Conversion in a Hollow Fiber Membrane/Enzyme Reactor

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The development of hollow fibers, tubular membranes with diameters of about 100 microns, has made it possible to design membrane separation systems of very high area-to-volume ratio. This same feature has suggested the possibility of designing an efficient catalytic reactor by immobilizing an enzyme within the membrane matrix (Waterland et al., 1974) or by enclosing or encapsulating an enzyme solution within the hollow lumen of the tubular membrane (Rony, 1971). This paper reports some preliminary experimental results obtained by immobilizing urease on a hollow fiber to produce a reactor suitable to the hydrolysis of urea.

Figure 1 shows a sketch of a single hollow fiber in radial and longitudinal cross section. The type of membrane used in this study is usually referred to as an *asymmetric* membrane. The membrane wall, usually made from a synthetic polymer, is rather porous and permeable. The inner surface, however, is a dense ultrathin membrane, perhaps half a micron thick, which determines the separating capabilities of the fiber but offers little resistance to the transport of permeable solutes.

The concept of a hollow fiber reactor is quite simple. The fiber is soaked in an enzyme solution to allow enzyme to diffuse into the porous wall region, where it is presumed to remain unless it is physically removed. The wet fibers are then arranged as tubes in a shell-and-tube configuration. If the shell-side is dry, enzyme cannot leave the fiber by moving in the shell direction. The ultrathin layer has a pore size too small to permit passage of relatively large proteins like enzymes. Hence the enzyme is effectively immobilized in the spongy annular fiber wall. Figure 2 shows a schematic of the reactor system.

The reacting substrate solution is then pumped through the inside of the fiber. If the substrate molecule is small enough, it will cross the thin membrane and diffuse into the enzyme solution where reaction occurs. Reaction products can diffuse back into the substrate solution or, if gaseous, out into the shell side of the reactor. The dynamics of substrate conversion in this reactor will depend on the enzyme kinetics, as well as on diffusion of substrate through the membrane matrix. In addition, if flow within the fiber lumen is laminar, diffusion within the flowing solution will play a role, though this might be minimal for slow reactions.

EXPERIMENTAL PROCEDURES AND EQUIPMENT

The hollow fiber membrane module was an Amicon PMD cartridge containing 4000 fibers mounted in a plastic shell. Fiber parameters are:

Inside diameter	2×10^{-2} cm
Outside diameter	3.3×10^{-2} cm
Dense skin thickness	5×10^{-5} cm
Fiber length	20 cm
Void volume of sponge wall	80-90%

The substrate solution was prepared by dissolving urea (2.0 g/L) in 0.2 M Na_2HPO_4 citrate buffer (*p*H 7.4).

Urease solution (Jack Bean, Sigma Chemical Company) was prepared by dissolving the enzyme in the same buffer as above. Cysteine (0.01 M) was added to the urease solution to reduce deactivation during preparation.

The urease solution was allowed to saturate the porous sponge region of the hollow fiber wall by filling the shell side of the hollow fiber membrane module and letting the fibers soak in the enzyme solution for one hour. All gas bubbles were removed by shaking the module and venting through the outlet nozzle. Any gas entrapped in the sponge region was removed by connecting the tube side of the module to a pump suction line and operating the pump until a small amount of solution was sucked through the fiber wall. The urease, which could not pass through the matrix of the ultrathin skin, was thereby immobilized in the porous sponge region of the hollow fiber membrane. Before the start of each test, the excess urease solution was drained from the hollow fiber module.

The urea concentration of the substrate solution was determined using a photometric procedure (Levine, 1961) with a Leitz Model M Photrometer with a #415 filter.

Substrate was pumped through the hollow fibers using a Cole-Parmer Masterflex tubing pump. Flow rates were in the range of 10 to 100 ml/min., corresponding to residence times in the range 1 to 0.1 min. All experiments were run at 25°C.

The kinetic parameters were determined by reacting urea with urease in a stirred-batch reactor at 25°C. The kinetics were found to be first order in the urea concentration in the range of interest. At enzyme concentrations of 1 and 2 g/L, respectively, the first-order constants were found to be 0.317 and 0.676 min^{-1}.

The hydrolysis of urea produces ammonia, and in several runs the ammonia concentration was measured, using the method in Boltz (1958). In all cases, concentrations were measured at the module outlet, after passage of substrate solution through the fibers.

