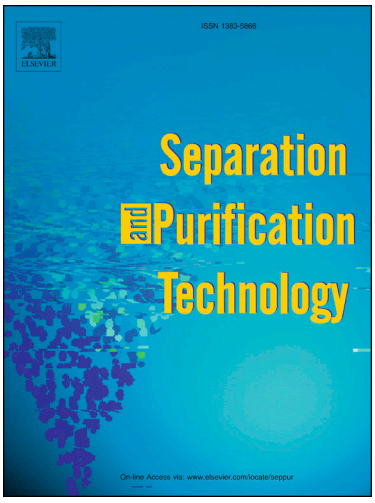
Journal Pre-proofs



Propranolol resolution using enantioselective biphasic systems

Ana R.F. Carreira, Ana M. Ferreira, Mafalda R. Almeida, João A.P. Coutinho, Tânia E. Sintra

PII: S1383-5866(20)32156-0
DOI: https://doi.org/10.1016/j.seppur.2020.117682
Reference: SEPPUR 117682

To appear in: *Separation and Purification Technology*

Received Date: 11 March 2020
Revised Date: 27 July 2020
Accepted Date: 10 August 2020

Please cite this article as: A.R.F. Carreira, A.M. Ferreira, M.R. Almeida, J.A.P. Coutinho, T.E. Sintra, Propranolol resolution using enantioselective biphasic systems, *Separation and Purification Technology* (2020), doi: https://doi.org/10.1016/j.seppur.2020.117682

Propranolol resolution using enantioselective biphasic systems

Ana R. F. Carreira[1], Ana M. Ferreira[1], Mafalda R. Almeida, João A. P. Coutinho* and Tânia E. Sintra

CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

*Corresponding author

E-mail address: jcoutinho@ua.pt

[1]These authors contributed equally to this work.

Abstract

The commercialization of chiral drugs is an increasing concern in the pharmacological field since the differences in the pharmacological activities of enantiomers may result in serious problems in the treatment of diseases using racemates. The resolution of chiral drugs is important for the development of safer and more active pharmaceuticals. This work aims to develop an enantioseparation platform for the resolution of propranolol (*R/S*-PRP) resorting to esters of tartaric acid and chiral ionic liquids (CILs) as chiral selectors in biphasic systems. More specifically, the efficiency of enantioselective liquid–liquid extraction (ELLE) systems, both aqueous and non-aqueous biphasic systems, are here studied, aiming to do a direct comparison between these two types of systems for the resolution of *R/S*-PRP. Studies were carried to evaluate the proper phase forming components of ELLE, *R/S*-PRP:chiral selector ratio, the potential of CIL over esters of tartaric acid, and the most suitable alkyl chain length for the esters of tartaric acid. It was found that the selected organic phase formers of ELLE, 1,2-dichloroethane and ethyl acetate, greatly impact the potential of the enantiorecognition of the system. The most efficient biphasic system identified was composed of 1,2-dichloroethane-water, and dipentyl-L-tartrate and boric acid as chiral selectors, with a enantioselectivity of 2.54. This system was further employed for the resolution of *R/S*-PRP in centrifugal partition chromatography, to assess its scalability potential, being shown that it was possible to increase the purity of *R*-PRP from 59% to 75%.

Keywords: Enantioseparation, esters of tartaric acid, chiral ionic liquids, aqueous biphasic systems, enantioselective liquid–liquid extraction, propranolol.

1. Introduction

Chirality plays an important role in the development of new pharmaceuticals. It is estimated that the global market for chiral technology enabling products can reach US$7.6 billion in 2022 [1]. Actually, racemates represent around 90% of the commercialized chiral drugs, which raises concerns by the FDA (Food and Drug Administration of United States) and EMA (European Medicines Agency) due to their possible differences in biological activity [2]. Despite enantiomers share the same chemical structure, they present a different spatial arrangement of atoms, only distinguishable by their optical rotation [3], being this fact responsible for their different interaction in the organism [4]. This may translate into different pharmacokinetic, pharmacodynamic and toxicological properties [5]. For that reason, the commercialization of enantiomeric pairs presents several disadvantages such as higher total drug dose, intricate dose-response relationship and possible toxicity of one of the enantiomers [5]. The commercialization of the therapeutically active isomer should thus be prioritized.

To overcome the mentioned issues, the pharmacological industry is mainly focused on two approaches: asymmetric synthesis and chiral resolution [6–9]. Asymmetric synthesis consists in the conversion of achiral molecules into chiral ones by using a proper catalyst and a chiral ligand [10]. The catalyst, which is frequently metal-based, and the use of chiral ligands, make this process expensive [6,11–13]. This approach is a unique way to produce pure enantiomers, which could not be otherwise synthesized, but it can be a complex and time-consuming task, which hampers its scale-up process [13,14]. Regarding the chiral resolution, chromatographic techniques such as high-performance liquid chromatography (HPLC) and simulated moving bed (SMB), are widely employed to resolve enantiomeric pairs [15,16]. The wide employment of HPLC is a consequence of its versatility and reliability [17]. As for SMB, this technique can be operated in a continuous mode, providing separations with high purity and low solvent consumption [18]. However, chromatographic methods have inherent disadvantages such as expensive equipment, high operational costs and environmental hazard, which hinders the effective scale-up of enantioseparation and stresses the urge for a novel cost-effective approach [19]. Enantioselective liquid–liquid extraction (ELLE) appears as a competitive and flexible alternative methodology that can be operated in a continuous mode [20]. A major advantage of the ELLE approach is that it comprises both enantiomeric recognition and solvent extraction on a single technique. Furthermore, conventional ELLE has been widely employed due to its simple scale-up and its tunability, enabling enantioseparation optimization [21]. These systems are conventionally composed of an immiscible organic and an aqueous phase. In order to avoid

the use of volatile organic solvents, Albertson introduced the aqueous biphasic systems (ABS) in 1958 [22]. ABS comprise two immiscible aqueous-rich phases based on polymer-polymer, salt-polymer or salt-salt combinations. In these systems both phases are mainly composed of water, thus affording an amenable media for the separation of (bio)molecules [23]. In general, ELLE needs the addition of a chiral selector, which interacts with the enantiomeric mixture and a complex is established preferably between one of the enantiomers and the chiral selector through intermolecular bonds [24]. The complex chiral selector-enantiomer will, ideally, have a different partition comparing to the free enantiomer, triggering the complex partition to the other phase and leading to an effective enantioseparation [25]. Thus, the enantiomeric recognition adds selectivity and the composition of the ELLE enables the different partition of the enantiomers in the system. The composition of the phases and the chiral selector are completely customizable, making of ELLE a versatile methodology. Both non-aqueous and aqueous biphasic systems have been successfully used for the purification of enantiomer molecules, such as mandelic acid, *α*-cyclohexylmandelic acid, phenylsuccinic acid, flurbiprofen, phenylalanine, amlodipine, among many others [26–31].

Over the years, several classes of chiral selectors have been studied. Cyclodextrin, copper-based metal complexes and tartaric acid derivatives are commonly selected to perform the chiral recognition on ELLE systems, some achieving promising outcomes [28,31–34]. Esters of tartaric acid are gaining increasing attention due to their synthesis from renewable feedstocks and their biodegradability, which makes them eco-friendly chiral selectors [35]. Another blooming class of chiral selectors is chiral ionic liquids (CILs), which are being widely explored on the enantioseparation field either as phase formers or as chiral selectors [29,36,37]. CILs are a subclass of ionic liquids that have a chiral moiety at the cation, anion or both. In general, they are non-volatile and thermally stable, with enormous structural diversity, allowing the design of task-specific chiral selectors [38]. The versatility of CILs is a key factor in enantiomers' separation, allowing the full customization of the chiral selector accordingly to the structure of the enantiomeric pair of interest. According to Ding *et al*. [39], the application of 1-butyl-3-methylimidazolium L-glutamate [BMIm][Glu] into n-decanol-buffer and n-octanol-buffer systems improved the selectivity of the system for amlodipine from 0.97 to 1.35 and from 1.04 to 1.21, respectively, which demonstrate the potential of CIL for enantioseparations.

Regarding the scale-up of liquid–liquid systems, currently, the countercurrent chromatography (CCC) is widely employed. CCC is a type of liquid–liquid chromatography

requiring two immiscible liquid phases, one of which acts as the stationary phase (maintained by centrifugal forces) and the other acts as the mobile phase [40]. There are mainly two different ways to obtain a liquid stationary phase using centrifugal forces: the hydrostatic and the hydrodynamic modes. Modern hydrostatic CCC columns are known and marketed under the name of centrifugal partition chromatographs (CPCs). A CPC column consists of several almost identical disks, which are mounted one above the other. Each disk has several engraved cells (chambers or channels) connected by narrow ducts and separated by a plate seal [41]. Through a small eyelet in this plate seal, the last cell of one disc is connected with the first cell of the next disc. As a result, this construction forms the space inside the rotor, where the column is formed, and the rotor is placed in a one-axis centrifuge. CPC can operate in the ascending (mobile phase rises through the retained denser stationary phase) and descending (mobile denser phases descends through the lighter phase) modes. It is considered a versatile, scalable and mechanistically simple approach, which permits the separation of structurally similar molecules in a continuous regime [21,42]. In fact, the application of liquid–liquid systems in CCC is very efficient in the separation of similar enantiomers [21].

In this work, aqueous and non-aqueous biphasic systems are proposed for the enantiomeric separation of *R/S*-PRP, aiming to do a direct comparison between the resolution ability of these two types of systems. More specifically, we formulated and optimized aqueous and non-aqueous biphasic systems for ELLE with different phase forming components and a chiral selector – CIL or tartaric acid esters derivatives – aiming to the enantioseparation of a β-adrenergic receptor blocker drug, propranolol (1-isopropylamino-3-(1-naphthyloxy)-2-propanol) (*R/S*-PRP). The aptitude of the systems to separate the propranolol enantiomers was studied by employing chiral selectors in ELLE using conventional biphasic systems (non-aqueous biphasic systems) and ABS (aqueous biphasic systems), with the quantification of the enantiomers on each phase performed by HPLC. The most promising result was scaled-up on CPC to assess its potential translation into industrial scales.

2. Experimental

2.1. Materials

In this work, six chiral selectors were synthesized, including two anionic CIL (di(tetrabutylammonium) L-tartrate $[N_{4444}]_2$[L-Tar] and 1-butyl-3-methylimidazolium (T-4)-bis[(α*S*)-α-(hydroxy-O)benzeneacetato-*κ*O] borate [BMIm][BSMB], and four esters of tartaric acid derivatives (dibutyl-L-tartrate, dibutyl-L-Tar; dipentyl-L-tartrate, dipentyl-L-Tar; dihexyl-

L-tartrate, dihexyl-L-Tar and dioctyl-L-tartrate, dioctyl-L-Tar). The chemical structures of the chiral selectors investigated are given in Figure 1.

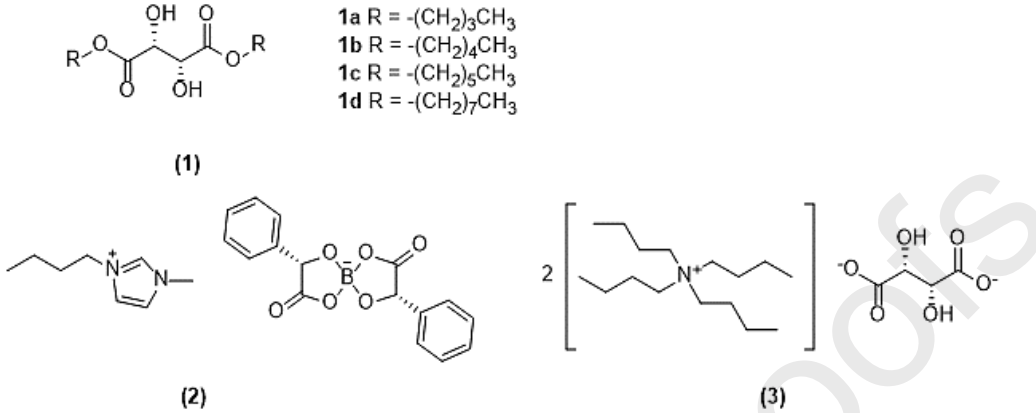


Figure 1. Structure of the chiral selector studied in this work, namely (**1**) tartaric acid derivatives, **1a**, **1b**, **1c** and **1d** corresponding to dibutyl-L-Tar, dipentyl-L-Tar, dihexyl-L-Tar and dioctyl-L-Tar respectively, (**2**) [BMIm][BSMB] and (**3**) $[N_{4444}]_2$[L-Tar].

