A self-powered vapor pressure delivery device for the controlled and continuous dispensing of an active agent employing in a preferred embodiment outer and inner chambers in functional relationships. The inner chamber is a sealed bag comprised of a flexible and substantially vapor and fluid impermeable material. The bag is freely positioned within an outer casing. The bag is filled with a volatile propellant and is expandably responsive to the vapor pressure of the propellant at the temperature of use, such as to cause the bag to distend so as to reduce the volume of the outer chamber. The active agent in the outer chamber is thereby caused to flow through a flow resistive means which is provided in the outer chamber.
SELF-POWERED VAPOR PRESSURE DELIVERY DEVICE

BACKGROUND OF THE INVENTION

This invention relates to a delivery device or pump and, more particularly, to a self-powered delivery pump which operates without any external energy source and which is capable of dispensing an active agent at a controlled rate over a prolonged period of time. The device employs vapor pressure as the motive force and it may be employed, in a preferred aspect, for internally administering medicaments in the body of an animal or human.

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 feeding 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 wherein it is desirable to use a delivery device to provide a slow release of drug to a recipient at a controlled rate over a relatively prolonged period of time in order 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 a 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 the drug from a drug 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 prior art to obtain such devices. One approach has been to enclose the drug within a capsule having a polymeric wall through which the drug can pass at a controlled rate by diffusion. An approach of this kind is set forth in U.S. Pat. No. 3,279,996. However, this type of delivery device has inherent shortcomings. For example, one difficulty is that release rates cannot readily be varied with a given polymeric material other than by changing the thickness of the material used to make the device which may cause fabrication difficulties in cases wherein very thin or very thick walls are required to achieve the desired release rate. Further, there are restrictions on the physical form of the active agent in that suspensions or the like cannot be delivered by a polymeric diffusion system. Additionally, few materials are satisfactory for the obtaining of desired release rates for relatively high molecular weight materials such as insulin.

Another approach has also been proposed in the form of a delivery device which is powered by vapor pressure. See Medical World News, Oct. 16, 1970, "A Lifetime Infusion Pump to Call His Own". The device is disclosed to be implantable within a human body and consists of a double walled chamber, containing a volatile liquid in the outer chamber. Liquid drug is placed within the innermost chamber formed by the inner walls of the double wall cylinder and is in the form of a collapsible, but rigid, accordion-type bellows made of stainless steel. For proper operation of the device, the chambers must be hermetically sealed from each other. Evaporation of the liquid in the outer chamber provides pressure so as to push the drug out from the innermost chamber. Other delivery devices comprised of cooperative chambers are known to the art, which also utilize a volatile material placed in an outer chamber as the motive force to dispense a liquid composition of matter placed in a collapsible inner chamber; see for example Krizka, U.S. Pat. No. 3,433,391 and Schultz, U.S. Pat. No. 2,876,768.

These prior art pressure-operated devices, however, have inherent disadvantages. These disadvantages result in part from the spatial relationship of volatile liquid and the composition of matter to be dispensed; that is, the former is placed in the annular space between the inner chamber and casing, whereas the latter is placed within the collapsible inner chamber, such that the pressure generates a mechanical deflating force on the inner chamber to thereby dispense the composition. In order to prevent the vapor from pinching the inner chamber and thus preventing the dispensing of the product, it is necessary to employ means so as to maintain the inner chamber in an erect position. Although this can satisfactorily be accomplished in a manner known to the art by the use of rigid supports or materials and the like, the resulting unit is relatively bulky and cumbersome. Moreover, the aforesaid described spatial relationship of volatile liquid and product to be dispensed in the prior art pressure-operated devices, necessitates inclusion of a discharge passageway from the inner chamber to the exterior of the device or alternatively, the mechanical securing in some manner of a part of the structure of the inner chamber to the outer casing, which in either case requires costly and difficult to make liquid-vapor seals between the chambers. Consideration of these factors will indicate that the usefulness of devices constructed in the manner so described are seriously limited for many applications.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide a self-powered vapor-pressure delivery device, simple in construction, inexpensive to manufacture, and therefore suitable for disposal after relatively short periods of use without undue economic hardship, and which exhibits all of the practical benefits of a constant continuous administration of various active agents both to animals and humans, and into other environments.

Another object of this invention is to provide an improved self-powered vapor-pressure delivery device which is suitable to be implanted or inserted in an animal or human.

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

A further object of this invention is to provide a delivery device which depends on vapor pressure for its motive force and which is particularly adapted to miniaturization so as to be suitable for installation at a wide range of sites with reasonable ease.

Yet another object of this invention is to provide an improved self-powered activated dispenser which over-
comes problems inherent in related devices heretofore proposed. Another object of this invention is to provide an improved method of administering an active agent to a recipient.

