_i}{l}\Delta p_i = \frac{Q_i}{l}(p_{i,\mathrm{f}} - p_{i,\mathrm{p}}) \tag{16.2}$$

where J_i is the flux of component i through the membrane, kg/(m^2 s); Q_i is the permeability of component i through the membrane, kg/(m s Pa); l is the effective membrane thickness, m; $p_{i,\mathrm{f}}$ is the partial pressure of component i in a gas stream in equilibrium with the feed liquid stream, Pa; $p_{i,\mathrm{p}}$ is the partial pressure of component i in the permeate, Pa.

The amount of component i that can be removed in time t from the feed stream is a function of the flux and the membrane area used to achieve the separation according to the following equation:

$$m_i = J_{i,\mathrm{ave}} A t \tag{16.3}$$

where m_i is the amount of component i removed, kg; A is the membrane surface area, m^2; t is the operating time, s; and an average value is used for the flux of component i to account for the fact that the flux declines as component i is removed from the feed stream to the permeate.

The permeability coefficient is dependent on the membrane material and varies with temperature and composition of the liquid feed stream. It is considered to be the product of the solubility and diffusivity of component i through the membrane

$$Q_i = S_i(T, C) D_i(T, C) \tag{16.4}$$

where S_i is the solubility of component i, kg/(m^3 Pa); D_i is the diffusivity of component i, m^2/s.

Although thermodynamic and transport models can be applied to calculate respectively the solubility and the diffusivity of a species through a membrane; in almost all practical applications, the permeability coefficient is estimated based on experimental data.

The partial pressure difference across the membrane is given by

$$\Delta p_i = x_i \gamma_i p_i^{\mathrm{sat}} - y_i P_{\mathrm{p}} \tag{16.5}$$

where γ_i is the activity coefficient of component i in the feed stream; p_i^{sat} is the vapor pressure of component i at the feed temperature, typically described by the Antoine equation.

Combining equations 16.2–16.5 a final expression for the flux of component i is obtained

$$J_i = \frac{S_i D_i}{l}\left(x_i \gamma_i p_i^{\mathrm{sat}} - y_i P_{\mathrm{p}}\right) \tag{16.6}$$

Equation 16.6 can provide an insight as to how the flux of the permeating species can be increased and hence the operation time needed to achieve a specified separation can be minimized. Four different cases and their combinations can be identified.

(a) *Increase the Permeability Coefficient*. Since the latter is dependent primarily on the membrane material, an increase of the flux can be achieved by selecting a membrane with a more open structure at the expense, however, of lower selectivity values. The allowable limits for this trade-off between flux and selectivity will generally depend on the intended application and can be decided by the process engineer during the process development stage.

(b) *Decrease the Effective Membrane Thickness*. This is also a membrane property, which has to be considered during the process development stage. Membranes with thin selective layers and open support layers to minimize diffusion limitations are the best choices.

(c) *Increase the Temperature of the Feed.* This action maximizes the vapor pressure of the permeating component and hence the partial pressure driving force across the membrane according to equation 16.5. Upper temperature limits are dictated by the boiling point of the liquid feed and the temperature stability of the active pharmaceutical ingredient. The second limitation is more severe in terms of process design. Boiling point limitations, which would result in cavitation of the feed pump and reduced process performance, can be partially overcome by pressurizing the feed. Such an action raises the boiling point according to the Clausius–Clayperon equation. This is the most effective and easy to implement modification to increase the flux of the permeating species due to the exponential dependence of vapor pressure on temperature.

(d) *Decrease the Partial Pressure of Component i in the Permeate Side*. This can be achieved by reducing the permeate's absolute pressure at the expense, however, of higher pumping costs. Alternatively, an inert gas can be pumped through the permeate side, which will reduce the mole fraction y_i to low levels. A combined approach, namely, starting by operating only the vacuum pump at the beginning of the process and then introducing a purge stream of an inert gas (i.e., N_2) toward the end of the process will be more effective since the partial pressure difference across the membrane is reduced throughout the process and becomes very small when most of the separation has been performed. This approach is similar to well established guidelines for conventional drying and is sometimes called the Combo Mode.

Equation 16.5 can be used to identify appropriate operating conditions with respect to the permeate pressure for a given separation. A positive flux and hence a separation is obtained if $\Delta p_i > 0$. For a given final concentration x_i in the feed stream, equation 16.7 then yields the maximum allowable operating pressure in the permeate side

$$P_{\mathrm{p,max}} = \frac{x_i \gamma_i p_i^{\mathrm{sat}}}{y_i} \tag{16.7}$$

Li et al. [12] used the above expression to calculate the permeate pressure for benzene dehydration at 70°C and select a vacuum pump appropriate for the desired levels of water removal. Such calculations require the estimation of the activity coefficient γ_i, which can be performed by group contribution or semi-empirical models such as UNIFAC and NRTL. Activity coefficient calculations are easy to perform for solvent–water systems but become more complicated for solvent–water–API/intermediate systems. The API or intermediate will alter the activity coefficient of water and will reduce or increase the water activity coefficient, depending on the nature of its interaction with water.

The flux of component i can also be expressed in terms of an overall mass transfer coefficient and concentrations

$$J_i = K_i(C_{i,\mathrm{f}} - C_{i,\mathrm{p}}) \tag{16.8}$$

where K_i is the overall mass transfer coefficient of component i through the membrane, m/s; $C_{i,\mathrm{f}}$ is the concentration of component i in the feed stream, kg/m^3; $C_{i,\mathrm{p}}$ is the concentration of component i in the permeate, kg/m^3.

The overall mass transfer coefficient can be expressed based on film theory as the sum of three resistances in series, feed side, membrane and permeate side:

$$\frac{1}{K_i} = \frac{1}{k_{i,\mathrm{f}}} + R_m + \frac{1}{k_{i,\mathrm{p}}} \tag{16.9}$$

where $k_{i,\mathrm{f}}$ is the mass transfer coefficient of component i at the feed side, m/s; R_m is the membrane mass transfer resistance, s/m; $k_{i,\mathrm{p}}$ is the mass transfer coefficient of component i at the feed side, m/s.

Equations 16.8 and 16.9 can be used to calculate fluxes based on film theory. In principle, mass transfer correlations can be used to calculate the feed and permeate side mass transfer coefficients with reasonable accuracy (see Ortiz et al. Ref. 13). Experimentation is needed to determine the membrane resistance. In practice, experimentation is performed and the overall coefficient is expressed as a function of the feed side mass transfer coefficient, since the membrane and permeate resistances are usually small compared to the feed side mass transfer resistance. The combined membrane and permeate resistance can then be obtained as the intercept in a Wilson plot [13].

The dependence of the flux of component i on temperature is usually expressed via an Arrhenius-type relationship [14]:

$$J = J_0 \exp\left(-\frac{E_{\mathrm{a}}}{RT}\right) \tag{16.10}$$

where E_{a} is the activation energy for permeation, J/mol; R is the universal gas constant, J/(mol K); T is the temperature, K.

