

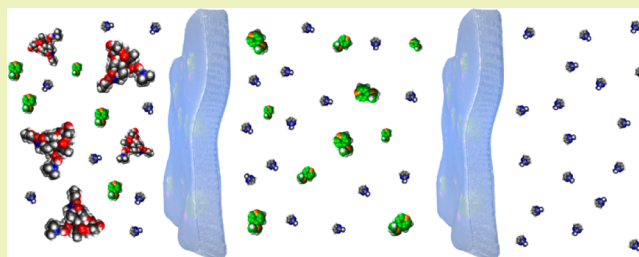
In Situ Solvent Recovery by Organic Solvent Nanofiltration

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ABSTRACT: Reducing solvent consumption in the chemical industries is increasingly becoming a topic of interest. The field of organic solvent nanofiltration (OSN) has markedly evolved in the past decade, and effective membranes are now available that can withstand aggressive solvents while completely rejecting small solutes at the lower end of the nanofiltration range (100–2000 g·mol⁻¹). With such membranes in hand and the advantages of membrane modularity, it is now possible to design innovative configurations to drastically reduce solvent consumption and enhance sustainability of downstream processes. Notably, a membrane-based solvent recovery configuration reported in our group has opened a new market for OSN membranes. In this work, the current state-of-the-art OSN membranes are screened, and a possible operation window for solvent recovery is identified. In tandem, to tackle the high solvent consumption challenge of membrane-based separation, we improved the solvent recovery configuration by combining both solute separation and solvent recovery in situ. The resultant system effectively performs the desired separation without any addition of extra solvent, thereby reducing solvent consumption to nearly zero. A model system comprising roxithromycin pharmaceutical and triphenylmethanol impurity is employed to illustrate that the proposed configuration allows constant volume diafiltration to be performed without any addition of fresh solvent. Parameters affecting the separation have been identified and validated experimentally or via modeling, and theoretical limitations are critically analyzed. The operability and carbon footprint have been compared with conventional solvent recovery units (e.g., distillation and adsorption). The present work reinforces that OSN is a leading separation technology in the process intensification movement of the fine chemicals sector.

KEYWORDS: Process intensification, Membrane, Solvent recovery, Organic solvent nanofiltration (OSN), Solvent resistant nanofiltration (SRNF)



INTRODUCTION

Chemical industries need to constantly improve their processes to (i) meet increasingly stringent regulations and (ii) increase their profit margins.¹ Process intensification is a movement to meet this challenge through process design innovation to lower waste generation, reduce environmental impact, and increase profit.²

Within the field of process intensification, solvent management is of particular interest,³ particularly in pharmaceutical manufacturing processes where solvents can account for 80–90% of total mass in the process.⁴ There has been a collaborative effort by pharmaceutical companies to gather plant data and to tackle unnecessary solvent consumption,⁵ and the top five waste solvents⁴ generated are summarized in Table 1. Whether incinerated onsite or disposed of through outsourced services, waste solvents produce a significant carbon footprint and associated expenditure. Instead, solvents can be recycled on site through various unit operations such as distillation, adsorption, or membrane processing. As the speed of time-to-market is an important factor, solvent recycling is not usually considered in the early stages of process development; however, once a process is well-established, solvent recovery (SR) is one of the key upgrades considered to improve profit margins.⁶

The membrane process is recognized as one of the key technologies to drive process intensification² due to its inherent simplicity and energy efficiency. The separation can proceed with a simple pressure gradient and, in most cases, without phase changes. Another advantage of the membrane operation, in terms of process intensification, is its modular nature.⁷ For instance, membrane units can easily be integrated with existing processes such as distillation,⁸ adsorption,⁹ and chromatography.¹⁰ Also, several membrane units can be advantageously arranged into different configurations, such as membrane cascades,^{11,12} to both reduce the solvent consumption and achieve high productivity separation.

In particular, organic solvent nanofiltration (OSN) is an established membrane technology that can achieve molecular separations in organic media at ambient temperature, separating solutes between 100 and 2000 g·mol⁻¹. OSN membranes are now stable in a variety of harsh solvents such as DMF, NMP, and DMAc¹³ and able to highly retain small solutes of MW down to 100 g·mol⁻¹.¹⁴

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Table I. Top Five Waste Solvents Generated by the Pharmaceutical Industry

solvent	rank	solvent generated [$10^6 \text{ kg}\cdot\text{y}^{-1}$]	CO_2 footprint [$10^6 \text{ kg}\cdot\text{y}^{-1}$]
methanol	1	44.8	18
dichloromethane	2	22.3	3
toluene	3	12.1	12
acetonitrile	4	7.9	3
chloroform	5	3.7	0.4

A common system for complete solute fractionation using membranes is constant volume diafiltration. A critical sustainability assessment of OSN technology has identified that OSN diafiltration is a highly solvent intensive operation and that implementation of an SR unit is critical to its sustainability.^{13,15} A back-of-the-envelope calculation illustrates this point in Figure 1.

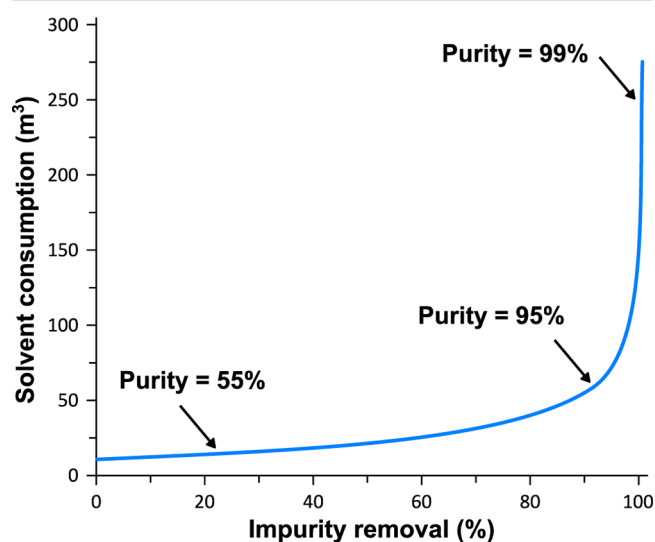


Figure 1. Diafiltration process solvent consumption as a function of impurity removal. Reaching high purity (>99%) requires exponential increase in solvent consumption (impurity rejection = 50%, product and impurity concentration = $1 \text{ g}\cdot\text{L}^{-1}$, system volume = 10 m^3).