In attaining the objects of this invention, one preferred aspect of this invention resides in a self-powered device for the controlled and continuous dispensing of an active agent, employing a pressure differential as the motive force, which comprises:

- a casing housing therein outer and inner chambers in functional operative relationship, the chambers being partitioned and sealed from each other by a bladder; the bladder comprised of a flexible and substantially vapor and fluid impermeable material and being freely positioned within the casing, the bladder being expandably responsive to an applied pressure emanating from the inner chamber at the temperature of use and being adapted to approximately conform to the shape and size of the inner surface of the casing;

and

- the outer chamber communicating with a discharge port having a low flow resistance means therein.

Other objects, features and advantages of this invention will become more apparent from the following description when taken in conjunction with the accompanying drawings, and wherein like reference numerals are used to indicate like or equivalent parts.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional view of an embodiment of a self-powered vapor-pressure delivery device of this invention.

FIG. 2A is a perspective view of the bladder element or inner chamber illustrated in FIG. 1, removed from the outer casing and containing a propellant therein. The bag is also shown inflated, in phantom position in the drawing.

FIG. 2B is a cross-sectional view through 2B—2B of FIG. 2A.

FIG. 3 is a perspective view of the device illustrated in FIG. 1, depicting the inner chamber in a collapsed condition before any of the active agent has been dispensed.

DETAILED DESCRIPTION OF THE INVENTION

Generally, the device can be viewed as a single unit comprising outer and inner chambers acting in a functional relationship for effective administration of agent. The outer chamber contains the active agent and an inner chamber containing the propellant, and is provided with a flow resistive means for releasing the active agent at a controlled rate to the exterior of the device. The inner chamber comprises a flexible and substantially impermeable bag which contains a volatile propellant and provides the power or energy for the device. The chambers are advantageously separated and sealed from each other by a wall or bladder which forms a part of the structure of the inner bag. The bladder is of such size and configuration that in its distended condition all, or substantially all, of the active agent will be discharged from the device.

Operation of the delivery device of the invention makes use of the scientific principle that a vapor in equilibrium with its liquid phase exhibits a constant pressure at a given temperature, irrespective of volume occupied by the vapor.

A preferred embodiment of the self-powered vapor-pressure delivery device, in accordance with this invention, is illustrated in FIGS. 1, 2A, 2B and 3, wherein the device 20 comprises casing 22 containing an inner sealed bag therein so as to define inner chamber 10, outer chamber 21 and bladder 12. Thus, the bladder is advantageously an integral part of the structure of the outer wall of the inner chamber and the inner wall of the outer chamber. More specifically, device 20 is comprised of hollow casing 22, housing bag 10 which is comprised of a flexible and impermeable material 12, termed a "bladder" herein. The space within bag 10 defines the inner chamber of the device and contains volatile propellant 18 therein, having a vapor pressure greater than that of the environment external to the device 20 at the temperature of use. It is freely positioned within casing 22. The volume of casing 22, other than that occupied by bag 10, defines the outer chamber 21 of the device 20 and is occupied by active agent 28. The wall of bag 10 is expandably responsive to the vapor pressure of the propellant 18 at the temperature of use and is adapted to approximately conform to the shape and size of the inner surface of casing 22 and preferably be substantially contiguous therewith when in a fully expanded condition.

Casing 22 is comprised of a rigid (or flexible, as described hereinafter), impervious structure having a removable bottom member 27 which is so provided for insertion of bag 10 and active agent 28. Member 27 can be threaded as shown or, alternatively, can be adhesively sealed or press-fit into place after insertion of the power source 10 and active agent 28. As an aid in maintaining a tight barrier between active agent 28 and the external environment of the device, a resilient O-ring 25 may be included. Discharge port 23 is bored into casing 22. Flow resistive metering means 24 snugly fits into discharge port 23 and is preferably adhesively secured or bonded therein. Alternatively, non-integral threaded member 27 can be eliminated entirely from casing 22 by employing port 23 as a means of ingress to the casing prior to assembling of flow resistive means 24. Thus, bag 10 can be temporarily folded up or otherwise compressed to a small object and inserted into casing 22 via port 23. In like manner, active agent 28 can be so incorporated into casing 22.

Optionally, casing 22 can be provided with an access port (not shown) to provide entry into the device 20 for purposes of refilling chamber 21 with active agent. The access port can be comprised of self-sealing needle penetrable material such as rubber and the like, or a suitable valve.

Bag 10 is easily fabricated, for example, by employing a rectangular piece of film sheeting 12 which is folded over and sealed with an appropriate sealant along its sides 14 and 16. Propellant 18 may then be introduced into bag 10 through side 17, and the bag sealed along side 17. Where the propellant has a vapor pressure of about one atmosphere at or below room temperature, the propellant is preferably introduced at reduced temperatures so that it does not vaporize. The inner chamber 10 is susceptible of embodiment in many different forms, other than that illustrated in FIG. 3, 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 sub-
stantially identical with the inner surface of casing 22. Additionally, it is preferred that inner chamber 10 be constructed such that it can be folded or compressed, or otherwise oriented in its initially collapsed state, to occupy only a small percentage of the total volume of the casing.

