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Removal of API's (Active Pharmaceutical Ingredients) from Organic Solvents by Nanofiltration

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Abstract: The removal of 5 specific active pharmaceutical ingredients (API's) with molecular weight of 189, 313, 435, 531, and 721, respectively, from toluene, methylene chloride, and methanol was studied by using solvent resistant nanofiltration. Three membranes of the StarMem series (120, 122, and 228), with cut-off values of 200, 220, and 280 respectively, were used in the experiments. Although the rejections expected from the size difference between solutes and membrane pores are high, the results largely depended on the solvent used. For toluene, rejections were rather small, due to the low molecular weight of the solutes of interest (all API's except for the largest compound). Modelling of the rejection curve showed that the minimum molecular weight of a solute to obtain a rejection of 90% in toluene with the membranes used, is ca. 600. The application in methylene chloride was unsuccessful

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due to partial dissolution of the membrane top layer; other polymeric membranes such as the Solsep series might be more successful. The rejections in methanol were sufficiently high (>90%) to allow implementation: the rejection can be significantly increased by using a module design with double membrane passage and recirculation of the retentate, as was calculated from mass balances. A comparison of a (single pass) nanofiltration system with a throughput distillation unit, currently in use, showed that the energy consumption is 200 times lower in the nanofiltration system.

Keywords: Solvent resistant nanofiltration, active pharmaceutical ingredients (API), solvent recovery

INTRODUCTION

Separation processes are of utmost importance for the chemical and pharmaceutical industry: 50 to 90% of the capital investments in the chemical industry involve separation processes, whereas organic syntheses in the pharmaceutical industry are often carried out in organic solvents and involve products with high added value that have to be separated from the organic solvents. Conventional separations are materials or energy intensive (in the chemical industry) or difficult to achieve at a large scale (pharmaceutical industry). Solvent (nano)-filtration is possibly an interesting alternative with benefits in terms of economy, environment and safety (1). An important reason for the pharmaceutical industry to adopt membrane technology is the ability to concentrate the pharmaceutical intermediate/end product at room temperature instead of high temperature, which may cause API degradation. However, experiences with solvent resistant nanofiltration are still scarce and some of the unknowns might impede a successful application. Among the reported difficulties are the membrane stability (2), prediction of the flux for a wide range of organic solvents (3–6), and often low solute rejections (7–9).

The pharmaceutical industry in Flanders is one of the major players in the region's economy. 29 pharmaceutical companies are hosted with a production department in Flanders; four companies are producing active pharmaceutical components (API's), whereas 25 are dealing with the formulation of drugs. API-production consumes much larger volumes of organic solvents than drug formulation. Organic solvents are mainly used as reaction medium, but also as raw material. As a consequence, large, and thus expensive, volumes of waste stream occur in the pharmaceutical industry. In 2004, the pharmaceutical industry in Flanders, Belgium, consumed approximately 18.5 kton of organic solvents for the production and the formulation of active pharmaceutical active ingredients. Organic solvents are not only used as reaction media, but also as raw materials or as catalysts. Typical solvents used in the pharmaceutical industry are methanol, ethanol, iso-propanol, toluene, and methylene chloride.

The use of organic solvents, either as raw materials, as reaction media or as catalysts, includes an important number of risks and possibly hazardous situations. Organic solvents have a different degree of toxicity for humans. A recurrent problem caused by VOCs is the so-called painter disease (CTE: Chronic Toxic Encephalopathy; or OPS: Organic Psycho Syndrome), the harmful effect of organic solvents on the central nervous system, resulting in tiredness, irritability, reduced ability to concentrate, or even dementia. Other potential health problems are skin disorders (eczema), cancers, multiple sclerosis, heart, kidney and liver complaints etc. The relative importance of possible effects of organic solvents on humans depends on the concentration and the time of exposure. High doses on a short term may lead to acute damage, whereas lower doses over longer periods of time can result in chronical effects.