Assuming that the product is fully retained by the membrane (rejection of 100%, eq 1) and the impurity permeates the membrane with 50% rejection (or 50% permeation), the required amount of solvent can be estimated as shown in Figure 1.

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

where $C_{P,i}$ and $C_{R,i}$ represent the concentration of solute i in the retentate and permeate, respectively.

It is evident from Figure 1 that in a typical diafiltration process, solvent consumption increases exponentially with impurity removal, or desired purity. In industries where product purity is of utmost importance, such as the pharmaceutical and fine chemicals sector, it is usually necessary to achieve product purity above 99%. As a result, membrane systems are often neglected during the development stage due to their high solvent consumption.

Promisingly, recent work coupled OSN diafiltration with an adsorptive SR unit using charcoal to recover the waste solvents.^{16,17} Although 100% SR could be achieved, it was shown that recovering 70% was the optimum point considering the amount of charcoal required as well as the solid waste generated.

Table II. Summary of OSN-Based Solvent Recovery

application	solute MW ($\text{g}\cdot\text{mol}^{-1}$)	rejection (%)	membrane	solvent
Lube oil Dewaxing ¹⁸	500	95	polyimide-based	MEK, toluene
API purification ¹⁹	>1000, 675	>99	DM 300, 1000	THF
catalyst recovery ²⁰	1044, 300	>99	DM 500, 300	THF
crystallization ²¹	600	>99	PuraMem 280	isopropyl acetate

Recently, the OSN membrane itself has shown potential for SR in a number of fields, summarized in Table II.

One of the first reported OSN-based SR processes is the solvent dewaxing unit known as Max-DeWax.¹⁸ MEK and toluene were recovered from lube oil ($\sim 500 \text{ g}\cdot\text{mol}^{-1}$) where 90% rejection of lube oil was sufficient to make the process economically viable. The process was a commercial success with a payback period of less than 1 year. Apart from the Max-DeWax process, Sereewatthanawut et al.¹⁹ reported a dual membrane diafiltration (DMD) process where impurities ($>1000 \text{ g}\cdot\text{mol}^{-1}$) are separated from the product ($675 \text{ g}\cdot\text{mol}^{-1}$) in the first stage and the product is subsequently concentrated in the second membrane stage by isolating the solvent, which is recycled to the first stage. Siew et al.²⁰ reported a similar process with a chiral organo-catalyst recovery application by first enlarging the catalyst (up to $1044 \text{ g}\cdot\text{mol}^{-1}$) through polyalkylation, allowing quantitative catalyst rejection. The enlargement of the catalyst was necessary for quantitative rejection. A second membrane stage was also implemented to concentrate the product ($300 \text{ g}\cdot\text{mol}^{-1}$) and recover the diafiltration solvent. While Sereewatthanawut et al. has clearly illustrated the potential for solvent recovery using a tight OSN membrane, two aforementioned cases required buffer tanks and extra pressure pumps in-between stages, making process control and operation cumbersome, especially during the start-up phase. It is particularly important to maintain good control with membrane processes, as the membrane performance is sensitive to operating pressure and concentration. For instance, poorly controlled membrane cascades often result in worse performance than a single membrane unit.²² An interesting work by Rundquist et al.²¹ explored the use of OSN instead of distillation to recover isopropyl acetate from crystallization mother liquor containing an API ($600 \text{ g}\cdot\text{mol}^{-1}$). The data showed that the recovered solvent had high enough purity for subsequent reuse but the extent of solvent recovery was limited by the API solubility. Again, a separate unit operation was required to recover the solvent with extra pump and a feed tank.

Reported applications in Table II have shown potential for OSN-based SR. In the fine chemicals industries, impurities are typically small ($<400 \text{ g}\cdot\text{mol}^{-1}$),²³ and membranes that can quantitatively reject such solute range were not available until recently. OSN membranes have improved drastically in the past years and it is now possible to reject molecules as small as $100 \text{ g}\cdot\text{mol}^{-1}$.¹⁴ Another important perspective is that in most of

the reported literatures, membrane SR processes have been treated as a separate unit operations, rather than integrated configuration, requiring additional equipment such as tanks and pumps, as well as handling and storage spaces.

In this work, we first screen through the current tightest state-of-the-art OSN membranes to identify suitable candidates in the range where OSN-based SR can be applied. Then, exploiting the modular nature of membranes, we present a membrane separation platform that purifies the product while recovering the solvents in a single unit operation in situ. By coupling the separation membrane stage to a SR membrane stage, the entire separation can proceed automatically in a closed-loop configuration. The proposed platform is tested with a pharmaceutical model mixture containing Roxithromycin (Roxi) and triphenylmethanol (TrOH), an active pharmaceutical ingredient (API) and a common protecting group impurity, respectively. Using the experimental data, membrane-based solvent recovery is compared with distillation and adsorption operations, and possible synergistic combinations are proposed.

EXPERIMENTAL SECTION

Materials and Membrane Fabrication. Methanol (MeOH) was HPLC grade and used as supplied from VWR. Triphenylmethanol (TrOH), Bisphenol A (BPA), cis-stilben (cS), naphthalene (Nphth), and *N,N*-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich, UK. 5,5',6,6'-Tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spriobisindane (TTSBI) was purchased from ABCR GmbH, Germany. Roxithromycin (Roxi) samples were kindly provided by Hovione FarmaCiencia SA, Portugal. DuraMem150 (DM150) was purchased from Evonik-MET, UK. Cross-linked 22 and 26 wt % PBI membranes (22DBX, 26DBX) were fabricated as described by Valtcheva et al.²⁴ Thin film composite (TFC) polyamide membranes were fabricated through interfacial polymerization as described by Jimenez-Solomon et al.¹⁴

Process Configuration and Modeling. The current tightest state-of-the-art OSN membranes reported in the literature (26DBX, TFC, DM150) were screened using solutes with MW in the range between 100–400 g·mol⁻¹ to characterize membrane performance in the lower nanofiltration range (Table III).

