United States Patent [19]

Brooke

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[54] **ZERO-ORDER RELEASE DEVICE**

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[73] Assignee: **Mead Johnson & Company,** Evansville, Ind.

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[21] Appl. No.: **405,616**

[52] **U.S. Cl.** **128/260,** 119/25, 128/272, 239/57, 239/60, 43/131

[51] **Int. Cl.** **A61m 31/00,** A61m 7/00

[58] **Field of Search** ..... 128/260, 130, 270, 268, 128/272 X, 2 R, 214 E; 119/156, 25 X, 26; 260/75, 86.1, 2.5; 222/386.5, 54; 239/60 X, 57 X, 44; 206/47; 23/267 A; 43/131 X

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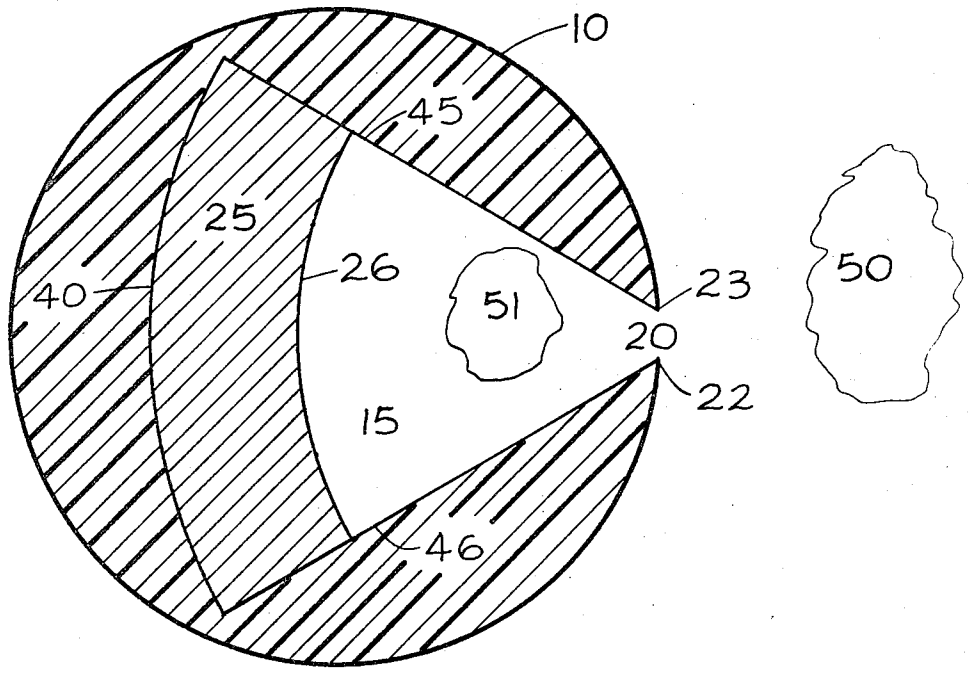
Primary Examiner—Aldrich F. Medbery
Attorney, Agent, or Firm—Robert E. Carnahan; Robert H. Uloth

[57] **ABSTRACT**

A diffusible solid is released by diffusion into a fluid medium from a cavity within a container through an opening therein at a rate which is independent of the amount of solid present in the container. Zero-order release is effected by the shape of the cavity and the opening. The rate is related to the solubility and to the diffusion constant of the solid in the fluid medium. For a given substance, the rate of release is determined by cavity shape and dimensions of the diffusion opening. The device is adapted for use in both liquid and gaseous media and can be used for the zero-order release of drug substances into the system of a living organism, and for non-medical uses.

