Enantioseparation of Racemic Mixtures Based on Solvent Sublation

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ABSTRACT A method of solvent sublation was developed for the enantioseparation of racemic ofloxacin (*rac* Oflx) and racemic tryptophan (*rac* Trp). In this method, dibenzoyl-*L*-tartaric acid (*L*-DBTA) and di-(2-ethylhexyl) phosphoric acid (D2EHPA) and sodium lauryl sulfate (SDS) were used as chiral coextractants and foamer, respectively. Several important parameters influencing the separation performances, such as pH in aqueous phase, concentrations of *rac* mixtures, *L*-DBTA, D2EHPA, and SDS, were investigated. Under the optimal operation conditions, the enantiomeric excess and enantioselectivity were 60.08% and 5.58 for Oflx and 65.09% and 6.31 for Trp, respectively. The yields of *D*-enantiomer and *L*-enantiomer were 34.23% and 8.54% for Oflx and 18.59% and 3.93% for Trp, respectively. The results suggest that the enantioselectivities have been enhanced compared with the traditional chiral extraction. This technique is an efficient chiral separation method, with many advantages such as low expenditures of organic solvent, low consumption of chiral extractant, and easy realization of multistage operation. *Chirality 00:000-000, 2012.*

KEY WORDS: solvent sublation; enantioseparation; chiral coextractants; *rac* Oflx; *rac* Trp

INTRODUCTION

Chirotechnology has promoted the development of global pharmaceutical industry, and the production of single-enantiomer drugs is one of the hot topics in the world. To provide single enantiomer with high quality and low cost is the key for the development of pharmaceutical industry.[1–4]

Solvent sublation technique is a kind of bubble separation process in which the hydrophobic compounds in water are adsorbed on the bubble surfaces of an ascending gas stream and then collected in an immiscible liquid layer (usually an organic solvent lighter than water) placed on the top of the bulk aqueous phase of the column.[5] This technique has many advantages, such as simultaneous separation and purification, high concentration efficiency and low expenditure of organic solvent, and so on.[6] Solvent sublation has attracted much attention in the fields of environmental analysis, wastewater treatment, and extraction of active constituents.[7–10]

In this work, solvent sublation technique was adopted for the enantioseparation of *rac* mixtures.[11] The paper was carried out in a conventional bubble column by taking racemic ofloxacin (*rac* Oflx) and racemic tryptophan (*rac* Trp) as the research models, while using sodium lauryl sulfate (SDS) as surfactant, *n*-octanol as diluent, and di-(2-ethylhexyl) phosphoric acid (D2EHPA) and dibenzoyl-*L*-tartaric acid (*L*-DBTA) as chiral coextractants, which were reported for the enantioseparation of amino acids with high enantioselectivity.[12,13] Compared with the traditional method of chiral extraction, our aim was to provide an efficient approach to chiral separation.[14–20] To our knowledge, no literature about the enantioseparation by solvent sublation is available.

MATERIALS AND METHODS

Materials and Apparatus

Rac Oflx (purity > 99.0%) was bought from Pulokangyu Institute of Fine Chemicals (Zhejiang, China); *Rac* Trp (purity > 98.0%) and D2EHPA were bought from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China); SDS (chemical-reagent grade) was purchased from Xilong Chemical Plant (Guangdong, China); *L*-DBTA (biochemical reagent, $[\alpha]_D^{28} = -114^\circ$ to -117°) was purchased from Lingxing Chemical Regents Co. Ltd. (Zhejiang, China); *n*-octanol (analytical pure) was purchased from Hengxing Chemical Material Co. Ltd. (Tianjin, China). All other chemicals were of analytical-regent grade, and water was deionized and bidistilled.

The apparatus of solvent sublation in this study is shown in Figure 1 (assembled by Hunan University Instrument Plant, China). It consists of four basic parts: (1) a sample cell (7×6 cm i.d.), which is used as the storage for sample solution, (2) an air introduction section with a rotameter to control the air flow rate, which is separated from sample cell and used to generate air into the column, (3) a glass column (40×2 cm i.d.) with ceramic raschig rings (1.5×1.5 cm i.d.) as packing material, which is used for the adsorption and interaction, and (4) a collection device, which is used to make bubbles flow into the container, where the aqueous phase can be collected and the organic phase be left.

Analytical Method

The quantification of Oflx enantiomers and Trp enantiomers in the aqueous phase was performed by high-performance liquid chromatography (HPLC) using an ultraviolet (UV) detector (Shimadzu, Japan) at the UV wavelength of 288 nm and 279 nm, respectively. The column was Kromail C_{18}, 5 μm particle size of the Packing Material, 250×4.6 mm i.d. (Hanbon Science and Technology Co. Ltd., China).

