Optical Resolution of (*R,S*)-2-Phenyl-1-propanol Through Enantioselective Ethycellulose Membranes

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ABSTRACT: Enantioselective membrane was prepared using ethyl cellulose (EC) as membrane material. The flux and permselective properties of membrane using aqueous solution of (*R,S*)-2-phenyl-1-propanol as feed solution was studied. The employed membrane process was a pressure driven process. All kinds of important conditions including preparation and operation of membranes were investigated in this experimentation. When the membrane was prepared with 18 wt % EC, 20 wt % *N,N*-dimethylformamide in casting solution, 13 min evaporation time and 0°C temperature of water bath for the gelation of the membrane, and the operating pressure and feed solution of (*R,S*)-2-phenyl-1-propanol were 0.2 MPa and 1.5 mg/mL, respectively, over 90% of enantiomeric excess (e.e.) and 44.2 (mg/m^2 h) of flux were obtained. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 2516–2521, 2009

Key words: (*R,S*)-2-phenyl-1-propanol; ethyl cellulose; enantioselective membrane; optical resolution

INTRODUCTION

Chiral specificity is fundamental in pharmacology and chemical biology because stereochemistry play a central role in controlling molecular recognition and interaction.[1] The often-encountered pharmacological differences between enantiomers justify the administration of chiral drugs as single enantiomers, and, therefore, the need of methods to produce them. Single enantiomer may be achieved either by the asymmetric synthesis of the desired enantiomer or by resolution of a racemic mixture. Although both approaches have undergone outstanding developments in recent years, industrial scale production for many specific enantiomer also are very difficult.[2]

Among the various conventional methods for resolution of the optical isomers are high-performance liquid chromatography, recrystallization, and extraction using chiral selector. Those methods have been known to have advantage and disadvantage at the same time.[3,4] Membrane technology is advantageous because it has high throughout, energy-saving, more economical than many other separation processes, and very easy to be scaled up.[5–21] Unfortunately, the optical resolution through an enantioselective membrane is just in the beginning stage and has to be improved much more for its practical use.

2-Phenyl-1-propanol enantiomer, having a chiral carbon atom, is an important intermediate reagent for synthesis of chiral compounds, such as medicine, pesticide, and chiral selector. Figure 1(a) shows its molecular structure. Cellulose derivatives have been widely used as preparation of polymer membrane for reverse-osmosis, nanofiltration, ultrafiltration, macrofiltration, etc.[22] Since ethyl cellulose (EC) is composed of glucopyranose units that contain a large amount chirally active carbons on the backbone structure [Fig. 1(b)] and is possible to form helical structures,[3] these characteristics could be the reason that EC membrane could form certain chiral environment and make the membrane capable of optical resolution. To the best of our knowledge, until now the most enantiomers separated by membrane are amino acid, and there is not example described of enantiomer separations by EC membrane. This is a report, for the first time, that the EC is used as optical resolution membrane material for isolating the optical isomers of (*R,S*)-2-phenyl-1-propanol.

EXPERIMENTAL

Materials

The EC was purchased from Acros (Geel, Belgium). *S*-2-Phenyl-1-propanol and (*R,S*)-2-phenyl-1-propanol were obtained from Fluka (Buchs, Switzerland). Tetrahydrofuran (THF) and *N,N*-dimethylformamide

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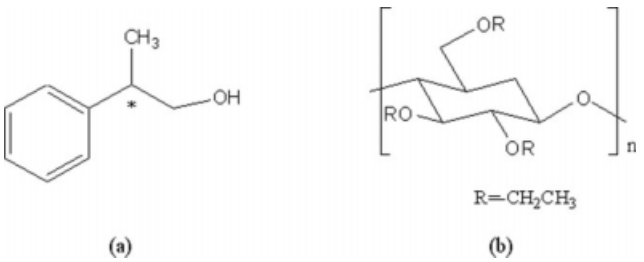

Figure 1 Molecular structures of 2-phenyl-1-propanol (a) and EC (b).

(DMF) were of analytical reagents. Pure water was used as solvent of feed solutions and coagulation bath. All other chemicals were used without any further purification.

