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Release Characteristics of Implantable Cylindrical Polyethylene Matrices

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Abstract

The geometrical relationship between a hemisphere and a cylinder has been investigated for controlled-release systems.

The relationship was tested by comparing dissolution results with results from mathematical calculation based on the principles of diffusion for matrix systems. A procedure has been developed for producing implantable, cylindrical, low-density polyethylene matrices, uncoated or coated with a thin impermeable film and a thick paraffin layer except for a hole on the flat faces of the cylinder. Drug matrices were prepared from a blend of sodium salicylate and polymer compressed in an appropriately designed stainless-steel mould at 150°C. Differential scanning calorimetry revealed that no decomposition product was formed in the matrix. When the surface area and the number of holes is increased, drug release also increases. When density is increased, however, drug release decreases significantly. Zero-order drug release was obtained from high-density covered one-hole and two-hole matrices. The diffusion coefficient was calculated as 0·067 day^{-1}.

The study suggested that true zero-order drug release could be obtained by drug diffusion from a hole, rather than from geometric shapes in the matrix systems. In addition, for constant release the diffusion area has to increase by approximately 25 mm^2 every day, compared to the area of the previous day, because the diffusion distance increases logarithmically.

Attempts have recently been made to regulate the dissolution behaviour of drug matrices by controlling their geometry; although spherical, cylindrical, circular cylindrical, planar, biconvex, square, clover leaf and cross have been investigated, constant drug release was obtained with circular cylindrical devices only (Brooke & Washkuhn 1977; Lipper & Higuchi 1977). Hsieh et al (1983), however, claimed that the rate of drug release from the circular cylinder was initially high and then began to approach, but not achieve, linearity. Some authors have proposed an oral tablet form with a central hole for obtaining zero-order drug release (Béchard & McMullen 1988; Hansson et al 1988; Sangalli et al 1993, 1994). In previous studies a hemispherical dosage form with the entire surface covered with an impermeable coating except for a small cavity in the centre of the flat surface was suggested, and zero-order drug release was achieved (Hsieh et al 1983; Doganay 1989). In a recent study cylindrical matrices with a hole in the flat surfaces, for oral administration, were prepared by compression of poly(vinyl alcohol) and sodium salicylate or theophylline. Although pseudo zero-order drug kinetics were obtained when the interior hole was the only uncoated surface, the origin of the zero-order kinetics has not yet been satisfactorily explained (Vandelli & Cameroni 1993). In this study, therefore, a new cylindrical implant was prepared from polyethylene and sodium salicylate containing a central hole on the flat surfaces. Drug–matrix systems were directly compressed at 150°C in an appropriately designed mould made of stainless-steel. Cylindrical devices thus obtained were initially coated with a thin impermeable polymer film then a thick paraffin coating except for the inner surfaces of the holes. Differential scanning calorimetry has been used to detect the presence of decomposition products formed in aminophylline suppositories (Pryce-Jones et al 1992) and so this method was also used in our study to determine whether any decomposition product of the drug was formed in the matrices at 150°C. In addition, the effect of matrix density on drug release was also investigated. Calculations of diffusion-controlled release from the geometric shape were in very good agreement with the zero-order drug release observed practically.

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Theory

Concept

We consider the cylindrical matrix to be two imaginary hemispheres with an uncontrolled region between them. If the cylinder is coated with an impermeable layer except for the holes on the flat surfaces, drug diffusion will occur only through these holes into solution (Fig. 1).

Information on drug diffusion from coated hemispherical matrices was given in a recent study (Hsieh et al 1983). For exact analysis of the process, the equation for the continuity in spherical coordinates must be written for the diffusion of the drug component. Then, assuming unidirectional (in the r

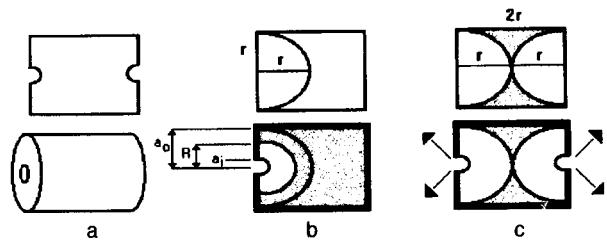

FIG. 1. Schematic diagrams of the cylindrical device and its cross section (a) and cross sections of imaginary hemispheres in the one-hole (b) and two-hole (c) cylindrical devices. The cross section of the one-hole device at time t is given in the lower part of b.

direction) mass transfer and applying appropriate boundary conditions, which include the moving boundary concept, the concentration distribution of the drug in the matrix can be evaluated at any time. Finally, the diffusional mass flux of the drug on the moving boundary at any time can be computed by using this concentration distribution function. As an alternative, Fick's first law equation can be directly applied to the diffusional flux of drug material in the matrix. In this paper this simplified approach has been adopted, rather than the complicated analysis.

