REVIEWS

Controlled Release of Polypeptides and Other Macromolecules

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Abstract: The use of polymeric matrices for the controlled release of polypeptides and other macromolecular drugs is reviewed. Three principal mechanisms of release include diffusion of the polypeptide through the polymer, erosion of the polymer matrix, and the application of magnetic fields to force more drug out of the matrix. The diffusion controlled systems generally utilize ethylene-vinyl acetate copolymer. The advantage of these systems is facile manipulation of the pore structure to obtain desired release kinetics. Release of many different polypeptides from these systems for periods of months has been demonstrated. Bioerosion provides the advantage that the polymer system does not need to be retrieved. Magnetism provides a mechanism whereby desired increases and decreases in polypeptide release rates can be achieved on demand.

The concept of controlling the release rates of pharmaceutical agents, as opposed to simply retarding their availability (e. g. slowly dissolving tablets) is relatively new. Since 1970, a number of polymeric systems have been developed to control the release of low molecular weight (<600 dalton) drugs (1,2). Examples include a one-week system for delivering a drug to combat glaucoma, a 1-year system for delivering a birth control drug, and 1-day and 3-day systems that can be placed on the skin to release nitroglycerin and scopolamine, respectively (3). In almost all cases, the mechanism of release is diffusion of the drug through a solid polymer. In general, diffusion rates for drug molecules through polymers are orders of magnitude less than the diffusion rates of the same molecules through water. Thus, the polymers serve as permeable barriers through which drug must cross before reaching the bloodstream.

Polymeric systems were at first believed to be unsuitable for the delivery of macromolecular drugs such as polypeptides. This was due to the fact that most polypeptides are simply too large to penetrate through most polymer chains, even after swelling of the polymer. Polypeptides are also excellent examples of drugs that generally require parenteral delivery (4). Most polypeptides are denatured or degraded by acids and/or enzymes in the gastrointestinal system, or are absorbed poorly, and thus exhibit low bioavailability when administered orally or transdermally. Simple parenteric administration is also problematic, due to the very short half-lives of the drugs once they reach the bloodstream. Table I lists macromolecular drugs of various classes, and their half-lives in the circulation. All of these drugs possess half-lives of less than three hours. Therefore, in order to obtain a long-term, constant therapeutic effect, a chronic, implantable dosage form is desired. Such a dosage form must serve two purposes: first to release the drug at a slow rate, and second to protect the drug from the body.

In this paper, efforts made to achieve controlled release of polypeptide drugs from polymeric systems are reviewed. We have classified the systems based on the primary mechanisms governing drug release: diffusion, bioerosion, and magnetism. The scope of this review does not include nonpolymeric delivery systems such as pumps. (The reader is referred to references (5, 6) for discussion of these devices).

Diffusion Mediated Release

In 1974–76 a number of polypeptides and other macromolecules were first released from biocompatible polymers such as poly(hydroxyethylmethacrylate) (Hydron®) and ethylene-vinyl acetate copolymer (EVAc) (7). The technique used for fabrication was later improved (8) to make the drug release kinetics more reproducible. At present, EVAc is the polymer of choice. EVAc is biocompatible (9), and has been approved by the Food and Drug Administration for use in several human controlled release systems. It is also hydrophobic and does not swell.

Fabrication procedures. There are currently two general methods for producing EVAc controlled release polymers. In the first procedure (8), illustrated in Fig. 1, EVAc is dissolved in methylene chloride. Polypeptide drug powder is suspended in the polymer solution and the suspension is poured into a cooled mold. The polypeptide particles are insoluble in methy-

Table I. Polypeptide Drugs and Their Half-Lives (4).

Polypeptide	Molecular Weight	Half-life
ACTH	~ 4700	<5 min
Angiotensin I	~ 1200	15 sec
Bradykinin	1060	30 sec
Calcitonin	~ 3600	< 40 min
Enkephalins	~ 600	2 min
Gonadotropic Hormones	~ 30000	.5–3 hr
Growth Hormone	~ 22600	< 25 min
Insulin	~ 6000	< 25 min
Oxytocin	1007	2 min
Parathyroid Hormone	9500	< 15 min
Vasopressin	~ 1200	4 min

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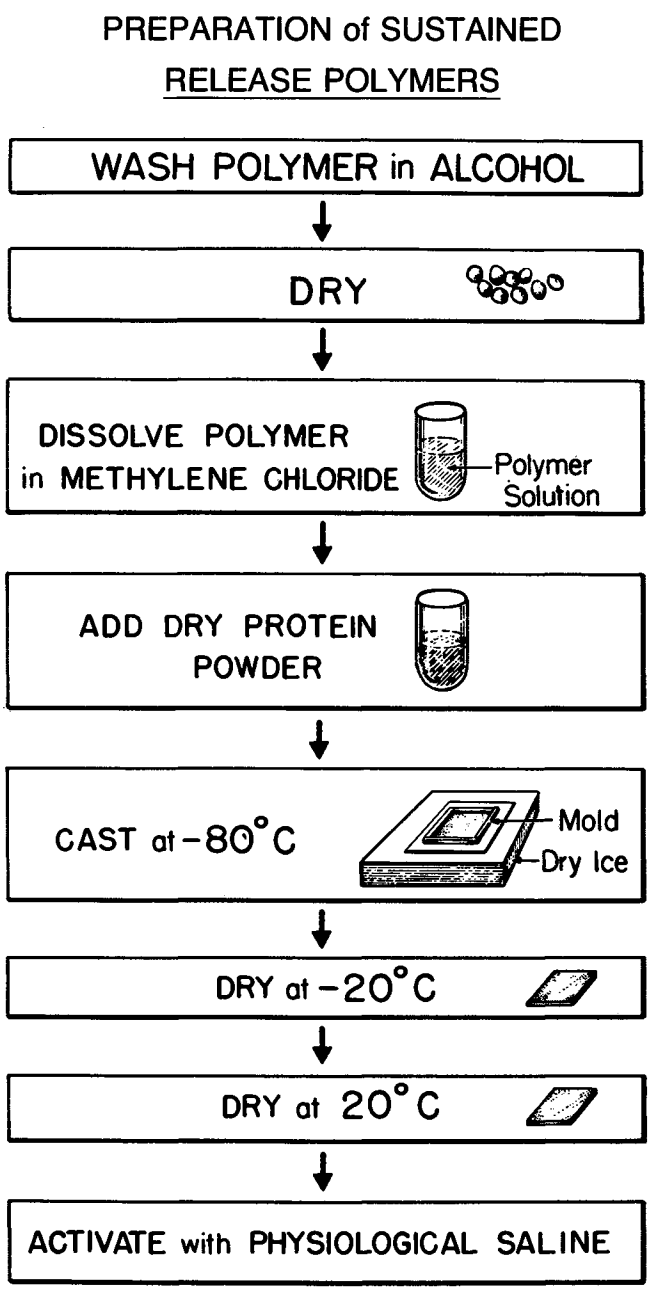