In addition to the health risk of human exposure to organic solvents, also indirect effects on the environment occur, due to diffuse or controlled emissions and discharges, which may be even more hazardous. The increase of historical pollutions of air, soil, and water resulted in the need for strict regulations in order to protect the environment and future generations. Over the last decades more attention has been paid to the substitution of dangerous solvents by safer alternatives, e.g. the use of toluene or xylene instead of the carcinogenic benzene. However, the large volumes required for formulation and separation processes remain.

In this work, the potential of nanofiltration as a separation tool in the chemical production process of active pharmaceutical components is evaluated. Due to strict regulations for pharmaceuticals, organic solvents used for chemical production of API's are required to be highly purified. Therefore, most of the organic solvents can not be reused and are discharged. Nevertheless, important volumes of waste streams are recovered by distillation. Solvents are distilled to virgin quality, which typically involves the following specifications: 99% chromatographic purity, clear colourless liquids, a water content of less than 0.1%, within predefined density and refractive index range and less than 10 ppm residual pharmaceutical intermediate/end product (API/IPI). Thus, the specific requirements for API's are much higher than the general specification for solvent purity (99%). The application of nanofiltration provides some interesting opportunities (a further reduction of the API/IPI content, impact on the solvent yield, flux in line with throughput distillation), allowing a faster throughput and an increase of the capacity of distillation, resulting in an increase of the number of solvent streams that can be distilled. Important economic and environmental benefits are feasible.

METHODS AND MATERIALS

Experiments

Three organic solvents used in the chemical production processes of Janssen Pharmaceutica-Johnson & Johnson (Company) (Geel, Belgium) were selected for this case-study: toluene, methanol, and methylene chloride. These solvents were of specific interest, as they correspond to the largest volumes of waste streams.

Five API's with a different molecular weight were selected for filtration experiments. Filtration experiments in methanol and methylene chloride were carried out with only one API. The components' names and properties were covered by a policy and secrecy agreement; however, the molecular weight of all components, which is the main factor determining separation performance, is known. The solutes used in the experiments had a molecular weight of 189, 313, 435, 531, and 721, respectively. For all experiments, StarMem-membranes (Membrane Extraction Technology, London, UK) were used, since significantly improved results were reported in literature for these membranes (10–12). Three different membrane types were tested: StarMem 120, StarMem 122 and StarMem 228. These membranes have a polyimide toplayer and a molecular weight cut-off of 200, 220 and 280, respectively. The permeability (toluene) is ca. 1 $\mathrm{L/(m^2 \cdot h \cdot bar)}$ for StarMem 120/122 and ca. 0.26 $\mathrm{L/(m^2 \cdot h \cdot bar)}$ for StarMem 228. In all experiments, the membranes were conditioned by immersion during 24 h in the solvent to be used in the experiment.

All experiments were carried out in triplicate at room temperature in a stirred dead-end filtration module (Sterlitech HP4750). The membrane surface has an active area of 0.00146 $\mathrm{m^2}$. The feed solution can be magnetically stirred with a (teflon coated) stirrer bar. The rotation of the stirrer was set at 1000 rpm. Pressure at the feed side is supplied by an inert gas (N_2). A transmembrane pressure of 15 bar was applied. Fluxes are determined by measuring the time difference Δt, required to collect a certain volume of permeate V_p (or mass m_p). Permeate collection started after a stabilization period of ca. 15 min. The flux was calculated as:

$$J\left(\frac{l}{h \cdot m^2}\right) = \frac{V_p(ml) \cdot 3600(s/h)}{1000(ml/l) \cdot \Delta t(s) \cdot A(m^2)} \tag{1}$$

Synthetic feed solutions of 10 ppm API were prepared. Table 1 summarizes the different solvent-solute combinations used in this case-study, together with the molecular weight of the APIs and the analytical technique for the determination of the API-concentration.