Membrane preparation

The EC membranes was prepared as follows: 9 g of EC was dissolved in 41 mL of the mixed solvent of *N*,*N*-dimethylformamide and tetrahydrofuran (10/31, v/v) with ultrasonic for 3 h at room temperature, the resulting solution was cast on the surface of a glass plate using a casting knife to control the thickness (0.5 mm) of the membrane. The nascent membrane was evaporated 13 min under the condition of 15°C temperature and 45% relative humidity, and then immersed into the water coagulation bath (0°C) at least 30 min. The membrane was washed in pure water at 5°C for 24 h to remove the *N*,*N*-dimethylformamide and tetrahydrofuran. Finally, the membrane was rinsed and stored in pure water until use.

To visualize the top surface and cross-sectional morphology of the membranes, a scanning electron microscope (XL30ESEM-TMP, Holland) was used. Before scanning analysis, the wet membranes prepared according to the experimental method was treated by using propanol and hexane, respectively, to retain their original structures, and then snapped in liquid nitrogen to give a generally clean break of the cross section for the cross section scan. The surface and cross section of resulting membranes were covered with a thin-layer of gold.

Permeation experiments

Permeation experiments were conducted by using a membrane cell which could hold one piece of membrane with an effective diameter of 3 cm, and an aqueous solution of 1.5 mg/mL of (*R*,*S*)-2-phenyl-1-propanol was used as feed solution. This cell possessed 100 mL volume and the constant pressure was applied through the knob located on the top of the cell, using nitrogen gas to apply the pressure wanted. The rate of feed solution was controlled adjusting the regulator attached to the gas container, confirming with the pressure gauge of the cell.

Sample analysis

For the pressure driven permeation experiments, the permeate solution was sampled, the concentration of *R*-2-phenyl-1-propanol and *S*-2-phenyl-1-propanol was measured by HPLC and the flux was calculated. The HPLC system was equipped with a LabTech LC600 liquid delivery pump, UV-vis detector. A personal computer equipped with a LabTech HPLC Workstation for the LC system was used to process the chromatographic data. The chiral analysis was performed using a chiral column CHIRALPAK IA (4.6 mm i.d. × 250 mm, Daicel, Japan) and a mixture of *n*-hexane/isopropanol (90/10, v/v) as mobile phase at 30°C. The detection was examined at 254 nm, and the flow rate of the mobile phase was 0.5 mL/min. The flux of racemic compounds was measured according to the equation as follows:

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

where, Q is the quantity of the solute permeated for a given time, t the permeation time, and A is the effective membrane area.

The percentage enantiomeric excess (%e.e.) of permeates was calculated from the peak areas of their two enantiomers, *R*-isomer (A_R) and *S*-isomer (A_S). The equation is as follows:

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

The permeation rate is the peak area ratio of the *R*- to *S*-isomer in the permeation as follows:

$$\text{Permeation rate}(\%) = A_R/A_S$$

RESULTS AND DISCUSSION

Morphological structure of EC membrane

SEM was used to characterize the optical resolution EC membrane to investigate the top surface and cross section morphological structure. The membranes were imaged with only representative samples presented. Scanning electron micrographs of surfaces and cross sections of membrane were shown in Figure 2. The surface of membrane was compact, and no pores were found. A sponge-like structure was found in the cross section, which became looser from the top down.

Optical resolution of (*R*,*S*)-2-phenyl-1-propanol

Optical resolution of (*R*,*S*)-2-phenyl-1-propanol through the EC membrane was performed by