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The mobile phase for Oflx enantiomers was 3 mmol/l $CuSO_4$ and 6 mmol/l *L*-phenylalanine aqueous solution: methanol (85:15, *v/v*) at a flow of 0.8 ml/min. The corresponding column temperature was 25 °C. The retention time of *L*-Oflx was less than that of *D*-Oflx.[21]

The mobile phase for Trp enantiomers was 3 mmol/l CuSO4 and 6 mmol/l *L*-phenylalanine aqueous solution: methanol (86:14, v/v) at a

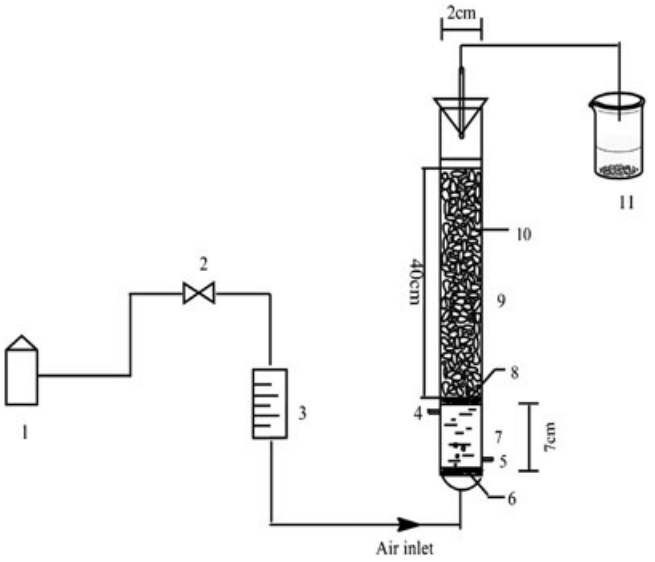

Fig. 1. Schematic showing the apparatus used in this work. (**1**) Air pump, (**2**) control valve, (**3**) rotameter, (**4**) inlet for solution, (**5**) outlet for solution, (**6**) gas distributor, (**7**) sample pool, (**8**) microporous plate, (**9**) glass column, (**10**) ceramic ring, and (**11**) bubble receiver.

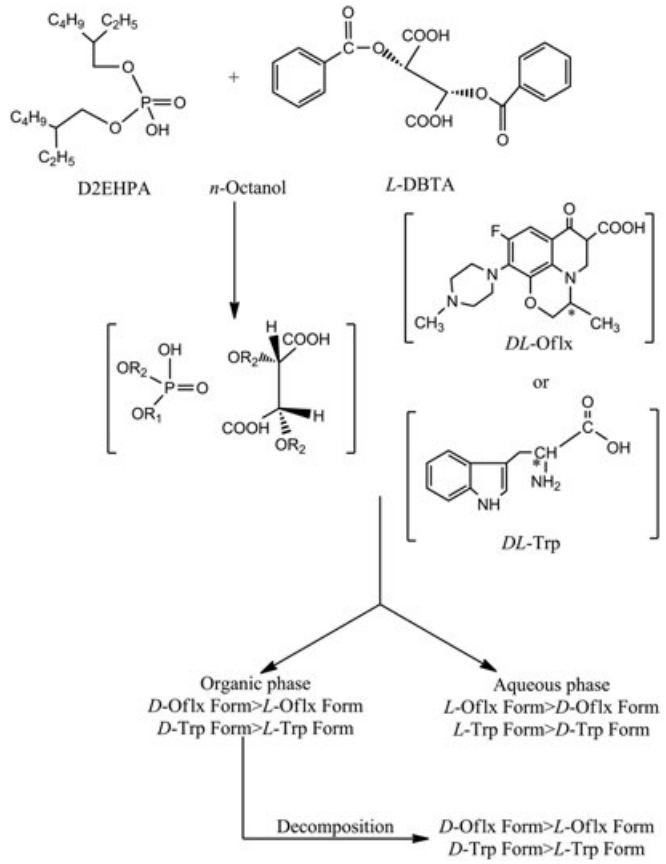

Fig. 3. Enantioseparation process based on solvent sublation. D2EHPA, di-(2-ethylhexyl) phosphoric acid; *L*-DBTA, dibenzoyl-*L*-tartaric acid; Oflx, ofloxacin; Trp, tryptophan.

