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Resolution of Racemic Propranolol in Liquid Membranes Containing TA-β-cyclodextrin

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Abstract: The pharmacological properties of propranolol enantiomers are quite different, the β-adrenergic blocking activity resides in the (*S*)-(−) isomer, while the (*R*)-(+)-enantiomer has only a membrane stabilizing effect. The inherent chirality of cyclodextrins (CDs) allows them to form diastereomeric complexes. In this work, a peracetylated β-CD (TA-β-CD) that preferentially interacts with the (*S*)-(−) isomer of propranolol was used. Two liquid membranes, bulk liquid membrane (BLM) and supported liquid membrane (SLM) were tested. A recovery of 30% and a enantiomeric excess of 12% were obtained, using a SLM with 10 mM of propranolol and a pH gradient between feed and stripping phases.

Keywords: Propranolol, cyclodextrins, liquid membranes, racemic resolution

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INTRODUCTION

In the synthesis industry, problems may arise due to the difficulty of racemic mixture resolution. This issue is very important for the chemical industry (purification of compounds) but for the pharmaceutical industry is even more critical as public health is involved.

Many pharmaceutical products are commercialized as racemic mixtures given the inherent difficulties of the physical and chemical separation of very similar substances or the difficulty in its enantio-selective synthesis.

However, in many cases just one of the enantiomers presents activity, the other is inactive or may even exercise an adverse secondary effect. The problems caused by thalidomide, where one of the isomers is active and the other is highly toxic, show how important it is, for cases like this one, to completely separate the isomers involved (1).

Enantiomeric resolution is usually performed by three major methods:

1. crystallisation processes, including direct crystallisation of racemates or diastereomeric salts, complexes or compounds;
2. chiral chromatography and
3. kinetic resolutions which can be performed either chemically or by enzymes (2, 3).

An attractive alternative method for separation of racemic mixtures may be liquid/liquid extraction using selective chiral carriers for each one of the enantiomers of the mixture. Some examples were described that evidence the possibility of using a chiral carrier agent dissolved in an organic phase (4, 5). Several carriers, such as cyclodextrins (CDs) (6), tartaric acid derivatives (7), and crown ethers (8) have been used.

CDs are cyclic water-soluble, non-reducing, macrocycle polymers, constructed from alpha-(1-4)-linked D-glucopyranose units, in a ring formation (9–11). The most important property of CDs is the possession of a doughnut-shaped hydrophobic cavity into which various types of drugs ("guest" molecules) may be clathrated (encased) forming non-covalently bonded inclusion complexes either in the solid phase or in aqueous solution (12–14) since their inherent annular structure is stable in both phases.

CDs and its derivatives have been employed to improve the separation of compounds with highly similar chemical structures, mainly positional and optical isomers (15). CDs have been reported to separate enantiomers of a wide range of chiral compounds. Examples include β-adrenergic and calcium channel blockers, anticonvulsants (16), carboxylic acids (17), and amino acid derivatives (18). Chiral separation is dependent upon a solute molecule entering the hydrophobic cavity such that a particular enantiomer interacts with its H_3 and H_5 groups and with the polar OH groups at the edge of the cavity, whereas the configuration of the alternative isomer

prevents it from entering into such interactions. So, for a racemic mixture to be resolved into its enantiomers there must be a difference in stability of the inclusion complex formed for each isomer.

Liquid membrane extraction has been the subject of many studies over the years for the recovery of fermentation products, removal of contaminants from industrial effluents or recovery of metal ions from aqueous solutions (19) since it offers the advantage of simultaneous extraction and stripping in only one equipment and the reduction of the amount of carrier to be used, thus reducing both capital and current costs.

In a liquid membrane system two miscible liquid phases, usually aqueous phases, are separated by an immiscible phase, the liquid membrane, through which selective transport of a solute from one miscible phase to the other may take place, if an adequate carrier is used (20). The liquid membrane may contain only liquid phases, which is the case of a bulk liquid membrane (BLM) or may contain, additionally, a polymeric membrane to support the organic phase, supported liquid membrane (SLM). These membranes have considerable potential since only a small amount of carrier is needed, but they can present stability problems due to leaching out of the organic solvent to the aqueous phases.

