Analytical Expression Pertaining to Concentration of Substrate and Effectiveness Factor for Immobilized Enzymes with Reversible Michaelis Menten Kinetics

S. Sevukaperumal
Department of Mathematics
Ganesar College of Arts and Science
Melaisivapuri-622403
Tamilnadu, India

A. Eswari
Department of Mathematics
The Madura College
Madurai-625011
Tamilnadu, India

L. Rajendran
Department of Mathematics
The Madura College
Madurai-625011
Tamilnadu, India

ABSTRACT

The mathematical model of immobilized enzyme system in porous spherical particle is presented. The model is based on non-stationary diffusion equation containing a nonlinear term related to Michaelis-Menten kinetics of the enzymatic reaction. A general and closed form of an analytical expression pertaining to the substrate concentration profile and effectiveness factor are reported for all possible values of dimensionless modules ϕ and α. Moreover, herein we have employed "Homotopy Perturbation Method" (HPM) to solve the non-linear reaction/diffusion equation in immobilized enzymes system. These analytical results were found to be in good agreement with simulation result.

Keywords: Diffusion-Reaction, Immobilised Enzymes, Modelling, Biosensors, Homotopy perturbation method; Michaelis-Menten kinetics; Effectiveness factor.

1. INTRODUCTION

Immobilization of enzymes helps in their economic reuse and in the development of continuous bioprocesses. Enzymes can be immobilized either using the isolated enzymes or the whole cells. Immobilization often stabilizes structure of the enzymes, thereby allowing their applications even under harsh environmental conditions of pH, temperature and organic solvents, and thus enables their uses at high temperatures in nonaqueous enzymology, and in the fabrication of biosensor probes. In the future, development of techniques for the immobilization of multienzymes along with cofactor regeneration and retention system can be gainfully exploited in developing biochemical processes involving complex chemical conversions.

The internal diffusional effects can be quantitatively expressed by the effectiveness factor η. The effectiveness factor is defined as the ratio of the actual reaction rate inside the particle to the rate in the absence of diffusional limitations [1]. The analytical solution for first-order kinetics, which provides the effectiveness factor value as a hyperbolic function of the Thiele modulus, is well known. For simple Michaelis-Menten kineties, a two-parameter model providing generalized plots of the effectiveness factor as a function of the dimensionless moduli [2, 3]. Immobilized enzyme system are also analysed for more complex kinetics: reversible reactions [4], competitive Michaelis-Menten kinetics [5] or two-substrate enzymatic reactions [6].

Rony [7] obtained the analytical expression of concentrations and effectiveness factor only for the limiting cases. Effectiveness factor for immobilized enzyme reaction are obtained using various numerical techniques [8-15]. But, since the calculus complexity increases as the reaction mechanism becomes more complex. When reversible or product competitive inhibition mechanisms have been considered, only external diffusional limitations [16] have been evaluated, otherwise unsatisfactory results were obtained [17-19].

Most theoretical models developed for estimating the effectiveness factor for heterogeneous enzymatic systems are based on the following assumptions: The catalytic particle is a porous sphere with a radius R. The enzyme is uniformly distributed throughout the whole catalytic particle. Diffusion reaction takes place at a constant temperature and under steady-state conditions. The substrate and product diffusion inside the catalytic particle can be modeled by Fick's first law and effective diffusivity is the same throughout the particle. The enzymatic reaction is monosubstrate and yields only one product.

The first model has been effectively applied in the devise of heterogeneous enzymatic reactors: fixed bed reactors [20], continuous tank reactors [21] and fluidized bed reactors [22]. Recently the methodology used in these papers has been applied to the simulation of a packed bed immobilized enzyme reactor [23, 24].

However, approximate analytical solutions have been obtained only in a limited range of the parameters [25-27]. Several numerical methods have been used to solve the boundary value problems outlined in Eq. (1) and (2). The most frequently used are finite differences [28] and orthogonal collocation [29], which transforms the problem into a system of algebraic equations. Recently, a two-dimensional flow model, incorporating mass transport has been developed to simulate a microchannel enzyme reactor with a porous wall using finite volume method [30, 31]. However, to the best of our knowledge, there was no rigorous solution for the substrate concentration has been reported. The purpose of this communication is to derive simple analytical expression for concentration and effectiveness factor for all possible values of reaction/diffusion parameters ϕ and α.