Fig. 1 Preparation of ethylene-vinyl acetate copolymer (EVAc) matrices by solvent casting.

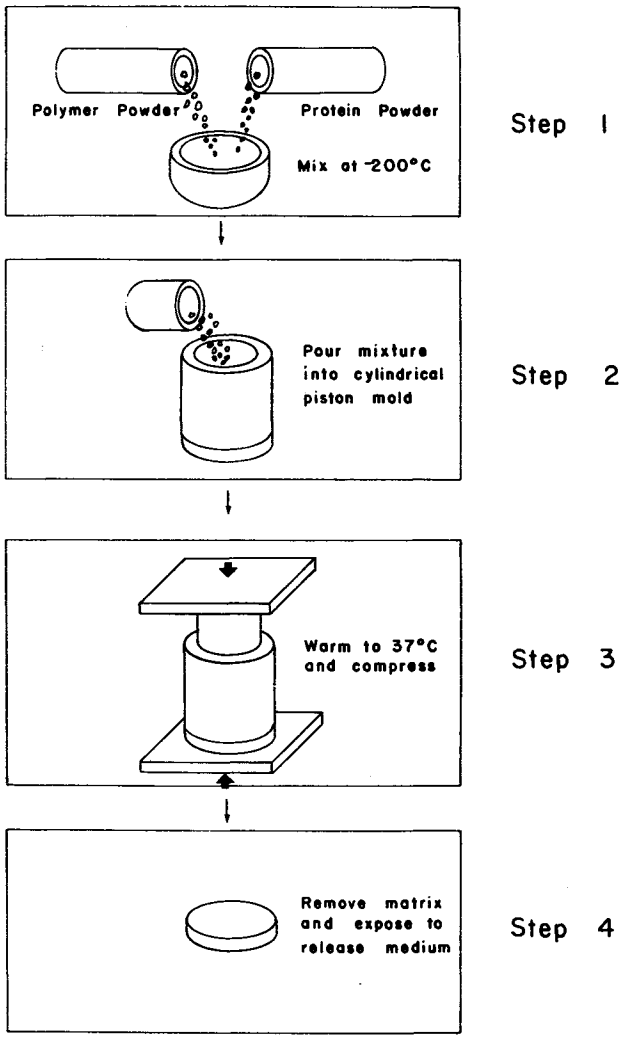

Fig. 2 Preparation of EVAc matrices by sintering.

lene chloride. The suspension congeals in the mold, and solvent evaporation can commence without settling of drug or convection currents. The polymer matrix is removed from the mold and vacuum dried. The process requires approximately 4 days. Most results discussed in this review are from matrices produced by this first procedure.

In the second procedure, illustrated in Fig. 2, polymer and polypeptide powders are mixed below the polymer's glass transition temperature, and are then sintered in a mold at room temperature (EVAc has a low glass transition temperature (−36°C) permitting it to flow readily at room temperature) (10). This second method requires approximately 1 hour, and possesses other advantages over the first method when problems of scale-up are considered (e.g. the second method does not require a solvent).

General release mechanism. It was at first puzzling that release could occur from such delivery systems. As stated before, polypeptides cannot diffuse through most polymer films. Serial microtomy and microscopy of matrices provide insights into the release mechanism. Fig. 3 a shows an EVAc matrix loaded with the polypeptide myoglobin and sectioned before release. Definite regions of polymer and polypeptide can be seen. (A pure EVAc matrix cast without any polypeptide appears as a non-porous sheet (11)). Fig. 3 b shows an EVAc matrix sectioned *after* release of incorporated polypeptides. Fig. 3 suggests the following mechanism of polypeptide release: water is imbibed into the matrix, dissolving the polypeptide powder. The powder granules, once dissolved, leave behind pores in the polymer matrix (Fig. 3 b). It is through these pores that polypeptide molecules are able to diffuse.

a. Before release.

b. After release

Fig. 3 5μ thick sections of EVAc polymers.