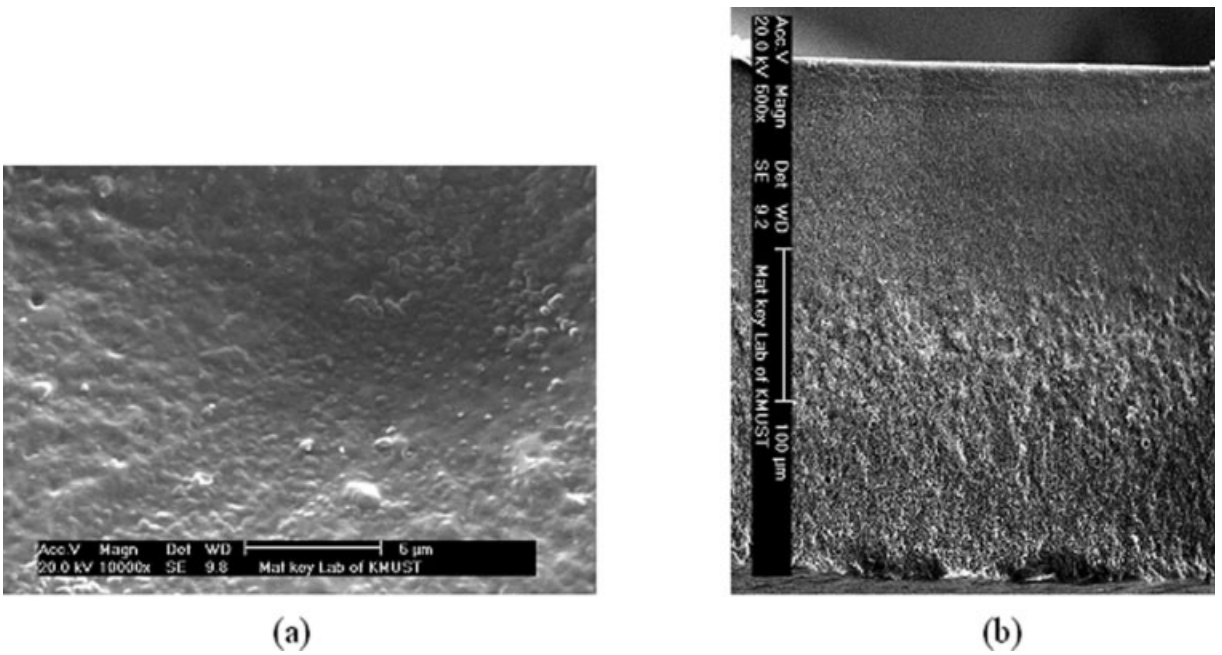

Figure 2 SEM images of chiral EC membranes prepared with 18 wt % EC and 20 wt % DMF. The evaporation time and temperature of water coagulation bath were 13 min and 0°C, respectively. (a) Surface of membrane and (b) Cross section of membrane.

employing 0.2 MPa pressure driven process at room temperature. Figure 3 showed that the enantiomeric excess value of *S*-2-phenyl-1-propanol changed with time from 0 to 150 h when 1.5 mg/mL of feed solution through a membrane, which was prepared from casting solution containing 18 wt % EC, 20 wt % *N*,*N*-dimethylformamide, with 13 min evaporation time and 0°C temperature of water bath for the gelation of membrane, over 90% of enantiomeric excess was obtained. From the results of HPLC analysis, it was found that the penetration rate of *S*-isomer was always much faster than that of *R*-isomer. Separation of the optical isomers can be explained by the interactions between the chiral environment formed in the membranes and the isomers being separated. EC used as membrane material contains a large amount of chirally active carbons on the backbone structure and is possible to form helical structure.[3,4] The helical structure will form chirally active small spaces in its main chain backbone structure, and their assembly will be possible to form certain larger chiral spaces in the membrane.[12] Chiral recognition was a result of steric fit of the enantiomers conformation in the chiral space of the membrane, and of dispersion, dipole–dipole, and hydrogen-bond interactions with the glucopyranose units in the EC.[3]

Effect of EC concentration on properties of EC membrane

Optical resolutions of (*R*,*S*)-2-phenyl-1-propanol using EC membranes prepared with different EC concentrations in the membrane casting solution were shown in Figure 4. When the EC concentration increased from 10 to 20 wt %, the enantiomeric excess value of *S*-2-phenyl-1-propanol increased, but the flux through the membrane and the permeation rate decreased. In the range of 15–20 wt % EC concentrations, the enantiomeric excess was over 90% and the change of flux was small for the membranes. From these results, it appeared that the appropriate concentration was necessary for a high optical resolution. The possible reason was that the membrane

