between particles, a lubricant initially present at particle surfaces would still exist at the interfaces formed by plastic flow where it could interfere with particle–particle bonding. The results of the present study help support this thesis, since microcrystalline cellulose and compressible starch appeared to exhibit a greater degree of plastic flow under compression than did sugar.

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Zero-Order Drug Delivery System: Theory and Preliminary Testing

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Abstract □ A new approach to zero-order drug delivery that includes geometric factors is described. An experimental device based on the theory was tested by following the release of stearic acid into ethanol. Three separate trials indicated that the solid was released *via* a zero-order process in a reproducible manner.

Keyphrases □ Drug delivery—zero-order system, geometric factors considered, experimental device tested □ Delivery, drug—zero-order system, geometric factors considered, experimental device tested □ Stearic acid—release into ethanol, zero-order drug delivery system, experimental device tested

Roseman and Higuchi (1) and, more recently, Roseman (2) treated the subject of drug release from silicone polymer matrixes containing suspended particulate drug. They developed equations for drug release from both planar and cylindrical surfaces (1). Roseman (2) showed that the fraction of drug release from a matrix with a planar surface was linear—not with time but with the square root of time. This finding confirmed an expectation published earlier (3). Roseman (2) also showed that the initial portion of a similar plot for a matrix of cylindrical shape was similar to that for the planar case. However, as more drug was released, the slope for the fraction *versus* square root of time plot decreased.

A study of these results indicates that polymer devices might be useful in dispensing drug to tissues or body cavities at fairly constant rates over reasonable periods of time. However, the ideal of a zero-order drug delivery system cannot be realized from planar or cylindrical devices of silicone polymer containing suspended particulate drug.

BACKGROUND

The planar case of a drug suspended in a polymer matrix fails as a zero-order drug delivery system because, as the drug is released, the boundary in the matrix at which drug dissolution occurs recedes from the surface from which the drug is released. The problem is one of a decreasing release rate due to an increasing drug diffusion path length within the matrix. For the cylindrical case, the situation is more complicated. Here, the diffusion path increases and the drug core within the matrix decreases in area.

The reduction of an effective dissolution surface, given a constant diffusion barrier, and its effect on drug dissolution, *e.g.*, from implants, are fairly well understood. In their derivation of the well-known "cube root law," Hixson and Crowell (4) showed an appreciation for the decreasing area of a single particle that maintained its shape during the dissolution process. Ballard and Nelson (5) related the rate of absorption from spherical implants to size. The same investigators (6) developed a graphical method of estimating the area of subcutaneously implanted cylindrical drug pellets.

More recently, Rippie and Johnson (7) attempted to regulate the dissolution behavior of drug pellets by controlling their geometry. However, their work involved dissolution in a turbulent flow, so that transport of the drug from the surface could not be considered limited to diffusion across a constant diffusion barrier.

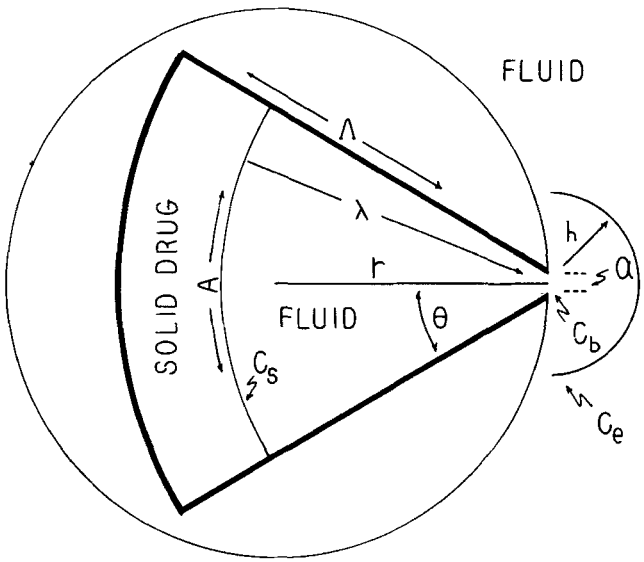

Figure 1—*Cross section of a zero-order drug delivery system containing solid drug. (See text.)*

