Chiral Separation of D,L-Mandelic Acid Using An Enantioselective Membrane Formed by Polycondensation of β-Cyclodextrin with 1,6-Diisocyanatohexane on A Polysulfone Membrane

Fei-Yu Tian, Jun- Hui Zhang, Ai-Hong Duan, Bang-Jin Wang and Li-Ming Yuan*

Department of Chemistry, Yunnan Normal University, Kunming 650500, P.R. China

Abstract: An enantioselective composite membrane was prepared by polycondensation between β-cyclodextrin (β-CD) on a polysulfone support (PS) and a heptane solution of 1,6-diisocyanatohexane (1,6-DCH). The flux and permselective properties of the composite membrane were studied using an aqueous solution of D,L-mandelic acid as the feed solution. The influences of a number of parameters, such as the air-drying time of the β-CD solution on PS, the time of polymerization, the operating pressure and the feed concentration of the racemate, were studied. Chemical characterization was carried out using Fourier transform infrared spectroscopy and the top surface/cross-section was analyzed by scanning electron microscopy. The results showed that when using the enantioselective composite membrane for the optical resolution of the D,L-mandelic acid racemic mixture, an enantiomeric excess of over 85% could be obtained. The paper thus details, for the first time, how a poly(β-CD crosslinked with 1,6-DCH)/PS composite membrane can be used as an optical resolution membrane material to isolate the optical isomers of D,L-mandelic acid.

Keywords: Chiral separation, enantioselective composite membrane, polycondensation, D,L-mandelic acid, poly(β-cyclodextrin crosslinked with 1,6-diisocyanatohexane).

INTRODUCTION

From the study and recognition of chiral compounds, it is well known that many pharmaceutical and flavoring compounds are racemic mixtures. Chiral isomers function differently because of rigorous chiral matching and identification with large molecules in the body, producing marked differences in their pharmacological activity, metabolic processes and toxicity. Therefore, the increasing need for single enantiomers in the pharmaceutical and chemical industries has stimulated a significant demand for efficient processes to resolve racemic mixtures. Compared with many other separation methods for chiral compounds, membrane technology is advantageous because it enables a high throughput, is energy saving and thus more economical, and is very easy to scale up [1-8].

A large number of composite membranes have been successfully developed from different polymers, such as polyurea [9], polyamides [10], polyurea-amides [11], polyester [12], polysulfonamide [13], polyimide [14], for reverse osmosis, gas separation and nanofiltration. β-Cyclodextrin (β-CD) and its derivatives have been widely used as stationary phases and an additive of mobile phases for chromatography due to their tridimensional selectivity [15]. Therefore, they have also been used as a membrane material to separate some compounds [16-18] and racemates. For example, β-CD modified membranes were applied in the chiral separation of salsolinol [19], D,L-tryptophan, D,L-phenylalanine and D,L-tyrosine [20]. Semi-interpenetrating network-structured chitosan/β-CD composite membranes were prepared to investigate the enantiomer separation of tryptophan racemate [21]. A membrane-based chiral separation system for the separation of racemic tryptophan solutions has been developed by covalently binding β-CD onto the surface of a commercial cellulose membrane [22-24].

The mandelic acid enantiomer is an important intermediate reagent in the synthesis of chiral compounds and as a chiral selector in solvent extraction [25]. To the best of our knowledge, most of the enantiomers separated by membrane were amino acids. No examples of enantiomer separations by an enantioselective membrane formed by polycondensation of β-cyclodextrin with 1,6-diisocyanatohexane on a polysulfone membrane have been described prior to this report of its use in isolating the optical isomers of D,L-mandelic acid.

EXPERIMENTAL

Materials

D,L-Mandelic acid was purchased from Acros (Belgium) and 1,6-diisocyanatohexane (1,6-DCH) from Alfa Aesar. β-Cyclodextrin (Guangdong Guanghua Chemical Factory, China) was purified with double distilled water three times, then dried and kept in a