17 Claims, 6 Drawing Figures



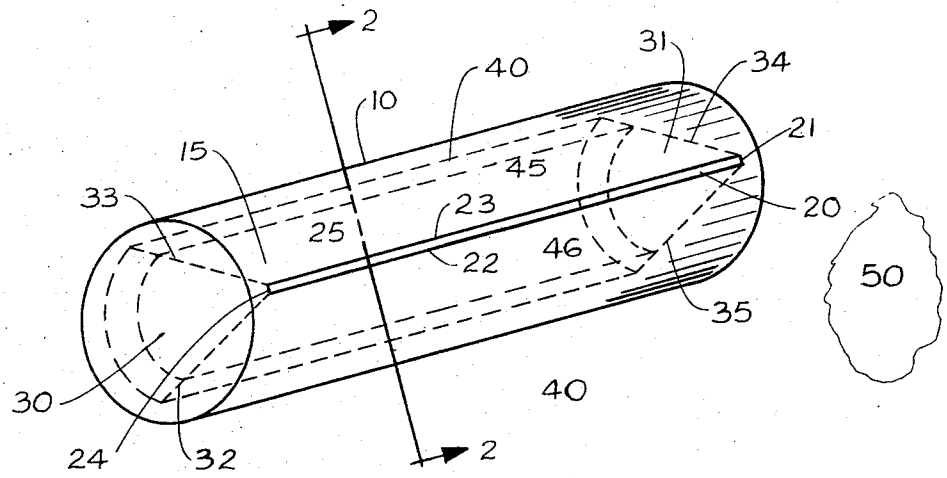


FIGURE 1

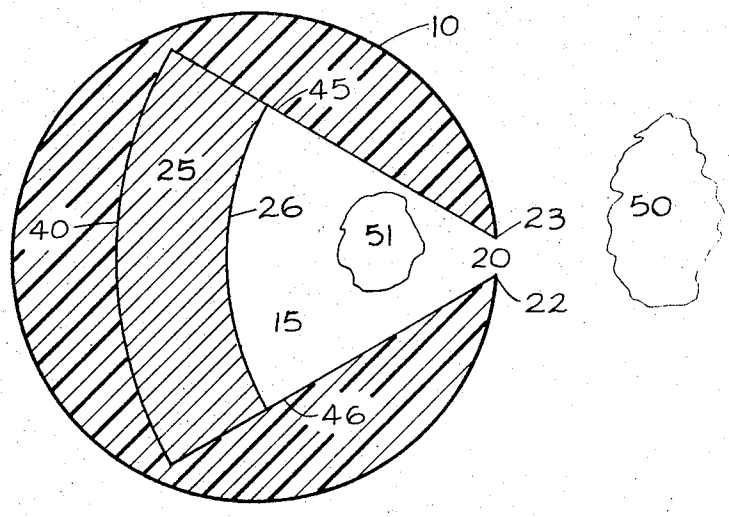


FIGURE 2

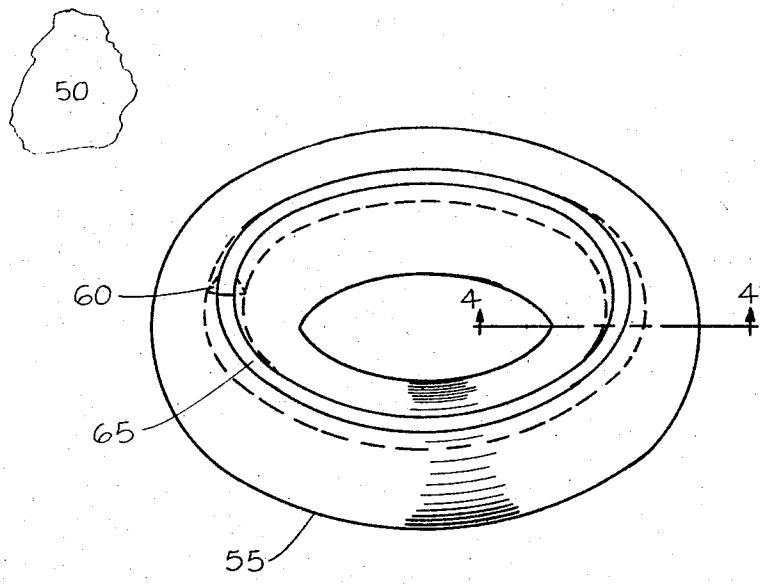


FIGURE 3

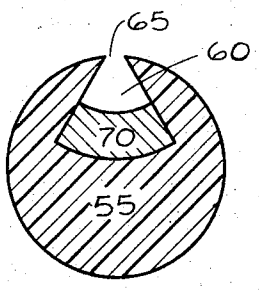
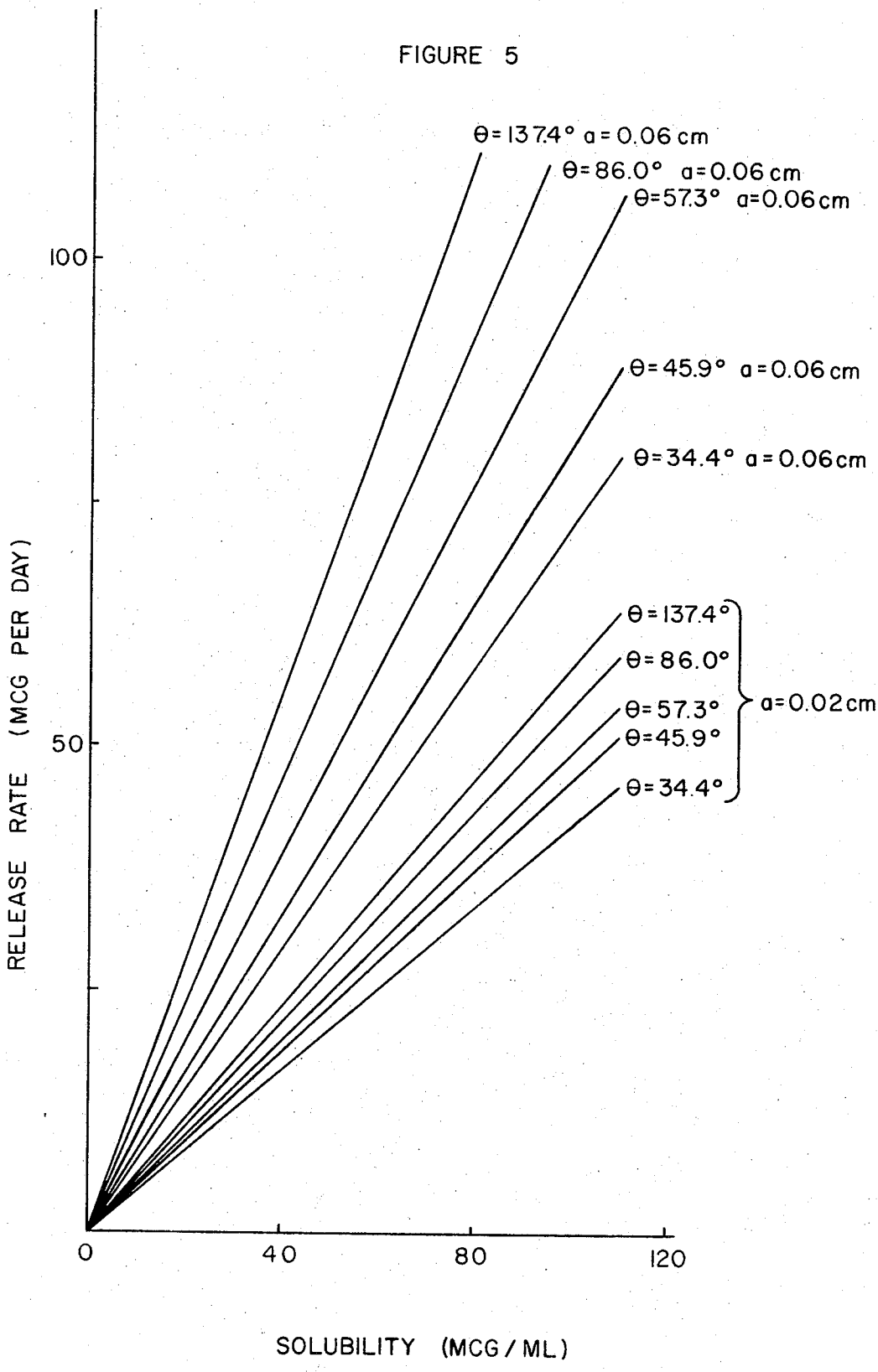