MATHEMATICAL MODELING

Within the spongy matrix of the hollow fiber, it is assumed that the urea concentration follows a simple diffu-

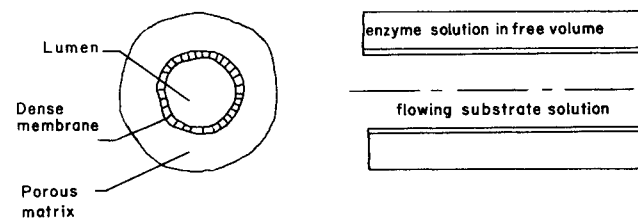

Fig. 1. Cross sections of hollow fiber membrane

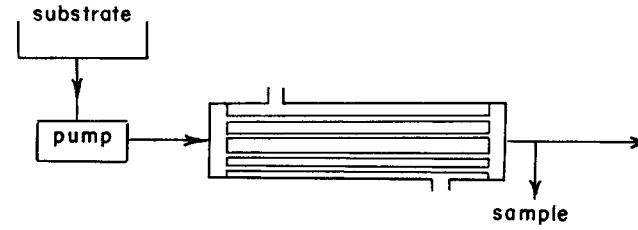

Fig. 2. Hollow fiber/enzyme reactor configuration

sion/reaction equation of the form

$$D_m \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_m}{\partial r}\right)=\frac{V_{\max} C_m}{K_m} \tag{1}$$

where first-order kinetics have been assumed.

Within the fiber lumen a diffusion/convection equation is written, assuming laminar Newtonian flow and negligible axial diffusion in the form

$$v_0\left(1-\frac{r^2}{R^2}\right)\frac{\partial C}{\partial Z}=D\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right) \tag{2}$$

Equations (1) and (2) are a coupled boundary value problem, the coupling appearing in the boundary conditions which express continuity of the radial flux at $r = R$,

$$D\frac{\partial C}{\partial r}\bigg|_R = D_m\frac{\partial C_m}{\partial r}\bigg|_R \tag{3}$$

and continuity of urea concentration across the membrane, or

$$C = C_m \quad \text{at} \quad r = R \tag{4}$$

Additional boundary conditions state:
no flux at the outer boundary of the fiber, or

$$D_m\frac{\partial C_m}{\partial r}\bigg|_{R_o} = 0 \tag{5}$$

symmetry along the lumen axis, or

$$\frac{\partial C}{\partial r}\bigg|_{r=0} = 0 \tag{6}$$

and an initial condition, of the form

$$C = C_0 \quad \text{at} \quad Z = 0 \tag{7}$$

Condition 4 assumes that urea has equal solubility in free solution as in the membrane matrix. In the absence of contrary data, and since the matrix is mostly aqueous-filled void space, this seems reasonable.

Solutions of this problem are discussed in a variety of sources. Waterland et al. (1974) discuss this problem in the context of a hollow fiber reactor and present some solutions for various parameters. They include nonlinear kinetics in their analysis. Even in the linear case, numerical techniques must be employed because of the coupling.

Davis et al. (1974) have discussed the same equations in the context of mass transfer between capillary blood and tissue. They present an exact solution in integral form based on an application of Duhamel's Theorem and offer a numerical scheme for computation of the relevant information.

For slow kinetics (in the sense of a small Thiele modulus) one might assume that the flowing substrate solution has a radially uniform concentration profile. In that case Equations (2) and (3) are replaced by a single equation of the form

$$D_m\frac{\partial C_m}{\partial r}\bigg|_R = \frac{v_0 R}{4}\frac{dC}{dZ} \tag{8}$$

The resulting solutions are then restricted to a certain range of Thiele modulus, defined by

$$\lambda^2 = \frac{V_{\max} R^2}{K_m D} < 1 \tag{9}$$

The advantage to be gained with this approximation is that relatively simple analytical solutions are available. This problem was considered and solutions were presented by Blum (1960) in the context of a blood-capillary exchange problem. A discussion of this and related problems is given by Middleman (1972).

The approximate analytical solution takes the form

$$\frac{C}{C_0} = \exp\left[-4B\lambda\zeta\right] \tag{10}$$

where

$$\zeta = zD/R^2 v_0 \quad \text{and} \tag{11}$$

$$B = \frac{-K_1(\lambda\rho)\,I_1(\lambda) + I_1(\lambda\rho)\,K_1(\lambda)}{K_1(\lambda\rho)\,I_0(\lambda) + I_1(\lambda\rho)\,K_0(\lambda)} \tag{12}$$

with $\rho = R_o/R$. $I_n(K_n)$ are modified Bessel functions of the first (second) kind of order n.