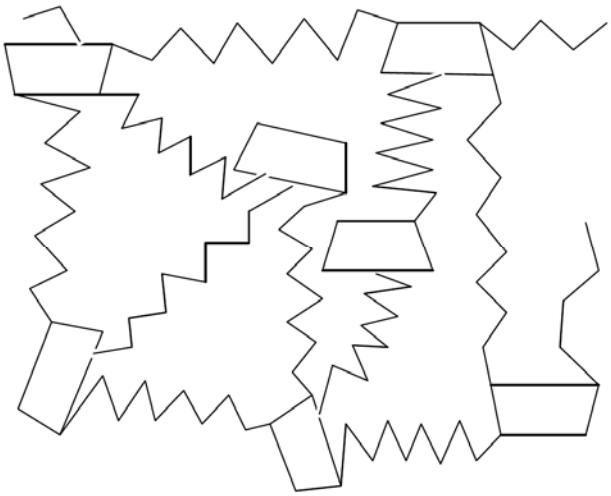
*Address corresponding to this author at the Department of Chemistry, Yunnan Normal University, Kunming 650500, P.R. China; Tel: 86-871-5941088; Fax: 86-871-5941088; E-mail: yuan_limingpd@yahoo.com.cn

E-ISSN: 1929-6037/12

desiccator before being used. Polysulfone ultrafiltration membranes (PS) were obtained from Vontron Membrane Technology Corporation (China). All the reagents were of analytical grade and were used without any further purification. Pure water was used as the solvent of the feed solutions.

Membrane Preparation

β-CD and 1,6-DCH were selected as the monomers for polycondensation (Scheme **1**) and the hydrophilic PS flat membrane was used as the substrate membrane. After the membrane was immersed in deionized water to be washed for at least 24 h, the treated support was immersed first in an aqueous solution containing 0.007% β-CD monomer at 20 ℃. Then the membrane was removed and air-dried at room temperature in a vertical position for 60 min, thereby forming a thin solid layer of β-CD on the substrate. The coated β-CD surface was then deposited onto 25 mL of 4% 1,6-DCH–heptane solution on a glass plate where the crosslinking reaction immediately took place at the solid–liquid interface. After 10 s of reaction time, the composite membrane was removed and the membrane surface was washed three times with heptane to remove the remaining 1,6-DCH from the membrane surface. After drying, the membrane was kept in deionized water at 4 ℃ until use.



Scheme 1: The schematic diagram of polycondensation between β-CD and 1,6-DCH.

In the process of polycondensation, the concentration of β-CD and 1,6-DCH were changed. However, when the aqueous solution contained 0.007% β-CD and the amount of 1,6-DCH in heptane solution was 4%, the highest enantiomeric excess was obtained.

Permeation Experiment

The permeation experiments were performed at 20 ℃ by using a membrane cell whose effective membrane area was 7.0 cm^2 and volume was 100 mL [4]. An aqueous solution of 50 mL of 0.5 mg/mL D,L-mandelic acid was used as the feed solution. Constant pressure was applied to the membrane cell using nitrogen gas input through a knob located on top of the cell. The 0.5 MPa of operating pressure was controlled by adjusting the regulator attached to a gas container and the operation time was 120 h. All membranes were used once only.

Chromatographic Analysis

The concentration of D,L-mandelic acid in feed solution and permeate were measured by high pressure liquid chromatography (HPLC). The HPLC system was equipped with a Waters 515 liquid delivery pump and a Waters 2489 ultraviolet-visible detector (Waters Company, USA). A personal computer equipped with a N2000 HPLC Workstation system was used to process the chromatographic data. The chiral column was CHIRALPAK OD (4.6 mm i.d. × 250 mm, 5 μm, Daicel, Japan) and n-hexane/isopropanol/ trifluoracetic acid (90:10:0.4, v:v:v) was used as the mobile phase with a 0.5 mL/min flow rate at 25 ℃. The detection wavelength was 254 nm and each injection volume was 20 μL.

The flux of D,L-mandelic acid was measured according to:

$$Flux(mg/m^2h) = \frac{Q}{At}$$

where Q represents the mass of the solute that permeated in a given time, t is the permeation time, and A means the effective membrane area.

The selectivity for enantioseparation was calculated in terms of the percentage enantiomeric excess (% e.e.) of the permeates:

$$e.e.(\%) = \frac{A_R - A_S}{A_R + A_S} \times 100$$

Where A_S is the S-enantiomer peak area and A_R is the R-enantiomer peak area obtained from HPLC in the permeation.