Fick's law of diffusion is:

$$dQ/dt = -DAdc/dr \quad (1)$$

Where Q is the mass of drug being transformed, t is the time, c is the drug concentration, D is the diffusion coefficient (constant), A is the area for mass transport and r is the distance from the diffusion source to the release surface. It can be seen from Fig. 1 that when r increases, drug release also increases, because the available diffusion area is increased, owing to the geometric structure, and this compensates for the increase in the diffusion distance of drug transport. The release rate for the hemisphere can be derived as described below:

$$dQ/dt = 2C_sDa_i\,[R/(R - a_i)] \quad (2)$$

where C_s is the solubility of the drug in the release media, a_i is the inner radius of the cavity and R is the radial distance to the interface between dissolved and dispersed drug within the matrix.

The approach to zero-order kinetics can be observed when $R \gg a_i$, $R - a_i$ becomes equal to R:

$$dQ/dt = 2DC_sa_i \quad (3)$$

Each of the terms in equation 3 is a constant. Thus for a hemispherical device with small a_i the release rate will essentially be constant. This equation can be used for our one-hole, covered cylindrical matrices. For a two-hole cylinder, this equation is multiplied by two.

$$dQ/dt = 2DC_sa_i \times 2 = 4DC_sa_i \quad (4)$$

Equation 1 is valid when the diffusion occurs from outside the hemisphere in the covered matrices. For high-density, one-hole devices D (0·067 day^{-1}) and A (3·227 cm^2) are constants, c is 1.1 g mL^{-1} and r increases from 0·7 cm to 1·2 cm, so constant release could not be observed.

Volumetric evaluations of imaginary hemispheres in the cylindrical matrix

The volumes of a cylinder and a hemisphere are given by equations 5 and 6, respectively.

$$V_{cyl} = \pi r^2 \times h \quad (5)$$

$$V_{hem} = 4\pi r^3/6 \quad (6)$$

If r is assumed to be 1 and h is 2r the equations become:

$$V_{cyl} = \pi \times 2 = 3{\cdot}146 \times 2 = 6{\cdot}292$$

$$V_{hem} = 4\pi/6 = 4 \times 3{\cdot}146/6 = 2{\cdot}097$$

and thus the percentage of the volume of the cylinder occupied by each hemisphere is:

$$(V_{hem}/V_{cyl}) \times 100 = 2{\cdot}097 \times 100/6{\cdot}292 = 33{\cdot}3\%$$

For two hemispheres, V is 66·6% and the region between the hemispheres is 33·3%.

Calculation of diffusion distances, diffusion areas and diffusion coefficient

The matrix mass was calculated on a percentage basis from the amount of drug released daily and the value obtained was divided by the density to find the matrix volume equivalent to the amount of drug released daily. The diffusion distance from the matrix volume and the diffusion area were then found by use of equations 7 and 8, respectively.

$$V = 4\pi r^3/6 \quad (7)$$

$$A = \pi R'2/2 \quad (8)$$

Where r is diffusion distance and R′ is the diameter of the sphere. The diffusion coefficient was found from the following formula for first-order kinetics:

$$D = m \times 2{\cdot}303 \quad (9)$$

where D is the diffusion coefficient and m is the slope of the line, which is given by:

$$m = \log y_2 - \log y_1/t_2 - t_1 \quad (10)$$

where y represents diffusion distance and t is the time.

