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Selective separation of salbutamol enantiomers with simultaneously synergistic extraction and stripping method

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ABSTRACT

Enantioselective separation of salbutamol enantiomers was carried out through the simultaneously synergistic extraction and stripping method with O,O-dibenzoyl-(2S,3S)-tartaric acid (+)-DBTA and di (2-ethylhexyl) phosphoric acid (D2EHPA) as chiral and non-chiral extractants, respectively. Chiral recognition mechanism of salbutamol enantiomers with (+)-DBTA was investigated using the Density Functional Theory (DFT) methods. The results showed that the chiral recognition in separation process was realized by the hydrogen-bond interaction. The binding energy of the complex resulting from (+)-DBTA and *R*-salbutamol was −86.14 kJ/mol, which was higher than that of the complex resulting from (+)-DBTA and *S*-salbutamol. The synergistic extraction experiment was preliminarily performed and the maximum separation factor was up to 1.65. Enantioseparation of salbutamol was conducted in the hollow fiber supported liquid membrane process. Various operating conditions, including the feed phase concentration, the component of membrane phase, the flow rate, and the pH of stripping side, were investigated. The results showed that the mass transfer resistance mainly focused on the membrane phase. The synergistic effect in liquid membrane system was also discussed. When the ratio of chiral to achiral extractant was 1.0:0.6, the separation factor was up to 2.0 in the stripping phase.

1. Introduction

Enantiomers show different biological and pharmacological responses in human body. Generally, one form of the enantiomer is active while the other form may be inactive. Nowadays, many pure enantiomeric drugs are demanded by the US Food and Drug Administration (FDA) [1]. Salbutamol, also known as Proventil or Ventolin, is a best-selling chiral drug for the treatment of asthmatic bronchitis, asthma and so on [2]. The therapeutic activity of salbutamol is mainly related to *R*-salbutamol (*R*-sal), whose affinity with receptor is more than 100 times of that of *S*-salbutamol (*S*-sal). The side effects or toxicity of salbutamol, such as lung damage, are often caused by *S*-salbutamol. Thus, to obtain optically pure *R*-salbutamol effectively is of great interest. Chiral separation is the most important method to obtain optically pure chiral drugs [3]. Many conventional chiral resolution methods, including preferential crystallization, stereoselective transformation by an optical resolution reagent, inclusion resolution, solid phase extraction resolution, and chromatographic separations, have been used to separate salbutamol enantiomer [4–7]. However, most of the above methods are more or less limited by the low productivity, low separation factor, complicated operation steps [8] and high energy consumption [9].

Enantioselective liquid–liquid extraction (ELLE), which integrates chiral separation and liquid–liquid extraction, has been proposed for the separation of racemic mixture. It can be easily performed with better separation effect, higher recovery efficiency and lower cost. It has become an attractive separation technology for separating enantiomers from racemic mixture [10–12]. Ren et al. [11] used the liquid–liquid extraction method for separating racemic ibuprofen enantiomers and also studied related chiral recognition mechanism. Sunsandee et al. [12] also developed a two-phase, chiral extraction system for the separation of racemic amlodipine. However, the enantioselectivity of most liquid–liquid extraction process is relatively low. Synergistic extraction, known as certain combination of two or more extractants, is derived from traditional liquid–liquid extraction. It has been used in the liquid–liquid extraction process [13,14] and some combined extractants could produce a synergistic effect which is benefit for the separation. Currently, synergistic extraction is mainly applied in the ion extraction process [13,14], but only a few reports are found in the chiral liquid–liquid extraction process. Luo et al. [15]

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developed a liquid–liquid extraction technique to separate chiral amino acid using a new chiral extractant complex of D2EHPA and ((−)-DBTA). A high chiral separation efficiency with a maximum enantioselectivity of 5.3 and an enantiomeric excess value of up to 57% in the aqueous phase were obtained.

Chiral liquid membrane technology is known as the coupling of membrane separation and chiral extraction technology, which can realize an effective simultaneous process to extract and recover compounds by a single unit operation. It has been widely investigated for the separation of enantiomers due to its high separation factor and mass transfer flux [16–20]. Liquid membrane technology can be mainly divided into three categories, i.e., emulsion liquid membrane [16], bulk liquid membrane [17] and supported liquid membrane. Among these three liquid membrane systems, emulsion liquid membrane [18] has a good separation performance, but it requires a complicated operation procedure and cannot effectively avoid membrane leakage. Bulk liquid membrane [16] is relatively stable, but its mass transfer rate is very low. Compared with emulsion liquid membrane and bulk liquid membrane, supported liquid membrane [19,20] has attracted a considerable attention recently because of its easy scaling-up, and low operating costs. Hadik et al. [21] used the hollow fiber supported liquid membrane for the separation of D, L-lactic acid and D, L-alanine. The maximum separation factors for D, L-lactic acid and D, L-alanine were 2.00 and 1.75, respectively. Jiao et al. [22] separated salbutamol sulfate enantiomers through the hollow fiber supported liquid membrane process, in which optically pure D-DTTA and toluene were used as the chiral resolution reagents and solvent, respectively. In the process, salbutamol enantiomers were effectively separated in the stripping side, which confirmed the feasibility of separating salbutamol sulfate enantiomers. The maximum separation factor and enantiomer excess value were 1.49% and 19.74%, respectively. The consumption of extractant was successfully reduced in the process but the separation factor was still around 1.5, leaving plenty of room to improve. To obtain better separation performance, synergistic extraction is considered to be applied in the chiral liquid membrane process. Besides, the chiral recognition mechanism and optimization of operating parameters of the chiral liquid membrane process need to be investigated systematically.

