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Separation of flurbiprofen enantiomers by biphasic recognition chiral extraction

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ABSTRACT

Based on our previous work, this paper reports enantioselective partitioning of flurbiprofen enantiomers in a biphasic recognition chiral extraction (BRCE) system combining a hydrophobic L-tartrate in organic phase and hydrophilic β-cyclodextrin derivative in aqueous phase which preferentially recognize *R*-enantiomer and *S*-enantiomer, respectively. The studies performed involve an enantioselective extraction in a biphasic system, where flurbiprofen enantiomers form four complexes with β-cyclodextrin derivative and L-tartrate, respectively. In these biphasic resolutions, the concentrations of the extractants and flurbiprofen enantiomers, the types of organic solvents and extractants, pH and temperature all exert a considerable influence on the biphasic recognition process. The maximum enantioselectivity for flurbiprofen enantiomers is 1.24 at the pH of 2.5, 5 °C, the flurbiprofen initial concentration of 0.0001 mol/L and the ratio of 2:1 of [L-*iso*-butyl tartrate] to [TM-β-CD]. By changing the monophasic recognition chiral extraction (MRCE) system into BRCE system, the enantioselectivities are greatly improved. Biphasic recognition chiral extraction is of strong chiral separation ability, and can be hopeful for separations of various enantiomers at a large-scale.

1. Introduction

The difference in the pharmaceutical properties of the enantiomers of a chiral drug is by no means a new notion. However, racemic compounds are still frequently marketed for medical application, assuming that the unwanted isomer is only a "stereo chemical ballast", devoid of any biological activity, accompanying the isomer in which the biological activity resides [1,2]. Last century the thalidomide incident dramatically drew attention to the consequences of chirality on pharmaceutical activity and the need to use enantiomerically pure chiral compounds for pharmaceutical purpose [3]. Therefore, the demand for single-isomer chiral drugs is now growing rapidly and the methods for their production are being actively investigated. However, since the enantiomers exhibit similarities in terms of physical and chemical properties, separation of enantiomers is not an easy work.

At present, the principle methods to obtain pure enantiomers are asymmetric synthesis and resolution of racemates. In spite of the advances in asymmetric synthesis of pure enantiomers [4–7], resolution of racemates is still the main method for the production of pure enantiomers in industry by crystallization [8], chromatographic techniques [9], etc. These methods accelerate researches about chiral compounds, but there still exist some drawbacks such as low versatility and high cost [10]. So, there is a definite need for new more effective chiral separation methods. Liquid–liquid extraction meets this demand because of being cheaper and easier to scale up to commercial scale [11].

As a potential large-scale production technique, a lot of researchers have been attracted to make great efforts on chiral solvent extraction in recent years [12–18]. Enantioselectivity (α) is the most important parameter for chiral extraction. For example, for a 99% pure product ($R/S = 100$) about 190 NTU (number of transfer units) are required for an enantioselectivity of 1.05, a number decreasing to approximately 30 when α increases to a value of 1.20 [19]. Enantioselectivity values are considered low when they are less than 1.10 [19]. However, the enantioselectivities for chiral liquid–liquid extraction are somewhat low, and a large number of transfer units are required in chiral solvent extraction process. To look for new extraction techniques with high enantioselectivity will speed up the application of chiral solvent extraction, and realize large-scale production with low energy cost. More recently, the chiral ligand-exchange concept has been applied to liquid–liquid extraction technology and obtained high enantioselectivities holding advantages over chiral ligand-exchange chromatography for large-scale applications [15]. Tartaric acid derivatives and cyclodextrins are normal selectors for separation of enantiomers. Cyclodextrins have been used for chiral recognition in liquid system [20], and used for extraction of toluene, *o*-xylene from heptane and benzyl alcohol from toluene [21]. We are trying to improve the enantioselectivities towards enantiomers by utilizing the separation abilities of both hydrophobic tartaric acid derivatives in organic phase and hydrophilic cyclodextrin deriva-