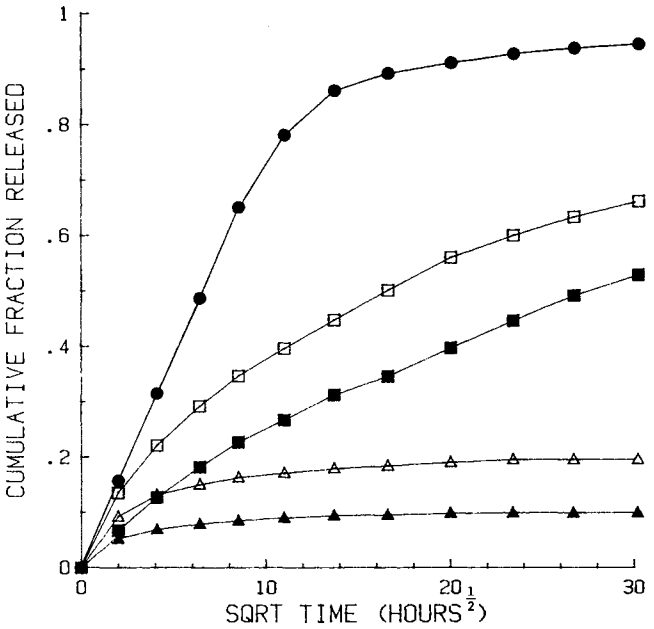

Fig. 4 Kinetics of release for bovine serum albumin (BSA) from EVAc matrices at various drug loadings and particle sizes. Abscissa is square root of time. Ordinate is cumulative fraction of incorporated BSA that is released.

▲ Loading = 0.10, particle size range = 150–180μ
△ Loading = 0.10, particle size range = 300–425μ
■ Loading = 0.30, particle size range = 150–180μ
□ Loading = 0.30, particle size range = 300–425μ
● Loading = 0.50, particle size range = 150–180μ

Fig. 4 shows kinetics of *in vitro* release for bovine serum albumin (BSA) from an EVAc polymer matrix plotted versus the *square root* of time. Note the long time scale over which release occurs (for example, 24 hours$^{t1/2}$ corresponds to 24 days, and 30 hours$^{t1/2}$ corresponds to 37.5 days). Both particle size and loading of the polypeptide can be varied to control the rate of release. It is also seen that at low loadings not all polypeptide is released from the polymer. This can be explained as follows: In the casting process, polypeptide particles become situated at random within the polymer matrix. The chance that two polypeptide particles will touch each other is very small when the polypeptide loading is low. Thus, most polypeptide particles will be completely surrounded by polymer, and the polypeptide molecules will be trapped. Only those polypeptide particles on the surface of the matrix will be able to be released. At higher loadings, polypeptide particles are more apt to touch each other, and large clusters of polypeptide particles can thus extend from the surface deep into the matrix. These clusters result in connected pore space upon dissolution of the polypeptide particles. Therefore, all polypeptide particles in these clusters can be released. These two situations are diagrammed in Fig. 5.

Fig. 4 also shows that an increase in polypeptide particle size also increases the total percentage of polypeptide released. This can be explained by noting that the larger the polypeptide particle, the more likely it will touch the surface of the matrix.

Time scale of release. The fact that much of the polypeptide can be trapped in the matrix provides further evidence that polypeptides do not diffuse through the polymer itself. The polypeptides are presumably diffusing through aqueous filled pores. Thus, one would expect that the relevant diffusion coefficient is that of polypeptide in water. However, if this were true, one might expect release times of shorter duration, as we shall now explain. Let L be the depth of a slab being tested for release, and D be the diffusion coefficient in water of the polypeptide being released from that slab. Assuming

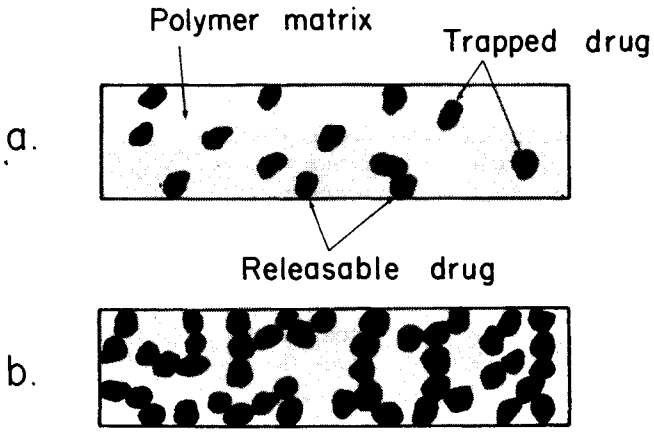

Fig. 5 Schematic of EVAc – polypeptide matrices before release.
a. Low loading – most drug is trapped by surrounding polymer.
b. High loading – almost all drug is connected to surface via other drug particles, and is therefore releasable.

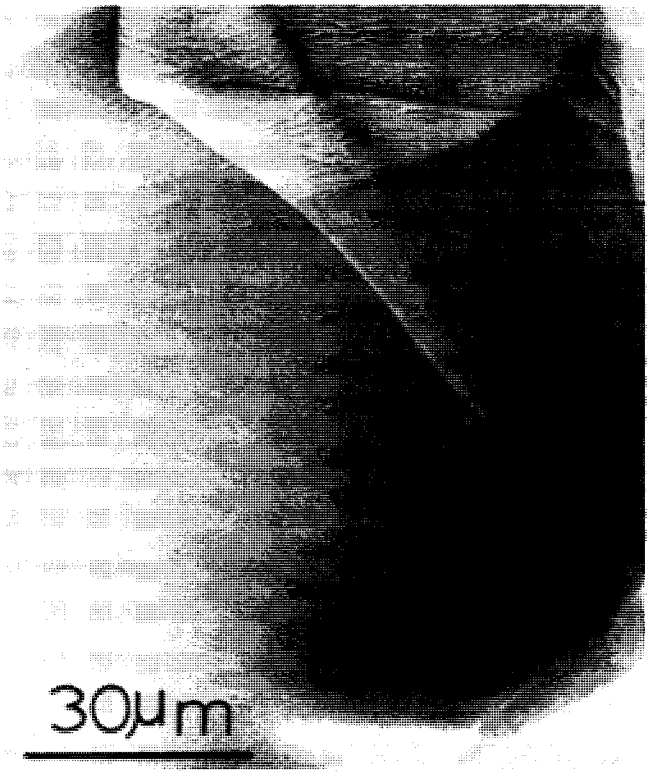

Fig. 6 Scanning electron micrograph of an empty pore in an EVAc matrix, featuring a constricted channel.