In this work, the resolution of a racemic mixture by extraction using these two liquid membrane configurations will be compared. Propranolol was selected as a model drug due to its enantiomers different properties: (*S*)-(−)-Propranolol is much more potent than (*R*)-(+)-Propranolol and mediates the antiarrythmic and antihypertensive activity of the racemic mixture, whereas only (*R*)-(+)-Propranolol appears to be beneficial in treating angina pectoris.

Water-based liquid membranes utilizing α-, β-, γ-CD were already employed for the separation of several hydrophobic isomers. That study was an important first step in demonstrating the feasibility of membrane-based isomer separations (21).

Since the propranolol is in aqueous phase a peracylated cyclodextrin, TA-β-CD, water insoluble, was chosen as carrier. The chemical structures of TA- β-CD and propranolol are presented in Fig. 1a. The enantioselective interaction takes place in the feed side membrane interface, where the (*S*)-(−)-propranolol enantiomer preferentially interacts with the TA-β-CD, and is transported across the membrane. Racemic propranolol is simultaneously transported through the organic solvent by diffusion. A schematic description of the transport of propranolol trough the liquid membrane containing the triacetyl-β-cyclodextrin. is shown in Fig. 1b.

Thus, the influence of

1. the propranolol concentration in the feed phase, and
2. the pH gradient between stripping and feed phases on the recovery of the propranolol and on the selectivity of the process were studied.

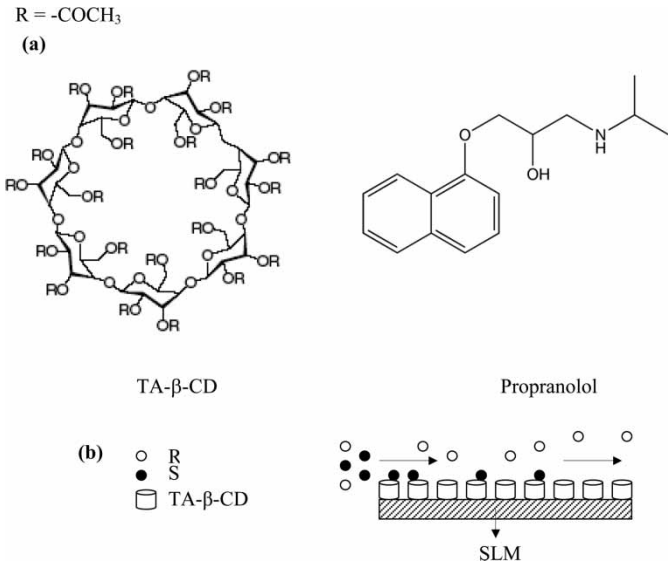

Figure 1. (a) Chemical structures of TA-β-CD and propranolol; (b) schematic description of the transport of propranolol trough the liquid membrane containing Triacetyl-β-cyclodextrin. S = (*S*)-(−) isomer of propranolol, R = (*R*)-(+) isomer of propranolol. SLM = supported liquid membrane.

EXPERIMENTAL

Materials

Racemic propranolol hydrochloride, p. a. grade, was supplied by Sigma-Aldrich (Germany). TA-β-CD and chloroform were supplied by Merck (Germany). All other reagents used (such as acids and inorganic salts) were of analytical grade. Doubly distilled water was used for all aqueous solutions.

A hydrophobic polypropylene membrane (Celgard 2400) was used as support. The membrane nominal pore size and thickness were 0.05 μm and 25 μm, respectively.

Transport Studies

Transport studies of racemic propranolol were carried out using two different membrane configurations: supported liquid membrane (SLM) and bulk liquid membrane (BLM).

Two different parameters were analyzed: the influence of the pH gradient between feed and stripping phases and the variation of concentration of propranolol in the feed phase. A blank experiment using the organic solvent without the carrier was also performed.

Bulk Liquid Membrane Experiments

The transport of the racemic propranolol through an organic solution by TA-β-CD and chloroform (liquid membrane) was investigated. A U-shaped tube with 1.5 cm inner diameter containing equal volumes (10 ml) of each phase was utilized (Fig. 2a). The contact area between the aqueous phase and the liquid membrane was 1.13 cm^2 and the mean distance between the two aqueous phases was 8.5 cm. A magnetic stirrer (300 rpm) was used to homogenize the liquid membrane and to cause turbulence in the aqueous organic interfaces. The influence of pH gradient between feed and stripping phases was studied for a 5 mM concentration of propranolol. The pH of the feed phase was maintained at pH = 5, while the pH of the stripping phase was also 5, in one experiment, and was adjusted to 3 using a phosphate buffer, in the other experiment.