A screening rig was set up in cross-flow configuration as described previously.²⁵ A solution containing the screening solutes (1 g·L⁻¹) was circulated around the rig at a flow rate of 100 L·h⁻¹. Two coupons of each type of membrane with an area of 14 cm² per membrane were tested. Samples were taken at steady state for pressures of 5, 10, 15, 20, and 25 bar.

Diafiltration is employed to fractionate solutes in a mixture, and the process typically proceeds at a fixed volume (sometimes referred to as constant volume diafiltration, or CVD), where the permeate volume is matched with fresh solvent (Figure 2). An impurity, typically exhibiting lower rejection than the product of interest, permeates through the membrane faster than the product, effectively separating the solutes.

Conventional diafiltration can be characterized by writing a system mass balance and integrating analytically to give the following equation:

$$C_i(t) = C_{i,0} \exp[-D(1 - R_i)] \quad (2)$$

where $C_i(t)$ and $C_{i,0}$ are the concentrations of solute i at time t and 0, respectively. R_i is the rejection of solute i , and the term diavolume (D) is defined as

$$D = \frac{JAt}{V_{\text{system}}} = \frac{V_{\text{P,total}}}{V_{\text{system}}} \quad (\text{eq } 3)$$

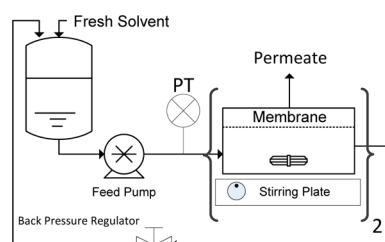
where J is the membrane flux (L·m⁻²·h⁻¹), A is the effective membrane area (m²), t is the time (h), V_{system} is the overall system volume (L), and $V_{\text{P,total}}$ is the total volume having permeated at time t .

The term diavolume (D) is a useful *timelike* dimensionless parameter, similar to the residence time concept, allowing different diafiltration

Table III. Solutes with Varying Size Used in the Present Study

Solute Name	Solute Structure	Abbreviation	MW (Da)
<i>N,N</i> -Dimethylaminopyridine		DMAP	122
Naphthalene		Nphth	128
cis-Stilbene		cS	180
Bisphenol A		BPA	228
Triphenylmethanol		TrOH	260
5,5',6,6'-Tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spriobisindane		TTSBI	340
Roxithromycin		Roxi	837

(A) Diafiltration



(B) Diafiltration + Solvent Recovery

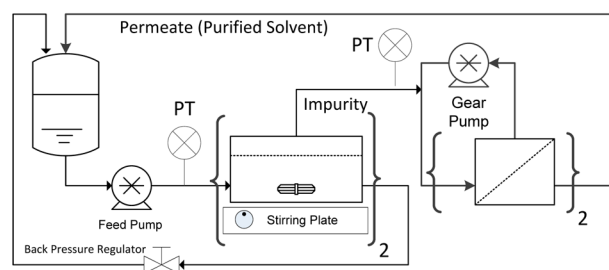


Figure 2. Schematic diagram of a diafiltration process without (A) and with (B) the proposed SR stage. Stirred cells and crossflow cells were used for the diafiltration stage and SR stage, respectively.

systems to be compared. In a system without solvent recovery, the progress of a diafiltration can be monitored by collecting the permeate volume (and replenishing solvent accordingly). As the flux through the membrane varies slightly over time, the level of the feed tank must be carefully, and precisely, controlled. The proposed configuration (Figure 2B) in this work connects the permeate from the first stage directly to a SR membrane stage, loaded with tight (highly rejecting) OSN membranes, and is described as follows.

$$\frac{dC_{i,1}}{dt} = \frac{\dot{V}}{V_1}(C_{i,2}(1 - R_{i,2}) - C_{i,1}(1 - R_{i,1})) \quad (4)$$

$$\frac{dC_{i,2}}{dt} = \frac{\dot{V}}{V_2}(C_{i,1}(1 - R_{i,1}) - C_{i,2}(1 - R_{i,2})) \quad (5)$$

where i can be any component, subscripts 1 and 2 refer to the respective stage, V_j defines the volume of that respective stage, and \dot{V} describes the volumetric flow rate through each stage (note that the permeate flow rates of each stage in this closed loop must be equal). Since the entire operation proceeds in a closed-loop, steady state conditions can be obtained by setting the differential equations to a value of zero. An analytical solution is thereby available for the maximum impurity removal fraction, as shown in eqs 6–8 (Results and Discussion section).

Conventional Diafiltration without Solvent Recovery. To fractionate Roxi from TrOH, two diafiltrations were performed independently with 22DBX membranes (51 cm² each) using the configuration shown in Figure 2A. The first diafiltration employed one membrane cell ($V_{\text{system}} = 200$ mL), and the second diafiltration employed two membrane cells connected in series ($V_{\text{system}} = 225$ mL). A crude solution containing 10 g·L⁻¹ of Roxi and 1 g·L⁻¹ of TrOH dissolved in MeOH were circulated around the system at 40 mL·min⁻¹ and 5 bar to initiate diafiltration. The temperature of the system stayed constant at 21 °C. The stirring rates were set at 750 rpm to ensure turbulence at the membrane surface and to minimize any effects of concentration polarization. The system volume was maintained at a constant level by matching the permeate flow rate with a pure solvent input into the system using a separate pump.

