United States Patent [19]

Buckles et al.

[11] **3,817,248**

[45] **June 18, 1974**

[54] **SELF POWERED DEVICE FOR DELIVERING BENEFICIAL AGENT**

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[22] Filed: **Nov. 6, 1972**

[21] Appl. No.: **303,773**

[52] **U.S. Cl.**..... **128/260,** 128/214 F, 128/349 B, 128/DIG. 12

[51] **Int. Cl.**..... **A61m 25/00,** A61m 31/00

[58] **Field of Search**.... 128/214 F, 129, 260, 349 B, 128/DIG. 12, 184

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[57] **ABSTRACT**

A self powered device for the continuous and controlled delivery of an agent over a prolonged period of time to an agent receptor is disclosed. The device is comprised of a pressure distendable receptacle formed of an elastic material, with the receptacle communicating with a discharge port having a flow resistive agent metering means for releasing agent in fluid form. The receptacle has an entry port providing access to its interior with the port having a sealing means. The receptacle is dimensioned for insertion in its collapsed state into a receptor site and it is expandably responsive to an applied pressure induced by forced infusion of agent through the port after the receptacle is in the receptor. The infusion of agent establishes an internal stress in the elastic material with the material maintaining as a result of the stress a substantially constant internal pressure in the receptacle throughout the discharge of the agent from the receptacle. The receptacle is adapted for easy removal from the agent receptor after the administration of agent.

