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

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ABSTRACT

A simplified mathematical model for determining the concentration of different components, including impurities, during the washing phase of an affinity ultrafiltration system is presented from a mechanistic approach. The results are compared with experimental data published in the literature. The good fit indicates that the model is closer to reality than those reported so far.

INTRODUCTION

The advent of the affinity ultrafiltration technique has opened up a new avenue in the field of bioseparations. As the name implies, it is a fusion of two separation processes: affinity adsorption and ultrafiltration. In practice, it involves carrying out affinity adsorption and ultrafiltration sequentially within an ultrafiltration module or in separate units. In this manner the specificity of affinity adsorption is combined with the high

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throughput of ultrafiltration to achieve a very powerful bioseparation technique.

Literature survey shows that there are several publications on affinity ultrafiltration (1–20). This technique has been used for purification of trypsin (1, 2, 5, 10, 11, 18, 19), concanavalin A (3, 4, 6), alcohol dehydrogenase (6, 14), β-galactosidase (7), urokinase (17), etc. In most of these papers the major emphasis is on the development and assessment of ligands, and description of process and equipment. Only a few (12, 19, 20) have made a mathematical analysis of such processes. Thus, it is believed that a simplified approach should be made to understand the different stages of affinity ultrafiltration from a mechanistic point of view. While the mechanism of solute–ligand binding is well understood, much work remains to be done on modeling and simulation of the washing and elution phases. In this paper an attempt is made to present a simple mathematical model for the washing phase of an affinity ultrafiltration process. The simulated results are compared with the experimental values published in the literature.

DEVELOPMENT OF MODEL

The model discussed here has been developed with the dead-ended mode of ultrafiltration in mind. However, with minor modifications this model may also be used for a crossflow mode. The mechanistic approach starts from affinity adsorption, which is well established.

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

$$B + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BL \tag{1}$$

$$K = \frac{k_1}{k_{-1}} = \frac{C_{BL}}{C_B C_L} \tag{2}$$

where K is the equilibrium constant and C_{BL} is the concentration of the biomolecule–ligand complex.

For this scheme, the following assumptions are necessary:

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.

Now

$$f = C_{BL}/C_{B_0} \tag{3}$$

where C_{B_0} = total biomolecule concentration
f = fraction of biomolecules bound

From the material balance

$$C_{L_0} = C_L + C_{BL} \tag{4}$$

where C_{L_0} = total ligand concentration
C_L = free ligand concentration

From Eqs. (2) through (4),

$$f^2KC_{B_0} - (1 + KC_{L_0} + KC_{B_0})f + KC_{L_0} = 0 \tag{5}$$

This quadratic equation adequately describes the affinity adsorption process and can be solved to obtain f.

Ultrafiltration Washing

The ultrafiltration module on which the present model has been based is shown in Fig. 1. The following assumptions have been made for this step:

1. Ideal mixing conditions exist within the vessel.
2. There is unhindered transport of the target biomolecule and impurities through the membrane (100% transmission).
3. The filtration rate is kept constant.
4. The volume within the module is kept constant by constant addition of washing buffer.
5. Concentration polarization of ligand molecule on the membrane surface is negligible under our operating conditions.

From a material balance of the target biomolecule during the washing step,

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

where C_{B_t} = free biomolecule concentration at time t
C_{BL_t} = bound biomolecule concentration at time t
V = working volume of the ultrafiltration unit
Q = filtration rate

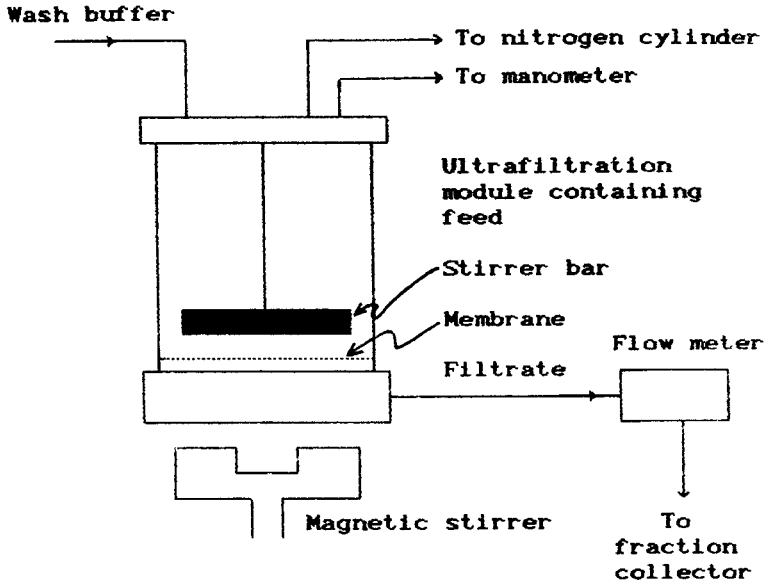

FIG. 1 Ultrafiltration module for affinity ultrafiltration.

Now

$$K = \left(\frac{C_{BL_t}}{C_{B_t} C_{L_t}}\right) \tag{7}$$

where C_{L_t} = free ligand concentration at time t.

