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Multistage enantioselective reactive extraction of terbutaline enantiomers by hydrophobic phase transfer: Experiment and modeling

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ABSTRACT

Terbutaline (TBTL) sulfate is hardly dissolved in organic solution, which made the enantioselective extraction of TBTL enantiomers by hydrophilic chiral extractant nearly impossible. In this paper, a phase transfer agent, sodium tetraphenylborate (NaTPB) was added to the multistage extraction system. TBTL cationic distributes in the organic phase through formation of an ion pair complex with NaTPB, which made the extraction of TBTL enantiomers possible and significantly improved the capacity of this process. TBTL enantiomers were separate by a fractional reactive extraction process performed on a cascade of centrifugal contactor separators (CCSs), where hydroxylpropyl-β-cyclodextrin and 1-octanol were employed as the chiral selector and organic solvent, respectively. A mathematical model based on equilibrium and mass balance analysis of the process was established. Model predictions agreed well with experimental results. Conditions for symmetric separation are optimized by this model and the optimal conditions are proposed at O/W of 0.6, O/F of 4, NaTPB concentration of 0.03 mol/L, HP-β-CD concentration of 0.1 mol/L, pH of 7 and temperature of 278 K. By modeling and optimization, the minimum stage number was 88 and 98 for $ee_{eq} > 98\%$ and $ee_{eq} > 99\%$.

1. Introduction

Chirality is now an active field for academic research as well as for pharmaceutical industry. Drug enantiomers often show different properties in pharmacology and toxicology [1]. At the present time, the enantiomeric separation is still a large challenge due to their nearly identical physical and chemical properties. Many impressive methods, such as diastereomeric salt crystallization [2,3], chromatographic technique [4–6], capillary electrophorsis [7,8], and kinetic resolution [9,10] have been investigated. The diastereomeric salt crystallization has the advantage of being robust and simple to operate and is still the most frequently applied technology for enantioseparation on an industrial scale and increasingly also the method of choice in the manufacture of active pharmaceutical ingredients (APIs). Nevertheless, the low versatility, excessive solids handling and a maximum yield of 50% of this method limit its application to some extent. There also exist some disadvantages for the kinetic resolution such as time-consuming and low product purity for most racemic compounds. Over the past decade, chromatographic techniques are widely used in industry to purify a small amount of target enantiomers at early development stages and are gaining their importance steadily in large-scale production when they are operated by simulated moving bed (SMB). However, chromatographic techniques should be further developed to increase the productivity and to reduce solvent consumption. Compared with the methods above, enantioselective liquid-liquid extraction (ELLE) has much more potential in the industrial-scale application [11–20].

The ELLE combines the functions of chiral recognition and liquid-liquid extraction in a single technique. Important features of this approach are its potential versatility and ease of continuous operation on different scales. At present, the studies on single-stage extraction equilibrium to seek for a new extraction system are ample. There are so many papers which contribute to development of the field and are summarized in Table 1. Generally, the enantioselectivity of liquid-liquid extraction in a single-stage extraction process is relatively low and multistage extraction is needed. But only several researchers attempt to study the ELLE in a multistage process to gain high purity of the final products and lay the foundations for industrial application of ELLE [14,20,21].

The centrifugal contactor separator (CCS) combines mixer and separator into one device. This integrated device possesses the beneficial properties of the large centrifugal forces and excellent mass transfer.

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Nomenclature

TBTL	terbutaline
HP-β-CD	hydroxyphenyl-β-cyclodextrin
NaTPB	sodium tetraphenylborate
P_0	physical partition coefficient for TBTL, dimensionless
K_a	acid-base dissociation constant, dimensionless
K	equilibrium constants of the complexation reaction between R- or S-TBTL and HP-β-CD, dimensionless
K_1	distribution equilibrium constant of NaTPB between organic and aqueous phases, dimensionless
K_2	dissociation-association equilibrium constant of the ion pair of AiH^+TPB^-, dimensionless
A_i	enantiomers of TBTL
O	organic phase
W	aqueous phase
F	feed phase
N	number of stage
ee	enantiomeric excess, dimensionless
Y	yield, dimensionless

Subscripts

i	index for TBTL enantiomers of different optical rotation, i = R or S
j	stage index
aq	aqueous phase
org	organic phase
0	initial value
eq	equal value

Table 1
Some important enantioseparation systems reported in literature.