As described above, since bag 10 is comprised of a flexible material and is only partially filled with volatile propellant 18, bag 10 can be folded up so as to occupy a very small volume, compared to the total expanded volume when bag 10 is distended. Usually, the volume of propellant which is required will not be more than about 5 percent of the volume of the bag 10 when expanded. Bag 10 with propellant 18 therein can be so constructed in most cases so as to initially occupy less than 10 percent of the effective internal volume of casing 22, advantageously resulting in the ability to substantially fill chamber 21 entirely with active agent 28. Additionally, it has been found to be desirable, in order to promote complete discharge of agent 28, to preform or pre-mold bag 10 such that it will conform with the shape and size of the internal surface of casing 22 and will be substantially contiguous therewith after the dispensing of active agent 28. This insures that no active agent is wasted by remaining in device 20 after use. Further, bag 10 can be independently manufactured so as to be available as required. That is, the bag can be fabricated, filled with a propellant or mixtures of propellants, depending on the particular requirements, and stored until required for use in the subject device. This provides for economical manufacturing procedures and low unit cost.

In assembling device 20, either bag 10 or active agent 28 can be first incorporated into casing 22, although it is preferred to initially incorporate bag 10 pre-cooled so that the propellant 18 is in a condensed state. Agent 28 may now be introduced to fill substantially all of the remaining volume within casing 22.

Metering of agent 28 from the device 20 is accomplished by flow resistive means 24 (more fully described hereinafter). Such metering element, in its preferred form, consists of a porous plug 24 inserted in discharge port 23. The element is preferably of a uniform porosity so as to function to control the flow rate of agent. The metering operation is preferably carried out in conjunction with highly permeable filter (not shown) disposed in port 23 in spaced relationship to plug 24, on the upstream side thereof. The calibration of the porous plug is a function of its built-in porosity, as well as its diameter and length, and these parameters and materials may be varied to meet required dispensing rate, as hereinafter more fully described. The function of the filter is to assure that the fluid passing through the flow resistive means shall be entirely free of sediment or precipitates which might otherwise clog the flow resistive means and alter the calibration value thereof. The filter element should be of greater size than the resistive element.

Device 20 may be stored at reduced temperature until ready for use or, alternatively, a cover or cap placed over porous element 24 to prevent the unwanted premature release of agent 28, if stored at higher temperatures. Device 20 is now ready for introduction into the environment in which it is to operate. A critical requirement of the environment is that it have a temperature at which the vapor pressure of the volatile propellant is greater than the pressure of the environment.

To use the delivery device of the invention, for example in cases wherein the active agent is a drug or other agent for treating a living organism, it is either physically inserted, orally ingested or surgically implanted in the body of the organism, typically a mammal. The particular method of introduction or retention of the device in the environment is not an aspect of this invention and is well known to those skilled in the art. Once in place, due to the heat transfer from the environment to the device 20, volatile propellant 18 will begin to vaporize and exert a pressure in excess of the environment causing the wall 12 (bladder) of bag 10 to expand. Because of the increase in volume of bag 10 suggested by the broken lines illustrated in FIG. 1, agent 28 will slowly begin to flow through porous plug 24 at a controlled rate into the external environment. As agent 28 is discharged, bag 10 will further distend to fill the space, the volatile liquid 18 vaporizing to maintain a constant pressure in bag 10. Bag 10 is of such a size, configuration and contour, so that when completely distended it will substantially fill the inner volume of casing 22. There is accordingly provided the gradual and controlled constant release of drug or similar agent directly to the body or affected organ thereof over a prolonged period of time.

In connection with the many uses of the present invention in the medical field and in other applications, it is quite important that the flow rate in the discharge line shall be steady and at a low and constant 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 a device which will discharge at a substantially constant rate over a period of time. The constant discharge flow rate of agent 28 is achieved due to the fact that the vapor pressure of the propellant providing the motive operating force remains constant under the isothermal conditions of the environment. Additionally, the viscosity of the active agent must be stable during storage and use.

In some instances the devices of this invention are of insufficient specific gravity to maintain placement at the desired location. For example, for use in the rumen of polygastric animals, the weight should be sufficient to provide a specific gravity of at least 1.5. In those instances of insufficient specific gravity, therefore, a weight or ballast can be placed in or attached to the device. Other suitable weights comprise iron plugs, iron ore tablets, brass plugs, ceramic plugs, or the like.

