



Recent Advances in Separation Techniques—III

AIChE
Symposium Series

Norman N. Li, editor
T. Alan Hatton, Sun-Tak Hwang,
Donald M. LaRue, Stephen A. Leeper,
Daryl L. Roberts, co-editors

250 *Volume 82, 1986*

AMERICAN INSTITUTE OF CHEMICAL ENGINEERS

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AIChE Symposium Series

Number 250

1986

Volume 82

Published by

American Institute of Chemical Engineers

345 East 47 Street

New York, New York 10017

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American Institute of Chemical Engineers
345 East 47 Street, New York, N.Y. 10017

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Library of Congress Cataloging-in-Publication Data

Main entry under title:

Recent advances in separation techniques III.

(AIChE symposium series ; no. 250, v. 82)

Includes index.

I. Separation (Technology)	I. Li, Norman N.	II. American
Institute of Chemical Engineers.	III. Series: AIChE symposium series ;	
no. 250.		
TP156.S45R432 1986	660.2'842	86-26513
ISBN 0-8169-0392-1		

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Printed in the United States of America by
Twin Production & Design

FOREWORD

Separation processes make purified products for mixtures and purify waste streams. They are involved in virtually all processing industries. Separation methods are also key parts of many analytical procedures. Because of the importance of separation science and technology in a broad spectrum of industries, the Program Committee "Novel Separation Processes" of the American Institute of Chemical Engineers scheduled six sessions on separations at the 1985 Summer National Meeting of American Institute of Chemical Engineers in Seattle. Most of the papers in the symposium volume were the papers presented at this meeting. A few papers in the volume were presented in the separations sessions of the AIChE's Summer National Meeting in Boston.

All together there are 21 papers in this volume. They discuss a wide range of topics on chromatography, distillation, extraction, electrophoresis, extractive distillation, processes using magnetically stabilized fluidized bed, and various membrane processes. Some of them focus on theories while others concentrate on recently developed applications. In combination, these papers represent some important aspects of recent advances of separation science and technology.

All of the co-editors of this volume are the session chairmen at the above-mentioned National Meetings, whose sessions have contributed papers to this volume. They are T. Alan Hatton of Massachusetts Institute of Technology, Sun Tak Hwang of University of Cincinnati, Donald M. LaRue of EG&G Idaho, Stephen A. Leeper of EG&G Idaho, Inc., and Darly L. Roberts of SRI International.

My co-editors and I would like to express our sincere appreciation to the authors and the reviewers for their effort in making this volume possible. We also wish to thank Ms. Maura Mullen and her staff at the American Institute of Chemical Engineers for their invaluable editorial assistance.

Norman N. Li
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ALCOHOL REMOVAL FROM BEER BY REVERSE OSMOSIS

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Full-bodied beer with reduced or "no" alcohol content can be produced from regular beer using sanitary design, spiral-wound reverse osmosis membrane elements. The elements contain a FDA approvable thin-film composite membrane and are operated in a semi-batch or continuous feed-and-bleed mode. Efficient production of low-alcohol beer is achieved by operating systems at low net pressure.

In 1980, food processing accounted for about 13% of all U.S. manufacturing gross national product with a market value of \$256 billion (1). In the last twenty years, value added in food processing has continued to increase independently of raw food prices, indicating a large potential market for membrane products capable of meeting food processing requirements. To infiltrate food markets effectively, membrane processes will have to reduce costs or give a product of superior quality, and they will have to satisfy regulations applicable to food processing.

For a technically feasible membrane food process to be commercially acceptable in many countries, all components of the membrane device must be made with raw materials which have been approved or are approvable for food contact by an appropriate governmental agency, such as the Food and Drug Administration (FDA) in the U.S. The device must also be constructed in a sanitary design with no stagnant areas and be easy to clean.

For certain food applications, membrane processes have been proven capable of giving lower cost, higher quality products, as a result of reduced energy requirements, decreased need for chemical preservatives, and lower operating temperatures. Since food processing using membranes does not require a phase change, heat sensitive fluids can be processed at lower temperatures, with

reduced operating expenses and reduced heat-related damage. By exploiting these advantages, sanitary design reverse osmosis (RO) and ultrafiltration devices have been successfully used for solution sterilization, dewatering applications and component separations. Of these, a commercially important membrane application is the production of milk-based products (2), such as the recovery and concentration of proteins in cheese whey. Other processing applications include the isolation and recovery of proteins, the sterilization of beer and fruit juices, the dewatering of sugar solutions, and the clarification and removal of tartrate from wines.

Of the many possible food applications for membranes, the production of low-alcohol beer has been investigated because of recent commercial interest. In the brewing industry there are two types of products: low-alcohol beer containing 2 wt% ethanol and "non-alcoholic" beer containing less than 0.5 wt%. The goal in producing low-alcohol beer by RO is selectively to remove ethanol from beer without losing extract or flavor components. These essential components, including proteins, carbohydrates, acetates, and higher alcohols, give the beer its characteristic aroma, body, and taste.

