that the excessive use of an excipient capable of complexing with a drug could result in a markedly reduced rate of delivery of that drug by simultaneously lowering the drug's activity and apparent diffusivity. Although such an effect is undesirable in most circumstances, it may be possible to use this effect to advantage in the design of slow-release preparations.

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Zero-Order Controlled-Release Polymer Matrices for Micro- and Macromolecules

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Abstract □ Theoretical and experimental analyses demonstrate that a hemispheric polymer–drug matrix laminated with an impermeable coating, except for an exposed cavity in the center face, can be used to achieve zero-order release kinetics. Hemispheric systems for low molecular weight drugs were prepared by heating and compressing polyethylene and drug (sodium salicylate) in a brass mold. Hemispheric systems for high molecular weight drugs were prepared by casting ethylene–vinyl acetate copolymer and protein in a hemispheric mold at −80°, followed by a two-step drying procedure (−20 and 20°). In both systems, cavities were made in the center face of the hemispheres and the remainder of the matrices coated with an impermeable material. Zero-order release for 60 days at a rate of 0.5 mg/day was achieved from polymer matrices containing bovine serum albumin (mol. wt. 68,000).

Keyphrases □ Drug delivery system—zero-order controlled-release polymer matrices, micro- and macromolecules □ Controlled-release delivery—zero-order, polymer matrices, micro- and macromolecules □ Polymers—matrices, zero-order controlled-release, micro- and macromolecules □ Sustained-release delivery—zero-order controlled-release polymer matrices, micro- and macromolecules

Diffusion-controlled matrix devices have been among the most widely used drug delivery systems, but a disadvantage frequently cited is their inability to achieve zero-order release kinetics (1–3). Most matrix devices have been designed in the form of a rectangular slab, and it has been observed that the cumulative release of drug is inversely proportional to the square root of time (4–8).

One possible means of altering release kinetics from matrix systems is to vary the matrix geometry. The influence of shape on kinetics of drug release from matrix tablets in spherical, cylindrical, and biconvex shapes has been evaluated (9, 10). It was predicted (11) that a matrix in the shape of a sector of a right circular cylinder would release drug at a zero-order rate. This analysis was more critically evaluated, and it was found that true zero-order kinetics were not achieved in practical cases but that this shape resulted in release rates that were initially high and then began to approach, but not achieve, linearity (12). A limitation cited in both studies was the need for effective procedures to fabricate these delivery systems and the requirement for further experimental testing.

In a previous study, a theoretical analysis suggested that a hemisphere with all portions laminated with an impermeable coating, except for a small cavity cut into the center of the flat surface, could achieve zero-order release kinetics (13).

In the present study, experimental results have been obtained that provide support for the theoretical analysis. Two types of fabrication procedures are presented here to demonstrate that the hemisphere design is universally suitable for either low or high molecular weight drugs.

THEORETICAL

Assuming that the drug is released from a solid matrix device by diffusion, a steady-state condition exists, and the area for mass transport,

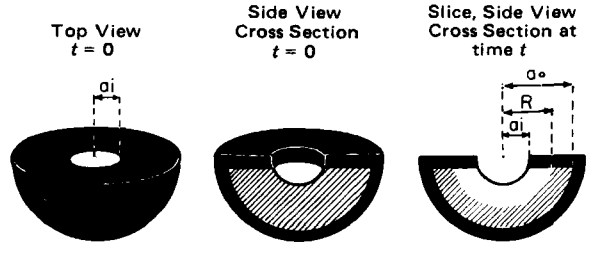

Figure 1—*Diagram of an inwardly-releasing hemisphere;* a_i *is the inner radius,* a_o *is the outer radius, and* R *is the distance to the interface between the dissolved region (white area) and the dispersed zone (diagonal lines). Black represents laminated regions through which release cannot occur.*

