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A COMPARISON OF SEMIPERMEABLE MICROCAPSULES AND STANDARD DIALYSERS FOR USE IN SEPARATION

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Introduction

Dialysers with membranes of the coil, plate, or capillary configurations are most commonly used in separation procedures. In recent years, there is the development of a new class of dialysis system in the form of semipermeable microcapsules (1,2,3, 4). It is the purpose of this paper to discuss this new dialysis system and to compare it with standard dialysers.

Movement of molecules across dialysis membranes

The movement of molecules across dialysis membranes involve three main steps: (1) the movement of the molecules from the solution to the interface of the membrane, (2) the movement of molecules through the membrane, and (3) the movement of molecules away from the interface of the membrane on the other side. The factor related to the movement of molecules to and away from the interface of the membrane will be discussed when the specific examples are given. The movement of molecules across the membrane are governed by factors expressed in the following equation:

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$$Js = \frac{ds}{dt} \cdot \frac{1}{A} = Ji - Jo$$

$$= \omega RT\ (C_s^o - C_s^i) + \{(1 - \sigma)\ \frac{C_s^o - C_s^i}{\ln \frac{C_s^o}{C_s^i}}\ Jv\}$$

$$= \frac{K}{dx\ (fsw + fsm)}\ RT\ (C_s^o - C_s^i) + \{(1 - \sigma)\ \frac{C_s^o - C_s^i}{\ln \frac{C_s^o}{C_s^i}}\ Jv\}$$

Where:

Js = net flux of solute

Ji = influx of solute

Jo = outflux of solute

$\frac{ds}{dt}$ = number of molecules crossing the membrane in unit time

A = membrane area available for diffusion

ω = solute permeability coefficient

dx = membrane thickness

fsw = friction coefficient of solute and solvent in membrane

fsm = friction coefficient of membrane and solute

R = gas constant

T = absolute temperature

C_s^o = solute concentration in compartment O

C_s^i = solute concentration in compartment i

σ = reflection coefficient

Jv = total flow of solute and solvent

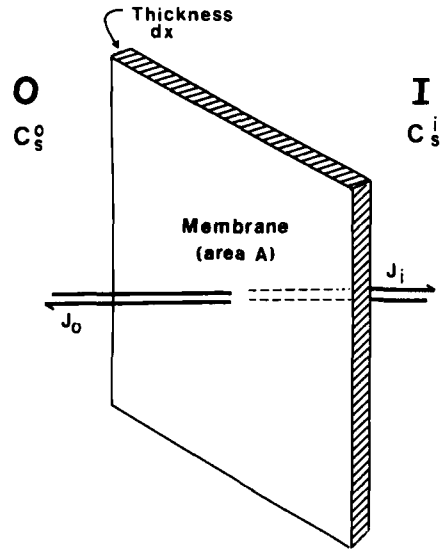
K = distribution coefficient for solute between membrane and aqueous phase

If the other factors remain constant then the rate of movement of molecules across the membrane is proportional to the total

membrane area (A), concentration gradient ($C_s^o - C_s^i$), porosity of the membrane, and inversely proportional to the membrane thickness (dx) (Figure 1).

Movement of molecules in standard dialysis system

Standard dialysers depend on the basic principle (Figure 1) where a semipermeable membrane separate two compartments. The solution with molecules to be separated flow through one compartment (0). The dialysate or washing solution flows through the other compartment (I). Dialysable molecules cross the membrane from compartment 0 to compartment I where they are removed by the



$$J_s = J_i - J_o = \frac{ds}{dt} \cdot \frac{1}{A}$$

FIGURE 1

Movement of molecules across a membrane. O - compartment O, I - compartment I, C_S - solute concentration, J - flux of solute across membrane, and s - solute.

dialyzing solution. The rate of movement of molecules across the dialysis membrane is facilitated by using a large membrane area which is made as thin and as porous as possible. In the case of the standard dialysers used as artificial kidneys in removing undesirable metabolites from blood, the total membrane area routinely used is 1 m^2 . Any extensive increase in the total surface area will result in an undesirable increase of the priming volume of the dialysers. In this type of system, the membrane thickness is usually about 20 microns, since with thinner membranes there would be problems of membrane leakage or breakage. In the standard dialysis system the movement of molecules to the surface of the membrane and the movement of molecules away from the membrane after crossing, is facilitated by appropriate adjustments of hydrodynamics.