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Nomenclature

α	operational enantioselectivity
α_{int}	intrinsic enantioselectivity
A_R^-	anion of *R*-flurbiprofen
A_S^-	anion of *S*-flurbiprofen
BRCE	biphasic recognition chiral extraction
β-CD	β-cyclodextrin
C	concentration of enantiomer (mmol/L)
[*C*]	concentration of selector C (mmol/L)
D	selector D
$-\Delta(\Delta G)$	difference in the Gibbs formation energies (kJ mol^{-1})
HA	flurbiprofen
HA_R	*R*-flurbiprofen
HA_S	*S*-flurbiprofen
HA_R–β-CD	complex of *R*-enantiomer and β-CD
HA_S–β-CD	complex of *S*-enantiomer and β-CD
HA_R–L	complex of *R*-enantiomer and selector L
HA_S–L	complex of *S*-enantiomer and selector L
HE-β-CD	hydroxyethyl-β-cyclodextrin
HP-β-CD	hydroxypropyl-β-cyclodextrin
k_R	distribution coefficient (*R*-enantiomer), org/aq concentration
k_S	distribution coefficient (*S*-enantiomer), org/aq concentration
L	selector L
Me-β-CD	methyl-β-cyclodextrin
MRCE	monophasic recognition chiral extraction
R	*R*-enantiomer
R–L	complex of *R*-enantiomer and selector L
S	*S*-enantiomer
S–L	complex of *S*-enantiomer and selector L
TM-β-CD	trimethyl-β-cyclodextrin

tives in aqueous phase which is named biphasic recognition chiral extraction (BRCE). Enantioselectivities towards some aromatic acid enantiomers have been improved greatly by BRCE in our recent work [22–24].

This work presents the results of separation of flurbiprofen (HA) enantiomers by biphasic recognition chiral extraction, which is commonly used as non-steroidal anti-inflammatory drug (NSAID) whose activity resides in *S*-enantiomer and *R*-enantiomer is used in treatment of Alzheimer's disease (Fig. 1) [25]. Each of flurbiprofen enantiomers has one carboxylic group and two aromatic groups. One dissociation equilibria for each enantiomer exists in aqueous solutions where HA exists in two states of neutral molecule and anion (Fig. 2). In a biphasic recognition chiral extraction system, flurbiprofen enantiomers form four complexes with β-cyclodextrin derivative and (D)- or (L)-tartaric acid ester, respectively (Fig. 2).

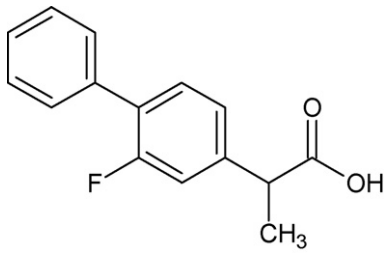

Fig. 1. Chemical structure of flurbiprofen.

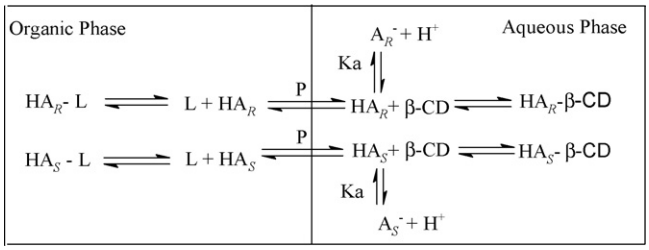

Fig. 2. Diagram of the resolution of enantiomers by biphasic recognition chiral extraction.

The monophasic recognition chiral extraction is carried out by the formation of two diastereomeric complexes between chiral selectors and (*R*) or (*S*)-enantiomers. The difference in free energy between the two diastereomeric complexes ($-\Delta(\Delta G)$) is the driving forces for separation of enantiomers which can be calculated by the following formula:

$$-\Delta(\Delta G)_L - \Delta G_{S-L} - (-\Delta G_{R-L}) = RT \ln \alpha_{int}, \quad \text{assuming} - \Delta(\Delta G)_L > 0 \tag{1}$$

In BRCE system for the separation of HA enantiomers, as hydrophilic β-CD derivative in aqueous phase preferentially recognizes *S*-HA, hydrophobic (L)-tartaric acid ester is added to organic phase as the chiral selector which preferentially recognizes *R*-HA (in Fig. 2).

Thus, the driving forces for separation of HA enantiomers in BRCE system are given by:

$$-\Delta(\Delta G)_{BRCE} = -\Delta(\Delta G)_L + (-\Delta(\Delta G)_{\beta\text{-CD}}) = RT \ln \alpha_{int} \tag{2}$$

where

$$-\Delta(\Delta G)_{\beta\text{-CD}} = -\Delta G_{R-\beta\text{-CD}} - (-\Delta G_{S-\beta\text{-CD}})$$

As $-\Delta(\Delta G)_L$ and $-\Delta(\Delta G)_{\beta\text{-CD}}$ are all over 0, the driving force $-\Delta(\Delta G)$ for separation of HA enantiomers is larger in BRCE system than that in MRCE system. As a result, α-values for BRCE are improved greatly. Therefore, in theory, it can be assumed that BRCE is of a stronger separation ability than MRCE.