Fourier transform infrared (FTIR) spectroscopy (Bruker Tensor 27, Germany) was used to characterize

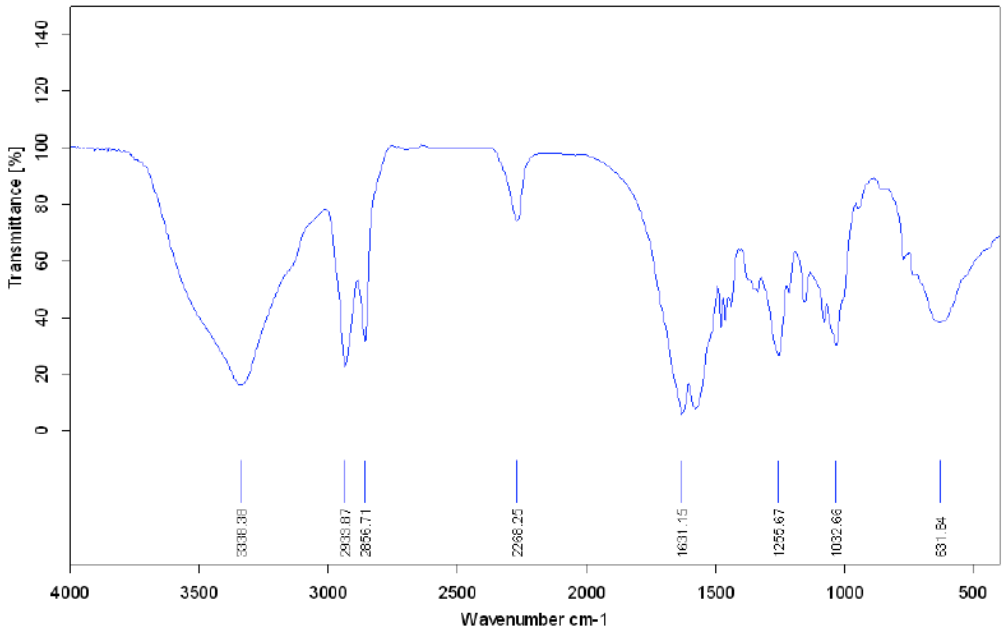


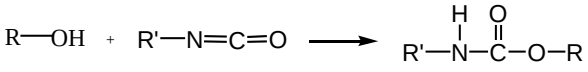
Figure 1: The FTIR spectrogram of membrane.

the membrane prepared by β-CD crosslinking with 1,6-DCH, and scanning electron microscopy (SEM) images of the composite membrane were obtained (XL30ES-EM-TMP, Holland).

RESULT AND DISCUSSION

Fourier Transform Infrared Spectroscopy

The FTIR spectra of the membrane prepared by the polycondensation between β-CD and the heptane solution of 1,6-DCH showed strong peaks at 1631.15cm^{-1}, which indicated the presence of the carbamate group (Figure **1**). This was formed by the reaction between –OH of β-CD and –N=C=O of 1,6-DCH.



Morphology of Composite Membrane

Figure **2** shows the morphologies of the cross-sections and top surfaces of the composite membrane as obtained from the SEM analysis. Before the analysis, the wet membrane was treated with propanol and heptane to retain the original structures, and then snapped in liquid nitrogen to give a generally clean break for the cross-section scan. The resulting membranes were coated with gold [5]. As can be seen by comparison with the cross-section of the PS membrane (Figure **2b**), the thin active surface layers were formed through the polymerization process on the PS membranes. Further, it could be seen that the film thicknesses increased with the increasing polymerization time (Figure **2d** and **f**). However, it is seen that there was little difference between the top surfaces of the composite membranes (Figure **2c** and **e**) and the top surface of the PS membrane (Figure **2a**) in Figure **2**.

Effect of Air-Drying Time of β-CD Solution on Polysulfone

Figure **3** shows the influence of the air-drying time of the β-CD solution on the PS membrane when held in a vertical position from 1min to over 60 min. With the increase in the air-drying time, the flux decreased and the % e.e. increased. Possible reasons may be that when the air-drying time was short, the PS substrate contained so much water and such a low concentration of β-CD that only a small amount of polymer was produced by β-CD and 1,6-DCH, resulting in low enantioselective selection and high flux. When the air-drying time extended beyond 60 min, thereby allowing the formation of a thin dry solid layer of β-CD on the substrate, the enantioselective composite membrane was created by interfacial polymerization on the surface, and over 85% e.e. was obtained.

Effect of Polymerization Time

As shown in Figure **4**, with the change in time of interfacial polymerization, the flux followed the order of 1 s ≈ 20 s > 10 s, and % e.e. value followed the order of 10 s>1 s>20 s. When this time was 10 s, over 85% e.e.

