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Characterization of a Supported Liquid Membrane Based System for the Enantioseparation of *SR*-Propranolol by *N*-Hexadecyl-L-hydroxyproline

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Characterization of a Supported Liquid Membrane Based System for the Enantioseparation of *SR*-Propranolol by *N*-Hexadecyl-L-hydroxyproline

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ABSTRACT

A supported liquid membrane (SLM) containing the chiral selector *N*-hexadecyl-L-hydroxyproline (HHP) was characterized for the enantioseparation of a β-blocking drug. *SR*-propranolol was the target racemic mixture to be resolved by the membrane separation system. The different affinity shown by the selected carrier, HHP, for the two propranolol enantiomers produced a discrimination of their transport through this SLM. We investigated the influence of various chemical parameters involved in that system, such as the acidity of feed and receiving phases,

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as well as the carrier concentration in the membrane. Valuable knowledge on the transport mechanisms within this system was thus attained.

Key Words: SLM; Enantioseparation; β-Blocking drugs; Characterization.

INTRODUCTION

It is now well known that the human body can, in certain cases, differentiate between the enantiomers of a racemic drug[1] due to their different biological activity. In most cases, only one of the enantiomers carries out a useful and necessary activity, while no specific activity is undertaken by the other; consequently, it is removed by the human body as an impurity. In certain (fortunately infrequent) cases, the second enantiomer is even found to have negative effects on human health. Since the demonstration of such effects, pharmaceutical industries have been forced to develop methodologies for producing pure enantiomers to ensure the desired activity in the administration of drugs. In the case of *SR*-propranolol, a β-blocking drug used for treating some cardiovascular anomalies, the *S*-isomer shows far more blocking activity than the *R*-isomer.[2,3]

To date, most methods employed principally in the pharmaceutical industry to elucidate enantiopure compounds, such as stereoselective asymmetric synthesis, biotransformation, the chiral separation processes based on the enzymatic kinetic resolution technique or diastereomeric crystallisation, have been shown to have several drawbacks from an industrial point of view. Some of these are the requirement of a considerable number of different steps, with the corresponding by-products and a high energy consumption consequent to this to produce a reasonable amount of one optically pure enantiomer.[4–6] In the case of certain chromatographic separations, e.g., HPLC, they are even not applicable at an industrial scale.

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.[7] Among such processes, membrane-mediated separation techniques are particularly promising, especially if we take into consideration the fact that they can be used in a continuous mode and that both the cost and related energy requirements are reasonably low.[4] In addition, most of the membrane processes are performed at room temperature, which makes them energy efficient. Of these processes, supported liquid membranes (SLM) have considerable potential, as only a very small amount of an expensive chiral carrier is needed to accomplish for resolution of the proposed enantiomer.[8]

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Different enantioselective carriers have already been tested for the enantioseparation of *SR*-propranolol by using liquid membrane (LM) systems, such as *N*-n-alkyl-hydroxyprolines,[9] or dialkyl tartrate.[10] In both cases, the carrier is present in the membrane phase and selectively forms a complex with one of the enantiomers, which is transported across the membrane by an ion pairing mechanism.[5,9] These transport systems are driven by a proton gradient between both feed and receiving aqueous phases. However, with respect to the influence of certain chemical parameters involved in these enantioseparation membrane systems, there is still a lack of all the information required to fully comprehend the process and for its optimization.

In the present work, SLMs impregnated with an isopropyl myristate solution containing *N*-hexadecyl-L-hydroxyproline as carrier were applied for the enantioselective transport of *SR*-propranolol. A study on the influence of certain chemical parameters in the liquid membrane system was carried out to characterize the chemistry of the transport system and to attain a better assessment of the required enantioresolution.

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EXPERIMENTAL

Chemicals

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). Figure 1 shows the molecular structures of both the carrier, HHP, and our target analyte, *SR*-propranolol.

All other reagents used (such as acids and inorganic salts) were of analytical grade. Doubly distilled water was used for all aqueous solutions. Organic and aqueous solutions were presaturated with each other before use.