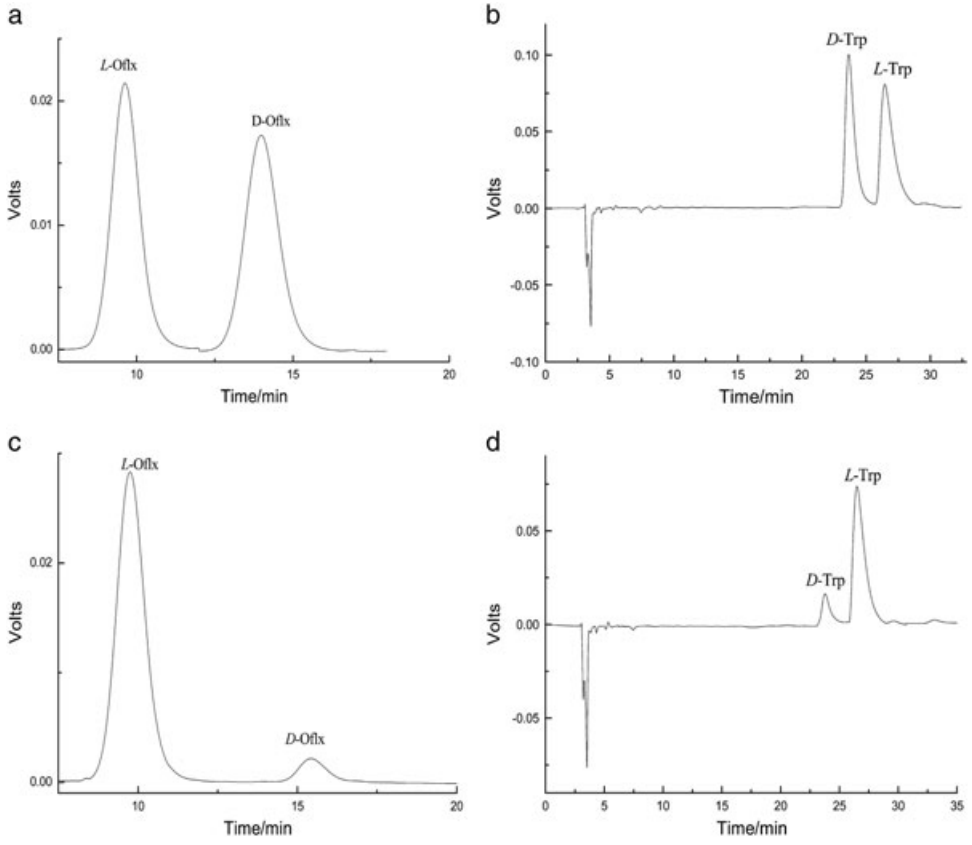

Fig. 2. High-performance liquid chromatography chromatograms of *rac* Oflx and *rac* Trp: (**a**, **b**) before and (**c**, **d**) after solvent sublation.

flow of 1.0 ml/min with pH 3.5 adjusted by acetic acid. The corresponding column temperature was 30 °C. The retention time of *D*-Trp was less than that of *L*-Trp.[22]

The chromatograms of these two racemic compounds are shown in Figure 2. It can be calculated that the peak area of *D*-enantiomer is equal to that of *L*-enantiomer, which indicates that the content of *D*-enantiomer is the same as that of *L*-enantiomer.

TABLE 1. Effect of reflux time on enantioselectivity

Reflux time (h)	Oflx[a]		Trp[b]	
	β	*e.e.*% (aqueous phase)	β	*e.e.*% (aqueous phase)
1	2.75	36.54	2.24	34.96
2	4.25	45.23	3.89	53.51
3	4.73	51.76	4.79	57.26
4	5.58	60.08	6.31	65.09
5	4.31	41.85	4.25	54.74
6	3.67	21.74	2.76	34.63

[a]Initial concentration of racemic ofloxacin (Oflx), dibenzoyl-*L*-tartaric acid (*L*-DBTA), di-(2-ethylhexyl) phosphoric acid (D2EHPA), and sodium lauryl sulfate (SDS): 1.67 mg/ml, 0.11 g/l, 0.91 mol/l, and 0.42 mg/ml, respectively. pH 7 in aqueous phase.
[b]Initial concentration of racemic tryptophan (Trp), *L*-DBTA, D2EHPA, and SDS: 1.40 mg/ml, 0.20 g/l, 1.51 mol/l, and 0.60 mg/ml, respectively. pH 6 in aqueous phase.

Experiment of Solvent Sublation

The aqueous phase was prepared by dissolving *rac* mixtures and surfactant SDS in water. The pH value was adjusted with phosphate salt buffer solution and measured using a pH meter before extraction for each experiment. *L*-DBTA and D2EHPA were used as the chiral coextractants whereas *n*-octanol as the diluent. We placed 140 ml of the organic and aqueous phases (1:6, *v/v*) into the sample pool under room temperature. Then, air was introduced into the aqueous phase to form bubbles. Refluxed for several hours, the bubbles were collected under a certain gas velocity. After static defoamed and phase separation, the concentrations of enantiomer in aqueous phase were analyzed using HPLC. Each experiment was duplicated under identical conditions, and the standard deviation is in the range of ±2%. Because the change in volume was very small, it could be seen as negligible. All the experiments were performed at a certain packing height and a steady air flow rate.

RESULTS AND DISCUSSION

As Tan's study in the suggested mechanism of chiral coextraction method, [12,13] the possible reaction mechanism in this paper is shown in Figure 3. According to that, some factors that affected the enantioseparation efficiency were investigated.