13 Claims, 6 Drawing Figures

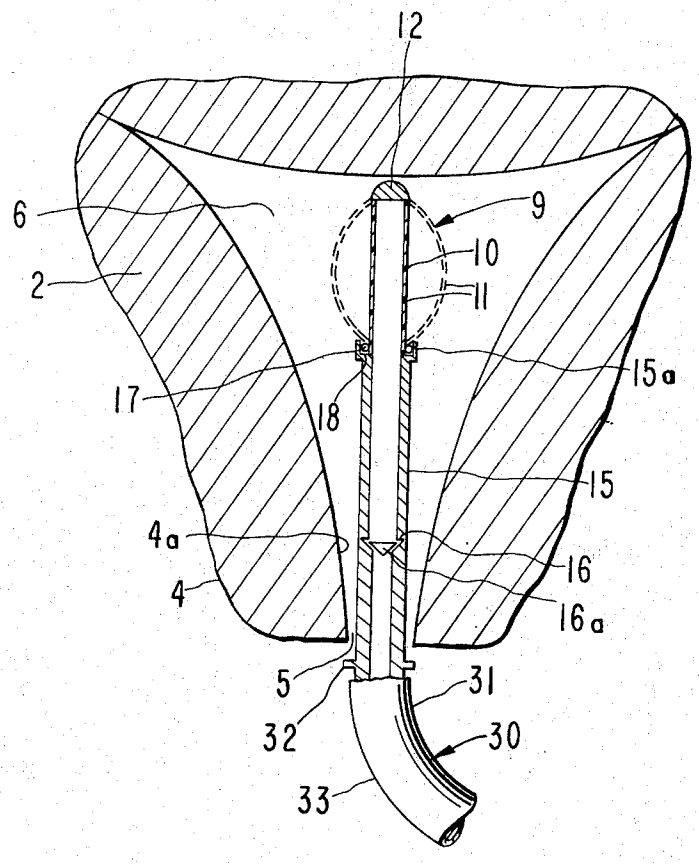


FIG. 1

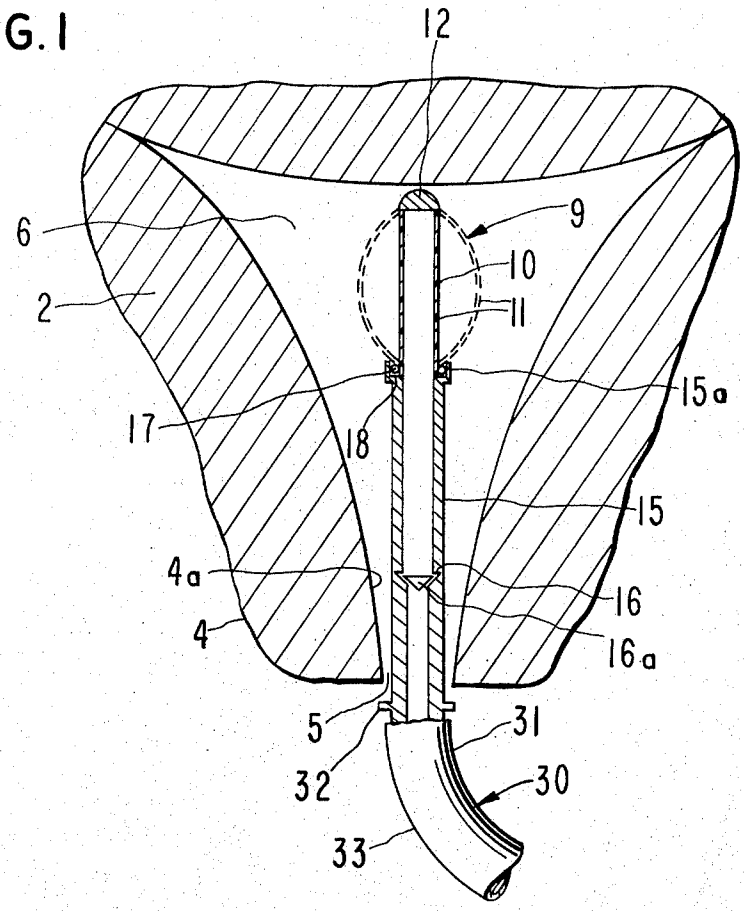


FIG. 4

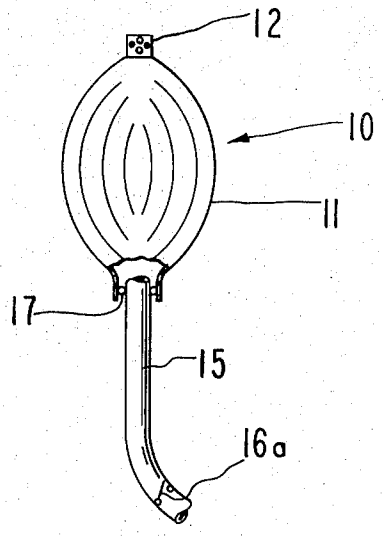


FIG. 2

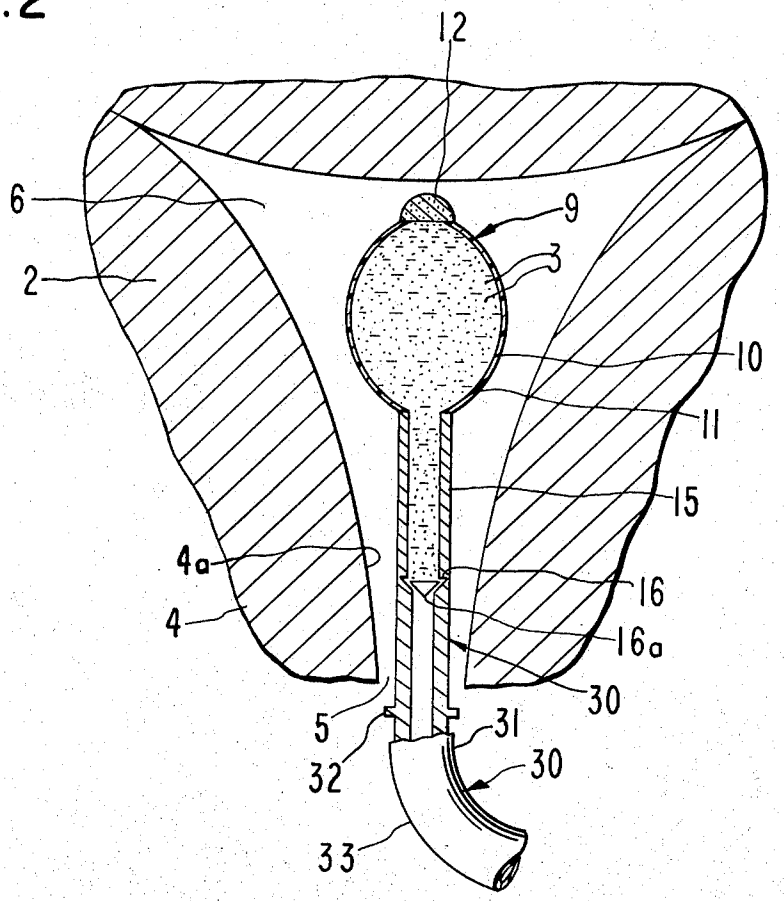


FIG. 3

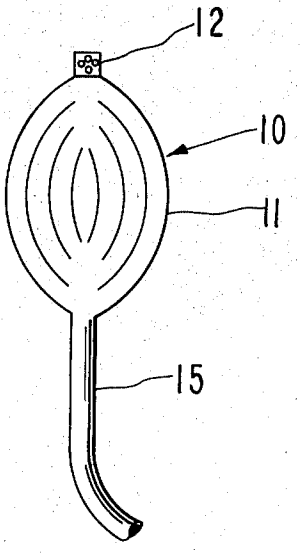


FIG. 5

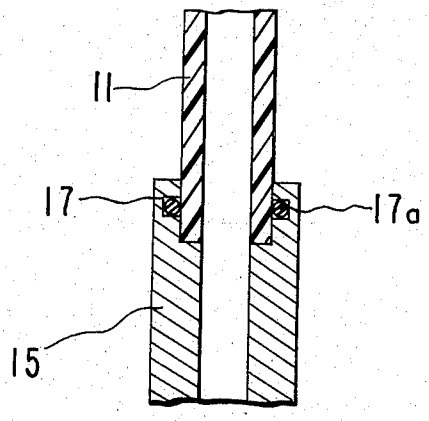
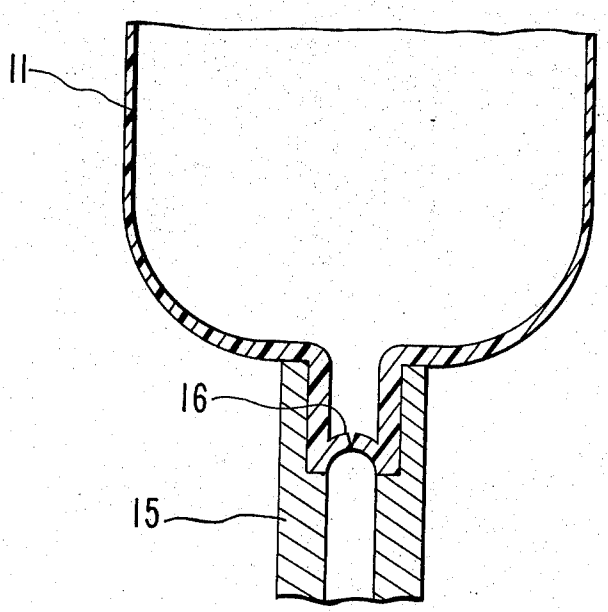


FIG. 6



SELF POWERED DEVICE FOR DELIVERING BENEFICIAL AGENT

BACKGROUND OF THE INVENTION

This invention relates to an agent delivery device, and more particularly to a self powered device for delivery of an agent which device operates without any external energy source and is capable of continuously dispensing an agent at a controlled rate over a prolonged period of time. The device uses energy stored in the materials employed to fabricate certain of its component parts as the motive force to dispense the agent. In a preferred aspect, the device is employed for internally administering a medicament to a drug receptor such as an animal, human or avian.