The activation energy E_{a} in equation 16.10 is a compounded parameter accounting for the variation of permeation flux with both the membrane permeability and the permeation driving force Δp_i, as pointed out by Feng and Huang [14]. Both the preexponential term and the activation energy can be expressed as functions of temperature, feed, and permeate mole fractions of component i by curve fitting laboratory experimental data obtained for the intended application. These expressions can then be substituted in equation 16.10 and used to perform scale-up calculations, as detailed in Section 16.2.4.2 [15].

16.2.3 Pervaporation Membranes

The nature of the pharmaceutical industry poses certain limitations to the selection of membranes for manufacturing

TABLE 16.1 Commercially Available Inorganic Pervaporation Membranes

Membrane Type	Selective Layer	Support Layer	ID/OD (mm)	Selective Layer Location	Manufacturer
Zeolite	Zeolite (A-, T-, Y-)	Alumina	9/12	Outside of tube	Mitsui Engineering & Shipbuilding Ltd.
Ceramic	Amorphous silica	Alumina, Titania	8/14	Outside of tube	Sulzer Chemtech
Ceramic	Amorphous silica	Alumina, Titania	7/10	Inside of tube	Pervatech BV

API or intermediates. First, the membrane must be compatible with the pharmaceutical stream to be processed. The use of harsh solvents (i.e., DMF, THF) is still widespread in the industry, although a turn toward greener chemistry has been experienced in the last few years. In addition, many times the active ingredient will make the stream acidic or basic or it might increase the interaction between the stream and the membrane. The question of leachables into the pharmaceutical stream and its impact on the final drug substance (DS) quality must then be addressed appropriately. Membranes with increased chemical and thermal stability are preferable. A second characteristic of the pharmaceutical industry is the generally low production requirement compared to the chemical industry and the fact that only one in nine new chemical entities entering phase I clinical trials reaches commercialization [16]. Many times the intended application will have to be abandoned. Therefore, a membrane, which can be used for a variety of processes/streams, will be clearly preferable. Membranes tailored to a specific process would make sense only if the intended application enters commercial production. In summary, the three desirable characteristics for a pervaporation membrane in the pharmaceutical industry are the following:

1. Good chemical stability
2. Good thermal stability
3. Ability to handle a variety of streams and/or process conditions without significant loss in performance.

Three types of membranes are available for pervaporation: polymeric, inorganic, and mixed matrix* membranes [17]. Only the first two types of membranes are available commercially. Both of them are asymmetric membranes, namely, they consist of a porous support layer and a thin dense selective layer coated onto the support layer. The selective layer is the one in contact with the process stream and hence must have good chemical and thermal stability. It is also the layer that will start leaching first to the process stream.

* Mixed matrix membranes consist of a polymeric base membrane impregnated with inorganic material.

Commercial polymeric hydrophilic membranes have a polyvinyl alcohol (PVA) selective layer. Sulzer Chemtech is the leader in the industry with probably more than 90% of market share. Spiral wound or hollow fiber modules are available. PVA membranes can tolerate temperatures of up to about 90°C and mild to relatively strong acidic and basic conditions. Fluxes reported for typical dehydration applications (water < 10 wt%) range between 1 and 2 kg/(m^2 h) [17, 18]. PVA membranes have a proven track record in a number of industrial dehydration applications. Their operating temperature limitations as well as stability issues when exposed to certain organic solvents should be taken into consideration. The above limitations make it unlikely that PVA membranes could be used as a general tool for dehydration problems in the pharmaceutical industry. However, they can still be useful in specialized applications. Recently, polymeric membranes with a fluoropolymer selective skin have been developed by Compact Membrane Systems (DE, USA) [19]. The selective layer can withstand temperatures of up to 200°C and a variety of different chemical conditions. It seems that this membrane can satisfy the performance criteria listed above and potentially be very useful for applications in the pharmaceutical industry. However, a suitable substrate must be selected for high temperature applications to avoid membrane damage due to thermal stresses.

Inorganic membranes can overcome the temperature limitations of polymeric membranes; certain types of inorganic membranes are resistant to a variety of chemical conditions also. Table 16.1 summarizes the commercially available inorganic membranes for dehydration applications. Two types of inorganic membranes exist: zeolite and ceramic. Zeolite membranes exhibit excellent selectivity and good fluxes [20–23], but they can only be used for a limited pH range, between 6 and 8 [1, 21]. These properties make zeolite membranes an excellent choice for solvent dehydration; however, in most cases zeolite membranes will be not able to withstand the presence of an API or an intermediate. Microporous silica membranes on the other hand can tolerate a much broader pH range, which makes them ideal for the dehydration of most pharmaceutical streams. The membranes manufactured by Pervatech BV can tolerate a pH down to 2–3, as has been confirmed with an actual pharmaceutical stream [24]. Silica membranes exhibit inferior separation factors compared to zeolite membranes but their flux

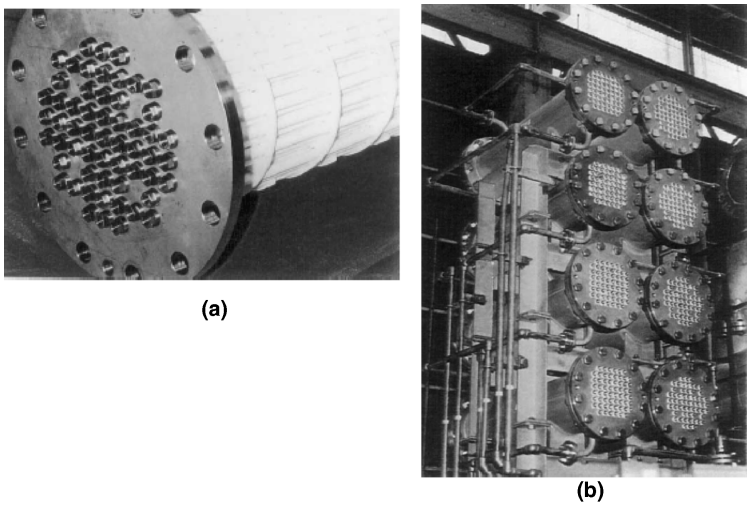

FIGURE 16.3 Zeolite NaA membranes from Mitsui Engineering & Shipbuilding Ltd. (a) Module configuration and (b) module layout (from Ref. 25, with permission).

is higher [20] and comparable if not better than polymeric membranes.

All commercially available inorganic membranes are of tubular geometry. Figures 16.3–16.5 show pictures of the membrane modules described in Table 16.1. The zeolite membrane modules from Mitsui have a typical shell-and-tube configuration [25]. The feed is introduced on the shell side and the baffles present force it to a path perpendicular to the tube length leading to higher feed side mass transfer coefficients. The permeate is collected in the tube side. The configuration of the Pervap® SMS module by Sulzer Chemtech is shown in Figure 16.4. The membrane tubes are placed inside the tubes of a heat exchanger to achieve isothermal operation and increase permeation rate. The feed flows in the annular space between the heat exchanger and the membrane tubes, while the permeate is collected inside the tubes. The membrane tubes can either be connected in series or in parallel. Both configurations yield acceptable pressure drops [26]. The modules by Pervatech BV have also a shell-and-tube configuration. They are made of 2 identical parts consisting of 54 tubes, 50 cm long, stacked one upon the other. The two parts are connected by a plate with machined channels connecting the individual tubes. The feed is introduced in the tube side and the permeate is collected at the shell side. The tubes are connected in series and the manufacturer recommends a linear velocity of 2 m/s through the tubes to minimize concentration polarization effects. This requirement results in a pressure drop of about 4 bar as measured for water by the manufacturer [27].