2. MATHEMATICAL FORMULATION OF THE PROBLEM AND ANALYSIS

The mathematical models for estimating the effectiveness factor in heterogeneous enzymatic systems are based on the following assumptions: (i) The catalytic particle is spherical and its radius is R. (ii) The enzyme is uniformly distributed throughout the whole catalytic particle. (iii) The system is in a steady-state and isothermal. Under these above assumptions, the differential mass balance equation for substrate and product in spherical co-ordinates are as follows [32]:

$$D_S \frac{d^2C_S}{dr^2} + \frac{2D_S}{r}\left(\frac{dC_S}{dr}\right) = V_S \qquad (1)$$

$$D_P \frac{d^2C_P}{dr^2} + \frac{2D_P}{r}\left(\frac{dC_P}{dr}\right) = -V_S \qquad (2)$$

The boundary conditions are

$$\frac{dC_S}{dr} = 0;\ \frac{dC_P}{dr} = 0 \text{ when } r = 0 \qquad (3)$$

$$C_S = C_{SR};\ \ C_P = C_{PR} \text{ when } r = R \qquad (4)$$

where

$$V_S = \frac{V_m\left(C_S - \left(C_P/K_{eq}\right)\right)}{K_M + C_S + \left(K_M/K_P\right)C_P} \qquad (5)$$

where C_S and C_P denote the dimensional substrate and product concentration, *r* is the radial co-ordinate and R is the radius of the particle. D_S and D_P are the effective substrate and product diffusivity inside the particle. C_{SR} and C_{PR} local substrate and product concentration at the particle surface. V_S is the local reaction rate per unit of catalytic particle volume and V_m is the maximum reaction rate per unit of catalytic particle volume. K_{eq} is the equilibrium constant. K_M and K_P are the Michaelis constant and competitive product inhibition constant. The form of V_S determines the mathematical method to solve the above equations and its complexity. Most of the already published articles on enzymatic solution were dealt with non-reversible Michaelis-Menten kinetics. The present model is an improvement based on the previously formulated three parameter model [33], since only two parameters are necessary to reach the solution. Adding Eqs. (1) and (2) and using the boundary conditions the following relationship can be established:

$$C_P = C_{PR} + \frac{D_S}{D_P}\left(C_{SR} - C_S\right) \qquad (6)$$

Substituting the value of C_P, we can obtain

$$V_S = \frac{\left[V_m\left(1 + \frac{1}{K_{eq}}\frac{D_S}{D_P}\right)\left(C_S - C_{SE}\right)\right]}{\left[\begin{array}{l} K_M + \frac{K_M}{K_P}C_{PE} + C_{SE} \\ + \left(1 - \frac{K_M}{K_P}\frac{D_S}{D_P}\right)\left(C_S - C_{SE}\right)\end{array}\right]} \qquad (7)$$

where $K_{eq} = \frac{C_{PE}}{C_{SE}}$,

$$C_{SE} = \frac{C_{PR} + \left(D_S/D_P\right)C_{PR}}{K_{eq} + \left(D_S/D_P\right)} \text{ and}$$

$$C_{PE} = K_{eq}C_{SE} = \frac{C_{PR} + \left(D_S/D_P\right)C_{PR}}{1 + \left(1/K_{eq}\right)\left(D_S/D_P\right)} \qquad (8)$$

where C_{SE} and C_{PE} are the equilibrium substrate and product concentration. We make the non-linear differential equations outlined in equations (1) and (2) dimensionless by introducing the following dimensionless parameters:

$$S = \frac{C_S - C_{SE}}{C_{SR} - C_{SE}},\ \rho = \frac{r}{R},$$

$$\phi = \frac{R^2V_m}{\left(C_{SR} - C_{SE}\right)D_S}\frac{\left(1 + \frac{1}{K_{eq}}\frac{D_S}{D_P}\right)}{\left(1 - \frac{K_M}{K_P}\frac{D_S}{D_P}\right)} \text{ and}$$

$$\alpha = \frac{K_M + \frac{K_M}{K_P}C_{PE} + C_{SE}}{\left(C_{SR} - C_{SE}\right)\left(1 - \frac{K_M}{K_P}\frac{D_S}{D_P}\right)} \qquad (9)$$