Diafiltration with Solvent Recovery. For the in situ solvent recovery system, the rig was reconfigured as illustrated in Figure 2B. The diafiltration stage was loaded with two 22DBX membranes (51 cm² each), and the SR stage was loaded with two DM150 membranes (51 cm² each). The diafiltration membrane cells were stirred with magnetic stirrers at 750 rpm, and the solution in the SR stage was circulated using a gear pump (Michael Smith, UK) at 54 L·h⁻¹. A solution containing 10 g·L⁻¹ Roxi and 1 g·L⁻¹ TrOH dissolved in MeOH was circulated around the diafiltration stage at 40 mL·min⁻¹ at 5 bar to initiate the diafiltration. The temperature of the system stayed constant at 21 °C. As the SR stage pressure increases, the diafiltration stage pressure is incrementally increased to maintain a transmembrane pressure of 5 bar. The steady operating pressures of the diafiltration stage and SR stages were 13 and 8 bar, respectively, giving transmembrane pressures of 5 and 8 bar, respectively. With no liquid leaving or entering, the system was run without further intervention until the steady-state purity was reached.

Analytical Method. All samples were analyzed by HPLC using an Agilent 1100 Series system equipped with an UV detector and Varian 385-LC ELSD detector. The pump flow-rate was set at 1 mL·min⁻¹, the injection volume was 50 μL, the column temperature was 30 °C, and an ACE C18 RP column was fitted. The column was eluted with a gradient of MeOH and water buffered with 5 mM ammonium acetate. The UV wavelength was set at 260 nm, evaporation temperature at 40 °C, nebulization temperature at 55 °C, and nitrogen gas flow at 1.5 SLM. All solutes were quantified against calibration curves using their UV response except for Roxi, for which the ELSD response was used. Besides the HPLC analysis of the intermediate permeate and retentate samples, the final permeate and retentate were evaporated to close the mass balance. Mass yield of Roxi was then calculated using eq 6.

$$\text{yield (\%)} = \frac{M_{\text{Roxi}}^{\text{final}}}{M_{\text{Roxi}}^{\text{initial}}} \times 100 \quad (6)$$

RESULTS AND DISCUSSION

Molecular Weight Limitations of Solvent Recovery by OSN. Solvent recovery (SR) is conventionally done by distillation and adsorption which are energy and waste intensive, respectively. On the other hand, membrane separations have low energy consumption and generate negligible waste. However, SR by nanofiltration membranes has not yet been widely

implemented in the fine chemical industries due to the fact that impurities in the waste streams are usually small with MW < 400 g·mol⁻¹.²³ Notably, PBI,²⁴ TFC,¹⁴ and DuraMem²⁰ membranes have recently been reported with excellent rejections and permeance in this range. Hence, these membranes were screened at pressures from 5 to 25 bar using solutes with MW of 100–400 g·mol⁻¹ (Figure 3). Methanol was chosen as a model solvent for the present study since it is the largest amount of waste solvent generated by the pharmaceutical industry (Table 1). Parallel to developing tight membranes, recent OSN development work focused on improving the stability of membranes in harsh solvents,^{24,26} allowing energy efficient recovery of high boiling solvents such as DMF or DMAc without phase change.

Figure 3A displays solute rejections on the test membranes at different transmembrane pressures. It can be seen that solutes above 200 g·mol⁻¹ can be virtually completely retained by the membranes. It can also be seen that a higher transmembrane pressure leads to higher rejection, allowing SR for solutes as small as 100 g·mol⁻¹ with the TFC membrane (Figure 3B). Furthermore, this type of TFC membrane not only exhibits the highest rejection but the highest flux too (Figure 3C), owing to its short permeation pathway.¹⁴ Despite the superior performance of the TFC membrane, the commercially available DM150 was chosen for the pharmaceutical case study of diafiltration coupled SR (See the following section).

Pharmaceutical Case Study: Effect of Solvent Recovery on Purification. Figure 4 shows the concentration profiles of TrOH following the expected, exponentially decreasing trend, as TrOH is removed from the first stage (separation stage). Up to 98% of TrOH was removed from the system without solvent recovery (Figure 4A). Further purification is possible by simply running more diavolumes; however, as expected from Figure 1, it takes significant amount of additional solvent to increase the product purity from this point. This inevitable trend is precisely the reason why a solvent recovery unit must be implemented for diafiltration process. The mass balance for the diafiltration closed within 2.2% with a high final yield of Roxi at 98.5% as the rejection of Roxi by the membranes was virtually quantitative. On average, the amount of solvent required can be normalized to 2700 ± 70 L·kg⁻¹ of product. As emphasized in previous work,¹⁶ the solvent accounts for more than 99% of the mass intensity in diafiltration process. To minimize solvent consumption, an in situ SR unit was then implemented to recycle solvent as shown in Figure 2B.

It can be seen in Figure 4B that the removal profile with SR is similar to the observed trend without the SR stage in Figure 4A. As expected from the model, the system reached steady state at 97% removal. This is because the rejection of TrOH in the SR stage is 99.8% allowing a small amount of TrOH to leach back into the first stage. The mass balance closed within 1% and the Roxi yield was 99%. It can be seen that with the SR unit implemented, the extra amount of solvent required for diafiltration was essentially zero, significantly reducing the overall solvent consumption and reaching virtually the same product purity. A comparison of the diafiltrations with and without the in situ SR stage is summarized in Table IV.

Apart from the significant solvent saving achieved, the proposed configuration in this work brings additional benefits. First of all, the entire system is closed-loop and no external control was necessary as the system operated on its own (Figure 2B). By setting the operating pressure of the first stage, the SR stage pressure is automatically determined (function of membrane area and permeability). In comparison, a conventional diafiltration