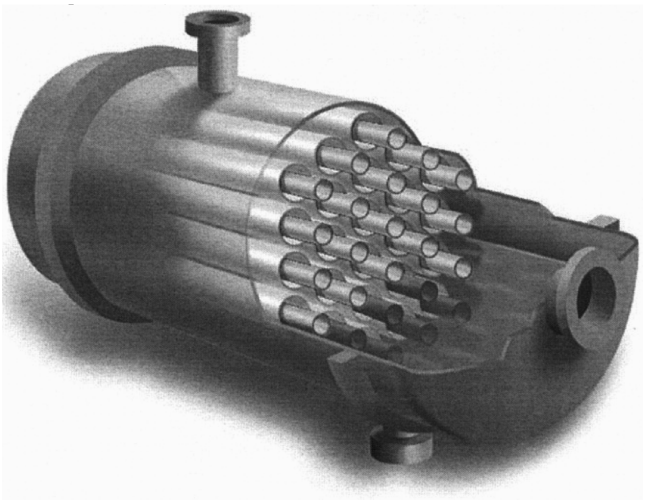

FIGURE 16.4 Pervap SMS silica membrane modules from Sulzer Chemtech (from Ref. 26, with permission).

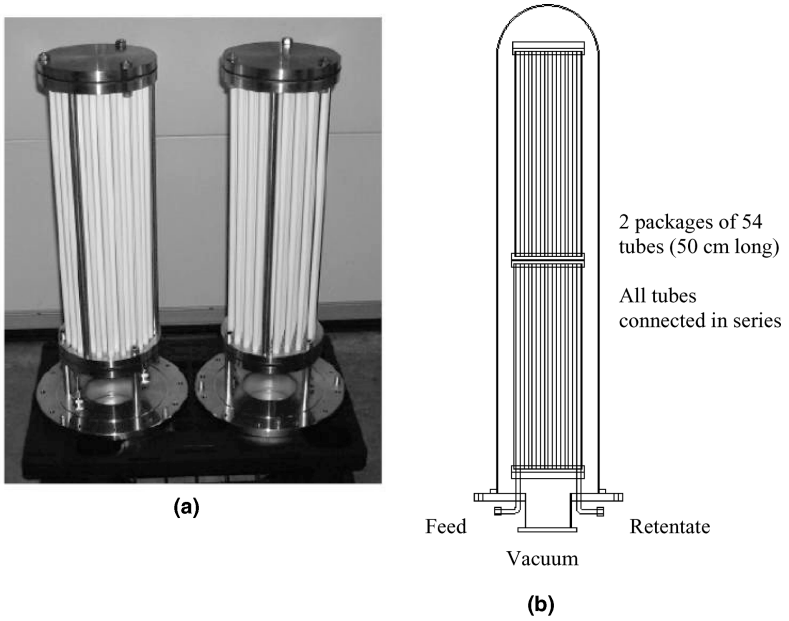

FIGURE 16.5 Silica membrane modules by Pervatech BV (a) Inner tube assembly and (b) module configuration.

16.2.4 Pervaporation Applications in the Pharmaceutical Industry

The majority of potential pervaporation applications in the pharmaceutical industry are related to dehydration of pharmaceutical streams. Pharmaceutical streams need to be dehydrated in the following cases:

1. *Removal of Moisture During Reactions*. Certain types of reactions, that is, esterification or condensation reactions, require the removal of water to increase conversion and yield. Such applications have already been demonstrated with nanofiltration membranes [28, 29]. In many cases, the presence of moisture is undesirable due to excess impurity formation and/or catalyst deactivation. The moisture can come from the API to be dissolved (hydrates or physically adsorbed water), the catalyst (in the form of adsorbed water) and/or the solvent itself.
2. *Removal of Moisture to Supersaturate Solutions in Crystallization Processes*. In many cases the solubility of pharmaceutical solids decreases with decreasing water content. If the nucleation kinetics is slow enough and a seeding step is envisioned for the process, these streams can be supersaturated by pervaporation and subsequently crystallized. Currently, batch distillation is used to achieve this goal.
3. *Dehydration of Waste Streams for Solvent Recovery*. These streams can originate from distillations or work-up procedures. Recovery of the solvent will make sense only in the case of large volume compounds and solvents with relatively high cost, for example, 2-MeTHF.

Another potential application of pervaporation is the removal of volatile organic compounds (VOCs) from pharmaceutical waste streams [30]. Since this application does not involve streams used in the production of an API, it will not be further explored here. The remainder of this section will explore in more detail the dehydration applications listed above.

16.2.4.1 Dehydration Applications of Pervaporation

This section will examine in more detail the work that has been performed up to now in the dehydration of organic solvents with ceramic membranes for two reasons. First, ceramic membranes are considered the most appropriate for applications in the pharmaceutical industry. Second, the work performed in pure solvents can serve as a basis for the design of applications with streams containing an API. The remainder of the section will focus on the operation modes that can be adopted in pharmaceutical manufacturing.

Dehydration in the pharmaceutical industry is primarily performed by distillation. Other means, for example, molecular sieves, can find only specialized applications and in many cases will not perform satisfactorily due to the presence of the pharmaceutical ingredient. The removal of water by azeotropic distillation can result in the intense use of solvents, even in the case where continuous** distillation is

** The term continuous is rather misleading; distillation is performed by continuously adding solvent and removing only distillate but not the batch, which is the heavy fraction.

used. One of the authors is aware of several examples where the removal of 100–200 kg of water requires the use of 2000–3000 L of solvent per batch. For an annual production of 20–50 batches, these numbers indicate that considerable savings in solvent cost as well as waste treatment costs can be achieved. The fiscal gains will increase with the cost of the solvent to be used. In addition to cost savings, pervaporation can lead to much greener solutions. In almost all cases, the cost savings from reduced solvent usage will be enough to repay the capital investment required to purchase the membrane modules.

Table 16.2 summarizes the results that have been obtained with commercial silica membranes during the dehydration of organic solvents by various researchers. Only solvents relevant to pharmaceutical applications are reported here; additional information can be found in the original references. The quoted fluxes can serve as a basis for initial design according to equation 16.3. A sample calculation is given in Example 16.1. As mentioned in Section 16.2.2, the presence of a pharmaceutical ingredient in the stream will alter its thermodynamics and especially the activity coefficient of water. According to equation 16.6, there will be an increase or decrease in the water flux depending on the nature of the interaction of the pharmaceutical ingredient with the rest of the stream components. The pressure required in the permeate side to effect a certain separation will also change accordingly. The presence of a pharmaceutical ingredient in a stream will also change its viscosity and hence the hydrodynamic conditions in the feed side. The latter can often negatively impact the flux through the membrane due to concentration polarization [26, 33]. Pervatech recommends a feed linear velocity of 2 m/s through the membrane to avoid concentration polarization [27]. From the above discussion, it follows that laboratory experimentation should be performed prior to scale-up to determine the actual flux and optimal operating conditions to adjust initial estimates of membrane surface area. As a rule of thumb, the flow should always be kept in the turbulent or at least in the transitional regime to avoid concentration polarization effects.