Technique	Ref.	Substrate	Selector	Separation factor
HFSLM[a]	[22]	D,L-phenylalanine	(+)-DBTA and D2EHPA[a]	1.71
HFSLM	[23]	Levocetirizine	(-)-DBTA[a]	Non reported
HFSLM	[24]	D,L-phenylalanine	N-decyl-L-hydropxy-proline : copper complex	1.6–1.7
Ultrafiltration	[25]	D,L-phenylalanine	DNA-immobilized chitosan membranes	≈1.6
BLM[a]	[26]	D,L-phenylalanine D,L-phenylglycine	Cinchona alkaloid derivatives	1.2–2.0
HFSLM	[27]	Ketoconazole	SBE-β-CD[a]	1.283
ELLE[a]	[19]	Racemic amlodipine	HP-β-CD and dibenzoyl-D-tartrate	> 10.00
ELLE	[28]	Oxybutynin	HP-β-CD	1.26
ELLE	[29]	α-cyclohexyl-mandelic acid	HP-β-CD	2.02
ELLE	[12]	Underivatized amino acid	N-decyl-L-hydropxy-proline : copper complex	1.28–1.56
ELLE	[14]	3,5-dinitrobenzoyl-(R),(S)-leucine	O-(1-*t*-butylcar-bamoyl)-11-octadecylsulfinyl-10,11-dihydro-quinine	≈3.4 (intrinsic value)
ELLE	[16]	Underivatized amino acid	Chiral ketone	Very high

[a] HFSLM = hollow fiber supported liquid membrane; BLM = bulk liquid membrane; ELLE = enantioselective liquid–liquid extraction; SBE-β-CD = sulfobutylether-β-cyclodextrin; (+)-DBTA = O,O-dibenzoyl-(2S,3S)-tartaric acid; (−)-DBTA = O,O′-dibenzoyl-(2R,3R)-tartaric acid; D2EHPA = di-2-ethylhexyl phosphoric acid.

Multistage ELLE in CCSs has received more and more attention in the last few years [14]. Recently, although a considerable amount of literatures have reported using CCS for some extraction processes [30,31], the studies on experiment and model of multistage ELLE are still very few [14,20,21].

Terbutaline (TBTL, see Fig. 1) as a β_2-adrenergic agonist is usually applied for cure of asthma and lung diseases in clinic. It has been reported that the (R)-terbutaline has agonistic effect and the less active (S)-terbutaline has no remarkable interaction [32,33]. However, the terbutaline is often used as a racemate and separation of TBTL enantiomers is desired for safe use and for improving the drug use efficiency. The separation of TBTL enantiomers has been carried out using several methods such as liquid chromatography [34,35], liquid membrane technique [36], and capillary electrophoresis [37]. Limitation of these methods is their scale up to commercial scale. Enantioselective extraction of TBTL enantiomers by hydrophobic extractant of tartaric-acid derivatives was reported before but the obtained enantioselectivity was 1.14 [38], which is difficult to be used in an industrial process. An equilibrium study for enantioselective extraction of TBTL enantiomers using hydrophilic extractant was reported in our early work and the obtained enantioselectivity was raised to 1.32 [39], which is helpful to design a large-scale extraction process.

This paper reports the use of CCSs for multistage enantioselective extraction of TBTL enantiomers. Hydroxylpropyl-β-cyclodextrin, was used as chiral selectors and sodium tetraphenylborate (NaTPB, see Fig. 1) was used as phase transfer agent. In order to describe the multistage phase transfer reactive extraction of TBTL enantiomers, the process was modeled. The experimental results are compared with the model predictions, and the model was also employed further to optimize the separation process.

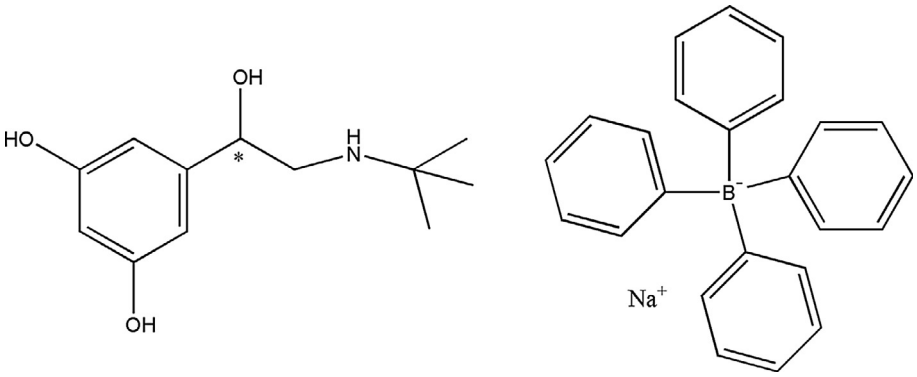

Fig. 1. Chemical structure of terbutaline (right) and sodium tetraphenylborate (left).