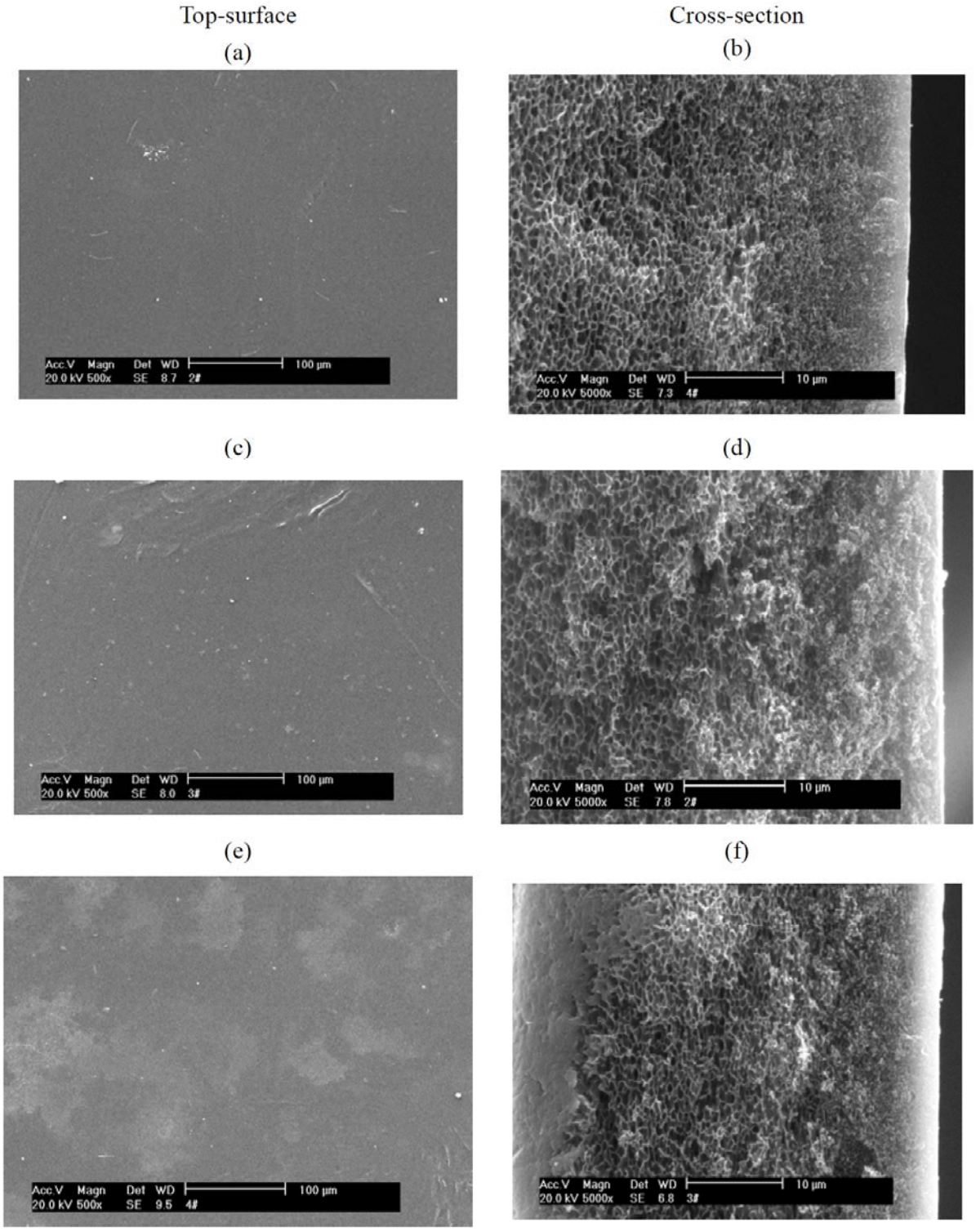


Figure 2: Scanning electron micrographs of polysulfone membrane and enantioselective composite membrane. Polysulfone membrane (**a** and **b**). Enantioselective composite membrane prepared using different polymerization times: (**c** and **d**) 1 s; (**e** and **f**) 10 s.

of enantioseparation was obtained, as the degree of crosslinking increased gradually from 1 s to 10 s. However, with the increase of the polymerization time to 20 s, the flux was increased and the enantioselectivity of the composite membrane significantly decreased, because we observed that the 1,6-DCH eroded PS, which resulted in the surface of the composite membrane being broken off. Therefore, the optimal time for interfacial polymerization was 10 s.