Materials and Methods

Preparation of cylindrical matrices

Sodium salicylate (Paninkret, Westerhorn, Germany; BP 1993) and low-density (LD) polyethylene (Pet-Kim, Izmir, Turkey, d = 0·921) were passed through a 40-mesh screen before use. Sodium salicylate and polyethylene, 30%:70%, were mixed in a cube blender for 5 min. A hollow cylinder mould was loaded with 1·75 g of this drug-polymer blend and placed in an oven preheated to 150°C. After 30-min heating a steel plunger was forced into the mould. By using this type of mould to compress the polymer-drug matrix, a small cavity was formed on the flat surfaces of the cylindrical matrix. After compression, the mould containing the cylindrical matrix was cooled to room temperature for 30 min. The mould was then dismantled and the matrix was removed from the mould. To protect the cavity within the cylindrical matrix during coating, a steel bead 2 mm in diameter was inserted into it. The outer surface of the cylindrical matrix was then coated with a thin film (Uhu, Colle Universale, made in Turkey under license of Ligner & Fischer GmbH, 7580 Bühl, Germany) by use of a brush, after which the device was plunged into paraffin at 60°C for the subsequent paraffin coating. Finally, the steel bead was removed from the cavity. The height of the matrices could be adjusted to three different levels by inserting the plunger to different distances into the mould.

In-vitro dissolution studies

The cylindrical matrices obtained were placed in a vial containing saline solution (0·9% NaCl; Merck, Darmstadt, Germany; 10 mL). The vials were then placed on a shaker (20 shakes min^{-1}, amplitude of shake 4 cm, shaking speed 0·8 $mmin^{-1}$) at 37 ± 1°C. After fixed time periods the dissolution medium was removed for analysis and fresh saline solution (10 mL) was added into the vial. Spectrophotometric

assay of the sodium salicylate (Unicam 8625 UV/Vis Spectrometer) was performed at 294 nm.

Matrix types

Three types of cylindrical matrix were prepared. The height of the cylinders were measured by use of callipers (calliper gauge, direct reading, 0·1 mm). The density (d) and surface area (S) of the matrices were calculated by use of the well known equations 11–13.

$$V = \pi r^2 \times h \quad (11)$$

$$d = M/V \quad (12)$$

$$S = 2\pi r^2 + 2\pi r \times h \quad (13)$$

Kinetic evaluations

The results thus obtained from dissolution studies were evaluated kinetically by first order, zero order, Hixon-Crowell, RRSBW and Higuchi methods (Hixson & Crowel 1931a, 1931b; Higuchi 1963; Langenbucher 1976; Alvarez & Villafuerte 1991). The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer program (Agabeyoglu 1971).

Differential scanning calorimetry (DSC)

The high density cylinder prepared from 70%:30% LD polyethylene-sodium salicylate (11·3 mg sample) in aluminium pans was scanned (DSC 92 scanning calorimeter; France) from 20 to 200°C at 10°C min^{-1} in air. The phase transition range of the prepared cylinder was determined.

Results and Discussion

The equation of the standard curve for sodium salicylate was $y = 44{\cdot}753x - 5{\cdot}915$ ($R = 0{\cdot}999$). The method is sensitive within the range of 1–12 μg mL^{-1} of drug. Matrix types prepared in this study and some data on height, surface area, density and matrix weights are given in Table 1. Normally when the height of the matrix increases, the surface area also increases, but the density decreases. The cumulative drug-release profiles for uncoated matrices are shown in Fig. 2. It is apparent that as the surface area increases, the release rate increases in accordance with Fick's law and drug release decreases with significant increases in the density of the matrix. Drug release continues for 3, 4 and 34 days with the low-, middle- and high-density matrices, respectively. It was established that RRSBW distribution best modelled the release profile of uncovered high density matrices (Table 2). Essentially, drug release continues beyond these days, but we ended the sampling when the drug concentration in the test solution fell below 0·1 mg mL^{-1}.

Table 1. Matrix types and their properties.

Matrix type	h* (cm)	S (cm^2)	d	M* (g)
High-density	1·20 ± 0·003	8·366	0·927	1·715 ± 0·004
Middle-density	1·65 ± 0·008	10·348	0·679	1·728 ± 0·003
Low-density	2·1 ± 0·025	12·330	0·534	1·730 ± 0·007

*Values are expressed as mean ± s.e.

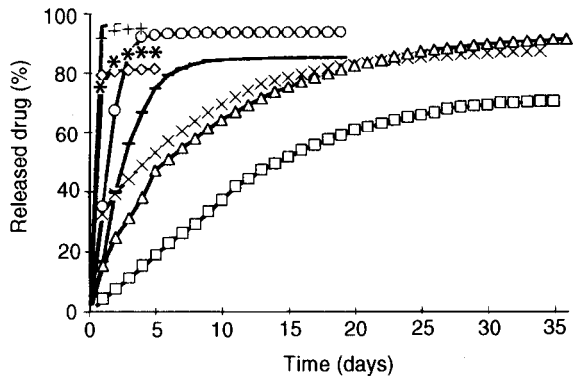

FIG. 2. Dissolution profiles of uncoated (× high density; ◇ medium density; – low density), coated one-hole (□ high density; – medium density; ○ low density) and coated two-hole (△ high density; * medium density; + low density) cylindrical matrices (n = 3).

