 DOI: 10.1002/masy.200850429

Polymeric Membrane Nanofiltration and Its Application to Separations in the Chemical Industries

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Summary: The application of membrane technology, particularly water-based nanofiltration, as a separation process in the chemical industries has increased tremendously in recent years. However, the use of membranes capable of molecular separation in non-aqueous systems (e.g. nanofiltration) is a relatively new and growing application of membrane technology. The main challenge in applying polymeric nanofiltration membranes to non-aqueous systems is that the polymers developed for water-based applications are not suitable. Polyimide is a particularly interesting polymer as it has excellent chemical resistance, and membranes produced from it provide desirable separation properties – i.e. economically viable flux and good separation of nanoscale molecules. Various research works have shown that commercial polyimide organic solvent nanofiltration (OSN) membranes, trademark STARMEM™,[1] are robust and suitable for performing molecular separations. This work will discuss in detail the use of STARMEM™ in a pharmaceutical application. The EIC-OSN process was developed for separating the enantiomers of chiral compounds in pharmaceutical applications. High optical purity (94.9%) of *(S)*-phenylethanol from *rac*-phenylethanol was achieved through the use of STARMEM™122. Process simulation of the ideal eutomer-distomer system predicted that the highest theoretical resolvability from this process would be 99.2%. Other application areas of OSN are varied, including purification and fractionation in the natural products industry, homogeneous catalyst recovery, monomer separation from oligomers, etc. Currently, OSN is used in a small number of processes including a very large petrochemical application, but it has the potential to be applied to a wide range of separations across the full spectrum of the chemical industries.

Keywords: chiral separation; EIC-OSN; membranes; polymeric membranes nanofiltration; separation techniques

Introduction to Membrane Technology

Separation technology is a fundamental aspect of the chemical industries. The majority of industrial separation processes, especially oil refineries, involves thermal operations such as distillation.[2] Distillation is not only an energy-intensive process, but in many cases the molecules being separated are degraded due to exposure to elevated temperature. In recent decades, membrane technology has emerged as an alternative separation process in various industrial applications, and is regarded as an effective and environmentally beneficial separation process as less energy is consumed due to the process being carried out at milder operating conditions. The vast majority of well-established applications have been in water-based solutions, e.g. desalination, process water recovery and protein clarification/concentration. However, the

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use of membranes capable of molecular separations (such as nanofiltration) in non-aqueous solutions is a relatively new and growing application of membrane technology. Of all membrane materials, polymeric membranes are the most advanced and widely used for industrial membrane applications.[3] However, the main challenge in applying existing polymeric membranes to non-aqueous solutions is that the polymers developed for water-based applications are not suitable — they dissolve or swell in most common non-aqueous solvents. Thus, to extend the technology's applicability into such applications, solvent-resistant polymers and membranes are needed.

Recent advances in membrane materials and engineering have allowed Organic Solvent Nanofiltration (OSN) to develop. OSN utilises solvent-resistant polymeric membranes to selectively retain nanoscale solutes (i.e. molecules with molecular weights in the range 200–1000 Da) and simultaneously allow smaller molecules to pass through the membrane. Polymers selected for OSN membranes are therefore required to exhibit (1) outstanding chemical and thermal stability, (2) the capacity to provide separations in the nanoscale range, and (3) good permeate flux. These membranes can be prepared from common high polymers like polyimide and poly(amideimide), poly(dimethylsiloxane), polyoctenamer, poly(ethylene-co-propylene-co-diene), and poly(acrylonitrile). Among these, polyimide is a particularly interesting polymer as it has excellent chemical resistance, and nanofiltration membranes produced from it provide desirable separation properties — i.e. economically viable flux and good separation of molecules in the 200–1000 Da range.[4] Various research works have shown that commercial polyimide OSN membranes, trademark STARMEM™, are robust and suitable for performing molecular separations in many applications, including but not limited to petrochemical, fine chemical, pharmaceutical and food industries.[5–7] This paper will discuss in detail the use of STARMEM™ in a pharmaceutical application.

Chiral Separation via EIC-OSN

Introduction

Enantioseparation is one of many established methods for the preparation and separation of chiral compounds, particularly in the pharmaceutical industry. The different biological activity of each enantiomer and the adverse side effect of the inactive enantiomer, essentially encourage the synthesis of enantiomerically pure compounds with specific biological activity. Resolution of the enatiomers by formation of diastereomers is one of the most popular techniques used in large-scale production of chiral pharmaceuticals. However, resolution can only be applied to molecules with base or acid functionality. Over the past decade, enantioselective inclusion complexation (EIC) has been introduced and developed by various researchers, including Toda and co-workers.[8] EIC seeks to expand the scope of chiral separations and to overcome the limitations of the resolution method. EIC employs the use of host compounds that derive from inexpensive hydroxyl acids such as tartaric or lactic acid. In principle, the host compound enantioselectively forms a complex with only one specific enantiomer of the guest species. Although this technique has been shown to be effective for certain enantioseparations, the subsequent complex separation of the host and the guest by distillation limits the applicability of compounds due to the volatility requirement – i.e. there must be adequate volatility difference between the guest and the host and/or one species must be volatile. Another drawback of EIC is the high energy requirement due to the use of distillation.

