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Demonstration of Molecular Purification in Polar Aprotic Solvents by Organic Solvent Nanofiltration

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Abstract:

Common separation challenges in the synthesis of active pharmaceutical ingredients (APIs) and production of high-value natural compounds (HVNCs) often involve molecules of molecular weight less than 1000 g·mol^{-1}. Examples are the removal of lower/higher molecular weight (MW) byproduct from an intermediate in API production, or the removal of free fatty acids (MW 200−300 g·mol^{-1}) from glycerides (MW 600−800 g·mol^{-1}) in natural oils. Here we show how organic solvent nanofiltration (OSN) can be applied to typical separation challenges. Two dyes, *Solvent Yellow 7* (MW = 198.2 g·mol^{-1}) (SY7) and *Brilliant Blue R* (MW = 826.0 g·mol^{-1}) (BB), are used in Case Study A as model product and impurity compounds, respectively. Case Study B is an actual separation challenge at Janssen Pharmacuetica NV involving an intermediate of a new drug candidate (API-INT, MW = 675 g·mol^{-1}) and its oligomeric impurities (MW ≥ 1000 g·mol^{-1}). Solutions to these separation challenges are demonstrated using organic solvent nanofiltration (OSN) spiral-wound membrane modules, applying diafiltration at kilo scale with typical organic solvents, *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF). For Case Study A, a final product with 99.7% purity of SY7 was generated from an initial starting solution of 91% purity, while recovering 90% of SY7. For Case Study B, 99% of the higher MW oligomeric impurities (i.e., tetramer and higher) have been removed from API-INT, whilst reducing the content of oligomeric impurities in the synthesis solution from 6.8 wt % to 2.4 wt %, which is below the allowed limit of 3 wt % oligomeric impurities, and recovering more than 99% of API-INT. By applying OSN, a solution is demonstrated to the tedious separation problem posed by Case Study B, which standard separation techniques (including chromatography, crystallization and charcoal treatment) cannot achieve. However, OSN diafiltration processes can require a large volume of solvent to achieve the target purity and yield of the desired compound. Coupling the purification process with a downstream OSN-solvent recovery system (dual membrane diafiltration (DMD)) provides a solvent-efficient process, which does not generate large volumes of waste and/or does not provide a dilute product solution that would require further processing. Operation of the spiral-wound modules in DMF and THF up to 10 days and 120 days, respectively showed that the membrane modules have stable flux and consistent separation performances over time. A simple mathematical tool is used to assist in membrane selection as well as in designing an efficient process configuration.

Introduction

Impurities are a hurdle in many pharmaceutical and nutraceutical production processes, where tiny amounts of impurities can adversely affect end-product quality. Therefore, the removal of impurities is a major concern.[1,2] State-of-the-art technologies primarily rely on crystallisation or column chromatography. Crystallisation is frequently used in active pharmaceutical ingredient (API) and high value natural compound (HVNC) production to isolate or purify materials. However, it can be a rather complex process that is difficult to control and scale-up due to the interlinked nature of chemical and physical effects, and requires significant optimization to generate acceptable process yields.[3,4] Preparative column chromatography is widely used in process development and is regarded as a reliable purification technology. However, it consumes large quantities of solvents, which require further downstream processing not only to recover the solvents but also to concentrate the diluted products.[5] In addition, when processing solutions containing some oligomeric impurities, the active sites of the stationary phase can become blocked by these oligomeric impurities, thus making the chromatography difficult and tedious.

Membrane technology, particularly nanofiltration, has attracted a great deal of attention as an alternative molecular purification technology for APIs and HVNCs.[6−15]

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By selecting suitable molecular weight cutoff (MWCO) membranes, this technology can be used to separate molecules of similar physical properties in the molecular weight range of 200 to 2,000 g·mol^{-1}. An additional benefit of nanofiltration processes compared to conventional thermal separation techniques is that the separation can be performed at near ambient or subambient temperatures, which is a considerable advantage for thermolabile compounds. Since many APIs and HVNCs are susceptible to thermal degradation, the flexible temperature operating window of membrane processes can minimise loss of activity and/or nutritive value due to thermal degradation.

Most established nanofiltration processes in industry are aqueous based, mainly in the dairy and sugar industries.[12] The application of nanofiltration in organic solvents is still limited, despite a wide range of potential opportunities in the pharmaceutical and natural products industries. Besides the relatively slow uptake of new technologies in the chemical industry, one of the main reasons for the slow technology breakthrough of membrane processes in organic solvents is the lack of robustness of commercially available membranes, especially in polar aprotic solvents. Since 1990, specialist organic solvent nanofiltration (OSN) membranes have been developed and the first large, industrial-scale OSN plant was installed at the ExxonMobil refinery in Beaumont (Texas, U.S.A.) to recover dewaxing solvents from lube oil filtrates.[16] These "first-generation" OSN membranes are reported to be stable in many apolar solvents including toluene, hexane, and ethyl acetate. Recently, a new "second generation" of highly stable nanofiltration membranes based on cross-linked polymers has been developed. These are reported to be stable in a wide range of key industrial solvents including tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and *N*-methyl-2-pyrrolidone (NMP).[17] Importantly, techniques to control the molecular weight cutoff (MWCO) of these membranes have made it possible to produce a range of membranes, from tight (MWCO around 200 g·mol^{-1}) to loose (MWCO around 1000 g·mol^{-1}).[18] Due to its excellent stability and availability with a range of different MWCO, this cross-linked membrane series (DuraMem) opens up many opportunities for applying OSN to molecular separations and, in particular, to purifying APIs/HVNCs using diafiltration processes.

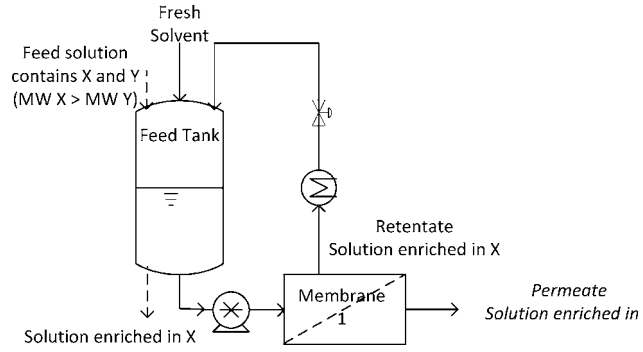

Figure 1. **Schematic diagram of an OSN membrane purification process of a mixture comprising compounds X (higher MW) and Y (lower MW).**

There are numerous applications of diafiltration processes in aqueous solution in the food and beverage, biotechnology and pharmaceutical industries.[5,19−21] The concept is depicted in Figure 1. Fresh solvent is added to a batch of feed which is undergoing filtration, so that the lower molecular weight species, compound Y, is flushed through the membrane whilst the higher molecular weight species, compound X, is held back (retained) by the membrane. The concentration of retained solute (compound X) is not allowed to increase during the diafiltration, which minimises concentration polarisation and fouling effects, and enables the permeating species (compound Y) to be flushed through the membrane more effectively.[22] In contrast, diafiltration of organic solvent solutions is rather unexplored. The use of OSN membranes in a diafiltration process for solvent exchanges has been reported.[22,23] However, to our knowledge, no literature has reported the use of OSN for diafiltration separations of two or more solutes in organic solvent solution.

The objective of this work is to demonstrate the use of OSN technology for diafiltration purification of APIs/HVNCs in harsh organic solvents such as DMF and THF. Two case studies of a typical separation problem are presented. The first case (Case Study A) is the separation of model compounds (organic dyes) - model product (4-phenylazophenol, *Solvent Yellow 7*) and model impurity ($C_{45}H_{44}N_3NaO_7S_2$, *Brilliant Blue R*). A practical application of OSN is demonstrated in Case Study B. Here the purification of an intermediate compound involved in the synthesis of a new drug candidate in the Janssen Pharmaceutica portfolio is performed by separating the desired product from oligomeric impurities. One of the main challenges facing the diafiltration processes in Case Studies A and B is that a considerable amount of fresh solvent is required to achieve a high yield of the product.