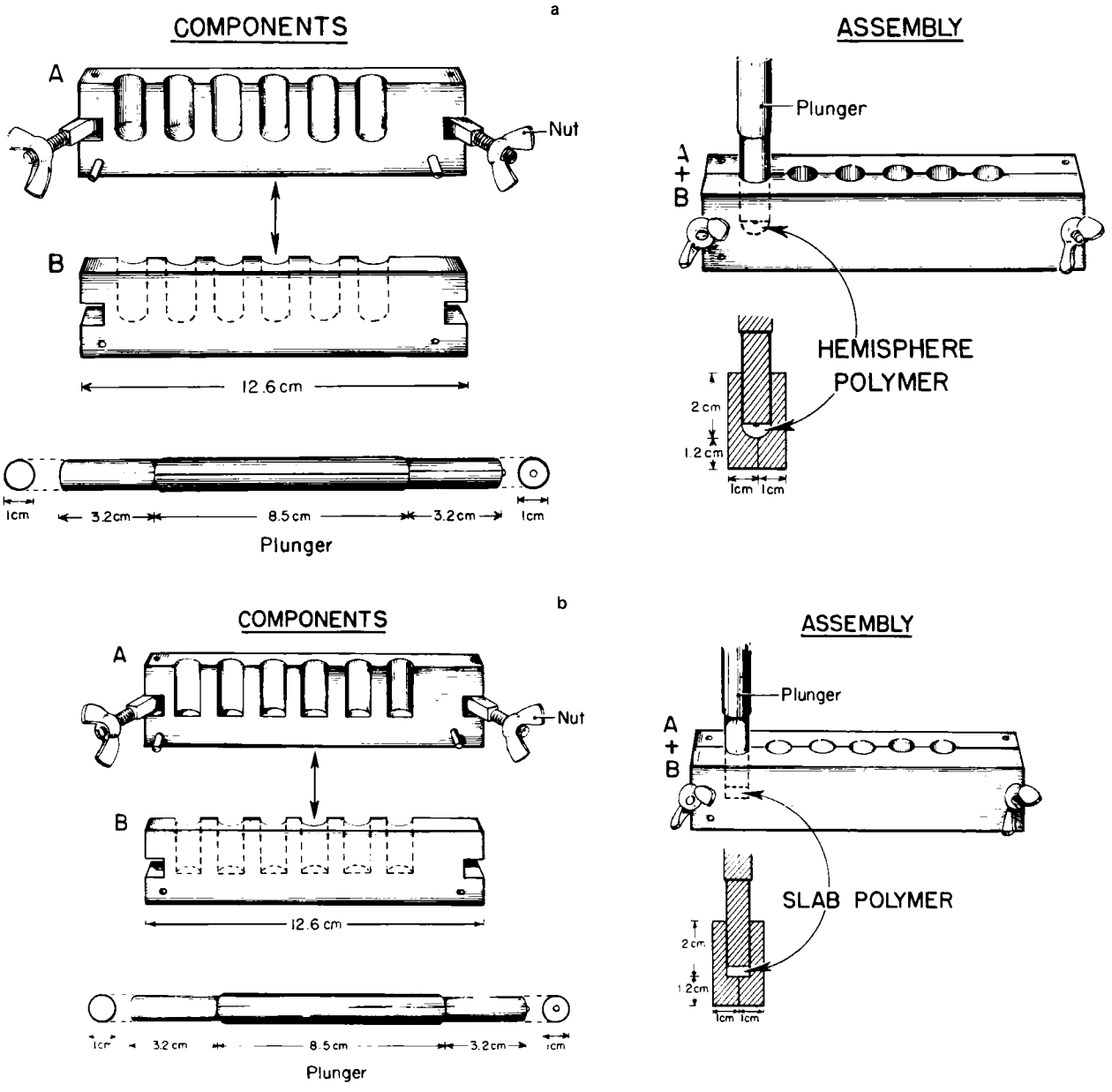

Figure 2—*Diagram of brass molds and plungers for making hemispheres and slabs containing low molecular weight drugs. (a) The brass mold (12.6 × 3.2 × 2 cm) had two halves (components A and B) fastened together with wing nuts (assembly). The mold had six hollowed cylinders (1-cm diameter and 11.4-cm length) with hemispheric bottoms (1-cm diameter). The brass plunger (1-cm diameter × 14.9-cm length) had two ends: one end was flat and the other end was press-fitted with a 2-mm (diameter) steel bead in the center in such a way that one-half of the bead was exposed and the other half was buried within the plunger. The plunger end containing the bead was used for making hemispheres. (b) The brass mold, with the same dimensions as those shown in Fig. 2a, had six hollowed cylinders with flat bottoms. The same plunger in Fig. 2a was used; however, this time the flat end was used for slabs.*

A, and drug diffusion coefficient, D, remain constant, then Fick's law of diffusion can be applied and is represented by:

$$\frac{dQ}{dt} = -DA\frac{dc}{dr} \qquad \text{(Eq. 1)}$$

where Q is the mass of drug being transferred, t is the time, c is the drug concentration, and r is the distance from the diffusion source to the release surface. From Eq. 1 it can be seen that the release rate decreases as the distance r increases; that is, the release rate is inversely proportional to the distance which the drug must travel from within the matrix to the matrix surface. The purpose of altering matrix geometry is to increase the available area of drug so as to compensate for the increase in diffusion distance of drug transport.

