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Brief

Chiral liquid membrane is an attractive separation method for racemic ibuprofen and the separation factor could be up to 1.38 under optimal experimental condition.

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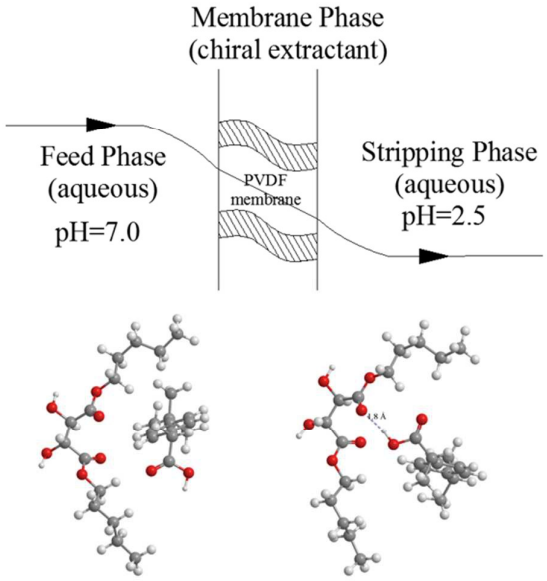

Chiral Liquid Membrane for Enantioselective Separation of Racemic Ibuprofen by *L*-tartaric acid derivatives

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Abstract

The chirality of drugs plays a significant role in most chemical and biochemical process. In this paper, chiral liquid membrane used *L*-tartaric ester solved in *n*-octane as liquid membrane phase and polyvinylidene fluoride hollow fibers as membrane support was investigated to separate racemic ibuprofen. To *L*-dipentyl tartrate ester, the separation factor were 1.18. The favorable *L*-dipentyl tartaric ester concentration was 0.20 mol/L. With the increase of flow rates on two sides, the flux change of mass transfer in stripping phase was not observed. The same trend is obtained in feed phase. The concentration of both *R*-ibuprofen and *S*-ibuprofen in stripping phase increased with the increase of pH value. The best pH in stripping phase was 2.5 and the separation factor was about 1.2. The best separation factor was up to 1.38 after six level experiment.

Key words: ibuprofen, chiral liquid membrane, chiral recognition, *L*-tartaric acid derivatives

1. Introduction

Ibuprofen((R,S)-a-methyl-4-(2-methylpropyl) benzeneacetic acid) is a nonsteroidal anti-inflammatory drug (NSAID) and has been used as an anti-inflammatory and antipyretic agent for the treatment of rheumatoid arthritis, degenerative joint diseases and other inflammatory rheumatic diseases. [1] The medical activity of *S*-ibuprofen is stronger than that of *R*-enantiomer, and *R*-ibuprofen can cause side effects or toxicity, such as gastrointestinal problems. The pure enantiomers and eutectic of ibuprofen have lower melting points than racemic ibuprofen, and therefore have a higher solubility in skin lipids and a greater percutaneous absorption. It is necessary to get pure *S*-ibuprofen for efficient and effective medical application. [2] Furthermore, many active pharmaceutical ingredients (API's) are also optically active, and in many cases, only one of these two enantiomers is pharmaceutically active. The different stereochemistry of chiral drugs between both drug enantiomers can lead to significant biochemical differences in their metabolism and efficacy. [3] It has been widely recognized as one of the most difficult technical problems in organic chemistry to separate optical isomers directly. Because of regulatory requirements and considerations on therapeutic effect improvement, the market for pure enantiomers of chiral drugs is growing. [4]

Now, the ways to obtain single-enantiomer drugs include chiral synthesis and racemic mixture resolution. [5] Racemic resolution has attracted more attention recently, including chiral liquid membrane, chiral column separation, capillary electrophoresis and etc. Chiral column separation and capillary electrophoresis methods have high separation ability and can be widely used and scaled up successfully, but the high cost and low yield obstruct the application of

both methods. The energy requirement and separation performance of chiral liquid membrane are often reasonable. [6] Pickering et al. studied the selective extraction of phenylalanine enantiomers, using copper(II) N-decyl-(*L*) hydroxyproline as chiral resolution in chiral emulsion liquid membrane process.[7] The membrane phase was pre-equilibrated with an equal volume of 5 mM copper nitrate in acetate buffer at pH=5.8. Krieg et al. used both single and multiple bulk liquid membrane (BLM), containing *β*-cyclodextrin (CD) as chiral mobile carrier for the chiral enrichment of racemic chlorthalidone. [8] Chiral enrichment was feasible, and the highest selectivity (1.41), was obtained with the multiple BLM at low pH and relative carrier concentration.