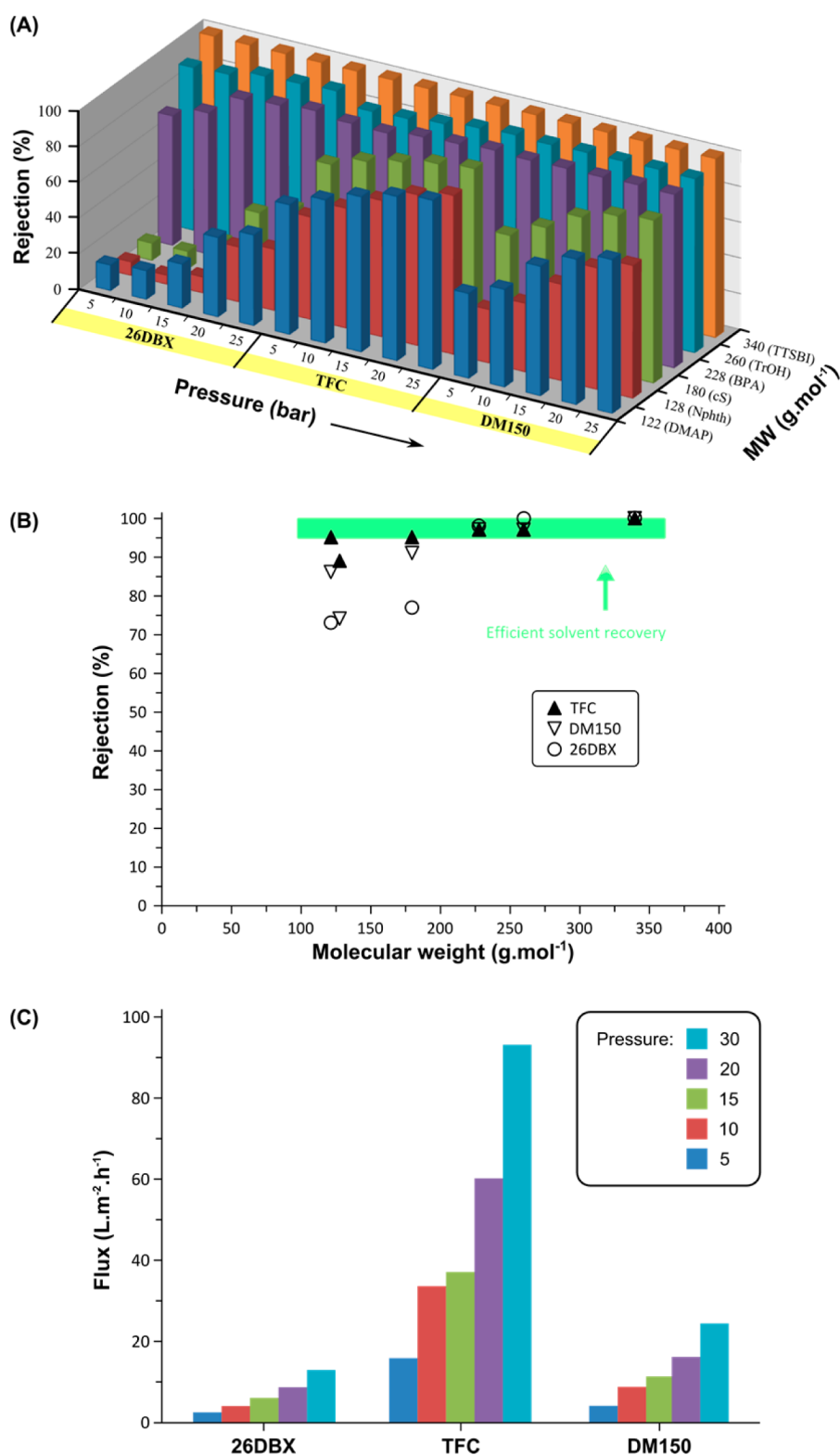


Figure 3. (A) Summary of solute rejections on tested membranes at different pressures. (B) Detailed rejection data at 30 bar. Solutes above 200 g·mol⁻¹ are virtually completely rejected and the green box indicates the MW range of effective SR (R > 95%) by the different membranes. (C) Flux data of the membranes given at different pressures.

system needs continuous monitoring and adjustment of the feed tank level through control of an additional pump (Figure 2A). Simpler process operability is one of the core aims of green process engineering. As pointed out earlier, such configuration is possible owing to the modularity of membrane units. Second, as

the operating pressure is essentially cascaded, there is no need for extra buffer tanks and pressure pumps in-between stages. Such advantage bypasses the need for high solvent inventory and the overall system volume can be minimized. In addition, this specific configuration can be considered as a single unit operation rather