In this work, a hollow fiber supported liquid membrane process based on the synergistic extraction experiment was constructed to separate salbutamol enantiomers. In order to understand the recognition process well, the chiral recognition mechanism between the chiral selector and salbutamol was preliminarily investigated by theoretical calculation with Gaussian03 software. The synergistic extraction experiment for salbutamol enantiomers was carried out with D2EHPA and (+)-DBTA as the synergistic chiral separation solvents. The effects of extraction equilibrium time, raceme solution concentration, and concentrations of chiral and achiral resolution solvents (+)-DBTA and D2EHPA on separation performance were investigated. The chiral liquid membrane process based on synergistic extraction was investigated for separating salbutamol enantiomers. The chiral selective extractant ((+)-DBTA) and achiral extractant D2EHPA were mixed together in the membrane phase for their synergistic effect. The effects of feed phase concentration, component of the membrane phase, flow state of the shell and tube side, and pH value of the stripping side on separating ability were studied. The mass transfer-controlling step and the synergistic effect were confirmed.

2. Experimental

2.1. Materials

The analytical reagents utilized in this work were as follows: > 99% pure Salbutamol (GlaxoSmithKline (China) Investment Co., Ltd., Tianjin, China), > 99% pure (+)-DBTA and D2EHPA (Tianjin GuangFu Fine Chemical Research Institute, Tianjin, China), n-caprylic alcohol, phosphoric acid, sodium phosphate and other reagents (Beijing Chemical Works, Beijing, China); PVDF membrane (asymmetric structure, Tianjin Polytechnic University, Tianjin, China).

2.2. Synergistic extraction experiment

All extraction experiments were performed in 25 mL conical flasks at 25 ± 2 °C. To each flask was added 10 mL of solvent mixture (consisting of (+)-DBTA and D2EHPA with n-caprylic alcohol) along with 10 mL of an aqueous solution containing salbutamol racemic samples with sodium phosphate buffer. The flask was then agitated for approximately 3 h and then left to settle for 30 min, during which time the two phases separated. Then all samples were centrifuged with 5000 r/min and the aqueous phase was filtered by filter head, which was used to determine the concentrations of salbutamol enantiomers by chromatographic analysis. Aqueous phase samples were analyzed for salbutamol enantiomers concentration using a high performance liquid chromatography (HPLC, SPD-20A, Shimadzu, Japan) with a 10 cm chiral-AGP column (100*4.6 mm*5.0 μm, Daicel, Japan). The chromatographic conditions are listed as follows: detection wavelength: 225 nm, column temperature: 283 K, mobile phase: 50 mmol/L sodium phosphate with pH 7.0, flow rate: 0.12 mL/min, sample quantity: 10 μL, sample: salbutamol sulfate aqueous solution. External standard method was used to determine the concentration of *R*-salbutamol and *S*-salbutamol under standard curves, which were depicted according to $C = 9.94313 \times 10^{-4}S + 1.13315 \times 10^{-4}$ and $C = 8.942 \times 10^{-4}S + 3.39118 \times 10^{-4}$ (*C*-the concentration of salbutamol, S-the peak area) with RSD of 2.0% and 1.1%, respectively. Raceme concentration could be measured in the range from 0.001 to 0.100 g/L, which shows good linear correlation. Assuming no loss of *R*-salbutamol and *S*-salbutamol in the liquid − liquid extraction process, the concentration of *R*-salbutamol and *S*-salbutamol in the organic phase can be calculated based on the mass balance of compounds. The pH value of the aqueous phase solution was determined by a pH meter (PXS-450, Dapu, China). To determine the effect of initial concentration of salbutamol raceme on synergistic extraction, the concentration of salbutamol raceme was considered as 0.02 g/L, 0.04 g/L, 0.06 g/L, 0.08 g/L and 0.10 g/L. Effects of the concentration of (+)-DBTA and D2EHPA in the synergistic extraction solvents on synergistic extraction were studied. The concentrations of both (+)-DBTA and D2EHPA in the organic phase were considered as 0 mol/L, 0.2 mol/L, 0.4 mol/L, 0.6 mol/L, 0.8 mol/L, and 1.0 mol/L. All the experiments were done three times. Preliminary experiments indicated that the deviations of the calculated values of salbutamol raceme concentrations were within ± 3%. The specific calculation formulas for distribution coefficient and separation factor were as follows,

$$D = \frac{C_O}{C_A} \tag{1}$$

$$\alpha = \frac{D_R}{D_S} \tag{2}$$

where C_O and C_A are the concentration of solute in the organic phase and the aqueous phase, g/L; D_R and D_S are the distribution coefficient of *R*-salbutamol and *S*-salbutamol.

2.3. Hollow fiber supported liquid membrane experiment

In the chiral liquid membrane experiments, hollow fiber