

- [54] **DRUG DELIVERY DEVICE WITH SELF
ACTUATED MECHANISM FOR RETAINING
DEVICE IN SELECTED AREA**

- [75] Inventor: **Alan S. Michaels**, Atherton, Calif.
[73] Assignee: **Alza Corporation**, Palo Alto, Calif.
[22] Filed: **Dec. 27, 1972**
[21] Appl. No.: **318,798**

Related U.S. Application Data

- [63] Continuation of Ser. No. 300,673, Oct. 25, 1972,
abandoned.
- [52] U.S. Cl. 128/260, 128/2, 128/272
[51] Int. Cl. A61m 31/00
[58] Field of Search 128/1, 1.2, 260, 271, 272;
119/1

[56] **References Cited**

UNITED STATES PATENTS

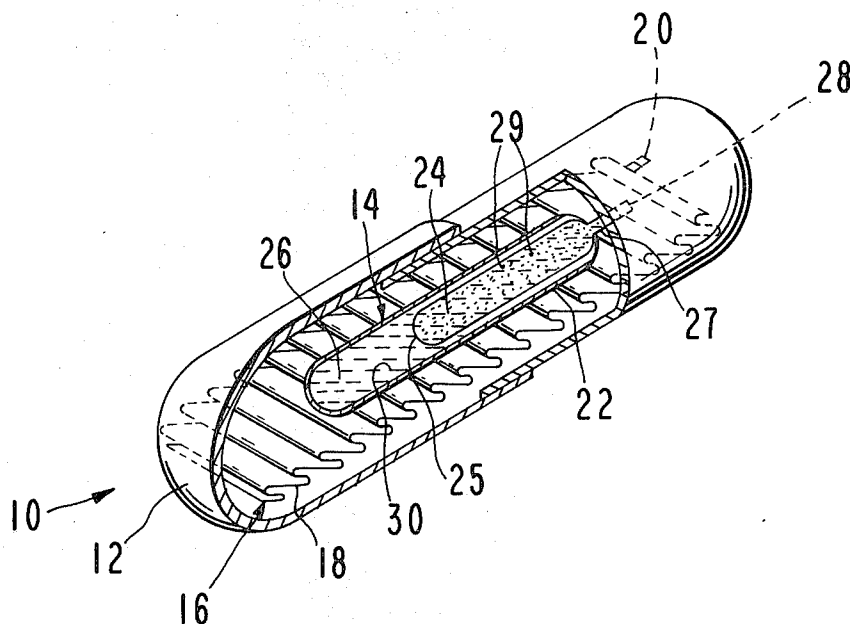
- | | | | |
|-----------|---------|-------------------|---------|
| 1,957,564 | 5/1934 | West..... | 128/272 |
| 3,485,235 | 12/1969 | Felson..... | 128/2 |
| 3,604,417 | 9/1971 | Stolzenberg | 128/260 |
| 3,701,351 | 10/1972 | Harvey..... | 128/260 |

Primary Examiner—Aldrich F. Medbery
Attorney, Agent, or Firm—Paul L. Sabatine et al.

[57] ABSTRACT

A device is disclosed for administering a drug at a controlled rate for a prolonged period of time to a drug receptor area to produce a nonsystemic or systemic physiological or pharmacological effect. The device is comprised of a hollow deformable member that is movable from a collapsed to an expanded position and returnable to a collapsed position after an extended period of time. A housing is attached to the deformable member and it is internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contains a drug and it has a discharge port for releasing the drug to the exterior of the device. The second chamber contains a means for generating pressure that is applied against the bladder. Drug is released from the first chamber through the discharge port by the bladder moving in response to pressure generated in the second chamber to increase its volume while simultaneously reducing the volume of the first chamber to release the drug at a controlled rate over a prolonged period of time. The device is initially optionally contained in a bioerodible container that erodes in the area to release the container.