For the synthesis of these compounds, the reagents used were the tetrabutylammonium hydroxide ($[N_{4444}]OH$, solution, 40.0 wt% in water), lithium carbonate (ACS reagent) and n-pentanol (> 99.0 wt%), all purchased from Sigma Aldrich, L-(+)-tartaric acid (L-Tar, ACS reagent grade) acquired from Acros Organics, boric acid (ACS reagent grade) from Panreac, (*S*)-(+)-mandelic acid (*S*-Man, 99.0%) supplied by Alfa Aesar, 1-butyl-3-methylimidazolium chloride ([BMIm]Cl, 99.0 wt%) from Iolitec, dichloromethane (99.9%) and toluene (99.8%), both purchased from Fisher Scientific. The synthesis also required the following reagents: p-toluenesulfonic acid monohydrate (> 98.0%) from TCI, n-butanol (99.6 wt%) acquired from VWR chemicals, n-hexanol (99.0 wt%) supplied by Carlo Erba, n-octanol (99.5 wt%) from Fluka and sodium hydrogen carbonate ($NaHCO_3$, 99.0%) acquired from LabKem.

For the formation of the phases of the liquid–liquid systems, the reagents used were ethyl acetate (EA, 99.8%) from Fischer Scientific, 1,2-dichloroethane (DCE, 99.8%), poly(ethylene glycol) Mw 8000 (PEG, BioUltra) and poly(acrylic acid sodium salt) solution Mw 8000 (NaPA, 45 wt% in water), from Sigma Aldrich and dextran Mw 60K-90K (Dex) from USB, all used without further purification.

For the enantioseparation assays, (±)-1-isopropylamino-3-(1-naphthyloxy)-2-propanol hydrochloride (*R/S*-PRP, > 99.0%) acquired from Sigma Aldrich, was used.

For the pH measurements of the ELLE phases, pH-indicator paper pH 1–14 universal indicator was acquired from Sigma Aldrich.

For the HPLC-DAD analysis, methanol (HPLC grade), acquired from Fisher Chemical, ultra-pure water (double distilled and then treated with a Milli-Q plus 185 water purification apparatus), sodium acetate (100.0%) from VWR, boric acid (ACS reagent grade) supplied by Panreac and acetic acid glacial (practical grade) from Fisher Chemical, were used for the mobile phase. (*R*)-1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride (*R*-PRP, > 98.0%) and (*S*)-1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride (*S*-PRP, > 98.0%) were both purchased at Sigma Aldrich and used to determine the calibration curve of each enantiomer.

2.2. Synthesis

The $[N_{4444}]_2$[L-Tar] was synthesized according to a procedure reported by Allen *et al*. [43]. $[N_{4444}]$OH (19.90 g, 40.0 wt% in aqueous solution) was added dropwise to an aqueous solution of 2.30 g of L-Tar, at room temperature. The reaction mixture was stirred at 60 °C and protected from light for 2 hours, producing the respective CIL and water as a byproduct. Most of the water was removed under reduced pressure. Finally, the obtained compound was dried under high vacuum for at least 48 hours. The chemical structure of $[N_{4444}]_2$[L-Tar] was confirmed by ^{1}H and ^{13}C NMR.

The [BMIm][BSMB] was synthesized as reported by Yu *et al*. [38]. Briefly, 0.92 g of lithium carbonate and 1.55 g of boric acid were dissolved in 24 mL of water, under constant stirring. Then, 7.32 g of *S*-Man was slowly added to the mixture. After 1 hour at 55 ºC, the mixture was cooled down until it reached room temperature. Then, 2.29 g of [BMIm]Cl was added, and two layers were formed. The mixture was stirred for 1 hour, at room temperature. After that period, 100 mL of dichloromethane was added and the desired compound was extracted to the bottom layer. The dichloromethane organic layer was washed with water (5 × 15 mL). The dichloromethane was reduced under pressure and the obtained product was dried under high vacuum for at least 48 hours.

The synthesis of the tartaric acid esters derivatives was adapted from Zawada *et al*. [35]. 15.10 g of L-Tar, 50 mL of toluene, 0.30 g of p-toluenesulfonic acid and 20.8 mL of n-butanol, n-pentanol, n-hexanol or n-octanol – depending on whether it was the synthesis of dibutyl-L-Tar, dipentyl-L-Tar, dihexyl-L-Tar or dioctyl-L-Tar, respectively – were refluxed for 2 hours. Then, the mixture was cooled down to room temperature and washed with a saturated solution

of $NaHCO_3$ (2 × 50 mL). The bottom layer was discarded, and the top layer was washed with double distilled water (2 × 50 mL). The top layer was dried under reduced pressure, to remove most solvents, and the obtained product was dried under high vacuum for at least 48 hours.

The structures of the synthesized chiral selectors were confirmed by ^{1}H and ^{13}C NMR, and the data can be consulted in the Supporting Information.

2.3. Conventional and aqueous biphasic systems for the separation of R/S-PRP enantiomers

Biphasic mixture points were selected to evaluate the systems' potential for the enantioseparation of *R/S*-PRP. Each system composition was determined by the gravimetrical quantification (± 10^{-4} g) of all the added components. The *R*/*S*-PRP solution added to each system had a concentration of 5 mg·mL^{-1}. On this work, several aspects were tested, namely, the impact of the chiral selector:*R/S*-PRP ratio, the potential of polymer-based ABS in comparison with the potential of the conventional ELLE systems, the influence of the structure of the CIL and the length of the tartaric acid esters' carbonated chain. The composition of all the studied systems is depicted in Table S1 in the Supporting Information. The initial mixture compositions were gravimetrically prepared (±10^{-4} g) and stirred at 15 rpm for 18 hours, at (25 ± 1) ºC, to promote contact between the chiral selector and the *R/S*-PRP. Afterward, the mixture points were centrifuged for 20 minutes at 3500 rpm to reach the equilibrium. After the complete phase separation, both the top and bottom phases were separated and weighed individually (± 10^{-4} g) and the amount of propranolol enantiomers in each phase was determined by HPLC-DAD. This procedure was done in triplicate. The percentage extraction efficiencies of each enantiomer, *R* and *S*-PRP ($EE_{R\text{-PRP}}$ and $EE_{S\text{-PRP}}$, respectively), was calculated separately by Equation 1:

$$EE_{R/S\text{-PRP}}\,(\%) = \frac{m_{\,top\ R/S-PRP}}{m_{\,total\ R/S-PRP}} \times 100 \qquad (1)$$

where $m_{top\ R/S\text{-PRP}}$ is the amount of *R* or *S*-PRP in the top phase and $m_{total\ R/S\text{-PRP}}$ is the total amount of *R* or *S*-PRP in the system. The partition coefficients (*K*) for each enantiomer were calculated separately through Equation 2:

$$K = \frac{m_{\,topR/S-PRP}}{m_{\,btt\ R/S-PRP}} \qquad (2)$$

where $m_{top\ R/S\text{-}PRP}$ is the amount of *R* or *S*-PRP in the top phase and $m_{btt\ R/S\text{-}PRP}$ is the amount of *R* or *S*-PRP in the bottom phase. Finally, the selectivity of each system (α) was calculated as described in Equation 3:

$$\alpha = \frac{K_{R-PRP}}{K_{S-PRP}} \quad (3)$$

where $K_{R\text{-}PRP}$ is the partition coefficient of *R*-PRP and $K_{S\text{-}PRP}$ is the partition coefficient of *S*-PRP. The purity achieved in the fractions collected from CPC was calculated as described in Equation 4:

$$Purity_{\ R\text{-}PRP} = \frac{Abs_{R-PRP}}{Abs_{R-PRP} + Abs_{S-PRP}} \times 100 \quad (4)$$

where $Abs_{R\text{-}PRP}$ is the absorbance value read by HPLC for the *R*-PRP and $Abs_{S\text{-}PRP}$ is the absorbance value read for the *S*-PRP. When the purity for more than one fraction is presented, the average of the purity of those fractions is calculated. As for the recovery percentage, this parameter was calculated as described in Equation 5:

$$Recovery_{\ R/S\text{-}PRP} = \frac{m_{Rec\ R/S-PRP}}{mtotal_{R/S-PRP}} \times 100 \quad (5)$$

where $m_{Rec\ R/S\text{-}PRP}$ is the mass of *R* or *S*-PRP quantified in the recovered CPC fraction and the $m_{total\ R/S\text{-}PRP}$ is the total amount of *R* or *S*-PRP injected in the analysis.

Note that in the studied ABS systems, the top phase is the PEG-rich phase and the bottom phase is mainly composed of NaPA or Dex. As for the conventional biphasic systems, more caution is required when analyzing data due to the inversion of the organic and aqueous phase in the DCE-H_2O in comparison to the EA-H_2O system. In the DCE-H_2O system, the top phase is mainly composed of H_2O and the bottom phase is rich in DCE. On the opposite, in the EA-H_2O system, the top phase is mainly composed of EA and the bottom phase by H_2O. The identification of the main components of each phase is depicted in Figure 2.

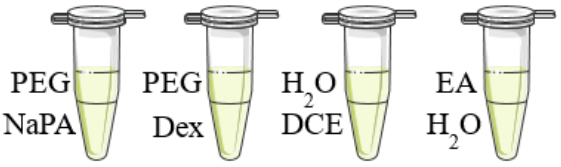


Figure 2. Identification of the main phase forming agent on each phase of the aqueous (the two systems on the left) and non-aqueous (the two systems on the right) biphasic systems.

2.4. Quantification of *R/S*-PRP by HPLC-DAD

The quantification of *R/S*-PRP enantiomers was performed by HPLC-DAD resorting to an adaptation of the procedure reported by Wang *et al*. [44]. The HPLC Elite LaChrom (VWR Hitachi) was accoupled to a diode array detector (DAD) l-2455. This HPLC was also equipped with a column oven l-2300, auto-sampler l-2200 and a pump l-2130. A Kinetex C18 reversed-phase (5 µm, 100 Å, 250 mm × 4.6 mm) analytical column was attached to a pre-column (5 µm, 4 mm × 3 mm) with the same stationary phase, both acquired at Phenomenex. The mobile phase was composed of methanol:water [54:46 (v/v)], 46 mM of boric acid, 11 mM of sodium acetate and 61 mM of dibutyl-L-Tar. The pH was adjusted on the aqueous solution composed by only sodium acetate to a value of 6 by adding acetic acid. The separation was performed on the isocratic elution mode at a flow rate of 0.8 $mL \cdot min^{-1}$. The injection volume was set to 10 µL and the wavelength was fixed at 275 nm. To enable propranolol enantiomers quantification, a calibration curve for each enantiomer was determined, using concentrations ranging from 0.1 to 1.0 $mg \cdot mL^{-1}$. The *R*-PRP enantiomer elutes first, at a retention time of around 13.1 min, followed by *S*-PRP eluting at around 15.8 min. Before all the assays, the equipment had a 5 hours stabilization time, which was monitored by the injection of an *R/S*-PRP standard sample.