Compared with emulsion and bulk liquid membranes, support liquid membrane could save the consumption of chiral resolution to save processing cost. Many reserach has been conducted for several decades. [9] Shinbo et al. investigated the effect of membrane solvent on transport efficiency and membrane stability in a crown ether-mediated enantioselective amino acid transport system. [10] The membrane stability was assessed by operating the membranes up to 90 days. It is found that the membrane solvent must have both a high dielectric constant and low solubility in water to make the support liquid membrane highly stable and permeable. Hadik et al. studied *D,L*-lactic acid and *D,L*-alanine solute resolution in supported liquid membrane with polypropylene hollow fiber module. [11] *N*-3, 5-dinitrobenzoyl-*L*-alanine-octylester dissolved in toluene was used as chiral resolution. The maximum *D, L*-lactic acid separation factor was 2.0, and that for *D, L*-alanine was 1.75, in both cases, the *D*-enantiomer flux dominated. Dzygiel et al. studied the transport of aromatic amino acids in supported liq-

uid membrane with chiral phosphate as the carrier. [12] The enantioselectivity of the process was moderate and dependent on the structure of carrier. Clark et al. studied the resolution of a racemic mixture of phenylalanine and methionine in supported liquid membrane. [13] The chiral carrier and transition metal were *N*-decyl-(l)-hydroxyproline and copper (II) respectively. The ratio of enantioselective equilibrium constants were determined based on initial experimental separation factors. The highest separation factors for phenylalanine and methionine were 1.8 and 1.9, respectively. Viegas et al. reported their study on the chiral resolution of propranolol with β-blockers. Propranolol was selected due to the distinct properties of its enantiomers among all β-blockers. [14] Extraction and stripping kinetic studies were performed in supported liquid membrane.

In this paper, chiral liquid membrane using *L*-dipentyl tartrate solved in octane as membrane phase was investigated to separate racemic ibuprofen. The membrane material was polyvinylidene fluoride (PVDF) hollow fiber. The feasibility of the process was studied at first. Then, the effect of chiral liquid membrane phase composition, flow rates on two sides and pH in stripping phase were investigated to determine the optimal experiment condition. Cascade experiment was conducted to improve the optical purity of ibuprofen enantiomer.

2. Materials and methods

2.1 Reagents

Ibuprofen racemic mixture was obtained from TSKF, Tianjin, with the purity over 99%. L-tartaric acid was obtained from GuangFu Fine Chemical, Tianjin, China. *p*-toluenesulfonic acid was obtained from YiLi Fine Chemical, Beijing, China. Other reagents, including n-

hexane, octane, *n*-octyl alcohol, and toluene were all obtained from Beijing Chemical Works, Beijing, China. All of above reagents were of analytical grade.

The *L*(*D*)-tartaric acid derivatives used in chiral liquid membrane process were obtained by esterification between *L*(*D*)-tartaric acid and relevant alcohol with *p*-toluenesulfonic acid as catalyst in our laboratory. Toluene was used to solve relevant alcohol. The reaction temperature was 140 °C for the removal of formed water. After cooling down to room temperature, reaction products were washed for several times by saturated sodium bicarbonate solutions and distilled water for *p*-toluenesulfonic acid removal. With drying to remove moisture and vacuum distillation to remove toluene, *L*(*D*)-tartaric acid ester was obtained. Structures of final products (*L*-dipentyl tartaric esters) were characterized by nuclear magnetic resonance (NMR) spectroscopy and Fourier infrared spectrometer.

2.2 Chiral Liquid Membrane Process

Polyvinylidene fluoride (PVDF) hollow fiber was used as the membrane material. The additional information about hollow fiber module was listed in Table 1.

Table 1

The chiral liquid membrane was prepared at room temperature by impregnating porous film with chiral membrane solution for at least 40 min in order to make the solution fully filled in the pores within fibers. The hollow fiber module was operated in a recycling mode, and the schematic of the process was showed in Fig. 1.

Fig.1

L-tartrate ester solved in *n*-octane was used as membrane phase solution. Ibuprofen solved in sodium phosphate-phosphoric acid buffer solution flowed through tube side. Sodium phosphate-phosphoric acid buffer solution flowed through shell side. The concentration of hydroxypropyl-beta-cyclodextrin was 0.1 mol/L. Samples were filtrated with 0.45 μm water system filtering header. All chiral liquid membrane experiments were carried out for three times to ensure enough accuracy.

For chiral liquid membrane process, the mass transfer flux of ibuprofen in both feed and stripping phase, J_f and J_s, were determined by the following equations [15]:

$$J_f = \frac{Q_f \times \Delta C_f}{A} \quad (1)$$

$$J_s = \frac{Q_s \times \Delta C_s}{A} \quad (2)$$

where Q_f is the volume flow rate of feed solution, Q_s is the volume flow rate of stripping solution, ΔC_f is the concentration variations of ibuprofen in feed solution, ΔC_s is the concentration variations of ibuprofen in stripping solution, and A is the membrane effective area

The separation factor (α) was calculated as,

$$\alpha = \frac{J_{S-S-ibu}}{J_{S-R-ibu}} \quad (3)$$

2.3 Analytical methods

The concentration of both ibuprofen enantiomers in aqueous phase was determined by HPLC using a UV detector (SPD-20A, SHIMADZU, JAPAN)) at a wavelength of 220 nm. A Chiral-AGP columns (100 × 4.6 mm×5.0 μm) and guard column (10×4.0 mm×5.0 μm) from

DAICEL (JAPAN) was used. The mobile phase was 0.1 mol/L sodium phosphate buffer solution: methanol with the volume ratio of 98:2 at a flow rate of 0.5 mL/min. Injection volume was 20 μL. The relative retention time of *R*-ibuprofen was about 8.4 min and *S*-ibuprofen was about 11.2 min. pH values in aqueous phases were measured with a pH meter (Shanghai Dapu Instruments Co., Ltd, PXS-450, China).

