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Organic Solvent Recovery and Reuse in Pharmaceutical Purification Processes by Nanofiltration Membrane Cascades

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The recovery and posterior reuse of organic solvents is a very important aspect to be taken into account during the production processes by chemical, petrochemical, food, and pharmaceutical industries. Organic solvent nanofiltration is becoming more relevant and appears as a very promising way to carry out solute fractionation, concentration and purification, which can be considered exigent separation operations in organic media. Under optimal design conditions, organic solvent nanofiltration can be also an effective unit process to reduce organic solvent consumption by incorporation of closed-loop solvent recycling systems.

Usually, single stage organic solvent nanofiltration processes can only be applied to relatively easy separations, so, most of the times, multiple membrane processes have to be integrated to carry out more complex separations. This research group has previous experience with the design of counter current membrane cascades to purify chemicals and has decided to make use of the acquired knowledge to advance in the design of continuous OSN membrane cascades with solvent recovery and reuse.

The purification of an intermediate API precursor in methanol medium has been selected as case study. After the formulation of a valid simulation model for the membrane cascade, the design of the process has been pointed to find the best cascade configuration in terms of sustainable solvent consumption. The proposed solution is based on solvent recovery from one extreme of the cascade, purification, and recirculation of the recovered solvent to the other extreme of the cascade in order to improve its performance by avoiding too concentrated streams, which could cause solubility problems, without any additional fresh solvent stream.

1. Introduction

Most of the production costs of pharmaceuticals can be imputed to purification tasks during the downstream processing. Adequate solute separation, concentration and, fractionation are critical to obtain very high purity products from dilute suspensions without excessive costs. The development of organic solvent resistant nanofiltration membranes has offered new opportunities for this membrane technology to be applied within the pharmaceuticals productive processes that employ organic solvents as reaction media (Darvishmanesh et al., 2011). Nevertheless, few studies report the adequate design of novel membrane configurations applied to solvent recovery (White, 2006), but some recent works are advancing in this field (Marchetti et al., 2014).

The separation of solutes by nanofiltration is based on differences among their respective molecular weights. Therefore, high separation performance can be expected when the solutes to be separated have different molecular sizes. However, when the molecular weights of the solutes are closer, the separation is more difficult and a unique membrane stage can be insufficient (Vanneste et al., 2013). In these cases which require more than a single stage, the way the multiple stages included in the network get connected becomes a crucial issue.

The typical multiple membrane installation consists of a network of modules designed to fulfil several technical, economic, and environmental requirements (Abejón et al., 2012a). Optimal systems must comprise optimal design of the individual modules (Kostoglou and Karabelas, 2011) and the entire network configuration

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(Alnouri and Linke, 2013), and optimal operation conditions (Abejón et al., 2012b). Integrated countercurrent membrane cascades were developed for gas separations, but they soon demonstrated their potential for liquid-phase membrane separations from microfiltration to reverse osmosis (Abejón et al., 2012c). Nanofiltration membrane cascades have been employed for wastewater treatment (Caus et al., 2009a), mono-saccharides fractionation in aqueous solution (Caus et al., 2009b), or advanced separations in organic media (Siew et al., 2013).

Although innovative membrane systems have been designed to consider water recovery and reuse for wastewater treatments or other separation processes (Barredo-Damas et al., 2010), the same efforts have not been applied so extensively to the recovery and reuse of organic solvents. Taking into account the low usage efficiency of organic solvents by the pharmaceutical industry, an increase in solvent recovery and reuse rates should be prioritized to advance in the sustainability of the sector. The main objective of this work is to analyze the application of organic solvent resistant nanofiltration membrane cascades to a pharmaceutical separation in order to reduce the corresponding solvent consumption.

2. Cascade design and modelling

Very diverse configurations of organic solvent nanofiltration membrane cascades can be implemented, but the final design would depend on the specific separation targets and the desired objectives. In this case, a dual cascade was selected. This type of cascades is characterized by an intermediate feed stage between two different separation branches. The general scheme of a dual cascade with a coupled final solvent recovery stage can be seen in Figure1.