Equation (10) was tested as an approximation to the exact numerical solutions of Waterland et al. (1974). In the range of $0.01 \leq \lambda^2 \leq 0.10$, the agreement was very good.

It was assumed that the diffusivities of urea in solution and through the fiber matrix were identical: $D = D_m$. Since the matrix is 80 to 90% solution-filled voids, this seems reasonable and it considerably simplifies the format of the solution.

EXPERIMENTAL RESULTS

The two independent variables controlled in these experiments were the Thiele modulus λ and the dimensionless fiber length ζ. Since fiber length was fixed, ζ was varied by changing the flow rate of substrate. The Thiele modulus was studied at only two levels and was varied by changing the enzyme concentration, which affects the first order rate constant directly.

Figure 3 shows data for fractional conversion of urea at the module outlet. In reducing the data to this form, it is necessary to have a value for diffusivity of urea in solution. The International Critical Tables (1929) value of 1.20×10^{-5} cm^2/s was used here.

It is apparent that the mathematical model describes the general features of the data quite well. Several factors which could cause failure of some of the model assumptions will be discussed below.

Figure 4 shows the level of ammonia appearing at the module outlet. The curve follows from the corresponding

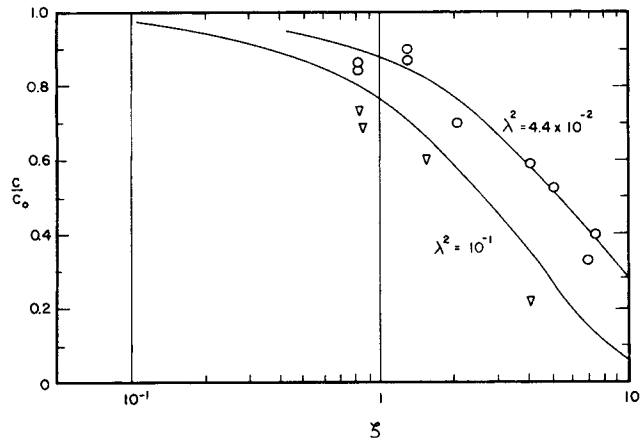

Fig. 3. Data for urea concentration in solution leaving reactor, normalized to inlet value. Curves are from theoretical model given by Equation (10).

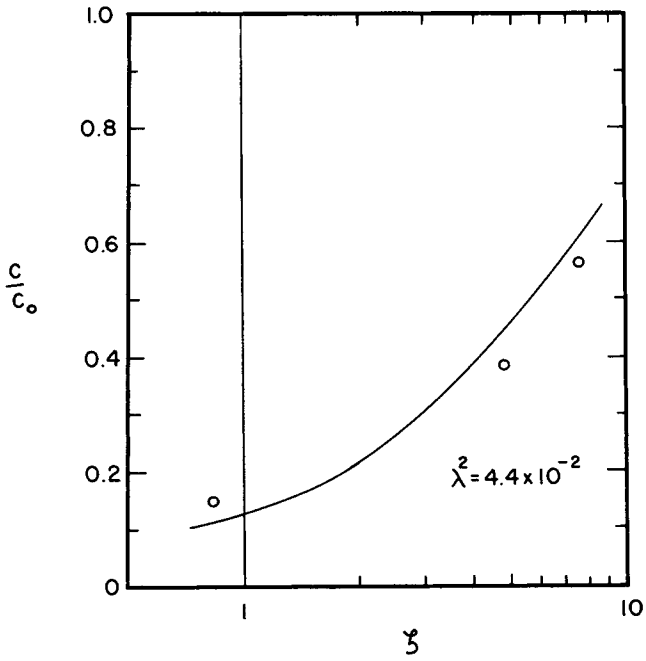

Fig. 4. Ammonia concentration in soution leaving reactor.

theoretical urea conversion curve of Figure 3, using the stoichiometry of this hydrolysis

$$(NH_2)_2CO + H_2O \rightarrow 2NH_3 + CO_2$$

In terms of the observed urea conversion, it is found that over 96% of the ammonia produced diffused back into the substrate stream. This is an important observation and will be discussed further.