EXAMPLE 16.1

A pharmaceutical stream of 5000 L contains an API, 6 wt% water and ethyl acetate. Stability concerns dictate that the removal of water must be performed in 24 h. Calculate the membrane surface area that is needed for the separation. Rearrangement of equation 16.3 for membrane area

$$m_i = J_{i,\text{ave}} A t$$

results in the following

$$A = \frac{m_i}{J_{i,\text{ave}} t}$$

A water flux from ethyl acetate can be obtained from Table 16.2. Based on a value of 3.16 kg/(m^2 hr) and $t = 24$ h and substituting values yields a membrane area of 3.56 m^2.

TABLE 16.2 Results Obtained with Commercial Ceramic Membranes in the Dehydration of Organic Solvents

Solvent	Feed Water Content (wt%)	Operating Temperature (°C)	Water Flux (kg/(m^2 h))	Water in Permeate (wt%)	Separation Factor	Membrane	Reference
Methanol	10.4	60	1.87	58.84	10	Sulzer Chemtech[a)]	[20]
	10.5	60	0.39	71.69	20	Pervatech	
Ethanol	10.3	70	2.33	86.37	60	Sulzer Chemtech	[20]
	11.0	70	2.00	95.26	160	Pervatech	
IPA	4.5	80	1.86	98.10	1150	Sulzer Chemtech	[31]
	10.2	75	2.76	91.06	90	Sulzer Chemtech	[20]
	9.8	75	2.55	95.33	190	Pervatech	[20]
Acetone	10.0	70	0.52	>99.5	n/a	Sulzer Chemtech	[32]
	10	70	2.72	>99.5	n/a	Pervatech	[32]
Acetic acid	10.4	80	1.91	86.80	60	Sulzer Chemtech	[20]
Ethyl acetate	2.0	70	3.16	93.71	750	Sulzer Chemtech	[20]
THF	11.8	60	3.47	96.53	210	Sulzer Chemtech	[20]
	11.5	60	3.30	99.91	8400	Pervatech	
Acetonitrile	11.9	70	2.73	96.36	200	Sulzer Chemtech	[20]
	9.7	70	3.90	97.27	330	Pervatech	
DMF	10.2	80	1.53	92.28	100	Sulzer Chemtech	[20]
	9.1	80	1.14	92.19	120	Pervatech	

In the original text the membrane is quoted as ECN. This membrane has been commercialized by Sulzer Chemtech and is referenced by this name here.

$$A = \frac{m_i}{J_{i,\text{ave}}\, t} = \frac{(5000\,\text{L})(0.9\,\text{kg/L})(0.06\,\text{wt\%})}{(3.16\,\text{kg/(m}^2\,\text{h))(24\,\text{h})}}$$

$$= \frac{270\,\text{kg}}{75.84\,\text{kg/m}^2} = 3.56\,\text{m}^2$$

This will give an initial estimate of capital cost to purchase the membrane modules. Additional laboratory experimentation with the actual pharmaceutical stream should be performed to obtain a more accurate estimate of water flux and hence membrane surface area.

Figure 16.6 shows a schematic for a typical pervaporation setup in the pharmaceutical industry. This setup will be useful when the pharmaceutical stream contains no solids. The batch is recycled between the reactor and the pervaporation module by means of a pump. A heat exchanger can be optionally used to ensure that the feed inlet temperature is maintained at appropriate levels. Alternatively, the reactor can be pressurized and its temperature increased to levels that will compensate any heat losses taking place between the reactor and the pervaporation module. A typical cartridge filter is installed prior to the pervaporation module to minimize membrane fouling and potential flux decline with time. The permeate side of the membrane module is connected to a condenser and a vacuum pump. In most cases, it will be practical to use chilled water (available at a temperature of about 6°C) for the condenser; however, glycol or Sylltherm® condensers can also be used. It will usually be better to use a dedicated vacuum pump to ensure that the appropriate vacuum levels are maintained in the permeate side during operation. However, house vacuum can also be considered if the intended application does not require permeate pressures lower than 30–40 mmHg. An option to use a nitrogen purge stream is also depicted in Figure 16.6; its use can be decided based on laboratory process development. A portable skid arrangement for the setup depicted in Figure 16.6 will be preferable, since it gives the flexibility to use the unit in multiple applications. This is important in an industry where the majority of the products scaled up will not reach commercial scale production.

Figure 16.7 shows a typical setup for vapor permeation. This mode of operation will be useful when solids are present in the pharmaceutical stream (i.e., heterogeneous reactions, insoluble catalyst), which would foul the membrane and render it useless. This mode of operation is not as energy efficient as the one depicted in Figure 16.6; the heat of vaporization needs to be supplied to effect the separation. However, this is of relatively small concern for the pharmaceutical industry, whose end-products are of high value. The membrane module is positioned between the reactor and the condenser. Water is removed from the vapor phase and the rest of the vapor is condensed and returned as reflux to the reactor. Concentration polarization will be of smaller concern with this operation mode since the mass transfer resistance in the vapor phase will be considerably smaller compared to the liquid phase.

16.2.4.2 Process Modeling As Figures 16.6 and 16.7 illustrate, pervaporation processes in the pharmaceutical industry operate batchwise. During operation, part of the pharmaceutical stream is removed through the membrane and the stream mass decreases by the amount permeated. The temperature of the stream entering the membrane module in such applications can be considered constant, since it is regulated in the reactor containing the batch and the amount of stream present inside the module and the recirculation loop is small compared to the total batch volume. However, a temperature decrease is experienced inside the module, since the heat required for the removal of water is supplied by the sensible heat of the stream. Therefore, the temperature of the stream will vary with axial position inside the module. From the above discussion, it is apparent that both the mole fraction of the permeating species and the stream temperature are functions of the axial position inside the module.

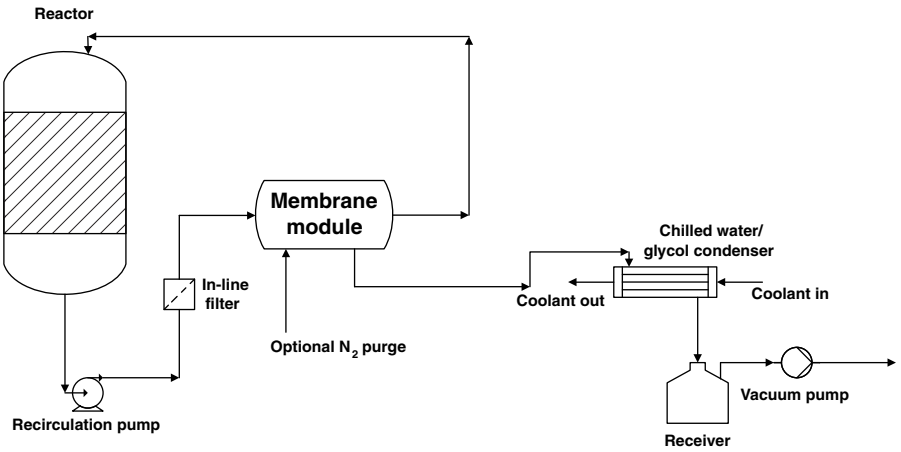

FIGURE 16.6 Typical pervaporation setup in the pharmaceutical industry.