Membrane System

The membrane cell configuration (Fig. 2) used for transport experiments (supplied by Prof. J. A. Jonsson, Lund University, Sweden) consists of two circular polytetrafluoroethylene (PTFE) blocks (diameter 120 mm and thickness 8 mm) with grooves arranged as an Archimedes' spiral (depth 0.25 mm, width 1.5 mm, and length 2.5 m, with a total volume of ca. 0.95 mL). Two aluminum blocks (thickness 6 mm) were placed on both sides of the

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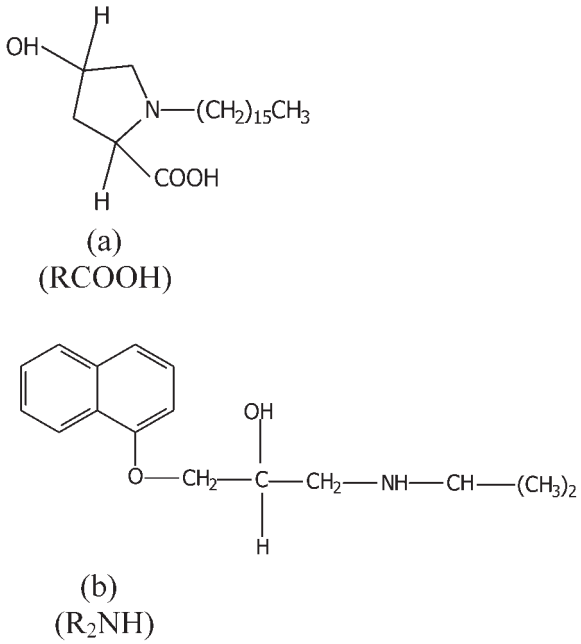

Figure 1. Structures of (a) *N*-hexadecyl-L-hydroxyproline (HHP) and (b) propranolol.

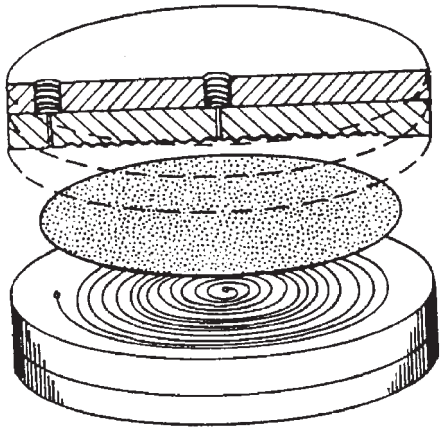

Figure 2. Schematics of the membrane cell configuration used for the experiments.

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PTFE blocks to stabilize the construction. Further details can be found elsewhere.[11,12] Porous polyvinylidenedifluoride (PVDF) membranes (Millipore GVHP, Millipore Corp., Germany), used as supports, were impregnated with a solution of HHP in IPM, by immersion of the solid polymeric support in the organic solution and sonication. In all the experiments, the amount of HHP in the membrane phase is expressed as the ratio of the quantity of HHP (in mols) in the membrane (taking into account the concentration of the HHP in the organic solution, and the effective volume of the porous support) to the amount of analyte (in mols) in the initial feed phase (C/A). The impregnated support is then placed between PTFE blocks and the whole construction is clamped tightly together with six screws. After installing the membrane and tubing, the excess solvent on the surface of the membrane was removed by passing doubly distilled water through both channels for 60 min, at 0.2 mL/min, which is the flux used for all the experiments. The total volume (20 mL) of each aqueous phase (both the feed and the receiving) was pumped with a peristaltic pump (Minipuls 3, Gilson, France) through acid-resistant tubing (Acid Manifold Tubing, Elkay Products, USA) connected to the membrane cell unit by screw plastic FIA fittings at both PTFE disks. Both aqueous phases were circulated throughout the whole experiment. The experiments started when both feed and receiving solutions entered the membrane cell. From that moment, samples of 0.5 mL were periodically withdrawn from the receiving phase channel, for about 5 h. In some cases, samples were also withdrawn after 20 h to confirm system behavior. A multimagnetic stirrer (A-03, SBS, Spain) was employed to stir both aqueous phases before entering the membrane cell unit, with the aim of supplying the membrane with homogeneous solutions. In all cases, the two solutions flowed in a counter-current mode. All experiments were performed at room temperature (24 $\pm$ 1°C).

SR-Propranolol Determination

A capillary electrophoresis (CE) system (P/ACE SYSTEM MDQ, Beckman, USA) was used to analyze the concentration of both enantiomers in the collected samples. Determination was performed in 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, doubly distilled 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).[13,14] The applied voltage was 23 kV and UV detection was carried out at 210 nm. Samples were injected using the hydrodynamic mode for 5 s, at 0.3 psi. The capillary was thermostated at 20°C. Between

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consecutive determinations, the capillary was rinsed with doubly distilled water. At the end of the day, the capillary was washed with 0.1 M NaOH, doubly distilled water, and MeOH, which was used for removing organic material and for facilitating capillary drying.