2.5. CPC experiments

A fast centrifugal partition chromatography (FCPC®) system, model FCPC-C, from Kromaton Rousselet-Robatel (Annonay, France), was used to investigate the continuous enantioseparation of *R/S*-PRP. The rotor consists of 13 associated disks, each one containing 64 twin cells, making a total of 832 twin cells. The total cell volume is 50 mL, with 10 mL or 20% of the column volume corresponding to the connecting ducts. The same equipment was used in a previous study, where phenolic compounds were purified in a continuous regime [45]. The FCPC separations were carried out using a system composed of

H_2O:DCE:dipentyl-L-Tar:boric acid [46.6:46.7:5.5:1.2 (wt%)]. This system was set to work in the ascending mode. The rotor was filled with the DCE-(bottom)-rich phase at 600 rpm to achieve homogeneous solvent re-equilibration on the rotor. Then, the rotation was set up at 1300 or 1750 rpm for appropriate stationary phase retention. After the working rotational speed was set up, the H_2O-rich-(top) phase was pumped through the stationary phase to reach the equilibrium, i.e. when only the mobile phase came out of the column and the signal baseline is stabilized. The mobile phase flow rate was studied to increase the enantiomers separation and, simultaneously, to decrease the purification time, and flow rates of 1.0, 1.5 and 2.5 $mL \cdot min^{-1}$ were applied. For the purification of *R/S*-PRP enantiomers, the sample loop was filled with 5 mL of an aqueous solution of *R/S*-propranolol with a concentration of 5 $mg \cdot mL^{-1}$. The *R/S*-PRP concentration on the collected fractions was quantified through HPLC.

3. Results and discussion

R/S-PRP is a chiral β-adrenoreceptor blocker used for the treatment of coronary artery disease, hypertension, angina pectoris, migraine and arrhythmia [46,47]. Therapeutically, the *R*-PRP is less effective than *S*-PRP or even inactive, making the commercialization of racemic *R/S*-PRP disadvantageous [48]. In some cases, according to the FDA, *S*-PRP is 100 fold more potent than *R*-PRP [47]. Still, the *R*-PRP is not always less active than *S*-PRP. In fact, *R*-PRP is more efficient in the blockage of the transcriptional activity of the SOX18 gene, meaning that whereas *R*-PRP has an anti-angiogenic action by interfering with SOX18, *S*-PRP cannot block the transcription of this gene. Altogether, this highlights the need to stop the commercialization of this drug as a racemic mixture.

Aiming at the chiral resolution of *R/S*-PRP, two non-aqueous and two aqueous biphasic systems were studied: DCE-H_2O and EA-H_2O, and PEG-NaPA and PEG-Dex, respectively. DCE has been widely employed in the separation of various chiral molecules, such as phenylalanine, phenylglycine, tyrosine, 3-chloro-phenylglycine and esmolol [32,49]. Considering its recognized performance as a medium for chiral resolution, DCE was selected to study the enantioseparation of *R/S*-PRP in this work. In order to study the impact of the organic medium on the enantioseparation of propranolol, EA was also assessed.

All the chiral selectors tested in this work were selected due to their potential to complex with boric acid, except for [BMIm][BSMB] which already has boric acid incorporated in its structure (Figure 1). According to the literature, this particularity is crucial since boric acid acts as an intermediate that enables the formation of a complex between esters of tartaric acid

derivatives and amino-alcohols (*R/S*-PRP) with the same configuration, as shown in Figure 3, allowing to obtain a good enantioselective distribution of the racemates [50,51]. The complexation of boric acid with esters of tartaric acid in non-aqueous systems has an interesting particularity, *i.e.*, the complexation does not seem to occur significantly in the absence of *R/S*-PRP, since boric acid is mainly in the aqueous phase, despite the presence of the tartaric acid derivative on the organic phase [51]. The addition of *R/S*-PRP alters its distribution in the system by increasing the concentration of boric acid in the organic-based phase [51]. Considering the chiral selectors selected in this work, it is expected that the *S*-PRP–boric acid–*S*-tartaric acid derivative complex partitions to the organic phase. To the best of our knowledge, there are not reports employing esters of tartaric acid derivatives in aqueous biphasic systems, so we cannot predict how the distribution of *R/S*-PRP will be affected in these systems.

In general, the pH seems to play a key role in the chiral resolution, since a better recognition ability is accomplished when enantiomers are in their ionic form [26,52]. In the study by Abe *et al*. [51], the enantioseparation of pindolol, *R/S*-PRP and alprenolol was achieved by using ELLE supplemented with boric acid and didodecyl-L-tartrate at pH 5.2. At that pH, *R/S*-PRP is protonated, suggesting that in systems using boric acid as an intermediate, the enantioseparation of *R/S*-PRP may occur in an interfacial ligand exchange mechanism [20]. Thus, all biphasic systems here studied (ABS and conventional biphasic systems) were chosen taking into account that *R/S*-PRP p*K*a value is 9.51 [53]. Since the pH for ELLE systems ranged from 5 to 8 (Supporting Information, Table S2), this means that at least 98% of the *R/S*-PRP was protonated, inducing a stronger affinity of *R/S*-PRP with the aqueous phase. This information is important since it allows to understand the impact of the chiral selectors on the distribution of *R/S*-PRP in the biphasic systems.

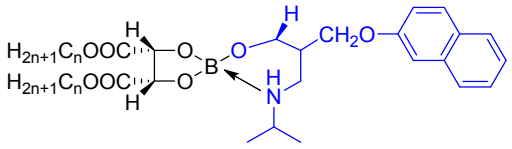


Figure 3. Structure of the tartaric acid derivative–boric acid–*R/S*-PRP complex, adapted from Abe *et al*. [51]. The *R/S*-PRP structure is represented in blue.

3.1. Effect of ratio chiral selector and R/*S*-PRP

To test if the ratio between the chiral selector and the *R/S*-PRP had an influence on the $EE_{R/S\text{-}PRP}$ and on the selectivity, three different dibutyl-L-Tar:*R/S*-PRP molar ratios (10:1, 45:1 and

91:1) were evaluated, as depicted in Figure 4. The $EE_{R\text{-PRP}}$ and $EE_{S\text{-PRP}}$ values and the obtained α for each case are detailed in the Supporting Information (Table S3). Boric acid and dibutyl-L-Tar were added in molar equivalents, similarly to the report of Abe *et al.* [51]. The increase of the ratio between the chiral selectors and *R/S*-PRP leads to a progressive increase of the selectivity ($\alpha_{\times 10}$ = 2.18, $\alpha_{\times 45}$ = 2.54). Notice that the selectivity of the system increases as the values diverge from 1. More specifically, when higher quantities of the chiral selector are available, more *S*-PRP tends to bind to it and, consequently, to partition to the organic phase, as expected by taking into account the results of Abe *et al.* [51]. However, a higher increase in the ratio does not translate into a higher selectivity since at higher ratios the selectivity decrease ($\alpha_{\times 91}$ = 2.18), thus the formation of more borate complex does not imply that the system will be further sensitive to the enantiomeric pair. Briefly, the best selectivity was achieved at the 45:1 ratio, suggesting that the saturation of the binding sites occurs somewhere between the 45:1 and the 91:1 ratio.

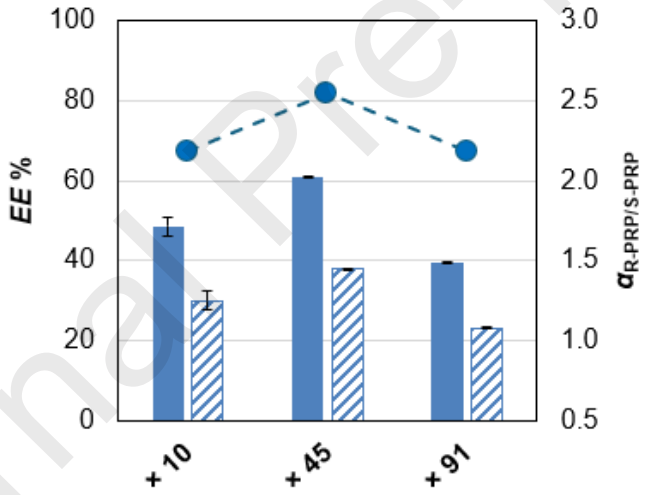


Figure 3. The extraction efficiencies ($EE_{R\text{-PRP}}$, solid background bars; $EE_{S\text{-PRP}}$ dashed bars) and selectivity (α, circles connected by a dashed line) for each DCE-H_2O system are presented. All the systems had dibutyl-L-Tar and boric acid as chiral selectors.

Furthermore, we also evaluate the effect of the ratio of CIL:*R/S*-PRP (10:1 and 45:1) on the enantioseparation efficacy, as depicted in the Supporting Information (Table S3). The results show that increasing the proportion of the [BMIm][BSMB]:*R/S*-PRP had a similar impact on the selectivity of the systems when comparing to the tartaric acid esters derivatives as chiral selectors (Table S3). More specifically, a selectivity improvement was achieved at the 45:1 ratio ($\alpha_{\times 10}$ = 1.24, $\alpha_{\times 45}$ = 1.76, for the system DCE-H_2O).

In conclusion, the best selectivity was achieved by using the ratio chiral selector:*R/S*-PRP 45:1, being that ratio used in the following studies.

3.2. Non-aqueous and aqueous biphasic systems as enantioselective systems

3.2.1. Esters of tartaric acid as chiral selectors

The capacity to separate the *R/S*-PRP enantiomers using biphasic systems with dibutyl-L-Tar (a tartaric acid ester derivative) as a chiral selector is investigated hereafter. The effect of the dibutyl-L-Tar on the *R/S*-PRP selectivity was evaluated in two types of biphasic systems, *i.e.*, the traditional organic solvent-water and ABS, enabling the comparison of the efficiency of both systems. The addition of esters of tartaric acids in ABS is poorly reported. Herein, we provide a practical way to compare their efficiency in conventional biphasic systems and alternative ABS. The extraction efficiency and selectivity of *R/S*-PRP in the various systems investigated are depicted in Figure 5, and the respective detailed data is reported in the Supporting information (Table S3).

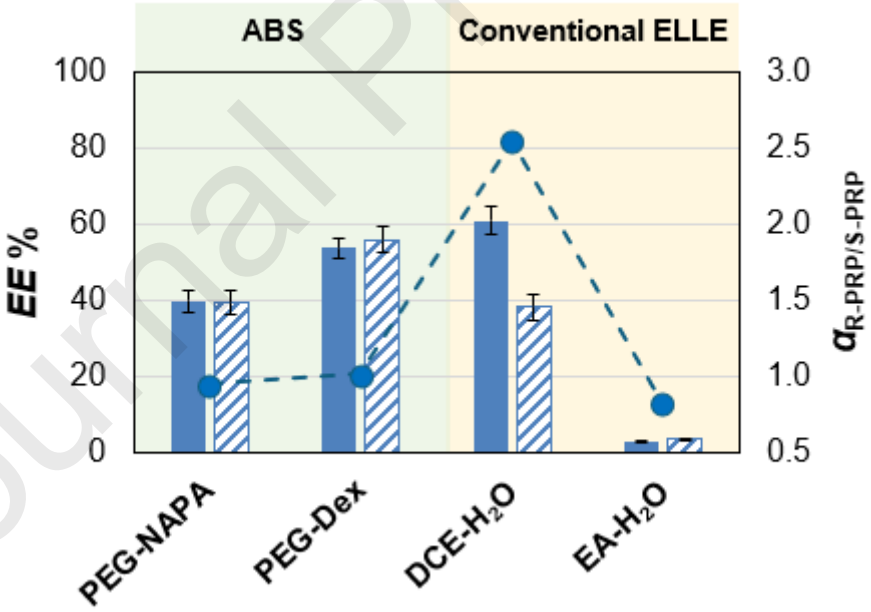


Figure 4. The extraction efficiencies ($EE_{R\text{-PRP}}$, solid background bars; $EE_{S\text{-PRP}}$ dashed bars) and selectivity (α, circles connected by a dashed line) for each system are presented. Conventional ELLE comprises the non-aqueous biphasic systems and ABS comprises the aqueous biphasic systems. All the systems had dibutyl-L-Tar and boric acid as chiral selectors.