Several methods have been tried unsuccessfully in an attempt to produce a full-

bodied, low-alcohol beer with acceptable taste. Two major problems encountered in the production of low-alcohol beer have been the addition of unwanted flavors and loss of beer body. Low-alcohol beer by dialysis was not successful as an unacceptable percentage of the beer's extract passed through the membrane resulting in a very light-bodied beer (3). Distillation methods (4, 5) have had only moderate success, mainly because they are expensive and the flavor components are altered during the process. Heat sensitive proteins and carbohydrates in the beer are denatured at distillation temperatures giving the beer an unacceptable taste. Brewers have also tried to modify their brewing process to obtain a low-alcohol beer, but this is unsatisfactory because a separate, modified brewing formula is required, and the reduced wort concentration in the new formulation results in a light-bodied beer. In contrast, production of low-alcohol beer by RO has the advantage of being able to remove the ethanol from the beer after normal fermentation without losing extract or altering flavor (5, 6).

The objective of the work presented here is to demonstrate the use of commercially acceptable, sanitary design RO spiral-wound elements for the production of low-alcohol beer. Performance characteristics for elements tested in pilot-scale systems are presented and used as a basis for specifying the preferred process design and for elucidating a novel membrane separation mechanism.

MATERIALS AND METHODS

Membrane Elements

The thin-film composite (TFC) membrane contained in the RO elements is a membrane specially formulated for use in food processing applications. Its use is in compliance with applicable FDA regulations for food-contact surfaces. All non-membrane components of the element are made from FDA grade raw materials. A detailed description of element components and design is given elsewhere (7).

For the spiral-wound membrane element to have a sanitary design it was necessary to eliminate the stagnant areas between the element and the housing. This is accomplished by perforating the u-cup carrier to create a bypass around the u-cup seal which prevents feed from flowing between the element and housing in conventional elements. Small

holes in the u-cup carrier allow 1 to 5% of the feed to leak past the element in the channel between the element and the housing. The controlled amount of feed bypassing the element can be modified by varying the number and size of the holes in the u-cup carrier. As can be seen in Figure 1, inlet cylindrical channels in the direction of flow have a diameter that is less than half that for the continuation channels through the u-cup carrier. This is done to prevent plugging of the channels downstream of the inlet. The inlet channels can also be designed to accommodate plugs containing holes of different sizes, thus allowing for adjusting the rate of bypass flow depending on the properties of the fluid being processed.

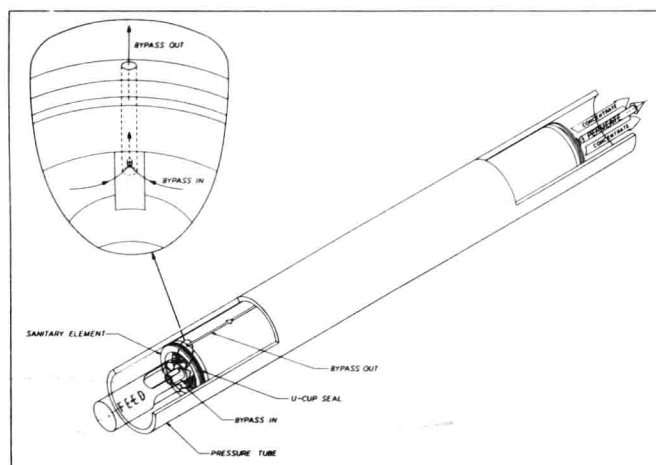


Figure 1. Sanitary design, spiral-wound element with perforated U-cup carrier for flow bypass.

Membrane System Process Design

Previous work has employed an approach for removing ethanol from beer using a membrane system operated in a batch-concentration mode whereby the beer being processed is either diluted with water before or after processing (5). Two disadvantages of this approach are that the concentrations of complex components in beer are altered and precipitates and other membrane foulants can form that affect the taste of the beer and reduce the membrane system productivity. Two approaches that were employed here that do not have these problems are the semi-batch and feed-and-bleed modes, which are shown schematically in Figures 2 and 3, respectively.

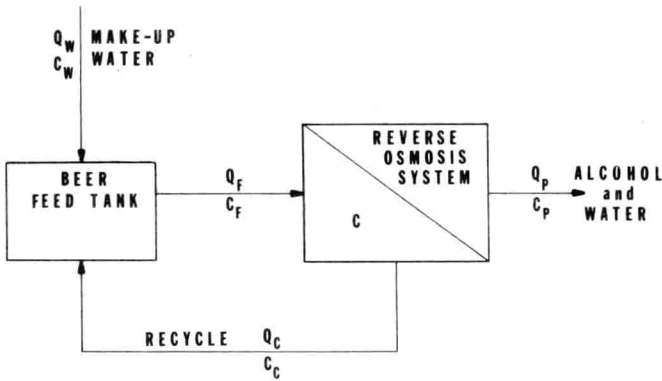


Figure 2. Flow schematic for semi-batch mode of operation for producing low-alcohol beer.