This report details the theory for a drug delivery system that might be incorporated into implants or devices to be placed into body cavities or tissues. Under ideal conditions, this system should release drug *via* zero-order kinetics for virtually as long as it contains drug. The principle involves a particular geometry which, in turn, keeps a constant relationship between the drug diffusion path and the effective area of the dissolution boundary. The rigid device can be charged with a drug pellet or a suspension of drug in an aqueous gel, a waxy matrix, or a polymeric matrix. It is postulated that the principle described would be useful, not only in drug delivery systems, but as a means of experimentally defining physical parameters such as diffusion coefficients.

THEORETICAL

The essence of the drug delivery system described is a cavity of length L having a uniform cross section with geometric properties like those depicted in Fig. 1. Here, the bold lines describe the cross section of a cavity that might be found within a rigid cylinder having a base of radius r. The cavity communicates with the fluid in which the device is placed only through a narrow opening of width a, which runs the length of the device. In Fig. 1, this width is indicated by a pair of dashed lines. Although the opening must have a finite width, for theoretical purposes the width should be considered negligibly small. The cavity may be considered as a portion of a right circular cylinder of radius Λ and altitude L. Thus, in the ideal construction, the wall opposite the opening will be arcuate.

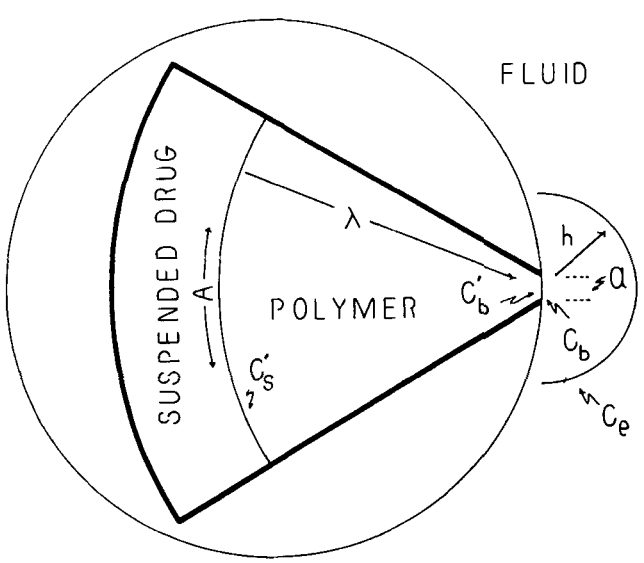

Figure 2—*Cross section of a zero-order device charged with a polymeric matrix containing suspended drug. (See text.)*

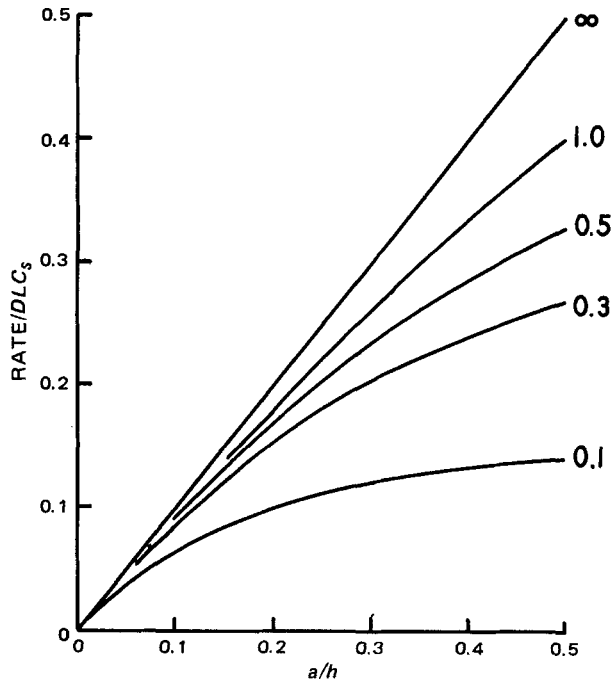

Figure 3—*Plot showing the interrelationships of a and θ in regard to release rate. The value for θ is indicated for each profile. (See text.)*