Then, experiments with two initial propranolol concentrations, 5 mM and 10 mM, were compared. An experiment using 2 mM was also performed. The solute concentration in the feed and stripping phases was monitored by sampling 1 ml of each phase at regular time intervals, during at least 168 hours.

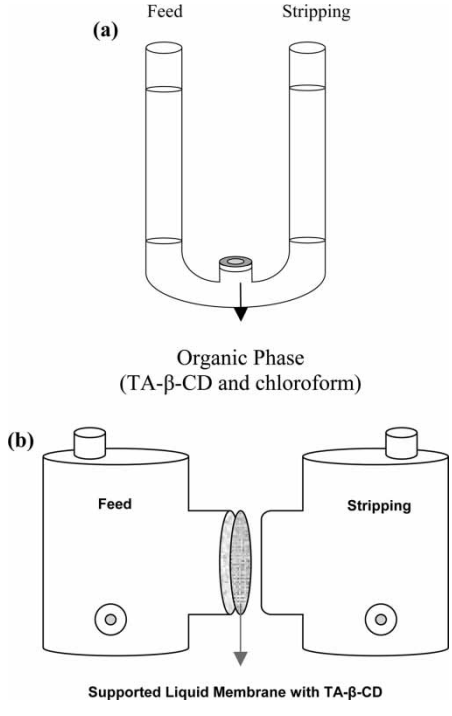

Figure 2. (a) Bulk liquid membrane cell; (b) supported liquid membrane cell.

Supported Liquid Membrane Experiments

The SLM was prepared by soaking the polypropylene membrane in a Petri dish containing a 100 mM solution of TA-β-CD in chloroform during one hour. The membrane, which was opaque, becomes transparent.

The transport studies were performed using a glass diffusion cell with two independent compartments of 160 ml each separated by the membrane (Fig. 2b). Both compartments were magnetically stirred at 300 rpm. This value was optimized in previous studies in order to have homogeneous aqueous phases and negligible boundary layers adjoining the membrane (22, 23). The effective membrane area was 12.56 cm^2.

The transport of the racemic propranolol through the SLM was evaluated. For the SLM the effect of the pH gradient between feed and stripping phases was also studied using a concentration of 2 mM. Then, the effect of the feed concentration was studied using different values of pH between feed and stripping phases. Two experiments were carried out, one using an initial propranolol concentration of 2 mM and another with a 10 mM concentration of racemic propranolol.

The solute concentration in the aqueous phases was monitored by sampling 1 ml of each phase at regular intervals, during at least 168 hours.

Propranolol Determination

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 288 nm. A Chiradex 5 μm LiChroCART 250-4 (Merck, Germany) column was used and the mobile phase consisted of a solution of acetonitrile/methanol/acetic acid/ammonia (95 : 4.5 : 0.4 : 0.1) (v/v) and the flowrate was 0.8 mL/min. The analitycal procedure was optimized by one of the authors (N. Ramalhete).

Calculation Methods

Solute Recovery

The recovery of the solute gives an idea of the extent of the extraction and stripping of propranolol. It is defined as the concentration of propranolol in the stripping phase divided by the initial concentration of propranolol in the feed phase, for each enantiomer, since equal volumes of feed and stripping phases were employed:

$$R = \frac{Cs}{Cf_0} * 100 \tag{1}$$

where Cs and Cf_0 are the propranolol concentrations in the stripping phase and in the feed phase in the beginning of the experiment, respectively. The solute recovery can be determined for both S and R enantiomers of propranolol.

Enantioselectivity

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

$$ee = \left[\frac{(C_{SS} - C_{SR})}{(C_{SS} + C_{SR})}\right] * 100 \quad (2)$$

where C_{SS} is the concentration of the S enantiomer of propranolol in the stripping phase and C_{SR} is the concentration of the R enantiomer of propranolol in the stripping phase.

According to Eq. (2) a positive value of the enantiomeric excess indicates a selective transport of the S-enantiomer of propranolol by the CD.

RESULTS AND DISCUSSION

Transport studies of racemic propranolol were carried out using two different membrane configurations: supported liquid membrane (SLM) and bulk liquid membrane (BLM).