The cumulative drug-release profiles for one-hole coated matrices are shown in Fig. 2. As the density of the materials increases, drug release decreases significantly as for the uncoated matrices. It is clear from Fig. 3 that at the beginning of the dissolution process zero-order drug release takes place for the first 11 days; drug release then proceeds according to the RRSBW distribution (Table 2). This release profile is in accordance with the coated one-hole cylindrical device with an imaginary hemisphere. Constant drug release will be seen only when drug release occurs from a hemisphere; constant release will not be observed for the rest of the dissolution. In theory, we had expected constant drug release for 9 days, because 33·3% of the drug content of the device would have been released in 9 days. The differences between theoretical and

Table 2. Kinetic distribution results from uncoated and coated high-density cylindrical matrices.

Kinetic model	Uncoated	Coated one-hole	Coated two-hole
First order	$k_{r1} = 2{\cdot}924$ (h^{-1}) $r = 0{\cdot}958$ $r^2 = 0{\cdot}919$	$k_{r1} = 2{\cdot}129$ (h^{-1}) $r = 0{\cdot}974$ $r^2 = 0{\cdot}950$	$k_{r1} = 3{\cdot}824$ (h^{-1}) $r = 0{\cdot}987$ $r^2 = 0{\cdot}975$
Zero order	$k_{r0} = 408$ mg h^{-1} $r = 0{\cdot}899$ $r^2 = 0{\cdot}792$	$k_{r0} = 553$ mg h^{-1} $r = 0{\cdot}940$ $r^2 = 0{\cdot}884$	$k_{r0} = 525$ mg h^{-1} $r = 0{\cdot}903$ $r^2 = 0{\cdot}816$
Higuchi	$r = 0{\cdot}957$ $r^2 = 0{\cdot}916$	$r = 0{\cdot}985$ $r^2 = 0{\cdot}971$	$r = 0{\cdot}986$ $r^2 = 0{\cdot}973$
RRSBW	$\beta = 0{\cdot}512$ $r = 0{\cdot}992$ $r^2 = 0{\cdot}986$	$\beta = 0{\cdot}963$ $r = 0{\cdot}992$ $r^2 = 0{\cdot}985$	$\beta = 0{\cdot}748$ $r = 0{\cdot}998$ $r^2 = 0{\cdot}997$
Hixson-Crowell	$r = 0{\cdot}939$ $r^2 = 0{\cdot}882$	$r = 0{\cdot}964$ $r^2 = 0{\cdot}931$	$r = 0{\cdot}967$ $r^2 = 0{\cdot}937$

practical drug release from the device were approximately 8% of drug content and 2 days release (Fig. 4).

With the two-hole devices constant drug release was seen for the first five days of dissolution; as a result of this 47·2% of the drug content was released ($r^2 = 0.994$) (Fig. 4). As for the one-hole device, RRSBW distribution was observed for the remaining dissolution (Table 2).

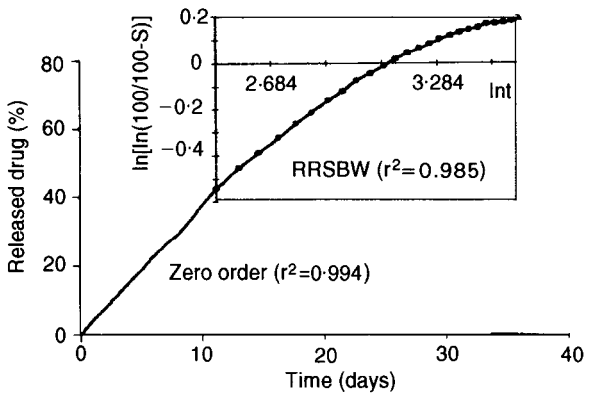

FIG. 3. Two-step kinetic model for drug release from one-hole devices.