The fundamental process design equation for the semi-batch mode (8) for producing low-alcohol beer is the following

$$\frac{C_F}{C_B} = e^{\frac{1}{k}[(1-k)^{1-R}-1]S} \quad (1)$$

where

C_F = Ethanol concentration in processed beer at time t

C_B = Ethanol concentration in unprocessed beer

$k = Q_P/Q_F$ = Recovery per pass through the membrane system

$R = 1 - C_P/C$ = Membrane rejection for ethanol

$S = Q_P t/V$ = Volume of make-up water per volume of beer processed

Q_P = Permeate flow rate

Q_F = Membrane system feed flow rate

C_P = Concentration of ethanol in permeate

C = Concentration of ethanol in beer during processing

V = Volume of beer being processed

t = Time

Equation (1) can be used to calculate the fractional reduction in ethanol concentration (C_F/C_B) as a function of membrane

rejection (R), recovery per pass (k), and the ratio of the volume of make-up water to the volume of beer processed (S). As S is determined by the flow rate of permeate (Q_P , equal to the flow rate of make-up water), the volume of beer being processed (V), and time (t), the fundamental equation can also be used to calculate the processing time required to give a specific reduction in ethanol concentration.

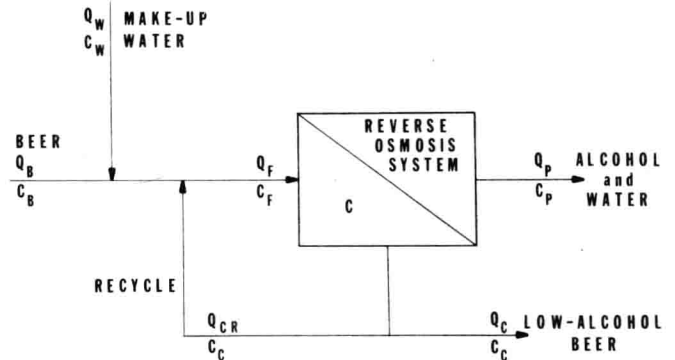


Figure 3. Flow schematic for feed-and-bleed mode of operation for producing low-alcohol beer.

In the continuous feed-and-bleed mode shown in Figure 3 for producing low-alcohol beer, the processed stream containing flavor components rejected by the membrane and reduced alcohol content is partially recycled (Q_{CR}) and mixed with fresh beer (Q_B) and make-up water (Q_W). The remaining processed stream (Q_C) is "bled" from the system and collected as product. To maintain a constant concentration of flavor components, volumetric flow rates are adjusted so that Q_C and Q_B are equal. The fundamental process design equation for calculating the reduction in ethanol concentration in processed beer (C_C) as compared to unprocessed beer (C_B) is given by

$$\frac{C_C}{C_B} = \frac{(1-k)-X}{(1-k)^R - X} \quad (2)$$

where

C_C = Ethanol concentration in processed beer

$X = Q_{CR}/Q_F$ = Fraction of feed that is recycle

Q_{CR} = Recycle flow rate

It can be seen from Equation (2) that the ethanol concentration change is a function

of the recovery per pass (k), the membrane rejection (R), and the fraction of system feed that is recycled, processed beer (X). The fraction of the processed beer that is recycled is given as $X/(1-k)$.

On comparing the two process designs, the semi-batch mode is an attractive design approach for small or pilot-scale units, but can be inappropriate for production or full-scale operation where a continuous mode of operation is preferred, such as a feed-and-bleed mode. An important disadvantage of the semi-batch mode is that for large systems, both incoming feed and recycle must be pressurized from atmospheric to operating pressure, while for the feed-and-bleed mode, the recycle pressure only has to be boosted to compensate for pressure losses incurred in the system. This can result in the energy cost for a feed-and-bleed mode being less than half that for a semi-batch mode. On the other hand, an important advantage for the semi-batch mode is that for a given ethanol concentration reduction, the volume of make-up water required per volume of beer processed is less than that for the feed-and-bleed mode.

Pilot-Scale Tests

Experiments were performed using sanitary design, spiral-wound elements operated in semi-batch and feed-and-bleed modes for reducing the ethanol content of beer. The pilot-scale system consisted of a positive displacement pump, six stainless steel pressure vessels with endplugs, two stainless steel reservoirs, and a propylene glycol cooling system. The cold feed was pumped from the feed tank through a manifold to three parallel arrays each containing two 2.5-in stainless steel pressure tubes. The concentrate was recycled back to the feed tank and the permeate containing ethanol, water, and carbon dioxide was discarded. The feed flow rate (Q_F) was adjusted to give acceptable recovery.

Beer is processed at 5 to 12°C as this temperature range allows for the greatest permeate flux without denaturing or precipitating beer proteins and other components. The pilot-system was operated at applied pressures of 690 to 4100 kPa (100 to 600 psig) while recovery per pass was varied from 1 to 10%. Feed and permeate flow rates were measured and the composition of samples was determined by chemical analyses. Data were collected for ethanol flux, ethanol

rejection, and permeate flux as functions of pressure.

The general experimental approach was to operate the system in a semi-batch mode, recycling concentrate and mixing it with water added at a flow rate (Q_W) equal to that of permeate (Q_P) until the desired concentration of ethanol was obtained in the feed. Steady state performance measurements could then be made by operating in either a once-through or total-recycle mode, or the water make-up rate could be adjusted, fresh beer added to mix with the recycled concentrate, and a portion of the concentrate collected as product in a feed-and-bleed mode.