According to the results obtained, ABS did not present any selectivity towards *R/S*-PRP ($\alpha_{PEG\text{-}NaPA}$ = 0.91, $\alpha_{PEG\text{-}DEX}$ = 1.02). Similarly, a report of Arai *et al.* [54] shows that the use of PEG-Dex for the separation of the racemic amino-alcohol carvedilol also resulted in poor selectivity (α = 0.92). Altogether, the application of polymer-polymer ABS may be unsuitable for the separation of amino-alcohols.

Regarding the results obtained with conventional systems, organic solvents seem to have a great influence on the distribution ratio and enantioselectivity of *R/S*-PRP (see Figure 5, $\alpha_{DCE\text{-}H_2O}$ = 2.54, $\alpha_{EA\text{-}H_2O}$ = 0.83). This may be because the formation of the ternary complex (tartaric acid derivative–boric acid–*R/S*-PRP complex) can be influenced by the organic solvent and its solubility in these organic solvents may be different [49]. Also, notice that since dibutyl-L-Tar is hydrophobic, the tartaric acid derivative–boric acid–*S*-PRP complex tends to partition towards the organic phase. These results are in good agreement with the literature, where other amino-alcohol (esmolol) also showed the same behavior when using conventional biphasic systems and dibutyl-L-Tar as selector chiral ($\alpha_{DCE\text{-}H_2O}$ = 2.00 and $\alpha_{EA\text{-}H_2O}$ =1.11) [49].

To better understand the impact of the organic medium on the chiral resolution, geometric parameters of both DCE and EA were analyzed (Table S4 in the Supporting information) [55,56]. Taking into account the Van der Waals surface area of DCE and EA (121.95 and 166.68 Å^2, respectively) and the results obtained herein, Van der Waals interactions do not seem the dominant interactions behind the enantioresolution of *R/S*-PRP in the studied conditions.

In summary, non-aqueous biphasic systems have shown to be more promising for the enantioseparation of *R/S*-PRP than aqueous biphasic systems, with the system DCE-H_2O presenting the best results.

3.2.2. CILs as chiral selectors

Different CILs were added to non-aqueous and aqueous biphasic systems to assess their potential for the enantiorecognition and resolution of *R/S*-PRP. The tested CILs were carefully selected for different reasons. [BMIm][BSMB] was tested due to its theoretical potential for the resolution of *R/S*-PRP [57]. Sedghamiz and co-authors reported computational studies showing [BMIm][BSMB] to be a good candidate for the enantiorecognition of *R/S*-PRP, being more selective for the *S*-PRP. According to c the *S*-PRP–[BMIm][BSMB] complex is more stable than the *R*-PRP–[BMIm][BSMB] complex since it has stronger π stacking interactions

and H-bonds. Regarding the $[N_{4444}]_2$[L-Tar], this CIL was selected due to its anion that may form a complex, preferably with *S*-PRP, in the presence of boric acid, enabling the enantioseparation of *R/S*-PRP. The CIL structure impact on the chiral recognition can be examined in Figure 5. (Supporting information, Table S3).

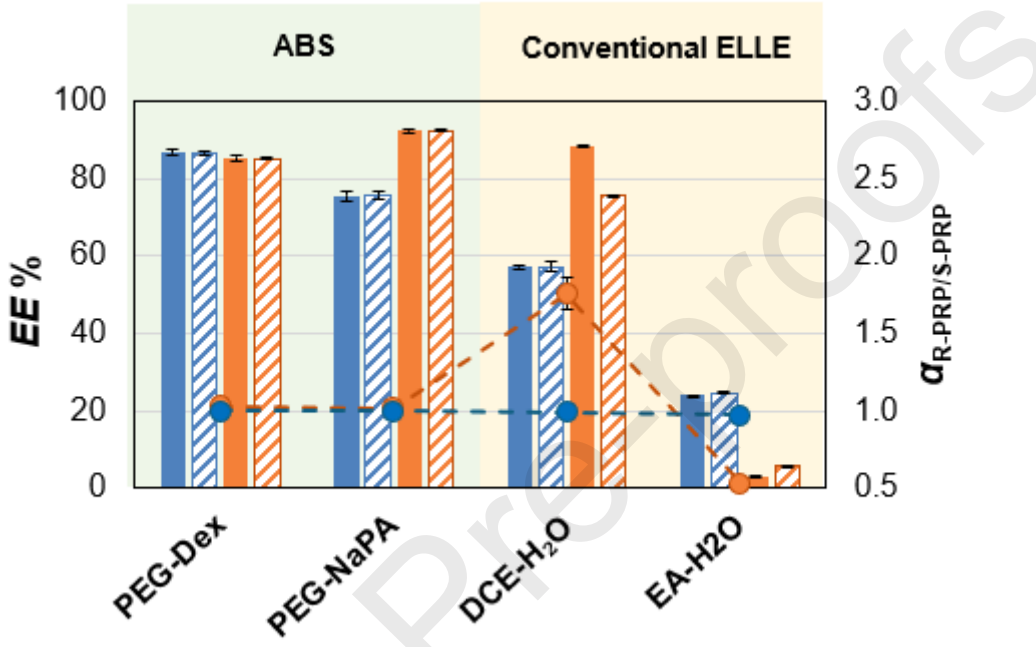


Figure 5. The blue bars and the blue dashed line correspond to the $[N_{4444}]_2$[L-Tar] data. The orange bars and the orange dashed line correspond to the [BMIm][BSMB] data. The extraction efficiencies ($EE_{R\text{-PRP}}$, solid background bars; $EE_{S\text{-PRP}}$ dashed bars background) and selectivity (α, circles connected by a dashed line) for each system are also shown. Conventional ELLE comprises the non-aqueous biphasic systems and ABS comprises the aqueous biphasic systems. All the systems with $[N_{4444}]_2$[L-Tar] as an adjuvant also had boric acid as a second chiral selector.

In all the studied ABS, no major differences are observed in the extraction efficiencies and selectivity (values around 1) for both CILs, suggesting that the selected CIL structure is not the most suitable to resolve *R/S*-PRP on these ABS. On the other hand, the partition in the conventional systems varies considerably with the CIL used as a chiral selector. The [BMIm][BSMB] showed good potential for the enantioseparation of *R/S*-PRP, leading to a selectivity of 1.76 and 0.53 for DCE-H_2O and EA-H_2O, respectively.

An opposite behavior was observed for $[N_{4444}]_2$[L-Tar], which did not present any selectivity in the conventional systems (α = 1.00). The $[N_{4444}]_2$[L-Tar] was not able to perform molecular

recognition between *R* and *S*-PRP and, thus, their distribution was unaffected. The results obtained may be related to the water solubility of the two CILs. [BMIm][BSMB] has a higher affinity towards the organic phase and $[N_{4444}]_2$[L-Tar] to the aqueous phase. In the case of the DCE-H_2O system, the $[N_{4444}]_2$[L-Tar] will be preferably on the upper aqueous phase, while [BMIm][BSMB] will prefer the bottom organic phase. Thus, the [BMIm][BSMB]–*R/S*-PRP complex will partition preferentially to the phase where the CIL has a higher affinity, causing the $EE_{R/S\text{-PRP}}$ differences, and consequently, the enantioseparation. The same principle applies to the EA-H_2O system, where the upper and bottom phases are the organic and aqueous phases, respectively. This data also shows that [BMIm][BSMB] has a preference for interactions with *S*-PRP, in agreement with the literature [57,58].

To the best of our knowledge, our report is pioneer in the experimental application of [BMIm][BSMB] for the enantioseparation of *R/S*-PRP in conventional biphasic systems and ABS. The results obtained herein show the good potential of this CIL for the enantiorecognition and separation of *R/S*-PRP, opening doors for future optimization of this CIL's structure, aiming at even better selectivities. Other reports using CILs with the same cation did not achieve selectivities as promising as the one delivered by [BMIm][BSMB], so proper optimization is needed. For example, the report by Cui *et al*. [29] employed [BMIm]-amino acid derived CILs for the enantioseparation of flurbiprofen, using a conventional system composed of DCE and phosphate salt buffer. The highest selectivity in that report was attained resorting to 1-butyl-3-methylimidazolium L-tryptophan [BMIm][L-trp] as a chiral selector ($\alpha_{[BMIm][L\text{-trp}]}$ = 1.21), a selectivity significantly lower than the one yielded herein with [BMIm][BSMB] for the *R/S*-PRP resolution ($\alpha_{[BMIm][BSMB]}$ = 1.76).

Concerning the results obtained using CILs in biphasic systems, it was possible to observe that non-aqueous biphasic systems are more promising than the aqueous biphasic systems for the *R/S*-PRP separation and the best conventional ELLE system is the one composed by DCE-H_2O ($\alpha_{[BMIm][BSMB]}$ = 1.76).

In conclusion, a high selectivity and suitable extraction efficiency are achieved when DCE is employed for all chiral selectors studied, except for $[N_{4444}]_2$[L-Tar] which presents no selectivity for *R/S*-PRP in any of the tested systems. Furthermore, comparing both types of chiral selectors used, the tartaric acid esters derivatives showed to be more promising for the chiral resolution of *R/S*-PRP than CIL ($\alpha_{dibutyl\text{-L-Tar}}$ = 2.54 and $\alpha_{[BMIm][BSMB]}$ = 1.76, for the system DCE-H_2O). Therefore, the conventional systems were selected as the most suitable for

extraction of *R/S*-PRP, as well as, the tartaric acid esters derivatives as chiral selectors and both were used for the subsequent investigations.

3.3. Alkyl chain length effect in the tartaric acid esters derivatives as chiral selectors

The chemical structure of tartaric acid derivatives may strongly influence the chiral recognition ability, as shown in the literature [51,59,60]. Thus, the effect of the addition of esters of tartaric acid with different alkyl chain lengths to conventional systems on the selectivity of *R/S*-PRP was addressed using the following esters of tartaric acid: dibutyl-L-Tar, dipentyl-L-Tar, dihexyl-L-Tar and dioctyl-L-Tar. Even though the system composed of DCE-H_2O presented the most promising results so far, we also studied the alkyl chain length effect in the system composed of EA-H_2O for comparison purposes. The outcomes for each of the four tartaric acid ester chiral selectors are depicted in Figure 7 (detailed information in the Supporting Information, Table S3).

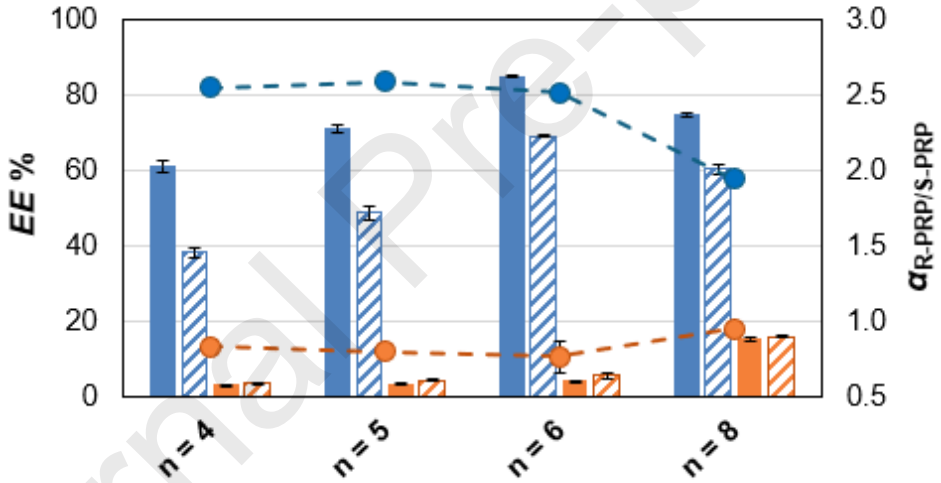


Figure 6. The blue bars and the blue dashed line correspond to the DCE-H_2O system's data. The orange bars and the orange dashed line correspond to the EA-H_2O system's data. The extraction efficiencies ($EE_{R\text{-PRP}}$, solid background bars; $EE_{S\text{-PRP}}$ dashed bars background) and selectivity (α, circles connected by a dashed line) for each system are also portraited. The dibutyl-L-Tar, dipentyl-L-Tar, dihexyl-L-Tar and dioctyl-L-Tar are represented as n = 4, n = 5, n = 6 and n = 8, respectively, as a reference to their alkyl chain length. All the systems had boric acid as a second adjuvant.