In a bulk liquid membrane (BLM) a large volume of organic phase is used (10 ml), thus the quantity of TA-β-CD available for transport is high but there is a long distance for solute transport between the two aqueous phases (8.5 cm). Although there is no limitation of carrier to transport the propranolol, the rate of transport may be low due to long diffusion path (19).

In a supported liquid membrane (SLM) the volume is much lower ($\approx$0.10 ml), but on the contrary the distance between the two aqueous phases is small (25 μm), corresponding to the membrane thickness. In this case, the transport rate of propranolol is expected to be high due to the small thickness of the support membrane and only a very small amount of carrier is needed to accomplish the separation (19).

Bulk Liquid Membrane

Influence of the pH Gradient between of the Feed and Stripping Phases

Figure 3(a) shows the recovery of propranolol, using the same value of pH (pH = 5) in feed and stripping phases, or using different values of pH, pH = 5 in the feed phase and pH = 3 in the stripping phase for an initial propranolol concentration of 5 mM. A higher recovery of propranolol can be noticed when different values of pH are used. The recovery is approximately

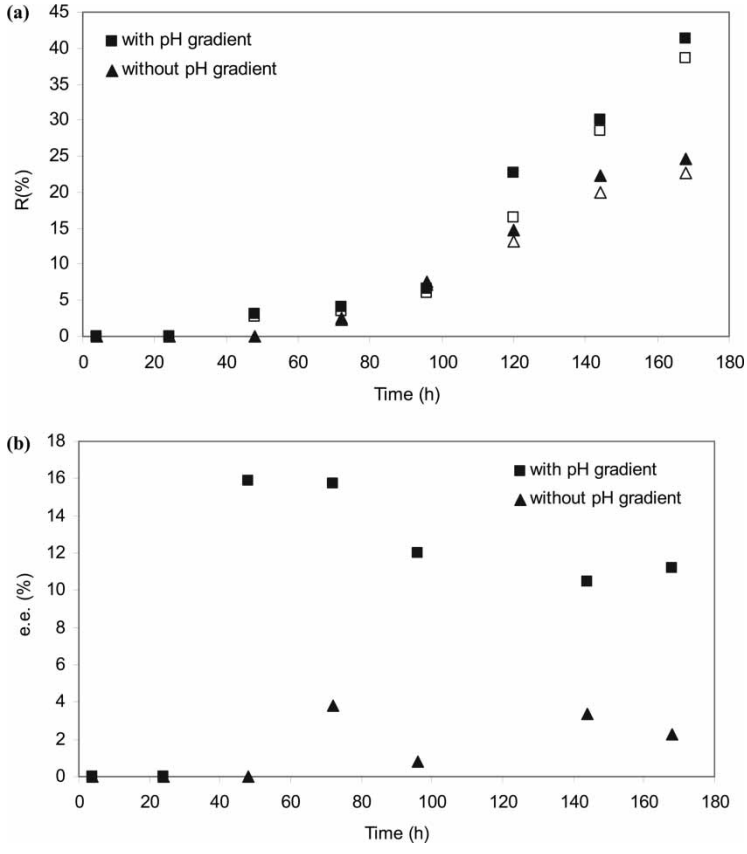

Figure 3. (a) Influence of the pH gradient between feed and stripping phases on the recovery, for an initial propranolol concentration of 5 mM. Open and filled symbols correspond to the R and S enantiomers, respectively; (b) enantiomeric excess for an initial racemic propranolol concentration of 5 mM with and without a pH gradient between feed and stripping phases.

double of the obtained when using the same pH in both phases (40% in the first case and 25% in the second case).

The transport is favored by the pH gradient between the feed and stripping phases, which enhances the propranolol extraction and prevents its retro-extraction into the feed phase. In fact, as in this system the TA-β-CD used, preferentially interacts with the (*S*)-(−) isomer of propranolol, it will be released in the stripping phase, due to the breaking of hydrogen bonds and higher solubility of propranolol in the stripping phase, at lower pH. This will lead to a higher recovery and higher enantiomeric excess. The same behaviour was observed by other authors (24), using N- hexadecyl-L-hydroxy-proline (HHP) as carrier.

Regarding the enantioselectivity, the values of the enantiomeric excess are much higher when a pH gradient between feed and stripping phases is imposed, than when using an equal value of pH in both phases. The values of the enantiomeric excess are in the range 16% to 10% in the first case, while a maximum value of 4% is obtained in the second case (Fig. 3(b)).