To verify that the alcohol content of the beer was actually reduced during the processing, samples of the processed and unprocessed beer were analyzed according to the protocol of the American Society of Brewing Chemists (9). The American pilsner beer used for the reduced-alcohol beer experiments was analyzed for original, real, and apparent extract, specific gravity, and ethanol content. The beer was also assayed for total protein and iso- α -acids. Beer samples were analyzed by gas chromatography for important flavor and aroma components including n-propanol and i-amyl alcohol.

RESULTS

In processing beer, the primary objective is to reduce the ethanol concentration in beer to a specified level with no loss of desirable components. The results of analyses listed in Table 1 show that by membrane processing the ethanol content of an American pilsner beer was reduced by 62 to 74% without loss of real extract, protein, or flavor components. The initial ethanol content of the beer was 3.4 wt%. After processing, the ethanol content of the "no-alcohol" beer was 0.9 wt%. Virtually all real extract was retained during processing. The value of the real extract was 3.7% for the initial sample, 3.9% for the low-alcohol sample, and 4.1% for the "no-alcohol" sample. The real extract increased during processing due to a proportional slight increase in volume. No substantial difference in the concentrations of taste and flavor components was observed between the processed and unprocessed beer. It is interesting to note that while the ethanol concentration decreased markedly, the concentrations of the higher alcohols remained nearly constant.

Table 1. Component analyses for American Pilsner beer as compared to low-alcohol and "no-alcohol" beer produced by RO from American Pilsner beer.

ANALYSES	REGULAR BEER	REDUCED ALCOHOL BEER BY REVERSE OSMOSIS	
		LOW-ALCOHOL BEER	"NO-ALCOHOL" BEER
ALCOHOL CONTENT (Wt %)	3.38	1.29	.85
REAL EXTRACT (Wt %)	3.74	3.92	4.11
TOTAL PROTEIN (mg/L)	.103	.108	.110
ISO- α -ACIDS (mg/L)	19.0	19.0	19.0
POLYPHENOLS (mg/L)	9.8	10.7	10.7
n-PROPANOL (mg/L)	19.7	19.2	21.8
i-AMYLALCOHOL (mg/L)	18.4	17.8	24.6

Figure 4 is a plot of TFC membrane ethanol rejection as a function of applied pressure (P_{applied}) using a beer feed at 10 to 12°C, which shows that ethanol rejection is not constant but increases with increasing applied pressure. For example, at an applied pressure of 1380 kPa the ethanol rejection is 34%, while at 3450 kPa the rejection is 68%. This increase in rejection with increasing pressure has an important effect on the selection of the preferred process pressure since at higher operating pressure more water will pass through the membrane with ethanol, adding to the processing costs. In contrast to the low, variable rejection for ethanol, the TFC membrane has a high rejection for chloride ion (>97% at 2760 kPa net), which is required to ensure that beer flavor components are not lost during processing.

A fundamental process parameter influencing flux and rejection for reverse osmosis systems is net transmembrane pressure differential (P_{net}). By expressing performance as a function of P_{net} , it is possible to relate results for different beers having different compositions. The term P_{net} is given as

$$P_{\text{net}} = P_{\text{applied}} - \Delta\pi \tag{3}$$

where $\Delta\pi$ is the transmembrane osmotic pressure differential. For beer, an expression for $\Delta\pi$ consists of two parts, one for highly rejected components such as

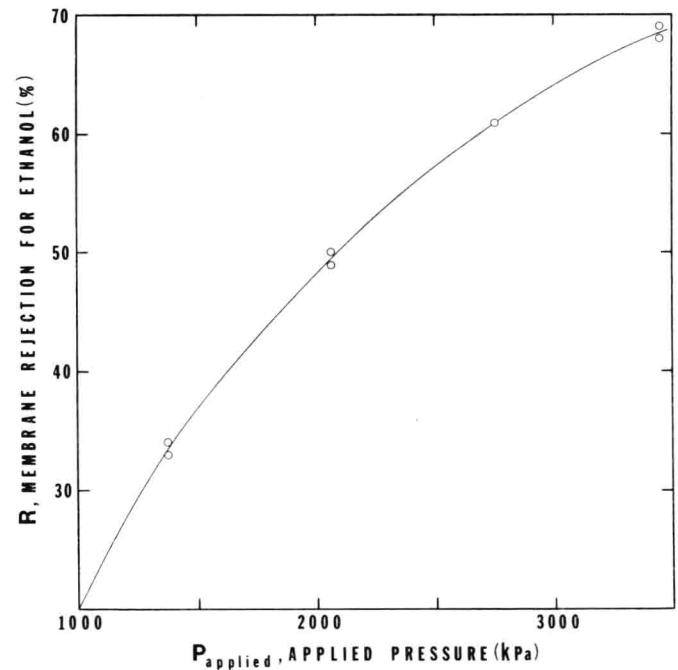


Figure 4. Membrane rejection for ethanol as a function of applied pressure for processing beer.

extract and one for modestly rejected species such as ethanol.

$$\Delta\pi = R C_{\text{EtOH}} k_{\text{EtOH}} + \pi_{\text{EXT}} \tag{4}$$

- where R = Membrane rejection at a given applied pressure
- C_{EtOH} = Ethanol concentration in feed
- k_{EtOH} = Osmotic pressure constant for ethanol
- π_{EXT} = Osmotic pressure of extract

As data in Figure 4 show that R is a function of applied pressure, $\Delta\pi$ is also a function of applied pressure and must be calculated for each P_{applied} used.