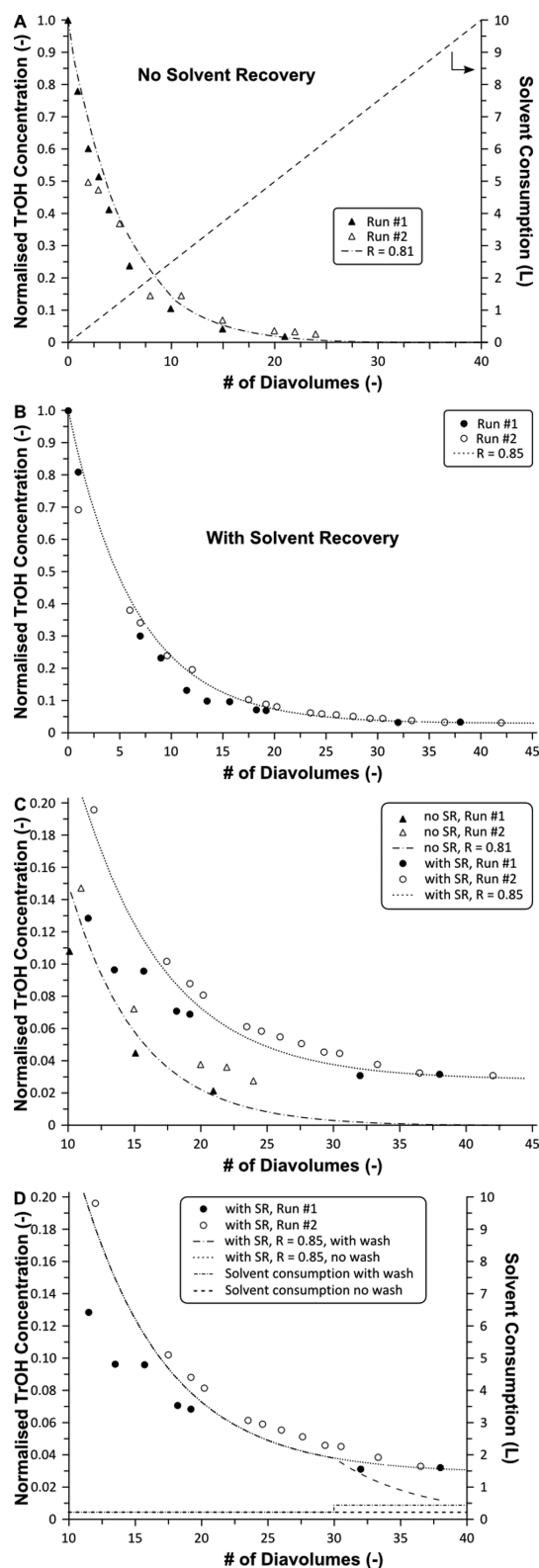


Figure 4. Impurity concentration profile of (A) conventional diafiltration without SR allowing the removal of 98% of TrOH up to 35 diavolumes using additional fresh solvent; (B) diafiltration coupled with SR stage up to 42 diavolumes without any addition of fresh solvent. The diafiltration and SR stages used 22DBX and DM150 membranes, respectively. (C) Magnification for normalized TrOH concentration below 0.20 of panels A and B combined. (D) Effect of washing the in TrOH removal, discussed in the following section.

Table IV. Summary of Diafiltration Data Including Yield, Impurity Removal, and Solvent Consumption

	yield (%)	TrOH removal (%)	mass balance (%)	solvent added ($L \cdot kg^{-1}$ product)
diafiltration without SR	98.5 ± 0.5	98 ± 0.1	2.2 ± 1.7	2700 ± 70
diafiltration with in situ SR	99 ± 0.1	97 ± 0.1	0.4 ± 0.6	0

than two separate operations. Apart from this configuration, many innovative designs that utilize different number of membrane cells can be envisioned such as membrane cascades.^{11,12,27}

Rejection Limitations of Solvent Recovery by OSN. In an ideal SR system, where rejection of every solute, particularly that of the impurity, is absolute ($R_{TrOH,2} = 1.00$), it is theoretically possible to remove all impurity from the first (separation) stage for an infinite number of diavolumes (Figure 5A). In practice,

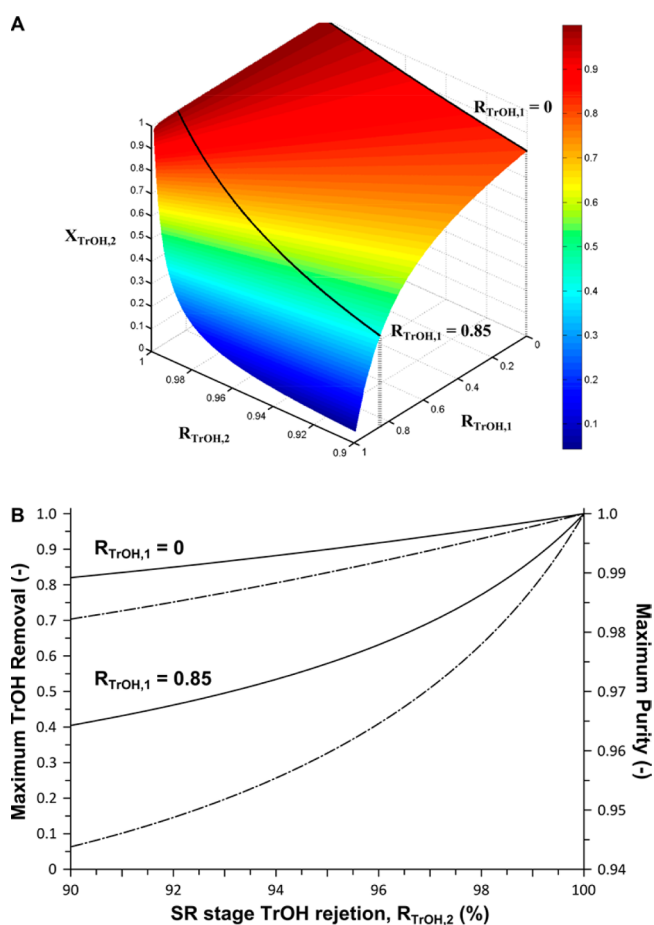


Figure 5. (A) Effect of first and second stage impurity rejection on the overall purity, fixing other parameters constant. (B) 2D projection of part A at $R_{TrOH,1} = 0$ and 0.85. Solid lines refer to the maximum TrOH removal, and dotted lines, to maximum purity.

quantitative rejection is difficult to achieve for any membrane due to inevitable formation of defects during membrane fabrication. As a result, for any given $R_{TrOH,2} < 1.00$, the impurity cannot be completely removed from the separation stage because some impurity will always leach from the SR stage back into the first separation stage. This phenomenon can be observed when having a closer look at the high diavolume range

in Figure 4C: while the concentration for the non-SR system asymptotically approaches zero, the SR system impurity concentration approaches some steady state value at around 3%.

We can establish that the maximum achievable purity of the solute to be purified is therefore dependent on the fraction of impurity that accumulates in the SR stage when the system is run for an infinite number of diafiltration volumes, i.e. at steady state. At this point, the removal of impurity from the first separation stage has become balanced by leaching of the impurity through the SR stage back into it. This steady state can be obtained by setting the system differential equations (eqs 4 and 5) to the value of zero. Either equation can be solved analytically to give the fraction of the impurity having accumulated in the SR stage ($x_{\text{TrOH},2}$, eq 9). The steady state of the system for an infinite number of diafiltration volumes, and the corresponding maximum impurity removal, can therefore be described as follows:

$$\frac{dC_{i,1}}{dt} = \frac{\dot{V}}{V_1}(C_{i,2}(1 - R_{i,2}) - C_{i,1}(1 - R_{i,1})) = 0$$

$$\frac{dC_{i,2}}{dt} = \frac{\dot{V}}{V_2}(C_{i,1}(1 - R_{i,1}) - C_{i,2}(1 - R_{i,2})) = 0$$

$$C_{i,2}(1 - R_{i,2}) = C_{i,1}(1 - R_{i,1}) \quad (7)$$

$$\frac{C_{i,2}}{C_{i,1}} = \frac{(1 - R_{i,1})}{(1 - R_{i,2})} \quad (8)$$

$$x_{i,2} = \frac{V_2 C_{i,2}}{V_2 C_{i,2} + V_1 C_{i,1}} = \frac{1}{1 + \frac{V_1 C_{i,1}}{V_2 C_{i,2}}} = \frac{1}{1 + \frac{V_1 (1 - R_{i,2})}{V_2 (1 - R_{i,1})}} \quad (9)$$

where $x_{i,j}$ represents the fraction of x_i that can be removed from the diafiltration stage into the SR stage.