The retentate stream R0 and permeate stream P0 from the feed stage 0 feed the initial stage of the multistage (retentate streams are connected in series) retentate branch of the cascade (Stage 1Rs) and the initial stage of the multipass (permeate streams are connected in series) permeate branch of the cascade (Stage 1Ps) respectively. The retentate branch purifies the most retained solute and avoids the loss of the most permeable solute. On the contrary, the permeate branch increases the purity of the most permeable solute, while reduces the amount of the most retained solute that leaves the cascade. The recirculation of streams to previous stages configures a countercurrent cascade that improves the efficiency of the system. The solvent recovery stage RO is a coupled solvent resistant reverse osmosis stage fed by the permeate leaving the last stage of the permeate branch (nPs) to recover solvent with very low solute content to recirculate it to the feed of the last stage of the retentate branch (nRs). The purpose of this solvent stream can be the improvement of the separation performance, the avoidance of appearance of new phases, the control of viscous solutions or the minimization of solute precipitation.

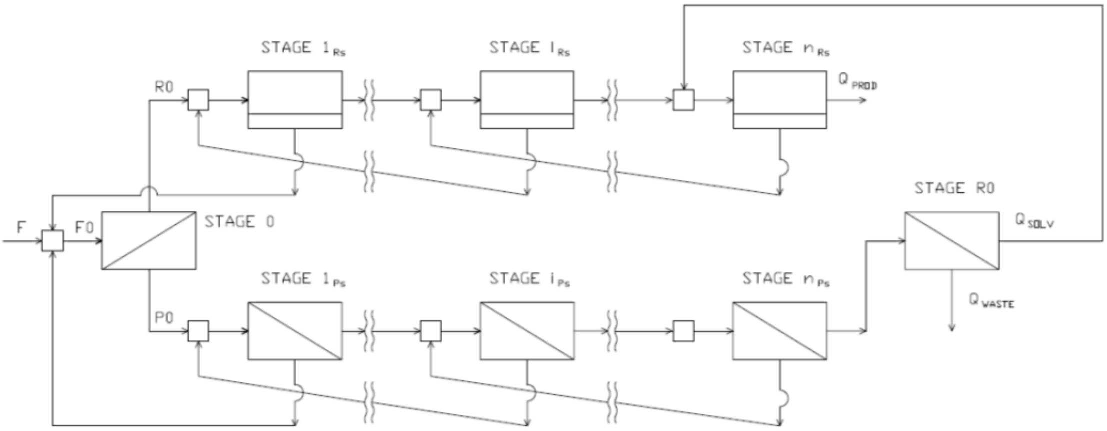

Figure 1: General scheme of a dual cascade with a coupled final solvent recovery stage

The proposed simulation model is based on the Kedem-Katchalsky transport equations for solvent and solute through membranes and the corresponding mass balances (overall and by components) for the membrane modules and mixers. The economic evaluation of the process is performed by a simple model that estimates the main costs of the process.

The Kedem Katchalsky model, simplified because of consideration of negligible osmotic pressure contribution, defines the characteristic variables of the nanofiltration membrane performance, the specific permeate flux (J_V) and the retention coefficient of each solute (R^{sol}) as functions of the applied pressure ΔP:

$$J_V = L_P \Delta P \tag{1}$$

$$R^{sol} = \sigma^{sol} \frac{J_V}{J_V + \omega^{sol}} \tag{2}$$

The characteristics of the permeate streams (flow P and solute concentrations cP^{sol}) can be calculated as function of the membrane area A of the corresponding stage:

$$P = A \cdot J_V \tag{3}$$

$$cP^{sol} = cF^{sol}(1 - R^{sol}) \tag{4}$$

The overall and component mass balances have to be applied to each stage for both membrane modules, Eq(5) and Eq(6), and mixers, Eq(7) and Eq(8):

$$F = P + R \tag{5}$$

$$F \cdot cF^{sol} = P \cdot cP^{sol} + R \cdot cR^{sol} \tag{6}$$

$$F_{in1} + F_{in2} = F_{out} \tag{7}$$

$$F_{in1} \cdot cF_{in1}^{sol} + F_{in2} \cdot cF_{in2}^{sol} = F_{out} \cdot cF_{out}^{sol} \tag{8}$$