8 Claims, 6 Drawing Figures



SHEET 1 OF 2

FIG. 1

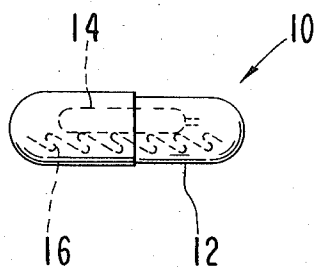


FIG. 2

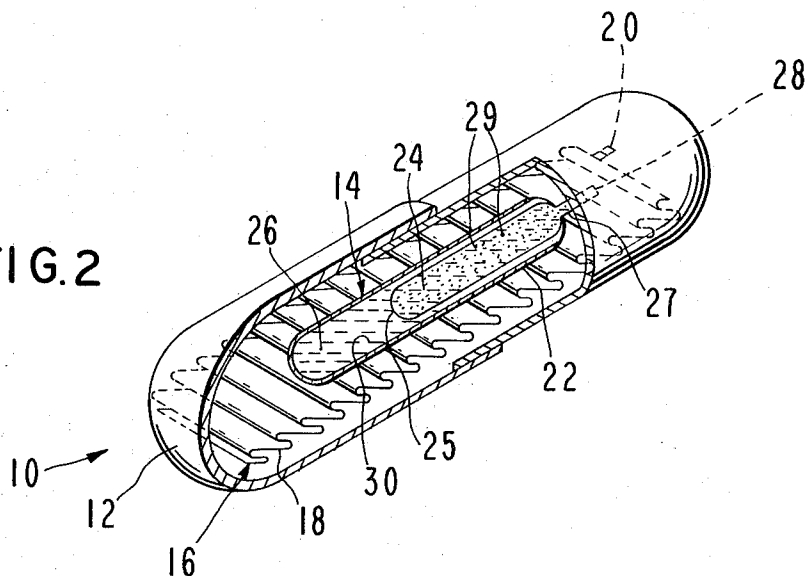


FIG. 3

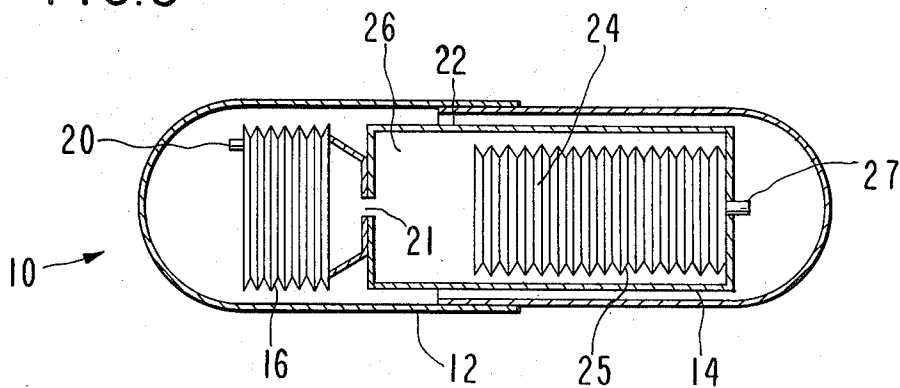


FIG. 4

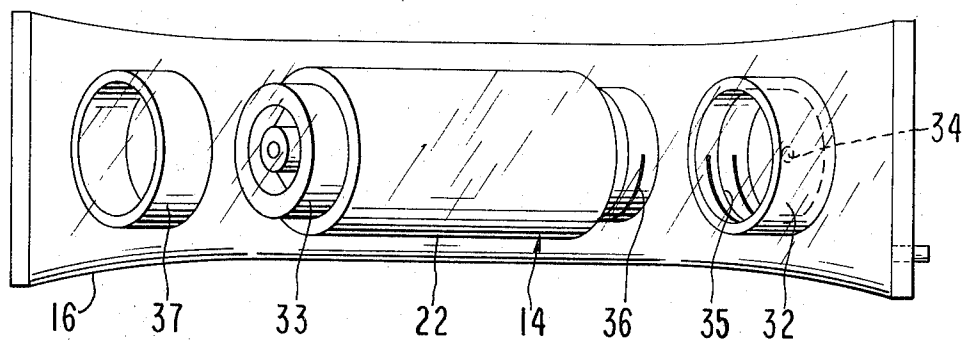


FIG. 5

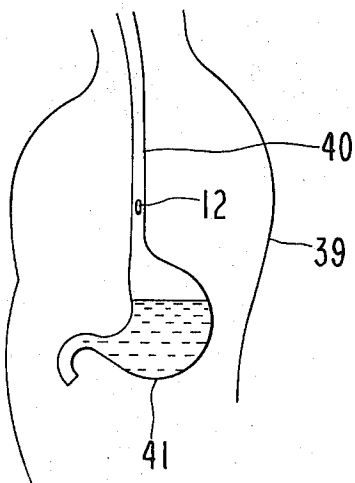
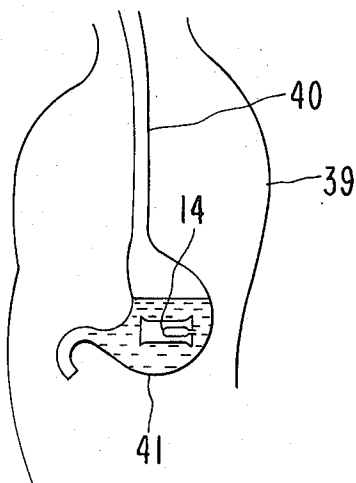


FIG. 6



DRUG DELIVERY DEVICE WITH SELF ACTUATED MECHANISM FOR RETAINING DEVICE IN SELECTED AREA

This invention is a continuation of application Ser. No. 300,673 filed on Oct. 25, 1972, now abandoned.

BACKGROUND OF THE INVENTION

It relates to a novel and useful drug delivery device for releasing drug in an environment of use, such as a biological drug receptor site, at a controlled rate for a prolonged period of time to produce a local or systemic physiological or pharmacological effect. The drug delivery device optionally is comprised of a bioerodible container housing a drug delivery device. The drug delivery device is secured to a deformable hollow member, which member is expandable from a collapsed state to an expanded state and collapsible to a collapsed state after an extended period of time. The device is comprised of a shell having a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contains a drug and a discharge control means for releasing the drug from the chamber to the exterior of the device. The second chamber contains a pressure generating source such as a gas in liquified form and having a vapor pressure greater than one atmosphere at the temperature of use, or it can be an osmotically effective solute phase which has an osmotic gradient in a fluid environment of use to allow a volume increase that generates pressure against the bladder. Drug is released from the first chamber through the discharge outlet by the bladder moving in response to pressure generated in the second chamber to increase its volume while simultaneously reducing the volume of the first chamber to release drug at a controlled rate over a prolonged period of time.

A critical need exists for a drug delivery device that can effectively administer a drug to a preselected environment, such as a body cavity or opening, for example the stomach, reliably at a controlled rate over a prolonged period of time. In many instances, such a rate of release of drug from a drug delivery device to the environment should have a preferred zero order time dependence, that is, the rate of drug release is independent of time. Different approaches have been tried by the prior art to obtain such a drug delivery device. However, the results obtained for these approaches have not led to their acceptance by the medical and veterinary arts for the management of health and disease. One approach, which has received attention for administering a drug to the gastrointestinal tract, is to mix a drug with a carrier material that is gradually broken down by the gastrointestinal fluids with the drug released as the carrier disintegrates. Numerous drug carriers have been used in such devices including waxes, oils, fats, soluble polymers, and the like. While some of these devices have provided for a delayed release of drug, the desired constant release rate for a prolonged period has not been achieved. One reason for this is as the carrier disintegrates the surface area of the dosage unit decreases, concomitantly exposing increasingly smaller quantities of the carrier to the surrounding fluids. This inherently results in a decline in the release rate over time.

