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Thermodynamic parameters and isotherm application on enantiomeric separation of levofloxacin using hollow fiber supported liquid membrane system

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ABSTRACT

The thermodynamic parameters ΔH, ΔS and ΔG on enantiomeric separation of levofloxacin were determined. The activation energy (E_a) of the reaction between levofloxacin and (-)-DBTA was 72.96 kJ mol^{-1}. Percentages of extraction and recovery of levofloxacin were 88.35% and 85.57%, respectively. Enantiomeric excess (% *e.e.*) was found to be 80.00%. Further, Langmuir isotherm was applied to the HFSLM system. Thus, it was noted that the Langmuir isotherm showed good agreement with the experimental data with a percentage deviation of 2.29%.

1. Introduction

Ofloxacin ((±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid) is a second generation broad-spectrum fluorinated quinolone antibiotic. It acts as a selective inhibitor of DNA gyrase antibacterial, resulting in greater bactericidal effects [1]. It can lead to the breakage of double strand DNA by selective inhibitor of DNA gyrase [2]. Ofloxacin has high potency, high stability, long half-life but low minimal inhibitory concentration and low toxicity. It has been successful in treating bacterial infections, such as acute bacterial infection of community-acquired pneumonia, chronic bronchitis, uncomplicated skin and skin structure infections [3]. It has been approved for the treatment of acute, uncomplicated gonorrhea and nongonococcal urethritis and cervicitis [4].

Ofloxacin is used as an enantiomeric mixture but the two enantiomers of ofloxacin have different pharmacological profiles [5–7]. As a racemic mixture, ofloxacin contains levofloxacin (Fig. 1(a)) and dextrofloxacin (Fig. 1(b)). Levofloxacin is the eutomer [5]. The antibacterial effect of levofloxacin is twice as effective as the racemic mixture. Further, the antibacterial activity of levofloxacin is 8–128 times greater than the dextrofloxacin [5–7]. Based on pharmacological research [7,8], many researchers have shown interest in determining and separating the two ofloxacin enantiomers. Regulatory authorities in the United States of America, Europe and Asia have indicated that the active enantiomeric drug should be recommended for use [9].

A review of the literature reveals that many researchers have attempted the separation of levofloxacin from its racemate. Techniques such as crystallization [10], semi-preparative enantiomeric separation [11], capillary electrophoresis [12] and chromatography [13–15] have been undertaken. Research has been carried out into enantiomeric compounds, but some deficiencies were found. Chromatography proved unsuitable for manufacturing on a large scale. The semi-preparative separation of enantiomer used many organic solvents [16]. Crystallization of levofloxacin proved to be time consuming and very costly requiring significant capital investment [17].

In recent years, the hollow fiber supported liquid membrane system (HFSLM) has attracted much attention. Many researchers have used this system for separation and wastewater treatment. Enantiomeric separation via HFSLM has been found to be a very interesting topic [18–20]. HFSLM can operate most effectively by means of a single-unit operation [21–23]. A lot of researchers have been attracted to separation using this system [24–26]. The application of HFSLM covers a wide range such as metal separation, organic and pharmaceutical compound extraction and enzymatic transformation [27–30]. The HFSLM process has much potential for enantiomeric separation. A summary of enantiomeric separation using HFSLM is given in Table 1.

The aim of this research is to demonstrate enantiomeric separation of levofloxacin using the HFSLM system based on an enantiomeric extractant (*O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid (Fig. 1(c)). The experiments were carried out under optimum conditions. Furthermore, an adsorption isotherm was applied to the HFSLM system. Finally, the

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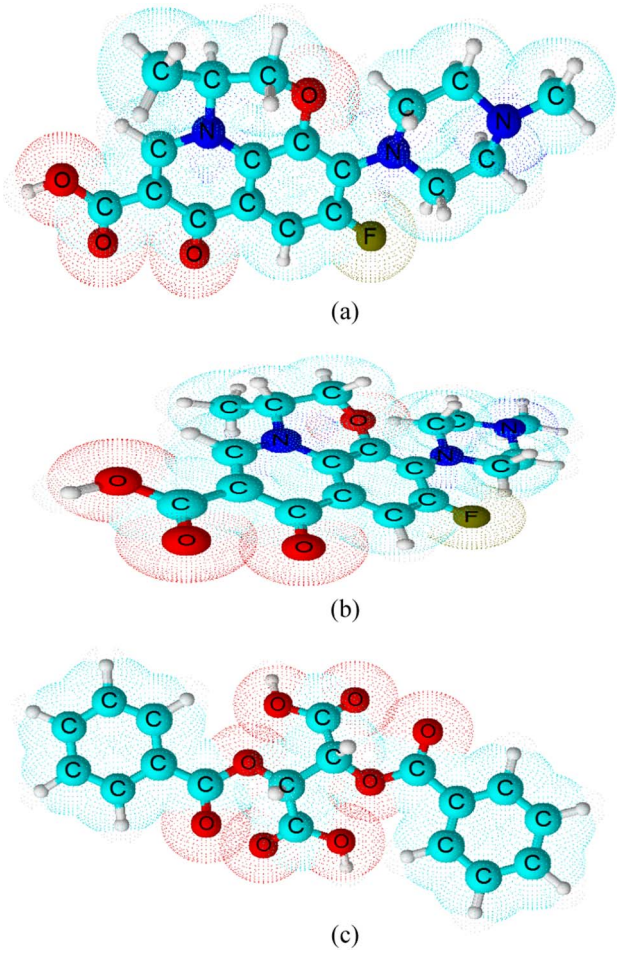

Fig. 1. The structures of (a) levofloxacin, (b) dextrofloxacin, (c) *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid ((-)-DBTA).

experimental results were compared with Langmuir and Freundlich isotherm adsorption models.