Parameters of Study

Determination of the Extraction Efficiency

The extraction efficiency (E) is the parameter determined in all the experiments to quantify the *SR*-propranolol transport across the SLM.[11] It is defined as the portion of analyte extracted in the receiving phase from the total amount of analyte in the initial feed phase, as shown in Eq. (1).

$$E = \left[\frac{C_{\mathrm{r,i}} * V_{\mathrm{r,i}}}{C_{\mathrm{f,0}} * V_{\mathrm{f,0}}}\right] \tag{1}$$

where $C_{\mathrm{r,i}}$ is the concentration of analyte in the receiving phase at time i, determined as explained above, $V_{\mathrm{r,i}}$ is the volume collected from the receiving channel, $C_{\mathrm{f,0}}$ denotes the concentration of analyte in the initial feed phase, and $V_{\mathrm{f,0}}$ corresponds to the initial volume of feed solution. Extraction efficiency was determined for both *S*- and *R*- pure enantiomers and is labeled as *Es* or *Er*, respectively.

Determination of the Enantiomeric Excess[15]

The enatiomeric excess (*ee*) is calculated from the previously obtained values of *Es* and *Er*, with the purpose of determining the enantioselectivity of the transport through the SLM system. The enantiomeric excess is defined as the ratio of the difference between the extraction efficiency of the two enantiomers to the total recovery of racemic analyte, within the receiving phase at time i:

$$ee = \left[\frac{Er_{\mathrm{i}} - Es_{\mathrm{i}}}{Er_{\mathrm{i}} + Es_{\mathrm{i}}}\right] * 100 \tag{2}$$

As seen from Eq. (2), a positive enantiomeric excess value will be obtained from a selective transport across the SLM of the *R*-enantiomer, and vice versa; negative *ee* will mean an enantioselective transport of *S*-enantiomer from the racemic mixture.

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RESULTS AND DISCUSSION

An SLM impregnated with an isopropyl myristate solution containing HHP as carrier was applied to characterize the expected enantioselective transport of SR-propranolol. The influence of various chemical parameters was systematically investigated to determine their influence on *SR*-propranolol enantiomeric transport through SLM. For this purpose, the pH of both aqueous phases and the carrier concentration, which are usually determinant parameters in these chiral systems,[5] were separately varied and the influence of the presence of ionic species in both aqueous solutions was also checked. Finally, different operation modes were assayed and membrane stability was also checked.

Influence of the Receiving Phase pH

Experiments with different pH in the receiving phase were carried out by using phosphate solutions at pH varying from 3 to 7. In all cases, the initial feed phase contained 0.05 g/L of racemate and was buffered with a borax solution at pH 8.[9] The carrier/analyte (C/A) ratio value was kept at about 1.4 throughout this set of experiments. Figure 3 shows experimental data

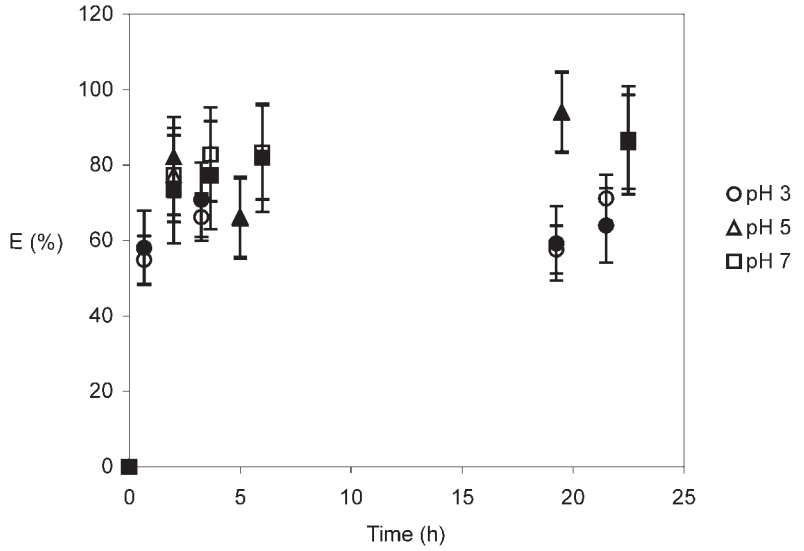

Figure 3. Comparison of the extraction efficiency between different pH of the receiving phase. Empty and full symbol apply for the *R* and the *S* enantiomers, respectively. Bars indicate the standard deviation of the values.