DISCUSSION OF RESULTS

For small Thiele modulus, $\lambda^2 < 1$, the analytical solution presented as Equation (10)is a good approximation to the more exact numerical solutions available. There are, however, several factors which have the potential to cause significant deviations between the model of this system and its actual operation.

Most membranes of the type used in hollow fibers have a finite permeability to water flow. Filtration of water was in fact observed in these experiments. At the highest substrate flow rate (110 ml/min.), an ultrafiltration rate of about 1 ml/min. was measured. This corresponds to a radial velocity, through the fiber matrix, of about 4×10^{-6} cm/s. In principle, radial convection due to this velocity could compete with diffusion as the major mode of substrate and product transport. For comparison, a diffusion velocity can be calculated as the ratio of diffusivity to fiber wall thickness. For the system used here, this velocity is about 2.5×10^{-3} cm/s. Hence it would appear that diffusion is still the dominant mode of radial transport, as assumed. If either the substrate or product had a very small diffusivity, or if a very high rate of ultrafiltration of water occurred, this situation could be altered.

A second effect of ultrafiltration is the potential washout of enzyme from the fiber. The fibers used in this study have a total capacity of about 20 ml of enzyme solution. With a maximum ultrafiltration rate of about 1 ml/min., significant washout of enzyme could occur over times of about several minutes. Data were obtained within the first few minutes of operation, and no attempt was made to see if the conversion decreased with continued operation. During the first few minutes conversion was observed to be steady in time, indicating that a steady state situation existed as assumed in the mathematical model. Hence it is not possible to evaluate the importance of ultrafiltration washout as a factor which reduces the efficiency of this design mode.

The appearance of product (ammonia) to a nearly complete extent in the exiting substrate (urea) stream has important consequences for design. In some applications one might wish to retain the product as the desired component in the circulating stream. In other applications, however, it might be necessary to separate products from reactants. For example, in artificial kidney design, where urea is to be removed from blood, a high level of ammonia in the blood would be intolerable. It would appear, however, that freely diffusible reaction products would indeed return to the fiber lumen, and this feature of the hollow fiber reactor must be taken into account.

CONCLUSIONS

A hollow fiber/enzyme reactor provides an efficient configuration for conversion of freely diffusible substrates. A relatively simple theoretical treatment is in good agreement with experimental data for the system urea/urease and provides useful information for design of such a system.

Some ultrafiltration of solute occurs, but not to such an extent as to effect the transport of the diffusible species in the system. However, the potential for ultrafiltration to cause washout of enzyme is recognized, and this feature may restrict the length of time during which an enzyme soaked hollow fiber system will retain its activity.

NOTATION

B = dimensionless function defined in Equation (12)
C_0 = entering concentration of substrate, mole/cm^3
C, C_m = concentration of substrate in lumen, or membrane, mole/cm^3
D, D_m = diffusivity of substrate in solution, or in membrane matrix, cm^2/s
r = radial variable, cm
R, R_o = radius of lumen, outer radius of fiber, cm
v_0 = maximum velocity, cm/s
V_{max}/K_m = effective first order rate constant, s^{-1}
Z = axial variable, cm

Greek Letters

ζ = dimensionless axial variable, Equation (11)
λ = Thiele modulus, Equation (9)
ρ = R_o/R

LITERATURE CITED

Boltz, D. F., (ed.), *Colorimetric Determination of Nonmetals*, pp. 84-94, Interscience, New York (1958).

Blum, J. J., "Concentration Profiles in and Around Capillaries," *Am. J. Physiol.*, **198**, 991 (1960).

Davis, E. J., D. O. Cooney, and R. Chang, "Mass Transfer Between Capillary Blood and Tissues," *Chem. Eng. J.*, in press (1974).

International Critical Tables, Vol. 5, p. 69, First Edit., McGraw-Hill, New York (1929).

Levine, J. M., R. Leon, and F. Steigmann, "A Rapid Method for the Determination of Urea in Blood and Urine," *Clin. Chem.*, **7**, 488 (1961).

Middleman, S., *Transport Phenomena in the Cardiovascular System*, Ch. 3, Interscience, New York (1972).

Rony, P. R., "Multiphase Catalysis II. Hollow Fiber Catalysts," *Biotech. Bioeng.*, **13**, 431 (1971).

Waterland, L. R., A. S. Michaels, and C. R. Robertson, "A Theoretical Model Enzymatic Catalysis Using Asymmetric Hollow Fiber Membranes," *AIChE J.*, **20**, 50 (1974).

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