diffusion is through water filled pores and channels (we define a pore as the space evacuated by a drug particle and a channel as the space connecting two pores), we can compute a characteristic time t_c for release, using the equation:

(1) $t_c = L^2/D$.

Our slabs typically have a depth of ~0.1 cm and a polypeptide such as BSA has an aqueous diffusivity of $\sim 7\times10^{-7}$ cm^2/sec. Thus we can compute.

$t_c = (0.1 \text{ cm})^2/(7 \times 10^{-7} \text{ cm}^2/\text{sec}) = 1.4 \times 10^4$ sec
$\cong$ 4 hrs.

However, as shown in Fig. 4, release continues for months.

Classically (12, 13), the retardation of diffusion through porous media is attributed to the "tortuosity" of the medium. The channels and pores through which a polypeptide must pass before it is released are very sinuous due to the randomness of the position of the pores. Thus, the effective distance that a molecule must travel is increased, and equation *(1)* should be modified to take this into account. A dimensionless tortuosity factor τ is introduced, and the effective depth of a slab becomes τL. Equation *(1)* is then replaced by

(1') $t_c = (\tau L)^2/D$.

A tortuosity factor τ of 2 would increase the characteristic release time by a factor of 4, while a tortuosity factor of 10 would increase the characteristic release time a hundredfold. Tortuosity factors of at least 10 are required to predict release that will continue for months.

However, it is unlikely that such large tortuosity factors could be due solely to the sinuousness of channels and pores. Typical values of tortuosities in porous media such as rocks and sands (14) and biological tissues (15) lie between 2 and 3. It would require a highly unusual organization of the channels and pores in a polymer matrix such that the channels and pores wind so much and also avoid each other (if channels and pores crossed each other they would create "short cuts" for the molecules). Given that matrices are cast such that the polypeptide particles, and hence the pores, are situated at random, it is unlikely that such organization could exist. Thus, alternative explanations for the retardation of release from these matrices must be considered.

It is unlikely that the retardation of release is due to adsorption of polypeptide onto pore walls. First, the pores have a large diameter (typically ~ 100μ), so the pore surface-to-volume ratio is quite low. A monolayer of polypeptide covering the pore walls would thus consist of an insignificant fraction (less than 1 %)[1] of the polypeptide within the pore. Second, release is not affected by the ionic strength of the pore water (16). Even at high ionic strength, release is retarded to the same degree as with low ionic strength, even though there is an excess of counterions that can "shield" the pore walls, thus preventing adsorption of polypeptides.

We have postulated that the sustained nature of polypeptide release is due to a geometrical feature of the pore structure in the matrix. The pores are formed because polypeptide particles are surrounded by polymer in the casting process. The

[1] Let R be the radius of a spherical pore and d be the diameter of a polypeptide. Then the volume of a monolayer is at most $4\pi R^2 d$, and the mass of polypeptide in the monolayer is then $4\pi R^2 d\varrho$, where ϱ is the density of the polypeptide. The volume of the spherical pore is $\frac{4}{3}\pi R^3$, and the mass of the polypeptide in the pore is thus $\frac{4}{3}\pi R^3 c$, where c is the polypeptide concentration. Thus the ratio of the mass of polypeptide in the monolayer to the mass of polypeptide inside the pore is $3\, d\varrho/Rc$. Typical values for the parameters are $R = 5 \times 10^{-3}$ cm, $d = 2\times10^{-7}$ cm, $\varrho = 1340$ mg/ml, and $c = 50$ mg/ml. Thus, the ratio for this case is

$$\frac{3 \times (2 \times 10^{-7}) \times (1.34 \times 10^3)}{(5 \times 10^{-3}) \times (5 \times 10^1)} = .003 < .01 = 1\,\%$$

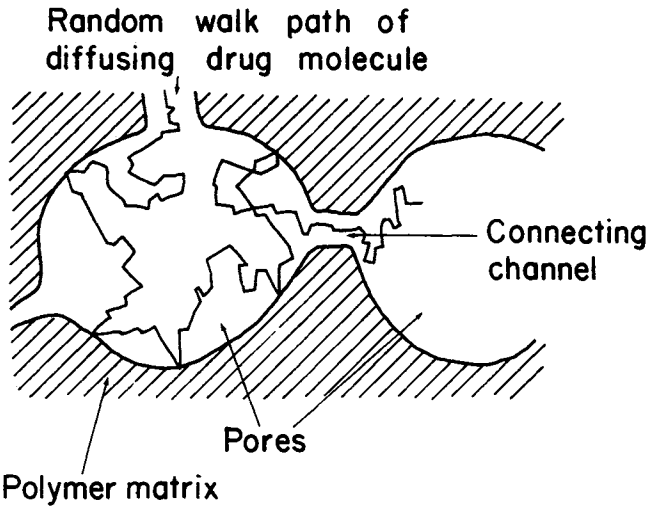

Fig. 7 Schematic of pores through which a diffusing drug molecule must pass. Bulging pores are connected via narrow channels. Due to the narrowness of the channel, the molecule has a difficult time finding its way into the next pore.