The mass balance differential equation for substrate in spherical co-ordinates for two parameter model is [32]:

$$\frac{d^2S}{d\rho^2} + \frac{2}{\rho}\left(\frac{dS}{d\rho}\right) - \phi\frac{S}{\alpha + S} = 0 \qquad (10)$$

where S is the substrate concentration and ρ is the dimensionless particle radial coordinate and ϕ and α are the dimensionless modules. The boundary conditions are represented as follows:

$$\frac{dS}{d\rho} = 0 \text{ when } \rho = 0 \qquad (11)$$

$$S = 1 \text{ when } \rho = 1 \qquad (12)$$

The effectiveness factor can be evaluated as [32]:

$$\eta = 3(\alpha+1)\int_0^1 \frac{S}{\alpha+S}\rho^2 d\rho \qquad (13)$$

3. GENERAL RESULT FOR CONCENTRATION S AND EFFECTIVENESS FACTOR η

The Homotopy perturbation method [34-40] is used to give the approximate analytical solution of non-linear reaction/diffusion Eq. (10). Using this method (see Appendix –A and B) we can obtain the concentration of substrate as follows:

$$S(\rho) = 1 + \frac{7\phi^2}{360\alpha^2}\left(1-\frac{1}{\alpha}\right) - \frac{\phi}{6\alpha} + \left(\frac{\phi}{6\alpha} - \frac{\phi^2}{36\alpha^2} + \frac{\phi^2}{36\alpha^3}\right)\rho^2 + \left(\frac{\phi^2}{120\alpha^2} - \frac{\phi^2}{120\alpha^3}\right)\rho^4 \qquad (14)$$

The Eq. (14) satisfies the boundary conditions (11) and (12). This equation represents the analytical expression of concentration provided $\frac{7\phi^2}{360\alpha^2}\left(1-\frac{1}{\alpha}\right)-\frac{\phi}{6\alpha}$ <1. Using Eqs. (13) and (14), the effectiveness response is given by

$$\eta = \frac{(\alpha+1)}{\phi A}\left[\begin{array}{l}\phi A - 18\alpha^2 A \\ + \arctan\left(\frac{\phi}{A}\right)\left(\begin{array}{l}108\alpha^3(\alpha+1) \\ -18\alpha^2\phi\end{array}\right)\end{array}\right] \qquad (15)$$

where

$$A = \sqrt{\phi\left(6\alpha^2 + 6\alpha - \phi\right)} \qquad (16)$$

Eq. (15) represents the new approximate analytical expression for the effectiveness factor for all possible values of parameters α and ϕ provided $A \neq 0$ and $\frac{7\phi^2}{360\alpha^2}\left(1-\frac{1}{\alpha}\right)-\frac{\phi}{6\alpha}$ <1.

4. NUMERICAL SIMULATION

The non-linear differential equation (10) is solved by numerical methods. The function pdex4 in SCILAB software which is a function of solving the boundary value problems for ordinary differential equation is used to solve this equation. Its numerical solution is compared with Homotopy perturbation method in figures and it gives a satisfactory result when $\alpha \geq 10$.

5. DISCUSSION

5.1 Effect of Thiele modulus ϕ in concentration of substrate

The Thiele modulus ϕ can be varied by changing either the particle radius or the amount of concentration of substrate. This parameter describes the relative importance of diffusion and reaction in the particle radius. When ϕ is small, the kinetics are the determining factor; the overall uptake of substrate in the enzyme matrix is kinetically controlled. Under these conditions, the substrate concentration profile across the membrane is essentially uniform. In contrast, when the Thiele modulus is large, diffusion limitations are the principal determining factor.