3. Result and discussion

3.1 Feasibility Study of Chiral Liquid Membrane

In the feasibility study of chiral liquid membrane, hydrophobic polypropylene (PP) and polyvinylidene fluoride (PVDF) hollow fibers were used as membrane materials. The membrane phase solution was *L*-dipentyl tartrate ester with relevant organic solution, *n*-octyl alcohol, *n*-octane and dichloroethane separately. The membrane leakage was observed when polypropylene was used as membrane support and *n*-octane was used as organic solution. This might be attributed to that the hydroxyl of *L*-dipentyl tartrate ester modified the hydrophobicity of polypropylene membrane material. The solution in feed phase could migrate across the hollow fiber membranes to stripping phase. As a result, polyvinylidene fluoride hollow fibers were used as membrane support in chiral liquid membrane process. When *L*-tartrate ester solved in *n*-octyl alcohol and dichloroethane was used as membrane phase, both *R*-ibuprofen and *S*-ibuprofen were accumulated in membrane phase significantly. The concentration of both ibuprofen enantiomers was low in both feed and stripping phases. This was mainly because both *R*-ibuprofen and *S*-ibuprofen preferred to solve in *n*-octyl alcohol and dichloroethane, which led to the concentration of both ibuprofen enantiomers in aqueous phase was low. So *L*-

dipentyl tartrate ester solved in *n*-octane was used as membrane phase solution. Ibuprofen solved in sodium phosphate-phosphoric acid buffer solution at pH=7.0 flowed through tube side, while sodium phosphate-phosphoric acid buffer solution at pH=5.0 flowed through shell side. The flow velocities on tube and shell side were 0.352 cm/s and 0.210 cm/s, respectively. Experimental results in Fig. 2 showed the changes of ibuprofen enantiomers concentration via time in feed phase and stripping phase.

Fig. 2

In feed phase, the concentration of *R*-ibuprofen was at the same level with *S*-ibuprofen. Combined with our preliminary study, the mass transfer of both ibuprofen enantiomers from feed phase to membrane phase was almost equal. [16] But the concentration of *S*-ibuprofen was apparently higher than that of *R*-ibuprofen in stripping phase. This was mainly because the stability of the complexes formed by both ibuprofen enantiomers and *L*-dipentyl tartrate ester was different, which led to different mass transfer rate between *R*-ibuprofen and *S*-ibuprofen. The complexes formed by *R*-ibuprofen and *L*-dipentyl tartrate ester was more stable in membrane phase, *i.e.* more *R*-ibuprofen was accumulated in chiral liquid membrane phase. At the meantime, the complexes formed by *S*-ibuprofen and *L*-dipentyl tartrate ester were transferred from membrane phase to stripping phase. As a result, more *S*-ibuprofen could be detected in stripping phase. In other words, *S*-ibuprofen was enriched in stripping phase by chiral liquid membrane process. The separation factor of *S*-ibuprofen in the process was 1.18.

3.2 Effect of chiral liquid membrane phase composition

The kind and concentration of chiral extractants with organic solutions had an apparent effect on experimental results.[15] Thus, several experiments had been conducted to investigate the influence of chiral liquid membrane phase composition.

3.2.1 Different Chiral Extractants in Membrane Phase

Ibuprofen solved in sodium phosphate-phosphoric acid buffer solution flowed through tube side at pH=7.0. Sodium phosphate-phosphoric acid buffer solution flowed through shell side at pH=2.5, the concentration of hydroxypropyl-beta-cyclodextrin was 0.1mol/L. The flow velocities of tube and shell side were 0.352 cm/s and 0.210 cm/s, respectively. To confirm the interaction of chiral recognition between *S*-ibuprofen and *L*-dipentyl tartrate ester, the contrast experiment was conducted while pure *n*-octane without chiral extractant was used as the membrane phase. The concentration of both ibuprofen enantiomers in stripping phase with and without chiral extractant in membrane phase were showed in Fig. 3.

Fig. 3

Concentrations of *R*-ibuprofen and *S*-ibuprofen remained constant in 11 h when pure *n*-octane was used as the membrane phase. *n*-octane showed no selectivity to both ibuprofen enantiomers, as the concentration of *R*-ibuprofen and *S*-ibuprofen was kept at same level throughout the experiment. This was mainly because there was no interaction of chiral recognition between *n*-octane and *L*-dipentyl tartrate ester. The results demonstrated that there was the interaction of chiral recognition between *L*-dipentyl tartrate ester and *R*-ibuprofen. After 8 h, the mass ratio of *R*-ibuprofen and *S*-ibuprofen in feed phase to those in striping phase could reach 85.9% and 88.4% with chiral extractant, respectively. But those values without chiral extract-

ant were much higher, which was 96.5% and 96.7%, respectively. In other words, without chiral extractant, there was almost no accumulation of ibuprofen in membrane phase.