pores are connected by channels whose radii are considerably smaller than the pore radii. A scanning electron micrograph of a typical pore is shown in Fig. 6, showing the existence of narrow connecting channels, or constrictions[2]. Now consider a typical polypeptide molecule trying to diffuse out of the matrix. To do so, it must traverse through several pores. To get from one pore to another, it must find its way out of the first pore, i.e. it must find a connecting channel. This process is illustrated in Fig. 7. If the channel radius is much smaller than the pore radius, the polypeptide molecule will have a difficult time finding the channel. This is because a diffusing molecule is executing a random walk and is unaware as to the location of the exit from the pore. Thus, the molecule will traverse into the pore wall many times before it exits that pore. The many attempts to find a pore exit lead to an extended confinement within the pore. The same process occurs in each pore through which the polypeptide molecule passes. The confinement of polypeptide molecules in several pores due to the constrictions could be a cause for the retardation of release from the polymer matrix.

Specific models of release kinetics. This section describes diffusion-mediated release. However, diffusion is not the only process occurring in such systems, although it is often the rate-limiting process. At the beginning of release, all the polypeptide is in powder form. In order for the polypeptide to diffuse out of the matrix, the matrix must first imbibe water and then the polypeptide particles must dissolve. The dissolution properties of polypeptides are highly variable. For example, many test polypeptides such as BSA and lysozyme have very high solubilities (i.e. over 300 mg/ml). Insulin (zinc form), on the other hand, has a very low solubility (less than 1 mg/ml). Rates of dissolution may also vary considerably. No single model can account for all these cases.

Models have been developed for the release of drugs of both high and low solubilities, assuming instantaneous dissolution of the drug where possible. The simpler case is that of high solubility. In this case all the drug in the matrix pore space dissolves quickly and the transient diffusion equation (17):

$$(2)\quad \frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left[D_e \frac{\partial c}{\partial x}\right]$$

describes the average polypeptide concentration c(x, t) within the matrix. We assume here that the matrix has a slab geometry, and all release occurs through the broad faces of the slab (see Fig. 8a). D_e, the effective diffusivity of the polypeptide in the matrix, is a function of polypeptide particle size and loading, since these determine the structure of the pores through which the polypeptide molecules diffuse. D_e increases with polypeptide particle size and with polypeptide loading.

For macromolecular drugs, the diffusion coefficient D_e is also a function of drug concentration. At high polypeptide concentrations, the solution becomes very viscous, and the polypeptides present excluded volume to each other. Thus the diffusion coefficient decreases as the polypeptide concentration increases (18).

Equation *(2)* can be solved, once initial and boundary conditions are imposed, i.e. (see Fig. 8b)

$$(2')\quad c(x, t = 0) = A,$$

where A is the initial polypeptide loading, and

$$(2'')\quad c(L, t) = c(-L, t) = 0,\ t > 0.$$

Once having solved for c, the total polypeptide released at time t, denoted M_t, can also be determined by[3]

$$(3)\quad M_t = [\text{Area of slab}] \times \left[2LA - \int_{-L}^{L} c(x, t)\, dx\right].$$

Because D_e is dependent on polypeptide concentration, equations (2)–(3) cannot be solved analytically, and a computer must be used. It can be shown, however, that M_t takes the form, for early release times:

$$(3')\quad M_t = at^{1/2}$$

where a is constant.

A second model has been developed by Higuchi (13) for the case where drug solubility C_s is low, but where diffusion is still the rate limiting factor in drug release. In this paper we present a form of the Higuchi equation in which we incorporate the concentration dependence of the diffusion coefficient:

$$(4)\quad M_t = 2 \times [\text{Area of slab}] \times \sqrt{2\bar{D}_e (A - \varepsilon\bar{C})\, C_s t}$$

where ε is the porosity of the matrix,

$$(4')\quad \bar{D}_e = \frac{1}{C_s}\int_0^{C_s} D_e(c)\, dc$$

and

$$(4'')\quad \bar{C} = \frac{\int_0^{C_s} cD_e(c)\, dc}{\int_0^{C_s} D_e(c)\, dc}$$

These equations are derived by assuming (see Fig. 8c):

[2] Other evidence for constrictions has been obtained using mercury intrusion porosimetry (28).

[3] The "area of slab" in eqs. *(3)* and *(4)* is the area of a single broad face of the slab in Fig. 8a.

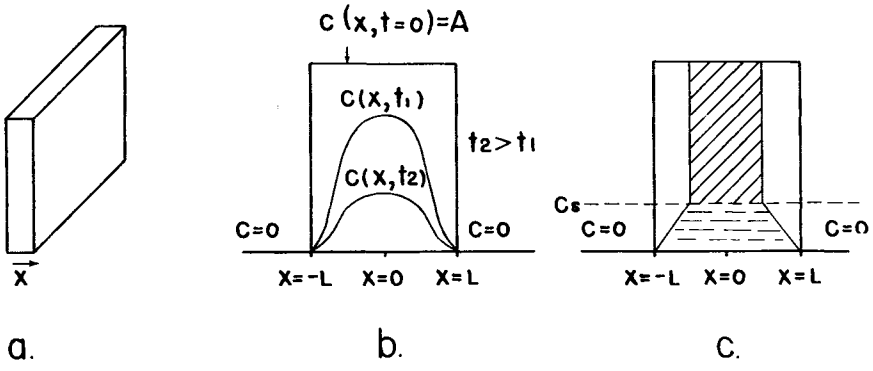

Fig. 8a Representation of slab. All diffusion is assumed to be in the x direction, and all release is through the broad faces perpendicular to the x axis.
b. Concentration profile of drug at various times for high solubility (transient diffusion) case. Assume perfect sink (c = 0 outside matrix). See text for symbol definitions.
c. Concentration profile of drug after release has started for low solubility (Higuchi) model. Diagonal hatching corresponds to solid drug. Horizontal hatching corresponds to drug in solution. See text for symbol definitions.