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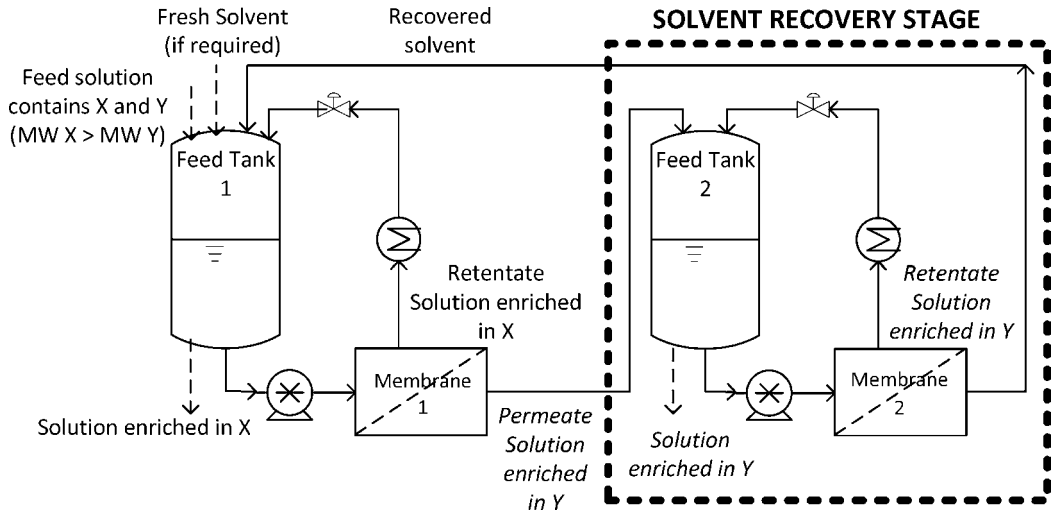

Figure 2. **Schematic diagram of dual membrane diafiltration (DMD) process, compound Y (lower MW) is separated from compound X (higher MW) in the primary stage using Membrane 1. In the secondary stage, compound Y is retained using Membrane 2, allowing solvent to be recycled back into the primary stage.**

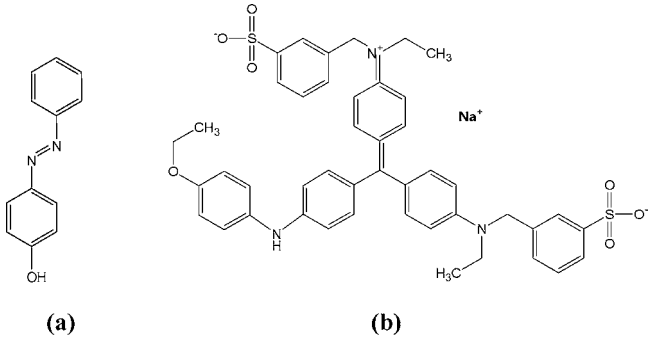

Figure 3. **Structures of model compounds used in Case Study A. (a) Model product, Solvent Yellow 7 (SY7) and (b) model impurity, Brilliant Blue R (BB).**

This is a generic problem in membrane diafiltration, since the permeating molecule is usually retained to some degree. We have reduced this limitation through using the dual membrane diafiltration (DMD) process, as illustrated in Figure 2. The DMD process combines two membrane stages, i.e. a purification stage combined with a solvent recovery stage. Here, instead of adding fresh solvent to the process, recovered solvent from the solvent recovery stage is returned to the purification stage to provide further purification. The feasibility of the DMD process is demonstrated through Case Study B.

Finally, commercially available spiral-wound modules are used to demonstrate the feasibility of the case studies at pilot scale. In addition to the feasibility of the membrane process, the stability of the membrane module and its components over time is essential if this technology is to be employed at industrial scale. This is demonstrated by testing the DuraMem membrane modules over an extended period of time in DMF and THF and by monitoring the separation characteristics (e.g., solvent permeability and molecular weight cutoff). Overall, this work demonstrates successful purification of API solutions in polar aprotic solvents such DMF and THF by diafiltration using highly stable OSN membranes.

Materials and Methods

The detailed process configurations and experimental procedures used for Case Studies A and B are described below.

Description. Case study A mimics a typical pharmaceutical/HVNC production challenge where purification of a product solution containing an API/HVNC and high molecular weight impurities is required. 4-phenylazophenol, *Solvent Yellow 7* (MW = 198.2 g·mol^{-1}) (SY7) and $C_{45}H_{44}N_3NaO_7S_2$, *Brilliant Blue R* (MW = 826.0 g·mol^{-1}) (BB) are used as model product and impurity compounds, respectively (Figure 3). When the selected model compounds are mixed, they provide distinctive visual properties; i.e. a mixture of SY7 (yellow) and BB (dark blue) is green. A schematic overview of Case Study A is shown in Figure 5a. The aim is to purify a solution containing 10 g·L^{-1} of the desired product compound, SY7, and 1 g·L^{-1} of the impurity, BB, to give a final purity of SY7 greater than 99.5% in the permeate whilst recovering ≥90% of SY7.

The yield of product i (Y_i) and purity of product i (P_i) are calculated using the following equations:

$$Y_i = \frac{M_{P,i}}{M_{F,i}} \times 100\% \quad (1)$$

$$P_i = \frac{M_i}{\sum M_i} \times 100\% \quad (2)$$

Case study B is a natural extension of Case study A, involving the separation of an API intermediate molecule from

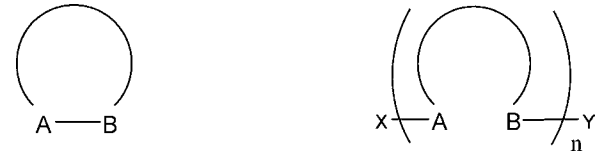

Figure 4. **Structures of API intermediate (API-INT) and its oligomeric impurities.**

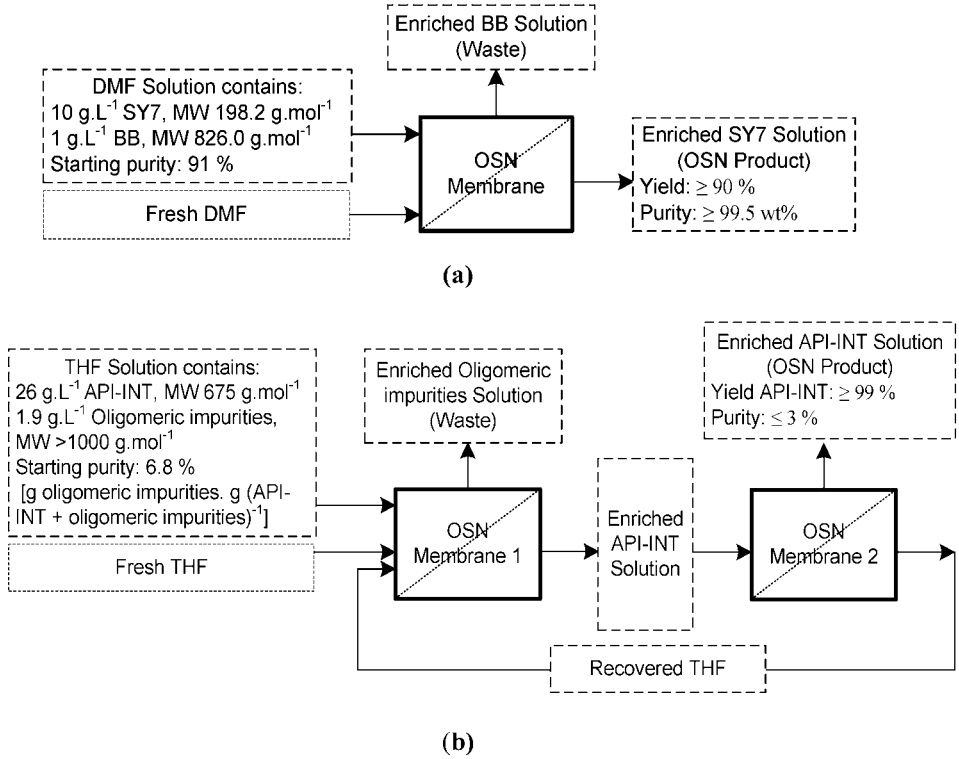

Figure 5. **Objectives of case studies presented in this article using OSN technology: (a) Case Study A - purification of organic dye SY7 from organic dye BB and (b) Case Study B - purification of an API-INT from its oligomeric impurities.**