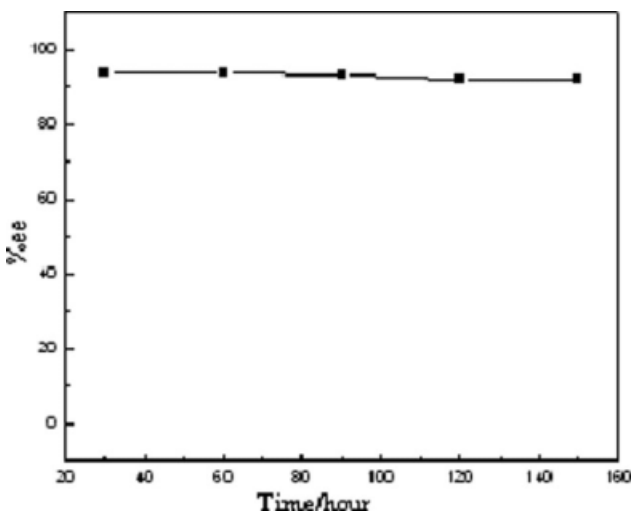

Figure 3 The e.e.% in the optical resolution of (*R*,*S*)-2-phenyl-1-propanol through the EC membrane. The operating pressure and feed concentration were 0.2 MPa and 1.5 mg/L, respectively.

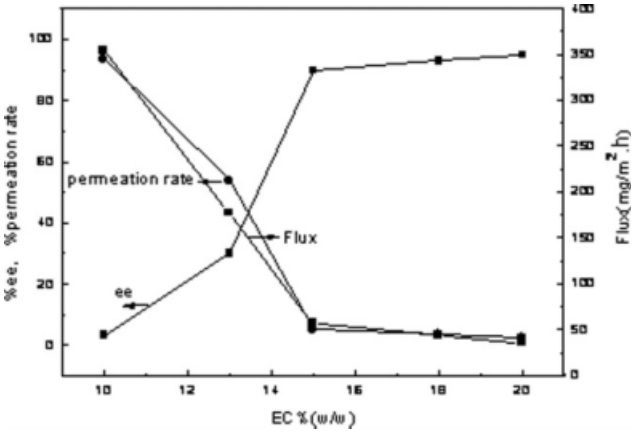

Figure 4 Effect of EC concentration on properties of EC membrane. The operating pressure and feed concentration were 0.2 MPa and 1.5 mg/L, respectively.

with low polymer, the structure of membrane became less compact with big aperture, resulting in the high flux of membrane, while decreasing the diffusion selectivity. Whereas, the structure of membrane became compact, resulting in less flux, also influencing the diffusion selectivity.

Effect of DMF content on properties of EC membrane

To investigate the effect of nonsolvent additive content of casting solution on the optical resolution property, the EC membranes were prepared using 15–30 wt % DMF content as nonsolvent additive. Figure 5 showed the effect of DMF content on the optical resolution of (*R*,*S*)-2-phenyl-1-propanol. Increasing the DMF content in the EC membrane casting solution, the membrane resulted in an increase in flux and permeation rate, but decreased in the enantiomeric excess value of *S*-2-phenyl-1-propanol. The enantiomeric excess values kept higher when the content of DMF was in the range of 15–25 wt %. The flux and permeation rate was great as the wt % DMF was more than 25%. The possible reason might be that when the exchange of the solvent (THF) with the nonsolvent (water) was complete, some DMF was still in the membrane due to higher viscosity of DMF to form the bigger hole on the surface of membrane.

Effect of evaporation time on properties of EC membrane

Figure 6 showed the effect of evaporation time of liquid membrane on the surface of a glass plate during the preparation of membrane on the optical resolution of (*R*,*S*)-2-phenyl-1-propanol. The flux and the permeation rate decreased with the increase of evaporation time. When evaporation time was more than 15 min, the flux was so low that there was little feed solution to permeate through membrane. The separation selectivity for (*R*,*S*)-2-phenyl-1-propanol increased with the increase of evaporation time. These behaviors could be explained because when the solvent of liquid membrane was vaporized, a skin layer was formed at the surface, in which the longer the evaporation time was, the denser the skin layer was. Therefore, when feed solution penetrated through this membrane, the low flux and permeation rate and the high enantioselectivity were obtained.

