Separation and Purification Technology 150 (2015) 170–178

Contents lists available at ScienceDirect

Separation and Purification Technology

journal homepage: www.elsevier.com/locate/seppur

Process optimization of continuous liquid–liquid extraction in centrifugal contactor separators for separation of oxybutynin enantiomers

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ARTICLE INFO

Article history:
Received 28 March 2015
Received in revised form 19 June 2015
Accepted 20 June 2015
Available online 22 June 2015

Keywords:
Multistage simulation
Optimization
Extraction
Chiral separation
Oxybutynin enantiomers

ABSTRACT

A model for multistage enantioselective liquid–liquid extraction (ELLE) of oxybutynin (OBN) enantiomers was built on the basis of single-stage model for chiral extraction of OBN enantiomers and the law of mass conservation in a counter-current cascade of centrifugal contactor separators (CCSs). A series of experiments concerning influence of the extract phase/washing phase ratio (W/O), extractant concentration, pH value, temperature and the number of stages were conducted to verify the multistage equilibrium model. High purity and yield of enantiomer can be obtained by optimizing W/O, extractant concentration, pH value or adding more stages. The model was applied to predict the symmetrical separation of OBN enantiomers. By simulation and optimization, optimal process parameters for the symmetrical separation of OBN enantiomers, namely, pH of 5, HP-β-CD concentration of 0.1 mol/L and W/F of 5 at temperature of 278 K are obtained. With the optimal process parameters, the ee_{eq} (equal enantiomeric excess) can be up to 97% with the number of stages (N) of 100.

1. Introduction

Chirality is playing an increasingly important role in people's life, for example in fragrance, pharmaceutical, and food industries, even in the military field [1]. In the past decades, chiral drugs have become the new target of profit for pharmaceutical companies around the world, with its market share expanding year by year. Usually, one of the two enantiomers is effective, another is ineffective or even harmful [2]. The drug administration department stipulates that only if the racemic form has no significant effect on drug efficacy and toxicity can they consider applications, or else should be made from single chiral compounds [3]. Thus, how to obtain the enantio-pure compounds has become a great challenge to the chemist [4]. Several technologies to obtain single enantiomer such as crystallization [1], gas chromatography [5], liquid chromatography [6], capillary electrophoresis [7,8], supercritical fluid chromatography (SFC) [9], membrane method [10–12], simulated moving bed chromatography (SMB) [13], enzymatic resolution and biocatalysis [14,15], are under development worldwide. Compared with other techniques, enantioselective liquid–liquid extraction (ELLE) has certain rules to follow [16–18] and more mature theory to guide, and it also makes the industrialization of the single enantiomer drug preparation easier to achieve. Therefore, ELLE may be the most promising technology which is cost-effective and easier to scale up to commercial scale.

Oxybutynin, 4-diethylamino-2-butynylalpha-phenylcyclohexa neglycolate (the chemical structure is shown in Fig. 1) [19], is applicable to the treatment of overactive bladder [20], urinary frequency and urgency, neurogenic urinary incontinence [21], idiopathic detrusor instability and nocturnal enuresis [22]. It has been revealed that racemic oxybutynin (Ditropan) exhibits classical antimuscarinic side effects, such as dry mouth. Moreover, preliminary biological results suggest that (*S*)-oxybutynin displays an improved therapeutic profile compared to its racemic counterpart [23]. Studies trying to obtain single OBN enantiomer have been reported in recent years, which are regularly achieved by synthesis [24], HPLC techniques [25,26] and capillary electrophoresis [27], which can only be applied to a small amount of preparation and analysis. Recently, we reported single-stage equilibrium and kinetics study on the reactive extraction of OBN enantiomers using HP-β-CD (Fig. 2) as chiral extractant [28–30]. The best operational selectivity is 1.26 and the intrinsic selectivity is 1.32 based on single stage extraction. Kinetic study shows the extraction accompanied by a fast reaction. The above research shows that full separation of racemic oxybutynin is promising by multistage extraction.

