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Enantioselective Separation of Propranolol by Chiral Activated Membranes

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Abstract: In this work, chiral activated membranes have been tested for the enantioseparation of the racemic drug propranolol. Polysulfone (PS)-based membranes have been prepared for this purpose, using N-hexadecyl-L-hydroxyproline (HHP) and L-di-n-dodecyltartrate (L-DDT) as chiral carriers, respectively. Kinetic experiments have been carried out using a membrane module with two rectangular channels separated by the membrane, which allows for a well-defined hydrodynamics of the feed and stripping phases.

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Propranolol transport across the membrane depends on its diffusion rate from the bulk solution to the membrane surface and also on the relative amount of carrier present in the membrane. Therefore, the influence of both the solute/carrier ratio and the flow rates of the feed and stripping phases on the rate of extraction and on the selectivity of the process was evaluated for both chemical systems. Modeling of kinetic experiments has been performed, and mass transfer coefficients obtained for both systems were compared.

Keywords: Fixed carrier membranes, enantioseparation, racemic propranolol, chiral resolution, facilitated transport

INTRODUCTION

It is known that chirality strongly influences some chemical and biochemical reactions due to the different behavior of the corresponding enantiomers. However, many chemical species with biological activity are prepared and used as racemic mixtures, despite the desired activity being often carried out by only one of the two enantiomers while the other undertakes no specific activity (1). In certain cases, the later enantiomer may inhibit the desired effect of the first enantiomer or even have adverse side effects (2). In the case of racemic propranolol, a β-blocking drug used for treating some cardiovascular anomalies, the *S*-isomer shows far more blocking activity than the *R*-isomer (3, 4). Thus, obtaining and identifying enantiopure compounds has become one of the most important demands, specially by pharmaceutical industries, which have been forced by regulatory agencies to develop methodologies for producing pure enantiomers.

Most methods employed up to date, in the pharmaceutical industry, to obtain enantiopure compounds, such as stereoselective asymmetric synthesis, biotransformation, chiral separation processes based on the enzymatic kinetic resolution technique, or diastereomeric crystallization, have been shown to have several drawbacks. They require a considerable number of different steps and a high-energy consumption in order to produce a reasonable amount of one optically pure enantiomer (5–7). Recently, other separation processes based on chiral stationary phases have increasingly gained attention at an industrial level, as both pure enantiomers can be obtained at the same time with far less difficulty (8). In this context, the use of membrane technology for chiral separations offers several advantages over traditional methods, namely, low time cost, simplicity of operation, and easy scale-up. Furthermore, when using chiral activated membranes only a small quantity of an expensive chiral selector is required (9).

Different enantioselective carriers have already been tested for the enantioseparation of racemic propranolol by using liquid membrane (LM) systems,

such as N-n-alkyl-hydroxyprolines (10, 11), or dialkyl tartrates (12). In both cases, the carrier is present in the membrane and selectively forms a complex with one of the enantiomers, which is transported across the membrane by an ion pairing mechanism (6, 10). These transport systems are driven by a proton gradient between both feed and stripping aqueous phases. However, liquid membrane systems have been shown to have problems of stability and short lifetime when tested under industrial separation conditions (13, 14). In an attempt to overcome these drawbacks, solid polymeric activated membrane systems have been proposed to resolve racemic mixtures (15–17).

In the present work, chiral activated membranes, based on a polysulphone polymeric support, containing N-hexadecyl-L-hydroxyproline (system A) or L-di-n-dodecyltartrate (system B) have been prepared and applied for the enantioselective transport of racemic propranolol.

Propranolol transport across the membrane is limited by its diffusion rate from the bulk solution to the membrane surface; therefore, the hydrodynamic conditions of the feed and stripping phases are important parameters.

On the other hand, for fixed site membranes the transport of solute is presumably achieved by diffusion in the membrane from a carrier site to a neighbor site. If the carriers are at a critical distance, the solute may be able to jump from site to site, thus increasing the transport rate significantly (18, 19).