According to the possible mechanism in BRCE for HA enantiomers, the types of organic solvents and extractants, the concentrations of the extractants and HA enantiomers, pH and temperature could affect the extraction efficiency. The factors affecting the extraction efficiency were investigated.

2. Materials and methods

2.1. Materials

Flurbiprofen (HA, racemate, purity ≥98%) was purchased from J&K Co. Ltd. (Beijing, China). Hydrophilic extractants, hydroxypropyl-β-cyclodextrin (HP-β-CD), hydroxyethyl-β-cyclodextrin (HE-β-CD), methyl-β-cyclodextrin (Me-β-CD) and trimethyl-β–cyclodextrin (TM-β-CD) were all obtained from Shandong Xinda Fine Chemical Co. Ltd. (Shandong, China). D- and L-tartaric acids with a purity of ≥99.85% were bought from Xinpu & Co. Inc. (Shanghai, China). Hydrophobic extractants, D- and L-tartaric acid derivatives, were synthesized as described in the literature [26]. 1,2-Dichloroethane was purchased from Shanpu & Co. Inc. (Shanghai, China). Solvent for chromatography was of HPLC grade. All other chemicals were of analytical-reagent grade.

Table 1
Screening of organic solvents.

Organic solvent	k_R	k_S	α
n-Octanol	29.98	28.38	1.06
n-Heptane	0.01	0.01	1.09
1,2-Dichloroethane	4.27	3.69	1.16
Methylene chloride	4.94	4.30	1.15
Methenyl chloride	10.57	9.15	1.16

Aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, pH = 2.5, and temperature 5 °C.

2.2. Analytical method

The quantification of HA enantiomers in aqueous phase was performed by HPLC using a UV detector (Merck, Hitachi, Japan) at the UV wavelength of 254 nm. The standard curve was used to quantify the enantiomers. The column was CHIRALCEL OJ-RH (150 mm × 4.6 mm i.d., 5 μm) (Hanbon Science & Technology Co. Ltd., China). The mobile phase was 0.5 mol/L sodium perchlorate buffer solution (pH 2.0): acetonitrile (65:35, v/v) at a flow of 0.5 mL/min. The pH of the aqueous phase was measured with a pH electrode and a pH meter (Orion, model 720A, USA).

2.3. Extraction experiments

HP-β-CD, HE-β-CD, Me-β-CD and TM-β-CD were used as the extractants in aqueous phase. Aqueous phases were prepared by dissolving β-CD derivative (HP-β-CD, HE-β-CD, Me-β-CD or TM-β-CD) and HA enantiomers in 0.1 mol/L phosphate salt buffer solution. (D)- and (L)-tartaric acid derivatives (*n*-butyl tartrate, *iso*-butyl tartrate, *n*-hexyl tartrate and *iso*-pentyl tartrate) were used as the extractants in organic phases and dissolved in organic solvents to prepare organic phases. The extraction experiments were performed in 25 ml glass-stoppered tube. Equal volumes (each 2 ml) of the aqueous and the organic phase were placed together, and shaken sufficiently (5 h) before being kept in a water bath at a fixed temperature to reach equilibrium. After phase separation, the concentrations of HA enantiomers in the aqueous phase were analyzed by HPLC. Each experiment was duplicated under identical conditions. Since the change in volume is very small, it can be seen as negligible. The concentrations of HA enantiomers in organic phase were calculated by subtractive method.

The distribution coefficients and enantioselectivity are important parameters to estimate the BRCE system, which can be calculated by the following formulas:

$$k_S = \frac{C_{O,S}}{C_{W,S}} \quad (3)$$

$$k_R = \frac{C_{O,R}}{C_{W,R}} \quad (4)$$

$$a = \frac{k_R}{k_S} \quad (5)$$

among which $C_{O,S}$ and $C_{W,S}$ represent concentration of *S*-flurbiprofen in organic phase and aqueous phase, respectively; $C_{O,R}$ and $C_{W,R}$ represent the concentration of *R*-flurbiprofen in organic phase and aqueous phase, respectively.

Table 2
Screening of β-CD derivatives.

β-CD derivatives	k_R	k_S	α
Me-β-CD	4.77	4.55	1.05
HE-β-CD	5.71	5.06	1.13
HP-β-CD	5.03	4.47	1.13
TM-β-CD	4.27	3.69	1.16

Aqueous phase: [Me-β-CD] = 0.1 mol/L, [HE-β-CD] = 0.1 mol/L, [HP-β-CD] = 0.1 mol/L, [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, pH = 2.5, and temperature 5 °C.