1) there is a moving front separating a region of completely dissolved polypeptide from a region in which the polypeptide concentration exceeds solubility;
2) diffusion in the solubilized region is in a pseudo-steady state;
3) polypeptide dissolves at the front as quickly as it is released from the matrix surface.

The two models just described are appropriate for the high and low solubility limits, respectively. Other models have been published (19, 20) which demonstrate how to interpolate between the two limits.

Zero order release. For most applications, it is desirable that the release rate be constant, i. e. zero order. Then M_t should be linear in time. However, for both models described above, M_t is linear with the *square root* of time. Note that in all cases thus far we have described release from slabs. It is possible, by altering the geometry of the matrix, to achieve zero order release (21, 22). The appropriate shape of the matrix, as shown in Fig. 9, is that of a hemisphere. The hemisphere is coated with an impermeable barrier everywhere except in a small aperture that is drilled in the center of the circular face. All release is through the aperture. Either the transient diffusion model or the Higuchi model, when cast in the appropriate hemispheric geometry, will lead to zero order release (21, 22). The use of hemispheres to produce zero-order release rates for polypeptides has been studied experimentally. Fig. 10 shows that BSA is released at a constant rate from a hemisphere (22).

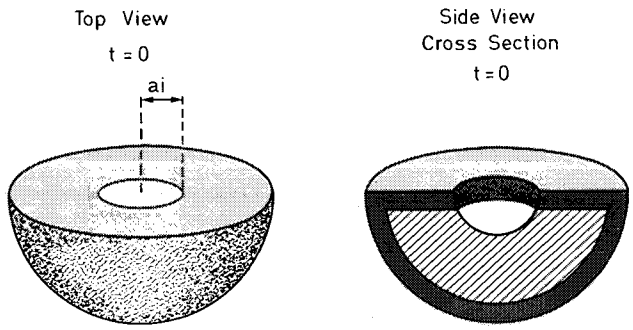

Fig. 9 Schematic of hemisphere device for zero order release.

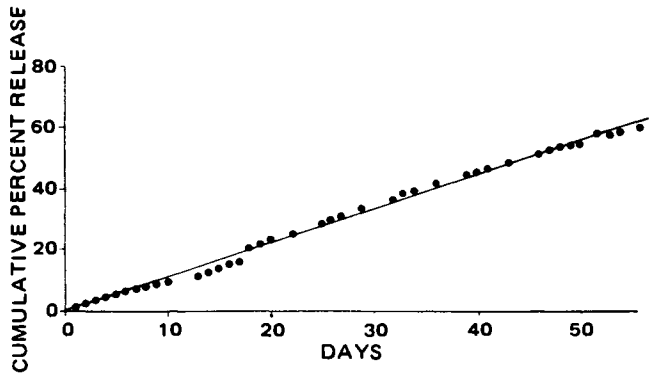

Fig. 10 Release kinetics of bovine serum albumin from EVAc hemispheres.

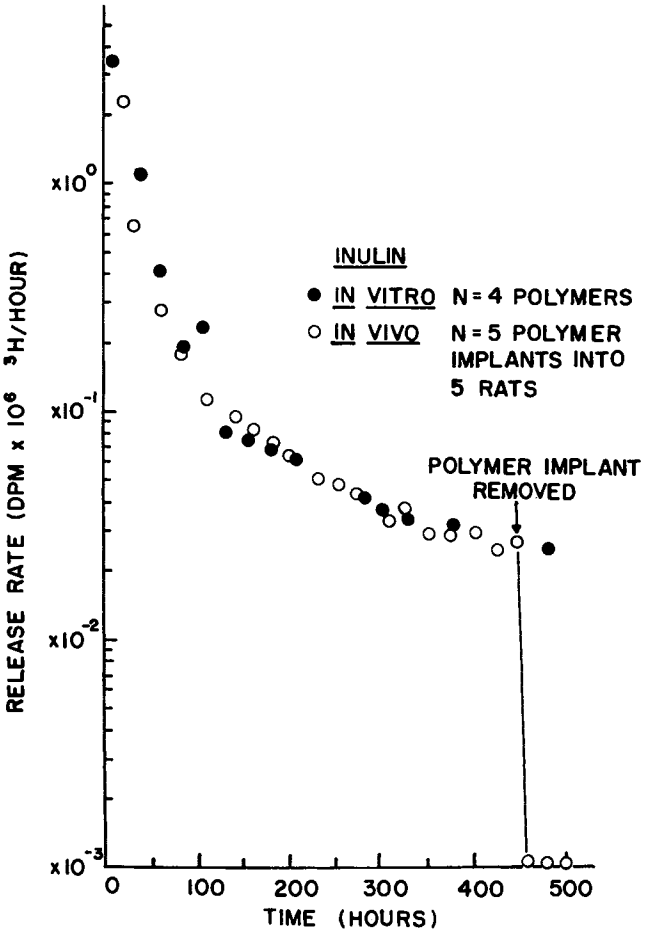

Fig. 11 Comparison of *in vitro* and *in vivo* (rats) release rates for inulin.