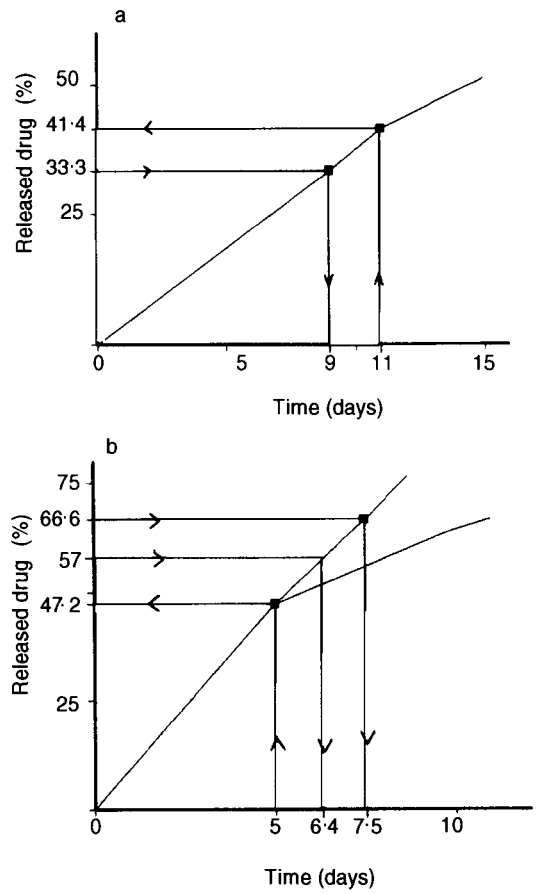

FIG. 4. Comparison of theoretical and practical drug release and release time for one-hole (a) and two-hole (b) covered matrices.

Graphically RRSBW distributions gave straight lines with slope $\beta = 0.512$, 0·963 and 0·748 and t = 7·2, 23·9 and 9·9 days for uncoated, coated one-hole and two-hole devices, respectively, for dissolution of the active ingredients up to 63·2%.

If the height of our two-hole device had been 1·4 cm, zero-order drug release would have proceeded for approximately 7·5 days, because 66·6% of the drug content of the device would have dissolved by this time. Owing to density adjustments, the height of our device was 1·2 cm and this 2-mm difference corresponds to 14·4% of the drug content of the device and the drug content of the two hemispheres are 57% (double percent calculations were used to obtain this value) and 6 days were, therefore, enough for the release of 57% of the drug of the device. In this case, there is difference of 10% of drug content and a difference of 1·4 days between the theoretical and practical drug release.

The results of the comparison of percentage cumulative drug release from one-hole and two-hole devices are given in Table 3 and Fig. 5. For the first five days practical drug release from the two-hole device is faster than that calculated theoretically. There is then a gradual reduction in drug release from the two-hole device until the eighth day. On the eighth day, drug release from the two-hole device is approximately twice that from the one-hole device (theoretical and practical drug release are nearly equal). Practical drug release from the two-hole device then continues to decrease gradually. This indicates that drug release is initially faster than expected for the two-hole devices. Hsieh et al (1983) claimed that zero-order drug release will be achieved after a short burst and maintained for the duration of release, because controlled release will begin when $R \gg a_i$ (Fig. 1). Rapid drug release can, therefore, be observed at the beginning of the release-rate studies. There is a burst of 0·5% for one-hole and 7·925% for the two-hole devices according to our calculations (the results for the first day were ignored when calculating the average daily value for the controlled-release amount). We assume that the difference between the theoretical and experimentally obtained release rates originates from the rapid release during the first day, as mentioned above. This concept is, moreover, verified by comparing the differences between the theoretical and the practical release rates for the second, third, fourth and fifth days.

The release times and amounts of drug dissolved during the first day from all the matrix systems are compared in Table 4. It is clear that as the amount of dissolved drug increases during the first day the release time decreases. The amount of drug implanted can be adjusted between 4·272 and 96·108 mg and release times vary between 3 and 36 days.

Table 5 shows the matrix volumes equivalent to the amount of drug released, the daily diffusion distances and the diffusion areas for the first eleven days of dissolution. The daily increase in matrix volume is nearly constant at 70 mm^3. There is a logarithmic relationship between the increase in the diffusion distance and the release time (Fig. 6). The slope of the line in Fig. 6 is 0·0295 and the diffusion coefficient was calculated from the slope of the line for first-order kinetics to be 0·067 day^{-1}. During eleven days, the diffusion area increased by approximately 25 mm^2 on each successive day.