The influence of both the solute/carrier ratio and the hydrodynamic conditions of the feed and stripping phases on the enantioselectivity and rate of solute transport were studied for the two systems (A and B). Mass transfer coefficients were calculated in order to be able to compare the two systems, operated under different experimental conditions.

THEORY

Transport Modeling

Transport mechanism schemes for the two systems propranolol/N-hexadecyl-L-hydroxyproline (system A) and propranolol/L-di-n-dodecyltartrate (system B) are shown in Figs. 1 and 2, respectively. Both chemicals systems were previously studied in other membrane configurations and as a result the transport mechanisms involved in both cases were proposed (4, 11).

In system A, the enantioselective interaction takes place in the feed side membrane surface, where the *S*-propranolol enantiomer preferentially forms an ionic pair with the carrier N-hexadecyl-L-hydroxyproline, and it is transported across the membrane. Propranolol transport is coupled by a proton antiport (11).

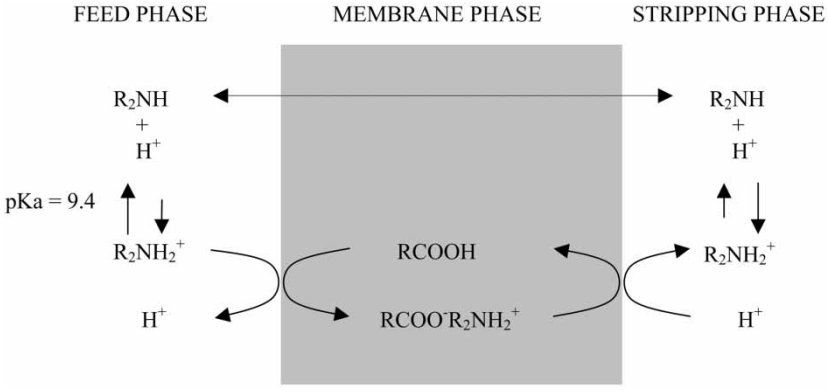

Figure 1. Scheme of steps taking place in the membrane for propranolol/N-hexadecyl-L-hydroxyproline (HHP) system A. The carboxylic group of the carrier (RCOOH) has a pKa of 9.5.

For system B, hydrophobic L-di-n-dodecyltartrate forms a nonpolar complex with boric acid and, preferentially, with the corresponding enantiomer of propranolol. Thus, both propranolol and boric acid are extracted and form a tetrahedral complex involving hydrogen bonding with the tartrate (4).

A membrane module with two rectangular channels separated by the membrane was used for the kinetic experiments (details are given next).

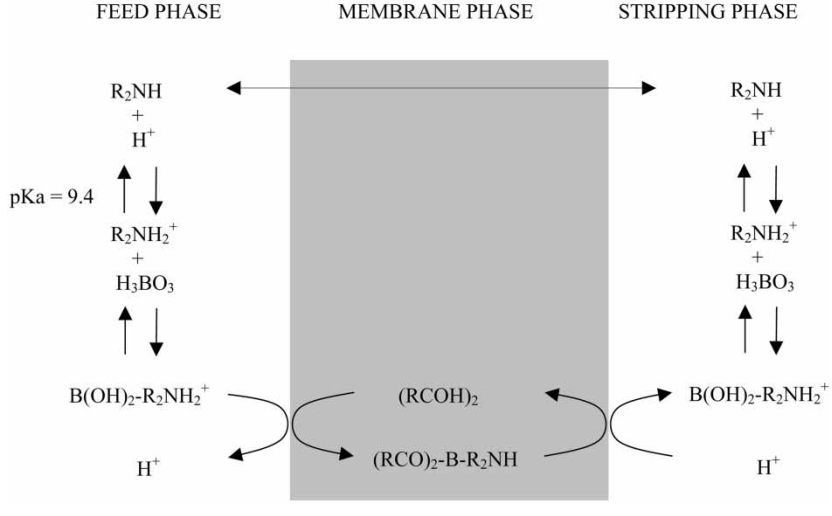

Figure 2. Scheme of steps taking place in the membrane for propranolol/L-di-n-dodecyltartrate (L-DDT) system B.

The well-defined hydrodynamic conditions established in both channels allow for a rigorous evaluation of the mass transfer coefficients.