Effect of temperature of water coagulation bath on properties of EC membrane

Figure 7 showed the effect of temperature of water coagulation bath on the optical resolution of (*R*,*S*)-2-phenyl-1-propanol. When temperature of water coagulation bath increased from 0 to 25°C, the flux

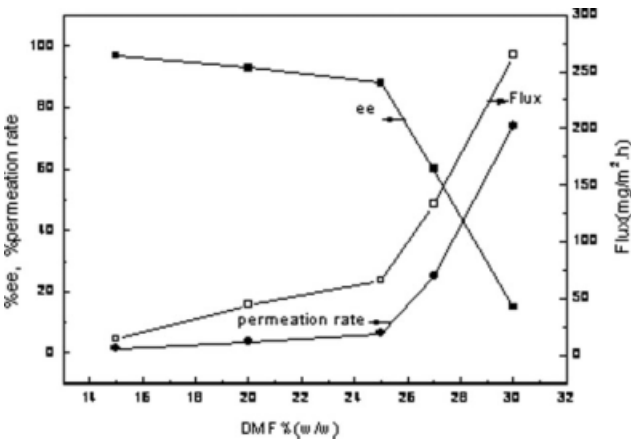

Figure 5 Effect of DMF content on properties of EC membrane. The operating pressure and feed concentration were 0.2 MPa and 1.5 mg/L, respectively.

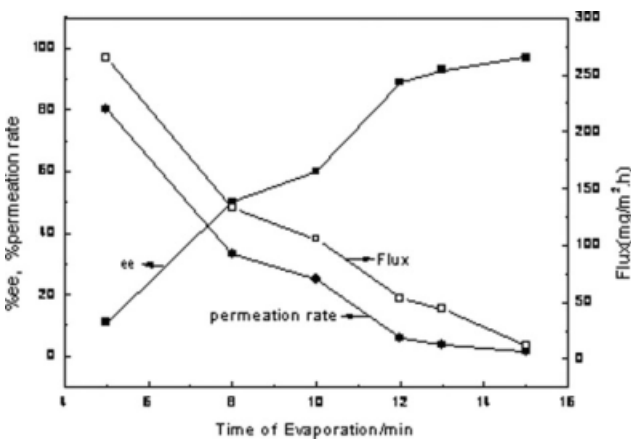

Figure 6 Effect of evaporation time on properties of EC membrane. The operating pressure and feed concentration were 0.2 MPa and 1.5 mg/L, respectively.

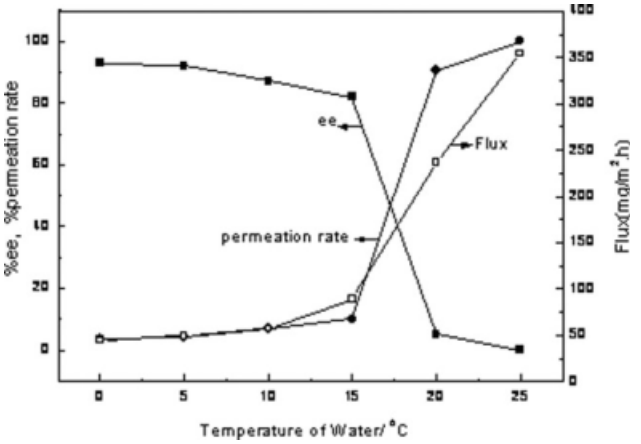

Figure 7 Effect of temperature of water coagulation bath on properties of EC membrane. The operating pressure and feed concentration were 0.2 MPa and 1.5 mg/L, respectively.