In a previous study (13), a theoretical analysis was conducted to derive release equations for a hemispheric device in which release only occurs through a cavity in the flat surface; all other surfaces would be laminated with an impermeable coating (Fig. 1). In the theoretical analysis (13), it was assumed as in a previous study (4) that the amount of drug present per unit volume, C_0, is substantially greater than the solubility of drug per unit volume of the vehicle, C_s. It was further assumed, as previously (4), that the solid drug dissolves from the surface layer of the device first; when this layer is depleted of drug, the next layer begins to be depleted. The interface between the region containing dissolved drug and dispersed drug moves into the interior as a front. Infinite sink conditions, no boundary layer effects, as well as other assumptions originally made (4) were considered applicable. The following notation is used:

a_i = inner radius or radius of the cavity
a_o = outer radius of device
R = radial distance to interface between dissolved and dispersed drug within the matrix (Fig. 1)
C_s = drug solubility in the release media [this also equals the concentration of drug at the interface between dissolved and dispersed drug (4)]
$Q(t)$ = drug released (wt) from the pellet at time t
D = diffusion coefficient of drug in matrix

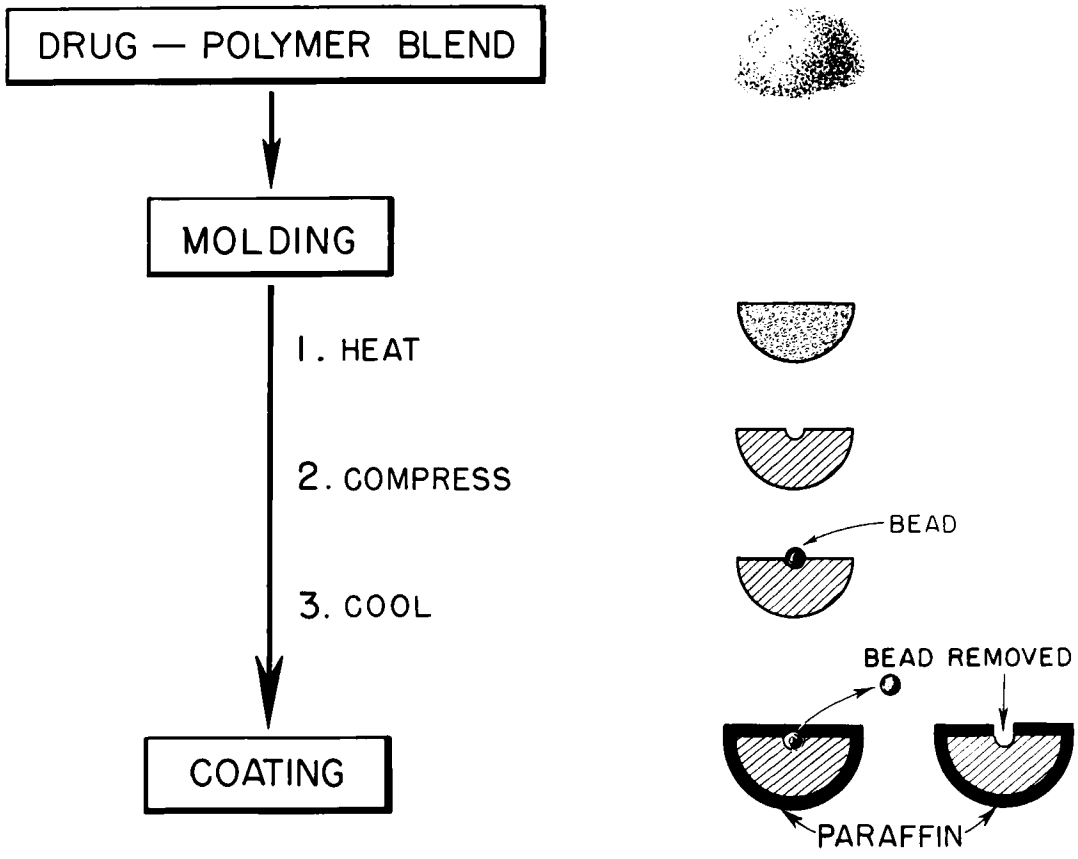

Figure 3—*Flow chart for preparing hemisphere-shaped devices for the release of small molecules. (Detailed procedures were recorded in the text.)*

Then, the release rate for the hemisphere can be derived as described previously (13) resulting in:

$$\frac{dQ}{dt} = 2\P C_s D a_i \left(\frac{R}{R - a_i}\right) \qquad \text{(Eq. 2)}$$

The approach to zero-order kinetics can be observed by examination of Eq. 2. In this equation, when $R \gg a_i$, $R - a_i$ becomes equal to R and:

$$\frac{dQ}{dt} = 2\P D C_s a_i \qquad \text{(Eq. 3)}$$

Each of the terms in Eq. 3 is a constant. Thus, for a hemispheric device with small a_i, release rates will be essentially constant. It can be calculated that for hemispheric devices designed so that the outer radius (a_o) is at least three times greater than the inner radius (a_i) zero-order kinetics will be achieved after a short burst and maintained for the duration of release (13).

