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Comparison of kinetic resolution between two racemic ibuprofen esters in an enzymic membrane reactor

Wei Sing Long, Phei Chia Kow, Azlina Harun Kamaruddin*, Subhash Bhatia

School of Chemical Engineering, Engineering Campus, Universiti Sains Malaysia, 14300 Seri Ampangan, Nibong Tebal, Seberang Prai Selatan, Pulau Pinang, Malaysia

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Abstract

The enantioselective hydrolysis of racemic esters and simultaneous separation of the corresponding optically pure (*S*)-acid as pure isomer is of considerable interest to the pharmaceutical industry as a route to non-steroidal anti-inflammatory drugs. In the present study, an enzymic membrane reactor (EMR) was employed for the optical resolution of racemic ibuprofen ester. EMR consisted of a lipase immobilized polymeric membrane, an organic phase dissolving ester and an aqueous phase to recover the reaction products. The catalytic behaviour of lipase immobilized in a polymeric hollow fibre membrane was investigated using 1-heptyl-ibuprofen ester and 2-ethoxyethyl-ibuprofen ester. The two ester substrates differ in the nature of the alkyl group of the alcohol moiety. The performance of the immobilized enzyme was studied as a function of temperature, pH of phosphate buffer solution and substrate flow rate. The operational conditions that favoured the enzyme selectivity for the (*S*)-ibuprofen esters, in order to obtain the corresponding (*S*)-ibuprofen acid as an optically pure single enantiomer, were identified. Lipase from *Candida rugosa* was used in the hydrolysis of racemic ibuprofen ester. (*R*)-Ibuprofen ester was found to be less reactive in the reaction. Highest enantioselectivity of enzyme was obtained with phosphate buffer solution of pH 8.0 at temperature of 40 °C and at lower substrate flow rate for both racemic 1-heptyl-ibuprofen and 2-ethoxyethyl-ibuprofen esters. The hydrolysis of racemic 1-heptyl-ibuprofen ester gave 4% ee_S, 90% ee_P and E value of 1–4, while the hydrolysis of 2-ethoxyethyl-ibuprofen ester resulted in 31% ee_S, 85% ee_P and E value of 9.5–13 by running the experiment under optimum operating condition in an enzymatic membrane reactor.
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Keywords: Membrane reactor; Ibuprofen; *Candida rugosa*; Hydrolysis; Enantioselectivity; 1-Heptyl-ibuprofen ester; 2-Ethoxyethyl-ibuprofen ester

1. Introduction

Ibuprofen, 2-(4-isobutylphenyl) propionic acid, constitutes the largest single group of drugs used in the treatment of rheumatoid arthritis and as general analgesics, which is a widely used for headache and minor pains [1]. Resolution of racemic ibuprofen by *Candida rugosa* lipase can be achieved through stereospecific esterification in non-aqueous media, while in aqueous media this approach is extended to stereospecific hydrolysis of the corresponding esters. The two enantiomers of racemic ibuprofen show physiologically different behaviour, the (*S*)-enantiomer form exhibiting an anti-inflammatory property [2]. This drug is a chiral molecule and was originally marketed as a racemate. The development and administration of (*S*)-ibuprofen was later in progress when the (*S*)-enantiomer of ibuprofen proved to be 100 times medically more active than the (*R*)-form [3]. The pharmacological activity of this chiral drug is primarily shown by the corresponding (*S*)-enantiomer. The (*R*)-enantiomer is the unwanted enantiomer as it is often the cause of side effects or toxicity. Pharmacological studies have indicated that gastrointestinal problems are the most frequent side effects associated with profens consumption [4]. Much emphasis has been therefore laid on the production of the useful (*S*)-enantiomer in pure form.

Kinetic resolution using enantioselective catalysts (enzymes) has been reported in the literature [5–10]. This process is a practical method for producing single enantiomers of chiral drugs because less energy is needed

* Corresponding author. Tel.: +60 4593 7788x6417; fax: +60 4594 1013.
E-mail address: chazlina@eng.usm.my (A.H. Kamaruddin).

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and is a comparatively cheaper process. In the production of chiral drugs by enzymic hydrolysis reaction, the racemic mixture undergoes a kinetic resolution in the presence of an enantioselective enzyme, i.e. lipase from *C. rugosa*. The kinetic resolution in this work is based on substrate selectivity since the lipase is enantioselective for only one of the two substrates (i.e. (*R*)- and (*S*)-enantiomers) present in a racemic mixture. The two enantiomers of a racemate react at different rates with the chiral catalyst (enzyme), in which the enzyme shows a greater stereopreference towards one of the two enantiomers. An example is the kinetic resolution of racemic ibuprofen ester via enzymic hydrolysis reaction as shown in Fig. 1.