3. Result and discussion

3.1. Screening of organic solvents

The influence of organic solvents on distribution behavior was investigated in various MRCE systems containing 0.1 mol/L TM-β-CD in aqueous phase and no extractant in organic solvents (Table 1). When *n*-octanol and methenylchloride are used as solvents, high distribution coefficients are obtained but low enantioselectivities are found. When *n*-heptane is used, TM-β-CD shows the enantioselectivity towards HA enantiomers but with small distribution coefficients. Enantioselectivity and distribution coefficients for HA enantiomers are relatively higher with 1,2-dichloroethane. With thorough consideration of distribution coefficients and enantioselectivities, 1,2-dichloroethane is a suitable solvent for extraction of HA enantiomers.

3.2. Screening of β-CD derivatives

Whether and to what extent a complex is formed, can be predicted on the basis of size, shape and polarity of the guest molecule and various interactions involving Van der Waals, dispersive forces, dipole–dipole interactions, electrostatic forces and hydrogen bonding [27]. The size of the guest determines whether it fits into the cavity, shape and polarity influence the possible stabilizing effects by interactions within the cavity or with side groups on the cavity rim [27]. The size of the guest of HA enantiomers fits into the cavity of β-CD derivatives, so β-CD derivatives can form complexes with HA enantiomers. But to what extent a complex is formed depends on the polarity of β-CD derivative. Therefore, four types of β-CD derivatives may show different enantioselectivities towards HA enantiomers.

Enantioselectivities and distribution coefficients for HA enantiomers were investigated in several MRCE systems containing different β-CD derivatives (Me-β-CD or HE-β-CD or HP-β-CD or TM-β-CD) in aqueous phase and without tartaric acid derivative in 1,2-dichloroethane (Table 2).

Table 2 shows that when Me-β-CD, HE-β-CD and HP-β-CD are used, relatively higher distribution coefficients are obtained but with low enantioselectivity. When TM-β-CD is used, relatively higher enantioselectivity is obtained with good distribution coefficients. It can also be found from Table 2 that k_R are always larger than k_S, which indicates that four β-CDs preferentially recognize *S*-enantiomer. Among the four β-CD derivatives, TM-β-CD has the highest enantioselectivity and is chosen as the suitable chiral extractant in aqueous phase.

3.3. Screening of tartaric acid derivatives

Distribution coefficients and enantioselectivities for HA enantiomers were examined in different chiral extraction systems containing 0.1 mol/L TM-β-CD in aqueous phase and 0.2 mol/L tartaric acid derivative in organic phase (Table 3).

It is observed from Table 3, that, in the biphasic recognition chiral extraction system, enantioselectivities towards HA enantiomers are improved by adding L-tartaric acid derivative in organic phase, but decrease by adding D-tartaric acid derivatives, which indicates that L-tartaric acid derivatives have stronger recognition abilities for *R*-HA than for *S*-HA, and D-tartaric acid derivatives have reversed recognition abilities for them. Among tartaric acid derivatives tested, L-*iso*-butyl tartrate is proved to be the best stereoselective additive. It is concluded that, in the biphasic recognition chiral extraction system for separation of HA enantiomers,

Table 3
Screening of tartaric acid derivatives.

Tartaric acid derivatives		k_R	k_S	α
n-Butyl tartrate	L	12.77	10.86	1.18
	D	10.96	9.56	1.15
iso-Butyl tartrate	L	11.35	9.19	1.24
	D	10.11	8.79	1.15
n-Hexyl tartrate	L	14.13	12.17	1.16
	D	15.24	13.68	1.11
iso-Pentyl tartrate	L	13.32	11.50	1.16
	D	14.19	13.76	1.03

Organic phase: [tartaric acid derivative] = 0.2 mol/L, aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, pH = 2.5, and temperature 5 °C.

L-*iso*-butyl tartrate and TM-β-CD should be chosen as chiral selectors in the organic phase and the aqueous phase, respectively. By changing the monophasic recognition chiral extraction (MRCE) system into BRCE system, the enantioselectivity has been increased to 1.24. In general, in the MRCE systems, the enantioselectivities with tartaric acid derivatives as chiral extractants are less than 1.1 [19].

3.4. Influence of TM-β-CD concentration

TM-β-CD and HA enantiomers can form two diastereomeric complexes with different stabilities, which not only enhances the solubility of the enantiomers in buffer solution, but also improves the enantioselectivities for HA. Therefore, the concentration of TM-β-CD has great influence on distribution coefficients and enantioselectivities. The influence of TM-β-CD concentration on distribution coefficients and enantioselectivities was investigated in Fig. 3. From Fig. 3, the following significant conclusions can be concluded: (1) the distribution coefficients remarkably decrease with the increase of TM-β-CD concentration. (2) The enantioselectivities all increase remarkably before the concentration of TM-β-CD is up to 0.1 mol/L. It is also observed that the distribution coefficients and enantioselectivities continuously decrease with a further increase in the concentration of TM-β-CD. (3) Enantioselectivity reaches maximum at the ratio of 2:1 of [L-*iso*-butyl tartrate] to [TM-β-CD]. These phenomena can be explained by the fact that TM-β-CD can form inclusion complexes with HA enantiomers, and the inclusion ability of TM-β-CD with *S*-HA is stronger than with *R*-HA.