There is an increasing interest and expansion of activity in the art directed to the development of devices which can provide a continuous and sustained administration of an active agent to a system. One field of endeavor to which such devices have applicability pertains to therapeutic programs relating to the management of health and disease where it is desirable to use a delivery device to provide a slow release of a beneficial agent, such as a drug to a recipient at a controlled rate over a relatively prolonged period of time to achieve a desired physiologic or pharmacologic effect. Such prolonged and continuous medication gives results which are far superior to periodic or intermittent administration that may be dangerous because of the high concentration of medicament at the time of administration, or of no therapeutic value because of the low concentration of medicament between the periods of administration. Frequently, it is advantageous to implant or insert such devices within the recipient at or near the area to be treated in order to avoid systemic administration of the drug. Further, in many instances, such a rate of release of drug from the delivery device should have a zero order time dependence, that is, the rate of drug release is independent of time.

Different approaches have been tried by the art to obtain such devices. Among such devices are those which dispense compositions of matter at a uniform delivery rate under a positively applied pressure developed by the use of elastomeric materials, as disclosed, for example, by Bierman in U.S. Pat. No. 3,469,578. Devices of the type disclosed in the patent dispense their composition by utilizing a pressure induced by internal stresses stored in elastic materials used to fabricate its component elements. An advantage of these devices is that, since the dispensing is effected under a positively applied pressure, it is not necessary to immobilize the drug receptor. The device is used by securing it to the receptor by straps and the receptor is allowed complete mobility and freedom of movement with full assurance that the device will continuously release its contents due to the positive pressure involved in actual operation. Nothwithstanding these advantages, however, these prior art elastomeric pressure operated devices have inherent disadvantages in that the device must be secured to the external surface of the receptor in some manner which is often cumbersome and awkward to accomplish. In addition, such placement often restricts ambulatory motions and, unless the device is hidden by clothing or the like, it can present an unsightly condition causing embarrassment and inconvenience to the user. Then too the devices are made without a means for regulating the flow of drug from the receptacle to the receptor. Moreover, such prior art devices are not adapted for implantation or insertion within many areas of the anatomy, such as the bladder, vagina, subcutaneously, rectum, ear, uterus or the like, which can only be reached by prior passage through a restrictive orifice or by surgical intervention. Such internal placement of the device is advantageous in that these local areas can be treated directly, thereby avoiding systemic administration of the drug while concurrently obviating other problems created by external placement.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide a self powered delivery device using energy stored in the materials employed to fabricate certain of its component parts, as the motive force, which overcomes deficiencies of prior art devices of this type as indicated above.

It is another object of the present invention to provide a device or an elastomeric pump for the continuous and controlled administration of a drug over a prolonged period of time to a drug receptor, such as body openings, cavities, subdermal and the like which device is adapted to be inserted or implanted in such receptor sites, including those areas of the anatomy readily accessible only via restrictive orifices, or via surgical intervention.

A further object of the present invention is to provide a self powered delivery device which does not require the use of auxiliary means to secure the device to the user.

Still another object of this invention is to provide a self powered delivery device which is suitable to dispense, for prolonged periods of time, beneficial active agents having a wide variety of chemical and physical properties and over a wide range of release rates.

Yet still another object of the invention is to make available to the medical and veterinary arts a device for releasing drug to a biological site which device has a flow resistant means for regulating the amount of drug released from the device per unit of time.

Still yet another immediate object of the invention is to provide a dispensing device for the administration of locally acting or systemically acting drugs to produce a physiologic or pharmacologic effect which device can dispense the drug at a rate produced by the use of a flow resistive means and a continuous, dischargeable, pressure set receptacle.

In attaining these objects, features and advantages, the invention resides in a self powered device for the continuous and controlled administration of a drug over a prolonged period of time to a drug receptor including body cavities, passages, subdermal areas, external areas such as nasal passages, the ear and the like comprising: a pressure distendable receptacle formed of an elastomeric material, the receptacle communicating with a discharge port having a flow resistive drug metering means therein, and having an entry port providing access to the interior thereof from an extracorporeal position, the entry port also having a means for sealing, the receptacle being dimensioned for insertion in its collapsed state into or onto a drug receiving animal including humans and avians and being characterized by being expandably responsive to an applied pressure induced by forced infusion of drug in the entry

port after insertion of the receptacle in the animal to establish an internal stress in the material, the receptacle when distended being of a size and configuration so as to promote retention thereof in the receptor, with the material maintaining, as a result of the stress exerted, a substantially constant internal pressure in the receptacle throughout a range of discharge of the drug, the receptacle being adapted for easy removal from the internal cavity after discharge of drug from the receptacle.

Other objects, features and advantages of this invention will become more apparent from the following description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

A preferred embodiment of this invention relates to the use of the device of the invention for administration of a drug to mammals, specifically to the uterus of an adult female. This embodiment has been arbitrarily chosen for ease of presentation in order to best explain the principle of the invention and its application so as to enable others skilled in the art to best utilize the invention. It will be appreciated that it is not intended to limit the invention to the specific embodiment disclosed.

FIG. **1** is a diagrammatic frontal view of the female uterus illustrating the first stage of installing the drug delivery device of this invention.

FIG. **2** is a diagrammatic frontal view of the female uterus region, illustrating the delivery device of this invention completely inserted, filled with drug and in position within the uterus.

FIG. **3** is an expanded view of the device of FIG. **1** made with the parts acting in combination.

FIG. **4** is a sectional view of another embodiment of the novel product delivery device of this invention.

FIG. **5** is a view of part of the structure of a device of the invention illustrating two components of a device united through an O-ring.

FIG. **6** is a view of part of the structure of a device of the invention illustrating a self closing valve integrally formed in the receptacle.

Corresponding reference characters in the drawings are indicated by responding numbers throughout several drawings.