Our research group recently developed and reported a novel enantioseparation process, coupling EIC with OSN separation.[9] The EIC-OSN process can be operated at room temperature and provides high to moderate yield and optical purity of products. The simplicity of the process and equipment, combined with the reusability of the host compounds, enhances the feasibility of this technique for use at both pilot and industrial scale.

This article will demonstrate separation of chiral compounds using EIC-OSN by:

1) developing a mathematical model which can predict the separation performance of EIC-OSN;
2) verifying the proposed mathematical model through a detailed investigation of the enantioseparation of the common drug intermediate racemic phenylethanol (**1**) (122 g/mol) using *(4R,5R)*-(-)-2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol (*(R,R)*-TADDOL) (467 g/mol) as the chiral host.

Process Description

To operate the EIC-OSN process (Figure 1), a racemic guest species in a non-interacting solvent is mixed with the chiral host. The mixture is stirred for 6 h to allow sufficient time for the chiral host to enantioselectively form a complex with one specific enantiomer ((*S*)-enantiomer, for this study) (Step A). Nanofiltration of the mixture results in an enantiomer-rich permeate of the uncomplexed enantiomer ((*R*)-enantiomer, for this study) (Step B). After elution of the (*R*)-enantiomer, a decomplexing solvent is added to dissolve the chiral host/(*S*)-enantiomer complex (Step C). Nanofiltration is again carried out to elute the (*S*)-enantiomer (Step D). In the final step, the decomplexing solvent is replaced by the solvent for Step A to allow the chiral host to precipitate and thus be available for the next operating cycle (Step E). Several nanofiltration operations can be employed in both step B and D in order to improve the yield and optical purity of the enantiomer-rich products.

Process Modelling and Optimisation

The model is based on two mechanisms; dilution and dissolution. The detailed equations are described in the literature.[10] For the distomer ((*R*)-enantiomer in this study), the dilution mechanism is applied to all filtration steps. For the eutomer ((*S*)-enantiomer in this study), two mechanisms were employed: (1) dissolution for filtration Step B and (2) dilution for filtration Step D.

The efficiency of the process was evaluated using the yield and optical purity of the desired product, which is expressed in term of enantiomeric excess (*ee*), and Fogassy's resolvability (*S*). The latter was introduced by Fogassy and co-workers and has proven to be effective for quantitative evaluation of optical resolution.[11] This parameter was calculated based on the yield and optical purity of the desired product.

Two interrelated optimisation approaches, namely distribution of nanofiltration and feed volume selection, are simultaneously employed using the resolvability as an objective function. The gPROMS simula-

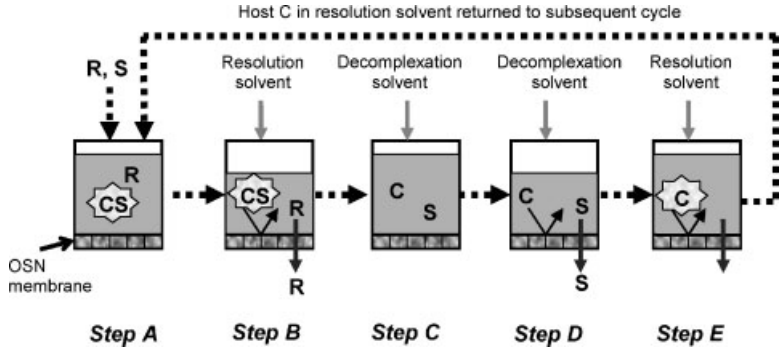

Figure 1.
Schematic diagram of enantioselective inclusion complexation-organic solvent nanofiltration (EIC-OSN) process structure. R and S represent (*R*)- and (*S*)-enantiomer (guest) while C represents chiral host.[9]

tion package (developed by Process System Enterprise Ltd, UK) was used to verify the optimal value of five different eutomer-distomer systems.

Results and Discussion

The results of EIC-OSN of the *rac*-**1** system are shown in Figure 2. It can be seen that for the first cycle, the combined yields and *ee*s of (*R*)-**1** at the resolution step (Step B) and of (*S*)-**1** at the decomplexation step (Step D) are predicted to be 98% yield with 36%*ee*(R) and 51% yield with 95%*ee*(*S*), respectively. The second cycle showed a similar trend with lower yield and *ee*s, which resulted from the increase in solubility of (*S*)-**1** due to the presence of some decomplexation solvent. Good agreement was achieved between experimental data and simulated results of both cycles with an average difference of 1.56% (with SD 3.50).

The optimisation of different eutomer-distomer systems is shown in Table 1. The results indicate that compounds with lower distomer solubility (K_s) give higher yield, purity, and subsequently resolvability. This implies that the highest possible *ee* can be obtained when all the eutomer binds with the host and entirely forms the solid inclusion complex (i.e. $K_s = 0$), whereas all the distomer remains in solution. This ideal best case scenario shows that it is possible to achieve 99.2% resolvability of the (*S*)-enantiomer using EIC-OSN.