Movements of molecules in a microcapsule dialysis system

Next, let us look at the more special case of dialysis systems in the form of semipermeable microcapsules. Semipermeable microcapsules are ultrathin membrane systems of microscopic dimensions (Figure 2). Their preparation, properties, and applications have been described in detail (2). Typically they have a membrane thickness of about 0.02 μ and a mean diameter of 5 to 2000 microns. The same factors governing the movements of molecules across a dialysis membrane determine the rate of movement of molecules across the microcapsule. However, the small particle size of the microcapsule is such that a very large membrane area to volume relationship is available. For example, 10 ml of 20 micron diameter semipermeable microcapsules have a total membrane area of more than 2 m^2. Furthermore, the membrane thickness is about $\frac{1}{1000}$ th of that of a standard dialysis membrane. This ultrathin membrane is made possible since in a microscopic spherical configuration the membrane can be made much thinner without becoming unstable. If one looks at the theoretical initial transport rate across 10 ml of microcapsules as compared to a standard dialyser, very surprising results are obtained

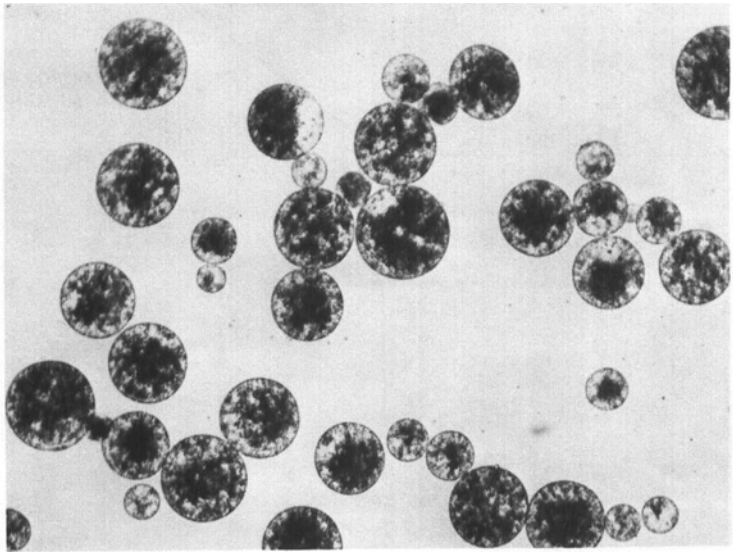


FIGURE 2

Microphotograph of semipermeable microcapsules containing enzyme. Mean diameter - 100 micron. Membrane thickness - 2 Å.

(Figures 3,4).For a conservative analysis, let us use a membrane thickness of 5 microns (instead of 25 microns) for the membrane of dialysers and 0.05 micron (instead of 0.02 micron) for the membrane of semipermeable microcapsules. The theoretical initial transport rate of standard dialysers with 1 m^2 membrane area and 5 micron membrane thickness is represented as unity. The theoretical initial transport rate of 10 ml of different diameter (10 - 2000 microns) microcapsules with 0.05 micron membrane thickness are computed and represented in the curve. It shows that 10 ml of 10 micron diameter microcapsules have a theoretical initial transport rate which is about 200 times greater than that of the standard 1 m^2 area dialysis system. Even 10 ml of microcapsules with a diameter of 2000 microns have a potential transport rate of about twice that of the standard 1 m^2 area dialysis system. If one were to use a volume of microcapsules comparable to the total