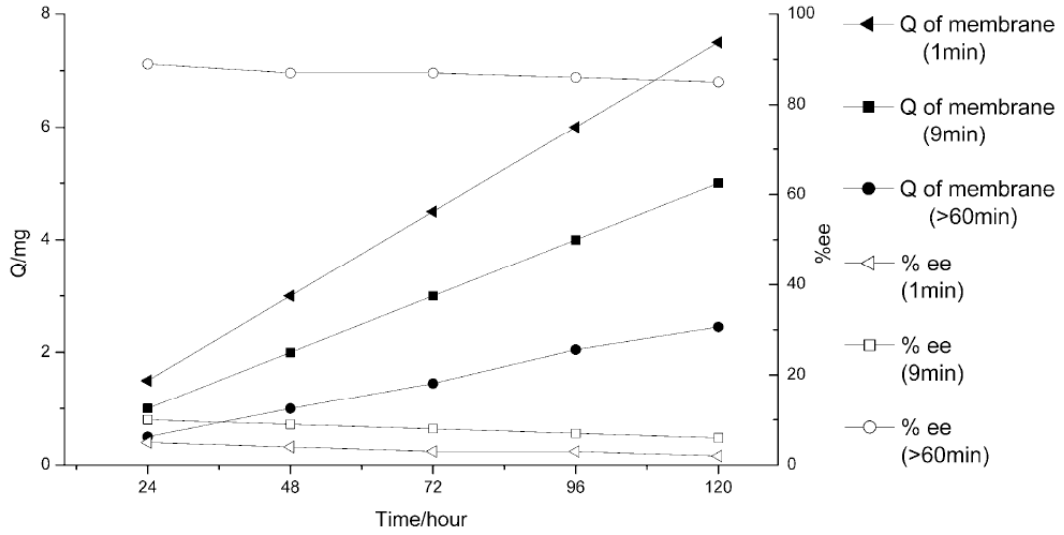


Figure 3: Mass of permeated solute (Q) and % enantiomeric excess in the chiral separation of D,L-mandelic acid through an enantioselective composite membranes prepared with 1 min, 9 min, and over 60 min of air-drying time of β-cyclodextrin solution on polysulfone in a vertical position. The time of interfacial polymerization, feed concentration and operating pressure were 10 s, 0.5 mg/mL and 0.5 MPa, respectively.

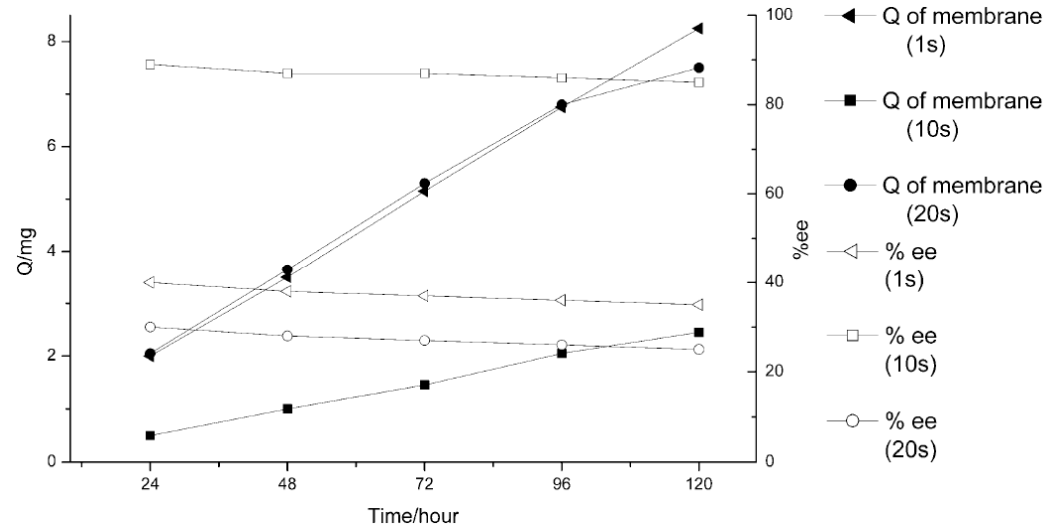


Figure 4: Mass of permeated solute (Q) and % enantiomeric excess in enantioseparation of D,L-mandelic acid through enantioselective composite membranes prepared with 1 s, 10 s and 20 s of interfacial polymerization. The air-drying time of β-cyclodextrin solution on polysulfone, operating pressure and feed concentration were 60 min, 0.5 MPa and 0.5 mg/mL, respectively.