Due to the small membrane area, the concentration change during a single pass is negligible. Therefore, in order to increase the change in concentration, extraction and stripping were carried out with recirculation of the feed and stripping phases through the module and back into the feed and stripping reservoirs, respectively. The solute concentration was measured along time.

The differential mass balances to each one of the enantiomers in the stripping phase are:

$$-Q_S\ dC_{SR} = K_{SR}dA(C_{SR} - C^*_{SR}) \tag{1}$$

$$-Q_S\ dC_{SS} = K_{SS}dA(C_{SS} - C^*_{SS}) \tag{2}$$

where Q_s is the stripping flow rate, C is the solute concentration, K is the overall mass transfer coefficient, and $dA = w\,dz$ is the differential membrane area, where w is the channel width and dz the differential length; the subscripts SR and SS refer to the enantiomers *R* and *S* in the stripping phase, respectively, and the superscript * refers to the equilibrium concentration.

The transient mass balances concerning the stripping reservoir may be expressed as:

$$-V_S(dC_{SR}/dt) = Q_S(C^{in}_{SR} - C^{out}_{SR}) \tag{3}$$

$$-V_S(dC_{SS}/dt) = Q_S(C^{in}_{SS} - C^{out}_{SS}) \tag{4}$$

assuming that the solute concentration in the reservoir and at the module inlet is identical for both enantiomers, $C_{SR} = C^{in}_{SR}$ and $C_{SS} = C^{in}_{SS}$.

These four equations can be reduced to only two, taking into account that the driving forces $(C^*_{SR} - C_{SR})$ and $(C^*_{SS} - C_{SS})$ can be considered constant along the membrane:

$$V_S(dC_{SR}/dt) = K_{SR}A(C^*_{SR} - C_{SR}) \tag{5}$$

$$V_S(dC_{SS}/dt) = K_{SS}A(C^*_{SS} - C_{SS}) \tag{6}$$

These equations may be integrated after substitution of the equilibrium concentrations, C^*_{SR} and C^*_{SS}. Since there is a very small quantity of carrier within the membrane and both the feed and stripping phases have equal volumes, then the stripping equilibrium concentration equals the feed phase

concentration for both enantiomers, $C^*_{SR} = C_{FR}$ and $C^*_{SS} = C_{FS}$, Eqs. (5) and (6) become:

$$V_S(dC_{SR}/dt) = K_{SR}A(C_{FR} - C_{SR}) \quad (7)$$

$$V_S(dC_{SS}/dt) = K_{SS}A(C_{FS} - C_{SS}) \quad (8)$$

The overall mass transfer coefficients K_{SR} and K_{SS} for each enantiomer are calculated by least-squares minimization of the residuals of the experimental data of C_{SR} vs. time and C_{SS} vs. time using Eqs. (7) and (8).

Enantioselectivity

The enantioselectivity of the membrane process is given in terms of enantiomeric excess. The enantiomeric excess is defined by the ratio of the difference between the concentration of both enantiomers in the feed or stripping phase to the total amount of both enantiomers present at any time, and was calculated according to (20):

$$\text{Enantiomeric excess} = [(C_{SS} - C_{SR})/(C_{SS} + C_{SR})]100 \quad (9)$$

EXPERIMENTAL

Reagents

R-propranolol hydrochloride, *S*-propranolol hydrochloride, and racemic propranolol hydrochloride, all p.a. grade, were supplied by Sigma-Aldrich (Germany). N-hexadecyl-L-hydroxyproline (HHP), isopropyl myristate (IPM), triethanolamine, and hydroxypropyl-β-cyclodextrin (HP-β-CD), all p.a. grade, were also purchased from Sigma-Aldrich (Germany). All other reagents used (such as acids and inorganic salts) were of analytical grade. MilliQ water was used for all aqueous solutions.

Propranolol hydrochloride and tartaric acid were purchased from Aldrich Chemical Co. (USA), boric acid from Riedel–de Haën AG (Germany), and chloroform from Merck (Germany). L-di-n-dodecyltartrate (L-DDT) was prepared as described by Abe et al. (21).