DETAILED DESCRIPTION OF THE INVENTION

Referring to devices of the invention, particularly to FIGS. **1** and **2**, the uterus **2** of an adult human female is schematically shown comprised of the uterus having a cavity **6** termed the fundus, which is a distendable muscular region having a volume of between 10 and 20 milliliters. At the entrance of the uterus there is located the cervix 4 which can be described as a short canal **4***a*, 3 to 6 millimeters in diameter, and between 2 and 4 centimeters long. The cervical os **5** is located at the entrance to the cervix and communicates with the vagina (not shown). The distance from the external cervical os **5** to the top of the fundus is from about 4 to 6 centimeters. Other details of the structure of the uterine area are not concerned with the invention and a detailed description is omitted in the interest of brevity.

The self powered delivery device **9**, as illustrated in its preferred form in FIGS. **1** and **2**, can be viewed as a single unit comprising a receptacle assembly **10** and catheter **15** joined together in functional relationship by a male-female couple at **15***a*, shown in one embodiment in FIG. **5** in detail, for the effective assembly of device **9** for administration of drug. Receptacle assembly **10** comprises an elonged container **11**, the walls of which are formed of a highly elastic material which is inert when placed in the body and not subject to deterioration by the action of body fluids. Flow resistive means **12** is secured by a discharge port positioned in the distal end of container **11**. The other or proximal end of the container **11** is joined with catheter **15** by placement thereover and securing therewith by means of an adhesive. An optionally seated O-ring **17** seen in FIG. **1** is tightly positioned about the end of container **11** in recess groove **18** also seen in FIG. 1 molded into the catheter body **15** as an aid in maintaining a seal and to assure retention of container **11** about catheter **15**. If desired, optionally seated O-ring **17** can be omitted, with sealing and retention being accomplished with adhesive, solvent sealed, heat sealed, or by any fluid tight assembly. In order that container **11** comfortably be able to pass through cervix **4**, the overall dimensions thereof, it its collapsed state, are quite small. Preferably, the overall length of container **11** for uterine use is approximately 5 to 40 millimeters, or the like with the diameter in the collapsed state being in the range of 1 to 10 millimeters. The diameter in the collapsed state corresponds to the diameter of the cervical os for easy insertion into the uterus. It will be appreciated that the dimensions noted above may be varied in accordance with different uteri and other body cavities.

Although container **11** is susceptible of embodiment in many different forms other than that illustrated, and can assume any shape when expanded such as elliptical, spherical, tapered, barrel, tubular, arcuate and the like, with the proviso that such shape be adapted, when filled with drug and inflated, to comfortably fit in the body cavity; for placement in the uterus, cylindrical configuration is presently preferred. The degree to which the container expands will be determined partly by the amount of drug injected therein after insertion in uterus **2** and its pressure-volume characteristics. Preferably, the container when expanded, as suggested by the broken lines in the drawings in FIG. **1** and seen in FIG. **2** in a charged state, should not occupy a volume which is greater than 70 percent of the volume of uterine cavity **2** when filled with drug **3** as in FIG. **2**, although this is not critical to the practice of the invention.

The material employed to fabricate container **11** must be elastomeric, at least in part, so as to be capable of storing the required energy in order to develop a positive pressure sufficient to discharge the contents from the interior of the container, and be substantially impermeable to drug **3** in FIG. **2** as contained therein. Further, the material must be such that it can be distended to a size and configuration which is greater than the size of ceruical os **5**, for reasons of retention of the device, as hereinafter described, and preferably, substantially conform to the shape of the uterine cavity. Still further, the material must be biologically inert, non-allergenic and chemically compatible with the medicament contained therein. The thickness can vary widely and is not a limitation on the invention. Typically, however, the container will have a thickness in the range of 0.5 to 50 mils, usually 1 to 20 mils thick, when deflated. The choice of materials will be chosen with reference to the compositions contained therein

and the required positive pressure necessary to operate the device, such as natural rubber as used for this invention. Containers suitable for the performance requirements of the invention are those materials that in normal air and atmospheric conditions at a temperature of 37° C have for a period of at least one month, generally 1 month to 1 year with the maximum desirable permanent radial set as 5 percent, and the maximum axial set of 5 percent, with the maximum change in steady state pumping rate under the defined parameters not exceeding 10 percent when a zero release is desired.

Catheter **15** comprises a hollow tube fabricated from non-elastomeric material, which is preferably rigid in nature, such as polyformaldehyde, nylon, polystyrene, poly(vinylchloride), high density polypropylene, segmented polyurethane, polyethylene, Kraton polymer, or the like, and it is formed at one end with retaining groove **16** adapted to receive a plug **16***a* which is held in position by a shoulder formed by groove **16.** It will be noted, by referring to the drawings, that when properly inserted in the uterus the catheter portion **15** of the device is positioned in the cervical canal **4***a* with catheter **15** and plug **16***a* in groove **16** extended out from the cervical os **5** into the vagina. In order that this be the case, the assembly unit is about 20 to 50 mm, the catheter **15** is about 20 to 50 cm and the catheter has a diameter of 1 to 10 mm. Plug **16***a* is comprised of a self-sealing rubber material and seals receptacle assembly **10** from the external environment. Another embodiment of a one-way value is seen in FIG. **6,** where it is an integral part of the elastomeric element **11,** as described later in the specification. However, plug **16***a* is capable of being penetrated by a needle of a syringe of the type conventionally employed in the medical field. Plug **16***a* acts to direct the flow of drug into balloon **11** and maintaining it there even though the unit can be drained with a syringe. Plug **16***a* is a uni-directional plug and it can be substituted with other sealing or closing means such as a one way valve or the like. A syringe, or the like, is utilized, after placement of this device in uterus **2,** to fill container **11** and catheter **15** with drug and maintain it under pressure of container **11,** with the container **11** expanding under such pressure as the drug is forced therein, as illustrated by the broken lines shown in FIGS. **1** and **2.** Upon withdrawal of the needle the drug is held under pressure in the assembly **10** of device **9** as seen in FIG. **2.**