Effect of Operating Pressure

Figure **5** shows the influence of the operating pressure on the optical resolution of the D,L-mandelic acid. When the operating pressure increased from 0.5 MPa to 0.7 MPa, the flux increased and the % e.e. underwent a major reduction. The reason was that as the operating pressure increased, the diffusion of the D,L-mandelic acid was strengthened and the sorption to the D,L-mandelic acid was weakened, so the selectivity to the racemates was decreased and the flux was increased. The optimum pressure was 0.5 MPa.

Effect of Feed Concentration of Racemate

Figure **6** shows the influence of the feed concentration on the chiral separation of D,L-mandelic acid racemates through the enantioselective composite membrane. The flux increased significantly when the feed concentration was raised from 0.5 to 1.5 mg/mL; however, the enantiomeric excess decreased. This was probably because more and more active points became covered by the isomer, thus leading to the permeation of the other isomer. Another possible reason was that with the increase in feed

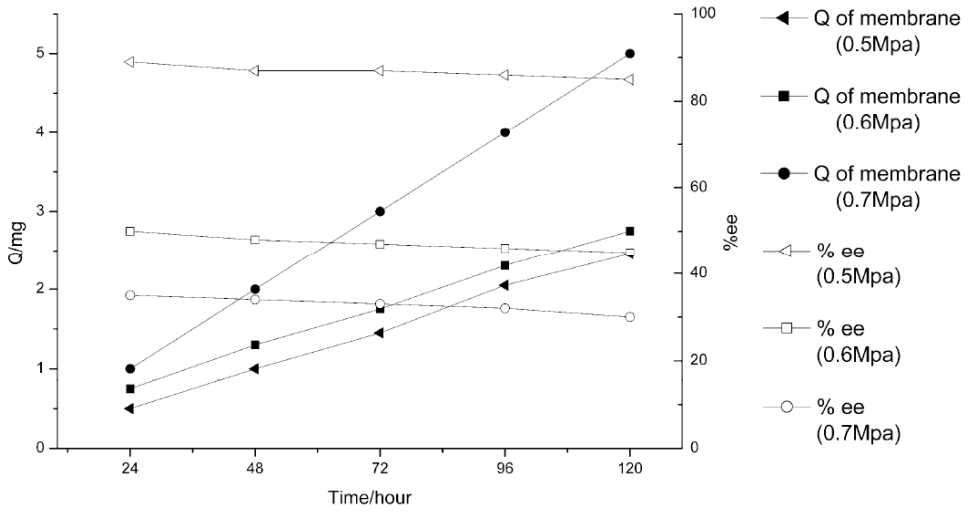


Figure 5: Mass of permeated solute (Q) and % enantiomeric excess in the chiral separation of D,L-mandelic acid through enantioselective composite membranes at 0.5 MPa, 0.6 MPa and 0.7 MPa of operating pressure. The air-drying time of the β-cyclodextrin solution on polysulfone, time of polymerization and feed concentration were 60 min, 10 s and 0.5 mg/mL, respectively.