Membrane Preparation

Polysulfone (PS) casting solution (15% wt.) was prepared by dissolving PS (Basf) in a.r. grade N,N-dimethylformamide (DMF, Sigma-Aldrich). PS membranes were obtained by phase inversion technique of the polysulfone

casting solution over a nonwoven fabric, which ensured re-enforced PS membranes (22). Membranes were chiral activated by addition of one of the two different chiral carriers investigated, to the casting solution; N-hexadecyl-L-hydroxyproline (HHP), previously dissolved in isopropyl myristate (IPM), or L-di-n-dodecyltartrate (L-DDT).

Apparatus

Experiments have been carried out using a membrane module with two rectangular channels separated by the membrane. This configuration allows for a well-defined hydrodynamics of the phases. Aqueous fixed volume feed and stripping solutions were pumped to each membrane side in countercurrent mode. All experiments were performed at $24 \pm 1^{\circ}C$. Figure 3 shows the experimental set-up.

Procedure

Two different chemical systems, N-hexadecyl-L-hydroxyproline (system A) and L-di-n-dodecyltartrate (system B), were characterized for the enantioselective resolution of racemic propranolol, by studying the influence of both the solute to carrier ratio (S/C) and the flow rate of the feed and stripping phases on the transport rate and on the selectivity through the chiral activated membranes. With this purpose, two different solute/carrier ratios (50 and 100) were investigated for system A and for system B (12 and 120). Two different flow rates (10 and 100 mL/min) were also assayed for both systems.

For system A, the influence of the solute to carrier ratio (S/C) was studied by varying the N-hexadecyl-L-hydroxyproline (HHP) concentration in the membrane, while in the case of system B it was the propranolol concentration that was varied.

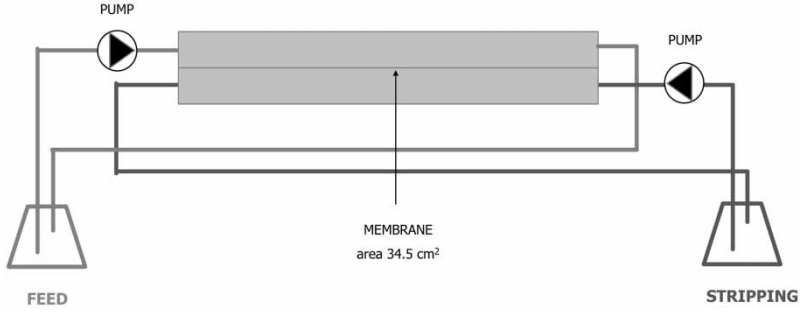

Figure 3. Experimental set-up.

The variation of S/C in system A was limited by the sensibility of the propranolol (solute) determination. Therefore, the carrier amount in the membrane should be varied to reach lower S/C ratios. On the contrary, the variation of S/C in system B was limited by the change of membrane properties with the carrier incorporation. Hence, in the latest case, solute concentration was varied.

In the case of system A, the feed phase contained 0.1 g/L (0.34 mM) of racemic propranolol and was adjusted at pH 8 with a borax buffer, and the stripping phase was buffered with disodium phosphate, at pH 7. For system B, the feed phase contained 1 mM and 10 mM of racemic propranolol in a 0.1 M boric acid media at pH 5.2, adjusted with acetate buffer, while the stripping solution was maintained at pH 2 with a 1 M solution of formic acid. A blank experiment using the polysulfone membrane without carrier was also performed for both systems.

Propranolol Determination

Two different detection techniques have been used to follow each chemical system (A and B). In the first case (A), a capillary electrophoresis system (P/ACE SYSTEM MDQ, Beckman, USA) was used to analyze the concentration of both enantiomers in the collected samples. Determination was performed using 50 μm internal diameter uncoated fused-silica capillaries of 60 cm (50 cm to the detector). Before each set of analyses, the capillary was rinsed with a 0.1 M NaOH solution, MilliQ water, and finally with the separation buffer solution. The latter consisted of 100 mM phosphoric acid adjusted at pH 4.4 with triethanolamine, containing 17.4 mM hydroxypropyl-β-cyclodextrin (HP-β-CD) (23, 24). The applied voltage was 23 kV and UV detection was carried out at 210 nm. Samples were injected using the hydrodynamic mode for 5s, at 0.3 psi. The capillary was thermo stated at 20°C. Between consecutive determinations, the capillary was rinsed with MilliQ water. At the end of the day, the capillary was washed with NaOH 0.1 M, MilliQ water, and MeOH, which was used for removing organic material and for facilitating capillary drying.