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expressed in terms of extraction efficiency (E) vs. time for each pH value investigated.

The high value of E attained in all cases after approximately 20 h indicates an almost complete transport of the entire analyte from the feed to the receiving phase. This can be explained by two factors: on the one hand, by the concentration gradient of analyte between both aqueous phases, which favors analyte transport across SLM to the receiving phase;[2,16] on the other hand, the transport is also favored by the pH gradient between both aqueous phases, which enhances the analyte transport extent[17] and prevents its retro-extraction to the feed phase[2] (buffered at a higher pH). This behavior can be better understood by considering the two proposed transport mechanisms involved in this SLM system:[5,16] a nonfacilitated transport mechanism that takes place by diffusion and a facilitated transport mechanism that takes place by ion-pair complex formation between the analyte and the carrier (HHP), together with the corresponding proton antiport. Both mechanisms are schematized in Fig. 4. As seen in Fig. 3, the pH 7 of the receiving phase was sufficiently low to ensure a complete[17] analyte transport from the feed to the receiving phase, and for preventing the analyte from being retro-extracted, due to the higher amount of H^+ present in the receiving phase compared to the feed phase (buffered at pH 8). A receiving phase buffered with Na_2HPO_4 at pH 7 was, therefore, employed for all other experiments.

The uncertainty of the obtained values may be related to the low C/A ratio used, which leads to higher relative errors in the impregnation step.

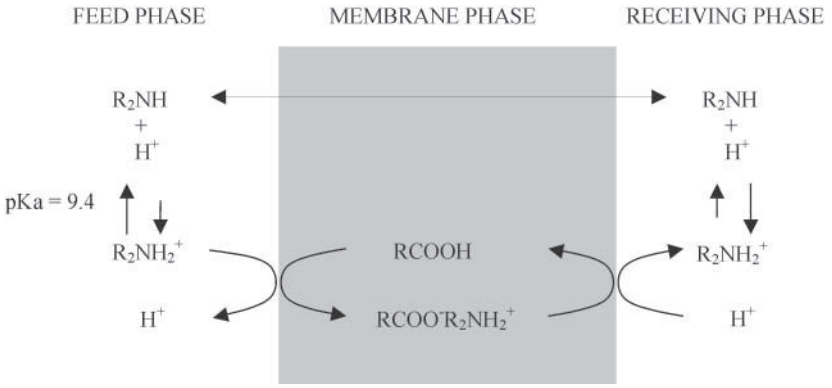

Figure 4. Scheme of steps and mechanisms taking place in the membrane system. The carboxylic group of the carrier (RCOOH) has a pKa around 9.5.

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Influence of the Feed Phase pH

In this case, different solutions buffered at different pH (7 to 10) were assayed as feed phases. Initial analyte concentration in the feed phase was 0.05 g/L of racemate, and the C/A ratio was maintained at 1.4. When investigating feed phase pH lower than 8, the corresponding receiving phase was lowered to pH 5 (instead of working at the optimum pH 7) to assure the necessary proton gradient between both aqueous phases. The results obtained are compared in Fig. 5.

The observed decrease of E when the feed phase pH is decreased can be explained by considering the HHP and propranolol acid–base properties; the carboxylic group of the carrier HHP has a pKa of about 9.5[18,19] and the secondary amine of SR-propranolol has a pKa of about 9.4.[20] Therefore, at pH 7, the chemical equilibrium of the carrier HHP is notably shifted to its protonated form and the exchange of this proton by the cationic propranolol is not favored. The formation of the ion pair with the analyte (see Fig. 4) is then restricted, avoiding analyte transport across the membrane by the facilitated transport mechanism. On the other hand, the analyte is most probably present in its acidic form (positively charged) at this pH, so diffusion of the neutral form of propranolol through the membrane phase can hardly occur. For these reasons, a low E is encountered and no selective transport is detected.