Modelling

Implementation of membrane processes at industrial scale requires a good descriptive and predictive model based on readily accessible physical property data. This model should be physically realistic and require a

Table 1. Solute-solvent combinations used in the case-study on solvent recovery in the pharmaceutical industry

Solute	MW (g/mol)	Solvent	Analysis
API-1	189	Toluene	GC
API-2	313	Toluene	UV/VIS-spectrophotometry
API-3	435	Toluene/Methylene chloride	UV/VIS-spectrophotometry
API-4	531	Toluene	UV/VIS-spectrophotometry
API-5	721	Methanol	UV/VIS-spectrophotometry

minimum number of assumptions. However, at a fundamental level, nanofiltration is a very complex process. Various models for the retention of (uncharged) organic molecules can be considered; all of these are based on nanosieving or on solution-diffusion. Whereas this approach seems to be fundamentally different, it can be shown that both models may lead to similar results, because the diffusivity of a given compound is inversely proportional to its size through the Stokes-Einstein equation:

$$D_s = \frac{kT}{6\pi\eta r_s} \tag{2}$$

where D_s is the diffusion coefficient (m^2/s), T is the temperature (K), k is the Boltzmann constant, η is the viscosity ($Pa \cdot s$), and r_s is the solute's radius.

Some of the models based on nanosieving are the Steric Hindrance Pore Model, the model of Zeman and Wales, the log-normal model, and the Verniory model.

The *Steric Hindrance Pore model* (SHP model) (13) assumes that all pores have the same diameter. This diameter corresponds with the pore size of an imaginary membrane with uniform pores, for which the retention of unchanged molecules is equal to the retention with the real membrane. In reality not every pore is cylindrical with the same diameter; the model is an approximation of the membrane structure as a bundle of cylindrical pores through which molecules in solution can permeate and encounter a certain amount of sterical hindrance and interactions with the pore wall.

The reflection coefficient can then be calculated as

$$\sigma = 1 - \mathrm{H_F S_F} \tag{3}$$

with

$$H_F = 1 + (16/9) \cdot \eta^2 \tag{4}$$

$$S_F = (1-\eta)^2(2-(1-\eta)^2) \tag{5}$$

$$\eta = d_c/d_p \tag{6}$$

H_F is a "wall-correction parameter" that represents the effect of the pore wall; S_F is a parameter that represents sterical hindrance during the transport through the pores. The diameter of a molecule and the diameter of a pore are symbolised by resp. d_c and d_p.

The model of *Zeman and Wales* (14) describes the retention of a sphere through a capillary (reflection coefficient) as:

$$\sigma = 1 - (\eta \cdot (\eta - 2))^2 \tag{7}$$

Pores are assumed to be cylindrical with a uniform diameter; a parabolic velocity dependence in the pore is assumed.

By introducing a sterical hindrance factor during convective transport, expressed as $\exp(-\alpha \cdot \eta^2)$, where α is a dimensionless constant, the equation becomes:

$$\sigma = 1 - [(\eta \cdot (\eta - 2))^2] \cdot \exp(-\alpha \cdot \eta^2) \tag{8}$$

In the *log-normal model* (15) the pore size is accepted to be not constant, in contrast to the SHP model and the model of Zeman and Wales. A log-normal distribution is assumed for the pore size. No sterical hindrance in the pores or hydrodynamic lag is taken into account, but it is assumed that a molecule permeates through every pore that is larger than the diameter of the molecule. Moreover, the diffusion contribution to the transport through the membrane is considered to be negligible. Therefore, the (maximal) retention can be expressed by the following equation:

$$\sigma(r_c) = \int_0^{r_c} \frac{1}{S_p \cdot \sqrt{2\pi}} \cdot \frac{1}{r} \cdot \exp(-\frac{(\ln(r) - \ln(\bar{r}))^2}{2S_p^2} dr \tag{9}$$

where $r_c = d_c/2$.

This equation comprises two variables, S_p and $\bar{r}$, where S_p is the standard deviation of the distribution. This standard deviation is a measure for the distribution of the pore sizes. As the reflection curve corresponds to an integrated log-normal distribution, a small S_p represents a large slope of the reflection curve; a large S_p represents a small slope. $\bar{r}$ is a mean pore size, namely the size of a molecule that is retained for 50%.