For system B, the quantification of both propranolol enantiomers in the aqueous phase was performed by HPLC using a UV detector (Merck, Hitachi, Japan) at a wavelength of 254 nm. A Chiralcel OD-R (Daicel, Japan) column was used and the mobile phase was a 0.1 M aqueous solution of potassium hexafluorophosphate: acetonitrile (60:40).

Calculation Methods

The overall mass transfer coefficients were evaluated by fitting the experimental data, i.e., the experimental values of C_s for both *R* and *S* enantiomers vs. time,

using Scientist® (Micromath Scientific Software, USA). The errors associated with the determined parameters were calculated for a confidence interval of 95%.

RESULTS AND DISCUSSION

Influence of the Solute to Carrier Ratio

With the purpose to investigate the influence of the solute to carrier ratio on the transport rate and on the enantioselectivity of racemic propranolol transport across the chiral activated membranes, the concentration of carrier within the membrane was adjusted to reach the solute/carrier ratios (S/C) of 50 and 100 for system A; the initial concentration of propranolol in the feed solution was also varied to obtain the solute/carrier ratios (S/C) of 12 and 120 for system B. The results obtained are shown in Fig. 4 (system A) and Fig. 5 (system B). It can be observed that the transport rate of propranolol across the membrane increases when decreasing the solute/carrier ratio in both membrane systems, i.e., when increasing the relative amount of carrier in the membrane. This behavior is usually present in membrane transport systems based in facilitated transport mechanism. Here, the amount of

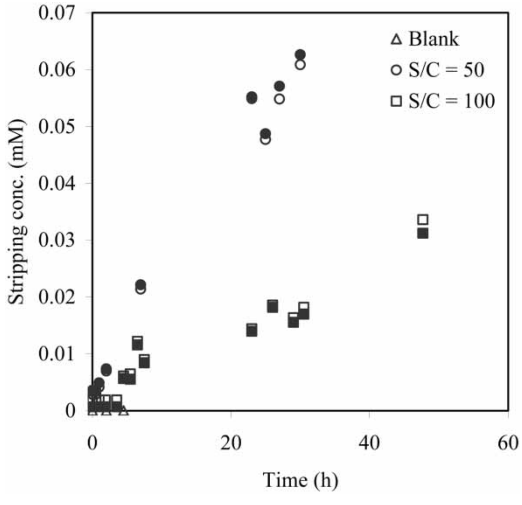

Figure 4. Influence of the solute to carrier ratio (S/C) on the propranolol transport across the chiral activated membrane for system A. Different symbol types apply for different (S/C) conditions, while within each given solute to carrier ratio assayed open and filled symbols correspond to the *S* and *R* propranolol enantiomers, respectively. Flow rates of feed and stripping phases were maintained at 100 mL/min.

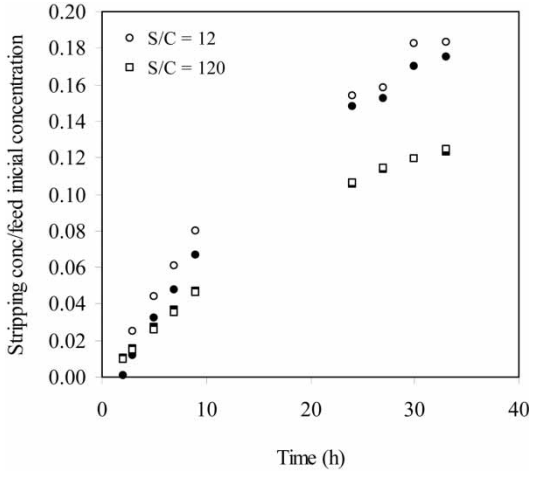

Figure 5. Influence of the solute to carrier ratio (S/C) on the propranolol transport across the chiral activated membranes for system B. Different symbol types apply for different (S/C) conditions, while within each given solute to carrier ratio assayed open and filled symbols correspond to the *S* and *R* propranolol enantiomers, respectively. Flow rates of feed and stripping phases were maintained at 100 mL/min.

active sites in the membrane (i.e., the amount of carrier) is the limiting step of the process (22, 25).