By analyzing the data for both systems studied, it seems that increasing the alkyl chain length of the chiral selector from four to six carbons has a low impact on the selectivity ($\alpha_{n=4}$ = 2.54, $\alpha_{n=5}$ = 2.59 and $\alpha_{n=6}$ = 2.51 for DCE-H_2O systems; $\alpha_{n=4}$ = 0.83, $\alpha_{n=5}$ = 0.80 and $\alpha_{n=6}$ = 0.76 for EA-H_2O systems). Yet, the selectivity of the systems dropped significantly for larger

alkyl chains, *i.e.*, when using the dioctyl-L-Tar ($\alpha_{n=8}$ = 1.94 for DCE-H_2O system; $\alpha_{n=8}$ = 0.95 for EA-H_2O system) as a chiral selector. This indicates that longer chains may be too bulky to properly form the borate complex. The results of Xu *et al.* [49] showed a similar behavior, *i.e.,* they used tartaric acid esters derivatives with different alkyl chain to extract selectively an amino-alcohol derivate (esmolol), and the selectors with bigger alkyl chain also showed less resolution ($\alpha_{n=4}$ = 2.10, $\alpha_{n=6}$ = 2.00, $\alpha_{n=8}$ = 2.09 for DCE-H_2O). Moreover, the extraction efficiencies of the studied systems are in agreement with Abe *et al.* [51], since the establishment of the complex between the tartaric acid esters derivatives and *S*-PRP is responsible for the partition of the *S*-PRP to the organic phase in both systems.

In summary, the experimental results showed that dipentyl-L-Tar presents the best selectivity ($\alpha_{n=5}$ = 2.59) along with a suitable distribution ratio for enantiomers of propranolol. Thus, the DCE-H_2O system with dipentyl-L-Tar as a chiral selector was further used in the study of the enantioseparation of *R/S*-PRP on CPC.

3.4. Enantioseparation of *R/S*-PRP on CPC

The best biphasic system identified before, composed of 46.6 wt% of H_2O + 46.7 wt% of DCE + 5.5 wt% of dipentyl-L-Tar + 1.2 wt% of boric acid (α = 2.54, corresponding to 59% of purity), was used to study the separation of *R/S*-PRP using a FCPC® system. This system presents partition coefficients (*K,* concentration of *R/S*-PRP between the H_2O-rich phase and the DCE-rich phase) in an adequate range for use in CPC ($K_{R\text{-PRP}}$ = 2.60 ± 0.14, $K_{S\text{-PRP}}$ = 1.00 ± 0.08) and has the highest selectivity values. The aqueous phase was used as the mobile phase, while the organic phase was used as the stationary phase. Several conditions to separate the enantiomeric pair were studied, such as different flow rates, 1.0, 1.5 and 2.5 mL·min^{-1} and also different rotation speeds, 1300 and 1750 rpm, to increase the purification of *R/S*-PRP and, simultaneously, decrease the purification time. The summary of the outcomes is reported in Table 1.

Table 1. Purity and recovery percentage of *R*-PRP at the different tested flow rates and rotation speeds.

		***R*-PRP**		
Flow rate ($mL \cdot min^{-1}$)	**rotation speed (rpm)**	**Fractions**	**Recovery (wt%)**	**Purity (wt%)**
1.0	1750	13–17	76.1	60.1
1.5	1750	13–17	75.2	70.6
2.5	1750	17–21	72.5	69.5
1.0	1300	14–20	76.0	69.0
1.5	1300	13–19	82.8	74.5
Recycle				
1.5	1300	14–20	83.4	72.0

As DCE was used as the stationary phase and dipentyl-L-Tar is dissolved on it, the *S*-PRP interacts more strongly with the stationary phase, being the *R*-PRP eluted first. Note that, as discussed previously, the *S*-PRP forms a complex with dipentyl-L-Tar using boric acid as an intermediate and this complex is more stable than the *R*-PRP–boric acid–dipentyl-L-Tar complex (see subsection 3.2.1.). Consequently, the first fractions recovered were richer in *R*-PRP than in *S*-PRP, achieving a maximal purity of 74.5%, when using a flow rate of 1.5 $mL \cdot min^{-1}$ and a rotation speed of 1300 rpm. For the assays performed at 1750 rpm, the purity of *R*-PRP obtained in each experiment is very similar, showing that the tested flow rates do not significantly influence the purity of *R*-PRP at this rotation. Regarding the recovery of *R*-PRP, at a rotation speed of 1750 rpm, higher flow rates result in better recoveries. Similarly, at the rotation speed of 1300 rpm, the best recovery of *R*-PRP was achieved at the highest tested flow rate (1.5 $mL \cdot min^{-1}$). It is important to mention that, individually, the first fraction of each assay usually possessed higher *R*-PRP purities (72.4–92.9%) than those reported in Table 1, but the recoveries are quite low (<11%) thus, a compromise was made, and fractions were added up and the average purity is reported.

No losses of the stationary phase were observed during the separation run, and the best separation of *R/S*-PRP was achieved with the *R*-PRP eluting in fractions 13–19 (the resulting chromatogram is depicted in Supporting Information, Figure S1). Since both compounds have the same wavelength, it was not possible to observe their individual characteristic peaks. The identification of these enantiomers in the respective fractions was achieved by HPLC (example

see Figure S2 and Figure S3 in Supporting Information). The CPC results are in agreement with the partition coefficients determined for the DCE-H_2O system, since *R*-PRP revealed to have the highest affinity to the water-rich phase and, consequently, being the first compound eluted.

Since the condition that afforded the best recovery (82.8%) and purity (74.5%) of *R*-PRP was the one with the rotation speed of 1300 rpm and flow rate of 1.5 $mL \cdot min^{-1}$, this assay was selected to perform the recycle of the stationary and mobile phases. The recycle aims to decrease the environmental impact of the *R/S*-PRP separation resolution. The recycle test presented a slightly minor purity in comparison to the assay using fresh stationary and mobile phase and a similar recovery rate of *R*-PRP.

4. Conclusions

Aiming at the enantioseparation of *R/S*-PRP, this work proposes an alternative approach for the resolution of this enantiomeric pair by applying esters of tartaric acid and CILs into aqueous and non-aqueous biphasic systems, facilitating the comparison of the efficiency of these biphasic systems for *R/S*-PRP enantioresolution. This work closes the gaps between conventional and aqueous biphasic systems, which is neglected throughout the literature. The optimized conditions evidence that the ratio between *R/S*-PRP:chiral selector of 45:1 is the best of the tested ratios. Among the tested chiral selectors, esters of tartaric acid revealed to be more promising than CILs in the tested conditions. Increasing the alkyl chain of the tartaric acid derivatives slightly improved the selectivity in the DCE-H_2O system ($\alpha_{n=4}$ = 2.54, $\alpha_{n=5}$ = 2.59 and $\alpha_{n=6}$ = 2.51) but only until a certain point since the chiral selector with the largest alkyl chain, dioctyl-L-Tar, presented the lowest selectivity ($\alpha_{n=8}$ = 1.94). The best liquid–liquid system studied, 46.6 wt% of H_2O + 46.7 wt% of DCE + 5.5 wt% of dipentyl-L-Tar + 1.2 wt% of boric acid, lead to a selectivity of 2.59. Although esters of tartaric acid presented better results, the CIL [BMIm][BSMB] also showed good potential for the *R/S*-PRP resolution, with a selectivity of 1.76 in the DCE-H_2O system. The most selective system, 46.6 wt% of H_2O + 46.7 wt% of DCE + 5.5 wt% of dipentyl-L-Tar + 1.2 wt% of boric acid, was evaluated in CPC, leading to a 75% purity for *R*-PRP.

Acknowledgments

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the

FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement. This work was also financially supported by the project POCI-01-0145-FEDER-030750 (PTDC/EQU-EPQ/30750/2017) - funded by FEDER, through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES. The NMR spectrometers are part of the National NMR Network (PTNMR) and are partially supported by Infrastructure Project Nº 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC). The authors thanks Mara G. Freire for allowing the use of the CPC equipment. Ana R. F. Carreira acknowledges FCT for the Ph.D. grant SFRH/BD/143612/2019.

References

[1] Chiral Technology Market Trends, Market Analysis, and Forecasts by Global Industry Analysts, Inc., (n.d.). https://www.strategyr.com/MarketResearch/market-report-infographic-chiral-technology-forecasts-global-industry-analysts-inc.asp (accessed February 24, 2020).

[2] A. Calcaterra, I. D'Acquarica, The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds, J. Pharm. Biomed. Anal. 147 (2018) 323–340.

[3] W. H. Brooks, W. C. Guida, K. G. Daniel, The Significance of Chirality in Drug Design and Development, Curr. Top. Med. Chem. 11 (2011) 760–770.

[4] S.W. Smith, Chiral toxicology: It's the same thing only different, Toxicol. Sci. 110 (2009) 4–30.

[5] I. Agranat, H. Caner, Intellectual property and chirality of drugs, Drug Discov. Today. 4 (1999) 313–321.

[6] M.M. Heravi, V. Zadsirjan, B. Masoumi, M. Heydari, Organometal-catalyzed asymmetric Friedel-Crafts reactions, J. Organomet. Chem. 879 (2019) 78–138.

[7] S. Konishi, Y. Ogura, H. Takikawa, H. Watanabe, Asymmetric synthesis of trans-p -menth-3-ene-1,2,8-triol, the monoterpene isolated from herbal plants, Biosci. Biotechnol. Biochem. 84 (2019) 1–6.

[8] O. Chantarasriwong, T.J. Dorwart, T.H. Morales, S.F. Maggio, A.L. Settle, A.T. Milcarek, M.L. Alpaugh, M.A. Theodoraki, E.A. Theodorakis, Chiral resolution of a caged xanthone and evaluation across a broad spectrum of breast cancer subtypes, Bioorg. Chem. 93 (2019).

[9] Y. Lin, J. Fan, L. Ruan, J. Bi, Y. Yan, T. Wang, H. Gao, X. Yao, K. Cheng, W. Zhang, Semi-preparative separation of dihydromyricetin enantiomers by supercritical fluid chromatography and determination of anti-inflammatory activities, J. Chromatogr. A. 1606 (2019).

[10] P.O. Carvalho, Q.B. Cass, S.A. Calafatti, F.J. Contesini, R. Bizaco, Review-Alternatives for the separation of drug enantiomers: Ibuprofen as a model compound, Brazilian J. Chem. Eng. 23 (2006) 291–300.

[11] W.F. Zheng, W. Zhang, C. Huang, P. Wu, H. Qian, L. Wang, Y.L. Guo, S. Ma, Tetrasubstituted allenes via the palladium-catalysed kinetic resolution of propargylic alcohols using a supporting ligand, Nat. Catal. 2 (2019) 997–1005.

[12] B.C. Calvo, A.J. Minnaard, Copper-Catalyzed Asymmetric 1,2-Addition of Grignard

Reagents to 3-Acyl 2 H -chromenes, Synlett. 28 (2017) 2624–2628.