The osmotic pressure of the extract can be estimated using a graphical procedure, as shown in Figure 5, a plot of permeate flux as a function of applied pressure for a beer feed and an ethanol-water feed. For a totally rejected entity, extrapolation of the lines to zero permeate flux will give the osmotic pressure of feed solutions. For ethanol feed (3.5 wt%), the extrapolation to zero permeate flux gives an osmotic pressure value of zero for the feed solution because the rejection of ethanol approaches zero at zero pressure. Because the extract is highly rejected by the membrane, a value for the

osmotic pressure of the extract can be deduced by extrapolating the beer feed line to zero permeate flux, shown on Figure 5 as about 500 kPa.

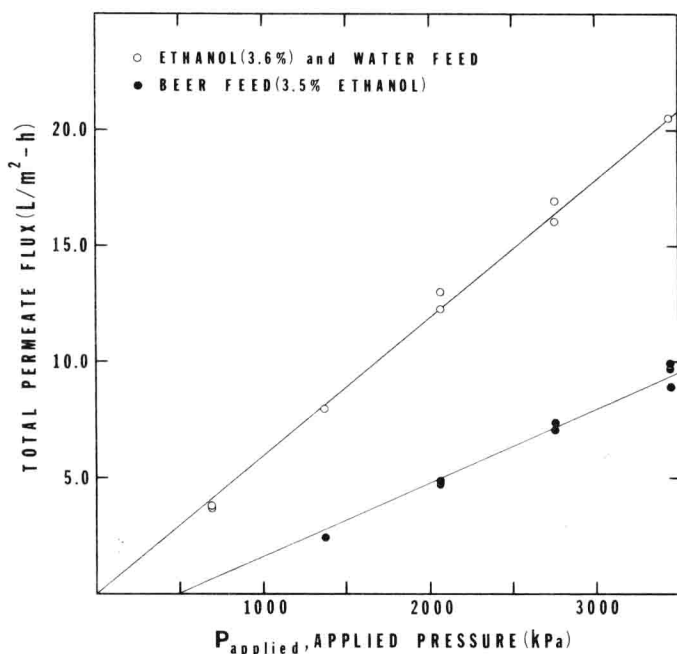


Figure 5. Permeate flux as a function of applied pressure for ethanol-water and beer feeds.

Figure 6 is a plot of ethanol flux and water flux as functions of net pressure, which was calculated using Equation (3). Water flux increases linearly with increasing net pressure. For example, at 250 kPa the water flux is 1.4 L/m²-h while at five times that pressure (1250 kPa) the water flux has increased by five times to 7.0 L/m²-h. On the other hand, it is interesting to note that while at low net pressure, ethanol flux also increases with increasing pressure, at high net pressures ethanol passage is nearly independent of net pressure. For example, at 250 kPa the ethanol flux is 0.05 L/m²-h, but above 1500 kPa ethanol flux reaches a plateau and increases very slowly with further increases in net pressure. This indicates that there would be no benefit to operating a system at a net pressure greater than about 1750 kPa. It is also interesting to note that the shape of the ethanol curve is not due to concentration polarization since the water flux line shows no change in slope. The difference in slopes for the water and ethanol flux curves in Figure 6 accounts for the variable ethanol rejection as a function of pressure shown in Figure 4.

Figure 7 is a plot of the ratio of ethanol concentration in processed beer at time t (C_F) to ethanol concentration in unprocessed beer (C_B) as a function of time and S value for a semi-batch mode of operation at about 690 kPa net. Very good agreement is shown between actual empirical

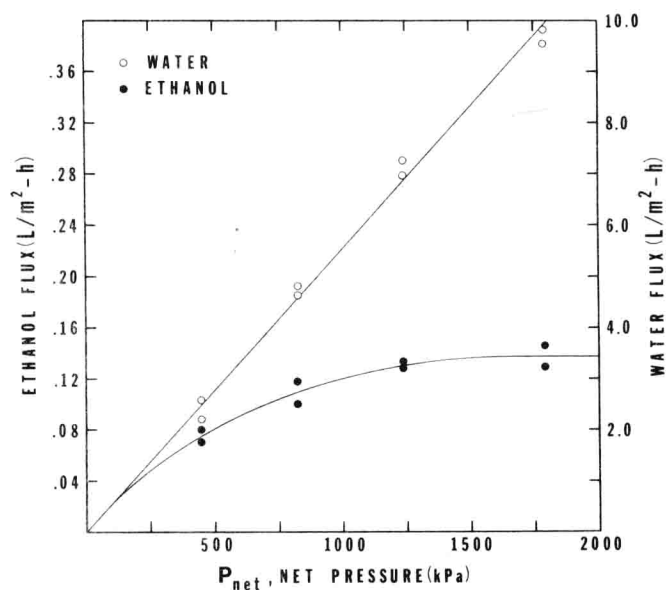


Figure 6. Flux for ethanol and for water as a function of net pressure.