FIGURE 4

FIGURE 5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θ=86.0° a=0.06 cm
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a=0.02 cm
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50
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40
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RELEASE RATE (MCG PER DAY)
SOLUBILITY (MCG / ML)

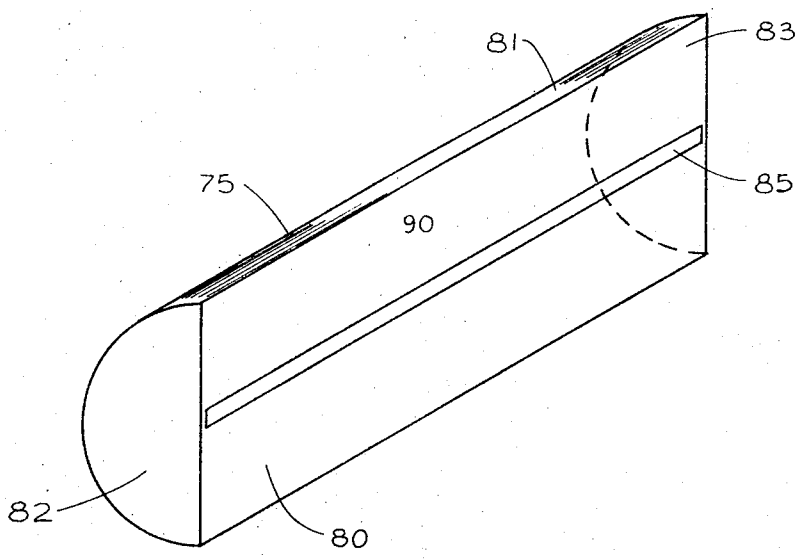

FIGURE 6

ZERO-ORDER RELEASE DEVICE

FIELD OF THE INVENTION

There is provided a device for dispensing a vapor from a subliming solid into a gaseous medium or a solid solute into a liquid medium at a constant rate during a prolonged period of time. The device may be used as a medicator such as a surgical implant, tampon, suppository, intrauterine device, or intravaginal device for delivery of a drug or growth regulating substance into the system of a living organism, or for other uses such as water or air treatment.

SUMMARY OF THE PRIOR ART

Certain pesticides are sublimable solids and various devices have been used for delivery of the vapor thereof such as decorative cannisters, pet collars, etc., to the locale to be treated. Moth proofing and insecticidal agents have been delivered in this fashion. Various means have been used for the delivery of drugs and other biologically active substances to the mammalian body by means of specifically fabricated tablets, implants, intrauterine devices, ocular inserts, catheter tubes, etc. which were designed to release the active substance at a predetermined rate. Examples of such devices are illustrated in the following patents. Levesque, U.S. Pat. No. 2,987,445 patented June 6, 1961; Long and Volkman, U.S. Pat. No. 3,279,996 patented Oct. 18, 1966; Rudel, U.S. Pat. No. 3,656,483 patented Apr. 18, 1972; Jacobs, U.S. Pat. No. 3,113,076 patented Dec. 3, 1963; Stephenson, et al., U.S. Pat. No. 3,146,169 patented Aug. 25, 1964; and Wepaic, U.S. Pat. No. 3,598,127 patented Aug. 10, 1971.