L-dipentyl tartrate ester and *D*-dipentyl tartrate ester solved in *n*-octane (0.20 mol/L) were used as membrane phase solution. As shown in Fig. 4, the concentration of ibuprofen enantiomers in feed phase showed the same trend with different types of chiral extractants in membrane phase. But the concentration of *R*-ibuprofen in stripping phase is higher than that of *S*-ibuprofen when *D*-dipentyl tartrate ester was used in membrane phase. An opposite tendency was observed compared with *L*-dipentyl tartrate ester. This was because the interaction between *S*-ibuprofen and *D*-dipentyl tartrate ester is stronger than that between *R*-ibuprofen and *D*-dipentyl tartrate ester. However, *L*-dipentyl tartrate ester showed different chiral recognition characters, which led to the accumulation of *R*-ibuprofen in chiral membrane phase. With *D*-dipentyl tartrate ester as the chiral extractant, the separation factor is 1.08 in 11 h. The results were much lower than that with *L*-dipentyl tartrate ester (1.18). This was mainly because the stability of the diastereomer formed with *L*-dipentyl tartrate ester was much stronger than that formed with *D*-dipentyl tartrate ester.

Fig. 4

3.2.2 Different Concentrations of *L*-dipentyl tartrate in Membrane Phase

L-dipentyl tartrate ester solved in *n*-octane was used as membrane phase solution. The concentrations of *L*-dipentyl tartrate ester was tested at 0.1 mol/L, 0.2 mol/L and 0.3 mol/L. The results were showed in Fig. 5 and Fig. 6.

Fig. 5

Fig. 6

The concentration of *R*-ibuprofen and *S*-ibuprofen in stripping phase increased with the concentration increase of *L*-dipentyl tartrate ester in membrane phase. This was mainly because more chiral extractant was solved in membrane phase with the increase of the concentration of *L*-dipentyl tartrate ester. As a result, the diastereomers formed by *L*-dipentyl tartrate ester and both ibuprofen enantiomers were increased, and more ibuprofen enantiomers were transferred into stripping phase.

The flux of ibuprofen in stripping phase increased with the increase of *L*-dipentyl tartrate ester concentration as showed in Fig. 7. The separation factor was the highest when the concentration of chiral extractant was 0.20 mol/L. When the concentration of chiral extractant was over 0.20 mol/L, the flux of ibuprofen in stripping phase kept the same trend while the separation factor stayed at the same level. This was mainly because that the stability of the diastereomers formed by *L*-dipentyl tartrate ester and ibuprofen enantiomers was different. Ibuprofen enantiomers were selectively extracted to organic phase with the increase of *L*-dipentyl tartaric ester concentration. When the concentration of *L*-tartaric ester was low, *R*-ibuprofen can be preferentially extracted from the organic phase due to competitive extraction. The result showed that two ibuprofen enantiomers can be separated. However, with the increase of *L*-dipentyl tartaric ester concentration, two ibuprofen enantiomers were extracted to organic phase equally. The performance of competitive extraction disappeared, which resulted in the consistent separation factor when the concentration of chiral extractant was over 0.20 mol/L.

So 0.20 mol/L was chosen as the favorable *L*-dipentyl tartaric ester concentration in this research.

Fig. 7

3.3 Effect of flow rates in two sides

The flow rates have a significant impact on the contact time and the thickness of liquid membrane layer. In chiral liquid membrane process, the flow rates also have impact on the mass transfer rate of the diastereomers formed by *L*-dipentyl tartaric ester and ibuprofen enantiomers. Several flow rates in two sides were investigated to study the mechanism of mass transfer. Ibuprofen solved in sodium phosphate-phosphoric acid buffer solution flowed through tube side at pH 7.0. Sodum phosphate-phosphoric acid buffer solution flowed through shell side at pH 2.5, the concentration of hydroxypropyl-beta-cyclodextrin is 0.1 mol/L. The flow rates in tube side were 0.352 cm/s, 0.704 cm/s, 1.056 cm/s and 1.408 cm/s, while the flow rates in shell side were 0.210 cm/s, 0.420 cm/s, 0.630 cm/s and 0.840 cm/s, respectively. The results were shown in Fig. 8 and Fig. 9.

Fig. 8

Fig. 9

With the increase of flow rates in two sides, no significant change of the mass transfer flux in stripping phase was observed. The same trend is obtained in feed phase. The experimental mass transfer resistances of ibuprofen enantiomers in both feed phase and stripping phase were not the major part. In other word, the major resistance of the process was in chiral liquid membrane phase. This was mainly because the diastereomers formed by *L*-dipentyl tartaric

ester and ibuprofen enantiomers were preferentially solved in organic phase, not in aqueous phase. The interaction of chiral recognition formed by hydrogen bond was stable, which made ibuprofen enantiomers accumulated in chiral liquid membrane phase.

3.4 Effect of pH in stripping phase

Ibuprofen molecule mainly exists at low pH, while the ibuprofen carboxylic acid ions are mainly emerged at high pH. The chiral recognition could achieve only between ibuprofen molecules and *L*-tartaric ester. In this experiment, pH values in stripping phase were tested at 2.5, 4.0, 5.5 and 7.0. The influence of pH in stripping phase on the concentration of *S*-ibuprofen and *R*-ibuprofen were showed in Supporting Information (Fig. S1 and S2). The mass transfer flux in stripping phase and separation factor in stripping phase were showed in Fig.10.

