Effects of simultaneous internal and external mass transfer and product inhibition on immobilized enzyme-catalyzed reactor

Ali E. AL-Muftah a,*, Ibrahim M. Abu-Reesh b

a Petroleum Engineering Department, Bahrain Petroleum Company (BAPCO), Awali, P.O. Box 25504, PETEX, Bahrain
b Department of Chemical Engineering, King Fahd University of Petroleum & Minerals (KFUPM), Dhahran 31261, Saudi Arabia

Received 13 February 2005; received in revised form 23 July 2005; accepted 2 August 2005

Abstract

A mathematical model has been developed for predicting the performance and simulation of a packed bed immobilized enzyme reactor performing lactose hydrolysis, which follows Michaelis–Menten kinetics with competitive product (galactose) inhibition. The performance characteristics of a packed bed immobilized enzyme reactor have been analyzed taking into account the simultaneous effects of internal and external mass transfer limitations. The model design equations are then solved by the method of weighted residuals such as Galerkin’s method and orthogonal collocation on finite elements.

The effects of simultaneous internal and external mass transfer coupled with product inhibition have been studied and their effects were shown to reduce internal effectiveness factor. The effects of product inhibition have been investigated at different operating conditions correlated at different regimes using dimensionless $\beta_{xo}$ ($St$, $Bi$, $\theta$, $\phi$). Product inhibition was shown to reduce substrate conversion, and to decrease effectiveness factor when $\beta_{s} > \beta_{xo}$; however, it increases internal effectiveness factor when $\beta_{s} < \beta_{xo}$. The effectiveness factor is found to be independent of product inhibition at crossover point at which $\beta_{xo}$ is defined. Effects of $St$ and $Bi$ have been investigated at different kinetic regimes and the results show their effects have a strong dependence on kinetic parameters $\theta$, $\gamma$ (i.e. $K_{m}/K_{p}$) and $\beta_{xo}$. The dimensionless residence time at crossover point, $\beta_{xo}$, has been correlated with kinetic and mass transfer parameters.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Biocatalysis; Enzyme bioreactors; Immobilisation; Immobilised enzymes; Product inhibition; Internal mass transfer

1. Introduction

Lactose is a disaccharide that occurs naturally in both human and cows milk which accounts for 40% of milk solids. It is widely used in baking and commercial infant-milk formulas. The hydrolysis of lactose, the sugar of milk to glucose and galactose has received much attention in recent years [1,2]. It is used for production of low lactose milk for consumers that suffer from lactose deficiency (70% of the world population is lactose deficient, Carrara and Rubiolo [3]). The hydrolysis product is sweeter and more soluble and biodegradable than lactose and can be used in further biotechnological processes.

The amount of lactose produced annually from whey is about 3.3 million tonnes [3]. It is produced as cheese whey, which is the liquid, separated after milk coagulation. It represents about 90% of the milk volume. The disposal of whey is considered a serious pollution problem facing dairy industry because of its high pollutant content (COD of about 70,000ppm). Acid hydrolysis of lactose is not favorable because of color formation and fouling of ion exchange resins used in processing. A better alternative is the use of enzymatic method. Enzymatic lactose hydrolysis is carried out by adding $\beta$-galactosidase commonly known as lactase to milk, skim milk or whey to hydrolyze lactose prior to pasteurization. Lactase is commercially available and used in large-scale processes. One problem associated with the use of lactase is that complete hydrolysis is difficult to achieve because of product (galactose) inhibition and production of isomer of lactose, allolactose. Several microbial sources of
Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>external surface of support per unit volume of reactor</td>
</tr>
<tr>
<td>$C_P$</td>
<td>product concentration in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$\langle C_P \rangle$</td>
<td>average product concentration in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$C_{Pb}$</td>
<td>product concentration in the bulk liquid (reactor phase)</td>
</tr>
<tr>
<td>$C_{P0}, C_P0$</td>
<td>product concentration at reactor inlet</td>
</tr>
<tr>
<td>$C_S$</td>
<td>substrate concentration in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$\langle C_S \rangle$</td>
<td>average substrate concentration in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$C_{Sb}$</td>
<td>substrate concentration in the bulk liquid</td>
</tr>
<tr>
<td>$C_{S0}, C_S0$</td>
<td>substrate concentration at reactor inlet</td>
</tr>
<tr>
<td>$D_{Sp}, D_{Pp}$</td>
<td>effective substrate and product diffusivity in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$D_{Sz}, D_{Pz}$</td>
<td>effective substrate and product axial dispersion coefficient</td>
</tr>
<tr>
<td>$K_e$</td>
<td>reaction equilibrium constant</td>
</tr>
<tr>
<td>$K_L$</td>
<td>mass transfer coefficient</td>
</tr>
<tr>
<td>$K_{La}$</td>
<td>volumetric mass transfer coefficient</td>
</tr>
<tr>
<td>$K_{LS}, K_{LP}$</td>
<td>mass transfer coefficient in substrate and product side, respectively</td>
</tr>
<tr>
<td>$K_m$</td>
<td>intrinsic Michaelis–Menten constant</td>
</tr>
<tr>
<td>$R$</td>
<td>length of the reactor</td>
</tr>
<tr>
<td>$r$</td>
<td>radial coordinate of distance in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$R_b$</td>
<td>dimensionless reaction rate at the surface of the spherical particles</td>
</tr>
<tr>
<td>$R_p$</td>
<td>local product production rate per unit of catalytic particle volume</td>
</tr>
<tr>
<td>$\langle R_p \rangle$</td>
<td>average product production rate</td>
</tr>
<tr>
<td>$R_s$</td>
<td>local substrate consumption rate per unit of catalytic particle volume</td>
</tr>
<tr>
<td>$\langle R_s \rangle$</td>
<td>average substrate consumption rate</td>
</tr>
<tr>
<td>$t$</td>
<td>time inside reactor</td>
</tr>
<tr>
<td>$u$</td>
<td>superficial fluid phase velocity inside the reactor</td>
</tr>
<tr>
<td>$v_{max}$</td>
<td>maximum reaction rate per unit of catalytic particle volume</td>
</tr>
<tr>
<td>$x, \xi$</td>
<td>reactor radial and axial coordinate</td>
</tr>
<tr>
<td>$Bi$</td>
<td>Biot number</td>
</tr>
<tr>
<td>$Da$</td>
<td>Damkohler number</td>
</tr>
<tr>
<td>$D_e$</td>
<td>inverse of the equilibrium constant</td>
</tr>
<tr>
<td>$P_e$</td>
<td>dimensionless product concentration in an immobilized enzyme support particle</td>
</tr>
<tr>
<td>$\langle P \rangle$</td>
<td>dimensionless average product concentration in an immobilized enzyme support particle</td>
</tr>
</tbody>
</table>