DSC study of the high-density cylinder prepared with sodium salicylate revealed no thermal event corresponding to the melting of drug crystals and no peak in the scan indicating

Table 3. Comparison of percentage cumulative drug release from one-hole and two-hole devices.

Time (days)	Cumulative drug release (%) Practical release from one-hole devices*	Theoretical release from two-hole devices†	Practical release from two-hole devices*	Differences
1	4·272 ± 0·576	8·544	15·511 ± 2·816	6·967
2	7·543 ± 0·648	15·086	24·611 ± 3·777	9·525
3	11·245 ± 1·281	22·490	31·309 ± 4·045	8·819
4	15·206 ± 1·232	30·412	38·101 ± 4·871	7·689
5	18·862 ± 1·115	37·724	47·211 ± 5·085	9·487
6	22·811 ± 1·555	45·622	50·978 ± 5·419	5·356
7	26·061 ± 1·437	52·122	54·572 ± 5·921	2·450
8	29·046 ± 2·235	58·092	57·910 ± 6·436	−0·180
9	33·197 ± 1·327	66·394	61·187 ± 7·017	−5·210
10	37·126 ± 1·702	74·252	64·232 ± 7·060	−10.020
11	41·451 ± 2·029	82·900	66·733 ± 7·215	−16·160

*Values are expressed as mean ± s.e. †Calculated by multiplying the values in the previous column by 2.

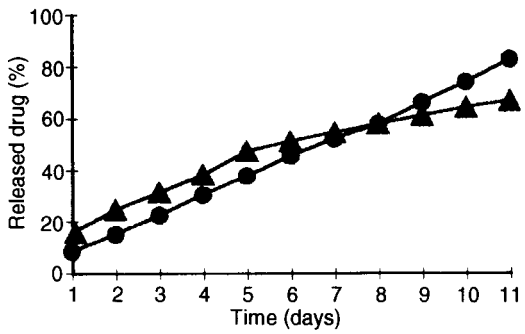

FIG. 5. Comparison of theoretical (●) and practical (▲) drug release from two-hole devices.

the presence of a decomposition product of the drug. It is apparent from Fig. 7 that the polymer begins to melt at 106·32°C and that melting ends at 130.15°C.

The fabrication procedure used for the preparation of the new cylindrical device is simple and useful and the products are reproducible. Developing a fabrication procedure for a well-functioning system is of crucial economic importance. Unlike the one-layered matrices reported in literature, our matrices were coated with two layers, so that if the outer layer is broken or fissured, the second layer can still guarantee the proper functioning of the system (Hsieh et al 1983; Hsu et al 1992). From this point of view, this system is reliable and highly resistant to external effects. Fickian drug release was observed from the matrices; for slabs, as the surface area increases, drug release also increases. The release behaviour of the covered matrices in serum simulates the imaginary hemispheres contained in the cylinder, and controlled release was observed. Drug release through the parts of the matrix other than the hemispheres was not constant. Kinetic evaluations are also in accordance with these opinions. A double-kinetic model contains two different kinetic models in the same figure (Fig. 3). For the first time, a double-kinetic model was given for dissolution profiles, showing that more than one kinetic model should be used for long-term dissolution parameters. In-vivo drug release from implanted matrix could be estimated by use of kinetic evaluations. The amount of drug released from two-hole devices is approximately twice that from the one-hole devices and these findings also conformed to our concept of imaginary hemispheres.

Hsu et al (1992) developed a cylindrical device with a vertical opening on its surface, but his proposed system is not ideal because the increase of diffusional area with time was limited. This system can, moreover, furnish real zero-order drug release for a very short time only at the beginning of the dissolution, because the surfaces of the cylinder becomes distant from the horizontal line (180°). In this system, if the vertical hole on the surface could be replaced by a central hole with two open ends, the results would have been more satisfactory. In a similar instance, constant drug release has been obtained in tablets with a central hole, which increased the release angle by 360° (Béchard & McMullen 1988; Hansson et al 1988; Sangalli et al 1993, 1994). Kuu & Yalkowsky (1985) described an approach to a near zero-order drug delivery sys-

Table 4. Comparison of the release times and amounts of drug dissolved from the matrix systems during the first day.