The devices of this invention need not have any particular shape. The devices in their original form ready for use may be cylindrical, oblong, oblate, prolute, spherical, polyhedral, etc. The shape of the device is primarily one of convenience, both as to manufacturing and the site of use. Moreover, the devices can be fabricated in shapes suitable for either physical insertion or implantation in the body, or for insertion via the gastro-intestinal tract, or for introduction into any other desired environment. Dimensions of the device can thus vary widely and are not of controlling importance. The lower limit of the size of the device is governed by the amount of the particular active agent to be supplied to the environment to elicit the desired response, as well as by the form the unit takes, e.g., implant, bolus, suppository, and in cases of specific body use, the location
The choice of materials, either individually or in combination, will be chosen in reference to the compositions contained in the chambers. Where a single material is not imperious to one or both of the active agent and the propellant, by using coatings or laminates of two or more different materials, substantial impermeability can be achieved. Illustrative materials include nylon, polyacrylonitrile, polyethylene, polypropylene, polyvinylidene chloride, e.g., Saran, cellophane, polyvinyl alcohol, etc. Laminates may be prepared, such as nylon-Saran, polyethylene-Saran-polyethylene, polyethylene-polyvinyl alcohol-polyethylene, Mylar-aluminum-polyethylene, polyethylene-polyvinyl alcohol-Saran; etc. In cases where the intended use is such that the overall size or cost of the device is not of controlling importance, rigid-type materials, e.g., thin metals such as stainless steel or the like, can be used. Flexibility can be imparted in these instances by employing a pleated accordion-type bellows construction. The choice of materials is further governed by its ability to retain the above discussed properties under the conditions of storage and use.

Many other materials are suitable for fabrication of the several component parts of the device of this invention. While the said several component parts of the device of the invention are preferred to be insoluble under the conditions are in the environment of intended use, it is also within the scope of the invention that such materials be insoluble only during the period of said intended use; thereafter dissolving away in the environment of the device. Thus, a dispenser is here contemplated which is unaffected by its environment, solubility-wise, at the site of use, or which is only slightly soluble during the period of intended use, such that once its active agent content has been discharged it will then dissolve or erode away leaving no objectionable residue or empty container at the said situs of use.

The term “active agent” as used herein denotes any drug (as exemplified, infra); composition in any way effecting any biological entity; substance having a nutrient or stimulating action, or growth inhibiting, destroying or any regulating action on plant growth, controlled or otherwise; substance to be assimilated by any organism, e.g., human being, animal, or lower order organism, for its nourishment or for regulating its growth; substance exhibiting any of the above activities to be directly applied to the habitat, surroundings, or environment of any of the above organisms; and substances having any other effect on any other environment.

The device of the invention is suitable for delivering active agents 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 compositions which are liquids, emulsions, gels, sols, suspensions, foams, gels, pastes, and the like. Suitable active agents for use with the dispenser of this invention include, without limitation, those which are generally capable of: 1. Preventing, alleviating, treating or curing abnormal and pathological conditions of the living body by such means as destroying a parasitic organism or limiting the effect of the disease or abnormality by chemically altering the physiology of the host or parasite; 2. Maintaining, increasing, decreasing, limiting or destroying a physiologic body or plant function, e.g., vita-
min compositions, sex sterilants, fertility inhibitors, fer-
tility promoters, and the like;
3. Diagnosing a physiological condition or state;
4. Controlling or protecting an environment or living
body by attracting, disabling, inhibiting, killing, modi-
ifying, repelling, or retarding an animal or microorgan-
ism, such as food and non-food baits, attractants and
lures, biocides, pesticides, algicides, parasiticides, ro-
denticides, insecticides, fungicides, and the like;
5. Preserving, disinfecting or sterilizing; and
6. Controlling or affecting generically an environ-
ment, as by introducing a catalyst or metering a reac-
tant into a reacting chemical system, or by effecting
any chemical process therein, such as a fermentation,
including propagation and/or attenuation of a microor-
ganism.

As indicated, of particular interest are active agents
which are drugs. Any of the drugs used to treat the
body, both topical and systemic, can be compartment-
alyzed as the active agent in any of the devices of this
invention. “Drug” is used herein in its broadest sense
as including any composition or substance that will pro-
duce a pharmacological or biological response.