Figs. (1) - (2) show the dimensionless steady-state substrate concentration for the different values of ϕ calculated using Eq. (14). From these figures, we can see that the value of the concentration increases when ϕ decreases. The concentration of substrate S increases slowly and rises abruptly when $\rho \geq 0.4$ and all values of ϕ. When $\phi < 1$ and $\alpha \leq 5$, the concentration of substrate $S \approx 1$ (steady-state value). The simulation result is compared with our simple closed analytical expression Eq. (14), in Tables 1. The average relative difference between our Eq. (14) and the simulation result is less than 0.5 % when $\alpha = 2.$

5.2 Effect of dimensionless module α in concentration

The dimensionless module α is parameter quantifying the degree of unsaturation/saturation of the catalytic kinetics since it describes the ratio of the substrate concentration within the film to Michaelis –Menten constant. When $\alpha << 1$, and so the kinetics are unsaturated (first order with respect to substrate concentration S). Alternatively, when $\alpha >> 1$, and the catalytic kinetics are saturated (zero order with respect to substrate concentration S). Figs. (3) to (4) show the dimensionless steady-state substrate concentration for the different values of α. From these figures, we can see that the value of the concentration increases when α increases for all values of ϕ.

5.3 Effectiveness factor η

Effectiveness is an important concept in immobilized enzyme system. Fig. 5 represents the effectiveness factor η versus dimensionless module ϕ for different values of dimensionless module α. From this figure, it is inferred that, a constant value of dimensionless module α, the effectiveness factor η decreases quite rapidly as dimensionless module ϕ increases, approaching zero at high ϕ values, which corresponds to internal diffusion controlled processes. Moreover, it is also well known that, a constant value of dimensionless module ϕ, the effectiveness factor η increases with increasing values of α.

Fig. 1. Influence of dimensionless module ϕ on the concentration profile of substrate S obtained from our approximate solution presented in this work (Eq. (14), solid line) and from the simulation result (plus line). The plot was constructed for $\alpha = 2$.

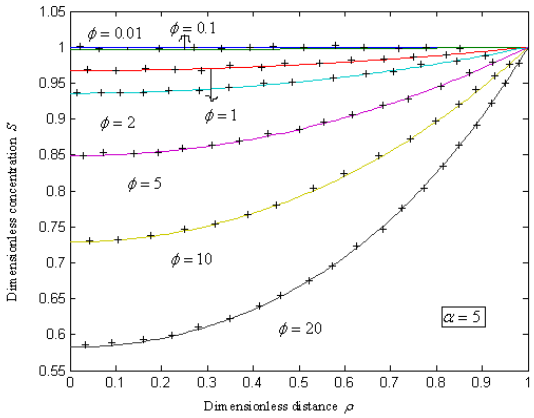


Fig. 2. Influence of dimensionless module ϕ on the concentration profile of substrate S obtained from our approximate solution presented in this work (Eq. (14), solid line) and from the simulation result (plus line). The plot was constructed for $\alpha = 5$.

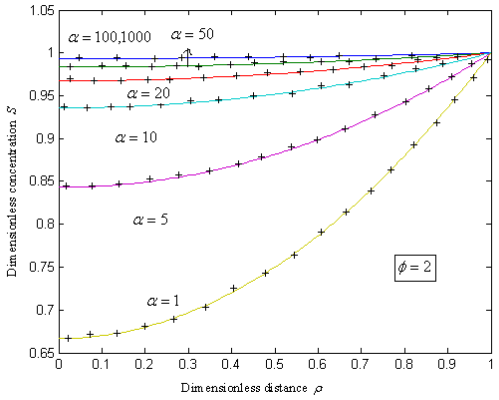


Fig. 3. Influence of dimensionless module α on the concentration profile of substrate S obtained from our approximate solution presented in this work (Eq. (14), solid line) and from the simulation result (plus line). The plot was constructed for $\phi = 2$.

