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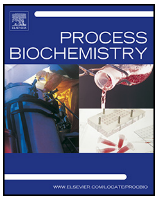

Kinetic study on reactive extraction of metoprolol enantiomers with cyclohexyl (D)-tartrate and boric acid as combined chiral selector

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ABSTRACT

This paper reports on the kinetic study on reactive extraction of metoprolol (MT) enantiomers using cyclohexyl (D)-tartrate (DT) and boric acid (BA) as combined chiral selector in a modified Lewis cell. An interfacial reaction model is applied to understanding the experimental data. The MT enantiomers are extracted enantioselectively from aqueous phase through the interfacial reaction among BA, DT and MT. Important factors that influence the kinetics of extraction are investigated. The optimal conditions for kinetic study were as follows: agitation speed of 75 rpm, interfacial area of 12.56 cm^2, pH of 6, initial DT concentration of 0.075 mol/L, initial BA concentration of 0.1 mol/L, and initial MT concentration of 5 mmol/L at temperature of 5 °C. Important parameters concerning extraction kinetics are evaluated through multiple linear regression analysis of the experimental data. The interfacial reaction is 0.4, 0.6 and 1 order separately with respect to BA, MT and DT, and the total order of reaction is about 2. The forward rate constants have been found to be 5.24×10^{-4} L/(mol s) for (R)-MT and 2.73×10^{-4} L/(mol s) for (S)-MT.

1. Introduction

Distinctive response is often observed when comparing the activities of a pair of pharmaceutical enantiomers, due to the fact that chirality is an intrinsic property of the “building blocks of life” [1]. Therefore, consideration of chirality is of prime importance for the pharmaceutical industry. During the last decades, there has been intense interest in the development and application of methods for obtaining single pure enantiomer drugs. Although the approach of asymmetric syntheses is intrinsically very powerful, its practical use is seriously hampered by its time-consuming development process [2]. This in turn brings a great challenge to the pharmaceutical industry to seek an efficient, reliable and economically feasible separation technique for manufacture of enantiopure products.

There are available techniques for separation of enantiomers, including crystallization [3,4], chromatography [5,6], membrane based approaches [7–13], and so on [14–17]. A comparison of this work with some other techniques is shown in Table 1. These available techniques have significantly contributed to the development of the field. However, some serious limitations, such as low versatility and limited yield of crystallization, high separation costs and low capacity of chromatographic techniques, low transport rate and structural instability of membrane techniques, hamper their wide use in production of single pure enantiomer [18–20]. When compared with the above methods, liquid-liquid reactive extraction is deemed to be an attractive alternative. It can be easily operated in a continuous countercurrent mode and the scales can be easily varied from laboratory separations to bulk processes in the chemical industry [21].

Liquid-liquid reactive extraction has been extensively studied in recent years. Most of the studies focus on seeking for a novel system with high enantioselectivity, but the reports on engineering study are rare [22]. For a reliable reactive extraction system, it requires not only the sufficiently high equilibrium selectivity and capacity, but also a sufficiently high rate of extraction. In a reactive extraction system, the rate of extraction may be determined by reaction kinetics or the mass transfer rate [23]. The rate determining step and the factors that influencing the extraction kinetics should be carefully investigated for selection and design of process equipment and for a reliable scale-up [24–26].

Metoprolol (MT), 1-*iso*-propylamino-3-[4-(2-methoxyethyl)phenoxy]propan- 2-ol (Fig. 1), is an important β-adrenergic blocking agent, which has gained widespread usage in the treatment of angina and hypertension. It is found that the two enantiomers of MT exhibit large difference in the affinity with

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Nomenclature

S	Interfacial area, cm^2
C	Concentration, mol/L
MT	Metoprolol
DT	Cyclohexyl (D)-tartrate
BA	Boric acid
MBD	Complex formed by metoprolol, boric acid and cyclohexyl (D)-tartrate
D	Distribution ratio
e	Enantioselectivity
k	Rate constant
R	Extraction rate, mol/(m^2 s)
t	Time, s
V	Volume of the bulk phase, l
[]	Concentration, mol/L

Subscripts

aq	Aqueous phase
org	Organic phase
+	Forward rate constant
−	Backward rate constant
0	Initial value