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, include, without limitation: for example, drugs
acting on the central nervous system such as hypnotics
and sedatives such as pentobarbital sodium, phenobar-
bital, secobarbital, thiopental, etc.; heterocyclic hyp-
notics such as dioxopiperidines, and glutarimides; hyp-
notics and sedatives such as amides and ureas exempli-
fied by diethylsoveralamide and α-bromoisooveralyl
urea and the like; hypnotics and sedative alcohols such
as carbomol, naphthoxethanol, methylparaphenol and
the like; and hypnotic and sedative urethans, disulfanes
and the like; psychic energizers such as isocarboxazid,
nialamide, phenelzine, imipramine, tranlypromine,
pargylene and the like; tranquilizers such as chloro-
promazine, promazine, fluphenazine reserpine, deser-
pidine, meprobamate, benzodiazepines such as chlori-
diazepoxide, and the like; anticonvulsants such as primi-
done, diphenyl-dimethion, ethotoin, pheneturide, etho-
suximide and the like; muscle relaxants and anti-
parkinson agents such as mephinesin, methocorbalom,
triethylphenidyl, 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, salicylamine, so-
dium salicylamide and the like; local anesthetics such
as procaine, lidocaine, naepaine, piperocaine, tetra-
caine, dibucaine and the like; antidepressives and anti-
ulcer agents as such as atropine, scopalamine, methscop-
alamine, oxyphenonium, papaverine, prostaglandins
such as PGA, PGE, PGF, PGE, PGA, and the like;
anti-microbials such as penicillin, tetracycline, oxy-
tetracycline, chlorotetracycline, chloramphenicol,
sulphonamides and the like; anti-malarials such as 4-
amino-quinolines, 8-aminoquinolines and pyrimeth-
amine; hormonal agents such as prednisolone, corti-
sone, cortisol and triamcinolone; androgenic steroids,
for example, methyltestosterone, fluoximesterone and
the like; estrogenic steroids, for example, 17β-estradiol
and ethinyl estradiol; progestational steroids, for exam-
ple 17α-hydroxyprogesterone acetate, 19-nor-
progesterone, norethindrone and the like; sympathomi-
metic drugs such as epinephrine, amphetamine, ephed-
rine, norepinephrine and the like; cardiovascular drugs,
for example, procaainamide, amyl nitrate, nitroglycerin,
dipyridamole, sodium nitrate, mannotol nitrate and the
like; diuretics, for example, chlorothiazide, flumethia-
ze and the like; antiparasitic agents such as benc-
phenium hydroxyxynphoate and dichlorophen, dap-
sone and the like; neoplastic agents such as mechlor-
ethamine, uracil mustard, 5-fluorouracil, 6-
thioguanine, procarbazine and the like; hypoglycemic
drugs such as insulins, protamine zinc insulin suspendi-
sion, globin zinc insulin, isophane insulin suspension,
and other art known extended insulin suspensions, sul-
fonlyureas such as tolbutamide, acetohexamide, tolaza-
mide, and chlorpropamide, the biguanides and the like;
nutritional agents such as vitamins, essential amino
acids, essential fats and the like; and other physiolog-
ically or pharmacologically active agents. Also, the
drugs can be present as the pharmaceutically accept-
able 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 the action of body enzymes assisted transforma-
tions, pH, specific organ activities, and the like.

When the active agent is other than a drug or similar
agent, or is intended for use other than in a living or-
ganism, the device is introduced into the desired envi-
ronment to produce the desired effect exactly as would
be any of the known means of accomplishing a like re-
sult. And this is generally a mere physical insertion,
such as by placing a pesticide containing device in a
river or stream, or a catalyst containing device in a re-
action medium.

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, in cases wherein the
active agent is a drug, suitable pharmaceutical carriers
include sterile water; saline, dextrose, dextrose in water
or saline; condensation products of castor oil and ethyl-
ene oxide combining about 30 to about 35 moles of
ethane oxide per mole of castor oil; liquid glyceryl tri-
ester of a lower molecular weight fatty acid; lower alka-
nols; 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, so-
dium carboxymethylcellulose; sodium alginate; poly-
vinylpyrrolidone); and the like, alone or with suitable
dispensing agents such as lecithin; polyoxyethylene ste-
rate; and the like. The carrier may also contain adju-
ivants such as preserving, stabilizing, wetting, emulsify-
ing, viscosity modifying agents, and the like.

It is essential to the successful practice of the inven-
tion that the flow resistive means be self-actuated when
the device is to be employed from continuous in vivo
administration from within internal body passages, al-
though the flow resistive element can be a convention-
al-type valve when the device is not so employed. By
the term “self-actuated” is meant that there is no re-
requirement for external manipulation to initiate the flow
of agent. Numerous types of flow self-actuated resistive
elements are available, such as porous plugs, micropo-
rous membranes, capillary tubes, etc. The flow resistive element may be of a wide diversity of materials, such as etched or perforated polymers, e.g., polyethylene, nylon, teflon, poly(vinyl chloride), poly(vinyl chloride), poly(methyl methacrylate), epoxy resin; sintered metals or ceramics. By proper selection of the flow resistive element, i.e., materials, diameter, length, pore size, and the viscosity of the medium for the active agent, 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 1,000 ml per hour, as desired, and for periods, for example, such as one day up to and in excess of one year. For satisfactory discharge rates, viscosities of the medium employed with the active agent 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.

The flow resistive element 24 can be inserted into port 23 by any convenient means which provides a non-leaking seal. For example, the means employed may be adhesives, mechanical means, e.g., threading, heat sealing or, alternatively, by making flow resistive element 24 an integral member of the casing structure.