Release rate expressions have been derived for several different shaped devices (13). In comparing such devices, the following statement provides a useful guideline: The hemisphere will more closely approximate zero-order release than other shapes (*e.g.*, a cylinder sector), if the inner radii (a_i) of both shapes are similar; if, however, the inner radius of the other device is much smaller than that of the hemisphere, the second device will more closely approximate zero-order release.

EXPERIMENTAL

To experimentally test the zero-order release concept for hemispheres, a polyethylene–sodium salicylate matrix was used. This matrix has been shown to follow the Higuchi model (6). For reference, release kinetics from a slab (in the present report any shape that has cross sections which were identical throughout the matrix was considered a slab) were also studied. In these studies a drug–polymer blend was molded into the different shapes; however, both the hemisphere and the slab were designed with dimensions such that similar apparatuses could be used and so that each would release approximately the same quantity of drug after the same time period.

Materials Used for Matrices Containing Low Molecular Weight Compounds—Sodium salicylate[1] and polyethylene[2] were passed through a 60-mesh screen[3] separately. These ingredients (30% sodium salicylate and 70% polyethylene) were then mixed together in a cube blender[4] for 5 min. The brass[5] mold[6] (Fig. 2) had two halves fastened together with wing nuts. The molds had six hollow cylinders (1-cm diameter, 11.4-cm long) that were either round-bottomed (with a 0.5-cm radius) for making hemispheres (Fig. 2a) or flat-bottomed for making slabs (Fig. 2b).

Hemisphere-Shaped Systems for Low Molecular Weight Compounds—A summary of the steps involved in the fabrication procedure for making hemispheres is shown in Fig. 3 and described in detail as follows. In the first step, each hollow cylinder mold (Fig. 2a) was loaded with 220 mg of a sodium salicylate–polyethylene blend and placed into a preheated oven[7] at 150° for 30 min. After heating, a brass plunger[6] (1-cm diameter) was forcefully inserted into each cylinder. Compression was complete within 30 sec. This plunger was flat-bottomed except for a central depression into which a 2-mm (diameter) steel bead[8] was press-fitted (press-fitting involves molding one metal object to another so that they are permanently attached) in such a way that half of the bead was exposed and the other half was buried within the plunger (Fig. 2a). By using this type of plunger to compress the polymer–drug matrix, a small cavity in the face of the hemisphere was formed. After compression the plunger was immediately removed. The mold containing hemispheric pellets was cooled at room temperature for 20 min. Then, the mold was disassembled. The hemispheric polymer–drug pellets were removed from the mold and trimmed with a scalpel[9] containing a surgical blade[10] to eliminate any irregular edges. The average weight of the hemisphere after trimming was 208 ± 3 mg.

[1] Fisher Scientific Co., Fair Lawn, N.J.
[2] PEP-315, Union Carbide Co., New York, N.Y.
[3] Dual Mfg. Co., Chicago, Ill.
[4] Type UG No. 16643, Erweka-G.M.B.H., Frankfurt am Main, West Germany.
[5] Admiral Metals Servicenter Co., Inc., Woburn, Mass.
[6] Mold and plunger made in machine shop of the Department of Nutrition and Food Science, M.I.T., Cambridge, Mass.
[7] Model 10, Precision Scientific Co., Bedford, Mass.
[8] Type 440C, Ultraspherics Co., Inc., Ann Arbor, Mich.
[9] Healthco, Inc., Medical Supply Division, Boston, Mass.
[10] No. 10 blade, Bard-Parker, Rutherford, N.J.