higher MW impurities. During the synthesis of a macrocyclic intermediate of a new drug candidate at Janssen Pharmaceutica (API-INT, MW = 675 g·mol^{-1}), its isomer (Isomer B), and a series of oligomeric impurities based on API-INT with MW > 1000 g·mol^{-1} (i.e., dimers, trimers, tetramers, pentamers, etc.) are also formed. Figure 4 presents the general chemical structures of API-INT and its oligomeric impurities. Isomer B and dimers and trimers of API-INT can be separated using conventional techniques such as preparative high pressure chromatography. However the presence of oligomeric impurities, especially the tetramers and higher oligomers of API-INT, block the active sites of the stationary phase and make this separation step tedious. A schematic summary of Case Study B is shown in Figure 5b. The main objective of this case study is to remove ≥99% of the tetramers and higher oligomeric impurities from API-INT, while recovering ≥95.0% of API-INT. Advantageously, by removing these oligomeric impurities to ≤3.0%, just one chromatography stage rather than multiple chromatography stages is required to generate high-purity API-INT for subsequent reaction steps in the production process. Reducing the number of chromatography stages provides major savings in time, equipment occupancy, and materials cost. The efficiency of other separation techniques such as charcoal treatment and crystallisation for the separation is also compared.

In this case study, the DMD concept is introduced for solvent recycle (Figure 2). Permeate containing the purified product from the primary membrane filtration (Membrane 1) is fed into the solvent recycle stage (Membrane 2). API-INT, isomer B, and the oligomeric impurities are retained by Membrane 2 in the solvent recovery stage, whilst the solvent freely passes through the membrane. The permeate from the solvent recovery stage (stage 2) is then returned to the purification stage (stage 1). This closed-system configuration allows solvent to be recycled and minimises the use of fresh solvent. The yield of API-INT ($Y_{\text{API-INT}}$) and impurity level in the OSN product (I) after the purification processes are calculated based on eqs 3 and 4, respectively. The impurity level in the purified product is based on the relative mass of API-INT and the oligomeric impurities (i.e., dimer, trimer, tetramer, and pentamer of API-INT) present in the product.

$$Y_{API-INT} = \frac{M_{R2,\text{API}-\text{INT}}}{M_{F,\text{API}-\text{INT}}} \times 100\% \quad (3)$$

$$I = \frac{M_{R2,\text{oligomeric impurities}}}{M_{R2,\text{API-INT}} + M_{R2,\text{oligomeric impurities}}} \times 100\% \quad (4)$$

Experimental Section. To identify a suitable membrane for this application, different nominal MWCO flat-sheet membranes from the DuraMem series were used.[24] DuraMem membranes are prepared by immersion precipitation of polyimide followed by further treatment with diamines for cross-linking to improve their stability.[17] Variation of the dope solution composition provides a range of different MWCO.[18] The screening solution is a mixture of 10 g·L^{-1} of SY7 and 1 g·L^{-1} of BB. A key industrial solvent, DMF, is used as the process solvent. Flat-sheet membrane filtration experiments are conducted using a MET*cell* crossflow filtration apparatus. The methodology for testing flat-sheet membranes is as discussed elsewhere by See Toh et al.[17,18]

Two parameters used to characterise the membrane performance in this study are flux and rejection. Solvent flux is

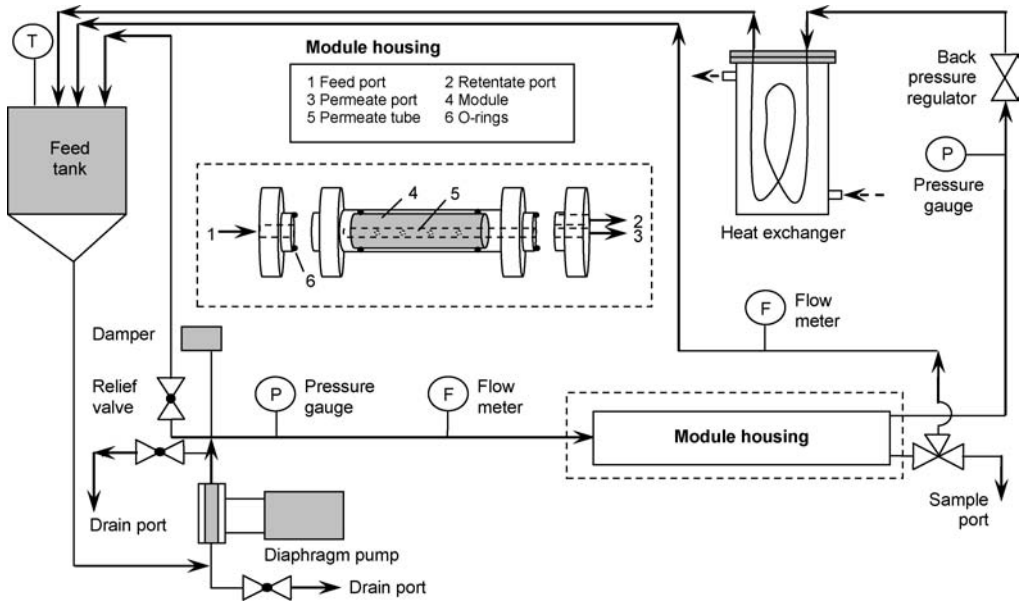

Figure 6. **MET kilo plant filtration unit.**

obtained by measuring the volume permeated per unit area of membrane per unit time using the following equation:

$$J_P = \frac{V_P}{A \cdot t} \tag{5}$$

Rejection of any species is used to assess the ability of the membrane to separate that species between the permeate and retentate solutions. The higher the rejection of species *i*, the more species *i* is retained by the membrane. Rejection of species *i* is defined by the following equation:

$$R_i = \left(1 - \frac{C_{P,i}}{C_{R,i}}\right) \times 100\% \tag{6}$$

Once a suitable membrane is identified, the selected membrane was fabricated into 1.8-in. diameter × 12-in. length spiral-wound modules. The effective membrane area of each element is approximately 0.27 m^2. Since the membrane module is operated in two different types of organic solvents, careful selection of all materials in addition to the membrane is required, i.e. all components used to fabricate the membrane module must be stable in the organic solvents. Before use, each membrane module requires conditioning with its process solvent (i.e., DMF and THF for Case Studies A and B respectively) at 2−10 bar to remove the preserving agent and other leachables from the spiral-wound module. Approximately 50 L of solvent is required to flush 1 m^2 of membrane area. The solvent requirement may vary depending on the solvent employed.