The amount of active agent 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, and in the case of drugs, to provide complete dosage regimens for therapy for a variety of maladies, there is no critical upper limit on the amount of drug incorporated in the device. The lower limit, too, will depend on the activity of the drug and the time span of its release from the device. In general, therefore, the amount of 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-desmethyloxyreserpine, about 5 to 40 mg in the device; for acetophenazine, an amount in the device of 100 to 200 mg; for methoxy promazine, about 600 to 750 mg in the device. Additionally, the amount of drug in the device can be 100 to 300 mg of thiopropazine 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 tranylcypromone 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, for example PGE1, PGE2, PGA2, PGF2α, 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.

Suitable volatile propellants for use in devices of the invention are well known in the art. A critical factor in selection of the propellant employed is that its vapor pressure at the temperature of use is greater than the pressure external to the device to ensure that a pressure differential will exist to provide the motive operating force for the device. Additionally, if the device is employed for internal drug administration, the propellant should be non-toxic and exhibit a pressure which is preferably not in excess of about 2 atmospheres at the temperature of use. Additionally, it is critical for this use that the propellant be such that activation is not required from an extracorporeal position. Exemplary of materials useful as propellants are liquefied gases. Suitable non-toxic gases are generally fluorochlorinated lower saturated aliphatic hydrocarbons, suitably halogenated lower alkanes containing one to four carbon atoms, preferably one or two carbon atoms, and at least one fluorine atom, including propellants such as dichlorodifluoromethane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114") and trichloromonofluoromethane ("Freon 11"). These propellants, or suitable mixtures thereof, will produce a propellant vapor pressure between about 1 and about 60 pounds per square inch at room temperatures (20°-25°C). Suitable mixtures of the propellants can be employed to give a preferred vapor pressure between about 1 and about 10 pounds per square inch at these temperatures.

When the device is to be employed for internal drug administration in mammals, the propellant should have a vapor pressure which is in excess of about one atmosphere at a temperature of about 37°C or physiological temperatures. Preferred propellants for this use include ethyl ether, Freon 11, n-pentane, butane, dimethyl ether, isobutane, etc. Further, for this use it is preferred that the volatile liquid have a vapor pressure of one atmosphere at a temperature above -10°C, more usually above 15°C, and most preferably in the range of about 15° to 40°C. Generally, the volatile liquid should have a vapor pressure of one atmosphere at a temperature at least about 5°C lower than the temperature of use and usually not more than about 40°C lower than the temperature of use. However, this is not critical, but is primarily a matter of convenience in handling and storage.

In order to achieve greater versatility as well as lower cost, propellant blends have been developed as known to the art. These blends consist of mixtures of fluorinated hydrocarbons and hydrocarbons. Blends are employed for a variety of reasons, including (1) obtaining a preferred vapor pressure, (2) reduction of cost, and (3) proper density. Further, blends of propellants can be prepared wherein the changes in vapor pressure with temperature are small.

If desired, long flexible tubing of polyethylene or the like can be extended from the discharge port 23 of the device. In such manner the device can be deposited at a site remote from the desired point of application and still release the active agent contents through the tube or conduit directly to said point. A modification of this aspect permits placement of the dispenser in an environment at one temperature to release the active agent into another environment which can be at a lower temperature, for example, at a temperature which is below the boiling point of the propellant. The dispenser can also be provided with a check valve, for example, a one-way ball valve, to prevent back flow of active agent or other materials from the external environment into the device.

The subject device can be suitably modified for the independent concurrent administration of more than
one active agent. This can be accomplished by employing a plurality of agent containing chambers within the same device separated and/or sealed from each other with each chamber having the same or separate flow resistive elements. Each agent containing chamber is placed in operative relation with the same or a plurality of pressure driven distendable bladders so as to discharge the agents as a mixture or separately, but concurrently.

The following in vitro examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, drawings and the accompanying claims.

EXAMPLE 1

Stainless steel shells utilizing a single small bore exit tube are employed; the exit tube functions as a flow resistant element. Propellant bags are made by heat sealing plastic film into a “pillow-type” structure of the type illustrated in FIG. 2 with propellant inserted before closing the final seal. The bags are made of one mil

The volume of the steel cylinder is varied by use of a plug or a syringe so that the size of the cell is the same dimension as the length of the bag. After placing the bag in the cylindrical stainless steel tube, the tube is then filled with Dow Corning 200 fluids per milliliter containing 5 percent by weight of progesterone.

The pump is tightly sealed and connected to an inverted graduated pipette through a stainless steel capillary tube by using Silastic tubing. Different sizes of capillary tube are employed. The pump and inverted pipette are immersed completely in a constant temperature bath, except for the short portion of the pipette tip. The pumping rate is determined from the rising level with respect to time of the Dow Corning fluid in the measuring pipette. For the “three-equilibrated” runs, the entire system is thermostated for 15 minutes, and then the fluid is released to be pumped out. For the “non-equilibrated” runs, the measurement of the pumping rate is started right after the pump is placed in the bath water. The measurements of the pumping rate are performed either by using a different bag for each run or by using the same bag for a number of runs.

