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Modeling and Simulation of the Elution Phase of an Affinity Ultrafiltration System

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ABSTRACT

A simplified mathematical model is proposed for the determination of concentration profiles of different components, including impurities, during the elution phase of an affinity ultrafiltration process. The model uses parameters which can be experimentally determined. The results have been simulated.

INTRODUCTION

Affinity ultrafiltration processes (1–10) have opened up a new avenue in the field of separation science. While this technique has a lot of potential for use in process industries, the mechanisms involved are not fully understood. In designing the equipment, empirical correlations rather than analytically derived equations must be relied on.

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An affinity ultrafiltration process can be divided into two phases:

1. Ultrafiltration washing
2. Ultrafiltration elution

In the washing phase the unbound impurity molecules are washed out of the affinity module by using a wash buffer. Some amount of the target biomolecule is also washed out in the process. In a previous communication (11) an attempt was made to explain the washing phase phenomenon from a mechanistic point of view. An equally important sequence in the affinity ultrafiltration process is the elution of the bound target biomolecule. A literature survey showed that only one correlation (10) on this sequence has been proposed. Again, this correlation is empirical in nature. It is therefore felt that an attempt should be made to explain the behavior of the system in the elution phase from a mechanistic approach. In the present investigation a mathematical model is proposed and the results are simulated. The simulation parameters used in the model can be experimentally determined. Thus, the use of adjustable parameters is avoided.

DEVELOPMENT OF MODEL

The model discussed here has been developed for the dead-ended mode of ultrafiltration (Fig. 1). However, with minor modifications this model

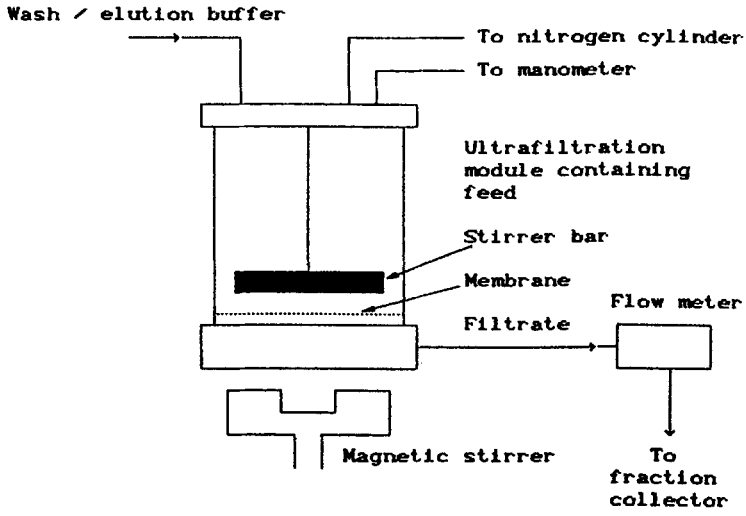

FIG. 1 Ultrafiltration module for affinity ultrafiltration.

may also be used for a crossflow mode. The two most fundamental assumptions necessary for development of such models are:

1. The binding of the target biomolecule to the ligand is a physical and reversible process.
2. The interaction between the target biomolecule and the ligand is not diffusionally limited.

The interaction between the target biomolecule (B) and the ligand (L) is described by

$$B + L \rightleftharpoons BL \tag{1}$$

$$K = \frac{C_{BL}}{C_B C_L} \tag{2}$$

where K = equilibrium constant
C_B = concentration of free biomolecule
C_L = concentration of free ligand
C_{BL} = concentration of target biomolecule–ligand complex

Ultrafiltration Elution

There are two possible mechanisms by which elution can be made to occur (12).

1. By reducing the value of the equilibrium constant (K) by a change of pH or by a change in the concentration of an eluting species (e.g., ions, chaotropic agents, deforming agents, polarity reducing agents, etc.).
2. By adding inhibitors which will displace the target biomolecule from the biomolecule–ligand complex (e.g., by competitively binding with the target biomolecule).

In this model the first mechanism has been considered. The following assumptions are made in order to develop the proposed model.

1. Ideal mixing conditions exist within the vessel.
2. There is unhindered transmission of the free target biomolecule and impurities through the membrane.
3. The filtration rate is kept constant.
4. The volume of liquid within the module is kept constant by the continuous addition of eluting buffer.
5. The concentration polarization of the ligand molecule on the membrane surface is negligible.

6. A "changing equilibrium" process is assumed in which the value of K changes with time, and the various concentration components adjust themselves according to the instantaneous value of K.
7. An "infinitely fast" reaction regime exists.

During the elution phase there is a gradual changeover of the pH or concentration of the eluting species inside the module. If the pH or concentration of eluting species of the initial (wash) buffer is denoted by C_{E_0}, and that of the eluting buffer by C_E^*, then from the material balance

$$C_E = C_E^* - (C_E^* - C_{E_0}) \exp(-Qt/V) \tag{3}$$

where C_E = concentration/pH inside the module at any time t ($t = 0$ at the start of the elution phase)
Q = filtration rate
V = working volume of the ultrafiltration module

Now

$$K = \psi(C_E) \tag{4}$$

Therefore

$$K = \phi(t) \tag{5}$$

From the material balance of the target biomolecule during the elution phase, one gets

$$-V \frac{d}{dt}(C_{B_t} + C_{BL_t}) = QC_{B_t} \tag{6}$$

where C_{B_t} = free target biomolecule concentration at any time t
C_{BL_t} = concentration of biomolecule–ligand complex at any time t