A blank experiment was also performed using an initial concentration of 5 mM of racemic propranolol and different values of pH, pH = 5 in the feed phase and pH = 3 in the stripping phase. Figure 4(a) compares the recovery

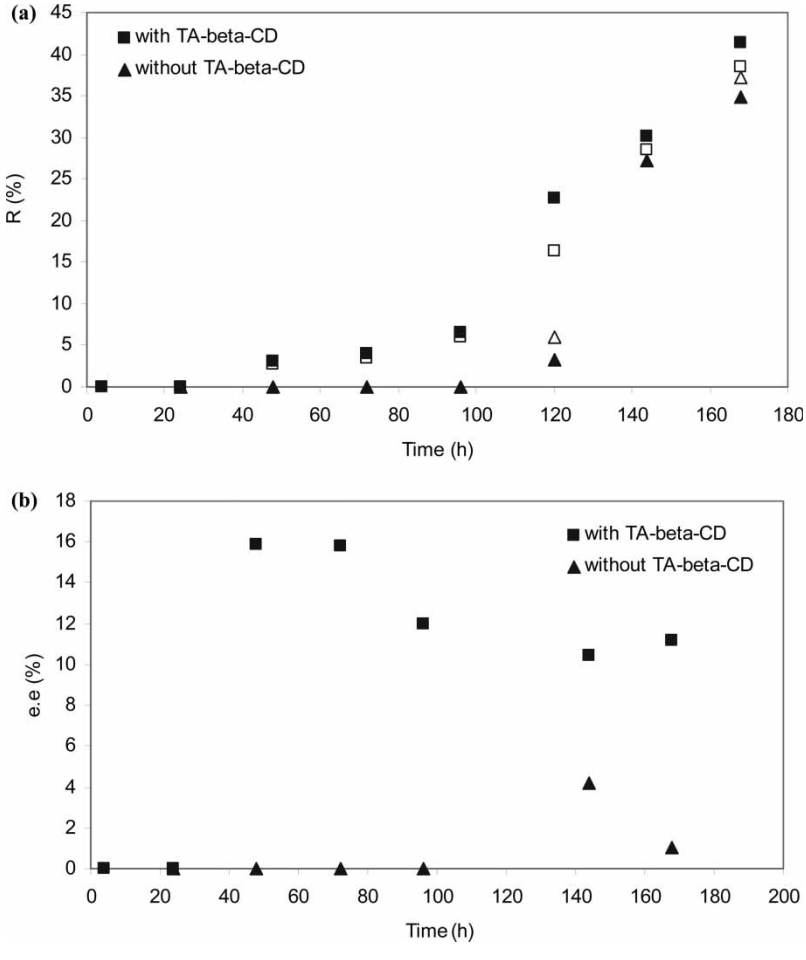

Figure 4. (a) Influence of the cyclodextrin concentration on the recovery, for an initial racemic propranolol concentration of 5 mM. Open and filled symbols correspond to the R and S enantiomers, respectively; (b) enantiomeric excess for an initial racemic propranolol concentration of 5 mM in the presence and in the absence of TA-β–CD.

profiles for the blank experiment and for the experiment using 100 mM of TA-β-CD. It can be noticed that the concentration of propranolol in the blank experiment is nearly null up to 100 h, but then it increases and in the end the concentration is similar to the one obtained in the experiment using 100 mM of TA-β–CD.

Regarding the enantiomeric excess (Fig. 4(b)), while the experiment using 100 mM of TA-β-CD shows values between 10% and 16%, the blank experiment evidences no enantioselectivity and only in the end of the experiment the enantiomeric excess reach values of 4% at maximum. These results show that the transport of both enantiomers of propranolol in the absence of the cyclodextrin may occur by diffusion through the solvent, therefore the transport rate is low and there is no enantioselectivity.

Influence of Propranolol Concentration in the Feed Phase

The effect of varying propranolol concentration in the extraction process can be observed in Figs. 5(a) and (b). The recovery is similar for both experiments (5 mM and 10 mM) between 38% and 44% and the final values of the enantiomeric excess are in the same range, from 12% to 14%, for both cases (Fig. 5(b)). However, the values of the recovery in the beginning of the experiment are very different, 10% for the 10 mM experiment and only 5% for the 5 mM experiment at 100 h. This is due to the higher driving force, the gradient of propranolol concentration between feed and stripping phases. When using 10 mM of propranolol the extraction is faster than for the 5 mM experiment. At 20 h the enantiomeric excess is 19% for the experiment using 10 mM of propranolol and for the 5 mM experiment at the same time (20 h), the stripping phase concentration was so low that it could not be detected, and so, the enantiomeric excess could not be evaluated. An experiment using an initial propranolol concentration of 2 mM was also performed, but the stripping phase concentration could not be detected through all the experiment (168 h).