3.5. Influence of L-iso-butyl tartrate concentration

To investigate the effect of L-*iso*-butyl tartrate concentration on distribution behavior of HA enantiomers, several initial concentrations of L-*iso*-butyl tartrate were used while the concentration of TM-β-CD was kept constant at 0.1 mol/L in NaH_2PO_4/H_3PO_4 buffer solution at pH 2.5. As expected, the following results were obtained from Fig. 4. When L-*iso*-butyl tartrate is not added to the

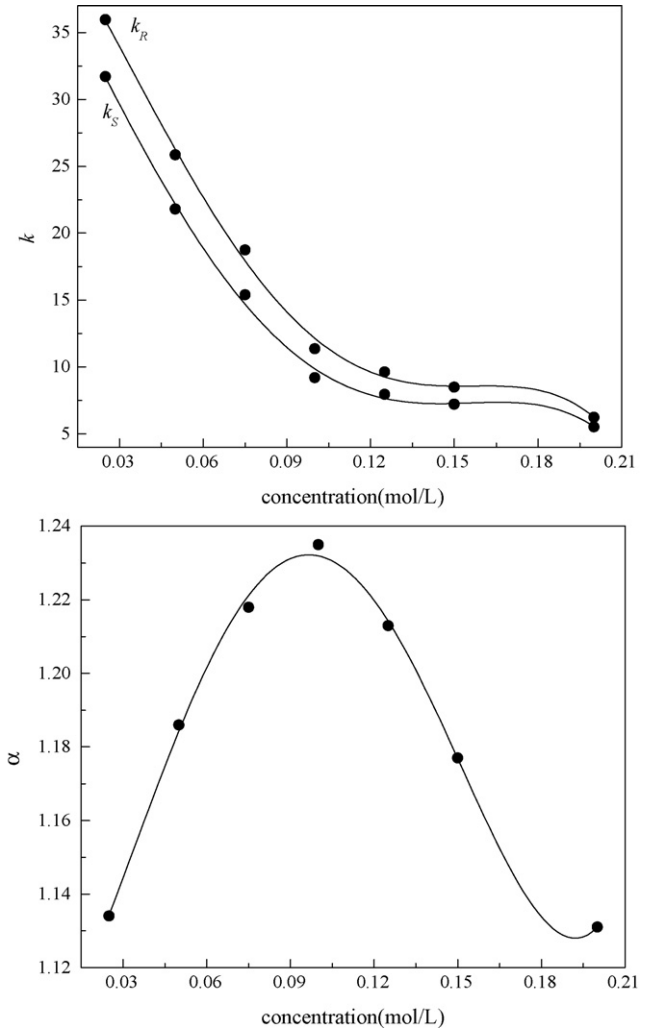

Fig. 3. Effect of TM-β-CD concentration on k and α. Organic phase: [L-*iso*-butyl tartrate] = 0.2 mol/L, [HA] = 0.0001 mol/L, pH 2.5, and temperature 5 °C.