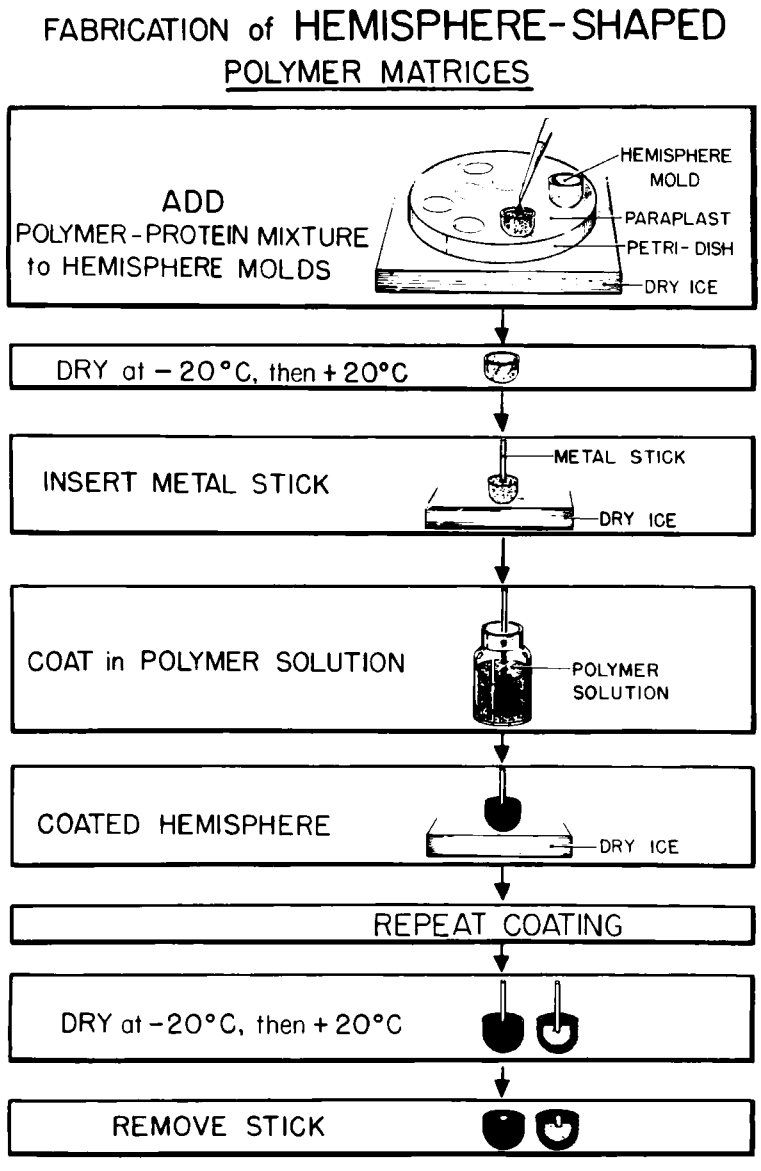

Figure 4—*Flow sheet for preparing hemisphere-shaped devices for the release of macromolecules. (Detailed procedures were recorded in the text.) In the last two blocks of the flow sheet, both the top view and a cross-sectional view of the same hemisphere device are shown.*

To protect the cavity within the hemisphere pellet during coating, a steel bead[8], 2 mm in diameter, was inserted (Fig. 3) into it with forceps[11]. The flat face of the hemisphere pellet containing the steel bead was then placed face down against a lid of a petri dish[12]. A total of nine pellets was placed in each dish. To coat the matrix, paraffin[13] was first melted in a glass beaker on a hot plate[14] until the temperature[15] of the paraffin was 50 ± 2°. Approximately 15 ml of melted paraffin was pipeted[16] onto the petri dish surrounding the pellets. This resulted in a block of paraffin[13] containing nine pellets. This block was removed with a laboratory spatula[11] and cut into nine pieces with a scalpel blade; each piece thus contained one hemisphere pellet. A drop of the melted paraffin was then layered over the flat surface of each of the hemisphere pellets, causing the pellets to be completely coated.

The final step in achieving the hemispheric design (Fig. 1) was to expose the cavity, yet leave the remainder of the pellet coated. This was accomplished by gently scraping off the paraffin covering the steel bead and removing the bead with a pair of forceps[11].

Slab Systems for Low Molecular Weight Compounds—The procedures to fabricate slabs followed methods similar to those described above. A sodium salicylate–polyethylene blend (800 mg) was loaded in the flat-bottomed brass mold[6], followed by heating in the oven and compressing with the flattened part of the plunger[6] (Fig. 2b). After compression, the resultant cylinder was cut lengthwise into two halves and trimmed to lengths of 7.4 ± 0.2 mm. The average weight was 210 ± 5 mg. The resultant pellet was placed with one of its flat faces down on the surface of a petri dish[12] and coated with melted paraffin. About 15 ml of the melted paraffin was poured over 10 pellets. The resultant slabs thus were coated on all sides except the flat faces. Each face had an exposed area of ~56 mm^2.

Hemisphere-Shaped Systems for Macromolecules—The molds used for fabricating hemisphere-shaped systems for macromolecules were composed of glass and had hemispheric bottoms[17] (13-mm diameter × 11-mm height). To prevent these molds from falling over, an embedding platform was made. This platform was constructed by pouring 15 ml of molten paraffin[13] into a bacterial petri dish[12], and then placing empty glass molds[17] into the paraffin so that they touched the bottom. After allowing the paraffin to harden, the molds were removed and the indentations left behind in the paraffin could be used to subsequently support the molds.

[11] Forceps and spatula were purchased from Healthco Inc., Medical Supply Division, Boston, Mass.
[12] Falcon 3003, Div. Becton, Dickinson and Co., Ornard, Calif.
[13] Paraplast tissue embedding medium, Lancer Co., St. Louis, Mo.
[14] PC-351, set at LO position, Corning Glass Works, Corning, N.Y.
[15] The thermometer was purchased from Fisher Scientific Co., Fair Lawn, N.J.
[16] Pasteur capillary pipets—disposable, Cat. No. 3575, Rochester Scientific Co., Rochester, N.Y.
[17] Glass molds were made using the bottoms of test tubes. These were cut in the Glass Shop, Surgical Research, Children's Hospital Medical Center, Boston, Mass.