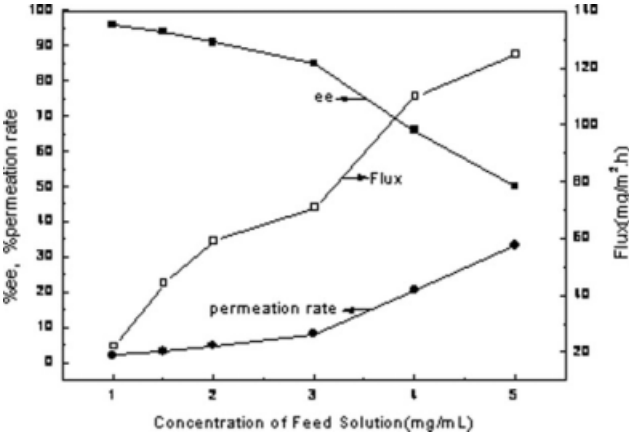

Figure 9 Effect of feed concentration of racemate on properties of EC membrane. The operating pressure was 0.2 MPa.

and the permeation rate increased and the enantiomeric excess decreased, This was due to the fact that with higher temperature of water coagulation bath, the solvent of membrane casting solution was faster diffused into the water. Thus, the membrane prepared under this condition was porous, which resulted in high flux and low selectivity.

Effect of operating pressure on properties of EC membrane

With increasing the operating pressure from 0.1 to 0.5 MPa, the experimental results by EC membrane was given in Figure 8. As shown in Figure 8, the flux of the membrane was very low as the operating pressure was 0.1 MPa. The permeation rate of the *R*-2-phenyl-1-propanol through the membrane increased with increasing the operation pressure, but the enantioselectivity of the membrane was very low as the operating pressure reached 0.5 MPa. This kind of result is one of the phenomena most commonly encountered in the membrane separation process. The solution-diffusion model has usually determined the selectivity of a dense membrane by both sorption and diffusion selectivity. The diffusion selectivity usually decreases with increasing driving force for the movement of solutes, eventually decreasing over all permselectivity.

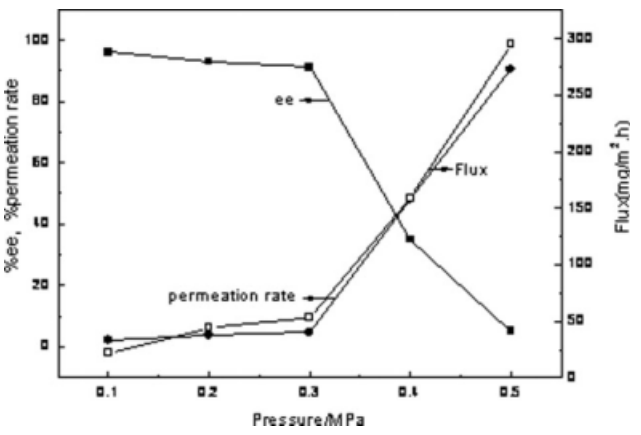

Figure 8 Effect of operating pressure on properties of EC membrane. The feed concentration was 1.5 mg/L.

Effect of feed concentration on properties of EC membrane

As the feed concentration increased from 1 to 5 mg/mL, the permeation rate of the *R*-2-phenyl-1-propanol penetrated through the membranes increased, whereas decreasing the enantioselectivity of membranes (Fig. 9). This result suggested that for the higher feed concentration, much of both *R*- and *S*-isomer were absorbed into the membrane, and then the *R*-isomers absorbed with slower diffusion rate interfered with the diffusion of the *S*-isomers, retarding the diffusion of *S*-isomers. On the other hand, the diffusion of *R*-isomers was helped by *S*-isomers. In consequence, the amounts of both *R*- and *S*-isomers penetrated through the membrane per unit time increased, but the difference in the permeation rates of *R*- and *S*-isomers became less, resulting in a low enantioselectivity.

CONCLUSIONS

The optical resolution of (*R,S*)-2-phenyl-1-propanol is possible through the EC membranes by a pressure driven process because EC contains a large amount of chirally active carbons on the backbone structure. Chiral recognition was a result of steric fit of the enantiomers conformation in the chiral space of the membrane, and of dispersion, dipole–dipole, and hydrogen-bond interactions with the glucopyranose

units in the EC.[3] The properties of membrane can be influenced by EC concentration, DMF content, evaporation time, temperature of water coagulation bath, operating pressure, and feed concentration of racemate.

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