Fig. 10

The concentrations of both *R*-ibuprofen and *S*-ibuprofen in stripping phase increased with the increase of pH value. This was mainly because the concentration of diastereomeric compounds, which were formed by *L*-tartaric ester and ibuprofen enantiomers, decreased with the increase of pH value. In Fig. 10, separation factor decreased with the increase of pH value. With the increase of pH value, the chiral recognition ability of *L*-tartaric ester decreased. The mass transfer rates of *S*-ibuprofen and *R*-ibuprofen were getting closer, which led to the decrease of separation factor. The mass transfer flux in stripping phase showed the opposite trend against separation factor. More *S*-ibuprofen and *R*-ibuprofen molecules were solved in

membrane phase, which would increase the distribution coefficient in stripping phase. As a result, fluxes of both ibuprofen enantiomers in stripping phase increased.

3.5 Transport results

To improve the optical purity of ibuprofen enantiomer, series operation was a common way to promote the separation performance. As series operation needs lots of membrane modules and space, cascade experiment used in this research needs only one membrane module. After every experiment, the membrane module was washed by deionized water thoroughly and dried by air pump. Then the membrane module was pretreated as before. The feed and stripping phase were introduced from previous experiment. Results were showed in Fig. 11.

Fig.11

The best separation factor was 1.38 after six level experiment. When the level of cascade experiment increased from 1 to 4, separation factor of ibuprofen enantiomers in stripping phase also increased accordingly. This was because the new chiral liquid membrane phase at every level can separate ibuprofen enantiomers apart. After 4 level cascade experiment, separation factor of ibuprofen enantiomers kept steady.

4. Conclusion

Chiral liquid membrane, used *L*-tartaric ester solved in *n*-octane as membrane phase, was investigated for separating ibuprofen enantiomers. *S*-ibuprofen was enriched in stripping phase with chiral liquid membrane. Polyvinylidene fluoride hollow fibers were used as membrane support in chiral liquid membrane process. With *L*-dipentyl tartrate ester, the concentration of

S-ibuprofen was apparently higher than that if R-ibuprofen in stripping phase, while that with *D*-dipentyl tartrate ester showed the opposite trend. With *D*-dipentyl tartrate ester, the separation factor was 1.08, which were much lower than that with *L*-dipentyl tartrate ester (1.18). The optimal concentration of chiral extractant was 0.20 mol/L. With the increase of flow rates on two sides, no significant change of the mass transfer flux in both feed and stripping phase was observed. The concentration of both *R*-ibuprofen and *S*-ibuprofen in stripping phase increased with the increase of pH value. The separation factor decreased with the increase of pH value. The separation factor was 1.38 in cascade experiment.

Acknowledgments

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Table captions

Table 1. Geometric parameters of membrane modules

Shell characteristics	
Material	Glass
Length, L /m	0.350
Internal diameter, d_i/m	0.016
Fiber characteristics	
Material	PVDF
Number of fibers, N	98
Effective length, L/m	0.300
Internal diameter, d^{int}/m	0.000610
External diameter, d^{ext}/m	0.000872
Fill factor	0.291

Figure captions

Fig. 1 Flow diagram of enantioselective separation of racemic ibuprofen by chiral liquid membrane.

Fig. 2 Changes of ibuprofen enantiomers concentration via time in feed and stripping phases.

Fig. 3 The concentration of ibuprofen enantiomers in stripping phase with and without chiral extractant in membrane phase.

Fig. 4 The concentration of ibuprofen enantiomers via time in feed and stripping phases with different types of chiral extractants in membrane phase.

Fig. 5 Influence of concentration of *L*-dipentyl tartrate ester in the membrane phase on the concentration of R-ibuprofen in stripping phase.

Fig. 6 Influence of concentration of *L*-dipentyl tartrate in the membrane phase on the concentration of *S*-ibuprofen in stripping phase.

Fig. 7 Influence of *L*-dipentyl tartrate concentration on flux in stripping phase and separation factor of chiral liquid membrane.

Fig. 8 Influence of flow rates of tube side on mass transfer flux in stripping phase.

Fig. 9 Influence of flow rates of shell side on mass transfer flux in stripping phase.

Fig. 10 Influence of pH in stripping phase on mass transfer flux in stripping phase and separation factor in chiral liquid membrane process.

Fig. 11 Influence of separation factor of ibuprofen enantiomers in stripping phase.

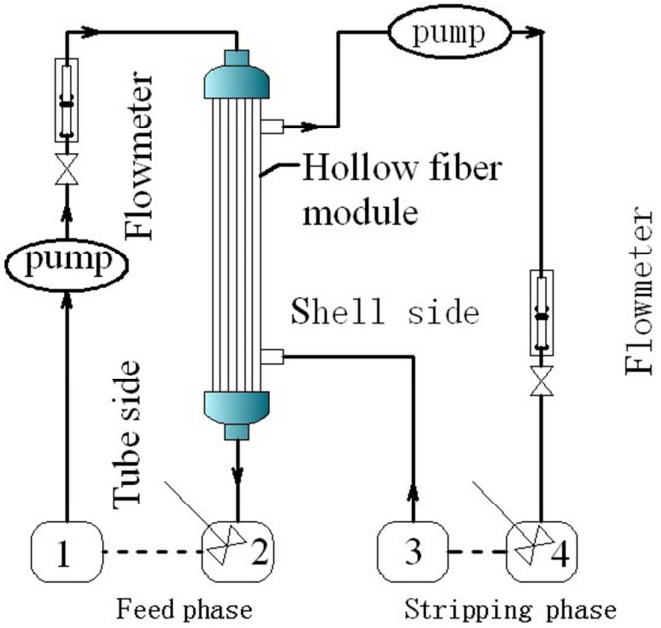

Fig. 1 Flow diagram of enantioselective separation of racemic ibuprofen by chiral liquid membrane.