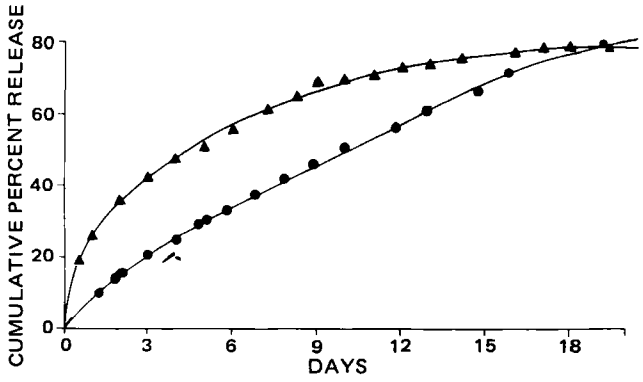

Figure 5—*Cumulative release of sodium salicylate* versus *time for the geometric shapes made as described in the text. Key: (●) hemisphere, (▲) slabs. Each point represents the mean of 10 samples for slabs and nine samples for hemispheres.* SEM *was 2% for slabs and 4% for hemispheres.*

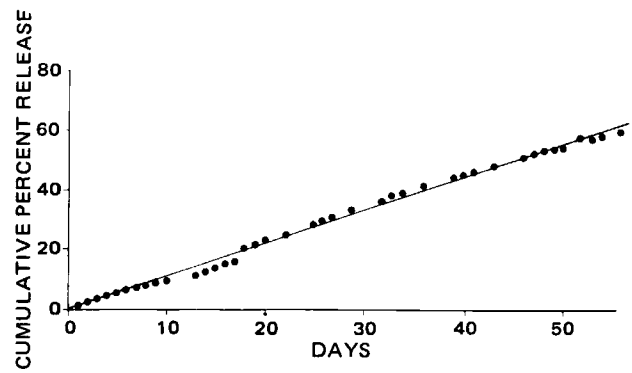

Figure 6—*Cumulative release of bovine serum albumin* versus *time. The matrix was made of ethylene–vinyl acetate copolymer and bovine serum albumin. Standard error of the mean of the cumulative release at each time point was within 12%.*

To make the hemisphere polymer systems, earlier methods of preparing polymer–macromolecule slabs (8) were adapted. The procedure is illustrated in Fig. 4 and described in detail as follows. First, empty glass molds were positioned in the indentations in the paraffin-embedding platform. Then, 6 ml of 20% ethylene–vinyl acetate copolymer[18] solution in methylene chloride[19] and 514 mg of bovine serum albumin[20] powder [particle size range (8) from 150 to 180 μm] were mixed in a glass vial at room temperature and vortexed[21] for 1 min to yield a uniform suspension. Into each hemispheric glass mold[17], 0.8 ml of the protein–polymer dispersion was pipeted[22]. The petri dish containing these samples was then transferred onto a block of dry ice for 10 min. The samples gelled within 1 min. The petri dish containing the samples was then dried first at −20° for 2 days and then at 20° for another 2 days as reported previously (8).

The hemisphere pellets were coated twice with 20% ethylene–vinyl acetate copolymer solution (containing no macromolecules) to form an impermeable barrier. The coating procedure is described as follows: (*a*) The tip of a cylindrical metal stick[23] (1.8-mm diameter × 30-mm length) was inserted into the center of the flat surface of each hemisphere pellet to a depth of ~3 mm. (*b*) Using the uninserted portion of the stick as a handle, the hemisphere pellets were placed directly on the surface of a block of dry ice for 10 min. (The round bottoms of the pellets were touching the dry ice.) (*c*) Again using the metal stick as a handle, the cooled hemisphere then was immersed into 20% ethylene–vinyl acetate copolymer solution at 20° for 10 sec, removed, and then placed immediately on the same dry ice for 10 min. (*d*) A second layer of coating was done in the same manner as described above. (*e*) The hemispheres were then put in the freezer[24] (−20°) for 2 days followed by further drying at 20° for 2 days in a desiccator[25] under a houseline vacuum (600 mtorr) to remove residual solvent (8). (*f*) Finally, to create the exposed cavity in the face of the hemisphere pellet, the metal stick[23] was removed by gently encircling the polymer surface immediately surrounding the stick with a scalpel blade.