Dimensionless variables

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathrm{Bi}$</td>
<td>Biot number</td>
</tr>
<tr>
<td>$\mathrm{Da}$</td>
<td>Damkohler number</td>
</tr>
<tr>
<td>$\rho$</td>
<td>mass density</td>
</tr>
</tbody>
</table>

Greek symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>effective diffusivity ratio of substrate and product in axial and interparticle, respectively</td>
</tr>
<tr>
<td>$\beta, \beta_s$</td>
<td>dimensionless residence modulus</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>reactor voidage</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Thiele modulus</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>dimensionless inhibition modulus</td>
</tr>
<tr>
<td>$\eta$</td>
<td>internal effectiveness factor</td>
</tr>
<tr>
<td>$\eta_e$</td>
<td>external effectiveness factor</td>
</tr>
<tr>
<td>$\theta$</td>
<td>dimensionless Michaelis–Menten constant</td>
</tr>
<tr>
<td>$\tau$</td>
<td>dimensionless time</td>
</tr>
<tr>
<td>$\xi$</td>
<td>dimensionless radial coordinate</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>dimensionless axial coordinate</td>
</tr>
</tbody>
</table>

$\beta$-galactosidase and reactor types have been used for the purpose of economic production of low lactose milk. Lactose hydrolysis in plug flow reactor gives higher conversion compared to continuous stirred tank reactor although the latter has good mixing and lower construction cost.

1.1. Kinetics of lactose hydrolysis

Kinetics of lactose hydrolysis has been studied extensively in the literature [1,2,4]. Michaelis–Menten model with competitive product inhibition by galactose is widely used to describe the hydrolysis [1]. Different types of bioreactor [5,6] and biocatalyst [1,2,7,8] have been investigated for lactose hydrolysis.

1.2. Modeling immobilized enzyme reactor

Enzyme immobilization offers a number of advantages over enzymes in suspension. Immobilization permits the reuse of the enzyme and may provide a better environment...
for catalyst activity and also it reduces the cost of down stream processing in addition to good product quality. These factors make it widely used in industry where many enzyme-catalyzed reactions are of industrial interest.

Continuous processes with immobilized enzymes can be carried out in different types of reactor. Lortie and Pelletier [9] have shown that plug-flow reactor model with external mass transfer resistance can represent adequately a fixed bed immobilized enzyme reactor for moderate or low dispersion. However, dispersed plug flow reactor model is superior in predicting the performance of packed bed reactor for isomerization of glucose to fructose [10]. Furthermore, a comprehensive model for a general rate expression such as reversible Michaelis–Menten kinetics was developed by Abu-Reesh [11] neglecting internal mass transfer resistance. A fluidized bed reactor model taking into account the reversibility of the reaction, inhibition by substrate and products or diffusional limitations was developed [12,13].

Among these reactors, packed bed enzyme-catalyzed reactors have promising applications in many biochemical processes [11,14,15] and biological processes [16] having advantages of longer solid retention times and ease of operation and relatively high conversion rates.

In spite of the well-established industrial application of packed bed immobilized enzyme reactors, little effort has been made toward mathematical modeling of such reactor with kinetics other than Michaelis–Menten equation. In most of the cases, enzyme immobilization is accompanied by mass transfer limitation. Different factors have to be taken into consideration in modeling of immobilized enzyme reactors:

1. Mode of operation, whether the steady state or transient.
2. Mass transfer limitations (external, internal and simultaneous).
4. The kinetics of enzyme catalyzed reaction.
5. The axial dispersion effects.
6. Types of reactors: packed bed, CSTR, hollow fiber bioreactor (HFBR) or fluidized bed reactor (FBR).
7. The stability of enzyme and effect of temperature on the enzyme activity.
8. Heat transfer effects.