In the separation process of solvent sublation, the extraction of *rac* Oflx and *rac* Trp by *n*-octanol can be considered as negligible. The distribution ratio (*D*), the value of enantiomeric excess (*e.e.*%), and enantioselectivity (β) at equilibrium as the evaluated parameters are defined by

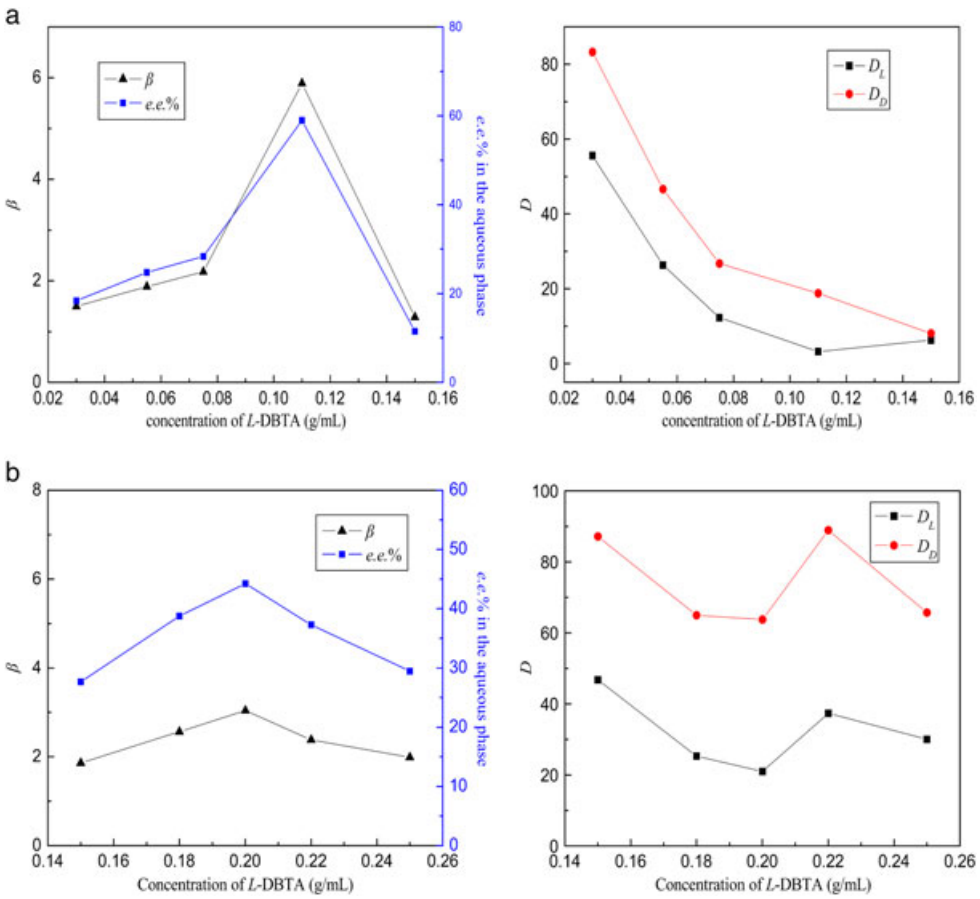

Fig. 4. Influence of the initial concentration of dibenzoyl-*L*-tartaric acid (*L*-DBTA) on the distribution behavior. (**a**) Initial concentration of racemic ofloxacin, di-(2-ethylhexyl) phosphoric acid (D2EHPA), and sodium lauryl sulfate (SDS): 1.67 mg/ml, 0.91 mol/l, and 0.42 mg/ml, respectively. pH 7 in aqueous phase and reflux time of 4 h. (**b**) Initial concentration of racemic tryptophan, D2EHPA, and SDS: 0.80 mg/ml, 1.51 mol/l, and 0.42 mg/ml, respectively. pH 5 in aqueous phase and reflux time of 4 h.

$$D_{D(L)} = \frac{\text{initial}[D]\text{or initial}[L]}{[D]or[L]} - 1 \quad (1)$$

$$\beta = \frac{\text{distribution ratio of } D \text{ enantiomer}}{\text{distribution ratio of } L \text{ enantiomer}} \quad (2)$$

$$ee\% = \frac{[L](or[D]) - [D](or[L])}{[L] + [D]} \times 100\% \quad (3)$$

Among which, [] was the concentration (mg/ml) of enantiomer in the aqueous phase.

Effect of Reflux Time

The influence of reflux time on enantioseparation is listed in Table 1. The results suggest that *e.e.*% and β increase with extending reflux time before up to 4 h and then decrease. It is because the interphase force and the contact area of interphase increase with extending reflux time; in that case, *e.e.*% and β show an increasing tendency. But, with continuous refluxing, the foam layer becomes thicker, which would increase the transfer resistance of enantiomers and decrease the extraction efficiency. Therefore, *e.e.*% and β decrease with the further increase of reflux time.[23] So, the relux time is fixed at 4 h in this work.