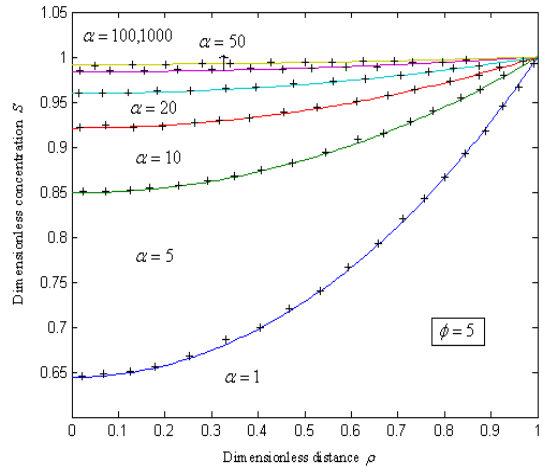


Fig. 4. Influence of dimensionless module α on the concentration profile of substrate S obtained from our approximate solution presented in this work (Eq. (14), solid line) and from the simulation result (plus line). The plot was constructed for $\phi = 5$.

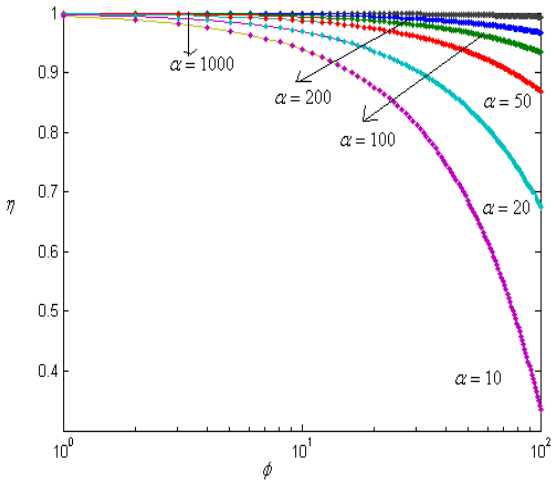
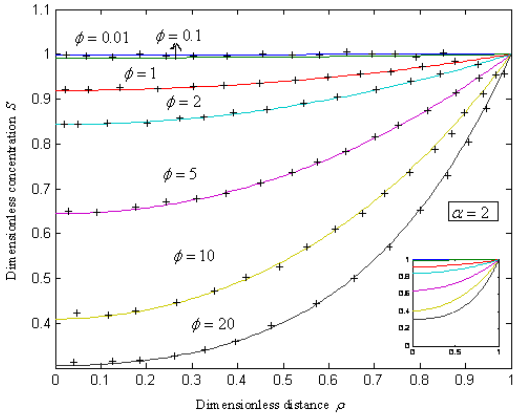


Fig. 5. Influence of dimensionless module α on effectiveness factor η obtained from our approximate solution presented in this work (Eq. (15), solid line) and from the simulation result (dotted line).



6. CONCLUSIONS

The time independent non-linear reaction/diffusion equation in immobilized enzyme system has been formulated and solved analytically. An approximate analytical expression for the concentration and effectiveness factor under steady state conditions are obtained by using the Homotopy perturbation method. The primary results of our work were simple approximate calculation of concentration and effectiveness factor for all values of parameters ϕ and α. This method can be applied to find the solution of all other non-linear reaction diffusion equations in immobilized enzymes for various complex boundary conditions.

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APPENDIX A.

Solution of the equation (10) using Homotopy perturbation method.

In this appendix, we indicate how Eq. (14) in this paper is derived. To find the solution of Eq. (10), we first construct a Homotopy as follows:

$$(1-p)\left[\frac{d^2S}{d\rho^2}+\frac{2}{\rho}\frac{dS}{d\rho}\right]+p\left[\begin{array}{l}\dfrac{d^2S}{d\rho^2}+\dfrac{2}{\rho}\dfrac{dS}{d\rho}\\ +\dfrac{S}{\alpha}\dfrac{d^2S}{d\rho^2}\\ +\dfrac{2S}{\rho\alpha}\dfrac{dS}{d\rho}-\dfrac{\phi S}{\alpha}\end{array}\right]=0 \quad \text{(A1)}$$