The device in Fig. 1 had been charged with a solid pellet of drug which dissolves isotropically. It is assumed that diffusion of drug out of the device and into the surrounding fluid is the rate-controlling process. In this case, about 60% of the initial charge has been released and fluid has diffused into the cavity. As drug continues to dissolve and diffuse from the curved surface through a distance, λ, to the opening, length A of the curve grows. It is clear from inspection that $A = 2\theta\lambda$ (for θ in radians). The fact that the relationship between the area of dissolving drug, AL, and the diffusion path length, λ, is a constant is the key to the zero-order performance of the device.

The rate equation describing the release of drug into the surrounding fluid can be derived by assuming that the rate of transport of drug to the opening of the device is equal to the rate of transport into the surrounding fluids. The concentration of drug at the dissolving surface is the solubility of drug, C_s, in the fluid. The concentration of drug at the opening is taken as C_b, and the concentration of drug at some distance, h, into the fluid is taken as C_e. The rate of transport of drug to the opening, R', is given in Eq. 1; the rate of transport away from the opening, R, is given in Eq. 2:

$$R' = \frac{DAL}{\lambda}(C_s - C_b) = 2D\theta L(C_s - C_b) \qquad \text{(Eq. 1)}$$

$$R = \frac{DaL}{h}(C_b - C_e) \qquad \text{(Eq. 2)}$$

Here, the diffusion coefficient for drug in fluid is indicated by D. By assuming that sink conditions prevail, *i.e.*, $C_e = 0$, and setting Eqs. 1 and 2 equal, it can be shown that the rate of drug release during steady state is described by:

$$R = \frac{2DaL\theta C_s}{a + 2\theta h} = \frac{DLC_s}{\frac{h}{a} + \frac{1}{2\theta}} \qquad \text{(Eq. 3)}$$

It is clear from Eq. 3 that, in a constant environment, *i.e.*, h constant, the release of drug occurs at a constant rate.

A different situation is shown in Fig. 2, where the cavity of a device has been filled with a suspension of drug in a polymeric matrix. The assumptions applied to this situation are those of Roseman and Higuchi (1). It is assumed that the total concentration of drug initially is large compared to the solubility of drug in the matrix, C_s'. It is assumed that steady-state conditions exist, that diffusion is the rate-controlling process, and that diffusion occurs through the matrix, not through pores.

The case depicted in Fig. 2 is one in which about 60% of the drug has been released, giving rise to a region depleted of solid drug particles. As drug dissolves at the boundary of the "zone of depletion," it must diffuse a distance, λ, to the opening where the concentration is C_b'. The rela-

Table I—Effect of a/h and θ on Rate × $100/DLC_s$

	θ						
a/h	0.1	0.3	0.5	0.7	1.0	3.0	∞
0.01	0.952	0.984	0.990	0.993	0.995	0.998	1.00
0.02	1.82	1.94	1.96	1.97	1.98	1.99	2.00
0.05	4.00	4.62	4.76	4.83	4.87	4.96	5.00
0.10	6.67	8.57	9.09	9.33	9.52	9.84	10.0
0.20	10.0	15.0	16.7	17.5	18.2	19.4	20.0
0.30	12.0	20.0	23.1	24.7	26.1	28.6	30.0
0.40	13.3	24.0	28.6	31.1	33.3	37.5	40.0
0.50	14.3	27.3	33.3	36.8	40.0	46.2	50.0

tionship between the area of the boundary where dissolution occurs, AL, and the diffusion path length, λ, is a constant since $A = 2\theta\lambda$. If the diffusion coefficient for drug in the matrix is D', the rate of transport of drug to the opening is given by:

$$R'' = \frac{D'AL}{\lambda}(C_s' - C_b') = 2D'\theta L(C_s' - C_b') \qquad \text{(Eq. 4)}$$