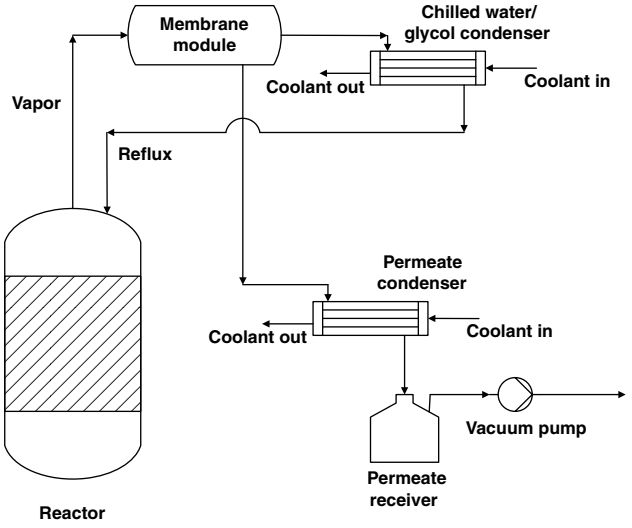

FIGURE 16.7 Typical vapor permeation setup in the pharmaceutical industry.

According to equations 16.6 and 16.10, the permeation flux also changes along the membrane module.

For a membrane module consisting of n tubes the following governing equations can be written [15]:

- *Overall system*
  Overall mass balance

$$dM = -J_t A_T dt \tag{16.11}$$

  Mass balance for water

$$d(Mx_F) = -J_t A_T y_M dt \tag{16.12}$$

  Combining equations 16.11 and 16.12, the following expression can be obtained

$$dx_F = \frac{(x_F - y_M) J_t A_T}{M} dt \tag{16.13}$$

- *Membrane module*
  Overall mass balance

$$dF = -Jn\pi D dz \tag{16.14}$$

  Mass balance for water

$$d(Fx) = -Jyn\pi D dz \tag{16.15}$$

  Energy balance

$$d(FH_f) = -J\Delta H_v n\pi D dz \tag{16.16}$$

  Equations 16.14 and 16.15 can be combined as follows

$$dx = \frac{(x-y)}{F} J n\pi D dz \tag{16.17}$$

  Equation 16.16 may be rewritten as

$$FC_p dT = -J\Delta H_v n\pi D dz \tag{16.18}$$

The following notations are used in the above equations: M is the mass of batch at time t, kg; J_t is the average flux through the membrane module for the time interval dt, kg/(m^2 s); A_T is the total membrane area, m^2; x_F is the water mole fraction in feed tank, dimensionless; y_M is the average water fraction in permeate for the time interval dt, dimensionless; F is the mass flow rate through membrane module at time t, kg/s; z is the axial displacement inside the membrane module from entrance, m; J is the local flux through a differential length dz of a membrane tube, kg/(m^2 s); D is the membrane tube diameter (inside or outside), m; H_f is the enthalpy of the stream entering the membrane module, J/kg; ΔH_v is the heat of vaporization of water, J/kg; C_p is the specific heat capacity of the stream entering the module, J/(kg K).

The model represented by equations 16.11, 16.13, 16.14, 16.17, and 16.18 neglects any heat losses due to vaporization of organic solvent. Its accuracy is not expected to deteriorate significantly due to this fact for the majority of organic solvents used with the exception of methanol, ethanol, and acetic acid, which as shown in Table 16.2 can permeate through the membrane to an appreciable extent. The system of equations 16.11, 16.13, 16.14, 16.17, and 16.18 can be solved by applying a finite difference scheme. Discretization is performed in both time and axial position inside the module domains. A prerequisite for this task is to have expressions of the flux J and the permeate water mole fraction as functions of feed water mole fraction and temperature

$$J = f(x, T) \tag{16.19}$$

$$y_M = g(x, T) \tag{16.20}$$

These expressions can only be obtained through laboratory experimentation. The latter should include permeation runs at different feed compositions and temperatures. Flux and permeate composition data will then need to be curve fitted against temperature and composition data. Equation 16.10 can be used for the flux, where the flux and/or activation energies are expressed as functions of feed composition; any expression for the water permeate fraction can be applied [15]. Based on the above discussion, the initial and boundary conditions to solve the following equations 16.11, 16.13, 16.14, 16.17 and 16.18 are as follows:

$$\begin{aligned} M(0) &= M_0 \\ x_F(0,0) &= x_0 \\ x_F(t,0) &= x_i \\ J(0,0) &= f(x_0, T_F) \\ J(t,0) &= f(x_i, T_F) \\ y(0,0) &= g(x_0, T_F) \\ y(t,0) &= g(x_i, T_F) \\ F(0,0) &= F(t,0) = F_0 \\ T(0,0) &= T(t,0) = T_F \end{aligned} \tag{16.21}$$

A simpler but less accurate model can be obtained if the variation of flux inside the module is neglected. In this case, only equations 16.11 and 16.13 need to be solved with the aid of equations 16.19 and 16.20. This is an initial value problem that can be solved by numerical integration (i.e., fourth order Runge–Kutta scheme). The initial conditions are summarized below

$$\begin{aligned} M(0) &= M_0 \\ x_F(0) &= x_0 \\ J(0) &= f(x_0, T_F) \\ y(0) &= g(x_0, T_F) \\ T_F &= \text{constant} \end{aligned} \tag{16.22}$$

This model will probably be adequate for scale-up calculations without the need to face the complexity of the more rigorous model presented previously. The approximation will be better for modules where the tubes are arranged in parallel. When tubes are connected in series the variation of composition and temperature along the tube length will be significant and the simple model will tend to overpredict the flux and hence underpredict batch-processing time.

16.3 ORGANIC SOLVENT NANOFILTRATION IN PHARMACEUTICAL INDUSTRY

The API solutes of interest in pharmaceutical synthesis vary in molecular weight between 200 and 1000 Da. Nanofiltration (NF) membranes originally developed for treatment of aqueous solutions are particularly suited for rejecting solutes in such a size range and passing water through [34]; the solute molecular weight range is said to vary between 150 and 1000 Da. Organic solvent nanofiltration (OSN) is directed toward achieving the same goal with organic solvents.