Now

$$C_{BL_t} = C_{L_0} - C_{L_t} \tag{7}$$

where C_{L_0} = initial total ligand concentration
C_{L_t} = free ligand concentration at any time t

Therefore

$$\frac{d}{dt}(C_{B_t}) - \frac{d}{dt}(C_{L_t}) = -\frac{QC_{B_t}}{V} \tag{8}$$

Again

$$C_{L_t} = \left(\frac{C_{L_0}}{1 + KC_{B_t}}\right) = \left(\frac{C_{L_0}}{1 + \phi(t)C_{B_t}}\right) \tag{9}$$

Therefore

$$\frac{d}{dt}(C_{B_t}) - \frac{d}{dt}\left(\frac{C_{L_0}}{1 + \phi(t)C_{B_t}}\right) = -\frac{QC_{B_t}}{V} \tag{10}$$

Simplifying and rearranging, one gets the canonical form

$$\frac{d}{dt}(C_{B_t}) = -(Q/V)\left(\frac{C_{B_t}(1 + \phi(t)C_{B_t})^2}{(1 + \phi(t)C_{B_t})^2 + C_{L_0}\phi(t)}\right) - C_{L_0}C_{B_t}\phi'(t)((1 + \phi(t)C_{B_t})^2 + C_{L_0}\phi(t)) \tag{11}$$

where

$$\phi'(t) = \frac{d}{dt}\phi(t) \tag{12}$$

Equation (10) is a first-order, nonlinear, initial value, ordinary differential equation. The initial value of C_{B_t} (at $t = 0$) is the free target biomolecule concentration at the end of the washing phase. Thus, if the function $\psi(C_E)$ is known, it is possible to determine the functions $\phi(t)$ and $\phi'(t)$. The function $\psi(C_E)$ can be determined from a plot of K versus C_E. Once these are known, Eq. (15) can be solved using suitable numerical techniques (e.g., 4th-order Runge–Kutta method) to determine C_{B_t} at any t, when all other parameters and constants are known. C_{B_t} is the concentration of the target biomolecule in the filtrate during the elution phase, and hence the validity of the differential equation can be directly verified by continuous analysis of the filtrate.

By using the material balance, the equation for determining the concentration of impurity during the elution phase is obtained as follows:

$$C_{I_t} = C_{I_0} \exp(-Q(t_w + t)/V) \tag{13}$$

where C_{I_0} = concentration of impurity at the beginning of the washing phase
C_{I_t} = concentration of impurity at any time t
t_w = duration of washing phase

SIMULATION

For the purpose of simulation it is necessary to know the exact functional relationship between K and C_E. One investigator (12) has indicated a sigmoidal relationship between the percentage recovery by elution and the concentration of eluent. It is also known that loss of enzyme activity (loss of the ability to bind a substrate to a catalytic site) due to a change in pH or a change in ionic strength is observed to follow an exponential decay pattern. Thus it is logical to assume an exponential relationship between the value of K and the change in pH or concentration. In its general form the relationship becomes

$$K = \psi(C_E) = K_0 \exp(-k_d(C_E - C_{E_0})) \tag{14}$$

where K_0 = value of K at $t = 0$
k_d = a decay constant

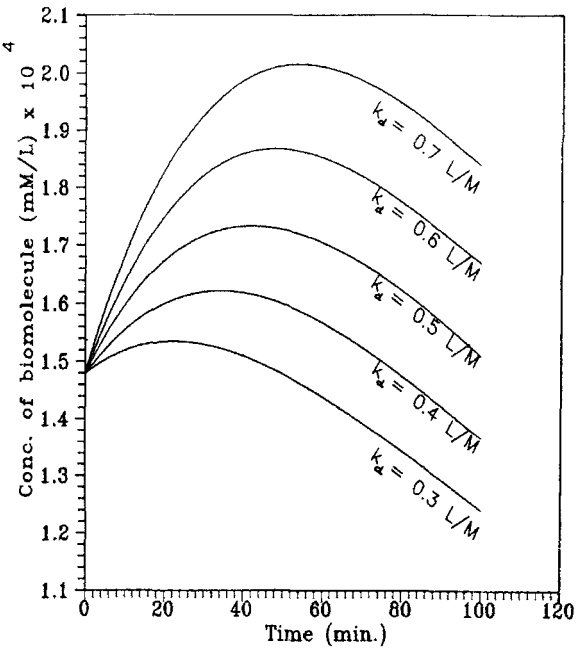

FIG. 2 C_{B_t} versus time profiles for the elution phase obtained using different k_d values. $C_{B_t}(t = 0) = 1.48 \times 10^{-4}$ mM/L, $C_{L_0} = 0.25$ mM/L, $K_0 = 17$ L/mM, $Q = 0.001$ L/min, $V = 0.04$ L, $C_{E_0} = 0$, $C_E^* = 0.05$ M/L.

Therefore, from Eqs. (3) and (14):

$$K = \phi(t) = K_0 \exp(-k_d(C_E^* - C_{E_0})[1 - \exp(-Qt/V)]) \quad (15)$$

Thus

$$\phi'(t) = K_0 \exp(-k_d(C_E^* - C_{E_0})[1 - \exp(-Qt/V)]) \times ((-Qk_d/V)(C_E^* - C_{E_0}) \exp(-Qt/V)) \quad (16)$$

Simulated concentration profiles of the target biomolecule in the filtrate during the elution phase using Eqs. (11), (15), and (16) are shown in Fig. 2.

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