SUMMARY OF THE INVENTION

This invention provides a device comprised of a container of rigid material which is impermeable to the fluid medium into which it is desired to dispense a diffusible solid which is contained within the device. The container may be of any convenient size and shape to fit the particular application under consideration. Housed within the container is a cavity communicating through a slot in the surface of the container with the exterior medium through which the contained solid is dispensed. The solid is dispensed by the processes of dissolution of vaporization within the container into the fluid medium which enters through the slot, and diffusion of the dissolved or vaporized solid outwardly through the slot into the surrounding medium. Zero-order release results from the configuration of the cavity and slot which is such as to provide an increasing surface area of diffusible solid exposed to the fluid medium within the container as the length of the path through which the dissolved or sublimed solid must diffuse to reach the exterior increases. A constant ratio of area of dissolution or sublimation surface to diffusion distance is maintained. The device is applicable to various drug delivery systems, and to non-medical uses such as the dispensing of insecticides, pesticides, perfumes, and water treatment with germicides in swimming pools, toilets, etc.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a perspective view of a device of the present invention which is cylindrical in form and contains a rectangular slot lengthwise on one side thereof which communicates with a cavity within the cylindrical container the cross-section of which is shaped like a slice of pie.

FIG. **2** is a view in cross-section of the device of FIG. **1** along line **2—2** showing the drug partially filling the cavity.

FIG. **3** is a perspective view of a device of the present invention in which the container is ring-shaped and the diffusion slot is arranged concentrically upon the upper surface thereof.

FIG. **4** is a view in cross-section of the device shown in FIG. **3** along line **4—4.**

FIG. **5** is a collection of graphs in which the rate of release of a diffusible solid from the device of FIG. **1** is related to its solubility, and the dimensions of the cavity and the slot.

FIG. **6** is a perspective view of a device of the present invention which is comprised of a hollow container in the form of a right circular cylinder bisected along the axis thereof and having an elongated diffusion slot located on the bisecting surface along the axis.

DETAILED DESCRIPTION OF THE INVENTION

In FIG. **1,** the cavity **15** is illustrated by broken lines and the slot through which it communicates with the exterior is indicated by **20.** The slot is of uniform length and width. The narrower dimension or width is situated at the ends **21** and **24** of the slot. The elongated dimension is located at the sides of the slot represented by **22** and **23.** Drug substance or other active ingredient to be dispensed **25** is contained within cavity **15** and is outlined by a broken line in the drawing. The cavity fill should be a solid under ambient conditions. The end walls of cavity **15** are represented by **30** and **31.** End walls **30** and **31** lie in parallel planes which are at right angles to slot **20,** adjacent to the ends thereof, and are congruent in shape. The side edges of end walls **30** and **31** of cavity **15** are represented by **32, 33, 34,** and **35.** They are of equal length and are arranged radially and inwardly divergent with respect to slot **20** so that end walls **30** and **31** are pie-shaped in the embodiment shown. Also, the rear wall **40** of cavity **15** is arcuate in contour defining a portion of the wall of a phantom cylinder whose axis lies substantially within slot **20** and the side edges **32, 33, 34,** and **35** of end walls **30** and **31** are substantially radii of the phantom cylinder. The side walls **45** and **46** of cavity **15** are situated. adjacent opposite sides **22** and **23** of slot **20** and in radial relation to said slot. They are congruent in shape.

FIG. **2** is a cross-section of the device of FIG. **1** taken along line **2—2** of FIG. **1** in a plane parallel with the planes of end walls **30** and **31** of cavity **15.** Like numbers in FIG. **2** refer to like features of FIG. **1.** Cavity **15** of the device shown in FIGS. **1** and **2** is only partially filled with drug substance **25, 26** representing the surface of drug substance **25** which is opposite slot **20.**

Cavity **15** houses drug substance **25** in bonded relation to side walls **45** and **46** and end walls **30** and **31** thereof. By bonded relation is meant in close contact so that fluid medium **50** and **51** which surrounds container **10** and which fills the void portion of cavity **15** cannot seep between the side walls or the end walls of said cavity and the drug substance **25.** In this fashion only one surface **26** of drug substance **25** is exposed to fluid medium **51** within cavity **15.**

The release of drug **25** from carrier **10** is controlled by dissolution and diffusion processes. This includes

dissolution of drug **25** into fluid medium **51** at surface **26** thereof, and diffusion therefrom in solution to slot **20** and thence into the surrounding medium **50.** The release rate of drug **25** through slot **20** into the surrounding medium **50** is a function not only of the solubility and diffusion coefficient of the drug in the receiving fluid **50** but also of the dimensions of slot **20** and of the angle between side walls **45** and **46** of cavity **15.** Initially cavity **15** may be filled flush with slot **20** with a single pellet of drug substance **25.** As the drug is dissolved and diffused from the carrier, fluid **50** from the surrounding medium diffuses into the cavity as shown by **51** in FIG. **2** to replace the drug which has dissolved and diffused out.