and the initial approximations are as follows:

$$\rho=0;\ dS_0/d\rho=0 \quad \text{(A2)}$$

$$\rho=1;\ S_0=1 \quad \text{(A3)}$$

$$\rho=0;\ dS_i/d\rho=0 \quad \text{(A4)}$$

$$\rho=1;\ S_i=1 \qquad \forall\ i=1,\ 2,..... \quad \text{(A5)}$$

and

$$S=S_0+pS_1+p^2S_2+p^3S_3+..... \quad \text{(A6)}$$

Substituting Eq. (A6) into Eq. (A1) and arranging the like coefficients of powers p, we can obtain the following differential equations

$$p^0:\quad \frac{d^2S_0}{d\rho^2}+\frac{2}{\rho}\frac{dS_0}{d\rho}=0 \quad \text{(A7)}$$

$$p^1:\quad \frac{d^2S_1}{d\rho^2}+\frac{2}{\rho}\frac{dS_1}{d\rho}+\frac{S_0}{\alpha}\frac{d^2S_0}{d\rho^2}+\frac{2S_0}{\rho\alpha}\frac{dS_0}{d\rho}-\frac{\phi S_0}{\alpha}=0 \quad \text{(A8)}$$

$$p^2:\quad \frac{d^2S_2}{d\rho^2}+\frac{2}{\rho}\frac{dS_2}{d\rho}+\frac{S_1}{\alpha}\frac{d^2S_1}{d\rho^2}+\frac{2S_1}{\rho\alpha}\frac{dS_1}{d\rho}-\frac{\phi S_1}{\alpha}=0 \quad \text{(A9)}$$

Solving equations (A7) to (A9) using reduction of order (see Appendix-B) for solving the Eq. (A8), and using the boundary conditions (A4) to (A5), we can find the following results

$$S_0(\rho)=1 \quad \text{(A10)}$$

$$S_1(\rho)=\frac{\phi}{6\alpha}(\rho^2-1) \quad \text{(A11)}$$

$$S_2(\rho)=\frac{\phi^2}{120\alpha^2}\left(\rho^4-1\right)+\frac{\phi^2}{36\alpha^2}\left(1-\rho^2\right)+\frac{\phi^2}{120\alpha^3}\left(1-\rho^4\right)-\frac{\phi^2}{36\alpha^3}\left(1-\rho^2\right) \quad \text{(A12)}$$

According to the HPM, we can conclude that

$$S(\rho)=\lim_{p\to1}S(\rho)=S_0+S_1+S_2..... \quad \text{(A13)}$$

After putting Eqs. (A10), (A11) and (A12) into Eq. (A13). The final results can be described in Eq. (14) in the text. The remaining components of $u_n(x)$ and $v_n(x)$ be completely determined such that each term is determined by the previous term.

APPENDIX B

In this appendix, we derive the solution of equation (A8) by using the reduction of order. The equation (A8) can be written in the form:

$$\frac{\mathrm{d}^2\overline{u_1}}{\mathrm{d}\rho^2}+P\frac{\mathrm{d}\overline{u_1}}{\mathrm{d}\rho}+Q\overline{u_1}=R \quad \text{(B1)}$$

where

$$P=\frac{2}{\rho};\ Q=0 \text{ and } R=\frac{\phi}{\alpha} \quad \text{(B2)}$$

Let the solution of Eq. (B1) be

$$u_1=c(\rho)v(\rho) \quad \text{(B3)}$$

Substituting Eq. (B3) in (B1), we get

$$\frac{\mathrm{d}^2v}{\mathrm{d}\rho^2}+P_1\frac{\mathrm{d}v}{\mathrm{d}\rho}+Q_1v=R_1 \quad \text{(B4)}$$

where

$$P_1 = P + \frac{2}{c}\frac{dc}{d\rho},\ Q_1 = \frac{1}{c}\left(\frac{d^2c}{d\rho^2} + P\frac{dc}{d\rho} + Qc\right) \text{ and}$$