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http://dx.doi.org/10.1016/j.seppur.2015.06.027
1383-5866/

Nomenclature

OBN	oxybutynin
HP-β-CD	hydroxypropyl-β-cyclodextrin
N	number of stages
ELLE	enantioselective liquid–liquid extraction
ee	enantiomeric excess
Y	yield
[ ]	concentration, mol/L
W	flow of aqueous phase (mL min^{-1})
O	flow of organic phase (mL min^{-1})
F	flow of feeding phase (mL min^{-1})
T	temperature (K)
k	distribution ratio, dimensionless
α	enantioselectivity
K	the interfacial complexation constant for OBN enantiomer
P_0	the physical partition coefficient of molecular species
P_i	the physical partition coefficient of ionic species

Subscripts

aq	aqueous phase
extract	the result in extract
eq	equal value
exp	experiment
raffinate	the result in raffinate
i	index for *R*, *S*
j	stage index
0	initial value
org	organic phase
R	*R*-oxybutynin
S	*S*-oxybutynin
sim	simulation

The centrifugal contactor separators possess the beneficial properties of excellent mass transfer and high centrifugal forces, and are suitable for continuous separation of enantiomers by ELLE. In recent years, centrifugal contactor separator devices have been applied in continuously enantioselective liquid–liquid extraction of enantiomers [31–33]. Steensma et al. performed the analysis and optimization of enantioselective extraction in a multi-product environment with a multistage equilibrium model [34].

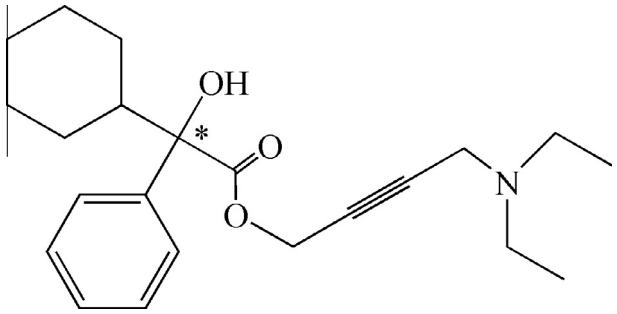

Fig. 1. Molecular structures of oxybutynin.

Multistage enantioselective liquid–liquid extraction is a very complicated chemical engineering process involving complexation, acid-base dissociation and physical partitioning (molecular and ionic OBN enantiomers). Many process parameters such as the extract phase/washing phase ratio (W/O), extractant concentration, pH value, and temperature and the number of stages, have significant influence on multistage ELLE performance. It is difficult to achieve optimal multistage ELLE conditions only by experiment. However, it is easier to obtain optimal extraction conditions by simulation and optimization. Recently, we reported on experiments and modeling on continuous separation of enantiomers by multistage ELLE in centrifugal contactor separators, and good agreements between the experimental results and the model

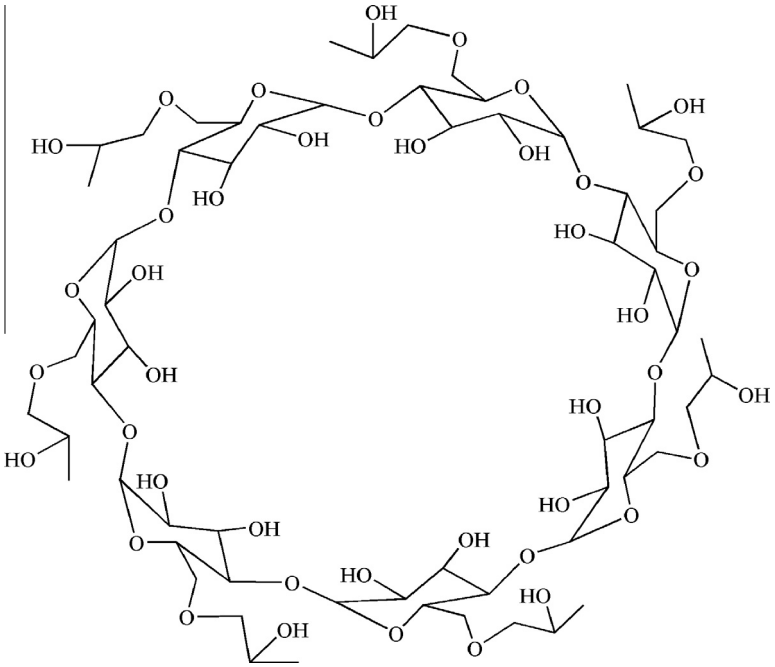

Fig. 2. Chemical structure of HP-β-CD.