It is essential to the successful practice of this invention that the flow resistive means **12** be self actuated, that is to say, requires no auxiliary means for initiation of flow, when the device is to be employed for continuous administration from within internal body passages. Numerous types of self actuated flow resistive elements for use as **12** are available, such as porous plugs, microporous membranes, compressed fabrics, capillary tubes, sintered plugs, pyrolyzed carbon, and the like. The flow resistive element can be fabricated from a wide diversity of materials, depending on the type, such as polyethylene, nylon, teflon, poly(vinylchloride), poly(methacrylate), epoxy resin, carbon, sintered metals or ceramics. Alternatively, the flow resistive means can be a small hole or orifice bored into the distal end of container **11** of predetermined calibrated size for releasing unit amount. Flow resistive element **12** can be inserted into container **11** by any convenient means which provides a non-leaking seal in fluid tight relation, for example, the means employed may be adhesive, mechanical, such as threading, heat sealing or, alternatively, by making flow resistive element **12** an integral member of the container structure.

In FIG. **3** there is seen an enlarged view of the drug release assembly **10** of device **9** of the invention. Assembly **10** is comprised of a balloon **11** that can move from a collapsed to inflated position suitably joined to a flow resistive means **12** and to a catheter **15.** Balloon **11** and catheter **15** can be integrally formed, as in FIG. **3,** or they can be formed in separate manufacturing operations and then joined into one assembly as in FIG. **4.** In FIG. **4** there is illustrated assembly **10** with a balloon **11** illustrated in the positions to which it can reversibly expand and collapse, a means **12** for controlling the flow of a drug from balloon **11** positioned at one end of the balloon **11** and at distant end an O-ring **17** for receiving catheter **15** in fluid tight relation for retaining positioning receptacle **11** to catheter **15.** Catheter **15** acts as a male member for insertion between O-rings **17** that function as a female couple within the terminal portion of receptacle **11.** A one way valve **16***a*, shown in hinged structure, is employed to fill container **11** by injecting drug through valve **16***a*, with container **11** expanding as the drug is forced therein. Typically, from 1 cc to 25 cc of drug more or less is injected into container. It is important to the successful practice of the invention that, prior to injecting the drug into the device, substantially all air be removed from the system. Air can be bled from the system by injecting an empty syringe through self-sealing valve or plug **16***a* to suck out the air. The syringe can then be removed, leaving the system evacuated and free of air. Alternatively, the device could be purged with liquid prior to insertion into the body cavity. The increase in volume of container **11,** suggested by the broken lines illustrated in FIGS. **1** and **2** and by circular type lines in **3** and **4** will serve to anchor the device within the uterine cavity. The critical aspect with regard to retaining the device in place during the drug administration period is the size of the limiting orifice, namely, the cervical os **5.**

FIG. **5** depicts in detail receptacle **11** catheter **15** couple, joined to operate as a unit device, as described for FIG. **1.** In FIG. **5** there is seen the terminal end of receptacle **11** received by catheter **15** and in intimate contact therewith. Catheter **15** is formed with a means **17** for housing a seal and retaining ring **17,** typically an O-ring or the like, for positioning, receiving and retaining member **11** within member **15.** Means **17** can be a groove, recess or the like, and it can be integrally formed or optionally machined in **15** by cutting or the like after catheter **15** is formed.

In FIG. **6** another embodiment of the invention is seen for positioning receptacle **11** within catheter **15.** In the figure, receptacle **11** terminates with an integrally formed one way valve **16,** that opens into receptacle **11** during filling of receptacle **11** and self closes by engaging its contactable, closable surfaces after the filling of **11.** Catheter **15** is also formed with a recessed area for receiving member **11.** The end of receptacle **11** comprised of valve **16** is fabricated for intimately engaging catheter **15** in nesting position for retaining **11** in leak tight manner within catheter **15.**

In practical use and delivery of a drug, the manner of operation of the delivery device of the invention makes use of the energy stored in the walls of container **11,** re-

sulting from the forced infusion of drug therein, to create an internal stress in the elastomeric wall material **11.** This stress in turn creates a positive pressure within container **11,** that is, a pressure greater than that of the environment external to the device, the uterus, to provide a uniform and controlled rate of flow of drug through the flow resistive element **12.** Positive pressures, for example pressures in excess of one atmosphere, such as from 100 to 400 mm of mercury, are suitable, although higher or lower values can be employed, depending on other flow parameters discussed hereinafter. As the drug is uniformly dispersed, container **11** will slowly deflate. When the agent or drug is fully discharged, container **11** will shrink back approximately to its original shape and volume, such that it can easily be removed from the uterine cavity, or any other cavity, using the proximal end of catheter **15** as an aid for this purpose.

In connection with the many uses of the present invention in the medical field, it is quite important that the flow rate in the discharge line be constant and at a low and steady pressure. An important feature of the present invention, accordingly, lies in the ability to realize a discharge having these characteristics, and these ends are effected through the development of the device which will discharge at a substantially constant rate over a continuous and prolonged period of time. The constant discharge flow rate of the agent is due to the internal stress in the elastic material of container **11** which provides the motive operating force and remains substantially constant throughout the discharge of drug from the device. Other delivery rates, for example pulsatile sinusoidal, can be achieved by suitable manipulations of the geometry and mechanical properties of the elastic materials.