Kinetic resolution occurs when k_R is not equivalent to k_S. In this work, the (*S*)-enantiomer of ibuprofen acid has a higher reaction rate than the (*R*)-enantiomer ($k_S >> k_R$). The pure product (*S*)-ibuprofen acid is transported through the membrane pores into the aqueous phase because the product (*S*)-ibuprofen acid has higher water solubility than (*R*)-ibuprofen acid.

The application of membrane technology in the fine chemical and pharmaceutical industry is of worldwide research interest [11,12]. Enzymic membrane reactors (EMR) comprise a combination of enzymic reaction, substrate recovery and product separation in one unit. The enzymic membrane reactor system consists of a polymeric hollow fibre membrane and the immobilized enzyme as catalyst. The membrane is used as separation medium and immobilization support to retain the enzyme. The hollow fibre configuration is widely used with enzyme immobilized on the membrane [11–15]. Immobilized enzymes are confined in a well-defined region, e.g. the spongy region. This configuration is more advantageous because of its longer contact time of reactants with the enzymes due to its high surface to volume ratio that permits high enzyme density in a small reaction volume. The reaction media in the enzymic membrane reactor can be non-aqueous (organic), two-liquid phases (organic-aqueous) or multiphase (enzymic reaction in an aqueous-organic medium with the enzyme present as the solid form). An added advantage of membrane reactor application is the reusability of the membrane by removal of inactivated enzymes and replacement with new enzyme.

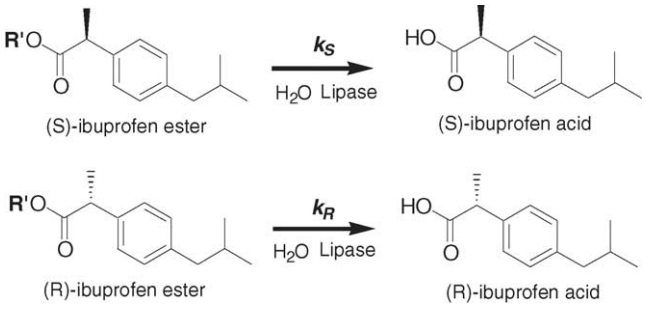

Fig. 1. Kinetic resolution of racemic ibuprofen ester, via lipase catalyzed hydrolysis reaction, *R′* designates an alkyl group.

The objectives of the present work are to compare the kinetic resolution of two different ibuprofen esters, viz. 1-heptyl-ibuprofen ester and 2-ethoxyethyl-ibuprofen ester and to identify the optimum operating conditions favouring the enzyme stereoselectivity to obtain the optically pure single enantiomer, i.e. the (*S*)-ibuprofen acid.

2. Biphasic organic/aqueous catalytic membrane reactor

The biphasic catalytic membrane reactor is a two-separated phase membrane reactor. The membrane separates the two immiscible phases with the two phases flowing along two separate circuits of the membrane module. The organic phase was recirculated in the shell side of the membrane, while buffer solution flowed in the lumen side. Fig. 2 shows the interaction of the enzyme–substrate (organic)-aqueous in the membrane spongy region with enzymic hydrolysis reaction taking place in the membrane. Substrate or racemic mixture in the organic phase partitioned from the shell side and reacted with immobilized enzyme in the membrane where the hydrolysis reaction took place and the product (*S*)-ibuprofen acid was extracted into aqueous phase as shown in Fig. 3. Bioconversion and separation of chiral compounds occur simultaneously, with the enantioselective enzyme as a chiral system and the membrane as a barrier that separates the converted enantiomer. The organic substrate could not pass through the membrane due to non-polarity and insolubility of the substrate as well as hydrophilicity of the membrane. The membrane is wetted by the aqueous phase because the membrane material is hydrophilic. The (*S*)-ibuprofen acid product is water-soluble and freely passed through the membrane into the aqueous phase in the lumen.

3. Experimental procedures

3.1. Materials and chemicals

Lipase from *C. rugosa* EC 3.1.1.3 (Type VII, 724 units per mg solids using olive oil as substrate) was supplied by Sigma–Aldrich (MI). (*R*,*S*)-ibuprofen acid 99% and (*S*)-ibuprofen acid 99% were purchased from Acros (Belgium). Other chemicals and reagents used were of analytical grade. 2-ethoxyethanol 99% and isooctane 99% were supplied by Acros (Belgium). 1-Heptanol 99 % was supplied from Merck (Germany).

3.2. Chemical synthesis of racemic ibuprofen ester

(*R*,*S*)-Ibuprofen acid (10 g, 0.048 mol), *p*-toluenesulphonic acid (0.2 g, 1.11 mmol) and 1-heptanol (5.57 g, 0.096 mol, 13.5 ml) were dissolved in 88.5 ml of isooctane. The solution was refluxed for 8 h using a Dean and Stark

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