

Encapsulation is another method of cell entrapment. Microcapsules are hollow, spherical particles bound by semipermeable membranes. Cells are entrapped within the hollow capsule volume. The transport of nutrients and products in and out of the capsule takes place through the capsule membrane. Microcapsules have certain advantages over gel beads. More cells can be packed per unit volume of support material into capsules, and intraparticle diffusion limitations are less severe in capsules due to the presence of liquid cell suspension in the intracapsule space. Various polymers can be used as capsule membranes. Among these are nylon, collodion, polystyrene, acrylate, polylysine-alginate hydrogel, cellulose acetate-ethyl cellulose, and polyester membranes. Different membranes (composition and MW cutoff) may need to be used for different applications in order to retain some high-MW products inside capsules and provide passage to low-MW nutrients and products.

Another form of entrapment is the use of macroscopic membrane-based reactors. The simplest of these is the hollow-fiber reactor. This device is a mass-transfer analog of the shell-and-tube heat exchanger in which the tubes are made of semipermeable membranes. Typically, cells are inoculated on the shell side and are allowed to grow in place. The nutrient solution is pumped through the insides of the tubes. Nutrients diffuse through the membrane and are utilized by the cells, and metabolic products diffuse back into the flowing nutrient stream. Owing to diffusional limitations, the unmodified hollow-fiber unit does not perform well with living cells. Modifications involving multiple membrane types (for example, for gas exchange or extractive product removal) or changes to promote convective flux within the cell layer have been proposed. Several commercial reactors for animal cell cultivation use membrane entrapment.

In addition to entrapment or encapsulation, cells can be bound directly to a support. Immobilization of cells on the surfaces of support materials can be achieved by physical adsorption or covalent binding.

Adsorption of cells on inert support surfaces has been widely used for cell immobilization. The major advantage of immobilization by adsorption is direct contact between nutrient and support materials. High cell loadings can be obtained using microporous support materials. However, porous support materials may cause intraparticle pore diffusion limitations at high cell densities, as is also the case with polymer-entrapped cell systems. Also, the control of microenvironmental conditions is a problem with porous support materials. A ratio of pore to cell diameter of 4 to 5 is recommended for the immobilization of cells onto the inner surface of porous support particles. At small pore sizes, accessibility of the nutrient into inner surfaces of pores may be the limiting factor, whereas at large pore sizes the specific surface area may be the limiting factor. Therefore, there may be an optimal pore size, resulting in the maximum rate of bioconversion.

Adsorption capacity and strength of binding are the two major factors that affect the selection of a suitable support material. Adsorption capacity varies between 2 mg/g (porous silica) and 250 mg/g (wood chips). Porous glass carriers provide adsorption capacities ( $10^8$  to  $10^9$  cells/g) that are less than or comparable to those of gel-entrapped cell concentrations ( $10^9$  to  $10^{11}$  cells/ml). The binding forces between the cell and support surfaces may vary, depending on the surface properties of the support material and the type of cells. Electrostatic forces are dominant when positively charged support surfaces (ion-exchange resins, gelatin) are used. Cells also adhere on negatively charged surfaces by covalent binding or H bonding. The adsorption of cells on neutral polymer support surfaces