The rate of transport away from the opening is given by Eq. 2. By assuming that the partitioning of drug at the matrix–fluid interface can be described by a constant, K, such that:

$$K = C_b'/C_b = C_s'/C_s \qquad \text{(Eq. 5)}$$

it can be shown that the rate of drug release is given by:

$$R = \frac{DLC_s}{(h/a) + (D/D'K)(1/2\theta)} \qquad \text{(Eq. 6)}$$

The similarity between Eqs. 3 and 6 is obvious.

Equations 3 and 6 are derived for an ideal case wherein the opening is infinitely small (*i.e.*, $a \to 0$) but presents no barrier to diffusion of drug. In the real case, the zero-order phase develops only after the diffusion path length, λ, becomes significantly larger than the slit width, a. That is, a constant release rate occurs only after all points within the slit opening are approximately equidistant from any one point on the dissolution boundary, A. It should be obvious that in the initial portion of the drug release profile, where a has a small but real value and $\lambda \simeq 0$, the situation approximates the planar model of Roseman and Higuchi (1). Thus, in the real case, the rate of drug release is initially higher than that of the subsequent "zero-order" phase.

Equation 6 should also describe the release of drug from a device charged with a thixotropic aqueous suspension of drug. In that instance, D' would be the diffusion coefficient of drug in the suspension and K would, in a steady-state circumstance, have a value of unity.

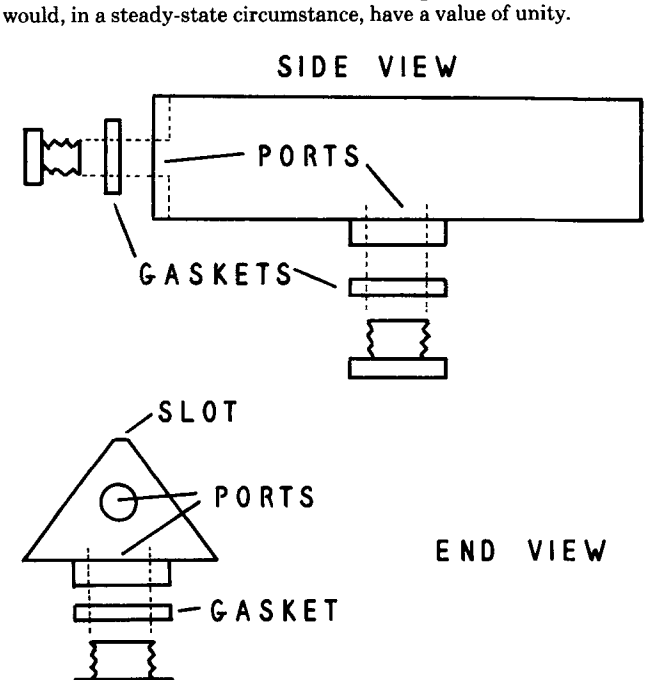

Figure 4—*Side and end views of an experimental stainless steel device used to test the zero-order theory.*

It is clear from Eqs. 3 and 6 that some latitudes prevail in the adjusting of the release rate through changes in a, θ, and L. The interrelationships of a and θ as concern the rate of release of drug from a cavity filled with solid material are depicted in Fig. 3 and Table I. Obviously, without specific knowledge of C_s, D, and h, exact values cannot be assigned. In general, however, the larger the values of a and θ, the larger is the rate. It is also clear from the equations that changes in the length, L, of the device result in proportionate changes in rate. Similar arguments hold for a cavity filled with a suspension of drug in a polymer.