The recovery ratio of each stage Rec is defined as:

$$Rec = P/F \tag{9}$$

The product purity and the process yield can be calculated as:

$$Purity = 100 \frac{cR(n)_{Rs}^{A}}{cR(n)_{Rs}^{A} + cR(n)_{Rs}^{I}} \tag{10}$$

$$Yield = 100 \frac{R(n)_{Rs} \cdot cR(n)_{Rs}^{A}}{F \cdot cF^{A}} \tag{11}$$

The total costs of the system are defined as the sum of the capital costs (CC) and the operation costs (OC). The capital costs attributable to membranes or to the rest of the installation are differentiated, while the operation costs are itemized into energy, labor, maintenance, chemical losses and waste treatment costs:

$$TC = CC + OC \tag{12}$$

$$CC = CC_{memb} + CC_{inst} \tag{13}$$

$$OC = OC_{en} + OC_{lab} + OC_{m} + OC_{loss} + OC_{waste} \tag{14}$$

For additional information about the modelling and the values of the employed parameters, a previous work of this research group can be consulted (Abejón et al., 2014).

3. Case study

As case study the purification of an API precursor was chosen. The Compound A is needed as intermediate chemical for the production of a synthetic opioid analgesic drug used for anaesthesia in surgery. Hence, it has to be separated from a main impurity (Compound I) after its synthesis process. However, it a quite challenging separation due to the similar molecular weights of both solutes (MW_A= 221 g/mol and MW_I=188g/mol).

The experimental results have proved that the Compound I is more permeable for organic solvent nanofiltration in methanol and the membrane performance for both compounds can be modelled according to the Kedem-Katchalsky transport equations. This way, the membrane permeability L_P can be considered as $5.43 \cdot 10^{-7}$ m/s bar, the solute permeability coefficients ω_A and ω_I take the values of $1.60 \cdot 10^{-6}$ and $5.38 \cdot 10^{-6}$ m/s bar, and the reflection coefficients σ_A and σ_I 0.688 and 0.172 respectively. On the other hand, the performance of the organic solvent reverse osmosis stage can be characterized by a lower solvent permeation when compared with the nanofiltration membranes: 45 % reduction in terms of the membrane permeability with a value of $2.44 \cdot 10^{-7}$ m/s bar (Abejón et al., 2014) and a higher retention of both solutes (the value of the rejection coefficients for both solutes is 0.995 at 35 bar).

The cascade was designed to be fed continuously with a 24 m^3/d stream containing 25 and 75 g/L of the compounds A and I respectively, which corresponded to a product purity of 25 %. The purity of the processed compound A had to be increased until 90 % (minimal purity requirement). In order to avoid any possible problems related to solute solubility, the maximal allowed solute concentration for whatever stream was fixed to be lower than 150 g/L.

Although ASPEN Custom Modeler was initially chosen as simulation software for the analysis of the designed cascades, it was decided the use of GAMS optimization software to guarantee the compliance of the requirements about minimal purity and maximal solute concentrations while consideration of only economically optimal conditions for each cascade configuration (minimal total costs). The maximum number of stages integrating the cascades was limited to 6 in order to avoid too complex systems.

4. Results

The commented results are focused on the comparison between the two most attractive cascades which incorporate 6 stages: the 3R2P+RO and 4R1P+RO configurations (the 2R3P+RO and 1R4P+RO configurations are more useful to obtain the more permeable solute as a high-purity product, but this is not the case).

Table 1 shows the economic results of both cascades under their corresponding optimal design and operation conditions. These optimal technical conditions are compiled in Table 2 and the resulting system performances can be observed in Table 3.