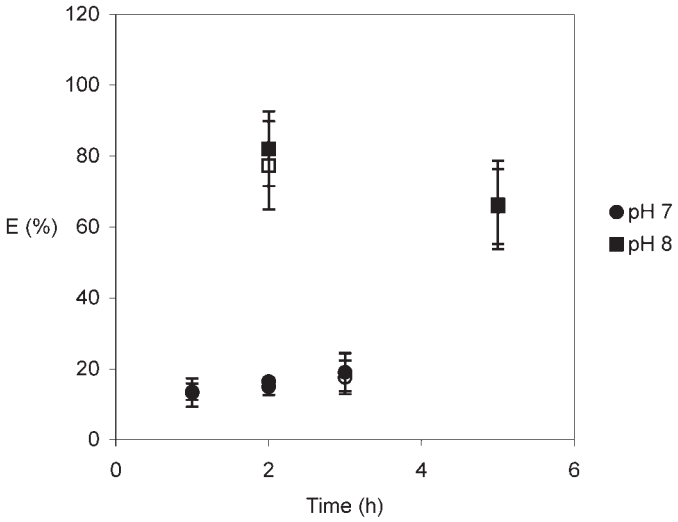

Figure 5. Comparison of the extraction efficiency for different pH values of the feed phase. Empty and full symbol apply for the R and the S enantiomers, respectively. Bars indicate the standard deviation of the values.

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The feed phase pH was also varied from 8 to 10. In this set of experiments, initial feed phase contained 0.1 g/L of analyte, receiving phase pH was maintained at 7, and NaCl was used to equal the ionic strength between both aqueous phases. High *E* values were obtained in all cases. At these high pH conditions (feed pH of 9 to 10), propranolol is a neutral molecule (R_2NH). Thus, it will be able to diffuse easily through the SLM membrane leading to high E values (see Fig. 4), but it will not be capable of interacting with the carrier HHP. Selective transport is, therefore, not detected in such cases, as can be seen in Fig. 6.

Clear *ee* is obtained only when working with feed phase adjusted at pH 8. At this pH, despite HHP being mostly protonated, it may exchange its proton by the charged form of propranolol (the predominant form at this pH) more readily than at 7 feed phase pH, and may, therefore, participate in the ion-pair formation that is the base of the selective transport.

Disodiumhydrogen phosphate was occasionally used to buffer feed phase at pH 8, instead of borax, to investigate whether the nature of the buffer in any way influences the analyte transport across the designed SLM. Similar *E* values were encountered in both cases. This emphasizes the importance of the feed phase pH and also indicates that borax (the usual buffer employed) neither participates in any transport-limiting process nor does it work as a complexing agent for the *SR*-propranolol. Therefore, a feed phase buffered with $Na_2B_4O_7$ at pH 8 was used for all subsequent experiments.

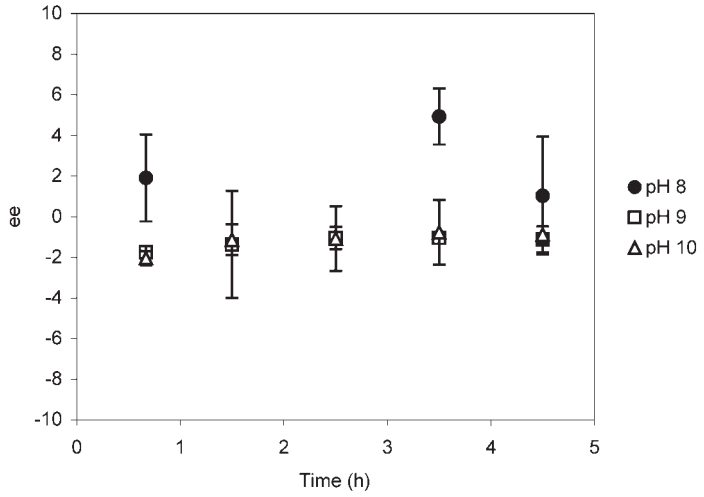

Figure 6. Comparison of enantiomeric excess at different feed phase pH. Bars indicate the standard deviation of the values.

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Influence of the Analyte Concentration

The influence of the analyte concentration in the feed phase on the membrane transport was investigated. Differences in extraction efficiency (E) or in the enantiomeric excess (*ee*) were not detected when comparing a set of experiments performed with different initial analyte concentrations varying from 0.05 to 0.1 g/L. This may be due to the fact that, relatively speaking, both transport mechanisms involved in this system are fast enough not to be influenced by the amount of analyte that may mostly affect thermodynamic factors. Feed phases with 0.1 g/L of analyte were, therefore, prepared for all the following experiments, as high analyte concentrations led to improved analyte detection by CE.