FIG. **2** represents the cross-section of a carrier from which about 50 percent of the initial drug fill has been released. The arcuate drug surface **26** shown in FIG. **2** is naturally formed as a result of the dissolution and diffusion processes. If it is desired to prepare a drug carrier which is only partially filled with drug substance at the outset as shown in FIG. **2,** then the surface of the drug substance should be provided with an arcuate contour as shown at **26** in FIG. **2.**

The reason for the arcuate contour of drug surface **26** is that the rate of diffusion of drug substance **25** through medium **51** to slot **20** is inversely proportional to the distance d separating drug surface **26** from slot **20** and directly proportional to the area A of drug surface **26.** The ratio of A to d remains constant so long as slot **20** lies along the axis of a section of a cylindrical surface **26** formed by drug substance **25.** The rate of release R of drug substance **25** from slot **20** is governed by the expression shown in Equation I.

$$R = DLCs/(h/a + 1/\theta)$$

EQUATION I

In Equation I, θ is the angle (expressed in radians, **1** radian = 57.3°) between side walls **45** and **46** of cavity **15.** D is the diffusion coefficient of drug **25** in medium **50** and Cs is the solubility thereof. The symbol a is the width of slot **20** and L is the length of slot **20.** The symbol h is the distance from slot **20** to that closest hypothetical point in medium **50** where the concentration of drug substance **25** is zero. As a practical matter, for drugs with relatively low solubilities a negligible or substantially zero concentration is reached at a relatively short distance from slot **20.** The values for D and h for a specific drug substance may be determined by the method of Roseman and Higuchi, J. Pharm. Sci., 59, 353 (1970). For release of the progestational steroid medroxyprogesterone acetate to vaginal tissues, they have calculated the values D=0.6 cm^2/day and h=0.058 cm.

The mathematical relationship of Equation I shows that since a, L, and θ are fixed by the dimensions of cavity **15,** then the rate of release R depends upon D, h, and Cs, all constants for any specific drug substance. Thus as long as drug is present and the arcuate surface **26** thereof is exposed to medium **51,** the rate of release will be constant. The mathematical relationship of Equation I further dictates that an increase in L will cause a proportionate increase in the release rate R. An increase in a will cause an increase in rate R but as a is made larger, its influence on rate declines. The rate R can be increased by increasing θ but like a and unlike L the effect is not linear. For a series of related drug materials having similar diffusion constants D and values h, the release rates of various members from devices having the same dimensions are substantially proportional to their solubilities Cs. If the values for D and h have not been previously determined as above, a trial and error approach to construction of the device to provide the desired release rate may be used.

It is preferred that rear wall **40** of cavity **15** have arcuate configuration as shown in FIGS. **1** and **2** similar to that of drug surface **26** such that rear wall **40** forms the wall of a cylinder the axis of which lies within slot **20.** In this circumstance a steady state of release of drug substance **25** will be maintained until the drug is entirely exhausted from the device. When rear wall **40** is flat or has another configuration other than the arcuate form shown, a constant rate of drug release will be maintained only until drug surface **26** intercepts wall **40** and exposes a portion thereof. From that time until all of the drug is exhausted, the release rate R from slot **20** will be less than the steady state zero-order condition. This may not pose a serious problem in some circumstances, and accordingly, the configuration of rear wall **40** is not limited in this invention to the arcuate form shown. Only drug surface **26** is required to be arcuate in form to provide zero-order release after dissolution and diffusion processes under operating conditions have reached equilibrium.

FIG. **3** illustrates another embodiment of the invention comprising an intravaginal ring **55** having an overall outside diameter of **6** or **7** centimeters and a cross-sectional diameter of about **1** centimeter. The ring serves as a container corresponding to **10** of FIG. **1** which houses a cavity **60** shown by broken lines in FIG. **3** corresponding to cavity **15** of FIG. **1.** Cavity **60** communicates with liquid medium **50** on the exterior of ring **55** through a slot **65** in the side thereof. Slot **65** in the device illustrated lies circumferentially on the uppermost surface of ring **55.** FIG. **4** is a cross-section of the intravaginal ring shown in FIG. **3** along line **4—4.** This illustrates the configuration of the slot and cavity along the uppermost surface of the ring in concentric position. In this instance, the length L of slot **65** corresponds to the circumference of the slot. In the configuration shown with the slot along the upper surface, a steady state of release is achieved by dissolution and diffusion of drug substance **70,** shown in FIG. **4** by the hashed mark area, since the length of exposed drug surface remains constant and equal to L. If the slot were placed on the outer or the inner surfaces of the intravaginal ring the exposed drug surface would decrease or increase respectively as drug substance **70** diffused from cavity **60** resulting in a slightly decreasing or increasing rate of release. A still further embodiment of the intravaginal ring not shown involves a ring similar to that of FIG. **3** with multiple cavities to provide for still higher rates of drug release, or for drugs having very low solubilities.

Referring again to FIG. **1,** drug substance **25** may be filled into cavity **15** in the molten state and then permitted to solidify. This is particularly suitable if the drug substance is stable at its melting point and solidifies in a form such that the dissolution properties are isotropic. A compressed solid may also be used as cavity fill. Another means of using the device of the present invention is to fill cavity **15** with a suspension of drug substance in a thixotropic gel or liquid monomer. In the latter instance, the monomer is caused to polymerize in place. In the former, a firm gel forms on allowing the

fill to stand in the quiescent state. So long as the drug substance diffuses through the polymer or gel matrix and the matrix is insoluble in the liquid medium in which the device is immersed, a steady state of release of drug substance through the diffusion slot will be achieved. In this instance, the diffusion coefficient of the drug substance through the polymer or gel matrix and the partitioning of drug between matrix and fluid is taken into account in calculating the release rate. In some instances, the release rate may be greater under these circumstances than when a solid pellet **25** of drug substance is used as illustrated in FIG. **1.**