Placement of the delivery device **9** within the uterine cavity **6** can be accomplished in various insertion methods. For example, receptacle **11** and catheter **15** can be integrally formed as in FIG. **3** for easy insertion by manually pushing it into uterine cavity **6.** Placement of delivery device **9** within uterine cavity **6** can also be assisted by the use of an inserting instrument represented generally in FIG. **1** by numeral **30.** Inserter **30** as shown is comprised of a sleeve or tube **31** which pushes against a protuberance which is integral to rigid catheter element **15.** That is, catheter **15** is formed with nobs or protuberances **32** and acts as a plunger for receiving receptacle **11** and insert **30.** Inserter **30** is easily removed while catheter **15,** now a plunger, is kept within the cavity during drug release. Tube **31** can also be catheter **15,** that is, this part of the drug delivery device is endowed with dual functionality for insertion of device **9** and delivery of drug **3.** Sleeve **31** can be straight or have a gradual turn or curved portion indicated as **33** which is slidably received by catheter **15** up to receiving means or plunger **32.** An alternative embodiment for insertion involves a separate tube of inside diameter larger than outside dimensions of said delivery system. It is used to enlarge the cervix prior to insertion of the delivery system and is subsequently removed after the drug is introduced to the device. Tube **31** may be made of a rigid material and it is perferably made of flexible plastic material such as one of the long-chain fluorinated polymers of ethylene such as tetrafluoroethylene, known under one trademark as Teflon polymer. In cross-section, not shown, the sleeve or tube **31** may be round or non-round such as being oblong. Plunger **15** with its protuberance **32** is made of a rigid or flexible material since it follows the contour of the tube **31.** The cross section of catheter **15** or plunger **32** generally corresponds to that of tube **31** or it is slightly larger for easily receiving tube **31.** It is preferred that the tube **31** have a diameter less than 2 to 10 millimeters for insertion to be accomplished painlessly through the cervical canal without dilation. In use, the instrument **30,** comprised of sleeve or tube **31,** which receives catheter **15** or plunger **32** are first separated. The body portion of the delivery device **9,** comprised of receptacle assembly **10,** are joined to catheter **15** and these are joined to catheter **15** or plunger at nobs **32** to tube **31.** The device is inserted therein from the end remote from curved portion **33.** With delivery device **9** so arranged in instrument **30,** the combined assembly is inserted through the vagina and partially into the uterine cavity **6** through the cervix **4.** Thereafter, plunger **32** is gradually pushed unto sleeve **31** in a two step insertion, or it can be previously assembled in a single step insertion. A the body of the container **11** enters the uterine cavity **6,** plunger **32,** which is longer than the sleeve or tube **31,** is continuously pushed inwardly thereof until the entire receptacle assembly **10** is accommodated within the uterine cavity **6** and the catheter portion **15** in the preferred embodiment is positioned with plug **17** extending outside ceruical os **5.** Thereafter, instrument **30** is slidably withdrawn from catheter **15** and from the body.

It will be appreciated that other equivalents of the device illustrated in FIGS. **1, 2, 3, 4, 5** and **6** will become apparent to those versed in the art in light of the present disclosure. For example, any appropriate body area, surface or cavity which is accessable by surgery or is positioned or surrounded by an orifice, that is, one having an opening which is dimensioned smaller than is the cavity itself, can be employed to house the delivery device while administering drug to the patient. Thus any area, such as subdermal, or cavity having an opening for ingress or egress, which is smaller than the size of the device when in its expanded condition, will serve to trap the device within such area or cavity for purposes of retention therein. Other areas and cavities in addition to the uterus included the bladder, vagina, anal spincter, trachea, nasal passages, ear, stomach, plumonary, subdermal, and the like. Of course, the dimensions and design of the device will have to be varied and adapted for use in the different situations. Exemplary of other modifications intended to be included within the spirit of the invention is to position the catheter so as to be extended from the discharge port as illustrated in FIG. **4.** Device **10** depicted in FIG. **4** is comprised of container **11** which can be filled to the various amounts as depicted by the paired unconnected elliptical lines as preferably formed of an elastomeric material having drug entry port **15** molded in one end therein and comprised of self sealing rubber, or formed separately for insertion into container **11.** Discharge port **12** formed of a flexible material such as small diameter polyethylene tubing leading therefrom or a porous body that rate controlls the passage of drug therethrough, advantageously also serving as the flow resistive means for the drug, is located on the other end of container **11.** A device of the design type illustrated in FIG. **4** is particularly suited for drug administration applications wherein it is desired to locate the device at a site remote from the desired point of application of

drug and where the device is accessible from an extracorporeal position such that it can be filled with drug with relative ease. This embodiment permits placement of the device in one environment, for example, an area of the anatomy having a cavity such as the vagina for purposes of retention of device **10** to release drug **3** to another area, the uterus, or it can be implanted under the skin for release of drug **3** that is absorbed and carried by the circulation to a distant body area for use. Thus, when the container is placed in the vagina, the transfer of drug **3** is effected from uniformly collapsable container **11,** located in the vagina, to the uterus by means of tube **12,** not seen in full length in FIG. **4,** that extends through the canal into the uterus. In operation, the device is placed in the vagina in a collapsed state, with delivery release tube **12** positioned in the uterus. Drug is injected by means of a medical syringe, not shown, through self sealing plug **16***a* to force drug into container **11.** When expanded, container **11** serves to anchor device **10** in the vagina and supply the required positive pressure by means of its elastomeric walls to discharge drug **3** at a constant rate through a polyethylene tube **12,** not shown in FIG. **4,** to the uterus. It will further be appreciated, in an alternative modification of the device illustrated in FIG. **4,** that for some applications it will be advantageous to locate the entry port and sealing means at **17** or a one way valve **16a** in catheter **15.**

The device of the invention is suitable for delivering agents, such as drugs which are fluids or which can be fluidized by use of mediums such as carriers, solvents, emulsifying agents or adjuvant materials and the like, and include drug compositions which are liquids, emulsions, gels, sols, suspensions, foams, pastes, and the like. Any of the drugs used to treat the body, both topical and systemic, can be incorporated as the drug in any of the devices of this invention. "Drug" is used herein in its broadest sense as including any composition or substance that will produce a local or systemic pharmacological or biological response.