To demonstrate this purification process, 3 L of DMF solution containing 10 $g \cdot L^{-1}$ of SY7 and 1 $g \cdot L^{-1}$ of BB was filtered through a spiral-wound membrane module in diafiltration mode using a kilo scale filtration unit (Figure 6). The system consisted of a 5 L capacity feed vessel and module housing(s) designed to hold the 1.8-in. × 12-in. spiral-wound module. The solution was pumped from the feed tank to the module housing by a high-pressure diaphragm pump fitted with a pulsation damper. The filtration pressure is controlled by a back pressure regulator located in the retentate line. The unit was operated in recycle mode (i.e., the permeate was recycled to the feed tank) at the selected pressure and temperature until a stable flux is achieved, before changing to diafiltration mode in which the permeate is discharged from the system and collected. Fresh DMF is charged to the system to maintain a constant feed volume. Samples are taken after each integer diafiltration volume (*N*), which is defined as

$$N = \frac{V_P}{V_F} \tag{7}$$

and flux and rejection are calculated using eqs 5−6.

Similar to the experimental procedure used in Case Study A, a series of flat-sheet DuraMem membranes were tested to identify the best membrane for purifying the starting solution of Case Study B and for recovering the process solvent (THF). On the basis of the screening test results, spiral-wound modules containing the selected membranes were fabricated. Two feed solutions were used in the screening experiments, for different purposes. Reaction mixture synthesised at Janssen Pharmaceutica (feed solution I) containing 26 $g \cdot L^{-1}$ of API-INT, 7.2 $g \cdot L^{-1}$ of Isomer B, and 1.9 $g \cdot L^{-1}$ of oligomeric impurities in THF was the feed solution for the purification stage. The oligomeric impurities in this mixture are given in Table 3. A purified material generated via OSN containing 8.4 $g \cdot L^{-1}$ of API-INT, 2.1 $g \cdot L^{-1}$ of isomer B, and ≤0.2 $g \cdot L^{-1}$ of oligomeric impurities (89.8% of dimers, 9.8% of trimers, 0.4% of tetramers, and 0% of pentamers) in THF (feed solution II) was used as feed solution for the solvent recovery stage.

Demonstration of the purification process of feed solution I via DMD was performed using two kilo scale filtration units as shown in the schematic diagram of Figure 2, with one 1.8-in. × 12-in. spiral-wound module and two 1.8-in. × 12-in. spiral-wound modules installed into the purification and solvent recovery stages respectively. This configuration allows a continuous filtration to be carried out since the permeate flux of the purification stage is almost double the permeate flux of

the solvent recovery stage. Concomitantly, with a larger dead volume in the solvent recovery stage, the feed volume was fixed at 3.5 and 6.5 L in purification and solvent recovery stages respectively. Feed solution I was initially purified with five diafiltration volumes of fresh THF. The process was then continued in parallel with the solvent recovery stage until the target yield was achieved. Overall, both stages were operated in constant volume filtration mode, achieved by adding permeate collected from the purification stage to the solvent recycle stage at the same rate as permeate was removed from the solvent recovery stage. Each stage in the DMD system was fitted with a facility to recycle permeate back to its respective feed tank to allow controlled permeate flow rates from both systems, and subsequently to operate the filtrations continuously. Samples were taken after each diafiltration volume for analysis.

Chemicals and Analytical Procedures. 4-Phenylazophenol, *Solvent Yellow 7* (MW = 198.2 $g \cdot mol^{-1}$) (SY7), $C_{45}H_{44}N_3NaO_7S_2$, *Brilliant Blue R* (MW = 826.0 $g \cdot mol^{-1}$) (BB), and HPLC grade ammonium acetate (MW = 77.2 $g \cdot mol^{-1}$) were purchased from Sigma-Aldrich (UK). All organic solvents used in this study, including DMF (Rathburn, UK), THF (Rathburn, UK), methanol (VWR, UK), acetronitrile (VWR, UK) were HPLC grade.

Concentrations of the dye compounds in solution were measured using a method reported by Yoshioka and Ichihashi (2008).[25] Analysis was performed with a reverse-phase C18 HPLC column (ACE5, 250 × 4.6 mm) using a UV detector. Solvent A was 0.1 $mol \cdot L^{-1}$ ammonium acetate aqueous solution, and solvent B was methanol/acetonitrile mixture (50:50 by volume). The flow rate was fixed at 1 $mL \cdot min^{-1}$, and the injection volume was 20 μL. As the dyes (SY7 and BB) have different absorption spectra, the samples were analysed at two wavelengths (350 nm for SY7 and 620 nm for BB). For both markers, the initial mobile phase composition was 97% of solvent B, and a linear gradient changed the mobile phase to 70% solvent B over 10 min. The 70% solvent B mobile phase was held for 1 min before returning to the initial 97% solvent B mobile phase over 1 min.

The reaction mixture (feed solution 1) containing the desired macrocyclic intermediate (API-INT), Isomer B and oligomeric impurities (as presented in Figure 4) was synthesised at Janssen Pharmaceutica. The concentrations of API-INT and Isomer B were measured using HPLC. The oligomeric impurities such as dimers, trimers, tetramers, and pentamers were determined by gel permeation chromatography (GPC). In addition, the presence of tetramers and pentamers of API-INT was also determined by means of thin layer chromatography (TLC). As the compounds are still under development, the public release of their detailed structure and analytical methods is not possible at the present time.

Process Modeling. A mathematical model was developed to predict process performance during the diafiltration. The model is based on mass balances at steady state using simplifying assumptions. The process parameters, variables, and equations are elaborated in the Support Information.

(24) DuraMem is supplied by and is a trademark of Membrane Extraction Technology Limited (www.membrane-extraction-technology.com).
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Table 1. **Summary of screening results for flat-sheet membranes using solution containing SY7 (10 $g \cdot L^{-1}$) and BB (1 $g \cdot L^{-1}$) in DMF[a]**

entry	operating pressure (bar)	membrane	permeate flux ($L \cdot m^{-2} \cdot h^{-1}$)	rejection (%) SY7	BB
1	10	DuraMem200	3	85.6	99.7
2	10	DuraMem300	18	83.8	99.6
3	10	DuraMem500	9	70.0	91.4
4	20	DuraMem200	4	86.6	99.3
5	20	DuraMem300	29	85.2	99.6
6	20	DuraMem500	17	74.6	94.6
7	30	DuraMem150	7	91.0	99.9
8	30	DuraMem200	11	88.1	99.9
9	30	DuraMem300	31	86.4	99.9
10	60	DuraMem150	9	93.9	99.9
11	60	DuraMem200	11	87.9	99.8
12	60	DuraMem300	51	93.3	99.9

[a] Filtrations performed at 30 °C in full-recycle mode (permeate and retentate returned to the feed tank). Rejections of each membrane disc are measured after 8 h.

The yield and purity of the process of Case Study A was calculated from eqs 1−2 using the predicted concentration profiles obtained from the following equations:

$$C_{R,i} = C_{F,i} \cdot e^{-N(1-R_i)} \tag{8}$$

$$C_{P,i} = \frac{C_{F,i} \cdot V_F(1 - e^{-N(i-R_i)})}{J_P \cdot A \cdot t} \tag{9}$$

Similar to a single-stage filtration model, by assuming the same volume and permeate flux of both filtration stages in a DMD process (purification and solvent recovery), the yield and impurity level of the process of Case Study B can be determined by eqs 3−4 using the concentration profiles of species *i* at time *t* in stage 1 and 2 derived from eqs 10 and 13 respectively:

$$C_{R1,i,t} = \frac{(\Omega_i \cdot C_{R1,i,0} + \Phi_i) \cdot e^{(J_P \cdot A \cdot \Omega_i \cdot t/V_1)} - \Phi_i}{\Omega_i} \tag{10}$$

where

$$\Omega_i = -[(1 - R_{i2}) + (1 - R_{i1})] \tag{11}$$

and

$$\Phi_i = (1 - R_{i2}) \cdot C_{R1,i,0} \tag{12}$$

$$C_{i,R2,t} = \frac{V_1(C_{R1,i,0} - C_{R1,i,t})}{V_2} \tag{13}$$

Membrane Module Stability. The stability of the DuraMem modules were tested over an extended period of time in DMF and THF following the method developed by See-Toh et al. (2007).[26] Flux and rejection were measured over the filtration period to monitor and measure any deterioration of separation properties of the membrane module.