Quantitative knowledge of the effect of these factors on the reactor performance and simulation is required for efficient design of immobilized enzyme reactor. Several isothermal steady state models have been considered using one or more of these phenomena in various combinations.

External mass transfer limitation is shown to have significant effect on the performance of immobilized enzyme reactor [17] using reversible enzyme reactions [18]. Analytical solution was given by Carrara and Rubiolo [4] and tested with experimental setup, for evaluation of mass transfer coefficient and conversion. However, Kobayashi and Mee-Young [19] were the first to apply the dispersion model to immobilized enzyme reactor. Dispersed plug flow reactor model (taking into account the effect of axial dispersion on flow reactor) is shown to be superior in predicting the performance of packed bed reactor for isomerization of glucose to fructose described by Michaelis–Menten [10,20]. Furthermore, dynamic behavior of plug flow reactor was studied and the kinetics parameters were estimated by fitting the experimental data to satisfy the dynamic response RTD curve. Michaelis–Menten kinetics is considered in experimental validation of PFR [21,22] and in spiral reactor [6]. Abu-Reesh [11] developed a general dimensionless model for predicting the steady state performance of immobilized dispersed plug-flow reactor performing reversible Michaelis–Menten kinetics. The effects of dimensionless parameters of Damkohler number (Da), Stanton number (St), Peclet number (Pe), the equilibrium constant and input substrate concentration were studied parametrically. Abu-Reesh [11] found that conversion is almost complete for high Da and St number especially in plug flow reactor which gives higher conversion compared to other reactor models. Furthermore, it is found that substrate conversion increases with increasing substrate external diffusion (i.e., decreasing diffusion resistance) and residence time. Moreover, the higher the St number, the higher the maximum conversion that can be achieved. The effect of the equilibrium constant on reactor performance was also studied. Carrara et al. [23] studied the behavior of fixed bed reactor considering steady-state conditions and external mass transfer resistance in the fluid around spherical catalyst particles. Their results showed the importance of hydrodynamic and kinetic reaction parameters for error reduction in the prediction of experimental behavior.

When enzyme is attached to a porous carrier matrix the internal mass-transfer limitations have a great influence on the intrinsic kinetics. It is necessary to develop comprehensive models that quantitatively account for the internal diffusional effects in addition to external one. The internal diffusional limitations with external diffusional effects can be quantified through the use of an effectiveness factor, η, or apparent kinetic parameters using the idealized plug flow reactor assuming Michaelis–Menten kinetics [24–30]. Isothermal, steady state and omission of the axial dispersion term were assumed in these analyses. The Biot number, effectiveness factor and Thiele modulus were studied numerically using Taylor expansion and orthogonal collocation methods. Theoretical analysis was incorporated with experimental data to correlate mass transfer coefficient [26].

Many researchers considered coupled internal and external diffusional limitation [12,31–37]. Coupled internal and external diffusional limitation were considered in development of a general CSTR model in which the effect of membrane diffusional resistance and Biot number were taken into account for prediction the effectiveness factor of an encapsulated enzyme particle [38]. Also, analytical solution of effectiveness factor was developed for Michaelis–Menten kinetics. Bódalo et al. [12] and Manjon et al. [39] considered the external and internal diffusional limitations and their model was solved numerically for reversible Michaelis–Menten kinetics with competitive product inhibition in a fluidized bed.
Mathematical analysis

2.1. Internal and external mass transfer—reaction model

Consider a packed bed immobilized enzyme reactor of length, \( L \), fluid velocity, \( u \), where \( C_{b0} \) and \( C_{p0} \) are the substrate and product inlet concentrations, respectively.

2.1.1. Assumptions

The mathematical model that describe the behavior of a packed bed immobilized enzyme reactor has been formulated using the following assumptions:

1. Isothermal packed bed immobilized enzyme reactor.
2. Enzyme activity is uniform throughout the reactor.
3. The enzyme is immobilized evenly inside porous spherical particles, which are uniformly packed in the reactor.
4. The convective velocity is uniform.
5. The hydrodynamics of the fluid bed is described by the dispersed plug flow model.
6. Pressure drop across the reactor and radiial concentration gradient in the bulk fluid phase are assumed to be negligible.

7. Assume no enzyme deactivation.
8. The enzyme can catalyze a specific reaction according to reversible Michaelis–Menten kinetics.
9. The enzymatic reaction is monosubstrate and yields only one product.
10. Fick’s law can model the substrate and product diffusion inside the catalytic particle. The effective diffusivity does not change throughout the particles and is independent of the concentration.

2.1.2. Mass balance on the reactor

Under these assumptions, the differential mass balance in the liquid bulk phase for the substrate and the product can be written respectively as,

\[
\frac{\partial C_{b0}}{\partial t} = D_{b0} \frac{\partial^2 C_{b0}}{\partial z^2} - \epsilon \frac{\partial C_{b0}}{\partial z} - (1 - \epsilon) \nu (C_{b0} - C_{b1}|_{z=L}) 
\]

\[
\frac{\partial C_{p0}}{\partial t} = D_{p0} \frac{\partial^2 C_{p0}}{\partial z^2} - \epsilon \frac{\partial C_{p0}}{\partial z} - (1 - \epsilon) \nu (C_{p0} - C_{p1}|_{z=L}) 
\]

where \( \nu \) is the reactor voidage, \( D_{b0} \), \( D_{p0} \) are the effective substrate and product axial diffusivity (or axial dispersion coefficients) and \( K_L \) is the overall mass transfer coefficient.