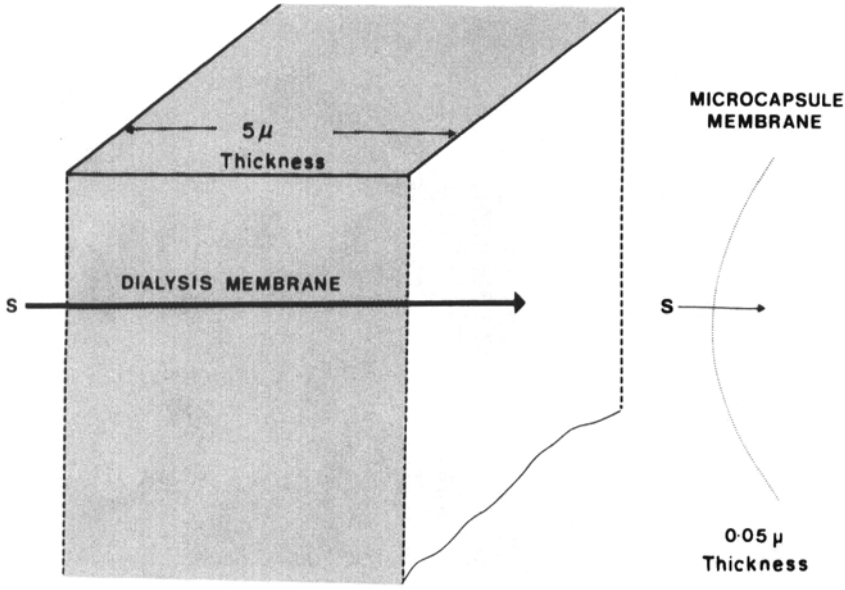


FIGURE 3

Schematic comparison of thickness of standard dialysis membrane with microcapsule membrane. s - solute.

priming volume of the standard 1 m^2 dialysis system (approximately 300 ml), the theoretical initial transport rate would be at least 6000 times higher in the case of the 10 micron microcapsule and 50 times higher in the case of the very large 200 micron microcapsule. These theoretical results would have to be considered together with the other factors of movement of molecules to the surface of the membrane and the movement of molecules away from the membrane interface. Vieth et al have recently analysed in some detail these two factors for semipermeable microcapsules (5).

The coefficient (K) for the molar flux (Jb) of molecules from the solution to the external membrane surface is expressed by the following equation (6):

$$Jb = K_L A (C_s^o - C_s^m)$$

Where: A is the surface area of the microcapsules

C_s^o is the concentration of solute in the suspending solution

C_s^m is the concentration of solute at the external surface of membrane

The coefficient K_L is related to the degree of turbulence of fluid around the external surface of the microcapsules. Adequate stirring in the case of a suspension or adequate flow distribution

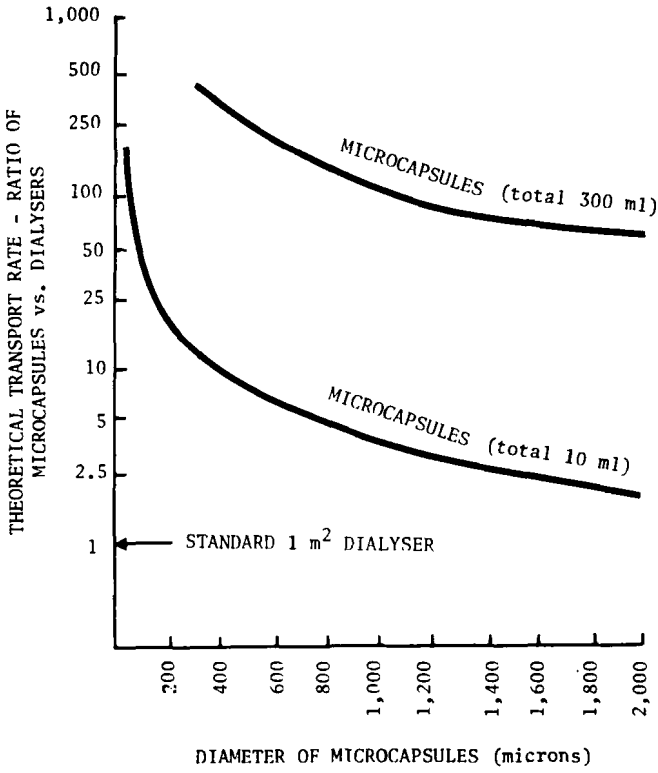


FIGURE 4

Ratio of microcapsule transport rate verus standard 1 m^2 dialyser transport rate. Standard dialyser rate being 1. Microcapsules of different diameters and with total volumes of either 10 ml or 300 ml are shown.