For this membrane configuration there is always a time (Fig. 5a) required to establish a stationary concentration gradient in the membrane, i.e., a constant flux through it.

Supported Liquid Membrane

Influence of the pH Gradient between the Feed and the Stripping Phases

For the case of the supported liquid membrane, the pH gradient between the feed and stripping phases has a great effect not only on the recovery of propranolol but also on the kinetics of the extraction process.

The recovery is much higher when using a different value of pH in the feed and stripping phases (30%), than when using the same value of pH in both phases (5%). In that case, the extraction process is very slow and a lag

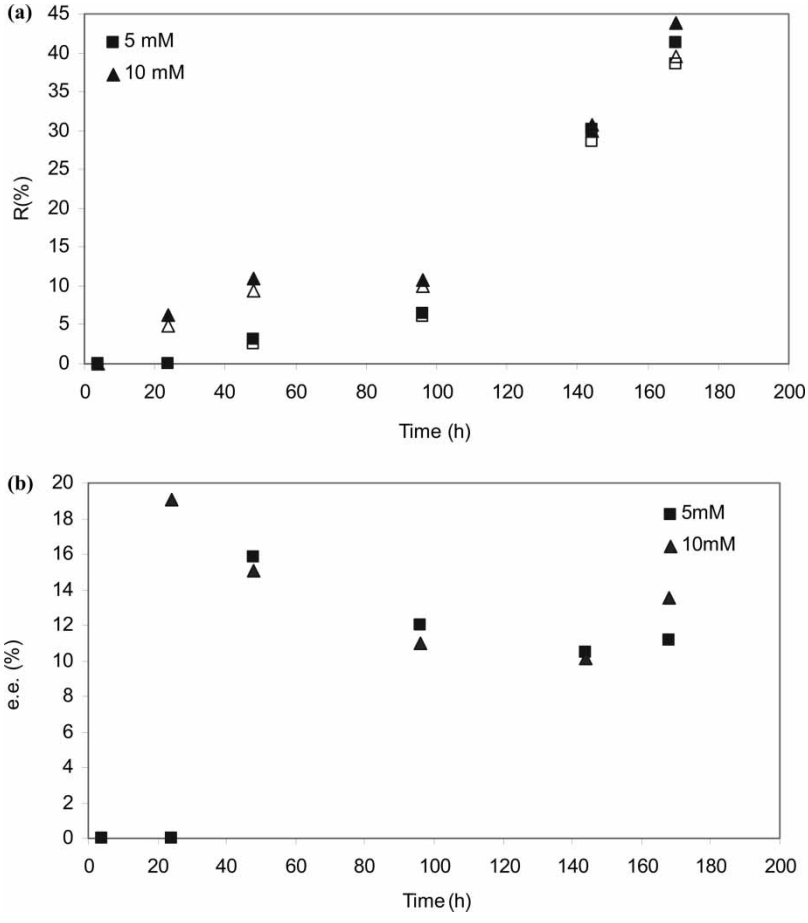

Figure 5. (a) Influence of the variation of the initial propranolol concentration in the feed phase on the recovery using a pH gradient between feed and stripping phases. Open and filled symbols correspond to the R and S enantiomers, respectively; (b) enantiomeric excess for initial racemic propranolol concentrations of 5 mM and 10 mM using a pH gradient between feed and stripping phases.

phase can be noticed of 120 h before the concentration of propranolol in the stripping phase is detectable (Fig. 6a). On the contrary, if a pH gradient between the feed and stripping phases is imposed, the recovery continuously increases from the beginning of the experiment until an equilibrium value of 30% is reached (Fig. 6a) and the enantiomeric excess varies between 6% and 11% throughout the experiment (Fig. 6b).