Equation 9 demonstrates, interestingly, that the maximum impurity removal possible is highly dependent on the *ratio* of the rejections and stage volumes.

V_1 and V_2 are parameters which can, in theory, be altered relatively freely. In practice, for most systems V_1 is kept as low as practically possible to keep the time required for a diafiltration volume low. On the other hand, V_2 can be chosen independently of all other system parameters, i.e. it can be increased as desired to facilitate more impurity removal by reducing the concentration of impurity in the second stage ($C_{\text{TrOH},2}$). Of course, increasing V_2 means more solvent will be contaminated with impurity at the end of the diafiltration and needing disposal. Hence, adjustment of V_2 therefore presents a classical trade-off for this solvent recovery system, as it holds impurity removal and solvent consumption in tandem.

Because rejection in the first stage, $R_{i,1}$, is largely a membrane parameter, it will be difficult to tune for efficient solvent recovery in a real system as the membrane in the first separation stage will be chosen mainly on the basis of what rejection is needed for the main product to be retained, in this case $R_{\text{Roxi},1}$. Lowering $R_{\text{TrOH},1}$ using a looser membrane would increase the maximum impurity removal but at the same time is likely to decrease the product yield by lowering $R_{\text{Roxi},1}$ as well.

Lastly, the rejection of the SR stage ($R_{\text{TrOH},2}$) should be as high as possible, ideally absolute (Figure 5). As opposed to $R_{\text{TrOH},1}$, the choice of $R_{\text{TrOH},2}$ is an economical trade-off, because tighter membranes usually have lower flux, necessitating a larger

membrane area which comes at a cost. The membrane screening (see previous section) revealed that TFC membranes have sufficiently high rejection at notably high flux (Figure 3C). Nevertheless, with commercial membranes, such as the DuraMem series used for the present study, a high $R_{\text{TrOH},2}$ goes hand in hand with lower permeability. Few membranes are currently available that provide a high flux for high rejection requirements and the membranes screened herein are exemplary.

For the typical separation stage rejection ($R_{\text{TrOH},1} = 0.85$) and stage volumes used in the SR study ($V_1 = 0.220$ L, $V_2 = 0.100$ L; see previous section), the maximum impurity removal of 97% corresponds to a SR impurity rejection of 99.8% ($R_{\text{TrOH},2} = 0.998$), where the deviation from quantitative rejection is likely from small inevitable defects.

$$x_{\text{TrOH},2} = \frac{1}{1 + \frac{V_1 (1 - R_{\text{TrOH},2})}{V_2 (1 - R_{\text{TrOH},1})}} = \frac{1}{1 + \frac{0.220 (1 - 0.998)}{0.100 (1 - 0.850)}} \approx 0.97 \quad (11)$$

It is clear that for a system where rejection of the SR stage is not absolute, complete removal of the impurity cannot be achieved due to trace amounts of TrOH leaching back into the first stage. The calculated and experimentally obtained TrOH impurity removal were identical (97%) confirming the validity of the model. Similar to the recrystallization or chromatography technique, one possible solution to improve the purity is to simply run the process again. For instance, the second loop can be washed out and the process can be repeated, effectively resetting the second stage impurity concentration to zero ($C_{\text{TrOH},2} = 0$) (Figure 4D). This way, the added solvent would be equal to the second stage volume, V_2 , and the TrOH removal fraction can be increased from 97% to 99.5% by repeating the purification. Incidentally, as only trace amounts of TrOH leaches out of the SR stage, an adsorption column can potentially be explored to achieve higher impurity removal.

Effect of Solvent Recovery on the Sustainability of Diafiltrations. The fairest way to compare the sustainability of downstream processes is via the carbon footprint since the energy and solvent consumption as well as the waste generated can all be incorporated. Figure 6A compares the reduction in carbon footprint in membrane diafiltration process by the proposed in situ SR with recent work which employed adsorptive SR.^{16,17} The batchwise adsorptive SR data in Figure 6A refers to the work of Kim et al.,¹⁶ where each diavolume solvent was collected and purified; the continuous adsorptive SR refers to the work of Peeva et al.,¹⁷ where an adsorptive column was implemented to continuously purify and recycle the solvent. The continuous OSN-SR refers to the current work. The calculation takes into account the CO₂ generated from operation parameters such as electricity (pump), waste adsorbent, solvent, and membrane. For the purpose of calculation, it was assumed that the recovered solvents had the same purity.

It can be seen in Figure 6A that implementing a SR unit in diafiltration process generally brings significant CO₂ footprint reduction, mainly from avoiding solvent incineration. For instance, OSN-based SR employed in this work reduced the CO₂ intensity from 3200 to 150 kg CO₂ per kg product which corresponds to 95% CO₂ reduction. The difference between the unit operations comes from the amount of solid waste (adsorbent, membranes) generated. In comparison, membranes generate less solid waste to adsorption where adsorbent waste can become a significant factor. The data obtained illustrates the significance of SR on the sustainability of diafiltration as predicted in Figure 1.