2. Theory

The HFSLM system contains many micro-porous polyethylene fibers. The membrane phase consists of an enantiomeric selector ((-)-DBTA) embedded into porous material in order to enhance separation. The feed solution and recovery solution are in contact with the organic membrane. Levofloxacin is transported across the membrane phase from feed solution to recovery solution. The transport mechanism of levofloxacin is shown in Fig. 2. The concentration of levofloxacin is the driving force between the feed and recovery solutions. In the membrane phase, (-)-DBTA can form diastereomeric complexes with enantiomeric drugs and can donate protons for hydrogen bonding by the carboxylic acid groups. The benzoyl groups of (-)-DBTA can take part in hydrophobic interactions. The other part of the (-)-DBTA molecule contains polar hydrophilic groups [23,29].

(-)-DBTA can form two diastereomeric complexes with levofloxacin and dextrofloxacin through coulombic interactions, hydrogen bonding and Van Der Waals interactions [23,38]. However, the low distribution ratio of (-)-DBTA limits its application in the field of enantiomeric separation. The conformation of (-)-DBTA preferentially recognizes levofloxacin [24]. When (-)-DBTA interacts with levofloxacin, levofloxacin-(-)-DBTA complex is formed and becomes more hydrophobic. After extraction, levofloxacin-(-)-DBTA complex is concentrated in the membrane phase. In the feed phase, dextrofloxacin is protonized. The reaction of dextrofloxacin and (-)-DBTA can be ignored. Only the feed phase contains dextrofloxacin. The transport mechanism of levofloxacin is shown in Fig. 2.

The elementary extraction reaction of levofloxacin with (-)-DBTA is shown below in Eq. (1) [23,29,38]:

$$[\text{levofloxacin}]_f + [(-)\text{–DBTA}]_m \underset{k_2}{\overset{k_1}{\rightleftarrows}} [[\text{levofloxacin}]\text{–}(-)\text{–DBTA}]_m \quad (1)$$

where

k_1 is rate constant of the reaction that occurs at the interface of the feed-membrane

k_2 is rate constant of the reaction that occurs at the interface of the membrane-feed

f is defined as feed phase

m is defined as membrane phase

The levofloxacin-(-)-DBTA complex diffuses through the membrane phase to the other side via the concentration gradient. Then, it reacts with hydrochloric acid in the recovery solution. Finally, levofloxacin is moved to the recovery phase as shown in Eq. (2) [23,29]:

$$[[\text{levofloxacin}]\text{–}(-)\text{–DBTA}]_m + [\text{HCl}]_s \underset{k_4}{\overset{k_3}{\rightleftarrows}} [\text{levofloxacin–HCl}]_s + [(-)\text{–DBTA}]_m \quad (2)$$

where

k_3 is rate constant of the reaction that occurs at the interface of the membrane-recovery

k_4 is rate constant of the reaction that occurs at the interface of the recovery- membrane

m suffix is defined as membrane phase

s is defined as recovery phase

Levofloxacin is moved to the recovery solution. The membrane phase contains the enantiomeric selector. Then, it is transferred by the difference in concentration to the interface of the feed-membrane phase.

From previous works [27,39], it is noted that the liquid volume of feed and recovery (receiving) solutions are the same and constant in the experimental setup. The extraction percentage is calculated by:

$$\%\text{Extraction} = \frac{C_{\text{f,in}} - C_{\text{f,out}}}{C_{\text{f,in}}} \times 100 \quad (3)$$

The recovery percentage is calculated as follows:

$$\%\text{Recovery} = \frac{C_{\text{s,out}}}{C_{\text{f,in}}} \times 100 \quad (4)$$

where $C_{\text{f,in}}$ is the initial inlet concentration of component i of the feed solution $C_{\text{f,out}}$ is the outlet equillibrium concentration of component i of the feed solution.

$C_{\text{s,out}}$ is the outlet equillibrium concentration of component i of the recovery solution.

The enantioselectivity of the HFSLM system is defined as the percentage of enantiomeric excess and is calculated according to Eq. (5):

$$\%\text{Enantiomeric excess} = \frac{C_{(levo)} - C_{(dextro)}}{C_{(levo)} + C_{(dextro)}} \times 100 \quad (5)$$

2.1. Estimation of mass transfer via HFSLM system

The estimation of mass transfer via the HFSLM system was determined in the same manner in accordance with Wannachod et al. [39]. The overall mass-transfer resistance (R) equals the sum of the feed phase mass-transfer resistance as in the feed phase, extraction reaction, liquid membrane phase, shell-side, stripping reaction and strip-side resistance. [30,39,40]:

$$R = R_{af} + R_e + R_m + R_o + R_s + R_{as} \quad (6)$$

where