Therefore from Eqs. (6) and (7),

$$\frac{d}{dt}\left(C_{B_t} + KC_{L_t} C_{B_t}\right) = -\frac{Q}{V} \tag{8}$$

again

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

Therefore

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

Integrate the above equation with the following boundary conditions:

$$C_{B_t} = C_{B_0}(1 - f) \qquad \text{at} \qquad t = 0$$

and the following equation is obtained:

$$(1 + KC_{L_0}) \log_e\left(\frac{C_{B_0}(1 - f)}{C_{B_t}}\right) - KC_{L_0} \log_e\left(\frac{1 + KC_{B_0}(1 - f)}{1 + KC_{B_t}}\right) + \left(\frac{KC_{L_0}}{1 + KC_{B_0}(1 - f)}\right) - \left(\frac{KC_{L_0}}{1 + KC_{B_t}}\right) = \frac{Qt}{V} \tag{11}$$

This equation can be solved numerically to determine C_{B_t} at any t when all other constants and parameters are known. C_{B_t} is also the concentration of the target biomolecule in the filtrate, and hence the validity of this correlation can be directly verified by continuous analysis of the filtrate. The target biomolecule content of the module at any time t is the difference between the initial total target biomolecule content and the cumulative amount of biomolecule lost with the filtrate. This can also be determined numerically.

The concentration of impurities which are not adsorbed by the ligand is given by

$$C_{I_t} = C_{I_0} \exp(-Qt/V) \tag{12}$$

where C_{I_t} = concentration of impurities at time t
C_{I_0} = initial concentration of impurities

A simulated concentration profile of different components as obtained using Eqs. (5), (11), and (12) is shown in Fig. 2.

In order to justify the validity of the proposed model, experimental data have been taken from a recent reference (19) where process parameters and experimental data are provided. A comparison among the experimental data (19), the predicted values based on the published model (19), and those obtained from the present model is shown in Fig. 3.

From the plot it is apparent that the present model gives a better fit with the experimental values. The sum of residuals (with respect to the experimental data) for the published model (19) is 50.3, while that for the proposed model is 47.3. Moreover, the published model (19) is valid only when C_{B_0} is much less than C_{L_0}. When C_{B_0} becomes comparable with

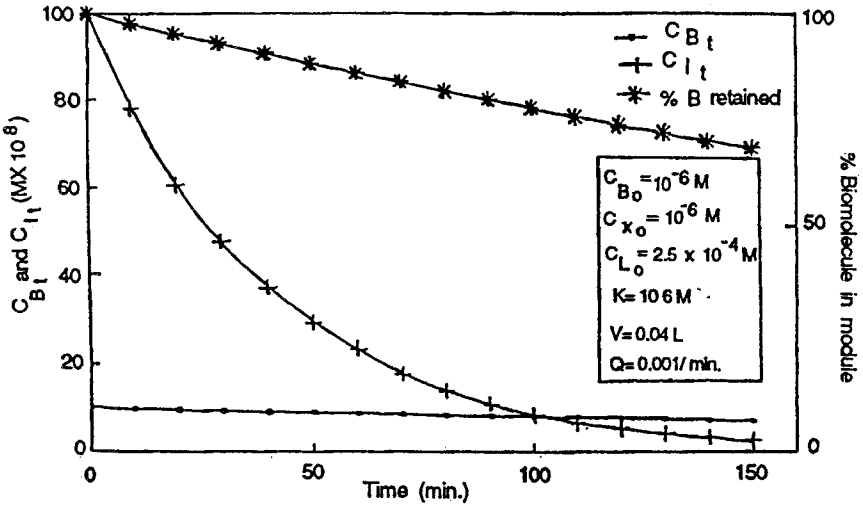

FIG. 2 Simulated concentration profile of various components during washing phase.

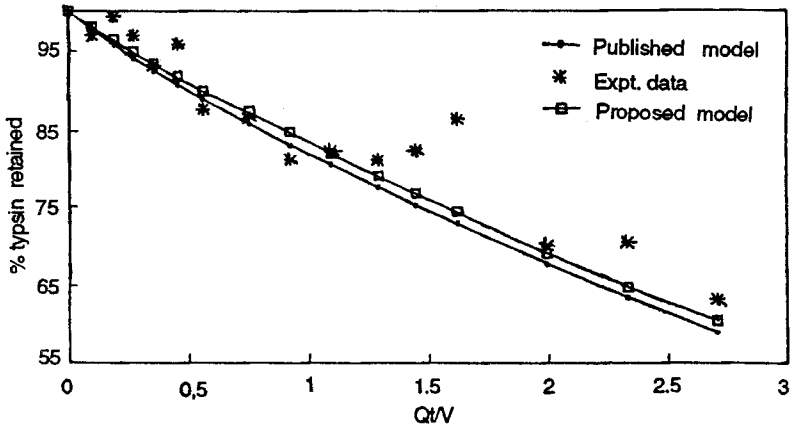

FIG. 3 Comparison between experimental data, published model, and proposed model.

C_{L_0}, it fails to give a true picture. Thus, the present model is closer to reality.

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