Matrix system	Amount of drug dissolved (mg day^{-1})	Release time (days)
One-hole device (high density)	4·272	36
Two-hole device (high density)	15·511	36
One-hole device (medium density)	16·863	19
Uncovered matrix (high density)	32·758	34
One-hole device (low density)	35·233	19
Two-hole device (medium density)	75·348	5
Uncovered matrix (medium density)	79·448	5
Two-hole device (low density)	91·751	4
Uncovered matrix (low density)	96·108	3

Table 5. The matrix volumes equivalent to the amount of daily drug released from one-hole devices, the diffusion distances and the diffusion areas for the first eleven days.

Day	Matrix volume (mm^3)	Diffusion distance (mm)	Diffusion area (mm^2)
0	2·09*	1*	6·28*
1	79·10	3·3	72·0
2	139·41	4·0	104·2
3	207·83	4·6	135·6
4	283·34	5·1	166·4
5	336·20	5·4	186·4
6	423·94	5·8	217·4
7	484·35	6·1	230·3
8	539·37	6·3	255·1
9	616·32	6·6	278·8
10	688·96	6·9	300·1
11	768·05	7·1	322·7

*Data for hole.

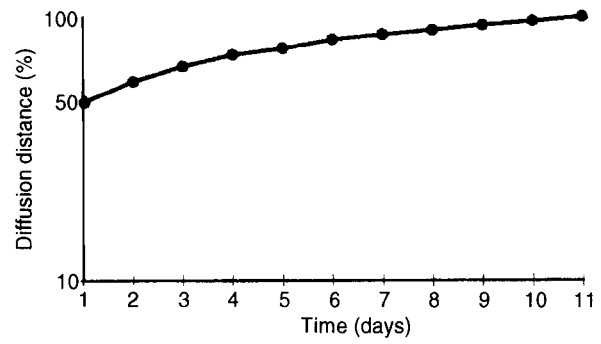

FIG. 6. Logarithmic increase of diffusion distance.

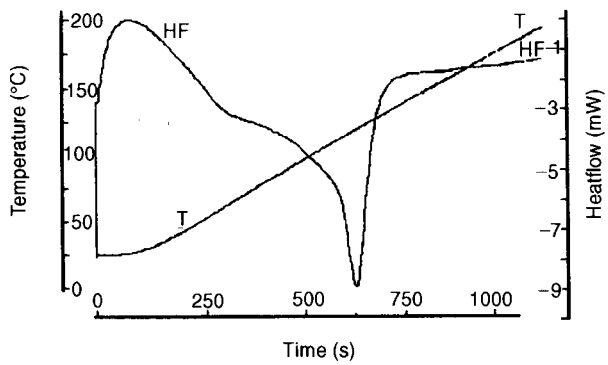

FIG. 7. DSC scan obtained from LD polyethylene containing sodium salicylate, showing the melting endotherm of the polymer. Enthalpy, 4·786 cal g^{-1}; onset temperature, 106·32°C; top of peak; 120°C.

tem which utilized a device consisting of multiple holes uniformly distributed on an impermeable membrane, but no supporting experimental data were available. Releasing angle was increased to the hole number × 180° by this system. Vandelli & Cameroni (1993) prepared a cylindrical matrix with a central hole on the flat surfaces by compression of poly(vinyl alcohol) and sodium salicylate or theophylline for oral administration. Pseudo zero-order kinetics were obtained when the interior hole was the only uncoated surface but only 11–13% of the drug content was released during 8 h. There is, moreover, no diffusional data on how to obtain zero-order kinetics. Marentette & Grosser (1992) also prepared a cylindrical reservoir device coated with permeable and erodible materials. By adjusting the permeabilities of the coatings, a constant drug-release rate was achieved in simulation studies, but the formation and working of diffusion-controlled membrane systems are different from those of matrix systems. In the light of these literature results and according to the results of our study, real zero-order drug release could be obtained by drug diffusion from a hole, rather than from matrix systems based on geometric shapes. In addition, if release is to be constant the diffusion area must increase by an amount sufficient to compensate for the increase in diffusion distance of drug transport. It was calculated that a daily increase in the diffusion area in the hemisphere of approximately 25 mm^2 was necessary for zero-order drug release. The increase in the diffusion distance decreases when the dissolution time increases, leading to a logarithmic increase in the diffusion distance (Fig. 6). The radius of the cylinder produced is 7 mm. The radius of the imaginary hemisphere was also calculated as 7·1 mm (Table 5) a result which confirmed the reliability of the data given in this study.

