Immobilization of Suspended Mammalian Cells: Analysis of Hollow Fiber and Microcapsule Bioreactors

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Model equations of substrate mass transfer and uptake have been formulated for two bioreactor systems: microcapsules and a hollow fiber reactor. Assumptions include time independence, Fickian diffusion, homogenous cell suspension, and kinetics described by the zero and first order limits of the Monod equation. Glucose and oxygen were the substrates chosen for investigation of the kinetic and diffusion limitations. For microcapsules, the resulting radial concentration profiles indicated the possibility of a necrotic core due to insufficient substrate in those cases where diffusion is low and/or uptake is high. The model equations provide a means of estimating the maximum capsule radius which will allow adequate diffusion of nutrients to all of the contained cells. The simulated concentration gradients developed for a hollow fiber reactor demonstrate that diffusion limitations may exist at the far end of the reactor. Concentration gradients are shown both in the fiber lumens (in the axial direction) as well as in the shell space (in the radial direction). Variation of model parameters provides information on system specifications to avoid these diffusion limitations.
1 Introduction

The development of novel bioreactors has flourished in recent years as efforts to produce more efficient and economical systems continue. Bioreactors are used for production of many different compounds from plant cells, microbial and animal cells, as well as from isolated enzyme systems. Conventionally, bioreactors have consisted of batch and continuous flow reactors, typically known as stirred tanks and chemostats, respectively. To improve the performance of these reactors, designs have focused on increasing productivity per unit volume and reducing the amount of expensive downstream processing. Immobilization of cells with various types of barriers or supports can satisfy both criteria. For suspended cells, immobilization primarily consists of two options:

a. entrapment of cells within a porous matrix; and
b. containment of cells behind a barrier.

The first option includes porous supports such as ceramics and gels, which can be either preformed or formed around the cells. This option will not be discussed further. The second option includes processes which retain the cells behind a barrier, typically a membrane. Hollow fiber and flat sheet reactors and microcapsules all utilize membranes for this purpose. In hollow fiber and flat sheet reactors, the membrane is preformed; in microcapsules, the membrane is formed around the cells. Because each of these systems protects the delicate outer membranes of animal cells from the shear forces which result from media flow or stirring, they have been used for cultivation of mammalian cells. Although most animal cells are anchorage dependent for growth, transformed cells, such as hybridoma cells, are grown in suspension culture. This is possible with the hollow fiber and flat sheet reactors as well as with the microcapsules. Each method, however, provides a different environment for the suspended cells, an environment which ultimately determines the productivity of the system.

Of major concern to the optimization of conversions in these bioreactors is whether, by instituting the separation or immobilization of the cells, the reactions are governed by kinetic or diffusional control. Models to determine the answer to this question can also provide insight toward shifting the mechanisms of control when the rate of production is dictated by diffusional limitations. This paper addresses current analyses of the problem and provides results from solutions of simplified continuity equations for the hollow fiber bioreactor and for the microcapsule using two substrates, glucose and oxygen.

2 Immobilization

2.1 Microcapsules

The encapsulation of living cells was first accomplished by Lim and Moss. Jarvis and Grdina have developed a modification of the original procedure which is patented under the trade name Encapcel. The process involves formation of a spherical polyanionic gel mold containing cells, onto which is deposited a polymeric membra-