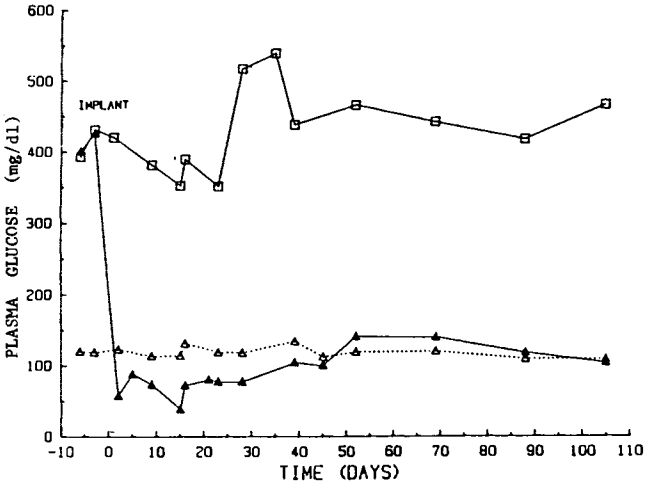

Fig. 12 Blood glucose response of diabetic rats to implanted insulin loaded EVAc hemispheres. Hemisperes were implanted at day 0.
□ – Untreated diabetic rats
▲ – Insulin hemisphere treated diabetic rats
△ – Normal (non-diabetic) rats

In vivo studies. Many *in vivo* studies have been conducted by different investigators using EVAc systems to release macromelecules. Fields of use include tumor biology (23), immunology (24), chemotaxis (25), and organ development (26). It has been shown (Fig. 11) that the *in vivo* release kinetics of EVAc matrices are identical to *in vitro* kinetics of identically formulated matrices due to the excellent tissue biocompatibility of these polymer systems (9, 27).

In vivo studies have been conducted in which insulin loaded polymer matrices were implanted into diabetic rats. Release periods of over 100 days using a hemispheric insulin polymer matrix have been observed (Fig. 12). Other potentially clinically important polypeptides such as interferon (16), vaccines (24), and anti-cancer drugs (23) have also been released using EVAc matrices.

Bioerodible Systems

In these systems, the drug is distributed uniformly throughout a polymer in the same way as in the diffusion controlled systems. The difference, however, relates to the fact that while the polymer phase in diffusion controlled systems remains unchanged with time, the polymer phase in bioerodible systems (in this paper, the words 'bioerodible' and 'biodegradable' are used interchangeably) erodes with time. As the polymer surrounding the drug is eroded, the drug escapes. This property offers a significant advantage over non-erodible systems in many applications because biodegradable polymers are eventually absorbed by the body, obviating the need for surgical removal. However, this advantage must be weighed against the potential disadvantage that the erosion products may be toxic, immunogenic, or carcinogenic.

There are only a few examples, at present, of bioerodible systems that have been used to release macromolecules. One such system was developed by Torchilin and coworkers (29). They used emulsion polymerization of polyvinylpyrrolidone to entrap the enzyme, chymotrypsin. N, N'-methylene bisacrylamide was used as a crosslinking agent. By varying the concentration of the crosslinking agent from 0.1 to 1.0% (w/w) with respect to the monomer, N-vinylpyrrolidone, during polymerization, they were able to synthesize a number of preparations that ranged from total solubility within several days to virtual insolubility. This permitted varying release rates (although not zero-order release rates) for the entrapped enzyme.

A second biodegradable polymer system used for releasing macromolecules has been developed by Heller and coworkers (30). Here cross-linked hydrogels were used to release bovine serum albumin. At low cross-linked levels, the hydrogels swell extensively and BSA is released very rapidly. At higher cross-link concentrations, the degree of swelling is reduced and the release of BSA slowed.

In a third example, Goosen et al. (31) have used biodegradable albumin microspheres to release insulin into diabetic rats; they were able to achieve glucose control for several weeks using these systems. The precise mechanism of release from these systems is not certain.

Magnetic Systems

For many polypeptide hormones, constant release may not be desirable. For example, insulin should be released at a constant rate most of the time, but supplemented by an increase near mealtime to control higher glucose levels. A system containing small magnetic beads has been developed in

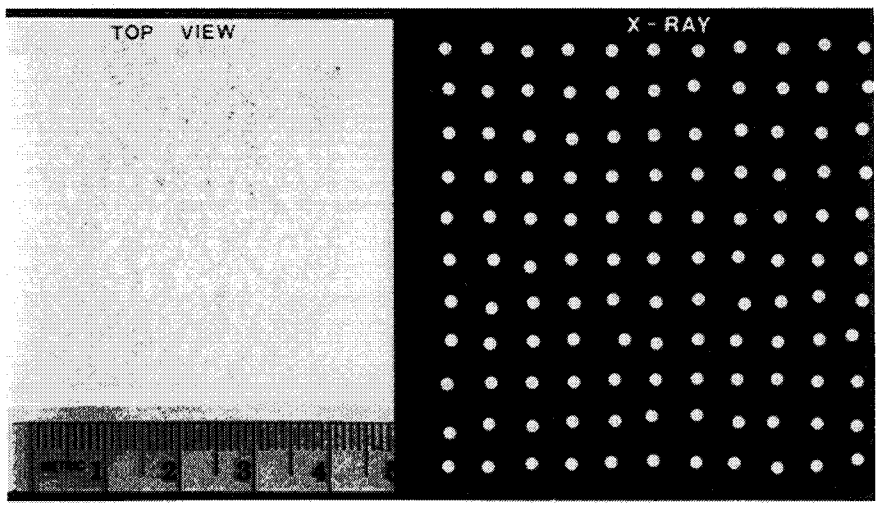

Fig. 13 Left – photograph of EVAc polymer matrix containing magnetic beads. Right – x-ray of same polymer matrix showing location of bead magnets.

which the release rate can be controlled by application of an oscillating magnetic field (32–34). Fig. 13 shows the polymer system under normal conditions and when exposed to x-rays to display the magnetic beads. Fig. 14 shows the triggering device which creates the oscillating magnetic field.