Influence of the Presence of Electrolytes in the Aqueous Solutions

To elucidate the chemical reactions involved in the membrane transport system, the role of proton and other cationic species was investigated. For that purpose, the influence of the presence of ionic species in the feed and receiving phases was evaluated by adding either NaCl or KCl to both phases and by maintaining all other parameters as previously indicated. No significant differences were observed between experiments with respect to the presence or absence of these electrolytes in the aqueous phases, when considering the variability of the data obtained corresponding to the uncertainty of the SLM system. In terms of *ee*, better performance of the SLM system was only detected when NaCl was added to the feed phase to balance the ionic strength on both sides of the membrane, with the aim of avoiding the effects of osmotic pressure.

We believe that the improvement in the *ee* that is observed in this case, by the comparison of Fig. 6 (pH 8) and Fig. 7 ($C/A = 1.4$), is due to a decrease in the resistance of the analyte against self-transport (especially in the case of facilitated transport) from the diluted to the more concentrated aqueous solution. This resistance is caused by the osmotic pressure phenomena previously referred to.[21]

Influence of the Carrier Concentration in the Membrane Phase

To investigate the influence of the concentration of the carrier in the membrane phase, different experiments were performed by varying the

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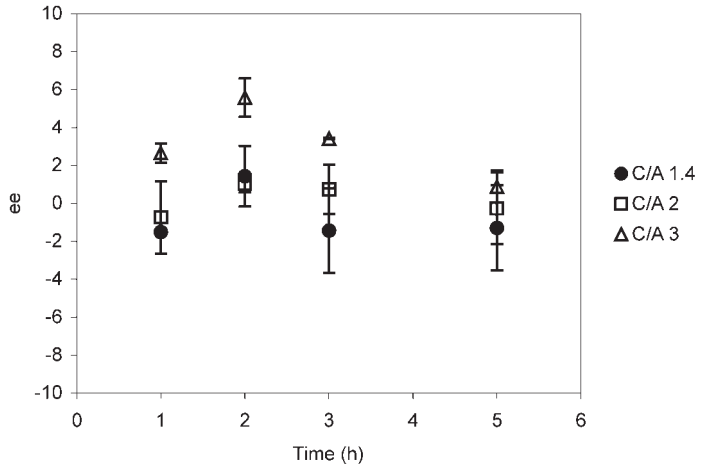

Figure 7. Influence of the carrier concentration in the membrane, in terms of C/A ratio, on the enantiomeric excess. Bars indicate the standard deviation of the values.

concentration of the HHP in the IPM organic solution, which impregnates the polymeric support. In each experiment, the feed phase, containing 0.1 g/L of analyte at pH 8, adjusted with borax buffer, and the receiving phase at pH 7, buffered with disodiumhydrogen phosphate, were pumped to the corresponding membrane side to determine the behavior of the SLM system. Experimental data are shown in Fig. 7 in terms of *ee* at the different carrier/analyte (C/A) ratio. C/A ratios higher than 3 were limited by the relatively low solubility of HHP in IPM.

An enantioseparation increase is observed when increasing C/A ratio; therefore, larger amounts of HHP enhance the contribution of the facilitated transport mechanism against the nonfacilitated mechanism. On the other hand, in the absence of a carrier, a similar diffusion of both enantiomers was detected.

Evidence of selective transport is obtained when a solution of HHP is impregnated in the membrane porous support. According to other research, the presence of secondary interactions (hydrogen bonding) in addition to ion pairing favors the affinity of the carrier for the *R*-enantiomer;[9] consequently, it is selectively transported to the receiving phase.

It is important to note that enantioseparation is only achieved during the first period of time in each experiment, corresponding to the period in which the facilitated transport mechanism occurs, up to the moment in which the difference in concentration of the two enantiomers within the aqueous phases of the SLM system is equaled by diffusion.[4,17] In the best case, when the C/A ratio is 3, an *ee* of 5.6% is obtained 2 h after starting the experiment.