For this membrane configuration and using a pH gradient between the phases there is no lag time because the liquid membrane thickness is very small and the transport is faster, as it was expected. For the bulk liquid

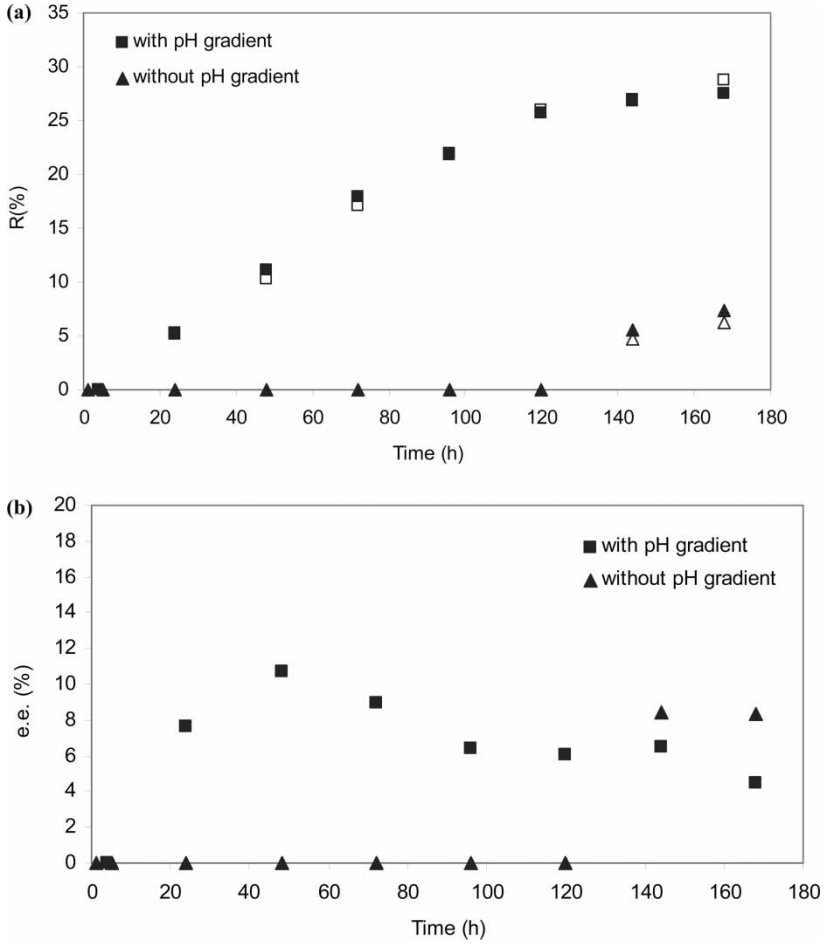

Figure 6. (a) Influence of the variation of pH gradient between the feed and stripping phases on the recovery, for an initial racemic propranolol concentration of 2 mM. Open and filled symbols correspond to the R and S enantiomers, respectively; (b) enantiomeric excess for an initial propranolol concentration of 2 mM in the presence and in absence of a pH gradient between feed and stripping phases.

membrane there is always a lag time (Fig. 4a) required to establish a stationary concentration gradient in the membrane, i.e., a constant flux through it.

A blank experiment, using chloroform without the TA-β-CD, was also performed for a concentration of 2 mM of propranolol and using different values of pH in the feed and stripping phases, pH = 5 in the feed phase, and pH = 3 in the stripping phase. The concentration of propranolol in the stripping phase could not be detected during the entire experiment (200 h). In the absence of the cyclodextrin there was no extraction of