16.3.1 Process Description and Principles

In nanofiltration, the feed solution is brought under pressure of as much as ≥ 35 bar to one side of the membrane (Figure 16.8). The solvent flows through the membrane to the other side at a lower pressure, generally atmospheric, called the permeate side. The liquid collected is called the permeate. The membrane is supposed to prevent the transmission of solutes of MW $> 150\sim200$ Da. If $C_{i\text{p}}$ is the molar solute concentration in the permeate side, kgmol/m^3 and $C_{i\text{f}}$ is the molar solute concentration in the feed side, kgmol/m^3, then the extent of solute retention by the membrane is described by solute rejection, R_i,

$$R_i = 1 - \frac{C_{i\text{p}}}{C_{i\text{f}}} \tag{16.23}$$

If the NF membrane retains the solute completely, then $C_{i\text{p}} = 0$ and $R_i = 1$. There are a variety of membranes; some membranes will reject higher molecular weight solutes/species/catalysts in the range of 200–1000 Da but not in the lower molecular weight range. The molecular weight cut off (MWCO) of the membrane is defined to be the solute molecular weight which will yield a value of $R_i = 0.95$; a smaller molecular weight will pass through the membrane more readily and have a lower R_i. An additional quantity of great interest is the solvent flux through the membrane N_i in gmol/(cm^2 s). It is reported often as a volume flux J_v in L/(m^2 h) (LMH); typical values at, say, 30 bar and 30°C may be between 10 and 150 LMH.

There are two general models for species transport through organic solvent nanofiltration membranes: (1) solution–diffusion model and (2) pore–flow model. The molar flux expression J_i suggested [35] for solution–diffusion of a species through a nonswollen selective layer of the membrane (analogous to that for reverse osmosis by Wijmans and Baker [36]) is

$$J_i = Q_{i,m}\left[x_i - \frac{\gamma_{i\text{p}}}{\gamma_i} y_i \exp\left(-\frac{\overline{V}_i(P_\text{f} - P_\text{p})}{RT}\right)\right] \text{ mol/(m}^2\text{ h)} \tag{16.24}$$

where $Q_{i,m}$ is the membrane permeability, mol/(m^2 h); $\gamma_{i\text{p}}$ is the activity coefficient of component i in the permeate at pressure P_p; x_i is the mole fraction of component i in the feed; y_i is the mole fraction of component i in permeate; $\overline{V}_i$ is the partial molar volume of species i; P_f is the feed pressure, Pa; P_p is the permeate pressure, Pa.

According to this model, each component i gets dissolved in the membrane at the feed interface, then diffuses through the membrane and is desorbed at the other interface without any consideration of other species being transported through the membrane.

In the pore–flow model of transport for cylindrical pore models, the solvent flux (or volume flux) expression is

$$J_v = -\frac{\varepsilon d_{\text{pore}}^2}{32\mu\tau}\nabla P \text{ m}^3/(\text{m}^2\text{ s}) \tag{16.25}$$

where d_{pore} is the diameter of the pore, m; τ is the pore tortuosity dimensionless; μ is the viscosity of the solvent, kg/(m s); ε is the porosity of the microporous membrane, dimensionless; ∇P is the pressure gradient, Pa/m.

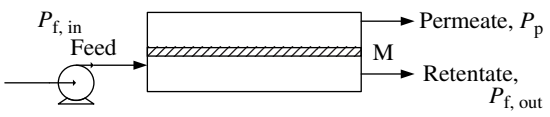

FIGURE 16.8 Schematic of a nanofiltration membrane unit for continuous operation.

If the pore structure cannot be modeled as consisting of effectively cylindrical capillaries of diameter d_{pore}, the solvent volumetric flux is characterized as

$$J_v = -\frac{Q_{\text{sm}}}{\eta}\nabla P \tag{16.26}$$

where Q_{sm} is the solvent permeability through the membrane. The molar solute flux in the pore–flow model is described via

$$N_i = -\alpha'_i C_{i\text{m}} J_v \tag{16.27}$$

where $C_{i\text{m}}$ is the molar concentration of solute i in the membrane and α'_i is a viscous flow characterization parameter [35]. Generally, membrane–solvent interactions occur and they would influence the parameters to be used in pore–flow models. The behavior of solute rejection R_i in such a model as a function of permeate volume flux (which increases essentially linearly with $-\nabla P$) has been illustrated for MPF-60 membrane in Whu et al. [28]. How to obtain various parameters for both models has been illustrated in Silva et al. [35] who have described the earlier literature. The local permeate solute concentration $C_{i\text{p}}$ for component i may be described via

$$\frac{C_{i\text{p}}}{C_{\text{sp}}} = \frac{N_i}{N_{\text{s}}} \tag{16.28}$$

where N_{s} is the molar solvent flux and C_{sp} is the molar solvent concentration in the permeate. We could rewrite equation 16.28 for a dilute solution of component i as

$$C_{i\text{p}} = \frac{N_i}{\overline{J}_v/\overline{V}_s} C_{\text{sp}} \cong \frac{N_i}{J_v} \tag{16.29}$$

where the partial molar volume of solvent is $\overline{V}_s$ yielding

$$R_i \cong 1 - \frac{N_i}{J_v C_{i\text{f}}} \tag{16.30}$$

Most performance data in OSN reported in literature were obtained with small membrane samples. In larger units, there will be variation of feed concentration along the membrane. There is very little information in the literature on analysis of such a situation. However, in any situation, with small or larger membrane sample, one has to account for concentration polarization. Since OSN is used often to reject a solute, which is an API while the solvent is going through, the rejected solute concentration will increase on the membrane surface to $C_{i\text{w}}$, which is larger than the feed concentration $C_{i\text{f}}$. The extent of this increase will depend on the solute mass transfer coefficient in the feed solution, $k_{i\text{f}}$ and the volume flux J_v as is observed in the processes of reverse osmosis and ultrafiltration

$$\frac{J_v}{k_{i\text{f}}} = \ln\left(\frac{C_{i\text{w}} - C_{i\text{p}}}{C_{i\text{f}} - C_{i\text{p}}}\right) \tag{16.31}$$

Therefore, when using the two models of membrane transport, $C_{i\text{w}}$ should be used instead of $C_{i\text{f}}$ unless the ratio $(J_v/k_{i\text{f}})$ is very small.

16.3.2 OSN Membranes

OSN membranes may be ceramic or polymeric in nature. There are no practical ceramic membranes whose MWCO value is less than 1000. Therefore, we will focus here on polymeric OSN membranes. Most polymeric membranes used in a variety of industries are prepared via the phase inversion technique in the first step of which the polymer is dissolved in a solvent. Therefore, most of those polymers are not suitable for OSN, since the membrane lacks solvent stability. Among those few that may be suitable, polyimide (PI) and polyacrylonitrile (PAN) stand out. A brief description of various aspects of the materials of OSN membranes is provided in Silva et al. [37].

The polymeric membranes of these materials may be of the asymmetric type or a composite membrane. In asymmetric membranes, a very thin skin at the top of the membrane is the solute-selective layer with the rest of the membrane providing a low transport resistance mechanical support; however, the whole membrane is of the same material and these are often described as integrally skinned. In composite membranes, the top selective skin is of a different material compared to the material of the porous support. This selective layer is cross-linked to impart substantial solvent stability. Cross-linked elastomeric barrier layers are often made out of polydimethylsiloxane on a PAN support.