Effect of Initial Concentration of L-DBTA

Figure 4 shows the influence of *L*-DBTA concentration on the distribution behavior. In this work, the chiral coextractants formed by *L*-DBTA and D2EHPA could form two diastereomeric complexes with *D*-enantiomer or *L*-enantiomer, respectively, which depends on the various molecular interactions during the process of solvent sublation. Therefore, it could be seen that β and *e.e.*% increase obviously with the increase of *L*-DBTA concentration and then reach maximum at a certain concentration. However, β and *e.e.*% would show a decrease tendency when the *L*-DBTA concentration exceeds a certain value because of the micelles formed by the excess *L*-DBTA, which could make the unexpected enantiomer be adsorbed. What's more, the initial concentration of *L*-DBTA also has an influence to *D*. Generally, except for the abnormality at the concentration of 0.22 g/ml for Trp, $D_{D(L)}$ tends to decrease with increasing *L*-DBTA concentration, which should be also attributed to the forming of complex by *L*-DBTA and D2EHPA. D2EHPA has relatively large extraction capacity but without any chiral recognition ability, and the extraction capacity might be impaired with the decrease of its concentration caused by increasing the *L*-DBTA concentration. The value of D_D is always larger than that of D_L, which suggests that *D*-Oflx and *D*-Trp are all preferentially extracted by the chiral coextractants.

Effect of Initial Concentration of Racemic Mixtures

Figure 5 shows the influence of concentration of *rac* mixtures on the distribution behavior. *e.e.*% and β are enhanced with the increasing initial concentration of *rac* Oflx, whereas *e.e.*% and β increase firstly and then decrease with the increase of initial concentration of *rac* Trp. The values of D_D

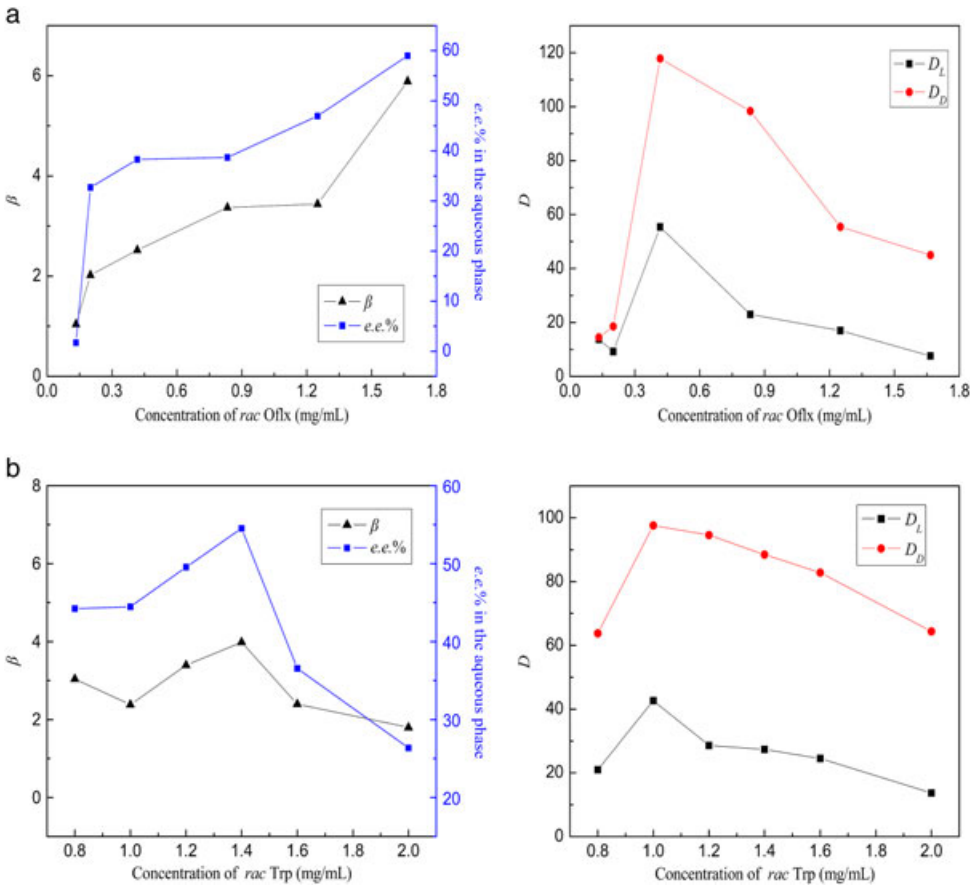

Fig. 5. Influence of the initial concentration of racemic ofloxacin (*rac* Oflx) and racemic tryptophan (*rac* Trp) on the distribution behavior. (**a**) Initial concentration of dibenzoyl-*L*-tartaric acid (*L*-DBTA), di-(2-ethylhexyl) phosphoric acid (D2EHPA), and sodium lauryl sulfate (SDS): 0.11 g/l, 0.91 mol/l, and 0.42 mg/ml, respectively. pH 7 in aqueous phase and reflux time of 4 h. (**b**) Initial concentration of *L*-DBTA, D2EHPA, and SDS: 0.20 g/l, 1.51 mol/l, and 0.42 mg/ml, respectively. pH 5 in aqueous phase and reflux time of 4h.

and D_L tend to decrease at the higher concentration of *rac* mixtures. The rather abrupt leveling-off of D_D and D_L at a certain concentration strongly suggests the formation of a D2EHPA-(*L*-DBTA) complex as efficient chiral coextractants, which we presume the complex to be mediated by hydrogen bonding. A reasonable explanation is that the Oflx (or Trp) complexes formed in organic phase are stronger extractants for Oflx (or Trp) than the initial chiral coextractants. If this is so, then it appears that the Oflx (or Trp) complexes in organic phase are inferior chiral coextractants. What's more, the salvation ability of *n*-octanol makes the enantioselectivity decrease at the higher concentration of *rac* mixtures.[3]