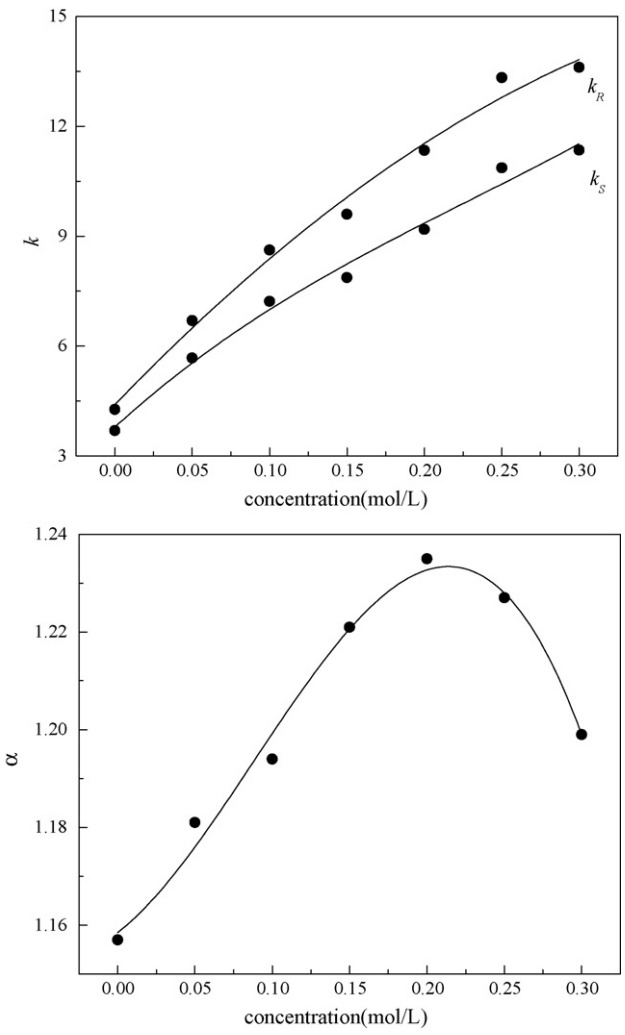

Fig. 4. Effect of L-*iso*-butyl tartrate concentration on k and α. Aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, pH 2.5, and temperature 5 °C.

organic phase, there is enantioselectivity towards HA enantiomers, but with small distribution coefficients. With the increase of L-*iso*-butyl tartrate concentration, the distribution coefficients are enhanced greatly. And the enantioselectivities all increase before the concentration of L-*iso*-butyl tartrate is up to 0.2 mol/L. When the concentration of L-*iso*-butyl tartrate is increased further, the distribution coefficients continuously increase, while the enantioselectivities follow an opposite tendency. It can be explained by the larger amount of complexes formed in the organic phase which leads to an increase in the distribution coefficients, and the enantioselectivities are the results of the cooperation of TM-β-CD and L-*iso*-butyl tartrate. It is also found that enantioselectivity reaches maximum at the ratio of 2:1 of [L-*iso*-butyl tartrate] to [TM-β-CD] which is in accordance with the above results.

3.6. Influence of pH

The pH is an important factor for consideration in the separation of enantiomers as it impacts the states of HA enantiomers. To better understand the effect of pH on the distribution behavior of HA enantiomers, distribution coefficients and enantioselectivities were studied in the BRCE systems with 0.2 mol/L L-*iso*-butyl tartrate in 1,2-dichloroethane and 0.1 mol/L TM-β-CD in 0.1 mol/L NaH_2PO_4/H_3PO_4 buffer solution at different pH values (Fig. 5). It is shown from Fig. 5 that the distribution coefficients and enantioselectivities all decrease obviously with the increase of pH.

The possible reasons for these may be that TM-β-CD and L-*iso*-butyl tartrate mainly have chiral recognition ability and affinity for molecular HA, but not for ionic HA. The amount of ionic HA increases with the rise of the pH, but molecular HA decreases. The amount of complexes formed by the selectors (L-*iso*-butyl tartrate and TM-β-CD) and enantiomers decrease with the increase of the pH. HA enantiomers mainly exist in aqueous phase in ionic state at high pH. As a result, distribution coefficients and enantioselectivities greatly decrease with the rise of the pH. Therefore, it should be kept at low pH to carry out the extraction process.