FIG. **6** is a drawing of another embodiment of the invention in which the container **75** is in the form of a right circular cylinder which is bisected lengthwise by a plane in which the axis of the cylinder lies. The planar bisecting face is represented by the numeral **80.** Diffusion slot **85** lies along the axis of the bisected cylinder on the planar face of the container. The inner side of the arcuate cylinder wall **81** constitutes the rear wall of cavity **90** which is the interior of the container. Rear wall **81** thus has the arcuate concave configuration as is preferred for zero-order release during the entire residence time of diffusible solid within the container while it is immersed in the medium into which it is desired to dispense the solid. End walls **82** and **83** are congruent and positioned adjacent the ends of slot **85** and at right angles thereto as is required. The portions of planar bisecting face **80** of container **75** on either side of slot **85** comprise the two side walls of cavity **90** corresponding to side walls **45** and **46** of cavity **15** of the device pictured in FIG. **1.** In this instance, the angle θ between the side walls is 180°. Other embodiments of the invention may be constructed with an angle θ from about 30° to about 270°. In such instance, the cavity is formed as in FIG. **6** in the shape of a segment of a right circular cylinder having the diffusion slot located along the axis.

For the cylindrical device of FIG. **1,** having diffusion slot **20** on the side thereof, the angle θ between side walls **45** and **46** of cavity **15** may vary from about 30° to about 140°. The angle employed is selected to afford the desired release rate. The cavity of maximum volume, and thus greatest total diffusible solid capacity, which can be constructed within a cylindrical device of the type shown in FIG. **1** has an angle θ of 1.36 radians or 78°. The foregoing is determined by geometric considerations.

Substances having a wide range of solubilities may be dispensed by the devices of the present invention. By the use of an intravaginal ring similar to that shown in FIG. **3,** a release rate of 50 mcg./day of a steroid or other substance having a solubility of as low as 1.7 mcg./ml. may be achieved. For an intrauterine device embodying a container as pictured in FIG. **1,** the same release rate can be assured for substances having solubilities of up to about 570 mcg./ml. Substances having this full range of solubilities may be dispensed with devices of the type shown in FIG. **6.** Release rates can be further manipulated by the use of wax, polymer, or gel matrices such as petroleum wax, cholesterol, silicone rubber, polymeric hydrophilic hydrogels, and thixotropic gels prepared from polyethylene glycol, carboxymethylcellulose, or carboxyvinyl polymer as the continuous phase of a suspension of crystalline diffusible solid to be dispensed within the cavity.

DESCRIPTION OF SPECIFIC EMBODIMENTS

FIG. **5** is a collection of graphs in which the rate of release R expressed in micrograms per day is plotted as ordinate and solubility Cs in micrograms per milliliter is plotted as abscissa for delivery of a drug substance from a cylindrical intrauterine device similar to that of FIG. **1** having radius 0.12 cm and slot length 3.2 cm. Each of the lines plotted on these coordinates is for a different device having the values for the angle θ and slot width a shown at the right hand side of the graph. The values of Roseman and Higuchi (loc. cit.) for medroxyprogesterone acetate of $D = 0.6$ cm²/day and $h = 0.058$ cm were used for these calculations. For drug substances having similar D and h values and solubilities of the order of **100** micrograms per milliliter release rates upwards of 100 micrograms per day may be achieved. Medroxyprogesterone acetate has a solubility of 3.25 mcg/ml (Roseman and Higuchi, loc. cit.) and release rates of from about 2.5 to 6 mcg/day can, therefore, be achieved with the devices referred to in FIG. **5.** Thus by reference to FIG. **5,** various release rates can be achieved for a drug of given solubility by selection of the appropriate angle θ and slot width a.

Experimental:

The system was tested experimentally by measuring the amount of stearic acid released from a device fabricated from stainless steel and immersed in USP alcohol. The prism-shaped device was 2.5 inches long, 1.0 inches wide at the base, and 0.63 inches high from the base to the slot. The sides, base, and one end were made of 18 gauge stainless steel. The other end was cut from three-sixteenths inch stainless steel and was drilled to provide a filling port which could be closed with a stainless steel bolt. All of the 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 in place a stainless steel nut to be closed with a stainless steel bolt. Solvent resistant gaskets were used at both filling ports. The slot width (a) was 0.030 inches and the effective slot length (L) was 2.263 inches. The angle θ was 80°.

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

The release of stearic acid from the device into USP alcohol was measured by placing the device in the bottom of a double-walled beaker with an inside diameter of 11.0 cm. containing 1,000 ml. of alcohol. The bolt used to close the port in the base served as a pedestal for the device. The beaker was kept at 30°C. and its contents were stirred with a three bladed propeller (radius 2 cm., blade pitch 30°) rotated at 50 rpm 2.5 cm. below the solvent surface. The distance between the top of the device and the propeller was 4.9 cm. A cover with a hole for the stirrer and one for the sampling port was kept on the beaker.