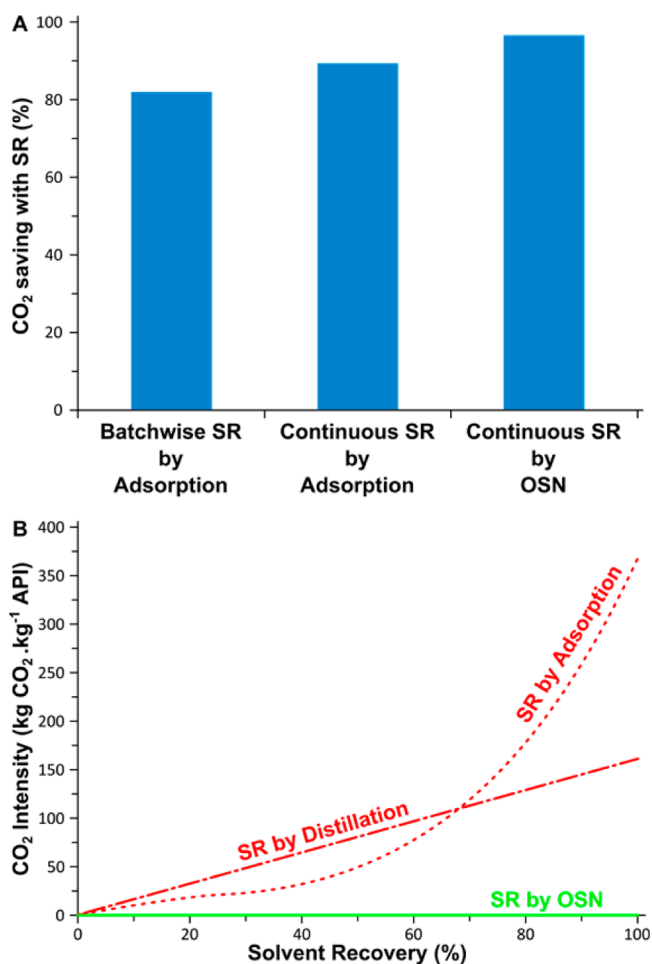


Figure 6. (A) Comparison of the carbon footprint improvement by the implementation of different SR approaches in membrane diafiltration process: batchwise SR by adsorption,¹⁶ continuous SR by adsorption,¹⁷ and the proposed continuous SR by OSN. (B) Effect of different means of SR on the carbon footprint calculated for methanol.

As expected, it was calculated that the solvents are essentially the main component of the overall diafiltration process CO₂ intensity (kg of CO₂ generated per kg of product), contributing up to >99% except for the case with adsorptive SR, where the carbon footprint from the waste adsorbent was significant (20%).

The carbon footprint profiles of the three possible means of SR, namely distillation, adsorption and OSN, are shown in Figure 6B. It can be seen that distillation has a higher CO₂ intensity up to 70% solvent recovery, mainly due to the high energy consumption. At that point the CO₂ generation by adsorptive SR exponentially increases as the last 30% of the waste solvent contains highly concentrated solutes,¹⁶ requiring excessive amounts of adsorbent. As mentioned before, adsorptive SR generates a considerable amount of solid waste, and if one wants to recover more than 70% of the solvent using adsorptive SR, solid waste adsorbent begins to outweigh the achieved solvent savings.¹⁶ Also, adsorbents get saturated and must be replaced frequently, affecting the overall process operation. On the other hand, membranes can be reused and its lifetime typically exceeds 2 years when properly maintained, contributing to negligible solid waste. An interesting feature about OSN membranes, contrary to other membrane processes, is that its inherent nature (harsh organic environment) prevents any potential biofouling, extending the lifetime of membranes. Apart

from the membrane solid waste, the only carbon contributor of a membrane-based SR stage is the pressure exerted by a pump. Hence, it can be seen in Figure 6B that membrane-based SR is virtually independent of the amount of solvent recovered. In addition, the modularity of the membrane units allowing the proposed configuration (Figure 2B) simplified the operability and controllability of the process, two important characteristics that should not be underestimated in regard to plant safety.

An interesting alternative would be to combine membrane and adsorption unit to improve the solvent purity while minimizing the solvent waste. Incidentally, as the adsorption unit is also modular, it can be fitted right after the membrane stage to achieve both high solvent purity and low energy consumption.

CONCLUSION

Organic solvent nanofiltration (OSN) membranes now can withstand aggressive solvents and sufficiently retain small solutes. Such features make OSN a good candidate for solvent recovery (SR) in the fine chemical industries where impurities are usually small with MW < 400 g·mol⁻¹. In this work, current state-of-the-art OSN membranes have been screened which showed it is now possible to implement an SR unit down to 100 g·mol⁻¹ range with appropriate configurations and operation protocols. Hence, a continuous and control-free in situ SR configuration has been implemented to recycle the waste solvent consumed during a membrane diafiltration process. The effect of impurity rejection by the membrane on the maximum achievable purity has been assessed and validated in a pharmaceutical case study, which gave almost quantitative product yield and 98% impurity removal with no additional fresh solvent. The product purity can be improved further by simply repeating the process without loss of yield. The operability and carbon footprint of the proposed membrane-based SR has been found advantageous compared to adsorptive- and distillation-based SR. The main advantages of the membrane-based SR, apart from its simplicity, are low solid waste generation and low energy consumption. It has been shown and emphasized that the modularity of the membrane processes allows convenient operation and the overall operability of the process can be significantly simplified.

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Notes

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GLOSSARY

$R_{\text{TrOH},1}$, rejection of TrOH impurity in the first stage (purification)

$R_{\text{TrOH},2}$, rejection of TrOH impurity in the second stage (solvent recovery)

$C_{\text{p},i}$, concentration of solute i in permeate

$C_{\text{r},i}$, concentration of solute i in retentate

V_1 , volume of the first stage (purification)
 V_2 , volume of the second stage (solvent recovery)
 C_i , concentration of solute i at time t
 $C_{i,0}$, initial concentration of solute i at time 0
 D , diafiltration volumes/diavolumes (–)
 J , solvent flux ($\text{L}\cdot\text{m}^{-2}\cdot\text{h}^{-1}$)
 A , effective membrane area (m^2)
 t , time (h)
 V_{system} , overall system volume (L)
 DMAP, N,N -dimethylaminopyridine
 THF, tetrahydrofuran
 MEK, methylethylketone
 Nphth, naphthalene
 cS, *cis*-stilbene
 BPA, bisphenol A
 TrOH, triphenylmethanol
 TTSTBI, 5,5',6,6'-tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spriobisindane
 Roxi, Roxithromycin
 SR, solvent recovery
 API, active pharmaceutical ingredient

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