When exposed to the magnetic field, polymer matrices released up to 30 times more drug (Fig. 15); release rates returned to normal when the magnetic field was discontinued (33). The magnetic controlled release systems did not damage sensitive animal tissues (32). While the mechanism of release is still under study, one possibility is that the magnetic field increases release rates because the beads alternately compress and expand the matrix pores, thereby "squeezing" out more drug. Such factors as magnetic field strength, magnetic field orientation, and the frequency of oscillation all influence the degree of modulation. The magnetic controlled release systems could perhaps be used to increase insulin delivery at desired times, such as after a meal (perhaps by placing the implant under the skin of the wrist and designing a triggering device in the form of a special watch). Other polypeptide hormones that are produced in a time-dependent manner by the body may also be amenable to improved therapeutic efficiency using modulated delivery systems.

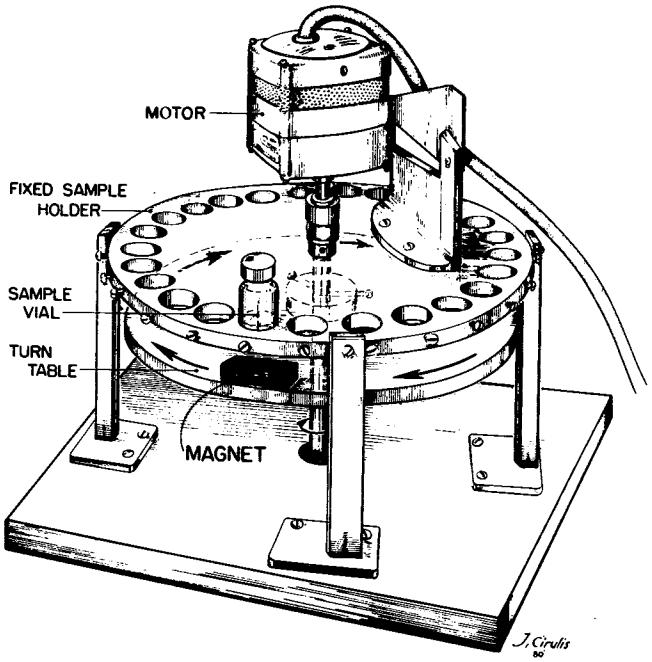

Fig. 14 Triggering device for magneting polymer matrices. Samples rest in slots of top table. Bottom table contains magnet. Bottom table is rotated by motor.

Future Directions

Other polymer systems also exist for controlling the release of drugs. These include polymers with the drug attached as a pendant chain (35) and swelling controlled systems (36). Such systems may also be useful for polypeptides, although they have yet to be explored. It is our expectation, however, that the thrust of research aimed at using polymers for the controlled release of polypeptides wil continue to be focused on diffusion controlled and bioerodible systems. In the former case, it will be desirable to understand how to control pore structure and to develop appropriate mathematical models to predict how best to do this for specific polypeptide candidates. In the latter cases, a goal will be to develop polymeric systems that erode heterogeneously even at high drug loadings, that are not toxic and that will not react with the incorporated polypeptides. Recent efforts in our laboratory have focused on the synthesis of novel polyanhydrides for this purpose (37).

Two developments in the pharmaceutical industry may lead to even greater interest in polymeric delivery systems for macromolecules in the future. First, the advent of genetic engineering may allow commercial production of numerous polypeptide drugs, such as growth hormones. Secondly, informational macromolecules normally produced by the body, including endorphins, enkephalins, luteinizing hormone-releasing hormone, and interferon are now being investigated as new pharmaceutical agents. Thus, it is possible that numerous new polypeptide drugs will emerge. However, since these are potent compounds, all with very short *in vivo* half-lives, it will be critical to develop effective delivery systems for them. In fact, the ideal candidates for controlled-release systems are molecules with short half-lives in the body (38), so that polypeptides may, in fact, be more suited to controlled-delivery systems than many long-lived, low molecular weight drugs.

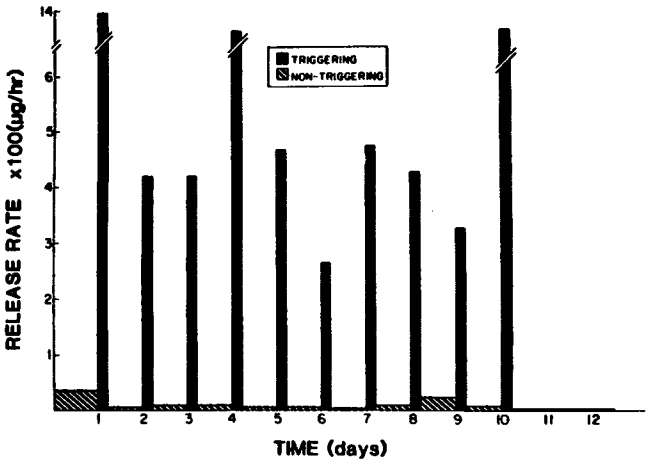

Fig. 15 Release rates for bovine serum albumin from magnetic polymer matrix. Hatched bars – no triggering. Black bars – release during triggering.

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