Another approach for administering a drug to a body cavity, for example the gastrointestinal tract, has been to enclose the drug within a single capsule having a permeable wall through which the drug can pass, for example, by diffusion. An approach of this kind is set forth in U.S. Pat. No. 3,279,996. These devices, too, have inherent difficulties. For example, one difficulty associated with the prior art is that different devices having different drug release rates cannot readily be made because the only variable parameter for the device is the thickness of the material used to make the device. Additionally, these prior art devices have generally been based merely on the high permeability of a single material as the diffusion control wall for some important drug molecule without a consideration of release rate controlling properties over a large number of hours which can defeat the primary object of an acceptable drug delivery device.

Another method widely used to obtain a necessary and beneficial drug level in a drug recipient over a large number of hours comprises orally administering a number of pills or tablets at regular time intervals to achieve a dose frequency response relationship. However, this method has certain inherent limitations that tend to defeat its purpose. For example, the pills may be rapidly cleared by muscular movement from the environment of use, for example the gastrointestinal tract, before they are fully utilized, or there can be an excessive amount of fluid present in the environment that can unfavorably dilute the concentration of the drug and prevent the reaching of the desired drug level. Also, the administration of a number of pills at set times requires attention and frequently a particular administration is inadvertently overlooked which diminishes the results of this method. Thus, a graphic illustration of the drug's concentration in the blood during a dosage schedule for this method has the appearances of a series of peaks and valleys; and, often these valleys may fall below the drug concentration needed to achieve the desired effects.

One other approach used by the art to administer drugs to a drug receptor and obtain controlled release over a prolonged period is the coated slow release bead technique. In this technique, the dose of drug is divided into a group of pellets about one to two millimeters in diameter, and each group is coated with a material resistant to fluids present in the environment of use, such as gastric and/or intestinal fluids. To time control the release, each group is coated with an increased number of coats, that is, the first group one coat, the second group two coats and so forth. However, this technique, as with the dose frequency response relationship technique described above, has those certain inherent limitations that tend to diminish its purpose. Therefore, these types of coated slow release beads are not suitable for releasing drug at a controlled rate for a prolonged period of time.

SUMMARY OF THE INVENTION

Accordingly, it is an immediate object of this invention to provide a drug delivery device for the administration of locally active or systemically active drugs to produce a physiologic or pharmacologic effect which device essentially overcomes the aforesaid disadvantages associated with the prior art modes of administration devices.

Still another important object of the invention is to provide a drug delivery for releasing drug at a controlled rate for a prolonged period of time.

Still yet another object of this invention is to provide a reliable and easily use drug delivery device for continuously administering controlled quantities of drug to the environment of use, such as body cavities and body opening.

A further object of this invention is to provide a complete dosage regimen for administering a drug to a drug receptor site such as the stomach, vagina or uterus for a particular time period, the use of which requires intervention only for initiation of the regimen, and in some instances removal of the device.

Still a further object of the invention is to provide a drug delivery device suitable for continuously administering drug to a body cavity such as the gastro-intestinal tract and remaining therein until the desired dosage regimen is essentially complete before the device is eliminated from the cavity, that is from the gastro-intestinal tract.

Yet still a further object of the invention is to provide a drug delivery device that is self-contained and self-powered and will remain in a preselected area, such as in the stomach for an extended time while administering drug from the device through a drug flow control outlet in response to pressure produced in the drug delivery device.

In attaining the objects, features and advantages of this invention, a device is provided for the continuous dispensing of a drug in the environment of use, such as the stomach, by using a pressure differential as the driving force for dispensing the drug from the device. The device is comprised of a first chamber and second chamber with the chambers separated by a vapor and fluid substantially impermeable, flexible bladder. The first chamber contains at least one drug and a discharge passage for releasing drug to the exterior of the device. The second chamber is in one embodiment essentially impermeable to a fluid or vapor and it contains a fluid with a vapor pressure in excess of one atmosphere at the temperature of use. In another embodiment the second chamber is comprised of a wall having controlled permeability to an external fluid, such as water, and it contains a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against the fluid. Drug is discharged from the device by the bladder urging and exerting a pressure against the drug as the bladder responds to pressure applied against it. The pressure arises in the second chamber by either the vapor pressure in excess of one atmosphere or by fluid diffusing into the chamber to increase its volume and concurrently exert a force toward the bladder to urge it to eject drug from the device. The device is bonded to a deformable, hollow member that can either expand or collapse. Optionally, the device is housed in a bioerodible container that bioerodes to reduce the device in the environment of use.

Other objects, features and advantages of the invention will be apparent to those skilled in the art from the following detailed description of the invention, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but rather are set forth to illustrate various embodiments of the invention, the drawings are as follows:

FIG. 1 is a plane, top view of a drug delivery device of the invention optionally housed in a bioerodible container.

FIG. 2 is an enlarged perspective view illustrating a drug delivery device in a container with a section of the container removed, to show a device in detail.

FIG. 3 is an enlarged view illustrating another drug delivery device of the invention confined in a container with a section removed.

FIG. 4 is an exploded view of a drug delivery device affixed to a deformable member in expanded position. The device in this figure is illustrated without a bioerodible container.

FIG. 5 is a view diagrammatically illustrating a contained drug delivery device passing to the environment of use, that is, the device is seen descending in the esophagus.

FIG. 6 is a view diagrammatically illustrating a drug delivery device in an environment of use such as the stomach.

In the drawings and specification, like parts in related figures are identified by like numbers. The items appearing earlier in the specification and in the description of the drawings as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various drug delivery devices of the invention, and which examples are not to be construed as limiting, one general example of a novel drug delivery device is indicated in FIG. 1 by numeral 10. Drug delivery device 10 in this embodiment is illustrated in side perspective view and it is comprised of a bioerodible container 12 housing a device 14 affixed to a deformable hollow member 16. In FIG. 1 drug delivery device 10 is depicted in miniature size to simplify one operative embodiment of the invention. In this figure, the device is illustrated within a container; however, it is to be understood that the container is not critical to successfully practice the invention. An enlarged detailed illustration of FIG. 1 is set forth in FIG. 2.