Superscript

Greek letter	Reaction order

β1 adrenergic receptor and the metabolic rates in body [27,28]. Therefore, it is interesting to investigate the separation of MT enantiomers. Enantioselective reactive extraction for separation of the enantiomers of some β-adrenergic blocking agents by simultaneous use of tartaric acid derivatives and boric acid as combined chiral selector was reported before [29]. The chiral recognition was derived from formation of a ternary complex by boric acid, tartaric acid derivative and enantiomer, and enantioselectivity higher than 2 was obtained. As a member of the β-adrenergic blocking agent family, it is possible to extend the use of the above reactive extraction system for separation of MT enantiomers. Furthermore, the extraction kinetics of such a system is not reported before, in which the extraction is accompanied by a borate-generation reaction and a coordination reaction. The aim of this paper is to study the kinetics of reactive extraction of MT enantiomers using DT and BA as combined chiral selector in a modified Lewis cell.

2. Materials and methods

2.1. Materials

Metoprolol (racemate) was purchased from Sigma-Aldrich Company. Boric acid was purchased from Titanchem Co., Ltd. (Shanghai, China). Cyclohexyl (D)-tartrate was synthesized in this laboratory with a method reported before [30]. Carboxymethyl-β-cyclodextrin (CM-β-CD) was supplied by Qianhui Fine Chemicals Co., Ltd. (Shangdong, China). And 1,2-dichloroethane was purchased from Huihong Co. Inc. (Hunan, China). More detailed information about MT and other main chemicals was listed in Table 2. Solvent for chromatography was of HPLC grade. All other reagents used in this work were of analytical grade and bought from different suppliers.

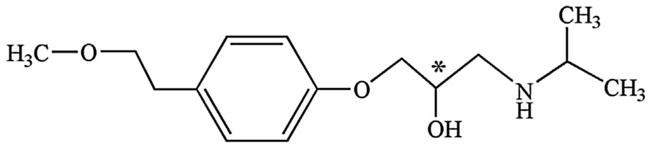

Fig. 1. Chemical structure of metoprolol (MT). The asterisk indicates the chiral carbon.

2.2. Apparatus

The modified Lewis cell used in this work was manufactured at the glass shop of Hunan Institute of Science and Technology. The cell was a glass cylinder with height of 7.5 cm and inside diameter of 6.8 cm and divided into two sections with a teflon circular disc. The interfacial area was altered by installing discs of different inner diameters. To maintain a uniform temperature in the cell, the cell was equipped with a thermo jacket through which water of constant temperature (5 °C) was circulated.

2.3. Analytical method

The quantification of MT enantiomers in aqueous phase was performed by HPLC (Agilent Technologies Corporation, Series 1260, USA) equipped with a UV/visible detector. The analysis was carried out on an Inertsil ODS-3 column (250 mm × 4.6 mm, 5 μm). The mobile phase was composed of 10 mmol/L Na_2HPO_4/H_3PO_4 buffer solution (pH = 5.0) and methanol containing 15 mmol/L CM-β-CD (84:16, v/v). The flow rate was set at 0.8 mL/min, the column temperature was set at 30 °C and wavelength of the UV/visible detection was set at 285 nm. The pH of the aqueous phase was measured with a pH electrode and a pH meter (Leici, PHSJ-3F, Shanghai REX Instrument Factory, Shanghai China). The analytical method is from reference and validated in this work [31].

2.4. Determination of extraction kinetics and screening of chiral selectors

Aqueous phase was prepared by dissolving MT and BA in 0.1 mol/L phosphate buffer solution. Organic phase was prepared by dissolving DT in 1,2-dichloroethane. 110 mL of organic phase was firstly introduced into the cell, and then an equal volume of

Table 1
The advantages and disadvantages of different techniques for enantioseparation of chiral compounds.

Technique	Reference	Advantages	Disadvantages
crystallization	Refs. [3,4]	cost-effective ease of operation	low rate of recovery low versatility
chromatography	Refs. [5,6]	high product purity good versatility	expensive low capacity difficulty in scale-up
membrane based approaches	Refs. [7–13]	ease of operation ease of scale-up cost-effective	instability of membrane low transport rate
chiral extraction	this work	ease of operation ease of scale-up cost-effective	high solvent consumption