Drug release normally decreases significantly when density increases. In this study, the amount of drug released and the release time can be varied by factors of 22 and 12, respectively, by changing the density. It is known that microcrystal drugs are highly resistant to high temperatures. Use of DSC showed that no decomposition products were formed at 150°C. For macromolecules, working at −80°C was recommended when using ethylene vinyl acetate as polymer (Hsieh et al 1983).

Our system has been devised for dispensing more than 1 mg drug day^{-1} by implantation. The implants produced in this study could be used in the subscapular lipoid tissue, musculus rectus abdominis and musculus rectus femoris of man, according to advice from surgeons. It must be mentioned in conclusion that work on the implantation systems awaits further improvements in the area of in-vitro and in-vivo release, and in microbiological and toxicological aspects, and these studies are indeed challenging and time-consuming.

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References

Agabeyoglu, I. T. (1971) In: Un Programme dans le Langue Basique de Microcomputer pour la Determination des Donneés de Dissolution. XVIIème Semain Medical Balkanique, Istanbul, 327

Alvarez, A. M. R., Villafuerte, M. A. H. (1991) Inert matrix tablets as a controlled release dosage form for carteolol hydrochloride. Eur. J. Pharm. Biopharm. 37: 147–153

Béchard, S., McMullen, J. N. (1988) Solute release from a porous polymeric matrix: inwardly tapered disk with a central releasing hole. J. Pharm. Sci. 77: 222–228

Brooke, D., Washkuhn, R. J. (1977) Zero-order drug delivery system: theory and preliminary testing. J. Pharm. Sci. 66: 159–162

Doganay, T. (1989) Hemispherical controlled-release dosage form suitable for oral use. J. Fac. Pharm. Gazi. 6: 75–94

Hansson, A. G., Giardino, A., Cardinal, J. R., Curatolo, W. (1988) Perforated coated tablets for controlled release of drugs at a constant rate. J. Pharm. Sci. 77: 322–324

Higuchi, T. (1963) Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52: 1145–1149

Hixson, A. W., Crowel, J. H. (1931a) Dependence of reaction velocity upon surface and agitation I. Theoretical consideration. Ind. Eng. Chem. 23: 921–931

Hixson, A. W., Crowel, J. H. (1931b) Dependence of reaction velocity upon surface and agitation II. Experimental procedure in study of surface. Ind. Eng. Chem. 23: 1002–1009

Hsieh, D. S. T., Rhine, W. D., Langer, R. (1983) Zero-order controlled-release polymer matrices for micro- and macromolecules. J. Pharm. Sci. 72: 17–22

Hsu, J. P., Ting, C., Lin, M. J. (1992) A theoretical analysis of a new drug delivery system: a cylindrical device with a vertical opening on its surface. J. Pharm. Sci. 81: 866–870

Kuu, W. Y., Yalkowsky, S. H. (1985) Multiple-hole approach to zero-order release. J. Pharm. Sci. 74: 926–932

Langenbucher, F. (1976) Parametric representation of dissolution-rate curves by the RRSBW distribution. Pharm. Ind. 38: 472–477

Lipper, R. A., Higuchi, W. I. (1977) Analysis of theoretical behaviour of a proposed zero-order drug delivery system. J. Pharm. Sci. 66: 163–164

Marentette, J. M., Grosser, A. E. (1992) Modeling of the kinetics of drug release from a binary system. J. Pharm. Sci. 81: 318–320

Pryce-Jones, R. H., Eccleston, G. M., Abu-Bakar, B. B. (1992) Aminophylline suppository decomposition: investigation using differential scanning calorimetry. Int. J. Pharm. 86: 231–237

Sangalli, M. E., Giunchedi, P., Gazzaniga, A., Conte, U. (1993) Erodible perforated coated matrix for extended release of drugs. Int. J. Pharm. 91: 151–156

Sangalli, M. E., Giunchedi, P., Maggi, L., Conte, U., Gazzaniga, A. (1994) Inert monolithic device with a central hole for constant drug release. Eur. J. Pharm. Biopharm. 40: 370–373

Vandelli, M. A., Cameroni, R. (1993) Selective coating of cylindrical matrices with a central hole. I. An interpretation of the swelling process. Int. J. Pharm. 100: 107–114