The active agents, such as 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, 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.; heterocyclic hypnotics such as dioxopiperidines, and glutarimides; 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, tranylcypromine, pargylene and the like; tranquilizers such as chloropromazine; promazine, fluphenazine reserpine, deserpidine, meprobamate, benzodiazepines such as chlordiazepoxide, and the like; anticonvulsants such as primidone, diphenyldantoin, ethotoin, pheneturide, ethoxuximide and the like; muscle relaxants and antiparkinson agents such as mephenesin, methocarbomal, trihexylphenidyl, biperiden, levo-dopa, also known as L-dopa and L-β-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; antispasmodics and anti-ucler agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine, prostaglandins such as PGE_1, PGE_2, $PGE_{1\alpha}$, $PGE_{2\alpha}$, PGA and the like; anti-microbials such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloramphenicol, sulfonamides and the like; antimalarials such as 4-aminoquinolines, 8-aminoquinolines and pyrimethamine; hormonal agents such as prednisolone, cortisone, cortisol and triamcinolone; androgenic steroids, for example methyltestosterone, fluoximesterone and the like; estrogenic steroids, for example, 17β-estradiol and ethinyl estradiol; progestational steroids, for example 17α-hydroxyprogesterone acetate, 19-norprogesterone, norethindrone and the like; sympathomimetic drugs such as epinephrine, amphetamine, ephedrine, norepinephrine and the like; cardiovascular drugs, for example, procainamide, amyl nitrate, nitroglycerin, dipyridamole, sodium nitrate, mannitol nitrate and the like; diuretics, for example, chlorothiazide, flumethiazide and the like; antiparasitic agents such as bephenium hydroxynaphthoate and dichlorophen, dapsone and the like; neoplastic agents such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine, procarbazine and the like; hypoglycemic drugs such as insulins, protamine zinc insulin suspension, globin zinc insulin, isophane insulin suspension, and other art known extended insulin suspensions, sulfonylureas such as tolbutamide, acetohexamide, tolazamide, and chlorpropamide, the biguanides and the like; nutritional agents such as vitamins, 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 lead 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 the action of body enzymes assisted transformations, pH, specific organ activities, and the like.

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. 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, e.g., 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 drug incorporated in the device varies widely depending on the particular agent, the desired effect, and the time span over which it is desired

to have the agent released. Since a variety of devices in a variety of sizes and shapes are intended to provide complete dosage regimen for therapy for a variety of maladies, there is no critical upper or lower limit on the amount of drug incorporated in 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 a period of time to achieve local or systemic effect is for various drugs, such as 11-desmethoxyreserpine, about 5 to 40 mg in the device; for acetophenazine, an amount in the device of 100 to 200 mg; for methoxypromizine, about 600 to 750 mg in the device. Additionally, the amount of drug in the device can be 100 to 300 mg of thiopropazate for releasing 15 to 30 mg over a 24 hour period; 200 to 400 mg in the device of phenyltoloxamine for a release of 150 to 200 mg per day; 100 to 200 mg of papaverine in the device for a topical release of 30 to 75 mg over a 24 hour period; 2.5 g to 4.0 g of mephenoxalone for a release of 1.0 to 1.5 g per day; 15 to 25 mg of tranylcypromane for a release of 10 to 15 mg as the standard dose; 1 to 2 gm of trimethadione present in the device for a release of 10 to 15 mg as the standard dose; 1 to 2 gm of trimethadione present in the device for a release administration of 0.5 to 1.0 g per day; prostaglandins, or example PGE_1, PGE_2, PGA_1, $PGF_2\alpha$, in amounts of 0.5 mg to 10 mg for release of 1 ng to 100 ng, and the like; for progestogen, progesterone, an amount of 0.01 to 20 mg; and the like.

The rate of release of drug from the device can be readily determined by those skilled in the art by standard techniques, such as measuring the release of drug per unit time, or as disclosed in *Mechanics of Materials*, by Papov, E. P., published by Prentice Hall, 1958. In this regard, by proper selection of the flow resistive element, of various materials, diameter, length, pore size are easily selected. The elastomeric container wall material and the viscosity of the drug formulation, a wide range of dispensing rates can be obtained, as well known to those skilled in the art. Rates may vary, for example, from 0.01 ml per hour to 100 mls per hour, as desired, and for periods, for example, such as one day up to and in excess of 1 year. For satisfactory discharge rates viscosities of the medium employed with the drug can be in the range, for example, of from 1 to 10,000 centipoise at the temperature of use, with the exact selection depending on the other fluid flow parameters and the desired delivery rate. In some instances, it may be desirable to assist retention of the device in the body cavity by attaching a weight or ballast to the device. Suitable weights, depending on the animal involved, include iron, brass, stainless plugs, or the like.

FIG. **3** represents a specific example of the manufacture of a delivery device of the invention used for the controlled and continuous administration of prostaglandin $PGF_{2\alpha}$ to the uterus of an adult female over a period of 1 day to 3 days with the preparation as follows and the device having the stated dimensions and specifications; a drug container **11**, is fabricated from commercially available peroxide-curved natural latex rubber linking with an internal diameter of 0.79 mm and outside diameter of 1.59 mm. The receptacle has a deflated initial length of 5 mm and it inflates to approximately 16 mm. The receptacle holds 3 cc of drug formulation. A medical grade polyethylene catheter **15** of 0.79 mm outside diameter leads into receptacle **11.** The inside diameter of the catheter is 0.6 mm and its length is 15 cm.

The drug is receptacle **11** consists of **7** mg of $PGF_2\alpha$ in 1 cc of sterilized isotonic saline mixed with the viscosity agent sodium carboxymethyl cellulose. The formulation has a viscosity of 10,000 cp at 37° C. The device is equipped with a flow control element **12,** distant from catheter **15.** The element is comprised of a porous polyethylene rod potted to the front end of receptacle **11.** The size of the flow control element is 0.9 mm in diameter and 1 mm in length. It has a porosity of 20 percent, a tortuosity factor of approximately 2.0 and an average pore size of 1 cc for the controlled, continuous administration of the prostaglandin to the uterus.