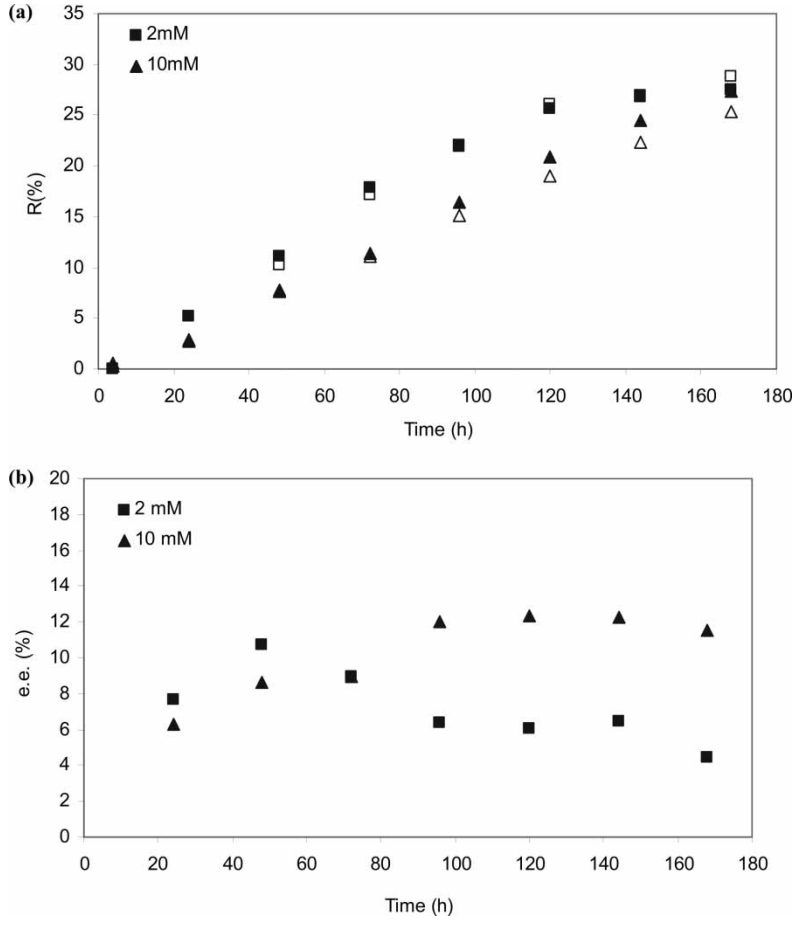

Figure 7. (a) Influence of the variation of the initial propranolol concentration in the feed phase on the recovery using a pH gradient between feed and stripping phases. Open and filled symbols correspond to the R and S enantiomers, respectively; (b) enantiomeric excess for initial racemic propranolol concentrations of 2 mM and 10 mM with pH gradient between feed and stripping phases.

propranolol by the solvent. The transport of propranolol is lower than that obtained with the BLM, due to the presence of the support membrane. For this configuration, propranolol can be also transported by diffusion through the polymer, but the transport through solids is always much lower than through liquids (25).

The SLM was stable, even in the absence of the carrier, because if it had collapsed it would imply equal propranolol concentrations in both aqueous compartments, which was not observed.

Influence of Propranolol Concentration in the Feed Phase

The effect of varying propranolol concentration in the extraction process can be observed in Figs. 7(a) and (b). The recovery profiles are very similar for both initial concentrations of propranolol (2 mM and 10 mM), although it is slightly higher for the 2 mM experiment. However, the propranolol concentration in the feed phase has a great effect on the enantioselectivity. The final values of the enantiomeric excess up to 100 h are almost double for the experiment using 10 mM of racemic propranolol (12%) compared to the value obtained using 2 mM of racemic propranolol (6%).

For this membrane configuration the initial propranolol concentration did not affect the recovery, since the transport rate is higher than that obtained with the bulk liquid membrane, due to the small diffusion path of the supported liquid membrane.

And since a similar performance in terms of recovery and enantiomeric excess was obtained for both membrane configurations using a concentration of propranolol of 10 mM, it seems very attractive to use the latter for the enantioseparation of propranolol, because only a very small amount of carrier is needed.

CONCLUSIONS

The enantioseparation of propranolol was accomplished using a peracetylated β-cyclodextrin, the heptakis (2,3,6-tri-O-acetyl)-β-cyclodextrin (TA-β-CD) that preferentially interacts with the (*S*)-(−) isomer of propranolol.

The propranolol concentration in the feed phase and the difference of the pH between stripping and feed phases influences the recovery of the propranolol and also the selectivity of the process.

The two different liquid membrane configurations, bulk liquid membrane (BLM) and supported liquid membrane (SLM) tested, showed a similar performance in terms of recovery and enantiomeric excess. However, due to the small thickness of the SLM only a very small amount of carrier is needed to accomplish the separation. On the other hand, there is no lag time and the transport is faster as it was expected. Thus, this membrane configuration seems more attractive for the enantioseparation of propranolol and proved to be stable in all the experiments.

A recovery of 30% and a enantiomeric excess of 12% were obtained, using a SLM with 10 mM of propranolol and a pH gradient between feed and stripping phases, i.e., pH = 5 in the feed phase and pH = 3 in the stripping phase.

These values were obtained with only one single theoretical stage of contact. A multi-step contact process will enable a more effective separation of the two enantiomers, easily enhancing both the recovery and the enantiomeric excess.

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