Referring to FIG. 2, drug delivery device 10 is seen in a bioerodible container 12 with a section removed to illustrate a device 14 housed in container 12 and mounted onto a deformable collapsed hollow bladder 16. Container 12 is advantageously formed of two parts with one part designed to telescope into the other for easily housing device 14 in container 12. Bioerodible container 12 in one embodiment is made from commercially available materials such as gelatin preferably so it can move quickly and easily through body passages such as the alimentary canal and quickly disintegrates when it reaches a drug receptor site, such as the stomach, wherein it frees the device 14. Containers made of other bioerodible materials can also be used for initially containing and subsequently releasing the device in animal, human or avian cavities. Device 14 as intimately joined to a deformable hollow member 16 and it is made of naturally occurring or synthetic flexible, polymeric materials that lend themselves to changes in shape and size. Member 16 in FIG. 2 is in

the form of a completely sealed envelope which is shown in collapsed state. The envelope is sealed at its margins and folded in a number of staggered folds 18. Member 16 contains a fluid that readily changes most of its volume at the temperature of use to a gas to inflate member 16. Member 16 thus acts as a floating support for device 14 to keep it in a preselected environment. Member 16 is equipped with a plug 20 formed of an erodible material that erodes after a predetermined time to release gas from member 16, thereby deflating it to a collapsed state so it can pass from the environment. In other embodiments, flat bags, balloons, tubes, foldable bags and the like can also be used as 16 for the purpose of the invention.

Drug delivery device 14, as seen in FIG. 2, is an osmotically functioning device and it is comprised of a housing or shell 22 having an internal space and at least a portion of the housing permeable to external fluids, such as water, gastric juice and the like. Device 14 is comprised internally of a unitary chamber divided into a first chamber 24 and a second chamber 26. A pressure responsive movable bladder 25 separates the chambers and it substantially defines and forms the first chamber 24. Bladder 25 is formed of a material that is substantially impermeable to vapor and fluid, and its geometric shape used for the drug delivery device is any shape that forms a container for containing drug. In the embodiment illustrated, bladder 25 defines chamber 25 in a balloon like container 24 for housing drug 29. First chamber 24, which serves as a drug reservoir for containing drug 29 is manufactured with a discharge outlet 27 for releasing drug 29. Discharge outlet 27 is closed with an erodible plug 28 that quickly erodes after device 14 is freed from container 22 upon its entry into the environment of use, such as the stomach. Second chamber 26 is occupied by a solution of an osmotically effective solute 30 which exhibits an osmotic pressure gradient against an external fluid.

Housing 22 which in at least a part exhibits controlled permeability to fluids, such as water, gastric fluids or the like, is made of a fluid permeable membrane adhesively secured, lined, laminated or cast in place on housing or shell 22. In another embodiment, all of shell 22 can be made of a fluid permeable membrane. In device 14 of FIG. 2, the fluid permeable membrane is cellulose acetate that is permeable to fluids but relatively impermeable to salts, thus permitting fluids to enter chamber 26 in an effort to reach osmotic equilibrium. Other materials such as those used for reverse osmosis processes, typically anisotropic membranes that are permeable to fluids but relatively impermeable to solute can optionally be used for the purpose of this invention.

In operation, device 14 is administered in one application into the stomach and after it is freed from container 12 and deformable member 16 inflates in the stomach, fluids, which will be absorbed from the body tissues or stomach, will diffuse through the reverse osmosis membrane of shell 22 and mix with solute 30 in an effort to establish osmotic equilibrium. As fluid enters chamber 26, the volume of the solution contained therein is increased and pressure is exerted against movable bladder 25 which urges drug 29 in chamber 24 through discharge outlet 27 at a controlled and constant rate into the external environment.

In FIG. 3 another embodiment of the invention is illustrated comprised of an assembled drug delivery device 10 consisting of an optionally used swallowable bi-

erodible container 12 made of two telescopically associated non-toxic envelopes having an interior cavity housing device 14. Container 12 is of standard pharmaceutical or veterinary design and it has a size and shape for swallowing and for passage by humans, farm animals such as cows, steers, pigs and the like, household pets such as dogs and sport animals such as horses to their stomach by normal peristalsis. In the stomach container 12, which is made from gelatin or the like pharmaceutically acceptable materials, quickly and easily disintegrates to release device 14 for discharging a medicament, not shown, into the stomach.

Device 14 of FIG. 3 is a vapor pressure activated device and it is comprised of a shell 22 with an internal space defining a first chamber 24 and a second chamber 26. Shell 22, in this embodiment, is made from a material essentially impermeable to fluids and gases, and it has a deformable hollow member 16 fixed to one end of said shell 22. Deformable bladder member 16 is optionally integrally formed, cemented or sealed to shell 22 and as shown it is a collapsible bag folded or having a plurality of bellows like folds made from a flexible or resilient material to allow it to freely expand and return to a collapsed state. Member 16 is also manufactured with both a bioerodible plug 20 that erodes after a period of time and with a passageway 21 for communicating with chamber 26. Chamber 24 is a means for storage of a drug, that is a drug reservoir, and delivery of it, and it is a movable bladder 25 preferably a bellows like foldable bag secured to a part of shell 22. Movable bladder 25 is essentially impermeable to fluids and gases and a flow control means 28 made of a porous inert material, a calibrated aperture or the like vents chamber 24 through shell 22 to the exterior of the device. The flow control means acts to release drug at a metered rate, for example, according to the Hagen-Poiseuille equation, at a constant rate over a period of time, despite its decreasing volume during the discharge of the drug. Chamber 26 is a pressure generating chamber and it contains a gas stored in liquified form for producing a vapor pressure in excess of one atmosphere at the temperature of use, that is, for example, the temperature of the stomach, to cause member 16 to inflate to a predetermined size and shape. The dimensions of member 16 in the inflated state will of course be different for animals but it should be large enough to retain the device in the stomach. It is slightly larger than the diameter of the pyloric canal which is about 1 cm to 4 cm, usually 2 cm in humans, until completion of the prescribed therapeutic regimen. Vapor pressures arising in chamber 26 also exert their pressure against bladder 25 causing it to fold, collapse and urge drug 29 (not seen in FIG. 3) through flow control means 27 to the exterior of the device at a controlled rate for a prolonged period of time. At the end of the prescribed therapeutic regimen, bioerodible plug 20 erodes to vent chamber 26 into the stomach causing it to collapse to a size smaller than the pyloric canal. Device 14 then passes through the alimentary tract and out of the body.