The blank experiments for both systems exhibited practically no transport, which was expected since the solute diffusion through the solid membrane without a carrier is extremely slow.

Influence of the Flow Rate

Two different flow rates of feed and stripping phases (100 and 10 mL/min.) were studied for both systems A and B, in order to determine its influence on the transport rate of propranolol across de chiral activated membranes. As can be seen in Figs. 6 (a and b) and 7, for systems A and B, respectively, lower flow rates cause a decrease of the transport rate of propranolol. This behavior may be due to the corresponding decrease of the Reynolds number, when decreasing the flow rate. The Reynolds number depends on aqueous phases densities, velocities and viscosities, and also on the module physical properties. Since the aqueous solutions are similar, decreasing the Reynolds number means decreasing the fluid velocity (flow rate). Lower flow rates imply low mass transfer velocities from bulk solution to membrane surface. Therefore, the propranolol transport across the membrane is limited by its diffusion rate from the bulk solution to the membrane surface.

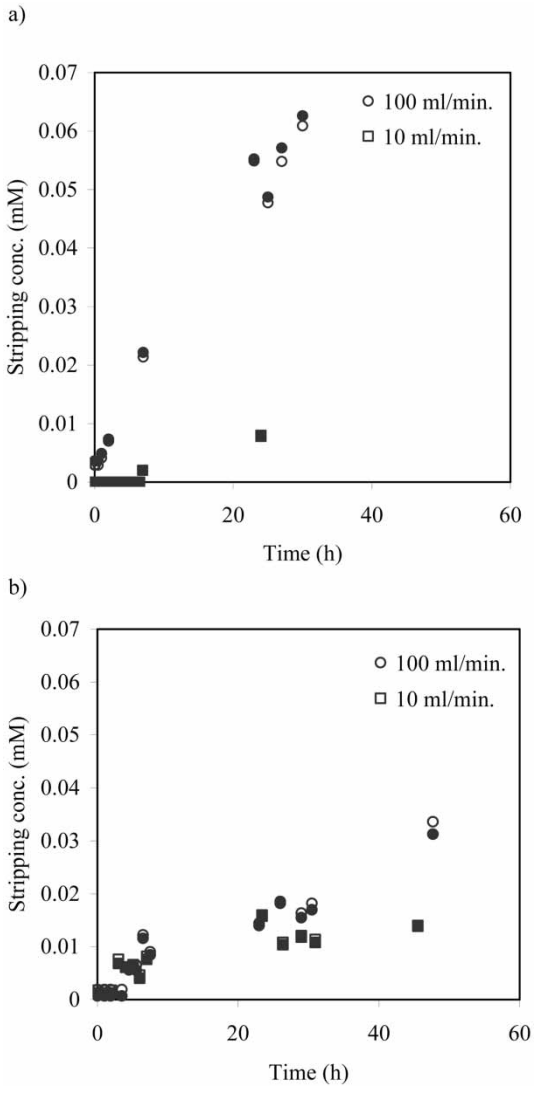

Figure 6. Influence of flow rates of feed and stripping phases on the propranolol transport across the chiral activated membranes for system A, with a solute to carrier ratio (S/C) of (a) 50 and (b) 100. Different symbol types apply for different flow rate conditions, while within each given flow rate assayed open and filled symbols correspond to the *S* and *R* propranolol enantiomers, respectively.