The initial condition for reactor start-up contains the immobilized enzyme particles suspended in a solution without substrate or product. At \( t=0^+ \), the substrate and product are continuously pumped into and out of the reactor at constant rate.

at \( z = 0^- \), \( C_{b0} = 0 \).

Eqs. (1) and (2) are subjected to the following boundary conditions requiring continuity of fluxes at both ends of the reactor [41] for both substrate and product

at \( z = 0^+ \), \( C_{b0}|_{z=0^+} = C_{b0}|_{z=0^-} + \frac{D_{b0} \epsilon}{u} \left. \frac{\partial C_{b0}}{\partial z} \right|_{z=0^+} \).

at \( z = L \), \( \left. \frac{\partial C_{b0}}{\partial z} \right|_{z=L} = 0 \).

The substrate and product mass balance equations in immobilized enzyme particles on a porous spherical particle support is given as:

\[
\frac{\partial C_{b0}}{\partial t} = D_{b0} \frac{\partial^2 C_{b0}}{\partial z^2} - \frac{1}{\rho} \frac{\partial}{\partial z} \left( \frac{\partial C_{b0}}{\partial z} \right) - R_b
\]

\[
\frac{\partial C_{p0}}{\partial t} = D_{p0} \frac{\partial^2 C_{p0}}{\partial z^2} - \frac{1}{\rho} \frac{\partial}{\partial z} \left( \frac{\partial C_{p0}}{\partial z} \right) + R_p
\]
where, $D_{SP}$, $D_{PP}$ are the effective substrate and product interparticle diffusivities.

2.1.3. Kinetic equation of lactose hydrolysis

Consider the general mechanism of reversible Michaelis–Menten kinetics. The reversible equation is able to explain irreversible Michaelis–Menten when $(K_r \to \infty$ and $K_P \to \infty$) and competitive inhibition by a product when $(K_P \to \infty)$. For example, enzymatic lactose hydrolysis has been modeled in the literature using soluble $\beta$-galactosidase [1]. Michaelis–Menten model with competitive product inhibition by galactose is widely used to describe lactose hydrolysis. The hydrolysis rate is given by

$$R = R_p = \frac{v_{max}}{K_m(1 + C_P/K_P) + C_S}$$

(7)

where, $R(C_S, C_P)$ is reaction rate, mol/h; $C_S$ is substrate (lactose) concentration, mol/l; $C_P$ is product (galactose) concentration, mol/l. $K_m$ is apparent Michaelis–Menten constant, mol/l; $K_P$ is inhibition constant, mol/l. $v_{max}$ is apparent maximum reaction rate, mol/h.

The rate constants $v_{max}, K_m$ and $K_P$ depend on temperature according to Arrhenius relationship [1].

The initial and boundary conditions are taken as,

at $t = 0, \quad C_S = C_P = 0$

(8)

at $t = R, \quad \frac{\partial C_S}{\partial r} = \frac{\partial C_P}{\partial r} = 0$

$D_{SP} \frac{\partial C_S}{\partial \zeta} |_{\zeta=0} = K_{SL} (C_S |_{\zeta=0})$

$D_{PP} \frac{\partial C_P}{\partial \zeta} |_{\zeta=0} = K_{LP} (C_P |_{\zeta=0})$

(9)

2.1.4. Governing equations in dimensionless form

Eqs. (1)–(9) can be reduced to the corresponding dimensionless forms by introducing the following dimensionless parameters (Table 1).

Substrate and product concentration variables

$$S = \frac{C_S}{C_{S0}}, \quad \frac{C_S}{C_{S0} |_{\zeta=0}}, \quad S_0 = \frac{C_{S0}}{C_{S0} |_{\zeta=0}}$$

$$P = \frac{C_P}{C_{P0}}, \quad P_0 = \frac{C_P}{C_{P0}}.$$  

(10)

Dimensionless axial, radial coordinate variables and dimensionless residence time

$$\xi = \frac{r}{L}, \quad \zeta = \frac{r}{R}, \quad \tau = \frac{v_{max} t}{C_{S0}}.$$  