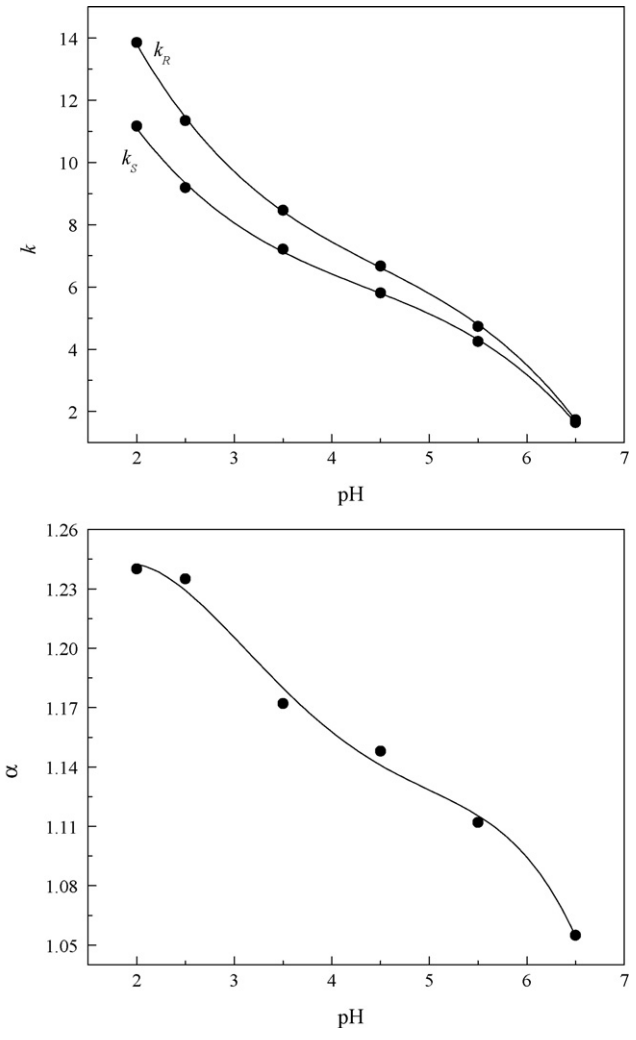

Fig. 5. Effect of pH on k and α. Organic phase: [L-*iso*-butyl tartrate] = 0.2 mol/L, aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, and temperature 5 °C.

3.7. Influence of HA enantiomers concentration

Fig. 6 shows the influence of HA concentration on distribution behavior of HA enantiomers. Distribution coefficients increase slowly with rise of HA concentration. This may be caused by non-selective partitioning due to the fact that 1,2-dichloroethane is used as the solvent. However, enantioselectivities are relatively higher at low concentration, which indicates a better enantioseparation efficiency at low initial concentration. This can be due to the fact that at low concentrations most extraction is through enantioselec-

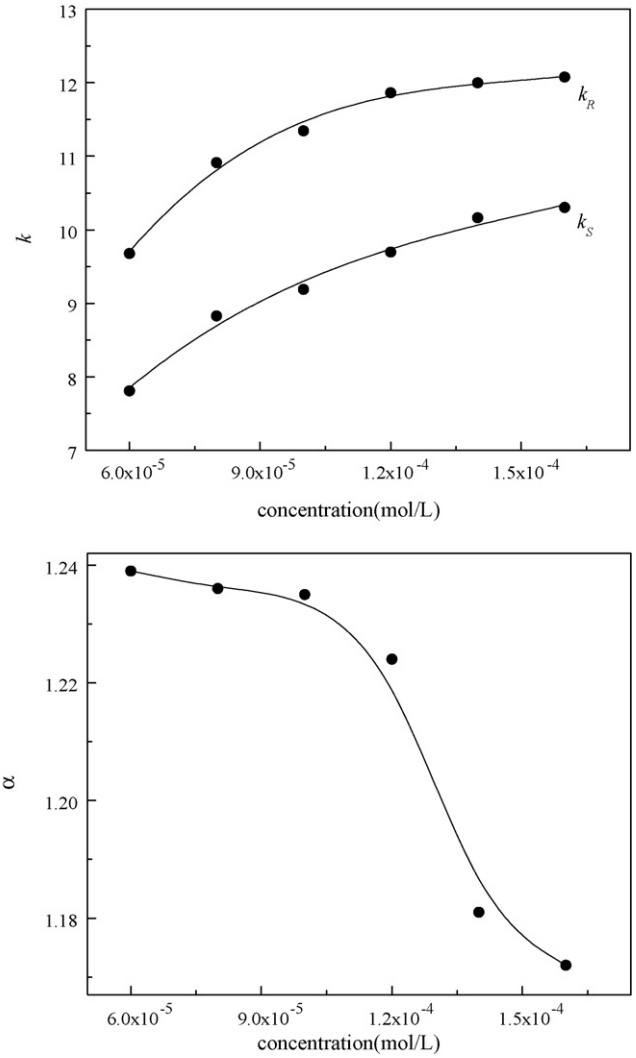

Fig. 6. Effect of concentration of HA on k and α. Organic phase: [L-*iso*-butyl tartrate] = 0.2 mol/L, aqueous phase: [TM-β-CD] = 0.1 mol/L, pH = 2.5, and temperature 5 °C.