(26) See Toh, Y. H.; Loh, X. X.; Li, K.; Bismarck, A.; Livingston, A. G. *J. Membr. Sci.* **2007**, *291*, 120–125.

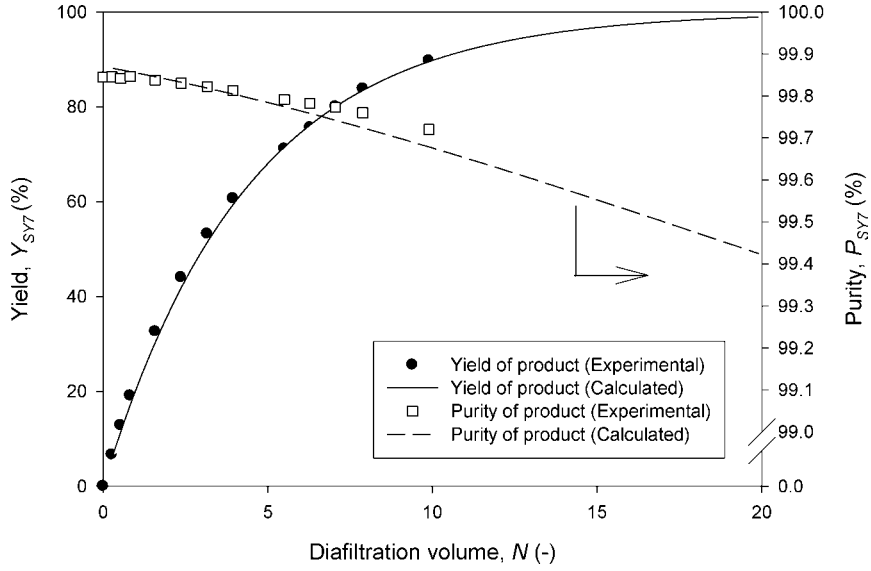

Figure 7. **Yield and purity profiles of Case Study A using a 1.8-in. × 12-in. DuraMem300 membrane module at 30 °C and 30 bar.**

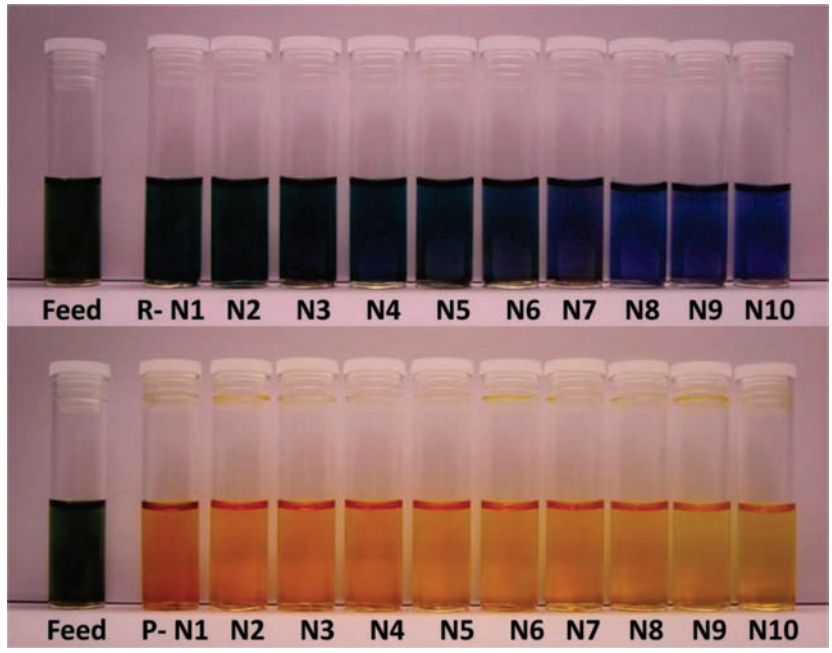

Figure 8. **Photograph of the initial solution, permeate, and retentate samples at each diafiltration volume (with 40 times dilution of feed and retentate).**

Results and Discussion

Case Study A. *Flat-Sheet Membrane Screening.* Four DuraMem membranes, DuraMem150, 200, 300, and 500 were tested at different operating pressures. The numbers following the name indicate the nominal MWCO of each membrane at 30 bar for DuraMem 150, 200 and 300; and 20 bar for DuraMem500.[27] The rejection of SY7 and BB and the permeate flux are summarised in Table 1. In general, rejections of SY7 and BB correlated well with the nominal MWCO of the membranes. Both rejections and fluxes increased at higher operating pressures for all entries. It is worth noting that the fluxes from DuraMem500 at 10 and 20 bar were lower than those from DuraMem300 at the same operating pressure which is not always the case for a more open membrane. This phenomenon may be attributed to fouling on the membrane surface, which was visually observed as a dye stain on the surface of the DuraMem500 but was not observed on the surface of the DuraMem 150, 200, and 300 membranes.

Since the aim of this purification process is to separate BB (model impurity) from SY7 (model product), the ideal membrane should completely retain BB whilst allowing SY7 to pass through unhindered. In addition to the rejection characteristics, a high permeate flux is desirable from the process economics point of view as this minimizes the required membrane area. Of the membranes tested, DuraMem500 (entries 3 and 6) gives the lowest rejection of SY7 (70−75%). However, it also provides a relatively low rejection of BB (91−95%) preventing

(27) The maximum operating pressures of DuraMem series supplied by Membrane Extraction Technology Ltd. are as follows: DuraMem 150, 200, and 300 (60 bar); and 500 and 1000 (20 bar).

Table 2. **Summary of screening results for flat-sheet membranes using feed solutions I and II[a]**

					rejection (%)[b]				
entry	feed solution[a]	operating pressure (bar)	membrane	permeate flux ($L \cdot m^{-2} \cdot h^{-1}$)	API-INT	dimer	trimer	tetramer	pentamer
1	I	10	DuraMem500	9	83.4	95.6	99.0	≥99.9	≥99.9
2	I	10	DuraMem500	14	80.1	95.7	98.6	≥99.9	≥99.9
3	I	10	DuraMem1000	20	59.7	93.1	96.2	≥99.9	≥99.9
4	I	20	DuraMem500	20	90.1	98.9	99.4	≥99.9	≥99.9
5	I	20	DuraMem500	27	93.4	99.3	99.6	≥99.9	≥99.9
6	I	20	DuraMem1000	32	80.0	95.7	98.2	≥99.9	≥99.9
7	II	30	DuraMem300	6	97.3	≥99.9	≥99.9	≥99.9	≥99.9
8	II	30	DuraMem300	7	96.9	≥99.9	≥99.9	≥99.9	≥99.9
9	II	60	DuraMem300	12	99.7	≥99.9	≥99.9	≥99.9	≥99.9
10	II	60	DuraMem300	13	99.5	≥99.9	≥99.9	≥99.9	≥99.9

[a] Feed solution I contains 26 $g \cdot L^{-1}$ of API-INT, 7.2 $g \cdot L^{-1}$ of Isomer B, and 1.9 $g \cdot L^{-1}$ of oligomeric impurities in THF (68.6% of dimers, 11.0% of trimers, 10.2% tetramers, and 10.2% pentamers). Feed solution II is a purified material generated via OSN containing 8.4 $g \cdot L^{-1}$ of API-INT, 2.1 $g \cdot L^{-1}$ of Isomer B and ≤0.2 $g \cdot L^{-1}$ of oligomeric impurities (89.8% of dimers, 9.8% of trimers, 0.4% of tetramers and 0% of pentamers) in THF. [b] Analysed by HPLC (API-INT and dimer) and GPC (dimer, trimer, tetramer, and pentamer). [a] Filtrations performed at 30 °C in full-recycle mode (permeate and retentate returned to the feed tank). Rejections of each membrane disc are measured after 8 h.

a good separation between the two compounds. Similarly, DuraMem150 is not suitable for this application due to its high SY7 rejection (>90%) and low permeate fluxes. The mathematical model suggests both DuraMem200 (entries 1, 4, 8) and 300 (entries 2, 5, 9) at 10−30 bar are good candidates for this application, and we selected DuraMem300 due to its higher permeate flux. No significant difference in rejection of SY7 by DuraMem300 was observed during operation at 10, 20, and 30 bar. However, 30 bar was selected since higher flux is preferable.