Further on, the Verniory model (16) is based on the incorporation of frictional drag forces acting in cylindrical membrane pores:

$$\sigma = 1 - g(\eta)S_F \tag{10}$$

with:

$$g(\eta) = \frac{1 - (2/3)\eta^2 - 0.2\eta^5}{1 - 0.76\eta^5} \tag{11}$$

$$S_F = (1 - \eta)^2\big(2 - (1 - \eta)^2\big) \tag{12}$$

For dense membranes, solution-diffusion models are to be used. These are derived from the fact that the flux is proportional to a gradient in solute concentration, which is the driving force. This approach is the most widely accepted basis for transport models in dialysis, reverse osmosis, gas permeation and pervaporation. White 2002 suggested to apply this model also on experimental data for dense nanofiltration membranes, used in toluene, resulting in the following transport model (17):

$$J_i = D_i K_i \left(\frac{c_{f,i} - c_{p,i} \exp\left((-V_i(P_f - P_p))/(RT)\right)}{\Delta x} \tag{13}$$

RESULTS AND DISCUSSION

Toluene

Experiments with toluene were carried out with API 1-4. StarMem membranes consist of a hydrophobic toplayer; as a consequence, the average permeabilities are relatively high for toluene: 1.1, 2.2, and 0.39 l/h $\cdot$ m^2 $\cdot$ bar respectively for StarMem-120, StarMem-122, and StarMem-228. These values are of the same order of magnitude as the values indicated by the manufacturer. Figure 1 presents the rejection of the different API's in toluene as a function of molecular weight. A clear correlation is observed between the molecular size of the solute and its rejection. This proves that the performance of the membranes can be evaluated based on molecular size, although deviations can be expected when for example more hydrophobic solutes are used. The three different membranes show similar rejection curves, but as can be expected on the base of the MWCOs, specified by the manufacturer, the rejections of a given component decreases in the following order: StarMem-120, StarMem-122, and StarMem-228.

Rejections of more than 80% were observed for solutes with a molecular weight of more than 400, which is reasonable for industrial application. However, the combination of toluene and API-1 (MW 189) was of special interest for Janssen Pharmaceutica, and only 43% could be obtained (with

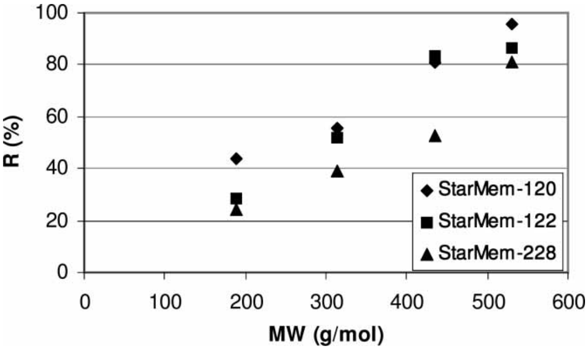

Figure 1. API-rejection in toluene (MW API-1 = 188, MW API-2 = 313, MW API-3 = 435, MW API-4 = 531).

StarMem-120). It was suggested (18) that for the removal of solutes having only twice the size of the solvent, approximately 50% is the upper limit with membranes currently available on the market. Nevertheless, it appears that the application of nanofiltration membranes may become a powerful separation tool in toluene for larger solutes.

The pore diameters of the three membranes in toluene were calculated using the Steric Hindrance Pore (SHP) model, the Zeman-Wales model, the Verniory model, and the lognormal model. Again, it is assumed that size is the most important factor in the separation. The three former models calculate an "effective" pore size, i.e., the pore size of a hypothetical membrane with uniform cylindrical pores, perpendicular to the membrane surface; the lognormal model takes a pore size distribution into account (17). The results are summarized in Table 2. Although the SHP model, the Ferry model and the Verniory model yield different results (with the smallest pore size predicted by the SHP model and the largest pore size predicted by the Verniory model), the order of magnitude is the same for each model, i.e., 1 nm. The lognormal model shows that the actual (average) pore size of the StarMem membranes is somewhat smaller, but a distribution of pore sizes exists. The rejection curve, calculated with the