Adjustments in the design parameters of a device might also prove useful in determining h and D. If one varies only the slit width, a, for a number of solid-filled cavities and plots the reciprocals of rates of release against $1/a$, a line with a slope of h/DLC_s and an intercept of $1/2\theta DLC_s$ is obtained. By dividing the slope by the intercept and multiplying by 2θ, one obtains a value for h. With a knowledge of C_s, θ, and L, one can calculate the diffusion coefficient, D, from the intercept value.

EXPERIMENTAL

The theory of the zero-order drug delivery system was tested experimentally by following the amount of stearic acid released from a device fabricated from stainless steel. The prism-shaped device used is illustrated in Fig. 4. Overall, it was 6.4 cm (2.5 in.) long, 2.54 cm (1.0 in.) wide at the base, and 1.6 cm (0.63 in.) high from the base to the slot. The sides, base, and one end were 18-gauge stainless steel. The other end was cut from 0.5-cm (3/16-in.) stainless steel and was drilled to provide a filling port which could be closed with a stainless steel bolt. All joints were silver soldered. A larger filling port was made in the base of the prism-like device by cutting a hole of appropriate size and soldering into place a stainless steel nut to be closed with a stainless steel bolt. Gaskets[1] were used at both filling ports. The slot width, a, was 0.08 cm (0.030 in.); the effective slot length, L, was 5.75 cm (2.263 in.). The angle, 2θ, was 80°.

For filling, the slot was covered with polyethylene and the device was inverted. Molten stearic acid[2] was added through the large port in increments. The device was rocked back and forth, and the portions were allowed to solidify after each addition. The device held approximately 9.5 g of stearic acid. After the port was closed, the polyethylene was removed carefully from the slit.

The release of stearic acid from the device into alcohol USP was followed by placing the device in the bottom of a double-walled beaker, 11.0 cm i.d., containing 1000 ml of alcohol. The port in the base and the bolt used to close it served as a pedestal for the device. The beaker was kept at 30°, and its contents were stirred with a three-blade propeller (radius of 2 cm and blade pitch of 30°) rotated at 50 rpm 2.5 cm below the surface. The distance between the top of the device and the propeller was 4.9 cm. A cover[1] with a hole for the stirrer and one for the sampling port was kept on the beaker.

Samples were withdrawn periodically. Alcohol at 30° was added to the beaker to maintain volume. The stearic acid concentration in the samples was estimated *via* an ion-pair extraction with methylene blue. A 5- or 10-ml aliquot of the ethanolic sample containing stearic acid was placed into a separator. A 50-ml volume of a 0.01 M pH 7.0 phosphate buffer containing 0.1% methylene blue (USP grade) and a 20-ml volume of redistilled reagent grade chloroform were added. If a 5-ml aliquot from the ethanolic sample was used, an additional 5 ml of alcohol was added. The separator was shaken, and the layers were allowed to separate. A 5-ml portion of the chloroform layer was diluted to 100 ml with methanol, and the density of the blue color was estimated at 640 nm against an appro-

[1] Teflon (du Pont).
[2] MC&B, SX950, 2733.

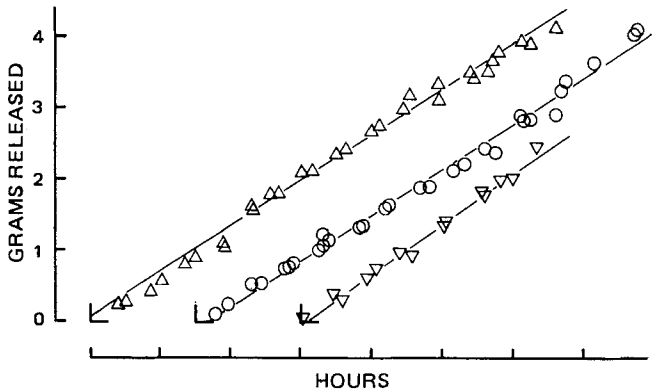

Figure 5—*Release of stearic acid* versus *time for three different trials [Trial I (○), Trial II (▽), and Trial III (△)]. The profiles are staggered for clarity, with the (0,0) point indicated by a right angle. Each division on the abscissa represents 50 hr. The lines for the profiles are the least-squares lines.*

priate blank. The blue color was stable after approximately 30 min. The absorbance was linearly dependent on the stearic acid in the sample.