Kinetic Studies—Studies were conducted to measure the release of salicylate into saline from polymer matrices. For these studies, each matrix was immersed in a scintillation vial[26] containing 10 ml of saline solution (0.154 *M* NaCl[27]). Each matrix was weighted down with five 9-mm stainless steel standard wound clips[28] stuck onto the wax coating. Any bubbles present on the uncoated, releasing surface were removed by aspiration with a pasteur pipet. The vials were placed on a shaker[29] at 20°. (Preliminary experiments have shown no significant difference between the release rates obtained with this mild shaking and those obtained using vigorous stirring.) At each time point, the matrices were transferred using a pair of forceps into 10-ml fresh saline-containing vials. During these transfers, excess solution on the matrix surface was removed by gentle blotting on a tissue. The released sodium salicylate concentration was determined spectrophotometrically[30] by measuring absorbance at 294 nm.

As controls, hemispheres of pure polyethylene were prepared uncoated and completely coated (including the cavity). Similarly, uncoated and completely coated hemispheres with the 30% salicylate–polyethylene blend were prepared. Identical controls were conducted for the ethylene–vinyl acetate copolymer system. All of these controls were tested for release kinetics.

The kinetics of albumin release from the hemisphere-shaped systems were followed by methods described previously (8). Albumin concentrations were measured spectrophotometrically[30] by determining absorbance at 280 or 220 nm (8).

RESULTS

The cumulative percentage release of sodium salicylate *versus* time from polyethylene matrices of these hemispheres and slabs is compared in Fig. 5. The hemisphere-shaped device closely approximates zero-order release. Standard error of the mean of cumulative release at each time point was within 2% for slabs and 4% for hemispheric devices.

Control matrices of coated and uncoated pure polyethylene hemispheres, as well as the completely coated sodium salicylate–polyethylene hemispheres, showed no material exhibiting spectrophotometric absorbance in the saline solution. The uncoated hemisphere-shaped device containing sodium salicylate prepared in the same manner as those used in the above study showed a rapid, nonlinear release and was nearly exhausted of its drug within 3 days.

To determine if the hemispheric design was applicable to macromolecules such as proteins as well as low molecular weight drugs, ethylene–vinyl acetate copolymer matrices containing bovine serum albumin were tested. Figure 6 shows the release kinetics of albumin from the hemisphere-shaped systems. Each point represented eight samples. A linear relationship between cumulative percentage release and the time of release was observed for 60 days. The release rate was ~0.5 mg of albumin/day. Standard error of the mean of cumulative release at each time point was within 12%. Control hemisphere-shaped devices completely coated twice with 20% ethylene–vinyl acetate copolymer solution did not release any protein. The media collected in the release experiments of the control hemisphere-shaped devices prepared from pure ethylene–vinyl acetate copolymer solution (without albumin) showed no spectrophotometric absorbance.

DISCUSSION

These studies demonstrate that hemispheric matrices can act as constant release systems for both low molecular weight drugs (Fig. 5) and high molecular weight compounds (Fig. 6). The fabrication procedures for these systems are relatively simple and can be performed without expensive apparatus. To fabricate the hemisphere-shaped devices, two different methods were employed: the fusion of polyethylene and drug

[18] Ethylene–vinyl acetate copolymer beads (Elvax 40, 40% vinyl acetate content w/w) manufactured by DuPont Chemical Co., Wilmington, Del., and extracted with hot water if the beads were clay coated.
[19] HPLC grade, Fisher Scientific Co., Fair Lawn, N.J.
[20] Sigma Chemical Co., St. Louis, Mo.
[21] Vortex-Genie, Fisher Scientific Co., Fair Lawn, N.J.
[22] Pipetman, Gilson Co., France.
[23] Becton, Dickinson and Co., Ornard, Calif.
[24] SciChem. Co., Howe & French Division, Boston, Mass.
[25] Bel-Art Co., Peguannock, N.J.
[26] No. 986548, Wheaton Scientific Co., Millville, N.J.
[27] USP grade, Mallinckrodt, St. Louis, Mo.
[28] No. 7032, Clay Adams, Paisippang, N.J.
[29] Clinical Rotating Apparatus, set at speed 4, Arthur H. Thomas Co., Philadelphia, Pa.
[30] Model 2400-S, Gilford Instrument Laboratories, Oberlin, Ohio.

by heating (14), and the gelation of ethylene–vinyl acetate copolymer by freezing at −80° (8). The selection of the fabrication procedure depended on the nature of the drugs. For example, the gelation of polymer at low temperature is more suitable for proteins or peptides because they may be denatured at high temperature.

