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Lipase-catalyzed dynamic kinetic resolution of racemic ibuprofen ester via hollow fiber membrane reactor: Modeling and simulation

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ABSTRACT

The enantio-separation of racemic ibuprofen ester via enzymatic membrane reactor is studied. The lipase-catalyzed resolution technique integrates kinetic resolution (KR) with *in situ* racemization resulting in 100% optically pure product. A mathematical model of lipase-immobilized hollow fiber membrane reactor incorporating dynamic kinetic resolution (DKR) of racemic ibuprofen ester is proposed. In the process of developing theoretical models for DKR, two zones were considered: (i) enzymatic hydrolysis of substrate in membrane matrix support and (ii) simultaneous racemization of unreacted substrate outside the membrane. The first part of the modeling work emphasized on the derivation of DKR rate equations for both enantiomers, based on the enzymatic resolution mechanism. The second part of the DKR model was derived by considering the mass transfer in the DKR rate equation. The model was solved using two numerical methods by means of MATLAB® build-in solver. The first numerical technique was based on the explicit Runge–Kutta to solve the system of non-linear first-order ordinary differential equations (ODEs) of DKR reaction rate. The second approach was a collocation technique for solving the non-linear second-order ODEs of the convective hydrolysis–racemization phenomena in the membrane layer. A number of process parameters were studied in order to investigate their effects on the concentration profiles and separation efficiency in terms of enantiomeric excess, i.e. ee_s and ee_p by simulating the models. The model parameters include Bodenstein number, B_0, Thiele modulus, Φ^2 and dimensionless racemization constant, γ. The simulation results showed that the hollow fiber membrane operates effectively at $B_0 = 8.68$, $\gamma = 10$, $\Phi^2 = 1$ with $ee_s = 2\%$ and $ee_p = 98.5\%$.

1. Introduction

In recent years, enantio-separation of chiral compounds via resolution approach has been practiced by many researchers [1–21]. However, only a few of them carried out chiral resolution in the hollow fiber membrane configuration [14–19]. There are limited numbers of models that have been developed to describe the resolution process, especially in enantio-selective dynamic kinetic resolution (DKR) of racemic ibuprofen ester. A simple time-course model proposed by Wen et al. [12] addressed the DKR process by considering the product inhibition and enzyme deactivation effects. Then, a better kinetic model was developed to investigate the effects of lipase activation and deactivation, racemization and reactive extraction of (*R*)- and (*S*)-enantiomers into the aqueous phase [14]. Unfortunately, emphases were not given to the mechanism of substrate transport in the proposed models. Besides, the DKR models reported in the literature are of the simplified version with a number of assumptions made [13,15,16].

On the other hand, typical kinetic resolution models demonstrated in the literature were based on the numerical solution of the dimensionless balanced equations [18,22]. The models are governed by the mass transfer and reaction kinetics with reference to the modified Michaelis–Menten rate equation that represents substrate and product inhibitions. However, the proposed kinetic resolution models without reversible racemization were not suitable to describe the DKR system. In this context, a complete model should be established in order to illustrate the chemo-enzymatic of DKR which incorporates the mass transport phenomenon in a hollow fiber membrane. The model should cover the coupled-reaction of the enzymatic hydrolysis and *in situ* racemization as well as the transport mechanism of (*R*)- and (*S*)-enantiomers on the membrane surface.

Enzymatic reactor has become particularly attractive in the production of optically pure compounds due to the milder condition and lower energy consumption [17]. Two types of commonly used biocatalytic reactors such as batch bioreactor and enzyme-immobilized membrane reactor have been employed in the resolution of chiral drugs [12–21]. In this work, the enzyme is immobilized on a 50 kDa hydrophilic synthetic membrane which is made of polyacrylonitrile (PAN). The high surface-to-volume