Integrally skinned polyimide membranes of the STARMEM® type are available from W.R. Grace, Columbia, MD, USA and Membrane Extraction Technology Ltd., UK. The composite polymeric membranes with silicone top layers are identified as MPF types and are available from Koch membranes, Wilmington, MA, USA in small sizes as well as spiral-wound modules. These membranes are good with many organic solvents such as toluene, methanol, and ethyl acetate. However, polar aprotic solvents such as methylene chloride, dimethyl formamide (DMF), *n*-methyl pyrollidone (NMP), tetrahydrofuran (THF) are demanding; successful OSN has been reported with these solvents using integrally skinned Lenzing P84 polyimide membranes chemically cross-linked with aliphatic diamines [38].

16.3.3 Potential Applications of OSN in Pharmaceutical Industry

Pharmaceutical synthesis of small molecules generally involves 4–20 reaction steps. There are many separation steps involved in between where one could use OSN. It may involve separation of the catalyst and its reuse/recycle, removal of solvent, and its exchange with a different solvent,

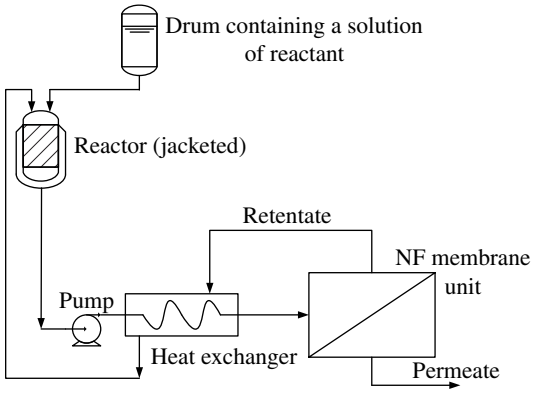

FIGURE 16.9 Schematic of a batch/semi-batch reactor coupled externally with an OSN unit (from Ref. 28, with permission).

concentration of a product/intermediate molecule rejected completely by the membrane, removal of smaller molecules/impurities from the reaction mixture along with the solvent through the membrane, recycling of resolving agents in chiral resolution processes, etc. These steps will most likely be implemented in a NF membrane unit external to the vessel/reactor where synthesis is being implemented (Figure 16.9) in a batch/semi-batch fashion with concentrate recycle.

There are two basic properties of successful membranes in OSN: (1) small molecular weight solvent and solutes pass through easily and the solvent flux is acceptable; and (2) molecules larger than the molecular weight cut off size of the membrane are essentially retained completely. The membrane MWCO may be 220/250, 400, 700 Da implying that species with molecular weight larger than the membrane MWCO is very likely to have a solute rejection (R_i) value ≥ 0.95. A basic expectation is also that the membrane performance will not change much with time either with respect to flux or solute rejection; therefore, membrane swelling in the solvents should be very low.

Scarpello et al. [39] demonstrated very high rejections of the following catalysts, Jacobsen catalyst (622 Da), Wilkinson catalyst (925 Da), and Pd-BINAP (849 Da) using STARMEM™ membranes of different kinds, STARMEM 122 (MWCO, 220 Da), STARMEM 120 (MWCO, 200 Da), and STARMEM 240 (MWCO, 400 Da) in the presence of different solvents, such as ethyl acetate and tetrahydrofuran. Usually STARMEM 240 showed higher rejection values, while STARMEM 120/122 showed very high rejection values >0.95 bordering onto 1. For smaller Pd-based catalysts used in Suzuki coupling, the leakage of catalyst through the STARMEM 122 membrane led to Pd levels in the product at a higher than the desired level [40]; Pd content was brought down to acceptable levels (<10 mg Pd kg/product) by using adsorbents on the permeate from OSN employed on the postreaction solution [41]. Adsorbents used alone for treating the postreaction solution were unsuccessful in achieving the desired level unless a very large amount was employed. Homogeneous Heck catalysts were recycled from postreaction mixtures using OSN [42]. Recovery and reuse of ionic liquids used as solvents was also demonstrated during these studies with OSN for pharmaceutical synthesis processes [43]. Phase-transfer catalysts such as tetraoctylammonium bromide was separated and successfully reused via OSN [44, 45]. Recycle and reuse of organic acid resolving agents such as di-*p*-toluoyl-1-tartaric acid (DTTA) used for resolution of chiral bases such as racemic amines was demonstrated via OSN [46].

Solvent exchange is an important step in pharmaceutical synthesis. It is usually performed by batch distillation, which results in an intensive use of energy and solvent. In addition, the separation achieved by conventional distillation is not very satisfactory. The room temperature exchange of the solvent ethyl acetate with methanol in a solution containing the solute erythromycin (734 Da) was demonstrated via discontinuous and continuous diafiltration [47, 48] using MPF-50 and MPF-60 membranes (Figure 16.10). In Figure 16.10, E represents erythromycin. This process avoids distillation processes where thermally sensitive APIs are likely to be affected. Toluene as the solvent for solutes such as tetraoctylammonium bromide (547 Da) was exchanged with methanol in batch distillation using STARMEM 122 membrane with the solute retention exceeding 99% [29] compared to average solute rejection of around 96.37% in Sheth et al. [47, 48]. A continuous countercurrent cascade of three nanofiltration membrane cells for the feed solution and the exchange solvent entering at two ends of the cascade was demonstrated for a test solute such as tetraoctylammonium bromide (547 Da) and the solvents methanol and toluene [49].

Membrane-assisted organic synthesis wherein NF membranes are utilized to remove undesirable by-products/intermediates from the reaction mixture as the reaction proceeds and concentrate the reaction product has not received as much attention. Whu et al. [28] pointed out via modeling how OSN may facilitate organic synthesis. Consider the reaction

$$\underset{(\mathrm{MW}\sim 400)}{\mathrm{A}} + \underset{(\mathrm{MW}\sim 50)}{\mathrm{B}} = \underset{(\mathrm{MW}\sim 400)}{\mathrm{C}} + \underset{(\mathrm{MW}\sim 50)}{\mathrm{D}} \qquad (16.32)$$

where the product D participates in a side reaction which consumes the reactant A to produce an undesired by-product E via

$$\mathrm{A} + \mathrm{D} = \mathrm{E} \qquad (16.33)$$

If we carry out OSN in an integrated fashion with a batch/semi-batch reactor, a few benefits are apparent. If reaction 16.32 is equilibrium limited, removal of D via OSN will shift the equilibrium to the right. Although reactant B is also removed through the membrane, one could continuously add reactant B from a drum in a solvent to replenish it. Removal of D reduces the extent of loss of A via side reaction 16.33. The concentration of C in the final reaction mixture can be