Purification Process. The experimental yield and purity profiles during the purification of a solution mixture containing 10 $g \cdot L^{-1}$ SY7 and 1 $g \cdot L^{-1}$ BB are plotted along with the calculated values as a function of diafiltration volume in Figure 7. The purity of the permeate and retentate streams can also be visually assessed from the photograph in Figure 8. Both permeate flux and rejections of SY7 and BB remained constant during the purification process. The initial permeate flux was 33.9 $L \cdot m^{-2} \cdot h^{-1}$, while the final permeate flux measured was 34.2 $L.m^{-2} \cdot h^{-1}$. The average rejections of SY7 and BB were 76.6 ± 0.9% and 99.6 ± 0.1%, respectively. The permeate fluxes and rejections are consistent with those obtained from flat-sheet screening, except for the rejection of SY7 which may have been lower in the flat-sheet testing due to concentration polarization effects. From Figure 7, a high product purity of 99.7% and a product yield of 90% were achieved after 10 diafiltration volumes. The calculated yield and purity are in good agreement with experimental values, suggesting that the model is valid for process prediction and scale-up. The calculated profiles show that after 20 diafiltration volumes, it is possible to recover 99% of the product whilst generating a final product of 99.4% purity. Concomitantly, the photograph in Figure 8 shows a clear separation between SY7 and BB, where the feed stream starts as a green colour (yellow plus blue) that evolves to intense blue as the yellow SY7 is removed, with the permeate stream remaining yellow at all times.

The results of Case Study A demonstrated that purification of organic solvent solutions containing products and impurities in the MW range 200−1000 $g \cdot mol^{-1}$ using OSN technology

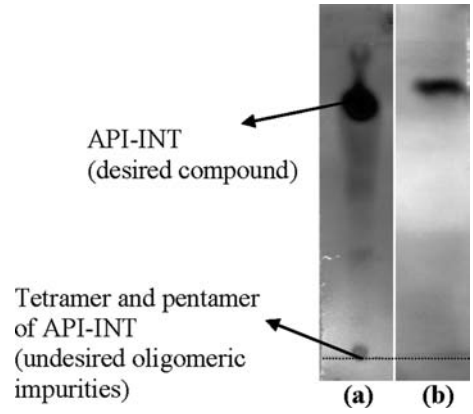

Figure 9. **Thin layer chromatography (TLC) traces of (a) feed solution I and (b) permeate collected from entry 3 in Table 2.**

is feasible. The system presented in this study mimics common industrial systems, and the concept can be readily transferred to various applications in pharmaceutical and natural products production (e.g., separation of API from lower/higher MW byproduct in the pharmaceutical industry and removal of free fatty acids (MW 200−300 $g \cdot mol^{-1}$) from glycerides (MW 600−800 $g \cdot mol^{-1}$) present in natural oils). Depending on the application target, the process can be customised to deliver the target yield and purity.

Case Study B. *Flat-Sheet Membrane Screening.* The performance of selected DuraMem membranes with API solutions in THF at 30 °C and operating pressures in the range 10−60 bar are presented in Table 2. Both DuraMem500 and DuraMem1000 are suitable to remove tetramer and pentamer impurities from API-INT in feed solution I, with tetramer and pentamer rejections ≥99.9% (entries 1−6, in Table 2). TLC analysis (Figure 9) confirmed that there was no presence of tetramer or pentamer in the permeate of entry 3, suggesting that the membranes are able to highly retain these larger oligomeric species. On the basis of the mathematical model derived above and using the experimental results obtained in Table 2, two systems are able to provide a purified API-INT solution with ≤3.0% of oligomeric impurities in the OSN product, while recovering ≥98% of API-INT. These include DuraMem1000 at 10 bar (entry 3 in Table 2) and

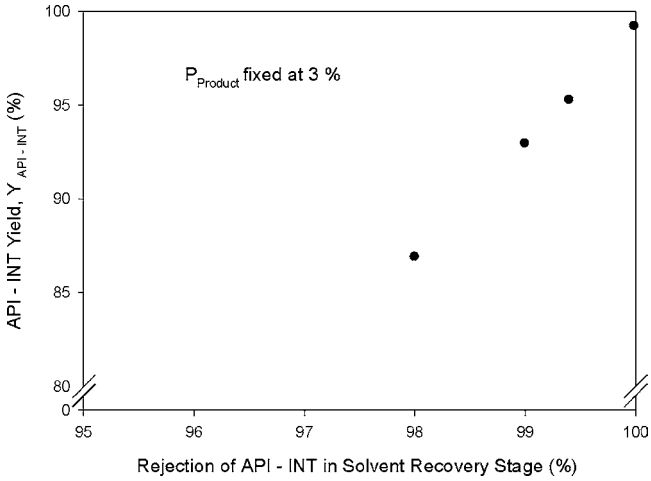

Figure 10. **Effect of API-INT rejection in the solvent recovery stage in a DMD process to the API-INT yield at a fixed impurity level of 3%.**

DuraMem500 at 20 bar (entries 4 and 5 in Table 2). However, the best membrane for removing ≥99% of tetramer and pentamer of API-INT and purifying feed solution I to the target purity while achieving the target yield is DuraMem1000 at 10 bar. DuraMem500 at 20 bar is not able to achieve all of the objectives of Case Study B since it is only able to remove ~95% of the tetramers and pentamers of API-INT from feed solution I. This is due to the higher number of diafiltration volumes required to achieve 98+ % recovery of API-INT. Effectively, DuraMem500 at 20 bar is more viable for removing lower MW oligomeric impurities such as dimers and trimers.

The potential of OSN technology to recover the process solvent from the diluted permeate generated from the purification process and to use the recovered solvent for further purification is evaluated here. Figure 10 presents the results of a mathematical model showing the influence of API-INT rejection in the solvent recovery stage of a DMD process on API-INT yield when the impurity level is fixed at 3%. It can be concluded that a minimum API-INT rejection of 99.4% is sufficient to generate a product purity of 3% whilst achieving the target API-INT yield of 95%. From Table 2, DuraMem300 provides the highest rejection of API-INT, 99.5−99.7% at 60 bar (entries 9 and 10 in Table 2), with an average permeate flux of 12.5 $L \cdot m^{-2} \cdot h^{-1}$. This membrane at 60 bar can therefore be used for the solvent recovery stage. However, since the permeate flux from the purification of feed solution I (entry 3, in Table 2) is 1.6 times the permeate flux of the solvent recovery of feed solution II (entries 9 and 10, in Table 2), the membrane area required in the solvent recovery stage of the DMD process will be ≥1.6 of the membrane area used in the purification stage.