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Nomenclature

a	fiber internal radius as indicated in Fig. 1 (mm)
b	fiber dense layer radius (mm)
c	fiber external radius (mm)
B_0	Bodenstein number
D_{eff}	effective diffusion coefficients for ibuprofen ester ($cm^2\ min^{-1}$)
ee_s	substrate enantiomeric excess
ee_p	product enantiomeric excess
F	volumetric flow rate of substrate stream ($mL\ min^{-1}$)
k_{cat}	hydrolysis reaction constant ($mmol\ L^{-1}$)
K_{rac}	racemization rate constant ($mmol\ L^{-1}\ h^{-1}$)
K_m	Michaelis–Menten constant for racemic ibuprofen ester ($mmol\ L^{-1}$)
K_{mA}	Michaelis–Menten constant for (*S*)-ibuprofen ester ($mmol\ L^{-1}$)
K_{mB}	Michaelis–Menten constant for (*R*)-ibuprofen ester ($mmol\ L^{-1}$)
K_{nI1}, K_{nI2}	non-competitive alcohol inhibition constant ($mmol\ L^{-1}$)
$K_{uS1}, K_{uS2}, K'_{uS1}$	uncompetitive substrate ester inhibition constant ($mmol\ L^{-1}$)
L	effective length of the hollow fiber (cm)
N	number of hollow fiber
$[E]$	enzyme concentration (g/L)
E	enzyme molecule in Fig. 3
E_T	total enzyme molecule
ES	enzyme–substrate complex
ES^*	enzyme–((*R*)-ester) complex
ESS^*	enzyme–((*S*)-ester)–((*R*)-ester) complex
EI	enzyme–inhibitor (alcohol) complex
ESI	enzyme–substrate–inhibitor (alcohol) complex
S	substrate (*S*)–ester molecule
S^*	substrate (*R*)–ester molecule
P'	product (*S*)–ibuprofen acid molecule
I	inhibitor (alcohol) molecule
r	fiber radius (mm)
R	dimensionless radial coordinate
s_{T0}	initial concentration of racemic ibuprofen ester ($mmol\ L^{-1}$)
s_i	substrate concentration of racemic ester ($mmol\ L^{-1}$)
s_{OH}	concentration of base catalyst (trioctylamine) ($mmol\ L^{-1}$)
s_A	concentration of (*S*)-ibuprofen ester ($mmol\ L^{-1}$)
s_{A0}	initial concentration of (*S*)-ibuprofen ester ($mmol\ L^{-1}$)
S_A	dimensionless concentration of (*S*)-ibuprofen ester
s_B	concentration of (*R*)-ibuprofen ester ($mmol\ L^{-1}$)
s_{B0}	initial concentration of (*R*)-ibuprofen ester ($mmol\ L^{-1}$)
S_B	dimensionless concentration of (*R*)-ibuprofen ester
s_{I0}	initial concentration of alcohol ($mmol\ L^{-1}$)
s_I, s_{by}	non-competitive alcohol inhibitor concentration ($mmol\ L^{-1}$)
S_{by}	dimensionless concentration of alcohol ($mmol\ L^{-1}$)
t	reaction time (min)
t_0	initial reaction time (min)
ν	reaction rate for hydrolysis of ibuprofen ester ($mmol\ L^{-1}\ h^{-1}$)
ν_{max}	maximum reaction rate for hydrolysis of ibuprofen ester ($mmol\ L^{-1}\ h^{-1}$)
ν_A	reaction rate for DKR of (*S*)-ibuprofen ester ($mmol\ L^{-1}\ h^{-1}$)
ν_B	reaction rate for DKR of (*S*)-ibuprofen ester ($mmol\ L^{-1}\ h^{-1}$)
V_{eq}	dynamic equilibrium rate ($mmol\ L^{-1}\ h^{-1}$)
$u(r)$	radial flow velocity of bulk substrate at the shell side of reactor ($cm\ s^{-1}$)

Greek letters

Θ_A	dimensionless Michaelis–Menten constant for (*S*)-ibuprofen ester
Θ_B	dimensionless Michaelis–Menten constant for (*R*)-ibuprofen ester
ξ_{IP}	dimensionless by-product (alcohol) inhibition constant
ξ_{IS}	dimensionless substrate (*R*)-ibuprofen ester inhibition constant
ξ'_{IS}	dimensionless substrate (*S*)-ibuprofen ester inhibition constant
ψ_A	dimensionless enzymatic DKR constant respect to (*S*)-ibuprofen ester
ψ_B	dimensionless enzymatic DKR constant respect to (*R*)-ibuprofen ester
τ	dimensionless time constant
φ	dimensionless product inhibition fraction
α_p	membrane porosity
Φ^2	Thiele modulus for enzymatic hydrolysis of ibuprofen ester
γ	dimensionless racemization constant

ratio in the hollow fiber membrane is an advantage for membrane reactor as it allows high biocatalyst density in a relatively small reactor volume. The hollow fiber membranes are assembled into a bundle of parallel tubes in a cylindrical cartridge. The porous membrane wall functions as a selective barrier, creates two distinct compartments inside the membrane reactor, namely luminal side and shell side. Both the substrate racemic ester and aqueous buffer streams flow separately at shell and lumen sides respectively during the operation of membrane reactor. The hydrophilic characteristic of the membrane prevents the organic phase to mix with the aqueous phase. Consequently, the excess racemic ester as well as the unreacted substrate ester ((*R*)-ibuprofen ester) remained in the shell side after the hydrolysis process, which took place in the membrane matrix. Simultaneously, an *in situ* racemization of the (*R*)-ibuprofen ester occurs at the shell side in the presence of trioctylamine (base catalyst). However, only the product ((*S*)-ibuprofen acid) which is highly soluble in aqueous phase diffuses through the membrane and enters the lumen side [17]. As a result, the product and substrate can be easily separated. Moreover, with the continuous racemization, 100% theoretical conversion and ee_p could be obtained at the end of the process.

The mathematical modeling and simulation for the DKR system are divided into two parts. Each part discusses a different DKR models: (i) reaction rate of DKR and (ii) DKR-incorporated mass transfer which describes the diffusion phenomena. Both parts are represented using the respective mathematical equations, which to be numerically solved using different approaches. In order to describe the DKR reaction, two first-order ODE equations, i.e. hydrolysis reaction with respect to (*S*)-ester and racemization with respect to (*R*)-ester, were proposed. These equations were numerically solved using the initial value problem (IVP) in order to simulate several concentration profiles. The incorporation of diffusion within the system introduces the complicated coupling reaction of hydrolysis and racemization respectively in the matrix support and outside the membrane. This convective hydrolysis–racemization phenomenon for a hollow fiber membrane module is transformed into a system