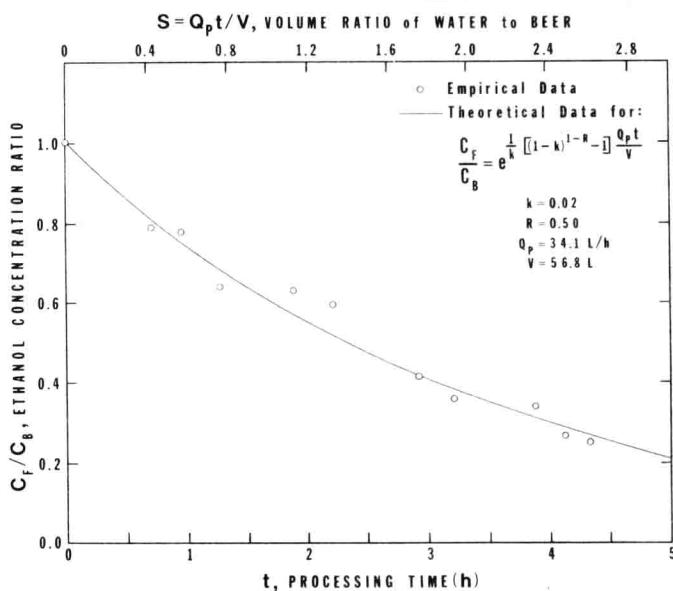


Figure 7. Ethanol concentration ratio for semi-batch operation as a function of time and S value.

data and theoretical predictions. For the conditions of the test, a reduction of 50% of the ethanol concentration required 2.3 h of processing. Had that been the goal of a commercial process either the semi-batch cycle would have been completed at this time or the process would have been converted to a feed-and-bleed mode for further processing in a continuous, steady state manner. The 50% ethanol reduction required 1.4 L water per L beer.

DISCUSSION

To design effective membrane systems, it is important to understand the factors that determine the flux and separating capability of the membrane. According to the widely held solution-diffusion mechanism, a distinction is made in aqueous membrane separations between the solution solvent (i.e., water) and the solution solute (e.g., salt). The driving force determining solvent flux is the net pressure differential across the membrane. For typical operating pressures, the solute flux is independent of net pressure differential and is determined by the transmembrane solute concentration gradient.

For the removal of ethanol from aqueous beverages, a TFC membrane has been developed that treats water as a conventional solvent, but treats ethanol as both a solvent (at low net pressure) and a solute (at high net pressure). This behavior is the basis for a novel approach for system design (6). A key additional feature of the TFC membrane is that it has an inherently high rejection for chloride ion (>97% at 2760 kPa net pressure). This is required to ensure that flavor components in beer are retained by the membrane.

The behavior displayed by the TFC membrane for ethanol separation could be due to several mechanisms. At low net pressure, ethanol flux is low and the transmembrane ethanol concentration gradient is relatively flat, with ethanol solubility being an important factor in determining the overall ethanol concentration in the membrane. For low net pressure, flux could increase with increasing pressure, like a solvent, due to pressure-effected displacement of ethanol in the polymer by ethanol in the feed. As pressure is further increased, water flux increases linearly, and the overall concentration of ethanol in the membrane could decrease due to the dilution affect of water. This dilution could result in

establishing a steeper transmembrane concentration gradient for ethanol and causing the ethanol concentration in the membrane to no longer be solubility limited. With a steeper concentration gradient created, the ethanol flux would become less dependent on pressure and would become more dependent on transmembrane concentration gradient diffusion like a solute.

Selection of optimal process conditions is determined by cost factors, several of which depend on the net pressure and the influence it has on the relative passage of ethanol and water. The preferred pressure must be high enough that there is a substantial permeation rate for ethanol to give an acceptable membrane system size, but not so high that there is a relatively large flow rate for valuable water that permeates along with the ethanol. Also, the recovery per pass must be low enough so as not to cause fouling or precipitation of beer components, yet high enough to give an acceptable recirculation rate, pump size, and energy costs.

The sanitary design, spiral-wound elements described here have been shown to be capable of reducing the ethanol content of beer when operated in either a semi-batch or a feed-and-bleed mode. For the semi-batch mode, the reduction in ethanol concentration can be changed by varying the cycle time. For the feed-and-bleed mode, the ethanol concentration in processed beer can be varied by employing multiple stages in series. More than one stage is preferred when a reduction of more than about 70% of the ethanol in beer is desired. For a given application, selection of the preferred mode of operation will depend on cost factors and the preference for a continuous versus a semi-continuous process. In comparing modes, two process distinctions are worth noting. One is the higher costs for energy and pumps for repressurizing all of the recirculated flow for a semi-batch mode. The other is the higher cost for make-up water for a feed-and-bleed mode.

For a given net pressure, membrane rejection, and recovery per pass, more water is required in a feed-and-bleed mode than in a semi-batch mode because the ethanol feed concentration the membrane contacts is less in the feed-and-bleed mode than in a semi-batch mode. An equation for calculating the ratio of the volume of water required for a feed-and-bleed mode to that for a semi-batch mode to reduce the alcohol

content by 50% (Z) is the following

$$Z = \frac{1.44[1-(1-k)^{1-R}]}{k-1+(1-k)^R} \quad (5)$$

For example, for a recovery per pass of 4% and a rejection of 50%, Z is 1.47, meaning that 47% more water is required for a feed-and-bleed mode than for a semi-batch mode.