From our solubility studies, it is also interesting to note that K_s does not increase at the same rate as the concentration, e.g. an 8-times increase in concentration leads to only a 3-times increase in K_s, and therefore the resolvability increases as the concentration increases. To demonstrate this, we

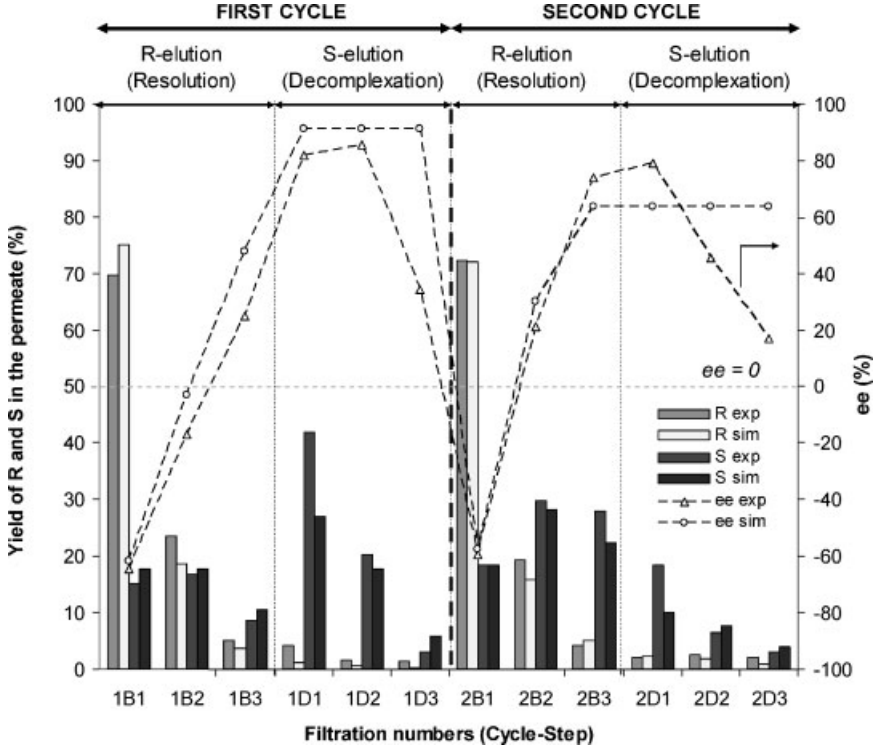

Figure 2.
Elution profile of resolution-filtration process and *ee* of the permeate stream in each filtration in two cycles. Step B is the elution of (*R*)-**1** and Step D is the elution of (*S*)-**1**. Positive *ee* indicates (*S*)-rich permeate while negative *ee* indicates (*R*)-rich permeate.

Table 1.
Simulated optimal resolvability of various secondary alcohols and amine racemate solutions in hexane at a concentration of 50 mM. Positive *S* indicates (*S*)-rich permeate and the calculation is based on using equimolar quantities of the TADDOL host.

System	*Ks* (mM)	Molecular Weight (g/mol)	Resolvability (%)	
			Step B (R-elution) (S_R^S)	Step D (S-elution) (S_D^S)
Ideal	0.0	–	−99.2	99.2
Phenylethanol	5.7	122.17	−64.7	64.7
Phenylpropargyl alcohol	6.7	132.16	−60.8	60.8
Phenylethylamine	18.9	121.18	−18.7	18.7
Phenylpropanol	25.0	136.20	0.0	0.0

simulated the phenylpropanol system at concentrations of 50 mM ($K_s = 25$ mM) and 400 mM ($K_s = 76$ mM), and the resolvability of both steps (Step B and Step D) increased from 0 to −50.3% and 50.3%, respectively with the increase of phenylpropanol concentration.

Conclusion

We have shown that the use of solvent decomplexation with OSN allows enantiomer purification and the reuse of the chiral host. The strengths of this process are the direct use of the chiral host (without derivatisation or immobilisation) and ambient temperature processing. By selecting appropriate OSN membranes with a suitable molecular weight cut-off it is possible to separate purified enantiomers and hosts. We regard the process presented here as having potential as an alternative technique for preparative-scale chiral separations, which could extend the scope of EIC from lab to pilot and industrial scale.

The Challenge and the Future

Currently, OSN is used in a small number of processes including a very large petrochemical application processing 11,500 m^3/d, but it has the potential to be applied to a wide range of separations across the full spectrum of the chemical industries. The current technological challenge is to develop membranes that demonstrate the ability to separate target compounds while maintaining their stability in organic solvents. Such membranes are not widely available in the market and when they are, they are typically more expensive than the equivalent membrane designed for use in aqueous systems. This therefore has led to a search for efficient, cost-effective polymeric materials having solvent resistance characteristics. The ongoing research in our group has extended the scope of OSN to applications included but not limited to purification and fractionation in the natural products industry, homogeneous catalyst recovery, colour removal from pharmaceutical products, and monomer separation from oligomers, etc.

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