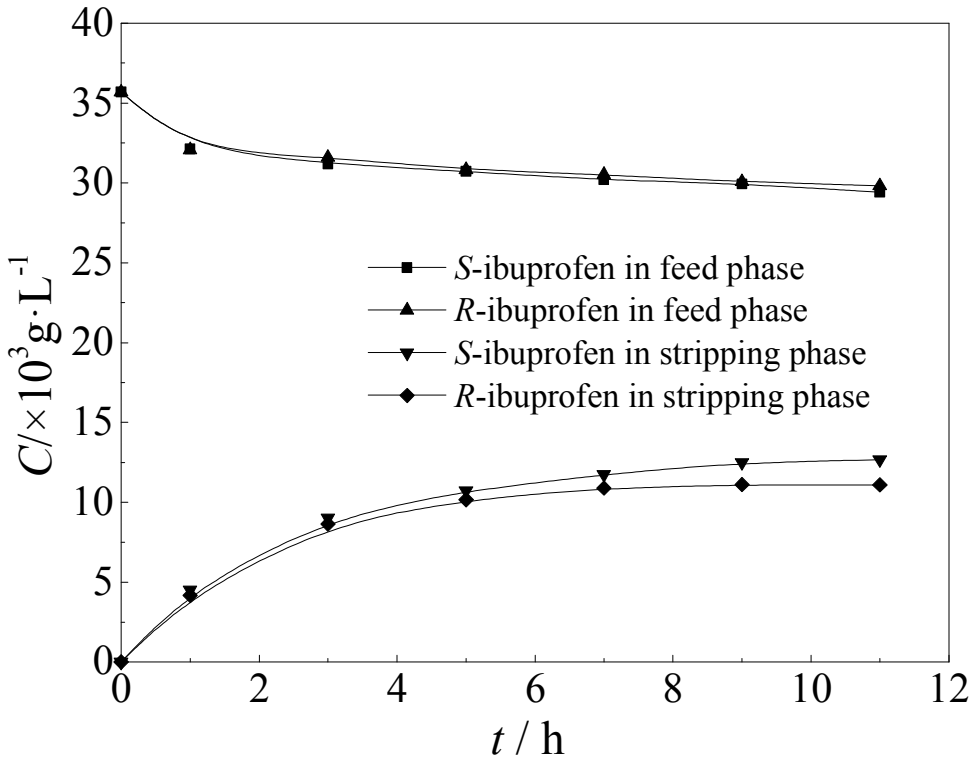

Fig. 2 Changes of ibuprofen enantiomers concentration via time in feed and stripping phases.

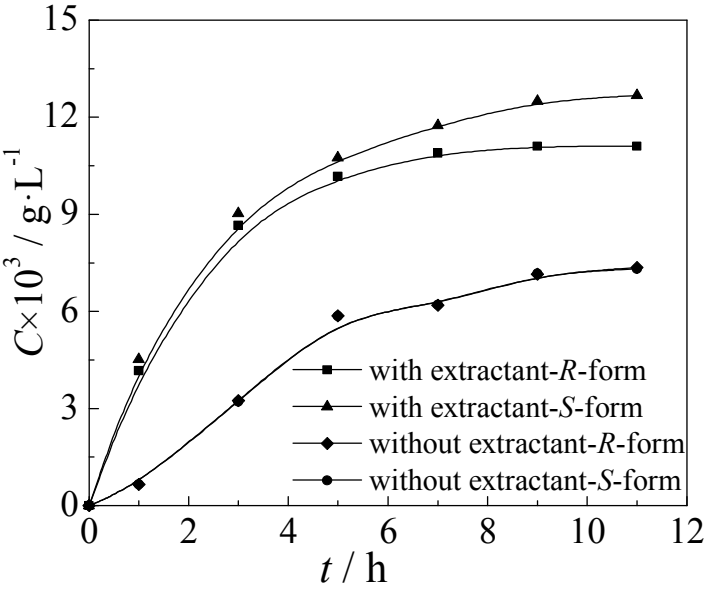

Fig. 3 The concentration of ibuprofen enantiomers in stripping phase with and without chiral extractant in membrane phase.