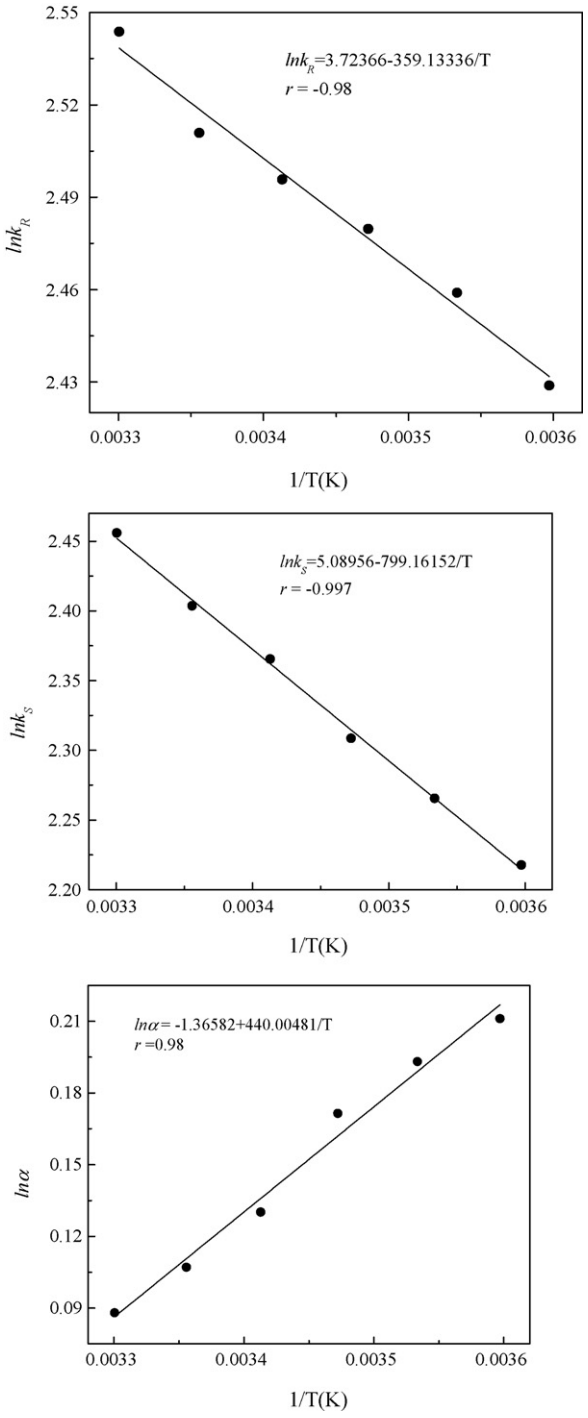

Fig. 7. Influence of temperature on the enantioseparation of HA. Organic phase: [L-*iso*-butyl tartrate] = 0.2 mol/L, aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, and pH = 2.5.

tive complexation and at higher concentrations more non-selective partitioning is occurring.

3.8. Influence of temperature

The influence of temperature on the distribution behavior of HA was carried out in the range of 5–30 °C. A peculiar effect is observed from Table 4 that higher temperature leads to an increase in distribution coefficients but a decrease in enantioselectivities. The fact that an increasing distribution coefficients is obtained indicates that the non-selective physical partitioning is increasing with temperature and CD complexation decreases with temperature. A decrease in enantioselectivities can be explained by the fact that the selector–enantiomer interaction weakens with temperature and the discrimination ability of the selectors for HA enantiomers weakens as well.

Table 4
Influence of temperature on the enantioseparation of HA enantiomers.

Temperature (°C)	k_R	k_S	α
5	11.35	9.19	1.24
10	11.69	9.64	1.21
15	11.94	10.06	1.19
20	12.13	10.65	1.14
25	12.32	11.06	1.11
30	12.73	11.66	1.09

Organic phase: [L-*iso*-butyl tartrate] = 0.2 mol/L, aqueous phase: [TM-β-CD] = 0.1 mol/L, [HA] = 0.0001 mol/L, and pH = 2.5.

Fig. 7 shows the variations of $\ln k$ and $\ln \alpha$ versus $1/T$. The absolute values of linear correlations (r) are all bigger than 0.95, which can be described as fitting very well with the Van't Hoff model, indicating that the complexes do not change in conformation and that enantioselective interactions remained unchanged in the temperature range studied.

4. Conclusions

Liquid–liquid extraction has been proved to be a promising alternative for chiral separation. However, optimization of the extraction process is required in order to obtain a high enantioselectivity. Based on our previous work, enantioselective partitioning of flurbiprofen enantiomers was investigated in a BRCE system containing hydrophobic L-*iso*-butyl tartrate in organic phase and hydrophilic TM-β-CD in aqueous phase, which preferentially recognize *R*-HA and *S*-HA, respectively.

It is found that the enantioselectivities in a BRCE system are greatly improved due to the utilization of the cooperations of the separation forces of L-*iso*-butyl tartrate and TM-β-CD. Higher temperature leads to an increase in distribution ratios but a decrease in enantioselectivities. Better enantioseparation efficiency is obtained at low pH and the ratio of 2:1 of [L-*iso*-butyl tartrate] to [TM-β-CD]. Full separation of racemic flurbiprofen enantiomers can be carried out by multistage extraction.

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