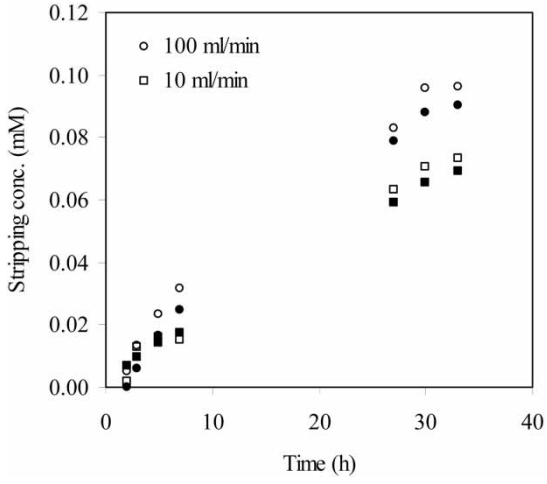

Figure 7. Influence of flow rates of feed and stripping phases on the propranolol transport across the chiral activated membranes for system B, with a solute to carrier ratio (S/C) of 12. Different symbol types apply for different flow rate conditions, while within each given flow rate assayed open and filled symbols correspond to the *S* and *R* propranolol enantiomers, respectively.

Furthermore, in the case of system A, the differences on the transport rate between the two flow rates investigated are, as expected, more important at low solute to carrier ratio, due to the faster transport step within the membrane, for this case. Under these conditions, the maximum transport rate that may be attained, in the absence of boundary layer resistances, is much higher than for high S/C ratios.

Enantiomeric Selectivity

In this study, enantioselectivity was only found for system B.

When working with system A, although the amount of carrier in the membrane relatively to the amount of solute in the feed solution was high, enantioselectivity was not observed due to the high transport rates obtained with the experimental conditions employed. Often, in these membrane systems, a compromise must be reached between both the external mass transfer conditions and the amount of carrier incorporated in the membrane. These two factors influence the transport rate of the solute through the membrane as well as the process enantioselectivity. The solute transport rate increases when increasing the Reynolds number and also when increasing the carrier concentration in the membrane, whereas the enantioselectivity

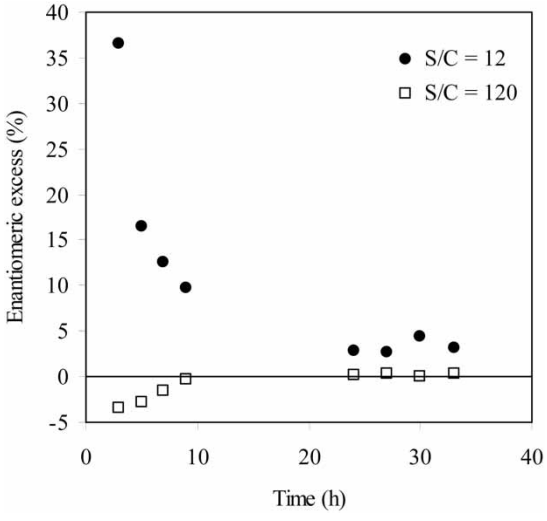

Figure 8. Enantiomeric excess for system B, with different solute to carrier ratios (S/C).

increases with the increase of carrier concentration just until an optimum. This can be related to an enhancement of transport rate at high carrier concentration, which makes the process less enantioselective (17).

For system B, and for the higher solute carrier ratio $S/C = 120$ there was no enantioselectivity (Fig. 8). However, an enantiomeric excess of 38% was obtained for the solute carrier ratio $S/C = 12$ which decreased to 3% at the end of the experiment. This behavior was also observed by other authors (1), showing that enantioselectivity is kinetically driven and no selectivity is noticeable once equilibrium is set in.

Transport Modeling

The overall mass transfer coefficients for the two enantiomers, K_{SR} and K_{SS}, were obtained by least-squares minimization of residuals of the experimental data of C_{SR} vs. time and C_{SS} vs. time using Eqs. (7) and (8).

Tables 1 and 2 show the values obtained varying the flow rate and varying the solute/carrier ratio for system A, and Tables 3 and 4 show the corresponding results for system B. For system A, Table 1 shows that for the lower flow rate (10 mL/min) the values of the mass transfer coefficients are 30% lower than the values obtained for the higher flow rate (100 mL/min).