Effect of pH in Aqueous Phase

To investigate the influence of pH on distribution behavior, *D* and enantioselectivities are studied at different pH. The results are shown in Figure 6, which could be seen that the influence of pH on distribution behavior is notable. [24]

For Oflx, β and *e.e.*% become larger at higher pH and reach the highest separation efficiency at pH 7 then decrease. Because at the acid medium of $2.0 < \mathrm{pH} < 7.0$, the structure of Oflx would be mainly in the form of quinoline instead of ketone because of the charge transfer reaction on the double bonds. At $\mathrm{pH} > 7.0$, the ionization extent of Oflx increases gradually with the increase of pH, so the intermolecular repulsive forces and solubility increase, which results in the decrease of enantioselectvities. At pH = 7, Oflx exists in the form of amphoteric ion and can be solvated into organic phase effectively by *n*-octanol. Therefore, pH = 7 is the better choice for Oflx.

For Trp, β and *e.e.*% reach the maximum values at pH = 5.8, which could be seen in Figure 6b. *D* (or *L*)-Trp has one carboxylic group, one amino group, and a side chain (β-indolyl). Because of its special structure, two dissociation equilibria exist in aqueous solution: [12]

$$\mathrm{RCH_2(NH_3^+)CHCOOH} \overset{K_{a1}}{\rightleftharpoons} \mathrm{RCH_2(NH_3^+)CHCOO^-} + \mathrm{H^+} \quad (4)$$

$$\mathrm{RCH_2(NH_3^+)CHCOO^-} \overset{K_{a2}}{\rightleftharpoons} \mathrm{RCH_2(NH_2)CHCOO^-} + \mathrm{H^+} \quad (5)$$

From the equilibria, we could find that a larger fraction of Trp^+ is available at lower pH. On the contrary, at higher pH, there would be many Trp^-. However, the chiral coextractants tend to complex with $Trp^{\pm}$, and therefore, only the amphoteric ion can be solvated into organic phase effectively. What's more, Trp exists as $Trp^{\pm}$ only at its p*I* ($pI = (pK_{a1} + pK_{a2})/2$), and the p*I* of Trp is 5.8. In that case, *e.e.*% and β are both enhanced with increasing pH and then decreased significantly. Therefore, pH = 5.8 is chosen as the optimum condition for Trp.

Effect of Initial Concentration of D2EHPA

The effect of concentration of D2EHPA in the organic phase on β, *e.e.*%, and *D* is shown in Figure 7. D2EHPA is suitable for a nonpolar solvent system, so *n*-octanol is selected as the extraction solvent. As could be seen from Figure 7, with the increasing D2EHPA concentration, both *e.e.*% and β keep an increase tendency firstly and then drop obviously. *D* begins to decrease and then increase with the increasing D2EHPA concentration. The reason for this phenomenon is also due to the chiral coextractants formation between *L*-DBTA and D2EHPA; therefore, the enantioselectivities increase,