$$R_1 = \frac{R}{c} \qquad \text{(B5)}$$

Now to remove the first derivative, we can choose the coefficient of the first derivative in Eq. (B4) is zero ($P_1 = 0$). We have

$$\frac{2}{c}\frac{\mathrm{d}c}{\mathrm{d}\rho} + P = 0 \qquad \text{(B6)}$$

Solving Eq. (B6), we can obtain *c* as follows:

$$c = e^{-1/2\int PdP} = \frac{1}{\rho} \qquad \text{(B7)}$$

Now the given equation (B4) reduces to

$$v'' + Q_1 v = R_1 \qquad \text{(B8)}$$

Substituting the value of Q_1 and R_1 in Eq. (B8) we obtain,

$$v'' = \frac{\phi x}{\alpha} \qquad \text{(B9)}$$

Solving the above equation (B9), we get

$$v = A\rho + B + \frac{\phi \rho^3}{6\alpha} \qquad \text{(B10)}$$

Substituting (B7) and (B10) in (B3), we have

$$u_1 = A + \frac{B}{\rho} + \frac{\phi \rho^2}{6\alpha} \qquad \text{(B11)}$$

Using the boundary conditions (Eqs. (A4) and (A5)), we can obtain the value of the constants *A* and *B*. Substituting the value of the constants *A* and *B* in the equation (B11) we obtain the equation (A11). Similarly we can solve the other differential Eq. (A9), using the reduction of order method.

NOMENCLATURE

Symbol	Meaning	Usual dimension
C_P	Product concentration inside the spherical particle	Mole/cm ^{3}
C_{PE}	Equilibrium product concentration	Mole/cm ^{3}
C_{PR}	local product concentration at particle surface	Mole/cm ^{3}
C_S	Substrate concentration inside the spherical particle	Mole/cm ^{3}
C_{SE}	Equilibrium substrate concentration	Mole/cm ^{3}
C_{SR}	local substrate concentration at particle surface	Mole/cm ^{3}
D_P	Effective product diffusivity inside the particle	Cm ^{2} sec $^{-1}$
D_S	Effective substrate diffusivity inside the particle	Cm ^{2} sec $^{-1}$
K_{eq}	equilibrium constant	none
K_M	Michaelis constant	Mole/cm ^{3}
K_P	Competitive product inhibition constant	none
r	radial coordinate of the particle	Cm
R	radius of the particle	Cm
S	dimensionless substrate concentration, defined as C_S/C_{SR} for the two-parameters model	Mole/cm ^{3}
V_m	maximum reaction rate per unit of catalytic particle volume	Mole/cm ^{3} sec
V_S	local reaction rate per unit of catalytic particle volume	Mole/cm ^{3} sec
Greek symbols		
α	dimensionless module for two parameter model	none
ϕ	dimensionless module for two parameter model	none
η	effectiveness factor	none
ρ	dimensionless particle radial coordinate	none

Table 1: Comparison of concentration profile of substrate S for various values of ϕ using equations (14) and simulation result when dimensionless module ($\alpha = 2$).

ρ	Concentration of S								
	S (when ϕ = 0.1)			S (when ϕ = 5)			S (when ϕ = 20)		
	Simulation	This work Eq. (14)	% of deviation	Simulation	This work Eq. (14)	% of deviation	Simulation	This work Eq. (14)	% of deviation
0	0.9900	0.9917	0.1714	0.6452	0.6441	0.0912	0.3051	0.3056	0.1636
0.2	0.9915	0.9920	0.0504	0.6570	0.6576	0.0912	0.3173	0.3176	0.0945
0.4	0.9935	0.9950	0.1508	0.6980	0.6986	0.0859	0.3600	0.3621	0.5799
0.6	0.9955	0.9958	0.0301	0.7679	0.7688	0.1171	0.4561	0.4568	0.1532
0.8	0.9968	0.9970	0.0201	0.8641	0.8647	0.0694	0.6514	0.6646	1.9862
1	1.0000	1.0000	0.0000	1.0000	1.0000	0.0000	1.0000	1.0000	0.0000
	Average		0.0705	Average		0.0758	Average		0.4962