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Construction and application of a model on the resolution of tropic acid enantiomers by enantioselective liquid-liquid extraction in centrifugal contactor separators

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ABSTRACT

This paper reports on the construction and application of a mathematical model on multistage liquid-liquid extraction of tropic acid (TA) enantiomers in centrifugal contactor separators (CCSs). An efficient extraction system was obtained, where HE-β-CD and butyl acetate was selected as the best extractant and organic solvent. The mechanism of reactive extraction of TA enantiomers by HE-β-CD was proposed and the thermodynamic constants such as physical partition coefficient and reactive equilibrium constants were obtained, which combined with the law of mass conservation gave the basis for construction of the model. The model was applied to predict and optimize the symmetrical separation of TA enantiomers. The optimal condition was obtained as follows, O/W volume ratio of 3.0, pH of 3.00 and HE-β-CD concentration of 0.05 mol/L, where ee_{eq} (equal enantiomeric excess) can reach up to 42%. The simulated results reveal that the minimum number of stages for $ee_{eq} > 97\%$ and $ee_{eq} > 99\%$ was 56 and 78, respectively.

1. Introduction

Recent chiral drug development is expected to extend the application of single molecule rather than enantiomeric/diastereomeric mixtures. In some drugs, one enantiomer exhibits the desired effects, whereas the opposite enantiomer has unanticipated negative side effects [1,2]. Therefore, the demand for single enantiomers in developing chiral drugs promotes the development for new strategy toward asymmetric synthesis and new methods of chiral separation.

Several chiral separation methods employed to produce optically pure compounds have been proposed including diastereomeric crystallization [3,4], chiral chromatography [5,6], supercritical extraction [7,8], simulated moving bed (SMB) [9,10], and membrane-based approaches [11,12]. However, the drawbacks of these separation methods limit the application, for example, the low versatility, excessive solids handling and a maximum yield of 50% of crystallization method [13], and the low capacity and high separation costs of chromatography [14]. Applying immobilized selectors in (liquid) membrane-based approaches can make the amount of selector needed reduced greatly, but the relatively low transport rates through the membranes requiring high membrane areas, delicate pressure control, and the risk of fouling limit its application. Therefore, developing a more effective chiral separation method is particularly important and highly desired.

Liquid–liquid extraction (LLE) is a mature technology that can easily be operated in a continuous counter-current mode to fractionate the racemate into its enantiomers, which is in favor of scaling-up. This possibility to operate at all scales, from laboratory separations to bulk processes in the chemical industry, makes the use of liquid-liquid extraction for enantioseparation especially interested. The first articles reported the use of LLE for enantioseparation in the English literature appeared in the late 1960's [15].

Enantioselective liquid-liquid extraction (ELLE) combines the concepts of enantiomeric recognition and traditional solvent extraction in a single technique, and it is closely affiliated to the large field of host-guest chemistry [16]. The mechanism of ELLE is that chiral selectors can selectively recognize single enantiomer and just dissolve in single phase. Therefore, the selection of enantioselective extractant is a key step for ELLE. Over the past few years, interesting supramolecular complexations have been used in chiral separations. Traditionally, various host molecules such as porphyrin [17], crown ethers [18], cyclodextrins (CDs) [19], tartaric acid derivatives [20], and calixarenes [21] were developed as representative extractants to separate organic species, metal ions, and proteins.

Recently, the studies providing the approaches for application of ELLE in multistage processes have drawn more and more attention from

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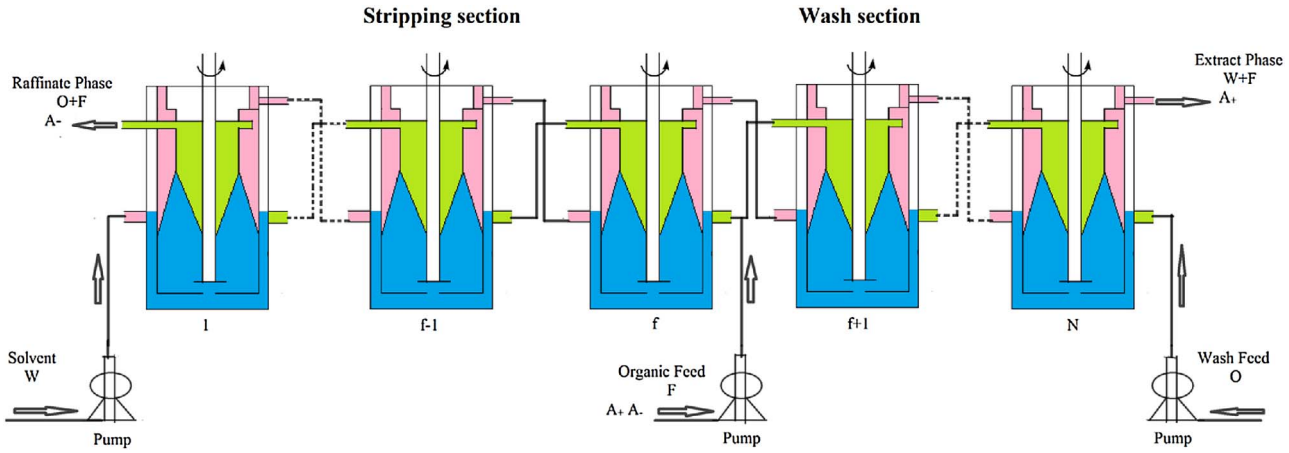