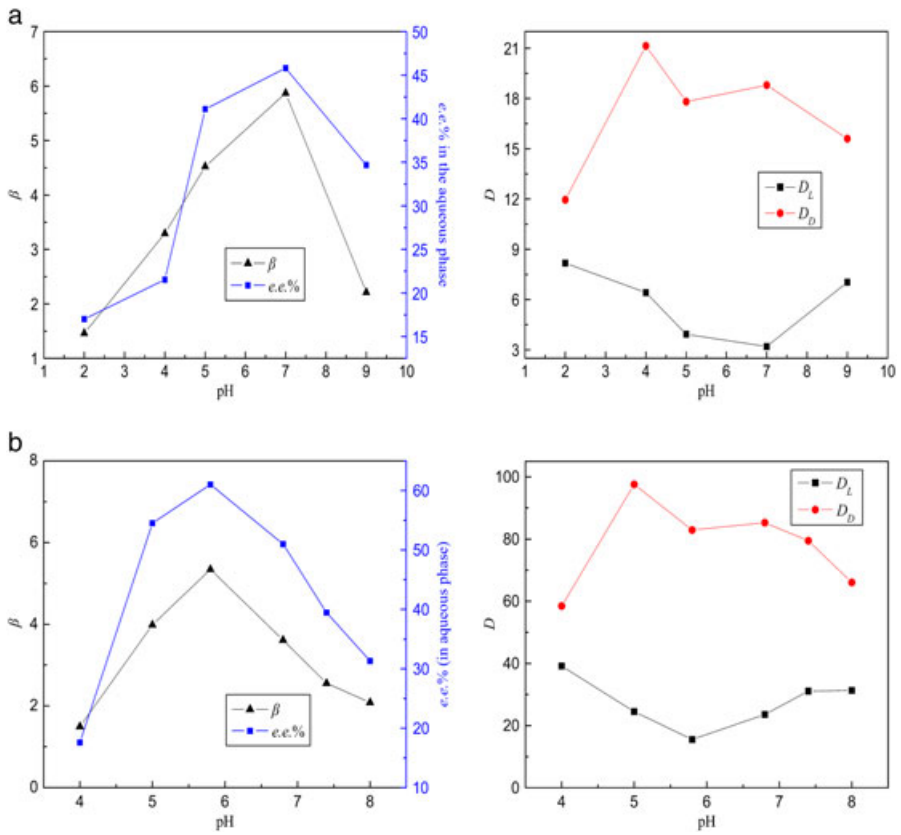

Fig. 6. Influence of pH on the distribution behavior. (**a**) Initial concentration of racemic ofloxacin, dibenzoyl-*L*-tartaric acid (*L*-DBTA), di-(2-ethylhexyl) phosphoric acid (D2EHPA), and sodium lauryl sulfate (SDS): 1.67 mg/ml, 0.11 g/l, 0.91 mol/l, and 0.42 mg/ml, respectively. Reflux time of 4 h. (**b**) Initial concentration of racemic tryptophan, *L*-DBTA, D2EHPA, and SDS: 1.40 mg/ml, 0.20 g/l, 1.51 mol/l, and 0.42 mg/ml, respectively. Reflux time of 4h.

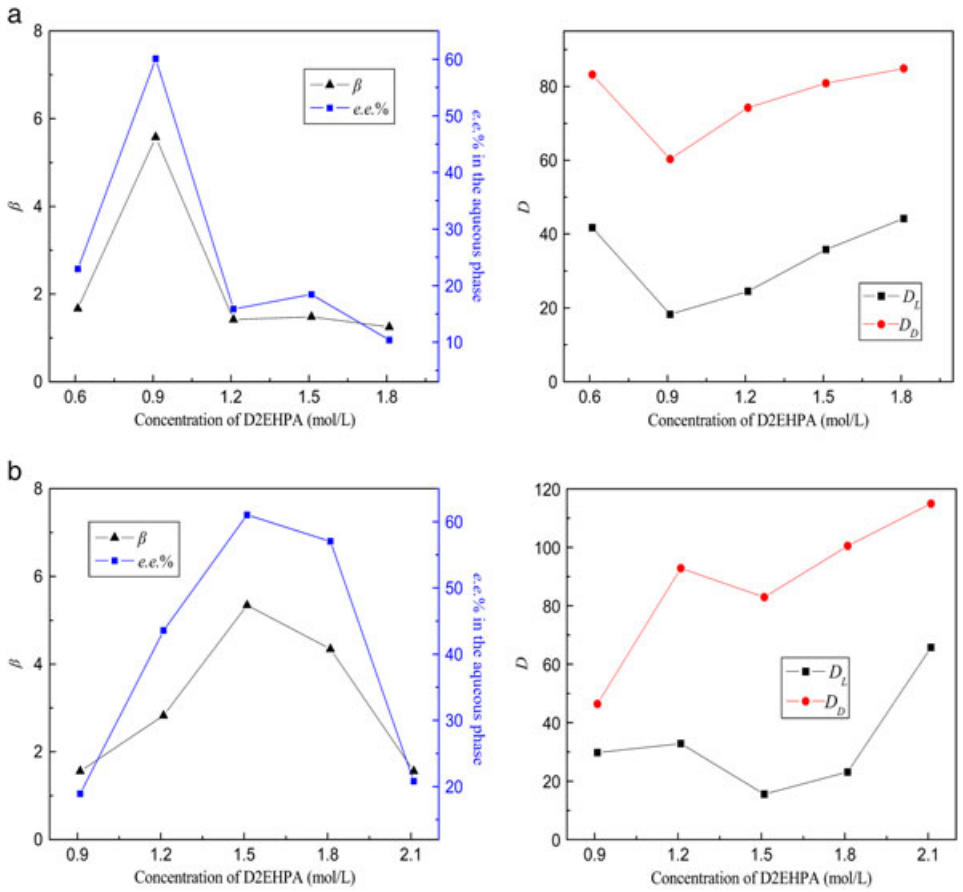

Fig. 7. Influence of the initial concentration of di-(2-ethylhexyl) phosphoric acid (D2EHPA) on the distribution behavior. (**a**) Initial concentration of racemic ofloxacin, dibenzoyl-*L*-tartaric acid (*L*-DBTA), and sodium lauryl sulfate (SDS) is 1.67 mg/ml, 0.11 g/l, and 0.42 mg/ml, respectively. pH 7.0 and reflux time of 4 h. (**b**) Initial concentration of racemic tryptophan, *L*-DBTA, and SDS is 1.40 mg/ml, 0.20 g/l, and 0.42 mg/ml, respectively. pH 5.8 and reflux time of 4 h.

whereas *D* decreases with the increase of D2EHPA concentration. However, D2EHPA does not have any chiral separation ability but could enhance the extraction capability. As a result, the enantioselectivities decrease, whereas *D* follows an opposite tendency. In addition, the excess concentration of D2EHPA in the organic phase could cause emulsification of the organic phase and increase the difficulty in phase separation, and it could increase the solubility of D2EHPA in the aqueous phase. So, the concentration of D2EHPA in the organic phase is fixed at 0.91 and 1.51 mol/l for Oflx and Trp, respectively.