FIG. 4 graphically represents an exploded view of a device of the invention as seen from a top view. In FIG. 4 a drug delivery device 14 is seen mounted on top of an inflated, support member 16. Member 16 is a long balloon, a balloon of pillow shape or the like. It serves as a floating dock for drug delivery device 14 in the environment of use. Device 14 is illustrated in exploded

view and the features of its housing, for one embodiment of the invention, are illustrated herein. Device 14 housing is comprised of a head 32 having a flow control opening 34 and internal threader 35 which threads onto external threads 36 of shell 22. Shell 22 houses an osmotically operated drug delivery system of the type seen in FIG. 2, and it has a fluid admitting head 33 and a holding member 37 to help retain member 33 in shell 22.

FIG. 5 and FIG. 6 diagrammatically illustrate the use of the device of the invention. In FIG. 5 there is seen the outline of a human 39 with a container 12 moving through the esophagus 40 and on into the stomach 41. In FIG. 6 the device 14 is seen in the stomach 41 administering a drug.

DETAILS OF THE DISCLOSURE

Drug delivery device 14 of this invention can be made into assorted sizes and shapes with these dimensions adapted for administering a drug to a particular animal and to the ease of manufacture. The shape of the device is usually tubular but other shapes such as cylindrical, oblong, oblate, prolate, spherical and the like can be made. The device is usually fabricated for oral administration into body openings or cavities, such as the stomach, and the size of the deformable hollow member 16 of the device in the inflated state will be slightly larger than the diameter of the opening or exit of the body cavity, such as the pyloric canal at the stomach's exit to let the device stay in the stomach during the period of drug release and on collapse of member 16 let it pass therefrom. The dimensions of various animal openings or cavities are recorded in standard anatomy textbooks. For example, for humans to retain the device in the stomach the device will be larger than the pyloric canal, that is, the inflated member will be about 3 cm in diameter to about 10 cm in length, with a usual diameter range of 2 cm by 4 cm. Devices of various sizes, such as 2 cm by 5 cm, 3.14 cm by 5 cm, 4 cm by 4 cm, and the like are also within the mode and manner of the invention.

Shell 22 of the device defining chamber 24 and 26 and confining the solute and gas in liquefied form can be flexible, semi-flexible or rigid or modifications thereof. Shell 22 is essentially impermeable to the gas in liquefied form and to solute but when the device is an osmotic actuated device it has at least one area permeable to fluids. The shell can be made from a wide variety of commercially available materials such as aluminum, teflon, poly(ethylene), laminates of poly(propylene), poly(methylmethacrylate), poly(formaldehyde), nylon, laminates of poly(styrene), metal foils such as aluminum foil, tin foils, poly(vinylidene chloride), copolymers of vinylidene chloride and vinyl chloride, or acrylonitrile, coated tin foil and the like. In an economical aspect, the devices of this invention are made of materials that lend themselves to single use devices and as such they are made from relatively inexpensive materials. The thickness of the shell can vary over a wide range, usually from 0.2 mils to 25 mils, generally in the range of 0.5 mils to 10 mils and the like.

Pressure responsive bladder 25 positioned in shell 22 defining the chambers and used to urge drug from the device is flexible, collapsable, essentially impermeable to vapors and fluids and the like, and it has a size and shape corresponding to the volume of drug employed. The bladder is made from naturally occurring or syn-

thetic materials and it is about 0.2 mils to 100 mils thick, or more, usually 0.4 to 20 mils and the like. The bladder can be made of a single material, a combination of materials in laminated form, elastomeric materials bonded on foils and the like. Illustrative materials include silicones, poly(urethanes), poly(acrylonitriles), poly(ethylenes), poly(propylenes), poly(vinylidene chlorides), copolymers of vinylidene chloride and vinyl chloride or polyethylene terephthalate, poly(vinylidene fluorides), acrylic elastomers, ethylene propylene terpolymers, laminates such as poly(ethylene)-poly(vinylidene chloride), nylon-poly(vinylidene chloride), poly(ethylene)-poly(vinylidene chloride)-poly(ethylene), poly(ethylene)-poly(vinyl alcohol)-poly(vinylidene)chloride, metal foils such as thin tin foil, thin aluminum foil, plastic coated foils such as poly(ethylene) on thin tin foil, poly(vinylidene chloride) on thin stainless steel foil and the like.

Member 16 is generally made from naturally occurring or synthetic materials that readily lend themselves to reversible change in size and shape. In one embodiment, when an erodible plug is used to deflate an inflated member, the material is an elastomeric polymer that is essentially impermeable to gases and fluids. In another embodiment, the material can be permeable to gases to let a gas diffuse through the material to deflate the member. The material is usually 0.2 to 100 mils thick and it can be natural rubber, silicone, poly(urethane), poly(acrylonitrile), poly(ethylene), copolymers of vinylidene chloride and vinyl chloride, or acrylonitrile, poly(ethylene terephthalate), acrylic elastomers, laminates such as poly(ethylene)-poly(vinylidene chloride), and the like.