Although the foregoing invention has been described in some detail by way of illustration of a preferred embodiment and examples, for purposes of clarity and understanding, it will be understood that certain changes and modifications may be practiced within the scope and spirit of the invention, as defined in the appended claims.

What is claimed is:

1. A device for the administration of a drug at a controlled and continuous rate over a prolonged period of time comprising: (a) a receptacle for containing a drug and adapted to be inserted into a body orifice of a warm blooded animal, said receptacle having a leading end for receiving a metering means and a trailing end for receiving a filling means, (b) a wall defining the receptacle and formed of a biologically inert, nonallergenic elastomeric material suitable for exerting a pressure on a contained drug by the wall moving from an expanded position when the receptacle is charged with drug to a collapsed position throughout the release of drug from the receptacle, (c) said metering means positioned in the leading end for controlling the rate of drug administration from the receptacle to its exterior, (d) a means for filling the receptacle positioned in the trailing end, the means having a tubular configuration and held in the end by the receptacle wall pressed against the tubular member, (e) a means for maintaining drug in the receptacle consisting of a unidirectional valve in the tubular member and wherein, (f) said elastomeric material defining a means for administering the drug from said charged receptacle by the wall moving from an expanded to a collapsed position to exert an internal pressure on drug and urge it through the metering means to administer it from the device at a controlled and continuous rate for a prolonged period of time.

2. A self powered device for the continuous and controlled administration of a beneficial agent over a prolonged period of time comprising: a pressure distendable receptacle for insertion into a biological environment and adapted to contain an agent and formed of an elastomeric material substantially impermeable to the agent, a discharge port integral with the receptacle, a flow resistive metering means for controlling the rate of agent administration from the receptacle by passage through the means with the means in communication with the discharge port and the receptacle, an entry port distant from the discharge port and the flow resistive means for providing access to the receptacle,

means housed in the entry port for internally closing the port and maintaining agent in the receptacle, a catheter tube for filling the receptacle with the agent in communication with the entry port and the receptacle, and wherein the receptacle is dimensioned for insertion and positioning in its collapsed state into an agent receptor biological environment, said receptacle expandably responsive to an applied pressure induced by infusion of said agent through the entry port into the receptacle after the receptacle is placed in the preselected environment of use to establish an internal stress in the receptacle material, and wherein in operation, when the receptacle is charged with said agent, the elastomeric material constitutes a means for maintaining, as a result of the induced stress, a preselected programmed pressure in the receptacle wall to move agent through said flow resistive means at a controlled and continuous rate throughout the discharge period of the agent from the self powered device.

3. A self powered device for the continuous and controlled administration of a beneficial agent over a prolonged period of time comprising: a pressure distendable receptacle for containing an agent, the wall of the receptacle formed of an elastomeric material substantially impermeable to the agent, a discharge port communicating with the receptacle, a flow resistive metering means in contact with the discharge port and the receptacle for controlling the rate of agent administration from the receptacle by passage of agent through said metering means from the receptacle, an entry port distant from the discharge port and flow resistive means for providing access to the receptacle, a catheter for internally receiving the receptacle at the entry port, selfclosing valve means internally positioned in the catheter distant from the entry port for providing entry to the receptacle and for maintaining agent in the receptacle, and wherein the receptacle is adapted for insertion and retention in its collapsed state into an agent acceptor biological environment, the receptacle being expandably responsive to an applied pressure induced by filling receptacle with agent through the entry port after the receptacle is placed in said preselected environment of use to establish an internal stress in the receptacle wall, said elastomeric material and the resultant internal stress when the receptacle is filled, defining an agent administrating means operative to maintain, as the result of said induced stress, a substantially constant pressure in the receptacle wall to move said agent through the flow resistive means at a controlled and continuous rate throughout the discharge period of the beneficial agent from the self powered device.

4. The device according to claim **3** wherein the entry port of the receptacle is positioned within the catheter, the catheter formed at the end that receives the entry port with an internal recess for housing an O-ring which contacts the end of the receptacle at the entry port and retains it within the catheter.

5. The device according to claim **3** wherein the entry port of the receptacle terminates within the end of the catheter, the catheter formed at this receiving end with an internal groove for containing an O-ring that abuts against the receptacle at its entry port to maintain it within the catheter, and the catheter formed at its distant end with at least one protuberance for receiving force for subsequently moving and positioning the device within a cavity.

6. The device according to claim **3** wherein the entry port is integrally formed with the catheter, said catheter comprised of an internal, one-way valve distant from the entry port with the valve self closing after the receptacle is charged with agent for maintaining it therein.

7. The device according to claim **3** wherein the device is adapted for insertion and positioning in the uterus.

8. The device according to claim **3** wherein the agent is an acceptable pharmaceutical agent that can produce a local or systemic physiologic or pharmacologic response upon administration from the device.

9. The device according to claim **3** wherein the environment of use is a mammalian bladder.

10. The device according to claim **3** wherein the wall material forming the receptacle is natural elastomeric non-toxic rubber.

11. The device according to claim **3** wherein the discharge port is tubular with a flow resistive means for controlling the flow of agent and it discharges agent into a receptor site distant from the sites of the device.

12. The device according to claim **3** wherein the receptacle when distended is of a size and configuration adapted to promote retention thereof in the environment of use and is adapted for easy removal from the environment of use and is adapted for easy removal from the environment of use after the administration of drug from the receptacle.

13. The device according to claim **3** where a one way valve is positioned in the catheter to maintain agent in the receptacle with the catheter made of a biologically inert material and having a length adapted for maintaining it within a mammalian cavity.

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