RESULTS AND DISCUSSION

The cumulative release of stearic acid from the device tested for three different trials is shown in Fig. 5. The linear regression analysis for each trial is summarized in Table II. A survey of Table II shows that the coefficient of determination (r^2) was 0.99 in each case, indicating that the data were zero order. The variations in the slopes and intercepts do not appear to be great when it is understood that it was difficult to fill the device uniformly. Problems included the trapping of air bubbles in the melted stearic acid and a slight shrinkage of the melt on cooling. In the ideal case, there must be no penetration of fluid between the cavity wall and the fill. Shrinkage might have allowed spaces to form between the fill and the cavity wall.

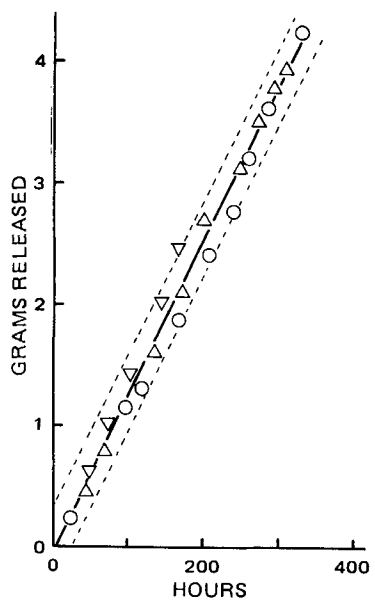

Figure 6—*Profile showing the amount of stearic acid released from the zero-order device. The regression line is based on a composite of all data from three trials, and the 95% confidence bounds are given as dashed lines. Selected points from Fig. 5 are shown. (See text.)*

Table II—Summary of Regression Analysis on Each Trial and on Composite of All Data

Parameter	Trial I	Trial II	Trial III	Composite Data
Release rate, mg/hr	12.73	14.24	12.89	12.72
SD (slope), mg/hr	0.23	0.41	0.24	0.18
r^2	0.990	0.990	0.991	0.985
Intercept, mg	−12.7	−48.3	+74.2	−21.9
SD (intercept), mg	44.5	41.3	47.2	33.1
n	32	14	30	76

Additionally, the theory requires that transport of solid within the cavity be diffusion controlled. If any currents arose in the fluid within the device during the experiment, then deviations from theory could occur. (Obviously this could not be a source of error in the case of a cavity filled with a polymeric matrix.)

It is calculated that the fabricated device, under ideal conditions, could release approximately 8.0 g of stearic acid at a zero-order rate. However, the trials were terminated after the release of 2.5–4.2 g when irregularities in the surface of the fill became obvious. The arcuate nature of the surface was always in evidence after a trial was terminated, but the surface did not show the perfect arc depicted in Fig. 1. Variations in the distance of the surface of the fill to the slot were also noted. Such variations, however, apparently "averaged out."

All data were collected under approximate "sink conditions" because the highest concentration of stearic acid achieved was about 0.4% compared to a solubility in ethanol of nearly 5% (8).

A summary of the regression analysis of a composite of all data for the three trials is given in Table II. The regression line and the 95% confidence bounds for single predicted values are shown in Fig. 6. Selected points from each individual trial are also given in Fig. 6 to illustrate the distribution of the data points.

Although the testing of the zero-order principle with stearic acid has been encouraging, a more critical approach will be necessary to validate the theory thoroughly. The filling of the device with a solid may prove to be more of an engineering problem than it is a pharmaceutical problem. A solid that is fused under high temperature and pressure in the process of filling the cavity should allow the most critical kind of test of the interrelationships of slit width, a, angle, 2θ, and length, L, of the device.

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