The portion of shell 22 that has permeability to fluids, for example, stomach juice, water or the like include a variety of materials permeable or semi-permeable to solvent but not to solute are suitable for construction of the osmotic power device. Typical membranes include the membranes known to act as osmosis and reverse osmosis membranes, such as unplasticized cellulose acetate, plasticized cellulose acetate, reinforced cellulose acetate, cellulose diacetate, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate propionate, cellulose acetate p-toluene sulfonate, triacetate of locust gum bean, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylized ethylenevinylacetate, cellulose acetate butyrate having a viscosity of from about 10 seconds to about 50 seconds, cellulose acetate butyrate containing about 17 percent of combined butyryl and about 29.5 percent acetyl and the like. Generally membranes having a permeability of 0.01 to 5 cc/cm²/hour/or day/or higher at atmospheric pressure against a saturated salt solution to a changing concentration solution of the temperature of use are within the spirit of the invention.

Representative of solutes suitable for housing in chamber 26 of an osmotically powered device include solutes, usually those soluble in aqueous type fluids, acidic fluids, uterine fluids, vaginal fluids, and the like. Various osmotically effective solutes include organic

and inorganic compounds such as magnesium sulphate, magnesium chloride, sodium chloride, potassium sulphate, sodium carbonate, sodium sulphite, calcium bicarbonate, potassium acid phosphate, calcium lactate, magnesium succinate and the like. The solid, present initially in excess, can be in any suitable physical form such as particles, crystals, pellets and the like.

Exemplary materials suitable for exerting a vapor pressure against pressure responsive bladder 25 when device 14 functions as a constant rate vapor pressure powered device are inorganic and organic compounds whose vapor is in equilibrium with its solid or liquid phase or a mixture of phases to exert a constant pressure at a given temperature regardless of volume. Representative of compounds are those that are liquids at ambient temperatures, usually 20° to 25° C or less, and have a boiling point, BP, above this temperature to exert a vapor pressure greater than one atmosphere at physiological temperatures. Exemplary materials useful for exerting a vapor pressure and also useful for inflating deformable hollow member 16 are halogenated hydrocarbons, fluorochlorinated lower saturated aliphatic hydrocarbons, halogenated unsaturated hydrocarbons, halogenated lower alkanes of 1 to 4 carbon atoms and the like, such as diethyl ether BP 34.6° C, methyl formate BP 31.5° C, methyl-n-propyl ether BP 39.1° C, methyl-isopropyl ether BP 32° C, tetramethyl silane BP 26.5° C, perfluoropentane isomers BP 31.0° C, n-pentane 36.0° C, iso-pentane 27.9° C, mixtures thereof, and the like. Usually, the amount of gas stored in the liquefied phase in the deformable hollow member 16 or in chamber 26 will be about 0.2 cc to 10 cc or higher, depending on the size of the device and the animal, generally 1 to 5 cc, and the volume of the vapor phase will be sufficient to inflate member 16 to about 20 to 80 percent of the volume of the chamber, or higher.

Materials suitable for use as bioerodible plug 20 are those materials that are commercially available and that bioerode in the environment of use, for example the stomach, at a predetermined given time. The materials are those that erode by known processes, such as chemical degradation, acidic hydrolysis, enzymatic action, oxidation, reduction, dissolution, slow solubilization, and the like. The bioerosion rate for suitable materials can be determined by standard assay procedures consisting of placing a section of material in natural or artificial body fluid, such as gastric juices at normal body temperatures and observing the rate of erosion over a period of time. By prolonged period of time is meant, for the present purposes, 2 hours to 20 days, usually 8 hours to 5 days.

Representative materials for use of plug 20 comprise hydrophilic polymers of uncross-linked hydroxylalkyl acrylates and methacrylates, hydrolytically biodegradable poly(anhydride) polymers as described in U.S. Pat. Nos. 2,073,799; 2,668,162; and 2,676,945; and in *Introduction to Polymer Chemistry*, Stille, J. K., Chapter 6, 1962, published by Wiley Publishing Co., bioerodible polyesters as described in *Industrial and Engineering Chemistry*, Vol. 36, No. 3, pages 223 to 228, 1964; *Macromol. Chem.*, Vol. 75, pages 211 to 214, 1964; U.S. Pat. Nos. 2,703,316; 2,668,162; 3,297,033; and 2,676,945, cross-linked gelatin prepared with a cross-linking agent reactive with the hydroxyl, carboxyl or amino functional groups of the gelatin molecule as described in *J. Polymer Science*, Part A-1, Vol. 5, No. 1,

1967, *J. Polymer Science*, Vol 54, pages 321 to 325, 1961; *Advances in Protein Chemistry*, Vol. VI, Cross Linkage in Protein Chemistry, 1961, published by Academic Press, Inc. Other materials include proteins and hydrocollides of animal and plant origins such as modified collagen, elastin, keratin, fibrin, karaya, algin, pectin, carrageenin, chitin, heparin, locust bean gum and the like. Also, synthetic polymers such as poly(ethylene oxide), poly(vinylpyrrolidone), poly(ethyleneimine), poly(acrylic acid) copolymers of acrylamide and methacrylamide up to 40% by weight of N-methylene bisacrylamide or N,N-dimethylol urea, and the like.