Table 1: Economic breakdown of the compared cascades

Cascade	**3R2P+RO**		**4R1P+RO**	
	Costs ($/d)	Contibution to Total Costs (%)	Costs ($/d)	Contibution to Total Costs (%)
TC	37,700		47,031	
CC	13,875	36.8	16,645	35.4
C_{memb}	1,577	4.2	1,891	4.0
C_{inst}	12,298	32.6	14,753	31.4
OC	23,825	63.2	30,386	64.6
OC_{en}	43	0.1	73	0.2
OC_{lab}	240	0.6	240	0.5
OC_m	694	1.8	832	1.8
OC_{loss}	15,097	40.0	21,485	45.7

It is clear than the 3R2P+RO option is much more advantageous in economic terms, as it can achieve the purity requirement with lower total costs (the save when compared to the 4R1P+RO cascade is close to 20 %). These savings are shared between the capital costs and the operating costs.

The preferred cascade needs a lower total membrane area (575 against 690 m²), and consequently, lower initial capital expenditure. However, this lower area is more effectively employed, as it is able to attain a higher product yield (calculated as the percentage of Compound A that is recovered in the product stream).

The difference between the achieved yields is the main reason that explains the higher operating costs of the 4R1P+RO configuration. The higher amount of Compound A that leaves the system in the waste stream implies higher costs due to chemical loss, which is the only component of the operating costs that is not similar between both cascades (the rest of them are actually comparable). It is worth mentioning that some operating costs, such as energy, labour and maintenance, can be considered negligible as their joint contribution to the total costs is lower than 2.5 %.

Table 2: Technical conditions of the compared cascades

Cascade	3R2P+RO						
Stage	3R	2R	1R	0	1P	2P	RO
Rec	0.673	0.835	0.817	0.897	0.900	0.147	0.739
ΔP (bar)	20	20	20	20	20	20	35
Area (m²)	27	29	31	83	322	47	36
Cascade	4R1P+RO						
Stage	4R	3R	2R	1R	0	1P	RO
Rec	0.671	0.836	0.818	0.883	0.900	0.105	0.738
ΔP (bar)	20	20	20	20	20	20	35
Area (m²)	27	28	31	71	450	47	36

The optimal operation conditions are characterized by maximum applied pressure in each nanofiltration stage within the defined range from 5 to 20 bar (for the reverse osmosis stage the applied pressure was fixed to 35 bar). The results regarding recovery ratios show high values (equal or close to the maximal value of 0.9 within the defined range) for most of the stages except but the last ones in the permeate branches. These stages work under very low recovery ratios, so high flow recirculated streams get back to previous stages.

Table 3: Performance of the compared cascades

Cascade	3R2P+RO	4R1P+RO
Purity (%)	90.0	90.0
Yield (%)	96.9	95.5

About the solvent recoveries, both configurations have a very similar performance: the flows of the streams with the recovered solvent from the reverse osmosis stage to the last stage in the retentate branches are 32.5 and 32.7 m^3/d for the 4R1P+RO and 3R2P+RO configurations respectively. Taking into account the flow of the preferred cascade and a solvent price (in this case methanol) of 250 \$/m^3, the resulting money save due to solvent recovery is 8,125 \$/d, which is more than 20 % of the total cost.

5. Conclusions

Different configurations of organic solvent nanofiltration membrane cascades can be designed for solute fractionation. Minimal solvent wastage and maximal solvent recovery and reuse have been integrated as desired aims, so a reverse osmosis stage has been incorporated to the six-stage configurations analysed in the present work for the purification of an intermediate API precursor in methanol medium.

A simulation model, based on the equations for solvent and solute transport through the membranes according to the Kedem-Katchalsky model and the mass balances (overall and by components) for membrane modules and stream mixers was formulated to represent the process performance. It was complemented with a simple economic model to assess the main costs of the process.

The results have demonstrated that both main configurations (3R2P+RO and 4R1P+RO) show a very similar performance for solvent recovery, with more than 32 m^3/d of recovered solvent. Under the operation conditions, no additional pure solvent stream is needed to control the maximal allowed solute concentrations. Nevertheless, the 3R2P+RO cascade appears as much more efficient, as it can achieve the imposed purity requirement with a higher yield when compared to the 4R1P+RO cascade. The main consequence of this higher yield is a reduction on the total costs of the process, close to 20 %.

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