[13] J.M. Hawkins, T.J.N. Watson, Asymmetric catalysis in the pharmaceutical industry, Angew. Chemie - Int. Ed. 43 (2004) 3224–3228.

[14] D. Martin, S. Kehrli, M. D'Augustin, H. Clavier, M. Mauduit, A. Alexakis, Copper-catalyzed asymmetric conjugate addition of Grignard reagents to trisubstituted enones. Construction of all-carbon quaternary chiral centers, J. Am. Chem. Soc. 128 (2006) 8416–8417.

[15] B. Zhu, M. Xue, B. Liu, Q. Li, X. Guo, Enantioselective separation of eight antihistamines with α1-acid glycoprotein-based chiral stationary phase by HPLC: Development and validation for the enantiomeric quality control, J. Pharm. Biomed. Anal. 176 (2019).

[16] S. Jermann, A. Alberti, M. Mazzotti, Three-column intermittent simulated moving bed chromatography: 2. Experimental implementation for the separation of Tröger's Base, J. Chromatogr. A. 1364 (2014) 107–116.

[17] J. Eijkel, Chip-based HPLC: The quest for the perfect column, Lab Chip. 7 (2007) 815–817.

[18] Y. Li, Z. Ding, J. Wang, J. Xu, W. Yu, A.K. Ray, A comparison between simulated moving bed and sequential simulated moving bed system based on multi-objective optimization, Chem. Eng. Sci. 219 (2020) 115562.

[19] J. Dingenen, Scaling-up of Preparative Chromatographic Enantiomer Separations, in: Prep. Enantioselective Chromatogr., John Wiley and Sons, (2007) 110–148.

[20] B. Schuur, B.J.V. Verkuijl, A.J. Minnaard, J.G. De Vries, H.J. Heeres, B.L. Feringa, Chiral separation by enantioselective liquid-liquid extraction, Org. Biomol. Chem. 9 (2011) 36–51.

[21] X.Y. Huang, D. Pei, J.F. Liu, D.L. Di, A review on chiral separation by counter-current chromatography: Development, applications and future outlook, J. Chromatogr. A. 1531 (2018) 1–12.

[22] P.Å. Albertsson, Partition of proteins in liquid polymer-polymer two-phase systems, Nature. 182 (1958) 709–711.

[23] Z. Li, Y. Pei, H. Wang, J. Fan, J. Wang, Ionic liquid-based aqueous two-phase systems and their applications in green separation processes, TrAC - Trends Anal. Chem. 29 (2010) 1336–1346.

[24] N.M. Maier, S. Schefzick, G.M. Lombardo, M. Feliz, K. Rissanen, W. Lindner, K.B.

Lipkowitz, Elucidation of the chiral recognition mechanism of cinchona alkaloid carbamate-type receptors for 3,5-dinitrobenzoyl amino acids, J. Am. Chem. Soc. 124 (2002) 8611–8629.

[25] M. Steensma, N.J.M. Kuipers, A.B. de Haan, G. Kwant, Modelling and experimental evaluation of reaction kinetics in reactive extraction for chiral separation of amines, amino acids and amino-alcohols, Chem. Eng. Sci. 62 (2007) 1395–1407.

[26] F.A. e Silva, M. Kholany, T.E. Sintra, M. Caban, P. Stepnowski, S.P.M. Ventura, J.A.P. Coutinho, Aqueous Biphasic Systems Using Chiral Ionic Liquids for the Enantioseparation of Mandelic Acid Enantiomers, Solvent Extr. Ion Exch. 36 (2018) 617–631.

[27] K. Tang, Y. Chen, K. Huang, J. Liu, Enantioselective resolution of chiral aromatic acids by biphasic recognition chiral extraction, Tetrahedron Asymmetry. 18 (2007) 2399–2408.

[28] X. Chen, J. Wang, F. Jiao, Efficient enantioseparation of phenylsuccinic acid enantiomers by aqueous two-phase system-based biphasic recognition chiral extraction: Phase behaviors and distribution experiments, Process Biochem. 50 (2015) 1468–1478.

[29] X. Cui, Q. Ding, R.N. Shan, C.H. He, K.J. Wu, Enantioseparation of flurbiprofen enantiomers using chiral ionic liquids by liquid-liquid extraction, Chirality. 31 (2019) 457–467.

[30] X. Chen, L. Liu, F. Jiao, Z. Wang, Extraction of phenylalanine enantiomers by aqueous two phase systems containing combinatorial chiral selector, Chinese J. Chem. 30 (2012) 965–969.

[31] N. Sunsandee, P. Rashatasakhon, P. Ramakul, U. Pancharoen, K. Nootong, N. Leepipatpiboon, Selective Enantioseparation of Racemic Amlodipine by Biphasic Recognition Chiral Separation System, Sep. Sci. Technol. 49 (2014) 1357–1365.

[32] X. Liu, Y. Ma, T. Cao, D. Tan, X. Wei, J. Yang, L. Yu, Enantioselective liquid-liquid extraction of amino acid enantiomers using (*S*)-MeO-BIPHEP-metal complexes as chiral extractants, Sep. Purif. Technol. 211 (2019) 189–197.

[33] K. Tang, Y. Chen, J. Liu, Resolution of Zopiclone enantiomers by biphasic recognition chiral extraction, Sep. Purif. Technol. 62 (2008) 681–686.

[34] Y. Wang, K. Tang, P. Zhang, J. Zhou, Y. Huang, P. Wen, G. Sun, Continuous Separation of Pantoprazole Enantiomers by Biphasic Recognition Chiral Extraction in Centrifugal Contactor Separators, Org. Process Res. Dev. 19 (2015) 1082–1087.

[35] K. Zawada, A. Plichta, D. Jańczewski, H. Hajmowicz, Z. Florjańczyk, M. Stępień, A. Sobiecka, L. Synoradzki, Esters of Tartaric Acid, A New Class of Potential "double Green" Plasticizers, ACS Sustain. Chem. Eng. 5 (2017) 5999–6007.

[36] H. Wu, S. Yao, G. Qian, T. Yao, H. Song, A resolution approach of racemic phenylalanine with aqueous two-phase systems of chiral tropine ionic liquids, J. Chromatogr. A. 1418 (2015) 150–157.

[37] F. Tang, Q. Zhang, D. Ren, Z. Nie, Q. Liu, S. Yao, Functional amino acid ionic liquids as solvent and selector in chiral extraction, J. Chromatogr. A. 1217 (2010) 4669–4674.

[38] S. Yu, S. Lindeman, C.D. Tran, Chiral ionic liquids: Synthesis, properties, and enantiomeric recognition, J. Org. Chem. 73 (2008) 2576–2591.

[39] Q. Ding, X. Cui, G.H. Xu, C.H. He, K.J. Wu, Quantum chemistry calculation aided design of chiral ionic liquid-based extraction system for amlodipine separation, AIChE J. 64 (2018) 4080–4088.

[40] A. Berthod, T. Maryutina, B. Spivakov, O. Shpigun, I.A. Sutherland, Countercurrent chromatography in analytical chemistry (IUPAC technical report), Pure Appl. Chem. 81 (2009) 355–387.

[41] M. Bojczuk, D. Żyżelewicz, P. Hodurek, Centrifugal partition chromatography – A review of recent applications and some classic references, J. Sep. Sci. 40 (2017) 1597–1609.

[42] S. Tong, Y.X. Guan, J. Yan, B. Zheng, L. Zhao, Enantiomeric separation of (*R*, *S*)-naproxen by recycling high speed counter-current chromatography with hydroxypropyl-β-cyclodextrin as chiral selector, J. Chromatogr. A. 1218 (2011) 5434–5440.

[43] C.R. Allen, P.L. Richard, A.J. Ward, L.G.A. van de Water, A.F. Masters, T. Maschmeyer, Facile synthesis of ionic liquids possessing chiral carboxylates, Tetrahedron Lett. 47 (2006) 7367–7370.

[44] L. Wang, X. Liu, Q. Lu, Y. Zou, Q. Liu, J. Yang, G. Yang, Enantioseparations of three amino alcohols using a di-n-butyl-l-tartrate- boric acid complex as the mobile phase additive by reversed-phase high performance liquid chromatography, Anal. Methods. 6 (2014) 4107–4114.

[45] J.H.P.M. Santos, M.R. Almeida, C.I.R. Martins, A.C.R.V. Dias, M.G. Freire, J.A.P. Coutinho, S.P.M. Ventura, Separation of phenolic compounds by centrifugal partition chromatography, Green Chem. 20 (2018) 1906–1916.

[46] S.A. Steenen, A.J. Van Wijk, G.J.M.G. Van Der Heijden, R. Van Westrhenen, J. De

Lange, A. De Jongh, Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis, J. Psychopharmacol. 30 (2016) 128–139.

[47] FDA, CDER, Inderal ® (propranolol hydrochloride) Tablets Rx only, n.d. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016418s080,016762s017, 017683s008lbl.pdf (accessed February 27, 2020).

[48] K. Stoschitzky, W. Lindner, W. Kiowski, Stereoselective vascular effects of the (*R*)- and (*S*)-enantiomers of propranolol and atenolol, J. Cardiovasc. Pharmacol. 25 (1995) 268–272.

[49] W. Xu, S. Wang, W. Wang, P. Zhang, K. Tang, Experiments and simulation on extraction of esmolol enantiomers from single stage to multistage, Sep. Purif. Technol. 203 (2018) 289–300.

[50] Y. Abe, T. Shoji, S. Fukui, M. Sasamoto, H. Nishizawa, Enantioseparation by dual-flow countercurrent extraction: Its application to the enantioseparation of (±)-propranolol, Chem. Pharm. Bull. 44 (1996) 1521–1524.

[51] Y. Abe, T. Shoji, M. Kobayashi, W. Qing, N. Asai, H. Nishizawa, Enantioselective Distribution of Amino-Alcohols in a Liquid-Liquid Two-Phase System Containing Dialkyl L-Tartrate and Boric Acid, Chem. Pharm. Bull. 43 (1995) 262–265.

[52] J. min Xing, F. fang Li, Chiral separation of mandelic acid by temperature-induced aqueous two-phase system, J. Chem. Technol. Biotechnol. 87 (2012) 346–350.

[53] W.J. Irwin, K.A. Belaid, Drug-delivery by ion-exchange: Part II: Physico-chemical properties of ester pro-drugs of propranolol, Drug Dev. Ind. Pharm. 13 (1987) 2033–2045.

[54] T. Arai, H. Kuroda, Distribution behavior of some drug enantiomers in an aqueous two-phase system using counter-current extraction with protein, 1991.

[55] Chemicalize - Instant Cheminformatics Solutions, (n.d.). https://chemicalize.com/app/calculation/C(CCl)Cl (accessed February 7, 2020).

[56] Chemicalize - Instant Cheminformatics Solutions, (n.d.). https://chemicalize.com/app/calculation/CCOC(=O)C (accessed February 7, 2020).

[57] T. Sedghamiz, F. Ghalami, E. Sedghamiz, M. Bahrami, Chiral recognition of propranolol enantiomers by chiral ionic liquid: A quantum chemical calculation analysis, Comput. Theor. Chem. 1140 (2018) 38–48.

[58] G. Absalan, Y. Alipour, Z. Rezaei, M. Akhond, Determination of enantiomer compositions of propranolol enantiomers by chiral ionic liquid as a chiral selector and

the UV-assisted spectrophotometric method, Anal. Methods. 4 (2012) 2283–2287.

[59] Z. Chen, W. Zhang, L. Wang, H. Fan, Q. Wan, X. Wu, X. Tang, J.Z. Tang, Enantioseparation of Racemic Flurbiprofen by Aqueous Two-Phase Extraction With Binary Chiral Selectors of L-dioctyl Tartrate and L-tryptophan, Chirality. 27 (2015) 650–657.