Table 2. Effective diameters of the StarMem-membranes in toluene, calculated with the Steric Hindrance Pore model (SHP), the Ferry model, the Verniory model and the lognormal model (^{a}: mean diameter, corresponding to a 50% rejection)

	SHP	Ferry	Verniory	Lognormal
StarMem-120	0.85	1.02	1.10	0.50^a
StarMem-122	0.89	1.09	1.89	0.54^a
StarMem-228	1.03	1.31	1.44	0.61^a

lognormal model, is given in Fig. 2 for the StarMem-122 membrane; the other membranes yielded a similar result. The effective pore size $d_{p,eff}$ used in Fig. 2 is calculated from the molecular weight of the solutes, using an empirical correlation and a constant ratio of the solute's diameter in water and toluene (17). From Fig. 2 it can be concluded that a rejection of 90% can be achieved when $d_{p,eff} > 0.8$, which corresponds to a solute with a molecular weight of ca. 600.

Methylene Chloride

None of the membranes used appeared to be resistant against methylene chloride. The toplayer of the StarMem-membranes dissolved from the support layer and low rejections were observed. Therefore, no further attention was paid to the separations in this solvent. It was concluded that the currently available polymeric membranes, even the most solvent resistant ones, cannot be applied for separations in methylene chloride. In other words, any membrane can only be applied in a specified set of solvents, although possibly specific membranes might be developed for this kind of applications, such as the SolSep series (19).

Methanol

Filtration experiments in methanol were carried out with API-5 (MW 721). StarMem-120 and StarMem-228 were used as membranes. Table 3 summarizes the results for these experiments. High rejections were observed (91–93%), which might be useful for industrial upscaling. A detailed estimation was made for this application, considering a full scale unit. Mass balances were calculated over the system (Fig. 3).

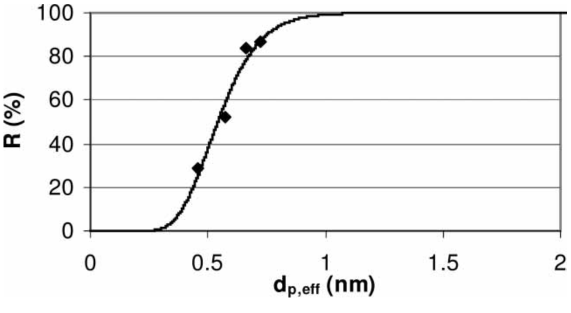

Figure 2. Rejection curve for StarMem-122 in toluene, calculated with the lognormal model (The effective pore size $d_{p,eff}$ is calculated from the molecular weight of the solutes, using an empirical correlation and a constant ratio of the solute's diameter in water and toluene (17)).

Table 3. Methanol permeability and API rejection (MW 721) using StarMem-120 and StarMem-228

	L (l/ $h \cdot m^2 \cdot bar$)	R (%)
StarMem-120	5.5	91
StarMem-228	3.6	93

Assuming that 80% of the feed stream is recovered in the permeate (a typical value for industrial applications) the mass balances are for this system are:

$$J_f = J_p + J_r \tag{14}$$

$$\frac{J_p}{J_f} = 0.8 \tag{15}$$

$$c_f J_f = c_p J_p + c_r J_r \tag{16}$$

$$R = 1 - \frac{c_p}{\overline{c_f}} = 0.91 \tag{17}$$

in which J_p, J_r, c_p, c_r and $\overline{c_f}$ are unknown.