For system B similar results are obtained. Table 3 shows that, for the lower flow rate the values of the mass transfer coefficients are 28% lower than the values obtained for the higher flow rate. Thus, as mentioned, the

Table 1. Mass transfer coefficients for two different flowrates with system A (S/C = 100)

Q (mL/min)	K_{SR} (m/s)	K_{SS} (m/s)
100	$(2.92 \pm 0.50) \times 10^{-8}$	$(3.12 \pm 0.50) \times 10^{-8}$
10	$(2.03 \pm 0.60) \times 10^{-8}$	$(2.10 \pm 0.60) \times 10^{-8}$

Table 2. Mass transfer coefficients for two different solute to carrier ratios with system A (Q = 100 mL/min)

S/C	K_{SR} (m/s)	K_{SS} (m/s)
50	$(1.26 \pm 0.10) \times 10^{-7}$	$(1.22 \pm 0.10) \times 10^{-7}$
100	$(2.92 \pm 0.50) \times 10^{-8}$	$(3.12 \pm 0.50) \times 10^{-8}$

Table 3. Mass transfer coefficients for two different flowrates with system B (S/C = 12)

Q (mL/min)	K_{SR} (m/s)	K_{SS} (m/s)
100	$(5.40 \pm 0.30) \times 10^{-8}$	$(5.30 \pm 0.30) \times 10^{-8}$
10	$(4.49 \pm 0.50) \times 10^{-8}$	$(4.33 \pm 0.50) \times 10^{-8}$

Table 4. Mass transfer coefficients for two different solute to carrier ratios with system B (Q = 100 mL/min)

S/C	K_{SR} (m/s)	K_{SS} (m/s)
12	$(5.40 \pm 0.30) \times 10^{-8}$	$(5.30 \pm 0.30) \times 10^{-8}$
120	$(2.13 \pm 0.50) \times 10^{-8}$	$(2.11 \pm 0.50) \times 10^{-8}$

propranolol transport across the membrane is limited by its diffusion rate from the bulk solution to the membrane surface at lower flow rates.

The solute to carrier ratio has a very high influence on the transport rate as expected, since the relative quantity of carrier is the limiting step of the process. For system A, the mass transfer coefficients obtained for the lower solute carrier ratio (S/C = 50) are four times higher than the values obtained for the higher solute carrier ratio (S/C = 100). It was expected that the transport of solute would be the double due to the double carrier concentration used. This high increase on the transport, also reported by other authors (19), is probably related with the decrease of the distance between the carrier sites allowing the solute to be transported by a more effective jumping mechanism.

For system B, the mass transfer coefficients obtained for the lower solute carrier ratio (S/C = 12) are 2.5 times higher than the values obtained for the higher solute carrier ratio (S/C = 120). In this case, the quantity of carrier was not changed but the quantity of solute decreased, so the transport rate is higher due to the higher availability of the carrier, corresponding to a relative increase of carrier in the system.

To sum up, it may be stated that the increase of transport rate experienced by both systems when lowering the S/C ratio depends not only on the solute to carrier ratio itself, but also depends on the absolute number of carrier sites inside the membrane, which actually is the rate determining step of the process.

CONCLUSIONS

The transport of propranolol across the membrane is limited not only by its diffusion rate from the bulk solution to the membrane surface but also by the relative amount of carrier in the membrane.

The decrease of the flow rate of the feed and stripping phases causes a decrease on the transport rate of propranolol in both systems A and B.

The transport rate of propranolol across the membrane increases when decreasing the solute to carrier ratio in both membrane systems, due to the relative increase of carrier amount in the membrane.

In both cases (systems A and B), the variation of the solute to carrier ratio has much more influence on propranolol transport rate than the variation of the aqueous phases flow rates. Enantioselectivity is only clearly observed when working with system B and for the lowest S/C ratio (S/C = 12), corresponding to the higher relative carrier amount in the membrane. Also a decrease of the enantiomeric excess with time for that experiment was observed. It appears that, enantioselectivity is kinetically driven and no selectivity is noticeable once equilibrium is set in.

The chemical conditions of system A do not allow achieving such lower S/C ratios, thus enantioselectivity could not be observed.

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