(11)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dimensionless parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Kinetic parameters</td>
<td></td>
</tr>
<tr>
<td>Michaelis modulus</td>
<td>$\theta = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
<tr>
<td>Product inhibition modulus</td>
<td>$\gamma = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
<tr>
<td>2. Internal mass transfer parameters</td>
<td></td>
</tr>
<tr>
<td>Dimensionless residence time</td>
<td>$\beta = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
<tr>
<td>Thiele modulus, $\phi$</td>
<td>$\phi = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
<tr>
<td>Diffusivity ratio in the internal sites of the enzyme particles</td>
<td>$\alpha_D = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
<tr>
<td>3. External mass transfer parameters</td>
<td></td>
</tr>
<tr>
<td>Damkohler number, $D_a$</td>
<td>$D_a = \frac{L}{u} \frac{v_{max}}{C_{S0}}$</td>
</tr>
<tr>
<td>Modified Damkohler, $D_a^*$</td>
<td>$D_a^* = \frac{L}{u} \frac{v_{max}}{C_{S0}}$</td>
</tr>
<tr>
<td>4. Simultaneous internal and external mass transfer parameters</td>
<td></td>
</tr>
<tr>
<td>Substrate, product Biosteady number</td>
<td>$B_S = \frac{K_{SP}}{D_{SP}}, B_P = \frac{K_{PP}}{D_{PP}}$</td>
</tr>
<tr>
<td>5. Axial dispersion on external fluid side</td>
<td></td>
</tr>
<tr>
<td>Peclet number</td>
<td>$P_e = \frac{L}{u} \frac{v_{max}}{C_{S0}}$</td>
</tr>
<tr>
<td>Diffusivity ratio with respect to the axial position</td>
<td>$\alpha_D = \frac{D_{SP}}{D_{PP}}$</td>
</tr>
</tbody>
</table>

The model can be described by the following dimensionless parameters

$$\theta = \frac{K_{m}}{C_{S0}}, \quad \gamma = \frac{K_{P}}{C_{P0}}$$

$$\beta = \frac{D_{SP}}{D_{PP}}, \quad \phi = \frac{L}{u} \frac{v_{max}}{C_{S0}}$$

$$\alpha_D = \frac{D_{SP}}{D_{PP}}, \quad P_e = \frac{L}{u} \frac{v_{max}}{C_{S0}}$$

Consequently, Eqs. (1)–(9) can be written in dimensionless form as follows,

$$D_{SP} \frac{\partial S}{\partial \tau} = \frac{1}{P_e} \frac{\partial^2 S}{\partial \zeta^2} - \delta \frac{\partial S}{\partial \zeta} - S (S_0 - S_{\uparrow=1})$$

(12a)

$$D_{PP} \frac{\partial P}{\partial \tau} = \frac{1}{\alpha_D P_e} \frac{\partial^2 P}{\partial \zeta^2} - \delta \frac{\partial P}{\partial \zeta} - S (P_0 - P_{\uparrow=1})$$

(12b)

with the following boundary conditions

at $\zeta = 0^+$: $S_0 |_{\zeta=0^+} = 1 + \frac{1}{P_e} \frac{\partial S_0}{\partial \zeta} |_{\zeta=0^+}$,

$P_0 |_{\zeta=0^+} = P_0 |_{\zeta=0^+} + \frac{1}{\alpha_D P_e} \frac{\partial P_0}{\partial \zeta} |_{\zeta=0^+}$

(13)
at $\xi = 1$, \( \frac{\partial S}{\partial \xi} |_{\xi=1} = 0 \).  

Mass balance for the substrate in immobilized enzyme particles supported on porous spherical particles is given by,

\[
\frac{D_a}{\alpha} \frac{\partial S}{\partial \xi} = \frac{1}{\alpha} \left[ \frac{\partial S}{\partial \xi} \right]_0 - Da R_S
\]

or,

\[
\frac{\partial S}{\partial \xi} = \left[ \frac{\partial S}{\partial \xi} \right]_0 - R_S
\]

and similarly the product concentration in immobilized enzyme particles is given by,

\[
\frac{\partial P}{\partial \xi} = \left[ \frac{\partial P}{\partial \xi} \right]_0 + R_P
\]

Dimensionless reversible Michaelis–Menten kinetics can be written as:

\[
R_S = R_P = \frac{S - K_p P}{S + K_p P}
\]

Eqs. (15) and (16) are subject to the following boundary conditions:

at $\xi = 0$, \( \frac{\partial S}{\partial \xi} |_{\xi=0} = 0 \)

and similarly the product concentration in immobilized enzyme particles can be obtained from the solution of the diffusion reaction equations. The average concentrations in the spherical particle can be obtained from the following expressions

\[
\langle C_S \rangle = 3 \int_0^R R^2 C_S r^2 dr \quad \text{or} \quad \langle C \rangle = 3 \int_0^1 S \xi^2 d\xi
\]

The average reaction rates are defined as:

\[
\langle R_S \rangle = 3 \int_0^R R^2 r^2 dr = 3 \int_0^1 R^2 \xi^2 d\xi
\]

2.2 Criteria for reactor performance

2.2.1 Average concentrations and average reaction rate

The calculations of the substrate and product profile along the radial and axial coordinates were obtained from the solution of the diffusion reaction equations. The average concentrations in the spherical particle can be obtained from the following expressions

\[
\langle C_S \rangle = 3 \int_0^R R^2 C_S r^2 dr \quad \text{or} \quad \langle C \rangle = 3 \int_0^1 S \xi^2 d\xi
\]

The average reaction rates are defined as:

\[
\langle R_S \rangle = 3 \int_0^R R^2 r^2 dr = 3 \int_0^1 R^2 \xi^2 d\xi
\]