Solvent samples were withdrawn periodically. Alcohol at 30°C. was added to the beaker to maintain volume. The stearic acid concentration in the samples was estimated colorimetrically after extraction from the sample. A 10 ml. aliquot of the ethanolic solution con-

taining stearic acid was removed from the beaker and placed in a separatory funnel. A 50 ml. volume of aqueous 0.01 M pH 7.0 phosphate buffer containing 0.1 percent methylene blue (USP grade) and 20 ml. of redistilled reagent grade chloroform were added. When a 5 ml. sample was used, an additional 5 ml. of alcohol was added to it. The separatory funnel 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 blue color was estimated photometrically at 640 nm against an appropriate standard. The blue color was stable after approximately 30 minutes. The absorbance was linearly dependent on the concentration of stearic acid in the sample. The complete data for three trials according to this procedure are listed in Table I.

TABLE I

RELEASE OF STEARIC ACID FROM ZERO-ORDER DEVICE

Trial I		Trial II		Trial III	
Time	Released	Time	Released	Time	Released
16 hr.	118 mg.	2 hr.	72.6 mg.	19 hr.	263 mg.
24 hr.	236 mg.	24 hr.	378 mg.	26.5 hr.	272 mg.
41 hr.	524 mg.	31 hr.	306 mg.	43 hr.	436 mg.
48 hr.	541 mg.	48 hr.	609 mg.	51 hr.	570 mg.
64 hr.	721 mg.	55 hr.	748 mg.	67 hr.	801 mg.
67 hr.	779 mg.	72 hr.	977 mg.	75 hr.	902 mg.
72 hr.	813 mg.	79.5 hr.	947 mg.	94.5 hr.	1110 mg.
89 hr.	1000 mg.	102.8 hr.	1360 mg.	95.5 hr.	1010 mg.
91 hr.	1230 mg.	103.5 hr.	1420 mg.	114 hr.	1600 mg.
93 hr.	1070 mg.	129.5 hr.	1840 mg.	115 hr.	1600 mg.
96 hr.	1150 mg.	130.5 hr.	1810 mg.	128 hr.	1770 mg.
118.5 hr.	1310 mg.	143 hr.	2000 mg.	134 hr.	1780 mg.
119.5 hr.	1310 mg.	151 hr.	2070 mg.	151 hr.	2090 mg.
137.5 hr.	1590 mg.	167 hr.	2450 mg.	158 hr.	2130 mg.
138.5 hr.	1600 mg.			175 hr.	2360 mg.
161.5 hr.	1850 mg.			182 hr.	2440 mg.
168 hr.	1870 mg.			199 hr.	2680 mg.
184.5 hr.	2100 mg.			206 hr.	2760 mg.
192 hr.	2170 mg.			223 hr.	2990 mg.
207.5 hr.	2400 mg.			230.5 hr.	3180 mg.
216 hr.	2350 mg.			247.5 hr.	3360 mg.
232.5 hr.	2860 mg.			248.5 hr.	3120 mg.
235 hr.	2830 mg.			270 hr.	3490 mg.
240 hr.	2810 mg.			271 hr.	3440 mg.
257 hr.	2870 mg.			282.5 hr.	3500 mg.
261 hr.	3210 mg.			285.5 hr.	3640 mg.
265 hr.	3350 mg.			290 hr.	3780 mg.
285 hr.	3620 mg.			307 hr.	3930 mg.
285.5 hr.	3610 mg.			314 hr.	3860 mg.
313.8 hr.	4010 mg.			331 hr.	4090 mg.
314.8 hr.	4070 mg.				
330 hr.	4240 mg.				

The linear regression analysis for each trial is summarized in Table II. The coefficient of determination (r^2) was 0.99 in each case indicating that the data for the release rate are zero-order.

TABLE II

SUMMARY OF REGRESSION ANALYSIS ON EACH TRIAL AND ON COMPOSITE OF ALL DATA

	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

The following compositions illustrate cavity fill solids for use in the present invention comprising dispersions of steroid compounds in solid matrices of various types.

Composition 1. Wax Matrix	
White Wax, USP	10.0 g.
Megestrol Acetate, microfine	2.0 g.

The white wax is melted and the megestrol acetate is added with mixing. The molten mixture is then poured into the cavity of a device such as is illustrated in FIG. 1, and rapidly solidified by cooling to ensure uniform drug dispersion. The amount of megestrol acetate employed in Composition 1 may be varied, and the white wax may be substituted by cholesterol.

Composition 2. Silicone Rubber Matrix	
Silicone rubber elastomer (viscosity 35000–70000 cps.; sp. gr. (25°C) 1.13 ± 0.03)	10.0 g.
Megestrol Acetate, microfine	0.1 g.
Stannous octanoate catalyst (tin content 26%)	0.05 g.

The megestrol acetate is suspended in the elastomer with thorough mixing, several drops of stannous octanoate catalyst are added. The mixture is promptly filled into the cavities of devices of FIG. 1 and allowed to polymerize.

The following compositions are for thixotropic gels which form solid matrices for dispensing a diffusible solid from a device of the present invention. These are employed while fluid to fill the cavity of the device and then allowed to set-up to form a firm matrix.