in the case of a fixed bed would ensure efficient transport from the solution to the membrane surface.

Another factor is the movement of solute away from the interface of the membrane on the other side. In the case of a rigid sphere with unmixed content, this can be represented by the equation for diffusion into a sphere (5):

$$Dr\left[\frac{\partial Cr}{\partial r^2} + \frac{\partial}{r}\frac{\partial Cr}{\partial r}\right] - (\text{rate of depletion of solutes by adsorption or catalysis})$$

Where: D is diffusion coefficient
C is concentration of solute
r is radial distance from center of microcapsules

The small diameter of the microcapsules results in an internal aqueous phase of microscopic dimension. This would allow for rapid diffusion and mixing of solute inside the microcapsules. Furthermore, the flexibility of the membrane also allows for mechanical mixing of the content of the microcapsules in a stirred suspension or in a fixed bed with pulsatile flow. All these factors would help to decrease the radial gradient inside the microcapsules as expressed by the above equation for a rigid unmixed sphere (2).

Another important factor is that the theoretical initial transport rate would diminish rapidly unless the concentration gradient ($C^1 - C^2$) across the microcapsule membrane is maintained. In the standard dialysis system the concentration gradient is maintained by the circulation of dialysate with a low solute concentration in the dialysate compartment. What machanism can one use in the case of the semipermeable microcapsules?

Types of semipermeable microcapsule systems

Let us look at the following examples (Figure 5): (I) In the first case, the semipermeable microcapsules are used as a simple microscopic dialysis system. The initial transport rate is such that solutes would very quickly equilibrate across the

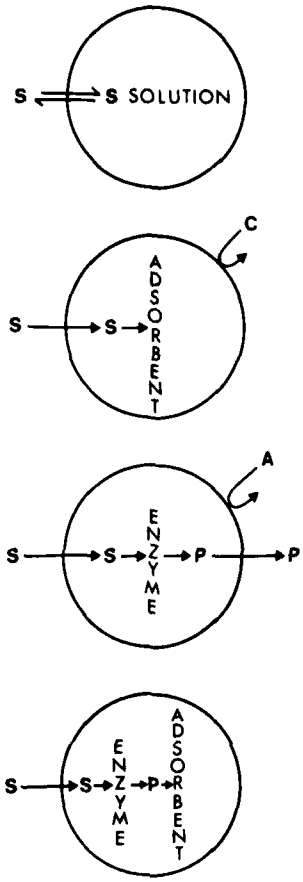


FIGURE 5

Schematic representation of four types of microcapsule systems. (1) microcapsules containing solution (2) microcapsules containing adsorbent (3) microcapsules containing enzyme (4) microcapsules containing enzyme plus adsorbent. s - solute, P - product of enzymatic reaction, C - cells, and A - antibodies.

membrane. For instance, in 100 micron mean diameter microcapsules the T 1/2 for equilibration is about 5 seconds for urea and 35 seconds for sucrose. This rate of equilibration would support the above theoretical analysis. Further variations in membrane properties (e.g. porosity, thickness, charge, lipid, etc.) could