2.2.2 Effectiveness factor

The internal diffusional limitations can be quantitatively expressed by the effectiveness factor, $\eta$, defined as the ratio of the average reaction rate to the rate which would be obtained if all enzyme molecules inside the particle were exposed to the same substrate concentration as that at the surface, i.e., in the absence of diffusional effects. The bulk reaction rate is the reaction rate at the bulk concentrations. Alternatively, the effectiveness factor may be defined as the ratio of the average reaction rate to the average bulk reaction rate, $R_b$. This relation is expressed by the following equation:

\[
\eta = \frac{R_S}{R_b} = \frac{\langle R_S \rangle}{R_b} = \frac{3}{\left( \frac{\int_0^1 R^2 \xi^2 d\xi}{R_b} \right)}
\]

2.2.3 Fractional conversion and yield

Conversion is a convenient variable and it is often used in place of concentration in engineering work. It is defined as the ratio between the total moles of substrate converted into product and the total moles of substrate fed into the reactor per unit time for a continuous reactor.

The following apparent conversions for the substrate and product can also be defined:

\[
X = 1 - \frac{C_{Sb}}{C_{Sb0}} = 1 - S_b
\]

Yield is defined as the ratio of the substrate converted to the maximum amount that could be converted during one residence time. Yield is used to measure the efficiency of enzyme utilization. It can be expressed as:

\[
Y = \frac{C_{Sb} - C_{Sb} \frac{\varepsilon L}{Pe}}{C_{Sb0}} = 1 - \frac{1 - S_{bL}}{\varepsilon L} = \frac{1 - S_{bL}}{\varepsilon L} \frac{1}{Pe} \frac{1}{\varepsilon}
\]

3. Results and discussions

The objectives of this study are to investigate the characteristics and behavior of packed bed immobilized enzyme reactors. These objectives can be achieved explicitly by studying the effects of kinetics parameters, internal and external mass transfer parameters, effects of reactor hydrodynamics and the effects of simultaneous diffusional effects.

Reactor conversion, yield and internal effectiveness factor are calculated as a function of dimensionless parameters Thiele modulus, $\theta$, St, Pe, $\eta$, and $\gamma$. Peclet number, $Pe$, which measures the degree of dispersion is assumed to be 2.0 for DPFR model, since at higher $Pe$ numbers the reactor performance tends to approach the PFR model. In order to evaluate the performance of packed bed immobilized enzyme reactors, numerical values of the process parameters were obtained from the literature [3,4,11,12,14,16,18,22,23,40]. Since a wide range of such values have been reported, the range of dimensionless Michaelis modulus, $\theta$, and Stanton number, St used in this simulation study of conversion, yield and internal effectiveness factor, was varied from 0.1 to 10. Similarly, the range of product inhibition modulus, $\gamma$, used in this analysis...
The differential mass balance equations have been written and normalized for both substrate and product in both external bulk phase and microenvironment phase (inside IME particles). The normalized PDEs are then solved using orthogonal collocation on finite elements (OCFE) and Galerkin’s method [42–46]. The number of collocation points and number of finite elements were chosen to give satisfactory convergence. Numerical simulation was performed to analyze the effect of transport and kinetic parameters on the reactor performance. The model equations were solved using the orthogonal collocation method. Twelve internal collocation points were chosen for the reactor bed axial direction and five collocation points were used inside enzyme particle. It is found that with these points a good accuracy can be obtained compared to those results with 15 collocation points.

### 3.1. Effects of Bi and φ

Biot number is defined as the ratio of intraparticle diffusion resistance to external mass transfer resistance [47–48]. The effects of Biot number on the substrate conversion will be studied with intraparticle limitations in Section 3.1. Moreover, effects of Bi and external mass transfer limitations with kinetic parameters θ and γ will be discussed in Sections 3.2 and 3.3, respectively.

Fig. 3 shows quantitatively the effects of Biot number on the substrate conversion as a function of Thiele modulus with θ = 1, γ = 1, Pe = 2.0 and St = 1.0. At low Thiele modulus, the effect of increasing Biot number on the substrate conversion is shown to reduce the substrate conversion. This takes place when the process is reaction rate controlled. At extremely high Thiele modulus, however, all curves of different Bi asymptotically approach constant value where the system becomes diffusion rate controlled. It also shows that the substrate conversion increases as a result of decreasing Bi when the process is kinetically controlled. This relation becomes independent of Bi when the process is mass transfer controlled. However, a weak relation is shown when both intraparticle diffusion and kinetic processes are dominating (i.e., in the mixed regime). Lower Biot number indicates the presence of strong external mass transfer resistance and hence both internal and external mass transfer resistances are important for the determination of substrate conversion. As the Biot number increases the external mass transfer resistance decreases in its importance. This occurs because the microenvironment substrate conversion approaches the bulk phase concentration and thereby the external mass transfer disappears. The effects of Bi are dominant in the reaction-controlled regime. However, the conversion is independent of Biot number when the process is diffusion rate.

Fig. 2 shows the effects of Biot number on the internal effectiveness factor as a function of Thiele modulus with θ = 1, γ = 1, Pe = 2.0 and St = 1.0. The trend of effectiveness factor versus Thiele modulus is shown to be a function of Biot number. The effectiveness factor approaches unity and it is independent of Bi when the process is kinetically controlled. Conversely, the effectiveness factor increases with increasing Biot number in the reaction controlled.