Effect of Initial Concentration of SDS

The effect of SDS concentration in the aqueous phase is shown in Figure 8. It suggests that β becomes larger with the increase of SDS concentration and then reaches maximum at the SDS concentration of 0.42 and 0.60 mg/ml for Oflx and Trp, respectively. But, with the further increasing SDS concentration, β decreases obviously. What's more, when the SDS concentration increases continuously, some white flocculent precipitates would be found in the sample cell, which in turn affect the results. Therefore, 0.42 and 0.60 mg/ml might be the optimal SDS concentration for Oflx and Trp, respectively.

Yields of Enantiomers under the Optimal Conditions

By investigating the factors that influence the enantioseparation process of solvent sublation, the optimal operational conditions for the chiral separation of Oflx and Trp can be easily found. In this situation, the enantiomeric excess and enantioselectivity were 60.08% and 5.58 for Oflx and 65.09% and 6.31 for Trp, respectively. Then, the yields of *D*-enatiomer and *L*-enantiomer in this study were defined as

$$D\% = \frac{\text{initial}[D] - [D]}{\text{initial}[D]} \times 100\% \tag{6}$$

$$L\% = \frac{\text{initial}[L] - [L]}{\text{initial}[L]} \times 100\% \tag{7}$$

According to the $[D]$ and $[L]$ under the optimal operational conditions, $D\%$ and $L\%$ were calculated to be 34.23% and 8.54%, respectively, for Oflx, whereas 18.59% and 3.93%, respectively, for Trp. Although the yields were not high to some extent, solvent sublation has still some advantages when used for enantioseparation purposes such as easy operation, low expenditure of organic solvent, little consumption of chiral selectors, and so on. Especially to be noticed, the aqueous phase after enantioseparation by solvent sublation can be very easily reused in the next stage still by using this method, so all the amount of the enantiomers can be separated in theory.

CONCLUSIONS

We found an effective method using solvent sublation for the separation of racemic mixtures. Both the distribution ratio and enantioselectivity were greatly improved with this technology

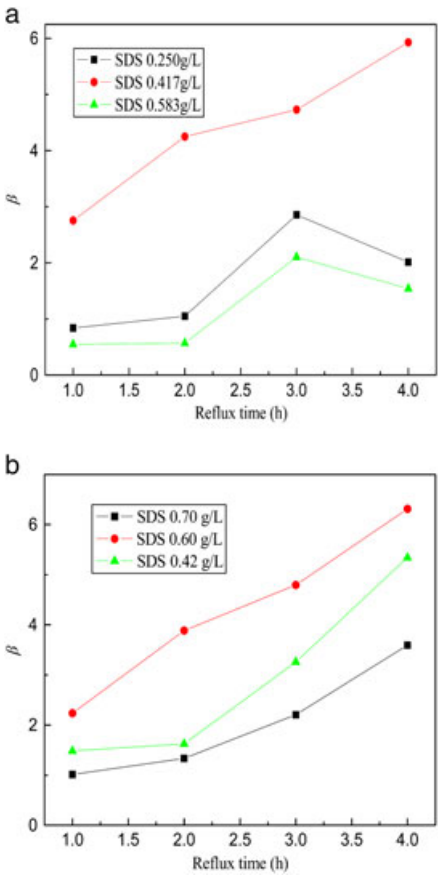

Fig. 8. Influence of the initial concentration of sodium lauryl sulfate (SDS) on β. (**a**) Initial concentration of racemic ofloxacin, dibenzoyl-*L*-tartaric acid (*L*-DBTA), and di-(2-ethylhexyl) phosphoric acid (D2EHPA): 1.67 mg/ml, 0.11 g/l, and 0.91 mol/l, respectively. pH 7.0 and reflux time of 4 h. (**b**) Initial concentration of racemic tryptophan, *L*-DBTA, and D2EHPA: 1.40 mg/ml, 0.20 g/l, and 1.51 mol/l, respectively. pH 5.80 and reflux time of 4 h.

when we used *rac* Oflx and *rac* Trp as study models. Several factors including reflux time, pH of aqueous, initial concentration of racemic enantiomers, D2EHPA, *L*-DBTA, and SDS, which influence the results of enantioseparation, were investigated. The results showed that the enantioselectivity was enhanced compared with the usual two-phase (O/W) recognition chiral extraction. Under the optimal operational conditions, the enantiomeric excess and enantioselectivity were 60.08% and 5.58 for Oflx and 65.09% and 6.31 for Trp, respectively. The yields of *D*-enatiomer and *L*-enantiomer were 34.23% and 8.54% for Oflx and 18.59% and 3.93% for Trp, respectively. What's more, this technique, with advantages of simultaneous foam adsorption and solvent extraction, very low expenditure of organic solvent, very little amount of chiral selectors, and easy realization of multistage operation, would have a considerable number of potential applications in chiral separation.

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