result in higher selectivity in regard to molecular size, charge of molecules, lipid solubility, etc. The use of semipermeable microcapsules as a simple microscopic dialysis system would be effective for rapidly separating a small volume of solution or for chromatographic separation. In order to maintain the concentration gradient and the capacity to remove an appreciable amount of molecules, other systems can be used in combination with the semipermeable microcapsules. (II) One of these involves the use of semipermeable microcapsules containing adsorbents (e.g. activated charcoal). In this case, molecules which dialyze rapidly across the semipermeable microcapsules are adsorbed by the adsorbents inside the microcapsules, thus maintaining a concentration gradient across the membrane. Proper selection of membranes and adsorbents would allow one a great deal of selectivity. (III) Another system is the use of semipermeable microcapsules containing enzymes. In such a system, the dialyzed substrate entering the semipermeable microcapsules is converted to products which can diffuse out, and in this way, the substrate concentration inside the microcapsules is maintained low, thus allowing a concentration gradient for substrates to continuously enter the microcapsules. The microencapsulated enzyme system unlike the microencapsulated adsorbent system, is not capacity limited, but acts continuously in the form of a microscopic reactor. (IV) Semipermeable microcapsules can be made to contain a combination of enzyme and adsorbent for its product, so that dialysable substrates can be selectively converted by the enzyme and the product selectively adsorbed.

The following are typical examples of how these different systems of semipermeable microcapsules are used in practice for separation and purification.

Selective separation of a specific type of molecules from a complex system

For this example let us take a complex situation in which blood, a complex suspension of blood cells, protein, and numerous types of solutes, circulate in the blood vessels of a living person.

SEMIPERMEABLE MICROCAPSULES AND STANDARD DIALYSERS

There are many cases when a person accidentally or intentionally takes a large quantity of drugs or toxins resulting in dangerously elevated blood levels. How does one selectively separate a specific type of drug or toxic molecules from this complex circulating blood in the body? The standard method for this includes the use of the standard dialysers. Here blood from the patient flows through one compartment where permeant molecules, including the drug, diffuse across the membrane to be washed away by dialysis solution on the other side. This method is only fairly effective for most of the commonly encountered poisonings. The efficiency of removal is of the order shown in Table I. In theory, one could put a column of adsorbent granules and pass the blood directly through it to remove the toxic material. In fact, this has been done using a column of free activated charcoal granules (7,8). Although the latter system is very effective in removing drugs, at the same time it removes essential blood elements (e.g. platelets) and releases charcoal powder into the blood stream causing adverse effects. These problems are eliminated when the adsorbent granules are placed inside semipermeable microcapsules (2,3,9). Thus, activated charcoal granules have been microencapsulated by coating with an ultrathin layer of blood-compatible polymer membrane. These are then retained in a column through which blood from the patient is

TABLE I

CLINICAL DRUG CLEARANCE COMPARISON

Methyprylon:	
ACAC microcapsules:	230 ml/min
Hemodialyzers:	80 ml/min
Glutethimide:	
ACAC microcapsules:	150 ml/min
Hemodialyzers:	60 ml/min
Methaqualone:	
ACAC microcapsules:	230 ml/min
Hemodialyzers:	29 ml/min

allowed to perfuse. The coating prevents powder from the charcoal granules from being released into the circulation, while the blood-compatible membrane coating prevents the removal of essential blood cells, such as platelets from the circulating blood. The very high transport rate of the ultrathin membrane of the semi-permeable microcapsules allows drugs to diffuse rapidly across the membrane to be removed by the enclosed activated charcoal. In this way, the microcapsule system is much more efficient than the standard dialysis system for the treatment of patients with drug poisoning (10,11) (Table I).

In addition to the above factors, the microencapsulated adsorbent system would also be effective in removing certain types of protein-bound toxic materials. Some drugs and toxins are bound to protein in the plasma. The proportion of protein-bound drug to unbound drug depends on the affinity of the protein for the drug and on the equilibrium constant. With most protein-bound drugs, it is mostly the unbound fraction that dialyzes across the standard dialysis system. In the case of microencapsulated activated charcoal, the charcoal has a varying degree of affinity for different drugs. For example is has a very high affinity for certain drugs like doriden. As a result, the drug equilibrates rapidly across the ultrathin membrane and is actively adsorbed on to the charcoal. This high affinity of the charcoal for doriden would appear to move the equilibrium of the drug into the direction of the activated charcoal, resulting in the unbinding of the protein-bound drugs. The efficiency of the removal of this drug by the microencapsulated charcoal system as compared to standard hemodialysis (Table I) shows that this is the case.