### 3.2. Effects of Bi, θ and St

Fig. 1 shows quantitatively the effects of Michaelis modulus, θ, and Stanton number on the substrate conversion as a function of Biot number with γ = 1.0, φ = 2.0 and Pe = 2.0. It shows that the conversion decreases upon increasing Biot number at a given St. A further decrease in Biot number results in the substrate conversion becoming independent of Michaelis modulus and the substrate conversion asymp-
Fig. 3. Effects of $St$ number on reactor conversion as a function of Biot number with $\theta=0.1$, 1, 10, $\gamma=1$, $\phi=2.0$ and $Pe=2.0$.

Fig. 4. Effects of $\theta$ on internal effectiveness factor for varying Biot number and Stanton number with $\gamma=1$, $\phi=2.0$ and $Pe=2.0$.

Table 1 shows the effects of $St$ on reactor conversion as a function of Biot number with $\theta=0.1$, 1, 10, $\gamma=1$, $\phi=2.0$ and $Pe=2.0$.

Fig. 5. Effects of Biot number on internal effectiveness factor as a function of Stanton number with $\gamma=1$, $\phi=2.0$ and $Pe=2.0$ for $\theta=0.1$, 1, 10.

Fig. 6. Effects of $St$ on internal effectiveness factor for varying Biot number and Stanton number with $\gamma=1$, $\phi=2.0$ and $Pe=2.0$.

3.3. Effects of $Bi$, $\gamma$ and $St$

A similar study was carried out to study the effects of Biot number for different product inhibition modulus, $\gamma$. The simulation results are shown in Fig. 7 for substrate conversion. Figs. 8–10 illustrate the effects of Biot number on the effectiveness factor.

Fig. 7 shows the effects of $\gamma$ on the substrate conversion for varying Biot number and Stanton number with $\phi=2.0$, $\theta=1.0$, $Pe=2.0$. As discussed earlier, it can be concluded that the substrate conversion increases with decreasing Biot number. The effect of product inhibition reduces the substrate conversion, and more significant effects occurs when both kinetic and mass transfer limitations are dominating factor, i.e., $Bi$ lies in the mixed regime.
Fig. 6. Effects of Stanton number on internal effectiveness factor as a function of Biot number for $\theta = 0.1, 1, 10$, $\gamma = 1$, $\phi = 2.0$ and $Pe = 2.0$.

Fig. 7. Effects of Stanton number on reactor conversion as a function of Biot number with $\gamma = 0, 1, 10$, $\theta = 1$, $\phi = 2.0$ and $Pe = 2.0$. The trend can be characterized by three distinct regimes. First, the process is kinetically controlled when the mass transfer resistances are negligible at very high Biot number and low Stanton number. In this regime, the effectiveness factor is independent of both Bi and St and is a function of $\gamma$ where the product inhibition reduces the effectiveness factor. Second, the kinetic and mass transfer are controlling the process when the effectiveness factor varies with Stanton number and it depends on $\gamma$ and Bi. In this regime, the effectiveness factor increases with increasing Stanton number when $\theta\gamma > 1$, with decreasing Stanton number at $\theta\gamma > 1$ and it is independent of Stanton number when $\theta\gamma = 1$. Third, the Stanton number is extremely high, when the effectiveness factor is independen

Fig. 8 shows the effects of $\gamma$ on the internal effectiveness factor for varying Biot number and Stanton number with $\theta = 1.0$, $\phi = 2.0$ and $Pe = 2.0$. The trend can be characterized by three distinct regimes. First, the process is kinetically controlled when the mass transfer resistances are negligible at very high Biot number and low Stanton number. In this regime, the effectiveness factor is independent of both Bi and St and is a function of $\gamma$ where the product inhibition reduces the effectiveness factor. Second, the kinetic and mass transfer are controlling the process when the effectiveness factor varies with Stanton number and it depends on $\gamma$ and Bi. In this regime, the effectiveness factor increases with increasing Stanton number when $\theta\gamma > 1$, with decreasing Stanton number at $\theta\gamma > 1$ and it is independent of Stanton number when $\theta\gamma = 1$. Third, the Stanton number is extremely high, when the effectiveness factor...
The effectiveness factor is independent of \( \gamma \) at certain values of \( St, Bi \) at crossover point. It is evident from Fig. 8 that the crossover points trajectory can be represented by dimensionless parameters at crossover point \( \beta_{eo} = St_{eo}/Bi_{eo} = 1.5 \), at \( \theta = 1.0 \) and \( \phi = 2.0 \) that satisfied all crossover points trajectory.

Further to investigate the effects of \( \theta \) and \( \phi \) on the crossover points trajectory, a similar study was conducted for different combinations of \( \theta \) and \( \phi \) and the simulation results are summarized in Table 2.