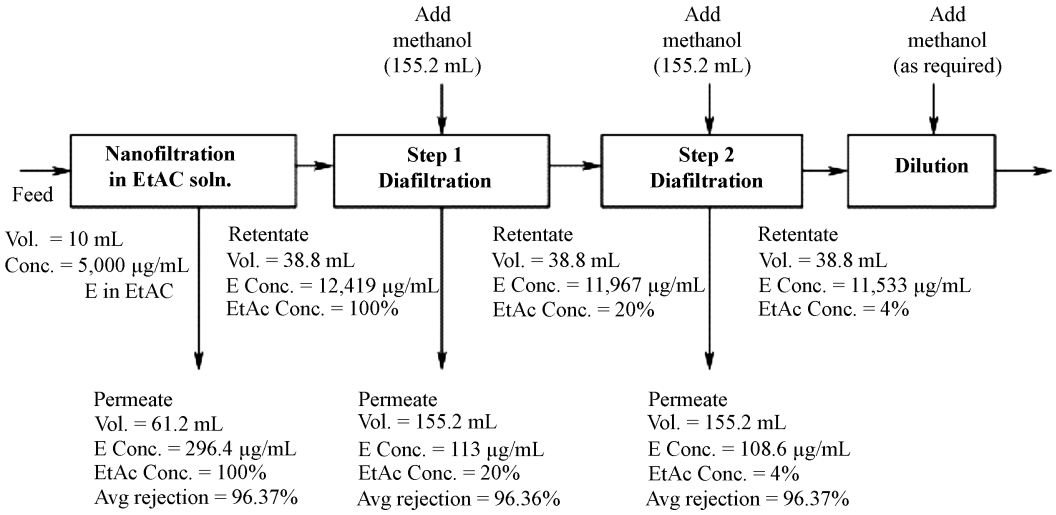

FIGURE 16.10 Mass balance during the preconcentration and discontinuous DF steps for the MPF-60 membrane in solvent exchange for erythromycin from ethyl acetate to methanol (from Ref. 48, with permission).

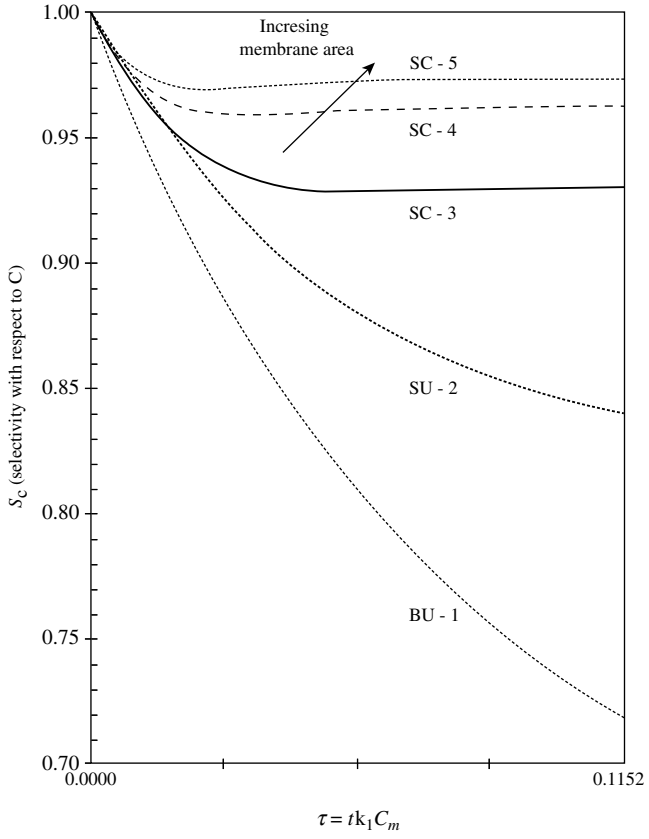

FIGURE 16.11 Selectivity with respect to the desired product C (S_c) as a function of time. See text for more details (from Ref. 28, with permission).

considerably enhanced. Further, the conversion time may be significantly reduced.

Figure 16.11 from Whu et al. [28] illustrates the enhancement of the selectivity with respect to species C as a function of dimensionless time for five modes of operation: BU-1 represents a batch reactor uncoupled from an OSN unit; SU-2 represents a semi-batch reactor uncoupled from an OSN unit; SC-3, SC-4, and SC-5 represent a semi-batch reactor coupled externally with an OSN unit with increasing membrane area and increasing concentration of species B in the drum as well as the volumetric rate of addition. This figure demonstrates that a much higher selectivity with respect to species C is achieved when the semi-batch reactor is coupled externally with an OSN unit to remove the solvent and the product D. Further, this enhanced selectivity is achieved in much less time.

16.4 NONDISPERSIVE MEMBRANE SOLVENT EXTRACTION

In pharmaceutical synthesis, sometimes one needs to extract a solute/API from an organic phase to an aqueous phase or vice versa. Much less frequently, one encounters extraction from a highly polar aqueous phase to a nonpolar immiscible organic phase or vice versa. Conventionally, these extractions are carried out in a mixer-settler type of extraction device by dispersing one phase as drops in another phase. Alternately, centrifugal extractors (Podbielniak) are employed. However, the possibility of a stable emulsion is a major problem in such processing. Nondispersive solvent extraction using microporous membranes has been developed to avoid such problems [50]. In this technique, the organic phase flows on one side of a porous hollow fiber

membrane and the aqueous phase flows on the other side. One of the phases preferentially wets the membrane pores. Hydrophobic membrane pores are wetted by the organic phase. Hydrophilic membrane pores are wetted by the aqueous phase. However, the phase not wetting the pores is maintained at a pressure equal to or higher than the pressure of the phase present in the pores. There is no dispersion. One can have a wide range of phase flow rates on the two sides of the membrane. The aqueous–organic or organic–organic phase interfaces at the pore mouths are stable as long as the required relative phase pressure conditions are maintained.

Examples of commercial exploitation of such a technique are provided in Sirkar [51] for aqueous–organic systems. The commonly used porous hollow fiber membranes to this end are made of polypropylene with the tube-sheet made out of polyolefin resins. Therefore, only some of the more common and less aggressive solvents can be used at lower temperatures. Large modules are commercially available (Celgard/Membrana, Charlotte, NC). High performance ceramic membranes having a fluoropolymer coating is available from Kühni AG (Allschwill, Switzerland; Stanley, NC (Kühni, USA)). These modules can be used up to a temperature of 150°C and can be steam sterilized.

In such membrane solvent extraction techniques, porous hydrophobic membranes provide mass transfer advantages when extracting solutes/APIs from an aqueous into a solute-preferred organic phase. On the other hand, when the solute/API in an organic phase prefers the aqueous phase and an aqueous wash is desirable, a porous hydrophilic membrane is desirable. Porous nylon-based membranes are quite suitable for this goal [52].

16.5 CONCLUDING REMARKS

Pervaporation for removing water from organic reaction medium is an attractive opportunity in pharmaceutical processing. Large membrane modules are available. Organic solvent nanofiltration can provide multiple processing opportunities of great relevance; these include catalyst recovery/recycle, solvent exchange, product concentration, enhancement of reaction conversion/selectivity, and reduction of reaction time. Large modules for nondispersive membrane solvent extraction can facilitate pharmaceutical processing as long as the membrane module has acceptable solvent resistance.

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