This example is one in which one has to separate one type of molecules from a complex suspension. This situation demands that the complex suspending solution should not be adversely affected in any way. For instance, neither by the addition of any material from the separating system, nor by the removal of essential material from the complex suspending medium.

Selective separation of a specific group of molecules from a complex suspension

In patients with kidney failure, the inability to excrete waste metabolites results in the accumulation of waste metabolites to toxic levels. It is not the purpose of this paper to discuss the exact toxins in uremia, nor is it the purpose of this paper to discuss the type of metabolites that need to be removed. In the past year, there has been some evidence that of all the accumulated waste metabolites, a group of molecules in the 300 - 1300 molecular weight range appear to contribute greatly to certain symptoms and problems in the patients. There is also evidence to indicate that the efficiency of removal of this group of molecules appears to be correlated with patients improvement.

The standard method of treating chronic renal failure involves the use of the standard dialysers to remove permeant molecules from the circulating blood. The standard dialysers, as we have described earlier, usually have a surface area of 1 m^2 and a membrane thickness of 20 microns. As such, the permeability to molecules is limited, especially with molecules of increasing molecular weights. If one draws a graph of the efficiency of the standard dialyser for removing molecules of different molecular weight, it can be seen (Figure 6) that the efficiency decreases rapidly with increase in molecular weight, so that in the molecular weight range of 300 - 1300, the standard dialyser is quite inefficient. This may explain why it is necessary to treat the patient 8 hours, 3 times a week when using the standard dialysers. Furthermore, as can be seen from the graph, in order to remove a sufficient amount of the bigger molecules, one has to remove a much large amount of the smaller molecules, some of which, like amino acids, might be essential to the body.

It would therefore be ideal to have a system which could selectively remove the specific group of molecules in the 300 - 1300 molecular weight range. Microencapsulation of activated charcoal within biocompatible membranes has been used in patients

for this purpose (12, 13, 14). The ultrathin membrane and the high transport rate allow the microcapsule artificial kidney (300 ml) to function at high efficiency for the removal of molecules between 300 - 1300 molecular weight range. The molecules diffusing rapidly into the microcapsules are adsorbed by the activated charcoal and thus allow for the continuous removal of the middle molecules. The result is shown in Figure 6 . In addition to this, the microencapsulated activated charcoal has some selective adsorbent characteristics so that it does not adsorb electrolytes or amino acids. The biocompatible membranes also prevent the removal of blood cells such as platelets. As a result, the removal of the middle molecules is fairly selective. Comparison of the efficiency of the standard dialysers and that of the semipermeable microcap-

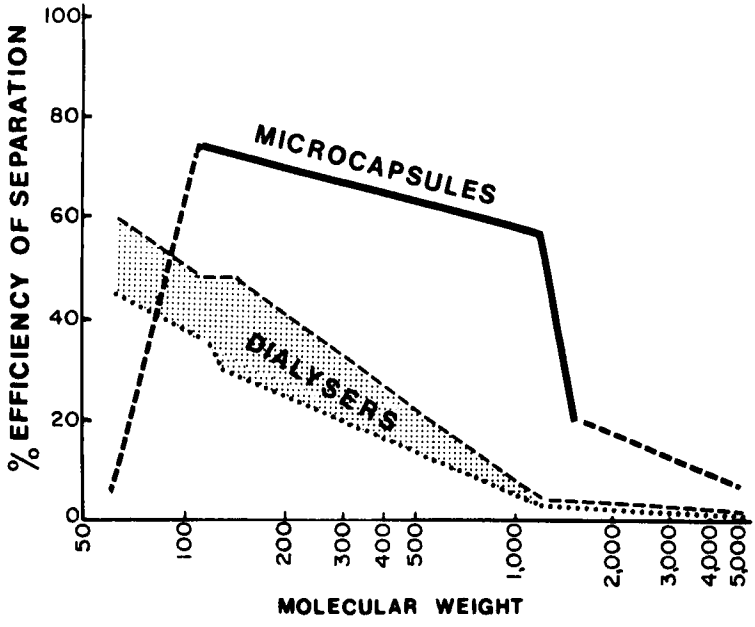


FIGURE 6

The comparative efficiency of the removal of solutes with different molecular weights. Comparison of the standard 1 m^2 dialyser with the microcapsule artificial kidney.