Furthermore, Fig. 9 illustrates the effects of product inhibition on the internal effectiveness factor as a function of \( St \) and \( Bi \) with \( \theta = 1.0, \phi = 2.0 \), and \( Pe = 2.0 \). As can be seen, the effects of product inhibition form a crossover points trajectory in \( St, \phi \) at given \( Bi = 0.1 \). Therefore, the \( \beta_{eo} \) at crossover points can be given by Eq. (26) at \( \theta = 1.0 \),

\[
\beta_{eo} \approx \frac{6.0}{\phi_{eo}}.
\]

The following equation can be correlated from Table 2 which can be used to approximate the \( \beta_{eo} \) at crossover point that relates to \( \theta \) and \( \phi \),

\[
\beta_{eo} = \frac{St_{eo}}{Bi_{eo}} \approx \frac{6.0}{\theta^{1/3} \phi_{eo}^{1/3}}
\]

Thus, the crossover points found in Fig. 10 can also be approximated by Eq. (27) at \( \beta_{eo} = 10 \).

\[
\beta_{eo} \approx \frac{0.776}{\theta^{1/6} \phi^{1/6}}
\]

Thus, the mixed regime can be characterized by \( \beta_{eo} \) at which the effectiveness factor \( \beta_{eo} \), whereas, when \( \beta_{eo} < \beta_{eo} \), the effectiveness factor decreases as \( St \) increases. However, when \( \beta_{eo} < \beta_{eo} \), the reaction kinetic factors are more significant where the effect of product inhibition has reduced the effectiveness factor by reducing reaction rate.

4. Conclusions

A mathematical model for a packed bed immobilized enzyme reactor has been developed considering Michaelis–Menten kinetics with competitive product inhibition. The effects of intraparticle diffusion, external mass transfer, axial dispersion and kinetic parameters have been taken into consideration in the model. The relevant equations were solved by the method of orthogonal collocation on finite elements and Galerkin’s method. The performance of packed bed immobilized enzyme reactor has been investigated parametrically for various operational parameters. The effects of \( \theta, \gamma, \phi, St \) and \( Bi \) have been identified quantitatively on the substrate conversion and internal effectiveness factor.

The following conclusions were drawn from simulation results:

1. Intraparticle diffusion resistance, external mass transfer resistances and axial dispersion were shown to reduce internal effectiveness factor.
2. Product inhibition was shown to reduce substrate conversion, and to decrease effectiveness factor when \( \beta_{eo} < \beta_{eo} \), however, it increases effectiveness factor when \( \beta_{eo} > \beta_{eo} \). The effectiveness factor is found to be independent of product inhibition at crossover point at which \( \beta_{eo} \) is defined, where \( \beta_{eo} \) is a function of \( St, Bi, \theta \) and \( \phi \).
3. Effect of Stanton number was shown to reduce the internal effectiveness factor when \( \theta \gamma < 1 \) (i.e., \( Kn < Kp \)), but it
favors the effectiveness factor when $\theta r > 1$. Due to these opposite trends, the effectiveness factor has been found to be independent of $\theta t$ at $\theta r = 1$.

(4) The effectiveness factor is only a function of $\theta t$ when the process is kinetically controlled at very high $B_i$ and extremely low $S_t$. In this regime, upon increasing $S_t$, the effectiveness factor becomes independent of $S_t$ and can be a function of $B_i$ and $\theta t$. However, at extremely high $S_t$, the effectiveness factor becomes independent of both $S_t$ and $\theta t$ and is characterized by $B_t$ when the process is mass transfer controlled. Between these two limiting cases, the effectiveness factor is a function of $\theta t$, $B_i$ and $S_t$ while other parameters remains constant.

(5) The effect of product inhibition reduces the effectiveness factor when the process is reaction rate controlled but it favors the effectiveness factor when the process is mass transfer controlled. Although the internal effectiveness factor is a function of $\gamma$ in these two regimes, the effectiveness factor is independent of both $S_t$ and $B_i$.

(6) In the mixed mode, however, the effectiveness factor increases with increasing Biot number and the trend is proportional when $\theta r > 1$. Whereas when $\theta r < 1$, the trend is inversely proportional.

(7) Due to existence of two opposite trends shown in the effect of $\gamma$ and $S_t$ on $\eta$, it is found that effectiveness factor is independent of $\gamma$ at certain values of $S_t$ and $B_i$ at crossover point. The crossover points trajectory can be represented by dimensionless parameters at crossover point $\beta_{ox} = S_{ox}B_{ox}$, and can be approximated by the following correlation:

$$ \beta_{ox} = \frac{S_{ox}}{B_{ox}} \approx \frac{6.0}{\gamma \frac{S_t}{B_i}}. $$

Therefore, the mixed regime can be characterized by $\beta_{ox}$ at which the effectiveness factor $\beta_t > \beta_{ox}$, whereas, when $\beta_t < \beta_{ox}$, the effectiveness factor decreases as $S_t$ increases. Therefore, when $\beta_t < \beta_{ox}$, the reaction kinetic factors are more significant where the effect of product inhibition has reduced the effectiveness factor by reducing reaction rate. However, when $\beta_t > \beta_{ox}$, the mass transfer limitations are dominant and the product inhibition favors the internal effectiveness factor since it reduces rate of mass transfer.

Acknowledgments

The authors gratefully thank Prof. Abdullah Shaikh, chairman of Chemical Engineering Department, and Dr. Kevin F. Laughlin for their technical support during the study. This work was funded by Scientific Research Department at King Fahd University of Petroleum & Minerals (KFUPM), Saudi Arabia, through grant ENZYME project.

References