[60] K. Tang, L. Song, Y. Pan, X. Jiang, J. Miao, Enantioselective partitioning of racemic ibuprofen in a biphasic recognition chiral extraction system, Chinese J. Chem. 28 (2010) 119–124.

Supporting Information

Propranolol resolution using enantioselective biphasic systems

Ana R. F. Carreira[1], Ana M. Ferreira[1], Mafalda R. Almeida João A. P. Coutinho* and Tânia E. Sintra

CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

*Corresponding author

E-mail address: jcoutinho@ua.pt

[1]These authors contributed equally to this work.

Experimental

Synthesis

Di(tetrabutylammonium)-L-tartrate ($[N_{4444}]_2$[L-Tar])

$[N_{4444}]_2$[L-Tar] was obtained as a colorless viscous liquid, 98% yield. ^{1}H NMR (D_2O, 300 MHz, [ppm]): δ 0.95 (t, J_{HH} = 7.3 Hz, 24H, $N(CH_2)_3C\boldsymbol{H}_3$), 1.36 (sext, J_{HH} = 7.3 Hz, 16H, $N(CH_2)_2C\boldsymbol{H}_2CH_3$), 1.65 (dt, J_{HH} = 15.7, 7.9 Hz, 16H, $NCH_2C\boldsymbol{H}_2CH_2CH_3$), 3.08 – 3.28 (m, 16H, $NC\boldsymbol{H}_2(CH_2)_2CH_3$), 4.30 (s, 2H, $C\boldsymbol{H}OHCO_2$). ^{13}C NMR (D_2O, 75.47 MHz, [ppm]): δ 12.80, 19.09, 23.06, 58.07, 73.75, 178.19.

1-butyl-3-methylimidazolium (T-4)-bis[(*αS*)-*α*-(hydroxy-O)benzeneacetato-*κ*O] borate ([BMIm][BSMB])

[BMIm][BSMB] was obtained as a colorless viscous liquid, 100% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, [ppm]): δ 0.82 (t, J_{HH} = 7.3 Hz, 3H, $-(CH_2)_3C\boldsymbol{H}_3$), 1.05 – 1.18 (m, 2H, $-C\boldsymbol{H}_2CH_3$), 1.50 – 1.60 (m, 2H, $-C\boldsymbol{H}_2CH_2CH_3$), 3.47 (s, 3H, $C\boldsymbol{H}_3N$-), 3.78 (t, J_{HH} = 7.4 Hz, 2H, $-C\boldsymbol{H}_2N$-), 5.27 – 5.32 (m, 2H, $-C\boldsymbol{H}C_6H_5$), 6.92 – 6.95 (m, 2H, $NC\boldsymbol{H}C\boldsymbol{H}N$-), 7.17 – 7.38 (m, 6H, $-C_6\boldsymbol{H}_5$), 7.48 – 7.66 (m, 4H, $-C_6\boldsymbol{H}_5$), 8.57 (s, 1H, $-NC\boldsymbol{H}N$-). ^{13}C NMR (D_2O, 75.47 MHz, [ppm]): δ 13.26, 19.22, 31.66, 35.89, 49.55, 121.95, 123.39, 126.13, 128.20, 135.66, 139.73, 178.12.

Dibutyl-L-tartrate (dibutyl-L-Tar)

Dibutyl-L-Tar was obtained as a pale yellow liquid, 53% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, [ppm]): δ 0.91 (t, J_{HH} = 7.4 Hz, 6H, $-C\boldsymbol{H}_3$), 1.25 – 1.49 (m, 4H, $CH_3-C\boldsymbol{H}_2$-), 1.57 – 1.75 (m, 4H, $CH_3CH_2C\boldsymbol{H}_2$-), 4.23 (dt, J_{HH} = 6.6, 1.4 Hz, 4H, $-COOC\boldsymbol{H}_2$-), 4.51 (s, 2H, $-C\boldsymbol{H}OH$). ^{13}C NMR ($CDCl_3$, 75.47 MHz, [ppm]): δ 13.57, 18.93, 30.46, 66.10, 72.17, 76.69, 171.63.

Dipentyl-L-tartrate (dipentyl-L-Tar)

Dipentyl-L-Tar was obtained as a colorless liquid, 59% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, [ppm]): δ 0.54 – 0.80 (m, 6H, $C\boldsymbol{H}_3$-), 1.25 – 1.49 (dp, J_{HH} = 7.1, 4.5, 3.5 Hz, 4H, $CH_3C\boldsymbol{H}_2C\boldsymbol{H}_2$-), 1.31 – 1.57 (m, 4H, $CH_3(CH_2)_2C\boldsymbol{H}_2$-), 1.31 (br s, 2H, O*H*-), 4.01 (t, J_{HH} = 6.7 Hz, 4H, $-O-C\boldsymbol{H}_2$-), 4.30 (s, 2H, $-C\boldsymbol{H}OH$). ^{13}C NMR ($CDCl_3$, 75.47 MHz, [ppm]): δ 13.90, 22.23, 27.83, 28.17, 66.49, 72.12, 171.65.

Dihexyl-L-tartrate (dihexyl-L-Tar)

Dihexyl-L-Tar was obtained as a colorless liquid, 61% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, [ppm]): δ 0.84 – 0.95 (m, 6H, CH_3-), 1.25 – 1.41 (m, 12H, $CH_3CH_2CH_2CH_2$-), 1.68 (p, J_{HH} = 6.7 Hz, 4H, $CH_3(CH_2)_3CH_2$-), 3.01 (br s, 2H, OH-), 4.25 (t, J_{HH} = 6.4 Hz, 4H, -OCH_2-), 4.53 (s, 2H, -CHOH). ^{13}C NMR ($CDCl_3$, 75.47 MHz, [ppm]): δ 13.95, 22.47, 25.37, 28.43, 31.32, 66.50, 72.14, 171.65.

Dioctyl-L-tartrate (dioctyl-L-Tar)

Dioctyl-L-Tar was obtained as pale yellow solid, 76% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, [ppm]): δ 0.80 – 1.01 (m, 6H, CH_3-), 1.18 – 1.43 (m, 20H, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.71 (p, J_{HH} = 6.8 Hz, 4H, $CH_3(CH_2)_5CH_2$), 4.27 (t, J_{HH} = 6.6 Hz, 4H, -O-CH_2-), 4.55 (s, 2H, -CHOH). ^{13}C NMR ($CDCl_3$, 75.47 MHz, [ppm]): δ 14.09, 22.63, 25.72, 28.49, 29.13, 37.76, 66.63, 72.04, 171.67.

Results

Table S1. Composition of all the prepared mixture points. Notice that the ratio between adjuvant:*R/S*-PRP was evaluated.

ADJUVANT	PHASE FORMERS	WEIGHT FRACTION COMPOSITION / WT%								
		Adjuvant	**H_2O**	**NaPA**	**PEG**	**EA**	**DCE**	***R/S*-PRP***	**Boric acid**	**Dex**
[BMIM][BSMB]	PEG-NaPA	2.1	64.0	21.4	6.4	-	-	6.1	-	-
[BMIM][BSMB]	PEG-Dex	2.1	73.7	-	7.5	-	-	6.1	-	10.7
[BMIM][BSMB]	DCE-H_2O	2.1	41.9	-	-	-	50.0	6.1	-	-
[BMIM][BSMB]	EA-H_2O	2.1	41.9	-	-	50.0	-	6.1	-	-
[BMIM][BSMB]	PEG-NaPA	2.1	42.9	21.4	6.4	-	-	27.1	-	-
[BMIM][BSMB]	PEG-Dex	2.1	52.6	-	7.5	-	-	27.1	-	10.7
[BMIM][BSMB]	DCE-H_2O	2.1	20.8	-	-	-	50.0	27.1	-	-
[BMIM][BSMB]	EA-H_2O	0.4	52.3	-	-	42.2	-	5.1	-	-
DIBUTYL-L-TAR	PEG-NaPA	5.4	38.3	21.5	6.4	-	-	27.2	1.3	-
DIBUTYL-L-TAR	PEG-Dex	4.9	40.0	-	6.9	-	-	25.0	1.2	22.0
DIBUTYL-L-TAR	DCE-H_2O	5.0	21.4	-	-	-	46.9	25.5	1.2	-

DIBUTYL-L-TAR	EA-H_2O	5.0	21.4	-	-	46.9	-	25.5	1.2	-
DIPENTYL-L-TAR	PEG-NaPA	5.0	42.6	20.0	6.0	-	-	25.3	1.1	-
DIPENTYL-L-TAR	PEG-Dex	5.0	51.6	-	7.0	-	-	25.3	1.1	10.0
DIPENTYL-L-TAR	DCE-H_2O	5.0	21.5	-	-	-	46.9	25.5	1.1	-
DIPENTYL-L-TAR	EA-H_2O	5.0	21.5	-	-	46.9	-	25.5	1.1	-
DIHEXYL-L-TAR	DCE-H_2O	6.1	19.9	-	-	-	47.2	25.6	1.2	-
DIHEXYL-L-TAR	EA-H_2O	6.1	19.9	-	-	47.2	-	25.6	1.2	-
DIOCTYL-L-TAR	DCE-H_2O	1.7	21.0	-	-	-	49.9	27.1	0.3	-
DIOCTYL-L-TAR	DCE-H_2O	7.1	19.7	-	-	-	46.7	25.3	1.2	-
DIOCTYL-L-TAR	EA-H_2O	7.1	19.7	-	-	46.7	-	25.3	1.2	-
DIOCTYL-L-TAR	DCE-H_2O	3.4	41.2	-	-	-	48.9	5.9	0.6	-
$[N_{4444}]_2$[L-TAR]	PEG-NaPA	12.1	35.4	20.0	6.0	-	-	25.3	1.2	-
$[N_{4444}]_2$[L-TAR]	PEG-Dex	12.1	44.2	-	7.0	-	-	25.4	1.2	10.0
$[N_{4444}]_2$[L-TAR]	DCE-H_2O	12.1	14.5	-	-	-	46.8	25.4	1.2	-

*Of an aqueous solution of *R/S*-PRP with a concentration of 5 $mg \cdot mL^{-1}$

Table S2. Assessed pH for the prepared mixture points. The values were collected resorting to a pH indicator paper.

ADJUVANT	PHASE FORMERS	PH
[BMIM][BSMB] (× 45)	PEG-NaPA	8
[BMIM][BSMB] (× 45)	PEG-Dex	8
[BMIM][BSMB] (× 45)	DCE-H_2O	5
[BMIM][BSMB] (× 45)	EA-H_2O	5
[BMIM][BSMB] (× 10)	PEG-NaPA	7
[BMIM][BSMB] (× 10)	PEG-Dex	6
[BMIM][BSMB] (× 10)	DCE-H_2O	5
[BMIM][BSMB] (× 10)	EA-H_2O	5
DIBUTYL-L-TAR (× 45)	PEG-NaPA	5
DIBUTYL-L-TAR (× 45)	PEG-Dex	7
DIBUTYL-L-TAR (× 45)	DCE-H_2O	5
DIBUTYL-L-TAR (× 45)	EA-H_2O	5
DIPENTYL-L-TAR (× 45)	PEG-NaPA	5
DIPENTYL-L-TAR (× 45)	PEG-Dex	7
DIPENTYL-L-TAR (× 45)	DCE-H_2O	5
DIPENTYL-L-TAR (× 45)	EA-H_2O	5
DIHEXYL-L-TAR (× 45)	DCE-H_2O	5
DIHEXYL-L-TAR (× 45)	EA-H_2O	6
DIOCTYL-L-TAR (× 45)	EA-H_2O	5
DIOCTYL-L-TAR (× 45)	DCE-H_2O	5
$[N_{4444}]_2$[L-TAR] (× 45)	PEG-NaPA	7
$[N_{4444}]_2$[L-TAR] (× 45)	PEG-Dex	7
$[N_{4444}]_2$[L-TAR] (× 45)	DCE-H_2O	7
$[N_{4444}]_2$[L-TAR] (× 45)	EA-H_2O	7

Table S3. Extraction efficiencies ($EE_{R\text{-}PRP}$ and $EE_{S\text{-}PRP}$) and selectivity (α), as well as the respective standard deviations, for each system. All the systems had boric acid as adjuvants, except for the ones containing [BMIm][BSMB].