Purification Process. In Case Study B, the purification process was initially performed using five diafiltration volumes of fresh THF (N = 0 to 5) and completed with recovered THF (N = 6 to 10) following the DMD process as described and shown in both Figures 2 and 5(b) until the target yield was achieved. The yield of API-INT and impurity level in the purified product during the purification process is summarised in Figure 11. The experimental yield of API-INT and impurity level in the OSN product closely follows the projected values estimated from a single stage purification system without solvent recovery. In fact, the purity of the product from diafiltration volumes (N) 5 to 10 deviates positively from the calculated values which are based on the initial rejection values. This is due to the improved rejections of the oligomeric impurities in the purification stage over time. Meanwhile, the rejection of API-INT remains consistent at 59.4 ± 6.1% during the purification process. This behavior may be attributed to compaction of the membrane over time, which is often observed with polyimide membranes.[28] A product with impurity level of 2.4% oligomeric impurities and product yield of 99.2% was achieved at the end of the purification process, whilst providing a consistent permeate flux of 28 ± 2.8 $L \cdot m^{-2} \cdot h^{-1}$ in the purification stage and an average of 11 ± 1.8 $L \cdot m^{-2} \cdot h^{-1}$ in the solvent recovery stage. The composition of oligomeric impurities in the purified material (OSN product) and the overall removal of each specific oligomeric impurity of API-INT is summarised in Table 3.

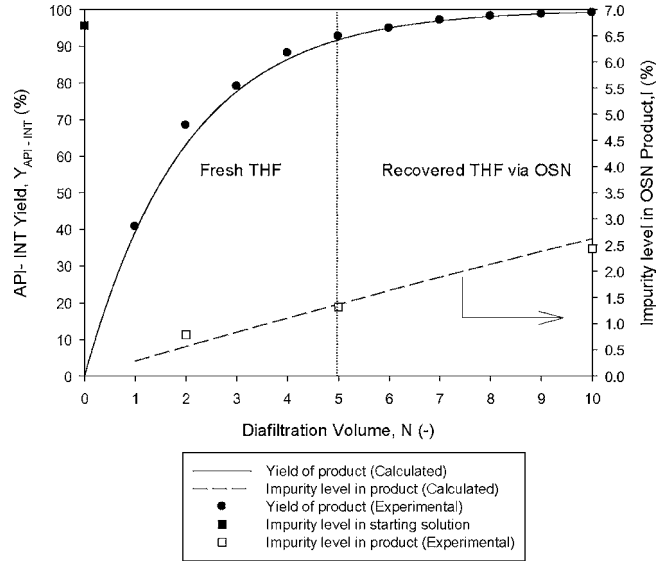

Figure 11. **Yield and purity profiles of Case Study B using the DMD process with a 1.8-in. × 12-in. spiral-wound DuraMem1000 module operated at 30 °C and 10 bar in the purification stage and two 1.8-in. × 12-in. spiral wound DuraMem300 modules operated at 30 °C and 60 bar in the solvent recovery stage.**

As alluded to previously, the DMD process is feasible to operate, without affecting the yield of API-INT and the impurity level in the purified product, as long as the purity of the recovered solvent is ≥99.99% and/or free

Table 3. **Composition of oligomeric impurities in feed solution I and purified material (OSN), and percentage of oligomeric impurities removed after purification through OSN using DMD process**

	Impurity level, I (%)			
solution	dimer	trimer	tetramer	pentamer
feed solution I	4.6	0.7	0.7	0.7
OSN product	1.8	0.2	≤0.1	≤0.1
removal (%)	60	69	99	99

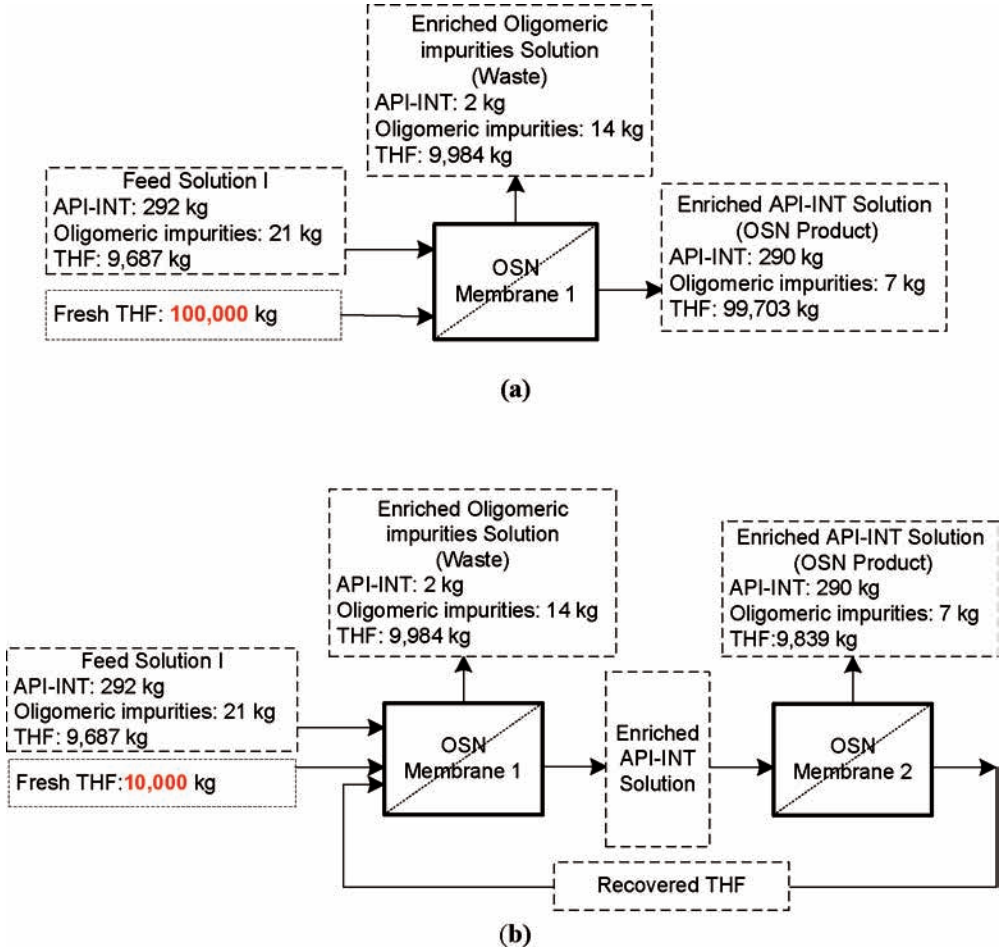

Figure 12. **Mass balance of Case Study B based on experimental results: (a) without solvent recovery and (b) with solvent recovery - DMD process, to process 10 batches of 1000 kg of feed solution I.**

Table 4. **Efficiency of OSN, crystallisation, and charcoal treatment in removing oligomeric impurities from feed solution I and yield of API-INT after purification treatment**

	efficiency		
separation method	removal of oligomeric impurities (e.g., dimers, trimers, tetramers and pentamers) (%)	removal of tetramers and pentamers (%)	yield of API-INT (%)
OSN (Case Study B)	67	99	99.2
crystallisation	30	26	85
charcoal treatment	45	60	98

of API-INT, which is achieved in Case Study B. The simple mathematical model employed here can be used to assist in membrane selection, as well as in designing an efficient process configuration.

The integration of solvent recovery in the DMD process can massively reduce the fresh solvent requirement for purifying a fixed mass of feed solution I by up to 90%, in an ideal process where 0% of solvent is lost from the system via evaporation and/or no dead volume is present in the system. Figure 12 presents the mass balance of Case Study B ((a) without the solvent recovery stage and (b) with the solvent recovery stage - DMD) to process 10 batches of 1 tonne of feed solution I. Further reduction in the THF usage of Case Study B is possible with the DMD process by optimising the solvent recovery stage, i.e. removing the retentate of the solvent recovery stage after processing several batches of feed solution I, which will not significantly affect the membrane performance (permeate flux, membrane fouling and etc.). Furthermore, DMD advantageously avoids generating a diluted product which would require further downstream processing. The efficiency of three optimised separation technologies (OSN, crystallisation, and charcoal treatment) to remove oligomeric impurities from API-INT is shown in Table 4. Overall these results show that OSN is a very promising technology as it successfully removed the problematic oligomeric impurities, while losing $\leq$1% of the desired and expensive API-INT from feed solution I.