The following table indicates the results of the test.

<table>
<thead>
<tr>
<th>Viscosity of Fluid (cp)</th>
<th>Temp. (°C)</th>
<th>Size of Bag Used</th>
<th>Q (exptl. cc/min)</th>
<th>Net Pumping Time (min)</th>
<th>Dimensions of Capillary Tubing (length cm)</th>
<th>Q (calc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65.10</td>
<td>37</td>
<td>F/16</td>
<td>0.117 ± 0.0202</td>
<td>7.0 ± 1.0</td>
<td>2.477 × 10^-2</td>
<td>0.84</td>
</tr>
<tr>
<td>65.54</td>
<td>37</td>
<td>F/16</td>
<td>0.013 ± 0.0025</td>
<td>62 ± 8.0</td>
<td>2.477 × 10^-2</td>
<td>0.78</td>
</tr>
<tr>
<td>6797.64</td>
<td>37</td>
<td>F/16</td>
<td>0.0038 ± 0.0005</td>
<td>161.25 ± 22.6</td>
<td>2.477 × 10^-2</td>
<td>1.12</td>
</tr>
<tr>
<td>65.10</td>
<td>37</td>
<td>F/32</td>
<td>0.185 ± 0.0035</td>
<td>1.44 ± 0.216</td>
<td>2.477 × 10^-2</td>
<td>0.76</td>
</tr>
<tr>
<td>65.54</td>
<td>37</td>
<td>F/32</td>
<td>0.031 ± 0.0037</td>
<td>8.25 ± 1.46</td>
<td>2.477 × 10^-2</td>
<td>1.14</td>
</tr>
<tr>
<td>6797.64</td>
<td>37</td>
<td>F/32</td>
<td>0.0029 ± 0.0046</td>
<td>83.33 ± 6.40</td>
<td>2.477 × 10^-2</td>
<td>1.07</td>
</tr>
<tr>
<td>6797.64</td>
<td>37</td>
<td>F</td>
<td>0.002 ± 0.0047</td>
<td>5061.7 ± 295</td>
<td>2.477 × 10^-2</td>
<td>1.11</td>
</tr>
<tr>
<td>56.40</td>
<td>40</td>
<td>F</td>
<td>1.98 ± 0.16</td>
<td>7.25 ± 0.5</td>
<td>2.477 × 10^-2</td>
<td>7.95</td>
</tr>
<tr>
<td>606.20</td>
<td>40</td>
<td>F</td>
<td>0.332 ± 0.021</td>
<td>36 ± 3.16</td>
<td>4.19 × 10^-2</td>
<td>0.93</td>
</tr>
<tr>
<td>6198.8</td>
<td>40</td>
<td>F</td>
<td>0.0305 ± 0.0005</td>
<td>367.5 ± 17.5</td>
<td>4.19 × 10^-2</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Notes: 1. Measured values with the Rotovisco Viscometer.
2. The data are obtained by the pumping system which is at room temperature until it is placed into bath water to start the pumping test. Q (exptl) is the over-all average slope of the line representing the accumulative volume of fluid pumped out versus time.
3. 95 percent of the time at which the release rate goes to zero.
4. F — Full size bag. It is the largest bag used in this program. Dia. ~ 2 cm and length ~ 5 cm.
F/16 — Expanded volume of this bag is approximately 1/16 of the full size bag. Dia. ~ 0.9 cm and length ~ 2.0 cm.
F/32 — Expanded volume is about 1/32 of the full size bag. Dia. ~ 0.55 cm and length ~ 1.4 cm.
5. Q (calc) are based on the Hagen-Poiseuille law.
6. Incomplete because of the lack of data for the temperature history inside the pump, and therefore, the vapor pressure of ether cannot be estimated accurately.

Capran 77 K film (Allied Chemical Co., nylon-six coated with Saran on one side), and reagent grade ethyl ether is employed as the volatile liquid.

Three difference sizes of bags are used, with 0.02 to 0.5 cc of propellant being introduced into the bags. The amount of air retained in the bags varies with the size of the bags. The largest sized bag has a diameter of two centimeters and a length of about five centimeters. The middle sized bag has an expanded volume approximately 1/16th of the full size bag and has a diameter of about 0.9 centimeters and a length of about 2.0 centimeters. The smallest bag has an expanded volume of about 1/32nd of the full size bag and has a diameter of 0.5 centimeters and a length of about 1.4 centimeters.

A number of conclusions are obvious from the above table. First, an extremely wide range of fluids of different viscosities may be employed in the subject invention with controlled release of the fluid. Secondly, very small bags may be used having extremely small amounts of a volatile liquid. Thirdly, long periods of time of continuous discharge of the fluid can be achieved, although the test is terminated after three and one-half days. Furthermore, good reproducibility is obtained, in that the results are amenable to mathematical analysis and predictability based on empirical formulations.