The active drugs that can be administered with the delivery device of the invention, in accordance with their known use and dose, and combinations of these drugs, as described in *The Pharmacological Basis of Therapeutics*, 14th Edition, Goodman, L. S. and Gilman, A., 1970, The Macmillan Co.; *Physicians' Desk Reference*, 25th Edition, 1971, Medical Economics, Inc., and, *Remington's Pharmaceutical Sciences*, 14th Edition, 1970, Mack Publishing Co., include without limitation: for example, drugs acting on the central nervous system such as hypnotics and sedatives such as pentobarbital sodium, phenobarbital, secobarbital, thiopental, etc; hetero-cyclic hypnotics such as dioxopiperidines, and glaucomimetics; hypnotics and sedatives such as amides and ureas exemplified by diethylisovaleramide and α -bromoisovaleryl urea and the like; hypnotics and sedative alcohols such as carbomal, naphthoxyethanol, methylparaphenol and the like, and hypnotic and sedative urethans, disulfanes and the like; psychic energizers such as isocarboxazid, nialamide, phenelzine, imipramine, tranlylcypromine, pargylene and the like; tranquilizers such as chlorpromazine, promazine, fluphenazine reserpine, deserpidine, meprobamate, benzodiazepines such as chlordiazepoxide, and the like; anticonvulsants such as primidone, ethosoin, pheneturide, ethosuximide and the like; muscle relaxants and antiparkinson agents such as mephensin, methocarbmal, trihexylphenidyl, biperiden, levo-dopa, also known as L-dopa and L- α -3-4-dihydroxyphenylalanine, and the like; analgesics such as morphine, codeine, meperidine, nalorphine and the like; antipyretics and anti-inflammatory agents such as aspirin, salicylamide, sodium salicylamide and the like; local anesthetics such as procaine, lidocaine, naepaine, piperocaine, tetracaine, dibucaine and the like; antiparasitics and anti-ulcer agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine, prostaglandins such as PGE₁, PGE₂, PGE_{1a}, PGE_{2a}, PGA and the like; anti-microbials such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloramphenicol, sulfonamides and the like; anti-malarials such as 4-aminoquinolines, 8-aminoquinolines, chloroquine and pyrimethamine; hormonal agents such as prednisolone, cortisone, cortisol and triamcinolone; antihistamines such as chlorpheniramine; androgenic steroids, for example, methyltestosterone, fluoximesterone and the like; estrogenic steroids, for example 17 α -estradiol and ethinyl estradiol; progestational steroids, for example 17 α -hydroxyprogesterone acetate, 19-nor-progesterone, norethindrone and the like; sympathomimetic drugs such as epinephrine, amphetamine, ephedrine, norepinephrine and the like; cardiovascular drugs, for example, procainamide, amyl nitrate, nitroglycerin, diprydamole, sodium nitrate, manitol nitrate and the like; diuretics, for example, chloro-

thiazide, trichloromethiazide, flumethiazide and the like; antiparasitic agents such as bephenium hydroxynaphthoate and dichlorophen, dapson and the like; neoplastic agents such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine, procarbazine and the like; hypoglycemic drugs such as sulfonylureas such as tolbutamide, acetohexamide, tolazamide, and chlorpropamide, the biguanides and the like; nutritional agents such as vitamins, such as vitamin A, essential amino acids, essential fats and the like; and other physiologically or pharmacologically active agents. Also, the drugs can be present as the pharmacologically acceptable derivatives, such as ethers, esters, amides, acetals, etc. that lend themselves to passage into the circulatory system. These derivatives can be prepared by art known techniques and then used in the practice of the invention. Of course, the drug derivative should be such as to convert to the active drug within the body through action of body enzymes assisted transformations, pH, specific organ activities, and the like.

The above and other beneficial agents can be used per se or they are conveniently formulated into a pharmaceutical form by mixing with a non-toxic carrier. Carriers acceptable for the purpose of this invention are the art known carriers that do not adversely affect the active agent, the host, or the material comprising the delivery device. For example, the suitable pharmaceutical carriers include sterile water; saline; dextrose; dextrose in water or saline; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid glyceryl triester of a lower molecular weight fatty acid; lower alkanols; oils such as corn oil; peanut oil; sesame oil and the like, with emulsifiers such as mono- or di-glyceride of a fatty acid, or a phosphatide, for example, lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence of a suspending agent, for example, sodium carboxymethylcellulose; sodium alginate; poly(vinylpyrrolidone); and the like, alone or with suitable dispensing agents such as lecithin; polyoxyethylene stearate; and the like. The carrier may also contain adjuvants such as preserving, stabilizing, wetting, emulsifying, viscosity modifying agents, and the like.

The amount of active agent incorporated in the device varies depending on the size of the device for a selected animal, the particular agent, the desired effect, and the time span over which it is desired to have the agent released. Since devices of different sizes and shapes are intended, to provide complete dosage regimen, there is no critical upper limit on the amount of drug incorporated in the device. The lower limit will depend on the activity of the drug and the time span of its release from the device. In general, therefore, the amount of the drug incorporated in the device is non-limited and it is an amount equal to or larger than, the amount of drug that on release from the device is effective for bringing about the drug's physiological or pharmacological local or systemic effects. For example, the amount of drug present in the delivery device when the device is used for adult humans for a period of time of 4 to 6 days to achieve local or systemic effect is for various drugs, such as propantheline 120 to 300 mg in the device; for glutamic acid hydrochloride an amount in the device of 240 to 300 mg; for pargyline hydrochloride 50 to 100 mg; for erythritol tetranitrate 50 to 100 mg; mannitol hexanitrate 75 to 100 mg; ephedrine sul-

fate 400 to 600 mg; nylidrin hydrochloride 12 to 48 mg; bethanechol chloride 120 to 480 mg; phenolamine 100 to 400 mg; quanethidine 100 to 1,000 mg; methyl dopa 3 to 12 gms; atropine 100 mcg to 1,250 mcg; and the like.