It should be noted that reservoir systems, in which a core of drug is surrounded by a membrane, can also be used as a zero-order release system. In these systems, if the drug is loaded above its solubility, the drug concentration at the inside of the membrane wall will be a constant (*i.e.*, the drug solubility); furthermore, the drug will always traverse the same diffusion distance (*i.e.*, the membrane thickness). Thus, the release rate will be constant. However, such systems have disadvantages such as expense, undesirable release properties for large molecular weight drugs, and danger in the case of leaks (1–3). The reservoir system principle also was applied to polymer matrices (15), where the rectangular matrices of polymer–drug were coated with pure polymer. Under appropriate conditions, the rate-limiting step for release was diffusion through the pure polymer coating rather than through the polymer–drug matrix, and constant release was observed. To ensure that the constant release rates observed for the experimental devices in this report were not due to a similar effect (caused perhaps by drug sedimentation towards the center of the matrix during fabrication leaving a film of pure polymer at the surface), a microscopic examination of the drug–polyethylene hemisphere was conducted. In this case, a colored compound, bromcresol green[1], was incorporated into the matrix, due to its ease of optical examination under a light microscope. The matrix was sectioned using a scalpel blade. The examination of the sections confirmed the assumption that the drug particles were evenly distributed in the polyethylene matrix. A similar microscopic examination was conducted for the ethylene–vinyl acetate copolymer–protein system using previously described methods (16). These matrices also showed a uniform drug distribution. Both tests ruled out the possibility that these matrices could act in any way as a reservoir type device.

In *Theoretical*, it was assumed that no boundary layer effects were present and that infinite sink conditions prevailed. In practice there may be significant drug concentration gradients between the matrix release surface and the surrounding media. However, the resultant bulk flow has been shown to bring the release kinetics even closer to zero order (12).

In matrix systems, the factors controlling release rates can be classified into two groups: the matrix parameters such as porosity and tortuosity and the properties of drugs such as solubility and diffusion coefficient. The former are closely related to the loadings and drug particle sizes; the latter are the inherent properties of the incorporated drugs and polymers. Higuchi (4, 5) was the first to design a mathematical model to predict the release kinetics for low molecular weight drugs from a matrix system; the theoretical predictions were proven (6) by measuring the porosity and tortuosity of the matrix from a model system consisting of polyethylene and sodium salicylate. It was also found that the porosity and tortuosity of the matrix were affected by the loading and particle size of the incorporated drugs (6). In a hemisphere-shaped matrix system, it is conceivable that release rates can be varied by a similar manipulation of these fabrication parameters. Additionally, the size of the opening is another governing factor. In situations where Eq. 3 applies, it can be seen that the release rate is directly proportional to the radius of the cavity, a_i.

The release rate of macromolecules or proteins, such as bovine serum albumin, from ethylene–vinyl acetate copolymer matrix slabs can be varied by as much as 2000-fold by manipulating three fabrication parameters, (*i.e.*, drug loadings, aggregate sizes, and matrix coating) (8). The release rate of macromolecules from a hemisphere-shaped device conceivably can be changed by manipulating the same fabrication parameters and the size of the opening. Although the hemisphere design resulted in zero-order release kinetics for macromolecules such as albumin, the release mechanism for these systems has not yet been fully established. However, evidence continues to indicate that the release of macromolecules from polymeric matrices occurs *via* diffusion through interconnecting pores (16). The present study is consistent with such a mechanism. However, a mathematical model that can be used to predict release kinetics from macromolecular release systems has not yet been developed.

Although only bovine serum albumin was used as a model macromolecule in the present study, initial results have also indicated that zero-order release rates were obtained for over 1 month for lysozyme and β-lactoglobulin when they were incorporated into hemispheric matrices. The hemisphere systems have not yet been tested *in vivo*. However, initial studies have demonstrated good correlation between *in vivo* and *in vitro* release rates of macromolecules from ethylene–vinyl acetate copolymer slabs (17).

The major problems encountered in the fabrication procedures in the present study are the techniques of both coating the matrix and opening the cavity uniformly. Paraffin was used to coat the hemispheres for small molecules; however, it may not be suitable as a coating material for an *in vivo* implant because of its brittleness and incompatibility with the tissue. A search is being conducted to find an appropriate coating material to replace paraffin. On the other hand, the ethylene–vinyl acetate copolymer system used for macromolecules has been shown to be highly biocompatible (18). The development of a technique for opening the hole on the flat face of the hemisphere is very critical to achieve reproducibility. Besides the methods practiced in these studies, improved techniques to create holes on the flat face of the hemisphere-shaped device should be explored. Techniques such as computer-aided drilling may prove useful in future studies.

In summary, both theoretical and experimental analyses have demonstrated that a hemisphere can act as a zero-order release system for both micro- and macromolecules. The achievement of constant release rates for macromolecules is particularly significant, since other approaches (*e.g.*, reservoir systems) have not yet been able to release macromolecules in a controlled fashion. This study appears to be the first demonstration that macromolecules can be released at a zero-order rate for long time periods from controlled-release polymer systems.

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