The cost of water has a major impact on the selection of the preferred process mode and the preferred applied and net pressures. If the cost of water is high, the preferred net pressure is low to reduce the amount of water expended during processing, the optimum net pressure being typically lower for the semi-batch than for the feed-and-bleed mode. For this case, overall annual costs can be lower for the semi-batch mode, primarily because the cost for expensive make-up water can be less than half that for the feed-and-bleed mode. This cost difference is due to the combined effect for the semi-batch mode of a lower rejection for ethanol at lower net pressure and a greater feed ethanol concentration driving force. Total costs for semi-batch can be lower than those for feed-and-bleed even though the electrical energy cost for semi-batch can be more than twice that for feed-and-bleed, and the pump capital cost is higher.

If the cost of water is low, the feed-and-bleed mode can be preferred because total costs are lower and because it is a continuous mode which can be more easily adapted to a commercial process. The optimum net pressure would be close to the plateau region on Figure 7 (e.g., 1380 kPa) to reduce the size of the membrane system, which would be the primary cost factor for the feed-

and-bleed mode when the cost of water is low.

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REVERSE OSMOSIS PROCESS FOR PRODUCING PHARMACEUTICAL-GRADE WATERS

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Pharmaceutical companies use a variety of high purity water such as USP Purified Water (PW) and Water for Injection (WFI). The processes utilizing the high purity water are drug manufacture, rinsing of autoclaves and process equipment, and formulations manufacture. Table 1 presents the minimum water quality requirements for the USP Purified Water and WFI as per criteria listed in the U.S. Pharmacopeia(1). The technologies employed to produce the Purified Water are ion exchange, reverse osmosis, and distillation; Water for Injection must be produced by distillation or reverse osmosis.

Currently, distillation is an overwhelming choice for producing the pharmaceutical grade waters. The reverse osmosis process is just beginning to make an impact on this industry, which demands sanitary design of system components, and a reliable, validatable process design. This paper will examine the use of reverse osmosis for the production of high purity water for the pharmaceutical industry. We will describe the development of sanitary design RO systems, present performance data from evaluation of a prototype unit and a field unit, discuss pretreatment options, and compare the operating and capital costs of comparable size distillation and reverse osmosis systems.

PHARMACEUTICAL RO SYSTEM DESIGN

An RO system designed to meet the stringent water quality requirements of the pharmaceutical industry must include features that minimize the growth of microorganisms (including pyrogenic by-products) and minimize the chemical contaminants that could leach into the water by system components. Also, "in-place" sanitization methods are essential to efficient and reliable operation.

Millipore has designed a series of single pass and two pass RO systems (Milli-RO S) specifically for the production of high purity waters(2). An example of the flow paths of two and single pass systems is given in Figures 1a and 1b. An illustration of a two pass system is shown in Figure 2.

A uniquely designed RO membrane module is a key component of the pharmaceutical RO systems. The RO module (spiral wound) has been designed to minimize stagnant areas within its structure and to be easily sanitized by chemical application.

The nominal module specifications are given in Table 2. The RO module contains materials selected to conform to appropriate FDA codes(3). A unique taper fit SS interconnector(4) is used to make all module connections (see Figure 3). The interconnec-

tor eliminates the use and potential for failure of O-ring seals. The module includes a controlled feed-to-reject bypass flow (see Figure 4) to maintain a water flow within the space behind the chevron seal. The outer wrap used is a heat shrinkable, fluorinated ethylene propylene which, unlike tape or wrapped fiberglass coverings, is smooth, crevice-free, and very low in extractables. Also, a flow channel has been incorporated between the outer wrap and cartridge surface.

System pressure vessels are 316L SS, hold three modules each, and are electropolished inside. All product piping is 316L SS, sanitary type (with no threaded or flanged fittings). The water flow velocity is maintained ≥ 1.5 m/s in the piping and tubing.

Multi-stage centrifugal submersible pumps are used in series on the two pass RO systems to provide up to 6200 kPa feed pressure to the first pass membranes. The pumps rely on the feed water for lubrication and thus there is no potential for oil leaks. All wetted metal parts are 316SS.

The RO unit is microprocessor controlled to aid in system operation and data storage. Validation of processes is a critical part of pharmaceutical operations. The microprocessor controller produces repeatable system operating conditions, monitors key parameters during operation, and provides a data base for validation procedures.

SYSTEMS PERFORMANCE

A variety of tests have been performed on a prototype two-stage RO system in our laboratory. These include an extractables test on the sanitary design RO module, a sanitization test on the system, and an operational test to produce WFI.

Testing was performed to demonstrate the efficacy of the module design (including the feed stream bypass) to facilitate flushing of residual sanitization agents (NaOCl , CH_3COOOH , or HCHO). Flush water flow rates were from 0.28 to 0.41 l/s at 2756 kPa feed pressure. For modules with the feed flow bypass, all residual sanitizing agents were flushed to below detectable levels in the product water within thirty minutes. For modules without the sanitary design features, including no feed flow bypass, residual chemicals remained in the product stream after one hour of flushing.