The throughput distillation currently in use deals with a feed flow (J_f) of 10,000 I a day, corresponding for methanol to a flow of 417 I/h of which 80%, i.c. 334 I/h, might be recovered. As can be seen in Table 3, the API-5 rejection is similar for StarMem-120 and StarMem-228. As the permeability is significantly higher for StarMem-120, it is opportune to select this membrane for further application and calculations. Assuming a permeability of 5.5 I/ $h \cdot m^2 \cdot bar$, and an applied transmembrane pressure of 15 bar, a permeate flux of 82.5 $I/h \cdot m^2$ is obtained. As a permeate flux of 334 I/h is required, a membrane surface of 4.05 m^2 is needed. A 8″ × 40″ module (20) provides

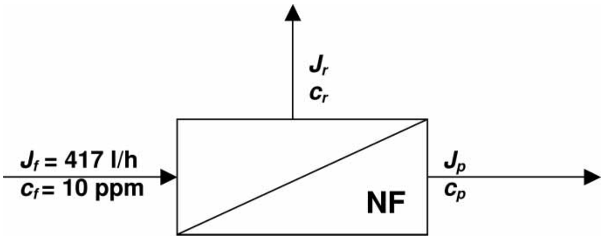

Figure 3. Design of a one-stage membrane process.

an active membrane area of $6.0\,\mathrm{m}^2$, so that a single element would be sufficient for this separation.

It was found in the experiments that StarMem-120 provides a 91% rejection for API-5. However, this can not be applied straightforward on the initial feed concentration of 10 ppm. As a high recovery is desired, the concentration of API-5 in the retentate is seriously increased when compared to the feed concentration, and the real feed concentration at the membrane surface ($\overline{c_f}$) lies between the initial feed concentration (c_f) and the retentate concentration (c_r). A possible assumption is that $\overline{c_f}$ is the average of the initial feed concentration and the retentate concentration:

$$\overline{c_f} = \frac{c_f + c_r}{2} \tag{18}$$

The solution of the mass balances then results in a permeate concentration of 2.3 ppm and a retentate concentration of 40.8 ppm. Thus, the observed rejection would be only 77%.

A more precise solution is obtained by calculating the dependency of the permeate concentration on the recovery in a more accurate way, by dividing the module into an infinite number of small segments, calculating the mass balances over these small segments and integrating the result over the entire membrane module, as presented by Mulder 1996. This method leads to the following equations:

$$c_p = \frac{c_f}{S}\left[1 - (1 - S)^{1-R}\right] \tag{19}$$

$$c_r = \frac{\left(c_f - c_p S\right)}{1 - S} \tag{20}$$

These equations show how the concentrations in the permeate and the retentate are related to the recovery (S) and the rejection (R). With a feed concentration of 10 ppm, a recovery of 80% and a solute rejection of 91%, the permeate concentration is 1.7 ppm, whereas the retentate concentration is 43.3 ppm. Thus, the observed rejection is 83%.

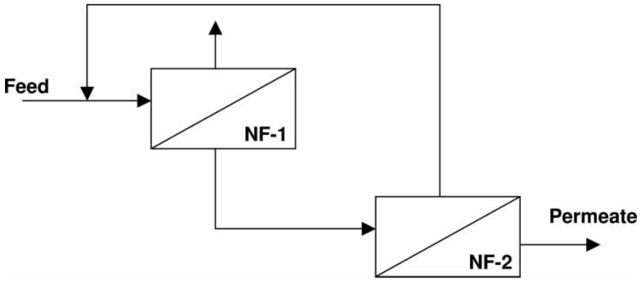

Figure 4. Design of a two-stage membrane process.

When a higher purification is required for solute reuse, a two-stage process can be considered, as shown in Fig. 4. It was shown (21) that the concentration that is left in the permeate fraction is approximately a factor 25 lower, whereas the recovery only decreases from 80% to 76.2%. A permeate flow of 317 l/h with a API-5 concentration of 0.07 ppm is then obtained. Thus, it can be concluded that the observed rejection, although incomplete, is sufficient for the removal of the selected API.

Membrane processes are much less energy consuming than traditional separation processes, such as the distillation unit currently in use. It is not the objective of this study to provide an entire cost analysis of a membrane process versus a distillation unit, for various reasons:

- the distillation column is already available, whereas the membrane module has to be constructed, and thus capital costs should be included;
- the use of a nanofiltration system gives the opportunity to treat other solvent streams in the distillation column;
- due to technical considerations, it is common to use at least two pumps in pressurised systems, a pressure pomp and a circulation pump; yet, the circulation pump requires considerably less energy.