The discharge outlet 27 suitable for the purpose of the invention includes flow resistive means for continuous administration of the drug in the body. The flow resistive elements are essentially self actuated, that is, no external intervention is needed to initiate the flow of drug. Numerous flow resistive means are commercially available, such as porous plugs, microporous membranes, capillaries, etched polymers, perforated polymers, and the like. The flow resistive means can be made from a variety of materials such as poly(ethylene), nylon, teflon, epoxies, poly(methyl methacrylate), metals, alloys, ceramics, sintered ceramics, stainless steel capillaries of 0.1 to 1 cm in length with a diameter of 20 microns, a stainless steel porous disk having a thickness of 0.1 cm, a diameter of 0.1 cm, a pore size of 0.1 micron, a porosity of 20 percent and tortuosity of 0.5, and the like. The rate of flow through the resistive means is governed by the Hagen-Poiseuille equation wherein $Q = \pi D^4 \Delta P / 128 \mu L$, where Q equals flow in ml/sec, D equals diameter in cm, μ equals viscosity in poise, ΔP equals pressure in dynes/cm², and L equals length of the means. The use of this equation allows the flow rate to be easily predicted and readily adjusted by changing the length and diameter parameters of the flow resistive means. Also, by altering the viscosity of the carrier the flow rate can easily be varied without altering the specifications of the flow resistive means. The viscosity of any carrier can easily be ascertained by employing standard viscometers, such as the Wells-Brookfield viscometer. The device of this invention can effectively meter from 0.001 ml/hour to 2 ml/hour, or more for various times such as 8 hours, a day, or longer. The viscosity of the carrier medium used to convey the drug can vary over a range of 1 to 10,000 centipoise at physiological temperature for administering a drug to a host.

A typical drug delivery device is fabricated according to the spirit of the invention as follows: first, a spherical collapsible balloon of approximately 4 cm in diameter is made from commercially available poly(ethylene terephthalate) by conventional vacuum forming and heat sealing process. Before the final heat seal is made, 0.25 cm³ of isopentane is metered into the balloon. Then, fabrication is continued by passing through the final heat seal a water poly(urethane) erodible seal of 3 mm in length and a poly(ethylene terephthalate)-monofilament to which is secured an osmotic delivery device. The device consists of a cylindrical poly(ethylene) drug reservoir bag open at one end which is filled with a drug formulation. In this device, 0.21 cm³ of a drug formulation consisting of 50 percent chlorpheniramine maleate and 50 percent polyethylene glycol were charged into the reservoir. This drug bag is then coated with 33 mg of potassium sulfate containing 2 percent ethyl cellulose. The just applied salt layer is then coated with 0.25 mm thick cellulose acetate having a degree of acetylation of 2.5, which then has a total surface area of 1.7 cm². At ambient temperature, 25° C, the collapsible balloon is easily folded around the osmotic delivery device and the whole assembly is placed within a number 000 gelatin capsule. Upon ingestion, the capsule dissolves, the poly(ethylene tere-

phthalate) balloon inflated as a consequence of vaporization of the isopentane. The drug polyethylene glycol formulation melts at physiological temperatures and it is pumped from the device as a consequence of fluid, gastric juice, permeating through the cellulose acetate membrane. The device delivers chlorophemiramine maleate at a rate of 0.84 mg/hour for five days. The water soluble poly(urethane) seal self-fails, that is, bioerodes, during the fourth to fifth day releasing the gas from the balloon allowing it to collapse. The spent device is then readily eliminated through the lower gastrointestinal tract.

Among the advantages of the device of the invention are the ease of construction by standard manufacturing techniques devices into units of different sizes, especially of a miniaturized size, also of shapes and forms that are suitable for delivering a drug internally to an animal or human. Another important advantage of the claimed delivery device is its ability to dispense at a controlled rate, a beneficial agent having a wide variety of chemical and physical properties and over a wide range of release rates. Still another important advantage of the invention resides in the device's ability to effectively control the rate of release of the drug from the device throughout the major portion of drug administration in a substantial zero order release rate. A further advantage of the device resides in the use of low cost substantially vapor and fluid impermeable materials for the power communicating element resulting in a unit suitable for disposal, after comparatively short periods of use, for example, a day or week, without undue economic hardship on the user, yet providing a continuous and controlled administration of drug without any external energy source. And, although the invention has been described in detail, it will be understood that certain changes and modifications can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. A drug delivery device for the controlled and continuous administration of a drug to an environment of use to produce a therapeutic effect comprising: a hollow expandable closed member having therein self-contained means for expanding the member and self-contained means for contracting the member after a given period of time of expansion, the member being affixed to drug delivering means for delivering a drug at a controlled rate over the given period of time, the delivering means comprising an outer housing defining an internal space including a first chamber and a second chamber, the first chamber containing drug and

having in communication therewith discharge means for releasing the drug to the environment of use, the second chamber containing means for generating a pressure, with means for separating the chambers and transmitting the pressure generated in the second chamber to the drug in the first chamber being interposed between the two chambers, the pressure thereby causing a therapeutically effective amount of drug to be released from the first chamber through the discharge means for the given period of time while the member is in an expanded state, thereafter the means for contracting causing the member to contract.

2. A drug delivery device for the controlled and continuous administration of drug according to claim 1 wherein the self-contained means for expanding the member comprises a liquid that vaporizes at physiological temperature to produce a gas which expands the hollow expandable closed member from a collapsed position to an expanded position.

3. A drug delivery device for the controlled and continuous administration of a drug according to claim 2 wherein the self-contained means for contracting the member comprises means for venting the interior of the member to the environment of use.

4. A drug delivery device for the controlled and continuous administration of drug according to claim 3 wherein the means for venting the interior of the member to the environment of use comprises a bioerodible plug.

5. A drug delivery device for the controlled and continuous administration of drug according to claim 3 wherein the means for venting comprises the hollow expandable closed member, the member being formed of a material that lets the gas slowly diffuse through the material to the environment of use.

6. A drug delivery device for the controlled and continuous administration of drug according to claim 2 wherein the hollow expandable member communicates with the second chamber, the means for generating a pressure in the second chamber comprises a means for producing a gas at physiological temperature, the gas expanding the member and also producing a pressure which is transmitted to the drug in the first chamber.

7. A drug delivery device for the controlled and continuous administration of drug according to claim 1 wherein the means for generating a pressure comprises means for generating an osmotic pressure.

8. A drug delivery device for the controlled and continuous administration of drug according to claim 1 additionally comprising an outer bioerodible container.

* * * * *