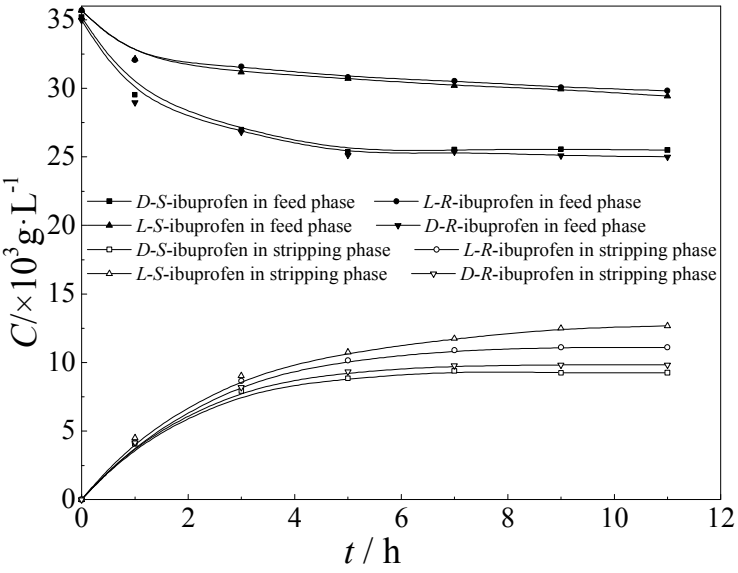

Fig. 4 The concentration of ibuprofen enantiomers via time in feed and stripping phases with different types of chiral extractants in membrane phase.

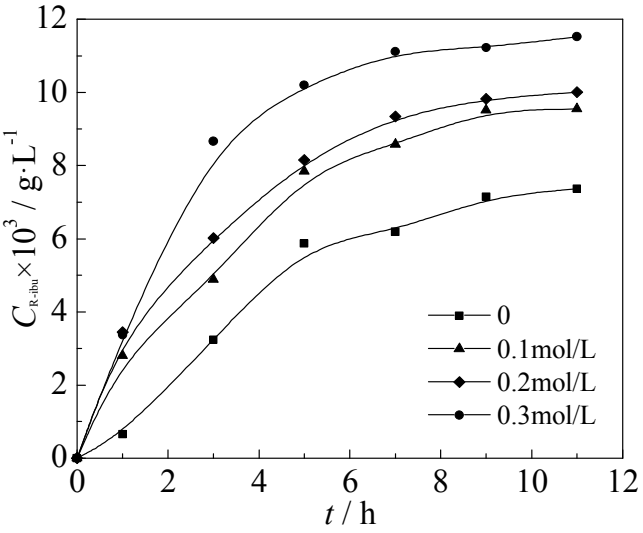

Fig. 5 Influence of concentration of *L*-dipentyl tartrate ester in the membrane phase on the concentration of R-ibuprofen in stripping phase.

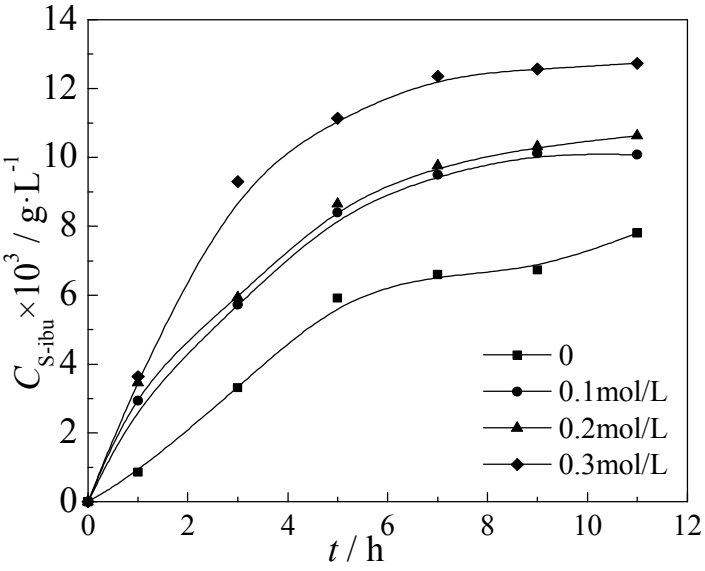

Fig. 6 Influence of concentration of *L*-dipentyl tartrate in the membrane phase on the concentration of *S*-ibuprofen in stripping phase.

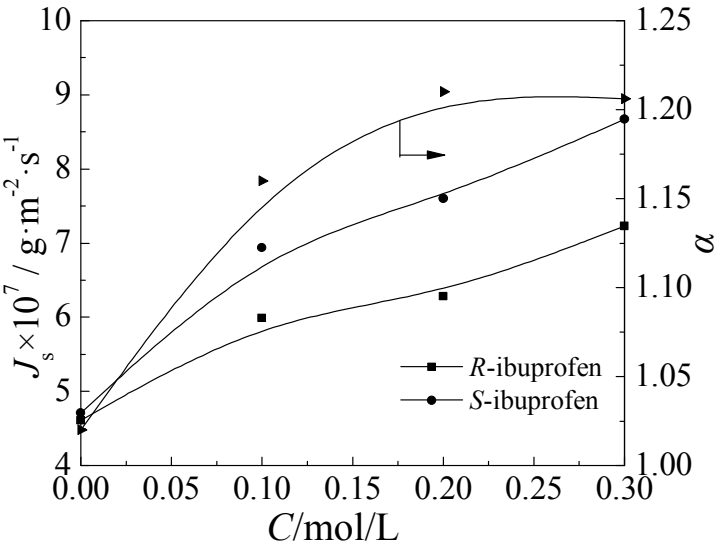

Fig. 7 Influence of *L*-dipentyl tartrate concentration on flux in stripping phase and separation factor of chiral liquid membrane.