System	Adjuvant	$EE_{R\text{-}PRP}$ (%)	σ	$EE_{S\text{-}PRP}$ (%)	σ	α	σ
PEG-Dex	[BMIm][BSMB] (× 10)	85.75	2.26	86.54	2.43	0.93	0.02
PEG-NaPA	[BMIm][BSMB] (× 10)	60.59	0.35	61.28	0.00	0.97	0.01
DCE-H_2O	[BMIm][BSMB] (× 10)	96.63	0.17	97.25	0.25	1.24	0.05
EA-H_2O	[BMIm][BSMB] (× 10)	42.43	0.42	25.76	1.17	0.47	0.02
PEG-Dex	[BMIm][BSMB] (× 45)	85.34	0.81	85.00	0.28	1.03	0.04
PEG-NaPA	[BMIm][BSMB] (× 45)	92.40	0.51	92.29	0.31	1.02	0.03
DCE-H_2O	[BMIm][BSMB] (× 45)	88.16	0.17	75.58	0.04	1.76	0.10
EA-H2O	[BMIm][BSMB] (× 45)	3.10	0.28	5.66	0.16	0.53	0.00
PEG-Dex	$[N_{4444}]_2$[L-Tar] (× 45)	86.53	0.78	86.52	0.69	1.00	0.01
PEG-NaPA	$[N_{4444}]_2$[L-Tar] (× 45)	75.44	1.30	75.47	0.95	1.00	0.02
DCE-H_2O	$[N_{4444}]_2$[L-Tar] (× 45)	57.07	0.42	57.24	1.09	0.99	0.03
EA-H_2O	$[N_{4444}]_2$[L-Tar] (× 45)	23.95	0.19	24.69	0.28	0.97	0.03
PEG-NaPA	dibutyl-L-Tar (× 45)	39.90	2.98	39.55	3.33	0.91	0.04

PEG-Dex	dibutyl-L-Tar (× 45)	53.71	2.58	55.95	3.62	1.02	0.02
DCE-H_2O	dibutyl-L-Tar (× 10)	48.60	0.50	30.04	0.85	2.18	0.01
DCE-H_2O	dibutyl-L-Tar (× 45)	60.95	1.44	38.17	3.28	2.54	0.13
DCE-H_2O	dibutyl-L-Tar (× 91)	39.61	1.04	23.23	1.01	2.18	0.00
EA-H_2O	dibutyl-L-Tar (× 45)	60.95	3.67	38.17	3.37	2.54	0.03
PEG-NaPA	dipentyl-L-Tar (× 45)	87.26	0.17	87.41	0.20	1.02	0.02
PEG-Dex	dipentyl-L-Tar (× 45)	40.67	1.17	40.31	1.61	0.99	0.00
DCE-H_2O	dipentyl-L-Tar (× 45)	71.04	1.13	48.71	1.88	2.59	0.05
EA-H_2O	dipentyl-L-Tar (× 45)	3.32	0.27	4.13	0.34	0.80	0.00
DCE-H_2O	dihexyl-L-Tar (× 45)	84.78	0.20	68.94	0.17	2.51	0.06
EA-H_2O	dihexyl-L-Tar (× 45)	4.72	2.88	3.95	2.10	1.14	0.14
DCE-H_2O	dioctyl-L-Tar (× 45)	74.63	0.68	60.27	1.29	1.94	0.03
EA-H_2O	dioctyl-L-Tar (× 45)	15.16	0.39	15.84	0.40	0.95	0.00

Table S4. Geometric parameters of the used organic solvents: DCE and EA [1,2]

	Van der Waals Volume (Å^3)	Van der Waals Surface Area (Å^2)	Solvent Accessible Area (Å^2)	Topological Polar Surface Area (Å^2)
DCE	73.3	121.95	257.92	0
EA	903	166.68	287.33	26.3

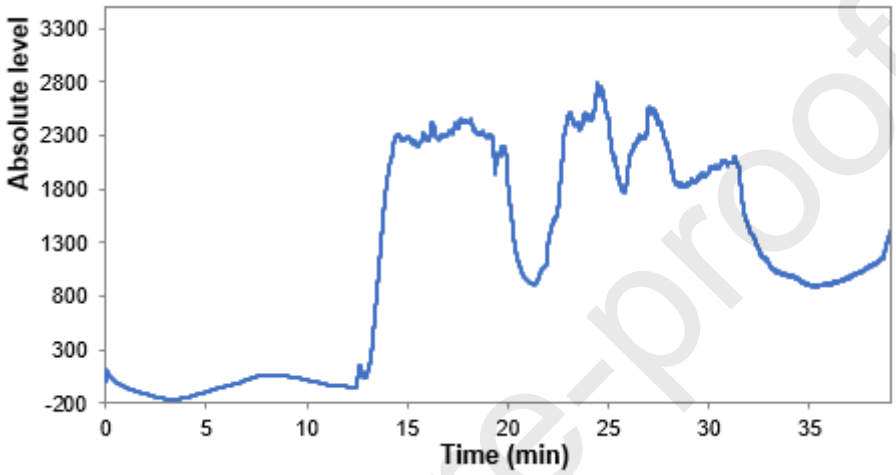


Figure S1. CPC chromatogram of the DCE-H_2O system containing dipentyl-L-Tar as an adjuvant. The used CPC conditions were: rotation speed 1300 rpm and flow rate of 1.5 mL·min^{-1}.

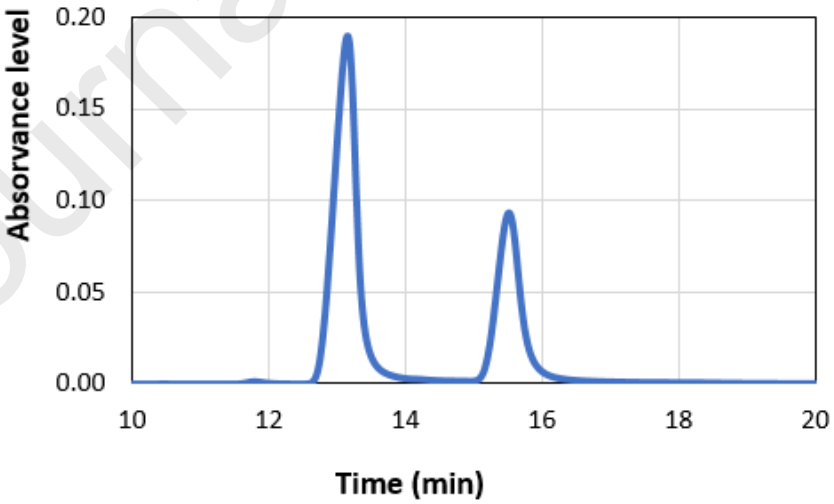


Figure S2. HPLC chromatogram of the DCE-H_2O system containing dipentyl-L-Tar as an adjuvant, fractions 13–19, affording a 75% purity of *R*-PRP recovered from the CPC under the conditions: rotation speed 1300 rpm and flow rate of 1.5 mL·min^{-1}.

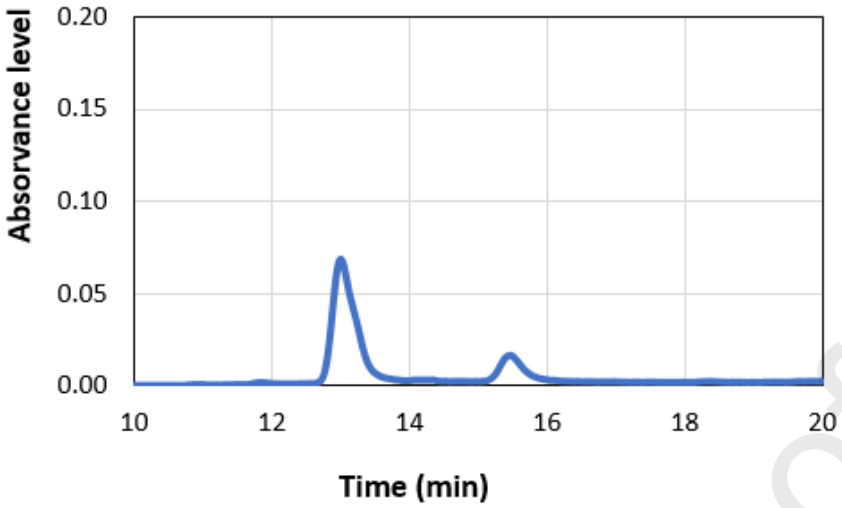


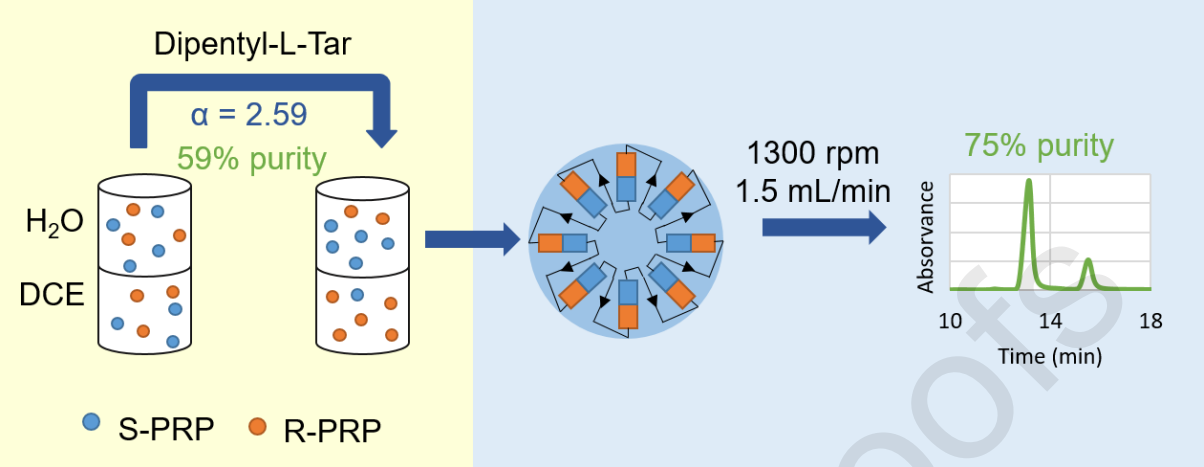
Figure S3. HPLC chromatogram of the DCE-H_2O system containing dipentyl-L-Tar as an adjuvant, isolated first fraction, affording a 82% purity of *R*-PRP recovered from the CPC under the conditions: rotation speed 1300 rpm and flow rate of 1.5 mL·min^{-1}.

References

[1] Chemicalize - Instant Cheminformatics Solutions, https://chemicalize.com/app/calculation/C(CCl)Cl (accessed February 7, 2020).

[2] Chemicalize - Instant Cheminformatics Solutions, https://chemicalize.com/app/calculation/CCOC(=O)C (accessed February 7, 2020).

Graphical abstract



Highlights

- Biphasic systems using chiral ionic liquids and esters of tartaric acid as chiral selectors were here proposed as enantioseparation platforms for chiral drugs.
- Two types of biphasic systems were evaluated, the aqueous biphasic systems and conventional organic-water systems.
- The organic-water systems and the esters of tartaric acid derivatives showed to be more efficient in the chiral resolution of the *R*/*S*-propranolol.
- Centrifugal partition chromatography (CPC) proved to be a valuable methodology to achieve an efficient scale-up of the enantioseparation developed.