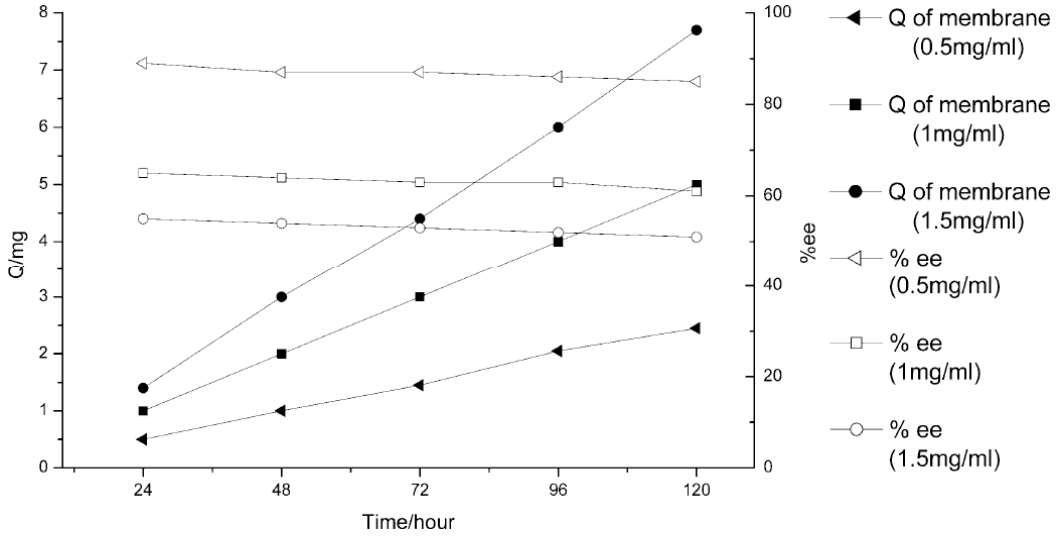


Figure 6: Mass of permeated solute (Q) and % enantiomeric excess in the chiral separation of D,L-mandelic acid through an enantioselective composite membrane prepared with air-drying times of β-cyclodextrin solution on polysulfone, polymerization time and operating pressure of 60 min, 10 s and 0.5 MPa, respectively. The feed concentrations of D,L-mandelic acid were 0.5 mg/mL, 1 mg/mL and 1.5 mg/mL, respectively.

concentration, the diffusion of the isomers interfered with each other. The enantioselectivity of composite membrane was at its best when the feed concentration was 0.5 mg/mL.

CONCLUSIONS

Chiral separation of D,L-mandelic acid was possible through a poly(β-CD crosslinked with 1,6-DCH)/PS composite membrane using a pressure driven process. Chiral recognition was a result of the steric fit of the conformation of the enantiomers in the chiral space of the membrane, and of the molecular interactions between the racemate and the membrane. The properties of the poly(β-CD crosslinked with 1,6-DCH)/PS composite membrane were influenced by the air-drying time of the β-CD solution on PS in a vertical position, the time of interfacial polymerization, the operating pressure, and the feed concentration of the racemate. When the crosslinking reaction for membrane preparation was took place for 10 s on the hydrophilic PS flat membrane with an 0.007% β-CD aqueous solution and 4% 1,6-DCH heptane solution, over 80% enantiomeric excess (e.e.) and 22.5 mg/m^{2}h of flux could be obtained.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation (No. 21075109) and the National Basic Research Program (No. 2011CB612312) of China.

REFERENCES

[1] Maier NM, France P, Lindner W. Separation of enantiomers: needs, challenges, perspectives. J Chromatogr A 2001; 906: 3-33. http://dx.doi.org/10.1016/S0021-9673(00)00532-X

[2] Xie R, Chu LY, Deng JG. Membranes and membrane processes for chiral resolution. Chem Soc Rev 2008; 37: 1243-63. http://dx.doi.org/10.1039/b713350b

[3] Romero J, Zydney AL. Staging of affinity ultrafiltration processes for chiral separations. J Membr Sci 2002; 209: 107-19. http://dx.doi.org/10.1016/S0376-7388(02)00283-1

[4] Zhao M, Xu XL, Jiang YD, Sun WZ, Wang WF, Yuan LM. Enantioseparation of trans-stilbene oxide using a cellulose acetate membrane. J Membr Sci 2009; 336: 149-53. http://dx.doi.org/10.1016/j.memsci.2009.03.034

[5] Xiong WW, Wang WF, Zhao L, Song Q, Yuan LM. Chiral separation of (R,S)-2-phenyl-1-propanol through glutaraldehyde-crosslinked chitosan membranes. J Membr Sci 2009; 328: 268-72. http://dx.doi.org/10.1016/j.memsci.2008.12.019

[6] Matsuoka Y, Kanda N, Lee YM, Higuchi A. Chiral separation of phenylalanine in ultrafiltration through DNA-immobilized chitosan membranes. J Membr Sci 2006; 280: 116-23. http://dx.doi.org/10.1016/j.memsci.2006.01.013

[7] Hazarika S. Enantioselective permeation of racemic alcohol through polymeric membrane. J Membr Sci 2008; 310: 174-83. http://dx.doi.org/10.1016/j.memsci.2007.10.055

[8] Sueyoshi Y, Fukushima C, Yoshikawa M. Molecularly imprinted nanofiber membranes from cellulose acetate aimed for chiral separation. J Membr Sci 2010; 357: 90-97. http://dx.doi.org/10.1016/j.memsci.2010.04.005