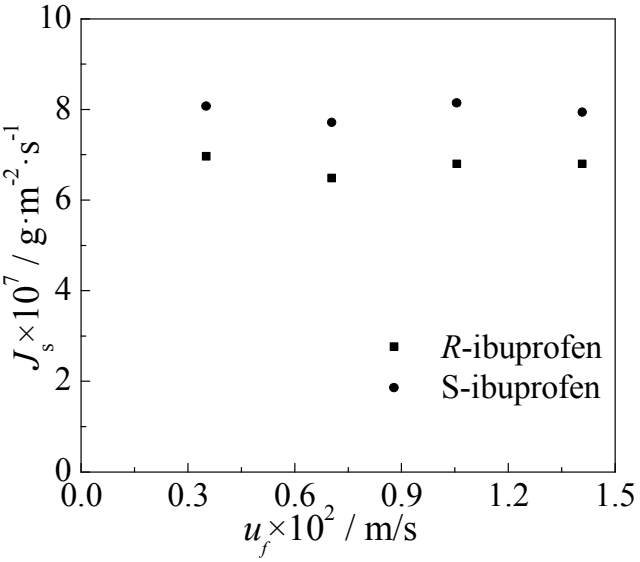

Fig. 8 Influence of flow rates of tube side on mass transfer flux in stripping phase.

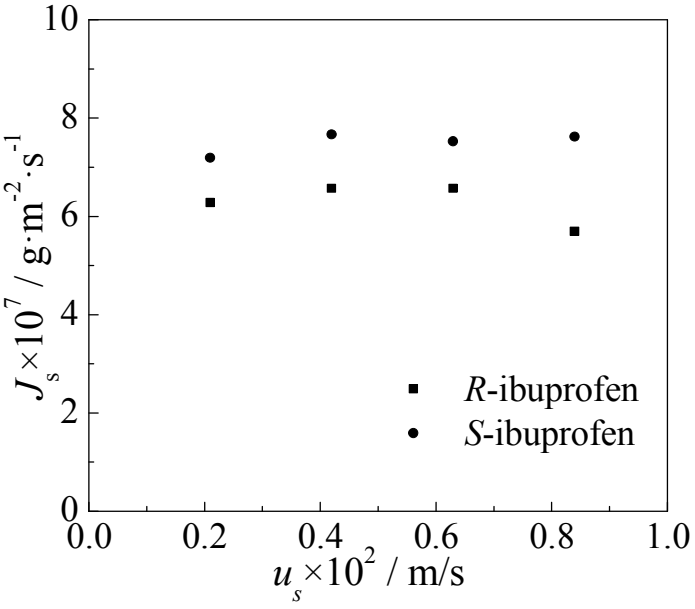

Fig. 9 Influence of flow rates of shell side on mass transfer flux in stripping phase.

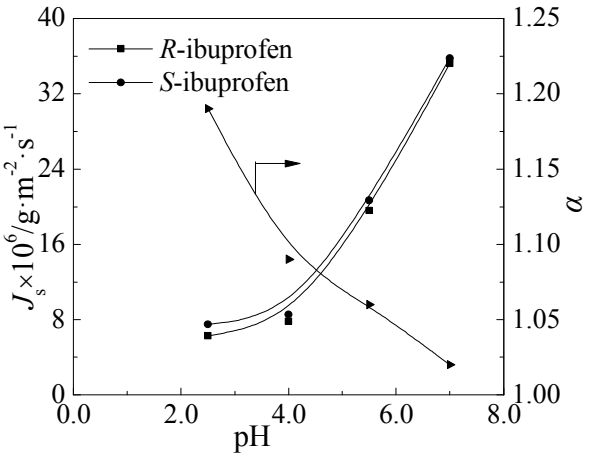

Fig. 10 Influence of pH in stripping phase on mass transfer flux in stripping phase and separation factor in chiral liquid membrane process.

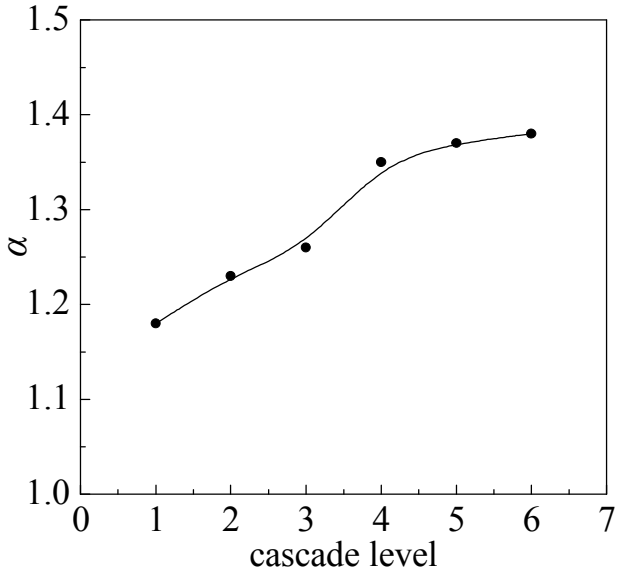

Fig. 11 Influence of separation factor of ibuprofen enantiomers in stripping phase.