Fig. 1. Flow diagram of the multistage centrifugal counter-current extraction of TA enantiomers.

researchers. Factors affecting the multistage processes are numerous and complicated, it will be a high consumption for studying the relationship of these factors on the separation performance in multistage extraction processes. Therefore, establishing a mathematical model to simplify the research fascinates researchers [22,23]. The established model can be a useful means for predicting the extraction performance and optimizing the separation process and will provide theoretical guidance and support for separation of enantiomers in industrial production.

Tropic acid (TA) is also called DL- scopolic acid. It is an improtant pharmaceutical precursor that can be used as starting materials for the synthesis of chiral drugs. The pharmacological active components of TA is S-TA, and it also carries anti-fugal properties or can be used to treat breast cancer by producing tamoxifen derivatives [24,25]. The traditional methods of chiral separation of TA are chromatography [26], kinetic resolution [27], capillary electrophoresis [28] and so on, but the common drawback of these methods is that they cannot be succeeded in carrying on industrialization.

In this work, we turned to describe a multistage model on the resolution of TA using ELLE in centrifugal contactor separator (CCS), which is a device that integrates mixing, reaction and separation of liquid-liquid systems and as such is an interesting example of process intensification [29,30]. The extraction system was screened firstly to obtain the suitable chiral selector, organic solvent and the operational conditions. According to the chemical and physical equilibrium of single stage, and mass balance, a multistage equilibrium model of ELLE was established. Multistage extraction experiments were carried out to verify the model. The verified model was applied to simulate and optimize the separation process, which can provide theoretical direction for industrial production.

2. Materials and methods

2.1. Materials and apparatus

2.1.1. Materials

Tropic acid (racemate, purity ≥ 98%) was purchased from Energy Chemical (Shanghai, China). Hydroxypropyl-β-cyclodextrin (HP-β-CD) and hydroxyethyl-β-cyclodextrin (HE-β-CD) were supplied by Qianhui Fine Chemicals Co., Ltd. (Shangdong, China). Carboxymethyl-β-cyclodextrin (CM-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD) were supplied by Zhiyuan Fine Chemicals Co., Ltd. (Shangdong, China). Solvents for chromatography were of HPLC grade. All other reagents used in this work were of analytical grade and bought from different suppliers.

2.1.2. Apparatus

HPLC (Series 1260) was supplied by Agilent Technologies Corporation (USA), and pH Meter (PHS-3F) was purchased from Shanghai Instrument Scientific Instrument Co., Ltd. (Shanghai, China). Thermostatic oscillator (SHA-2) was purchased from Pu Dong Physical Optical Instrument Co., Ltd. (Shanghai, China) and CCS (Model V02) was supplied by Yaskawa Electric Co., Ltd. (China). Pump for constant flow was purchased from Tong Tian Biotechnology Co., Ltd. (Shanghai, China). Thermostat bath (DC-1030) was purchased from Ningbo scientz thermostat Co. Ltd. (China). Ultra-pure water system (Heal Force NW) was purchased from Heal Force Instrument Co., Ltd. (Shanghai, China).

2.2. Analytical method

The determination of tropic acid (TA) enantiomers concentrations in extraction phase was analyzed by HPLC (Agilent Technologies Corporation, Series 1260, USA). The quantitive analysis is performed by UV–vis adsorption detector at the wavelength of 225 nm. An Inertsil ODS-3C_{18} column (250 mm × 4.6 mm I.D., 5 μm) is employed and the column temperature is maintained at 25.0 °C. The mobile phase consists of methanol and 23 mmol/L HE-β-CD aqueous solution (pH = 3.00, adjusted with triethylamine and glacial acetic acid), in which the volume ratio is 96:4. The flow rate is 0.6 mL/min. The retention time of (+)-TA was less than that of (−)-TA. This analytical method was adjusted according to the reference [31].

2.3. Extraction experiments

2.3.1. Single-stage extraction experiments

A single-stage extraction experiment was performed according to the reference [32]. All the experiments were carried out in triplicate under the identical condition.

2.3.2. Multistage extraction experiments

Fig. 1 shows the flow diagram of multistage countercurrent extraction of TA enantiomers using a series of CCSs. The substrate (TA racemate) is fed to the multistage system through a constant flow pump at the feed stage (f). The aqueous phase is a phosphate buffer solution with HE-β-CD and the phosphate concentration is maintained at 0.1 mol/L. The aqueous phase is transported into the multistage system at the first stage. In the current system, butyl acetate is used as organic phase. The organic phase is transported into the system from the last stage. In the overall multistage extraction system, Stages 1 to f are the stripping section and Stages f + 1 to N are the wash section. Through the countercurrent extraction process, (+)-TA and (−)-TA are enriched separately in the organic and the aqueous phases.