EXAMPLE 2

A self-powered delivery device for the controlled and
continuous administration over a period of three days of tetracycline hydrochloride to the rumen of a cow weighing 1,000 pounds is prepared having the following dimensions and specifications:

**Casing**

| High density rigid polyethylene | Inside diameter | 2.3 cm |
| Wall thickness | 0.2 cm |
| Inside length | 5.0 cm |
| Inner volume | 21 cc |

**Inner bag**

Polyethylene-polyvinyl alcohol-polyethylene laminate film, 1 mil thick charged with 0.2 cc of propellant; propellant mixture of Freon 11 and Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane); mole fraction of Freon 11 is 0.5; vapor pressure of propellant is 900 mm Hg at 38°C; the bag is of the type illustrated in FIG. 2A, having dimensions, when flat, 5 cm x 3.14 cm.

**Active agent**

15 grams of tetracycline HCl in suspension medium of polyethylene glycol 200 (40 weight percent). Concentration of drug is 0.75 gram/cc, having a particle size of less than one micron; viscosity of formulation at 38°C is 10,000 centipoise.

**Flow Control Element**

The flow control element is comprised of five stainless steel hollow capillary tubes sealed in discharge port of the pump. The dimension of each tube is as follows: length = 0.5 cm; diameter of the lumen = 20 micron.

The device prepared above is inserted into the rumen of a cow and will continuously administer the agent at a controlled rate over approximately a 3 day period.

**EXAMPLE 3**

A self-powered delivery device for the controlled and continuous administration of digitoxin to a human adult patient over a one day period is prepared having the following dimensions and specifications:

**Casing**

| High density rigid polyethylene shell | Inner volume | 0.4 cm³ |
| Inside diameter | 0.6 cm |
| Inside length | 1.4 cm |
| Wall thickness | 0.1 cm |

**Inner bag**

Polyethylene-polyvinyl alcohol-polyethylene laminate film 0.5 mil thick charged with 0.05 cc of propellant mixture of Freon 11 - Halothane; mole fraction of Freon 11 equal to 0.5; vapor pressure of the propellant mixture is 850 mm Hg at 37°C; the bag is of the type illustrated in FIG. 2A, having dimensions, when flat, of 1.4 cm x 0.9 cm.

**Active agent**

0.1 mg of digitoxin in carrier medium of ethyl alcohol (17 weight percent) and sodium carboxyl methyl cellulose (1.5 weight percent). Concentration of drug is 17 mg/cc; viscosity of drug carrier formulation is 10,000 centipoise at 37°C.

**Flow Control Element**

The flow control element is 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 a tortuosity of 0.5
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3,840,009

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pandable in response to a pressure increase within the inner chamber from an initial state in which the volume defined by the outer surface of the bladder is less than the volume of said chamber to an expanded state in which the outer surface of the bladder conforms approximately to the shape of said chamber and the volume defined thereby is approximately the volume of said chamber;
d. a self-actuated active agent flow resisting means within said outlet for metering the discharge of agent from said chamber at a substantially constant rate; and
e. a liquified gas propellant having a vapor pressure greater than one atmosphere at the physiological temperature of the mammal contained within said inner chamber;
whereby when said dispenser is placed internally of the mammal said propellant vaporizes in response to said physiological temperature causing said bladder to expand continuously from said initial state to said expanded state and thereby concurrently and continuously displace active agent from said chamber via said outlet and said means in vivo at a controlled rate.
2. The dispenser of claim 1 wherein the outer surface of the bladder in said expanded state is substantially contiguous with the inner surface of the casing.
3. The dispenser of claim 1 including:
f. an inlet in said casing communicating from said exterior to said chamber for charging active agent to said chamber.

4. The dispenser of claim 1 wherein the casing is constructed of a flexible material.
5. The dispenser of claim 1 wherein the same has a specific gravity of at least 1.5 and is of a size, weight and shape which enables it to be retained in the rumen of polygastric mammals.
6. The dispenser of claim 1 wherein the bladder is comprised of a polymeric film material.
7. The dispenser of claim 6 wherein the polymeric film is a laminate.
8. The dispenser of claim 6 wherein the bladder is in the form of a pleated accordion bellows.
9. The dispenser of claim 6 wherein the bladder is comprised of a metal foil.
10. The dispenser of claim 1 wherein the bladder is comprised of polyethylene, polyvinylidene, polyvinylidene chloride, aluminum foil, polypropylene, nylon, polytrifluorochloroethylene, polytetrafluoroethylene, polyvinylacetate, polyvinylchloride, or combinations thereof.
11. The dispenser of claim 1 including:
f. a conduit connected to said outlet and leading to the administration site of the agent.
12. The dispenser of claim 1 wherein the active agent substantially fills that portion of the volume of said chamber not occupied by said bladder in its initial state.

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