Stability of Membrane Modules. The membrane characterisation technique introduced by See-Toh et al.[26] has been adapted to evaluate the chemical and mechanical

(28) White, L. S. *J. Membr. Sci.* **2002**, *205*, 191–202.

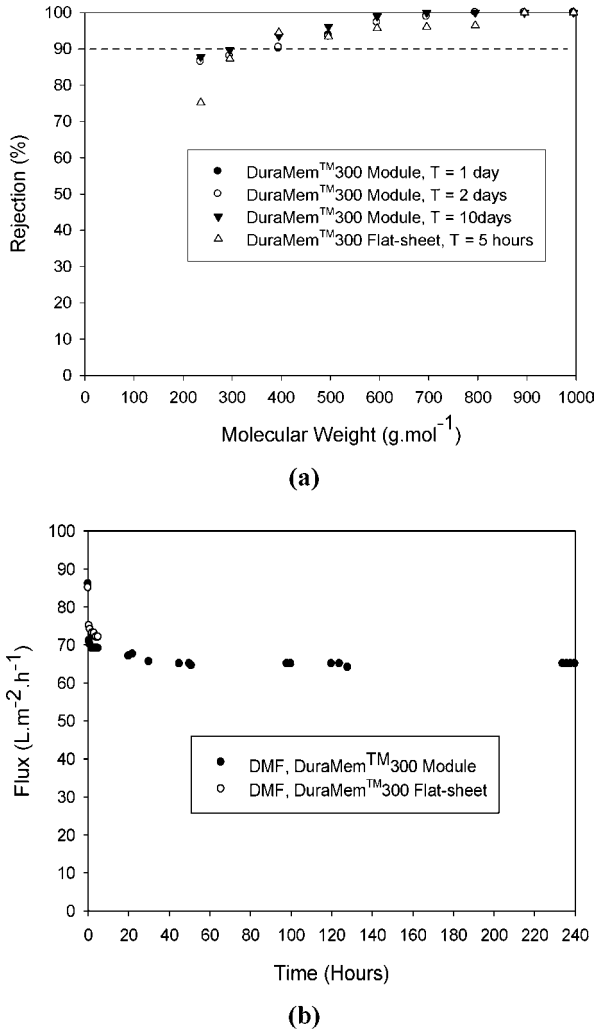

Figure 13. **(a) Rejection profile and (b) DMF flux of 1.8-in. × 12-in. DuraMem300 membrane module at 30 bar and 30 °C over a period of 10 days in DMF, using polystyrene oligomers as markers.**

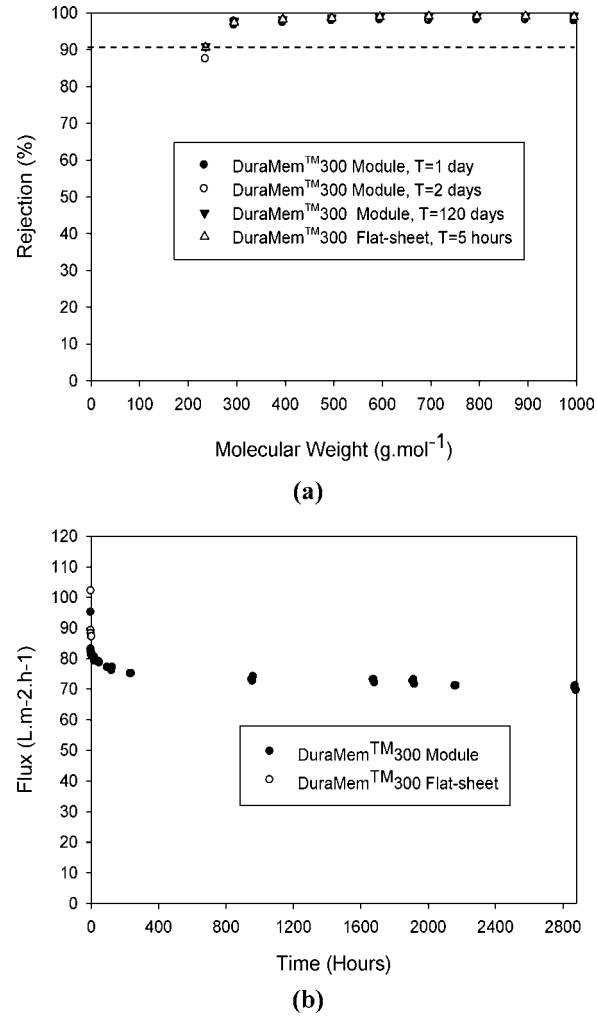

Figure 14. **(a) Rejection profile and (b) THF flux of 1.8-in. × 12-in. DuraMem300 membrane module at 30 bar and 30 °C over a period of 120 days in THF, using polystyrene oligomers as markers.**

stability of membrane modules. Figures 13 and 14 present (a) the rejection profile and (b) flux of DuraMem300 membrane modules in DMF and THF at 30 bar and 30 °C respectively. The continuous testing was carried out over 10 days in DMF and 120 days in THF with flux and rejection measurements taken periodically. The membrane modules of DuraMem300 reached a stable permeate flux after 5 h of compaction, giving a final flux of 65 $L \cdot m^{-2} \cdot h^{-1}$ and 70 $L \cdot m^{-2} \cdot h^{-1}$ in pure DMF and THF respectively (since the feed solutions are dilute and contain approximately 2 $g \cdot L^{-1}$ of solute in solution). Maximum compaction of the membrane in the modules is observed in the first 0.5 h of filtration, resulting in about 24 − 27% reduction in permeate flux in both cases. The membrane modules also showed a MWCO of 300 $g \cdot mol^{-1}$ in DMF and 200 $g \cdot mol^{-1}$ in THF (MWCO is the molecular weight at which 90% rejection is obtained). The data unequivocally demonstrates the stability over an extended test period of the membrane module in these harsh conditions whilst still affording good separation performance.

Conclusion

The application of OSN using DuraMem membrane modules for purifying a model solution containing product (SY7) and impurity (BB) in DMF (Case Study A), and an organic synthesis solution containing API intermediate (API-INT) from its oligomeric impurities such as dimer, trimer, tetramer and pentamer in THF (Case Study B) has been demonstrated. In Case Study A, a purified product with purity of 99.7% SY7 was generated from the model solution, while 90% of SY7 was recovered. In Case Study B, the overall content of oligomeric impurities in an organic solution synthesised at Janssen Pharmaceutica was reduced from 6.8% to 2.4%, which is below the target limit of 3.0% oligomeric impurities, as well as removing 99% of the particularly challenging higher oligomeric impurities (i.e., tetramer and higher of API-INT). Integrating a downstream OSN-based solvent recovery system into the diafiltration purification process via Dual Membrane Diafiltration (DMD) massively reduced fresh solvent consumption. The DMD process also solves the problem commonly encountered in membrane purification techniques, i.e. by retaining the desired product with the

solvent recovery membrane, the DMD process does not generate a dilute product solution that requires further processing. Extended testing of the DuraMem300 membrane modules in DMF for 10 days and in THF for 120 days showed the membrane modules to be stable with consistent separation characteristics over the testing period.

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Nomenclature

A	membrane area (m^2)
C	concentration ($g \cdot L^{-1}$)
J	volumetric flux ($L \cdot m^{-2} \cdot h^{-1}$)
M	mass (g)
N	diafiltration volume (−)
P	purity (%)
R	rejection (%)
t	time (h)
V	volume (L)
Y	yield (%)

Subscripts

F	feed
i	compound i
P	permeate
R	retentate
t	time

Supporting Information Available

Mathematical model for process prediction. This material is available free of charge via the Internet at http://pubs.acs.org.

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