sules for the removal of the middle molecules serves to explain why treatment using the microcapsule kidney requires less than 1/3 the time needed for the standard dialysers (Figure 6).

Selective conversion of a specific substrate in a complex system

In the above two examples, the removal of molecules from a complex suspension is fairly selective. A much more selective separation procedure would be using semipermeable microcapsules containing enzymes. Here the selectivity can be extremely refined since one enzyme system can be used to act selectively on the conversion of only one dialysable substrate in a very complex suspension or solution. As an example of this application, let us take a complex system in the form of an experimental animal. If one wants to selectively remove or convert one substrate from a living animal, how can one go about doing this? One can inject an enzyme solution into the body, thereby converting selectively the substrate directly and quite efficiently. However, the introduction of a foreign protein enzyme into the body, sometimes creates problems, like allergic reactions. Furthermore, once injected, the enzyme could be quickly removed by various systems in the body which normally remove foreign proteins and thus removing the activity very quickly. Furthermore, with repeated injection of the enzyme, the body would react to the foreign protein by the production of antibodies which would inactivate subsequently injected enzymes. On the other hand, if an enzyme is placed inside semipermeable microcapsules (Figure 5), then at no time is the enzyme in direct contact with the body and thus cannot produce allergic reaction. Furthermore, the enzyme in the microcapsules cannot be directly removed by systems in the body that remove foreign proteins. Since the enzyme is enclosed within the semipermeable microcapsules, if there are any antibodies present in the body fluids, they cannot enter the microcapsules to inactivate the enzyme. However, the substrate can equilibrate rapidly across the membrane to be acted on by the microencapsulated enzyme. Studies have been carried out showing that semipermeable

microcapsules containing various types of enzyme can act efficiently in converting body substrates (1,2). Thus, urease has been used to selectively convert urea in the body (1,2) while microencapsulated asparaginase is used to selectively convert asparagine in the body (2,15,16). Microencapsulated catalase have also been used to selectively convert peroxide in the body of experimental animals (2,17,18). In all these cases, the substrate is converted to a product which is allowed to recycle in the body. In many cases, this is what is desired, but in other cases, it may be necessary to remove the product of the enzymatic reaction.

Selective removal of a specific substrate and its enzymatic product

In cases where it is desired to convert a specific substrate and at the same time remove its enzymatic product, one can microencapsulate a combination of enzymes and adsorbents for the enzymatic product (2,3). In this way, the product produced by the enzymatic conversion of the substrate is adsorbed in the microcapsule. A typical example of this is the experiment in which microencapsulated urease and ammonia adsorbent are used. Urea diffusing into the microcapsules is converted by the encapsulated urease into ammonia and the ammonia produced is then adsorbed by the ammonia adsorbent. The net effect is the removal of a specific substrate, urea. Other examples of this combination approach are also possible.

DISCUSSION AND GENERAL SUMMARY

The examples given above mostly involve using one of the most complicated systems is illustrate the feasibility of the new microdialysis system. The semipermeable microcapsules would be most effective in the special examples mentioned where the suspending medium for separation is extremely complex. However, there are other conditions where the situation is less complex in which the semipermeable microcapsule system is also effective. In conclusion,

the semipermeable microcapsule system is a new dialysis system of microscopic dimensions which has a transport capacity many times greater than the standard dialysers. The possibility of combining the microcapsule dialysis system with enzymes or adsorbents would further extend its possible application.

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