[9] Liu LF, Yu SC, Zhou Y, Gao CJ. Study on a novel polyamide-urea reverse osmosis composite membrane (ICIC-MPD). I. Preparation and characterization of ICIC-MPD membrane. J Membr Sci 2006; 281(1-2): 88-94. http://dx.doi.org/10.1016/j.memsci.2006.03.012

[10] Kim JH, Lee KH, Kim SY. Pervaporation separation of water from ethanol through polyimide composite membranes. J Membr Sci 2000; 169(1): 81-89. http://dx.doi.org/10.1016/S0376-7388(99)00335-X

[11] Zhou Y, Yu SC, Liu MH, Gao CJ. Preparation and characterization of polyamide-urethane thin-film composite membranes. Desalination 2005; 180(1-3): 189. http://dx.doi.org/10.1016/j.desal.2004.12.037

[12] Seman MNA, Hayet MK, Hilal N. Nanofiltration thin-film composite polyester polyethersulfone-based membranes prepared by interfacial polymerization. J Membr Sci 2010; 348: 109-16. http://dx.doi.org/10.1016/j.memsci.2009.10.047

[13] Dickson JM, Childs RF, McCarry BE, Gagnon DR. Development of a coating technique for the internal structure of polypropylene microfiltration membranes. J Membr Sci 1998; 148: 25. http://dx.doi.org/10.1016/S0376-7388(98)00142-2

[14] Higuchi A, Tamai M, Ko YA, Tagawa YI, Wu YH, Freeman BD, *et al*. Polymeric menbranes for chiral separation of pharmaceuticals and chemicals. Polym Rev 2011; 50: 113-43. http://dx.doi.org/10.1080/15583721003698853

[15] Yuan LM. Chiral recognition materials. Beijing: Science Press 2010; pp. 121-254.

[16] Jiang LY, Chung TS. Homogeneous polyimide/cyclodextrin composite membranes for pervaporation dehydration of isopropanol. J Membr Sci 2010; 346: 45-58. http://dx.doi.org/10.1016/j.memsci.2009.09.014

[17] Rölling P, Lamers M, Staudt C. Cross-linked membranes based on acrylated cyclodextrins and polyethylene glycol dimethacrylates for aromatic/aliphatic separation. J Membr Sci 2010; 362: 154-63. http://dx.doi.org/10.1016/j.memsci.2010.06.036

[18] Yudiato A, Dewi E, Kokugan T. Separation of isomers by ultrafiltration using modified cyclodextrins. Sep Purif Technol 2000; 10: 103-12. http://dx.doi.org/10.1016/S1383-5866(00)00055-1

[19] Dai RJ, Su CL, Wu HY, Deng YL. Separation of salsolinol using β-cyclodexytrin-modified chiral membrane. Trans Beijing Inst Technol 2008; 28: 557-57.

[20] Long YD, Huang TB. Enantioselective Permeation of Amino Acids Through β-Cyclodextrin Polymer Membranes. Chem J Chin Univ 1999; 20: 884-86.

[21] Wang HD, Chu LY, Song H, Yang JP, Xie R, Yang M. Preparation and enantiomer separation characteristics of Chitosan/β-cyclodextrin composite membranes. J Membr Sci 2007; 297: 262-70. http://dx.doi.org/10.1016/j.memsci.2007.03.055

[22] Xiao Y, Chung TS. Functionalization of cellulose dialysis membranes for chiral separation using beta-cyclodextrin immobilization. J Membr Sci 2009; 290: 78-85. http://dx.doi.org/10.1016/j.memsci.2006.12.016

[23] Xiao Y, Lim HM, Chung TS, Raj R. Acetylation of β-cyclodextrin surface-functionalized cellulose dialysis membranes with enhanced chiral separation. Langmuir 2007; 32: 12990-96. http://dx.doi.org/10.1021/la7026384

[24] Zhou ZZ, Xiao YC, Hatton TA, Chung TS. Effects of spacer arm length and benzoation on enantioseparation performance of β-cyclodextrin functionalized cellulose membranes. J Membr Sci 2009; 339: 21-27. http://dx.doi.org/10.1016/j.memsci.2009.04.015

[25] Choi WJ, Lee KY, Kang SH, Lee SB. Biocatalytic enantioconvergent separation of racemic mandelic acid. Sep Purif Technol 2007; 53: 178-82. http://dx.doi.org/10.1016/j.seppur.2006.06.024

Received on 03-12-2012 Accepted on 24-12-2012 Published on 31-12-2012

DOI: http://dx.doi.org/10.6000/1929-6037.2012.01.02.1