Therefore, a simple comparison is made for the energy consumption of the two processes, based on a pressure pump for the nanofiltration system, and a total reboiler for the throughput distillation.

The brake horsepower (BHP) of one pressure pump required to provide a pressure difference ΔP for a feed flow F is given by (22, 23):

$$BHP = \frac{F \cdot \Delta P}{\eta} \tag{21}$$

with η the overall pump efficiency.

When a pressure difference of 15 bar is applied on a feed flow of 0.417 m^3/h, and an overall pump efficiency of 0.3 is assumed, the BHP is 0.58 kW.

The energy required in a throughput distillation consists of two contributions: heating the fluid to the boiling point, and evaporate the liquid at the boiling point:

$$Q = Q_{boil} + Q_{vap} \tag{22}$$

$$Q = F_m \cdot c_p \cdot \Delta T + \Delta H^{vap} \cdot F_m \tag{23}$$

with F_m the molar flow, c_p the heat capacity at constant pressure, ΔT the difference between the temperature of the feed flow and the boiling point and ΔH^{vap} the molar heat of vaporisation.

For methanol, a flow of 417 l/h corresponds to a molar flow of 2.856 mol/s. The heat capacity is 81.6 $J/mol \cdot K$, the boiling temperature

64.7°C, and the heat of vaporization 37.6 kJ/mol. The average temperature in Flanders is 9.8°C. This results in a reboiler duty of 120 kW.

At this time, yearly 451 tons of methanol are recovered by distillation, which corresponds to a process time of 1371 h at a feed flow of 417 l/h. The total energy consumption then is 162 MWh, whereas the nanofiltration set-up requires only 795 kWh, which is more than 200 times less. It is indeed clear that a membrane process is advantageous in terms of energy consumption, and might become a lucrative alternative for a traditional distillation. In addition, reducing the energy consumption is not only important in terms of process costs, but has also environmental relevance and contributes to a more sustainable use of resources.

However, it must be emphasized that the comparison of the process (energy) costs cannot be generalized because of variable prices and differences in energy cost for heat and work. A complete and careful economic analysis still remains necessary, and the payback period must be calculated. Membrane modules are expensive (6,000 Euro/module) and the optimal operating pressure must therefore be determined. A higher transmembrane pressure enhances the flux, which allows a reduced membrane surface, but the energy consumption of pumping increases too then. For a complete analysis, also indirect gains must be brought into account, such as the increased number of solvent streams that can be distilled, the safety, and the environmental aspects.

At first sight, it appears that the methanol volume to be treated is too small to account for economic feasibility. However, the membrane installation can also be used for other solvent streams: e.g. API-1 was rejected for 43% in toluene. This can be increased to approximately 80% (or 2 ppm in the permeate) in a two-step filtration process. It depends on further applications whether this meets the specifications or not.

Furthermore, pharmaceutical companies are more likely to explore a new technology in a small scale application and scale up from the experience with this process.

If methanol was completely not recovered, the total cost for the purchase, at the rate of 0.5 Euro/I, and the incineration at the rate of 86.5 Euro/ton, would be 325 000 Euro for the volume of 451 tons.

CONCLUSIONS

The application of nanofiltration for the removal of API's from organic solvents is feasible, but the success of the operation depends on the solute-solvent combination. On the solvent side, the selected membrane should be resistant against the solvent(s) used in the application, which might be difficult when aggressive solvents are considered. On the solute side, the envisaged API's should be large enough, the threshold being given by the rejection curve for the membrane/solvent combination.

The economic advantage, in addition to environmental and safety advantages, is obvious from a calculation of the energy requirements for a solvent resistant nanofiltration system and a conventional throughput distillation system: energy consumption is two orders of magnitude lower for nanofiltration. In view of a further optimization in terms of energy consumption and product quality, a possible further improvement to be studied would be the use of a hybrid process nanofiltration-distillation.

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