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Influence of the Mode of Operation

An assay in batch mode was carried out to investigate the influence of the operation mode on the extension of the transport and on its enantioselectivity. In this case, a feed phase containing 0.1 g/L of analyte, buffered with borax at pH 8, was pumped to both membrane sides for 2 h. The C/A ratio value was 3.0. Subsequently, this solution was replaced by a receiving one, adjusted at pH 7, and was also pumped to both membrane sides. After 2 h, E was measured. The results obtained are set out in Table 1 and are compared with the common continuous mode usually employed. That comparison makes clear the well-known advantages of the continuous mode, according to the extent of transport. The continuous mode, which has simultaneous extraction and reextraction mechanisms, permits the enhancement of transport extent by properly displacing the equilibriums involved in the SLM transport mechanism, making them efficient enough to be of promising potential at an industrial level. However, the operation mode shows no influence on the enantioselectivity of the transport under the tested conditions, as it is principally governed by the system's chemical parameters (pH of feed and receiving phases, and carrier concentration in the membrane).

Membrane Stability

Separate experiments were carried out to evaluate the stability of the membrane by determining extraction efficiency, E, in successive experiments over a period of 14 days, using the same impregnated support. Initial feed phase was maintained as reported previously,[9] and the C/A ratio value was 1.4 throughout all the experiments. Two samples were withdrawn from each experiment; the first of these after 1 to 2 h of starting the experiment, and the second sample just before terminating the experiment. To determine the stability of the SLM system, 16 experiments were carried out over 14 correlative days. Figure 8 shows the evolution of E over time (in hours) for

Table 1. Comparison of the extraction efficiency between experiments performed in continuous and batch operation modes.

Experiment type	*Es* (%)	*Er* (%)
Continuous mode	73.6 (30.4)	78.4 (30)
Batch mode	9.2 (1.2)	9.6 (1.2)

Note: Values in brackets represent the standard deviation of the data obtained.

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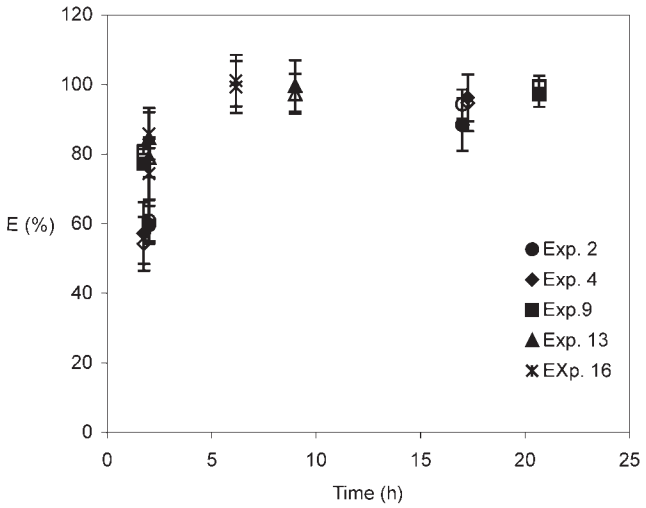

Figure 8. Comparison of the extraction efficiency (E) for the different sequential experiment and time. Empty and full symbols apply for the *R* and the *S* enantiomers, respectively. Bars indicate the standard deviation of the values.

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various experiments. No differences are observed between E values obtained for all the experiments. After the last experiment, membrane appearance was still acceptable, as it presented some organic impregnation.

These results are very promising, taking into account the drawbacks and performance of SLM.[22,23] It may be a consequence of the organic solvent's good impregnating properties for the porous support used, together with the properties of the membrane cell configuration that minimize the leaching out of organic solution to the aqueous phases, and also supplementarily reduce the volatility of the organic solution. This makes the application of this system to semi-industrial levels genuinely attractive. Enantiomeric excess values show a high variability between experiments (but not a specific tendency) due to the fact that the C/A ratio employed here was relatively low, as the principal focus of this study was to determine membrane lifetime.

CONCLUSION

SR-propranolol enantioseparation was carried out through SLM system containing HHP as chiral selector. The system was characterized in terms of extraction efficiency (E) and enantiomeric excess (ee). The operation

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conditions together with the chemical parameters of the feed and receiving phases were investigated.

Two of these studied parameters, namely the feed phase pH and the concentration of analyte within the membrane, have the greatest influence on the enantioseparation of the *SR*-propranolol racemic mixture. The pH of the feed phase governs the feasibility (or not) of the selective ionic-pair formation. The concentration of carrier in the membrane phase, when sufficiently high, facilitates the enantioseparation of the propranolol enantiomers across the SLM system. Additionally, good stability was encountered for the supported liquid membranes under study. A transport mechanism for the enantioseparation the *SR*-propranolol was then proposed.

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