Organic extractables tests were performed under normal service conditions and after repeated sanitization cycles (with either NaOCl or CH_3COOOH). During all tests, the product water met the USP criteria for total oxidizables.

A sanitary design prototype RO system was operated in our laboratory for a period of nine months. During that time, biological and chemical data were collected in order to study the performance of the unit. Figure 5 shows the pretreatment used and the flow path of the entire system.

The operating conditions for the RO system were: Feed pressure 345 kPa, 1st stage pressure 4500 kPa, 2nd stage pressure 1900 kPa, feed flow 1.07 l/s, product flow 0.57 l/s, and reject flow 0.50 l/s. The water temperature was 20°C.

Samples for bacteria analysis were obtained three times a week. Samples for chemical and pyrogen analysis were obtained twice a week. Water samples for bacteria were taken after the sampling ports were flamed and water flushed through them for one minute. The MF technique using SPC agar was used during the test period for bacterial recovery.

Ionic contaminants were determined by either specific ion electrodes or an inductive coupled plasma (ICP) apparatus. Total solids were obtained from conductivity readings in microsiemens.

Pyrogen levels were determined by the Limulus Amoebocyte Lysate assay.

To determine the salt rejection performance of the unit, a challenge test using 1500 mg/l NaCl was performed before and after the nine-month test under the same conditions. These results were 99.7% overall rejection before and 99.5% rejection after the test, indicating no loss of rejection during the test period.

Bacteria samples were taken at various times after chemical sanitization to determine if the levels increased as a function of time.

The chemical and microbial analyses of the feed and product streams (Table 3) indicate that over the nine months of testing, the prototype system consistently produced water quality that met the specifications outlined in Table 1.

During the test, two types of sanitizing agents were used, either 10 mg/l of NaOCl (pH = 5-6) or 100 mg/l of CH_3COOOH (pH = 4-5). The results indicated that right after sanitization, the bacteria levels were quite low, approximately 0-6 cfu/100 ml.

Bacteria and pyrogen levels in the product were compared to the feed in an attempt to correlate the results. A statistical analysis found the levels in the feed had no relation to the levels in the product. Such a correlation test may be useful in confirming module integrity. Since both sanitizing chemicals sanitize rather than sterilize, total bacteria kills will not be obtained at the stated concentrations.

Evaluation of a two pass unit that has operated at a customer location for five months indicates that USP chemical requirements for WFI have been easily met (data in Table 4). In addition, pyrogen concentrations have been below the limit of 0.25 EU/ml and bacteria counts in the 2nd stage product have been in the range of 1 to 2 cfu/ml (based on a weekly sanitization cycle).

PRETREATMENT CONSIDERATIONS

A proper pretreatment of feed waters is critical to maintaining an efficient and reliable operation of RO systems. A pretreatment process should be designed to accomplish the following: It must reduce the contaminants level to enable the RO systems to produce PW or WFI; it should protect RO system components (pump, membrane/module), and the treated water quality should improve with each treatment stage. A list of recommended treatment processes for the removal of commonly occurring RO feed water contaminants is provided in Table 5. A pretreatment capable of producing RO feed of enhanced quality should employ these processes in the right sequence.

COST OF PRODUCING PHARMACEUTICAL GRADE WATER

The reverse osmosis membrane-based process offers significant economic advantages over the distillation process for producing the pharmaceutical grade waters(2). The key advantages among these are energy costs and initial capital costs.

In distillation the greatest energy consumption takes place in vaporizing the water (latent heat of vaporization 540 cal/g @ 100°C.) The overall energy consumption of a still depends on its efficiency. The simplest

(single effect) still designs are the least efficient and are used only on a laboratory scale. For large volumes, distillation columns are staged to provide increased flow rates at a higher level of efficiency. The staging of columns results in a multi-effect still.

The key factors which determine operating costs for distillation are: (1) Energy, (2) Feed water, (3) Cooling water, (4) Discharge water (sewer cost) and (5) Pretreatment.

Reverse osmosis utilizes a pump and a membrane to purify the feed water. The process occurs at ambient temperature. Unlike distillation, there is no phase change. The impurities are removed by passing water through a membrane, using pressure as the driving potential.

The key components of operating costs for a reverse osmosis system are:

1. Energy consumption by the high pressure pump
2. Annual membrane replacement
3. Tap water (product and reject)
4. Discharge water (sewer costs)
5. Pretreatment

Table 6 summarizes the capital and operating costs of a reverse osmosis system (Milli-RO S, 0.8 l/s) and a comparable size multi-effect distillation system. The capital costs include the purchase price of the systems and pretreatment equipment. The data show the capital cost of the distillation system is 52% higher than the Milli-RO S system (\$5733/1000 liters/day for distillation vs. \$3000/1000 liters/day for RO). The operating costs data indicate the Milli-RO S process costs \$4.70/1000 liters while the distillation process costs \$20.90/1000 liters. The total of the operating cost and capital cost suggests the Milli-RO S system costs approximately 28% of the distillation costs (\$7.00/1000 liters vs. \$25.00/1000 liters). The payback period for the Milli-RO S process is calculated to be 1.2 years.

DISCUSSION

The development of the pharmaceutical RO systems presented in this paper now facilitates the production of pharmaceutical grade water at a much lower cost than the traditional distillation process.