Composition 3. Carboxypolymethylene Gel	
Active ingredient, microfine	2 to 10%
Sorbital solution, USP	40%
Dioctyl sodium sulfosuccinate	0.02%
Carboxypolymethylene	1.2%
Thiomerosol	0.004%
Sodium hydroxide, q.s.	pH 6.5
Water qs	100.0 ml.
Composition 4. Carboxymethylcellulose Gel	
Active ingredient, microfine	2 to 10%
Carboxymethylcellulose	3.5%
Glycerin	8.0%
Polysorbate 80 USP	0.1%
Methyl parabens	0.2%
Water qs	100.0 ml.
Composition 5. Polyethylene Glycol Gel	
Active ingredient, microfine	2 to 10%
Polyethylene glycol 4000	10%
Methylcellulose USP, 4000 cps	0.3%
Water qs	100.0 ml.

What is claimed is:

1. A device for the automatic release at a substantially constant predetermined rate of a diffusible solid into a fluid medium into which said solid has a propensity to diffuse when said device is immersed in said medium which comprises,

a container which is insoluble in said medium, impermeable thereto, and impermeable to said solid,

said container having a slot in the surface thereof defining an elongated opening of uniform length and width having two ends and two sides with the narrower dimension at the ends and the longer dimension at the sides, said slot communicating in its entirety with

an internal cavity within said container said cavity being defined by an accuate wall and

a pair of parallel congruent planar end walls arranged at right angles to said slot and adjacent the ends thereof,

and a pair of inwardly extending congruent planar side walls adjacent the opposite sides of said slot and in substantially divergent radial relation to said slot, and extending to said rear wall.

a means for diffusing said solid from within said cavity into the immersing medium including a diffusible solid housed within said cavity as a homogenous mass in bonded relation to the inner wall surface of the cavity and having a surface thereof facing and opposing said slot opening to expose the diffusable solid surface to said fluid medium when said device is immersed therein.

2. The device defined in claim **1** wherein the entire volume of the cavity is occupied by said solid.

3. The device defined in claim **1** wherein less than the entire volume of said cavity is occupied by said solid such that the rear wall of said cavity is entirely covered thereby and the surface thereof opposite said slot is of arcuate concave configuration defining a segment of a cylinder wall the axis of which lies within said slot.

4. The device of claim **1** wherein the side walls of said cavity are positioned with respect to one another at an angle in the range of from **30°** to **270°**.

5. The device of claim **1** wherein the rear wall of said cavity is of arcuate concave configuration defining a segment of a cylinder wall the axis of which lies within said slot.

6. The device of claim **1** adapted for use in a gaseous medium and said solid possesses a vapor pressure such that sublimation thereof occurs under ambient conditions.

7. The device of claim **1** wherein said fluid medium is a liquid.

8. The device of claim **1** wherein said solid is biologically active and release thereof into said medium is for the purpose of exerting a biological effect in the medium.

9. The device of claim **8** wherein said solid is a drug substance and said medium is a biological liquid.

10. The device of claim **8** wherein said solid is a suspension or a dispersion of a particulate pure drug substance in an inert carrier solid wherein said carrier solid is substantially insoluble in said medium but permeable to diffusion of said drug substance.

11. The device of claim **1** wherein said device is sized and shaped for placement and retention within the uterine cavity of a mammal and said solid is a biologically active substance.

12. The device of claim **11** wherein said solid possesses hormonal activity.

13. The device of claim **11** wherein said container is a cylinder approximately 3.2 cm. in length and 0.24 cm. in diameter.

14. The device of claim **13** wherein said slot is arranged in an axial direction on the side of said cylinder, the width of said slot is from about 0.02 to about 0.06 cm., the angle formed by said side walls of said cavity is from about 30° to about 140°, and said solid has a solubility in said medium from about 1.7 mcg./ml. to about 570 mcg./ml.

15. The device of claim **1** wherein said container is a ring adapted for placement and retention within the vagina of a mammal, said solid is a biologically active substance, and said slot and cavity are positioned concentrically on said ring.

16. The device of claim **15** wherein said slot traverses the entire circumference of said ring.

17. The device of claim **15** having multiple concentrically positioned slots and cavities.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,851,648 Dated December 3, 1974

Inventor(s) Dana Brooke

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 9, line 33, delete "an accute" and replace it with -- a rear --; lines 44 and 45, correct "surface", first occurrence, to read -- surfaces --.

Column 10, lines 44-48, rewrite Claim 15 to read as follows:

15. A device for the automatic release at a substantially constant predetermined rate of a diffusible solid into a fluid medium into which said solid has a propensity to diffuse when said device is immersed in said medium which comprises

a ring-shaped container which is insoluble in said medium, impermeable thereto, and impermeable to said solid,

said container having a slot in the surface thereof defining an elongated opening of uniform width having two opposing sides concentrically positioned and traversing the longer dimension of said opening, said slot communicating in its entirety with an internal concentrically positioned cavity within said container said cavity being defined in cross-section by

a rear wall, and

a pair of inwardly extending side walls adjacent the opposing sides of said slot and in substantially divergent radial relation to said slot, and extending to said rear wall,

a means for diffusing said solid from within said cavity into the immersing medium including a diffusible solid substance housed within said cavity as a homogenous mass in bonded relation to the inner wall surfaces of the cavity and having a surface thereof facing and opposing said slot opening to expose the diffusable solid surface to said fluid medium when said device is immersed therein,

wherein said diffusible solid is a biologically active substance and said ring-shaped container is adapted for placement and retention within the vagina of a mammal.

Signed and Sealed this

fourteenth Day of *October 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks