United States Patent [19]

Theeuwes

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[45] **Sept. 25, 1973**

[54] **OSMOTICALLY POWERED AGENT DISPENSING DEVICE WITH FILLING MEANS**

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[73] Assignee: **Alza Corporation,** Palo Alto, Calif.

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[52] **U.S. Cl.**..... **222/95,** 128/260, 222/386.5, 222/389

[51] **Int. Cl.**..... **B65d 35/28**

[58] **Field of Search**..... 222/94, 95, 190, 222/386.5, 389, 394; 129/213, 214 R, 218 R, 218 A, 260, 272; 141/3, 30

[56] **References Cited**

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Primary Examiner—Robert B. Reeves
Assistant Examiner—Larry Martin
Attorney—Paul L. Sabatine et al.

[57] **ABSTRACT**

A device is disclosed comprised of a wall formed of a material collapsable in response to mechanical force and surrounding a closed compartment for containing an agent, a dispensing passageway communicates with the compartment and the exterior of the device for dispensing agent therefrom, a filling passageway communicates with the exterior of the device and the compartment for filling the device, a layer of an osmotically effective solute is despoited on the collapsable wall's outer surface, said solute capable of exhibiting an osmotic pressure gradient against an external fluid and increasing its volume as fluid diffuses by osmosis into the solute, an outer wall surrounding the layer of solute formed of a material having shape retaining properties, permeable to the fluid and substantially impermeable to solute, and wherein the filling passageway houses a material penetrable to a means for filling the compartment which material self closes on removal of the means to maintain the compartment in closed condition for subsequent collapsing thereof in response to mechanical or hydrostatic force generated by osmotic pressure arising in the solute layer, as fluid diffuses therein to increase its volume and generate forces that are exerted between the collapsable wall of the agent containing chamber and the more rigid outer semipermeable wall, which collapsing force in turn dispenses an agent through the dispensing passageway when the compartment is charged with drug and the device is positioned in the environment of use.

5 Claims, 7 Drawing Figures

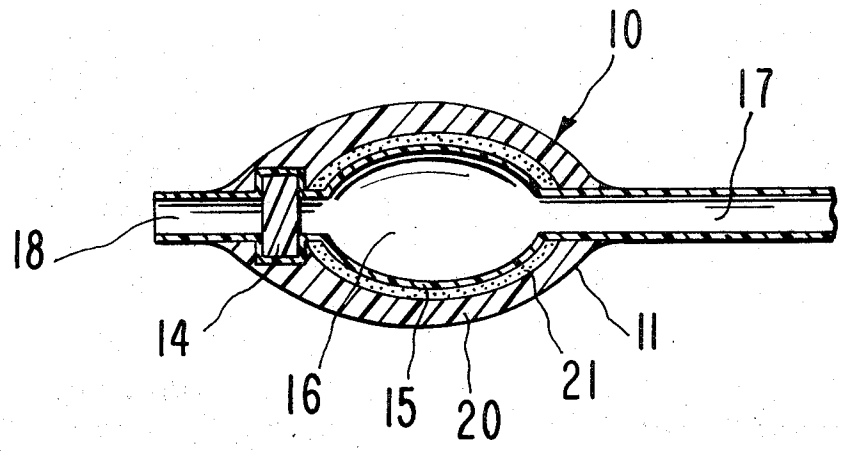


FIG. 1

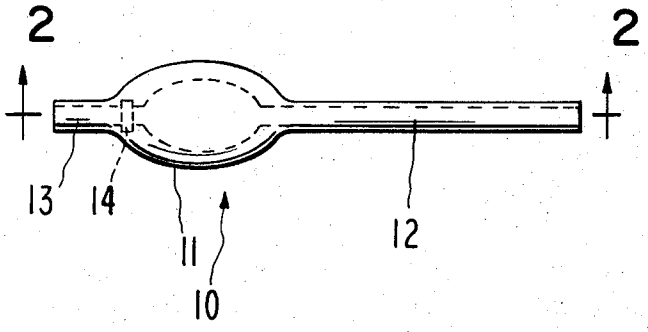


FIG. 2

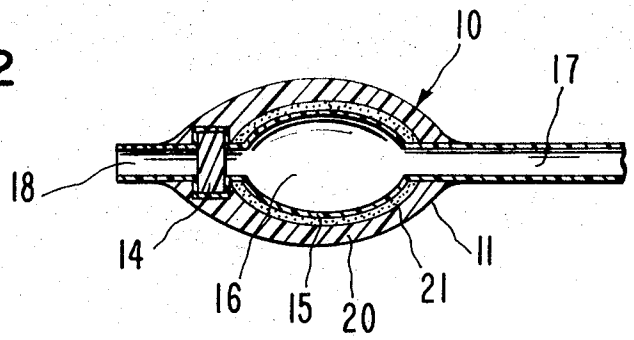
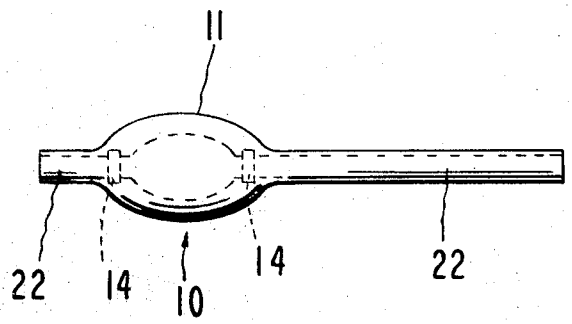
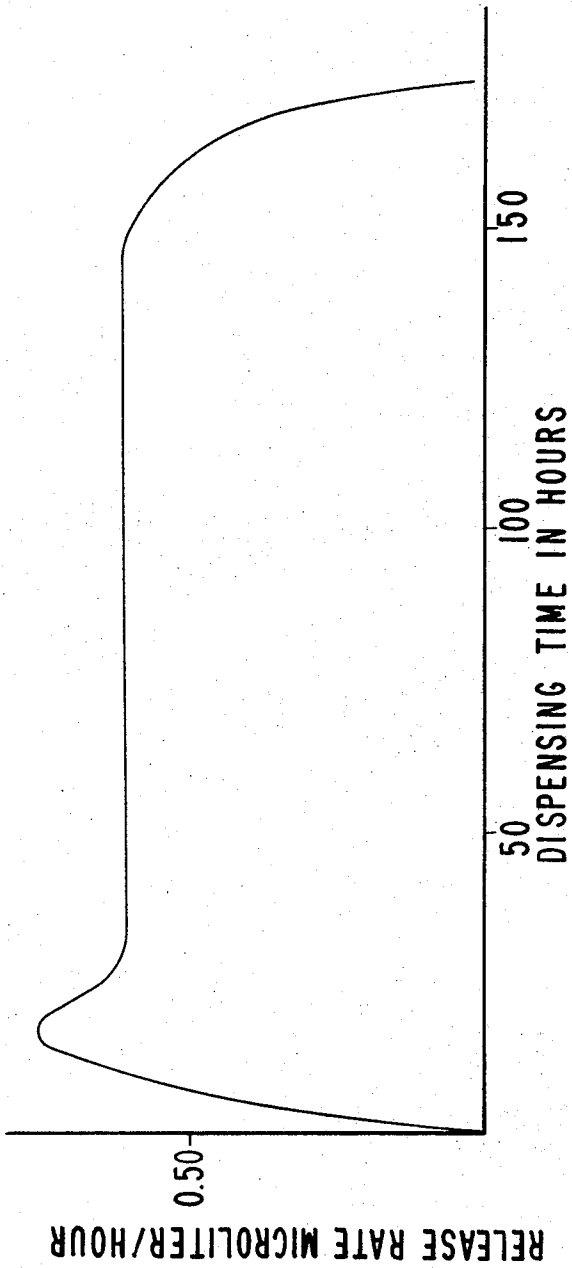


FIG. 3

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50
100
150
DISPENSING TIME IN HOURS

FIG.4

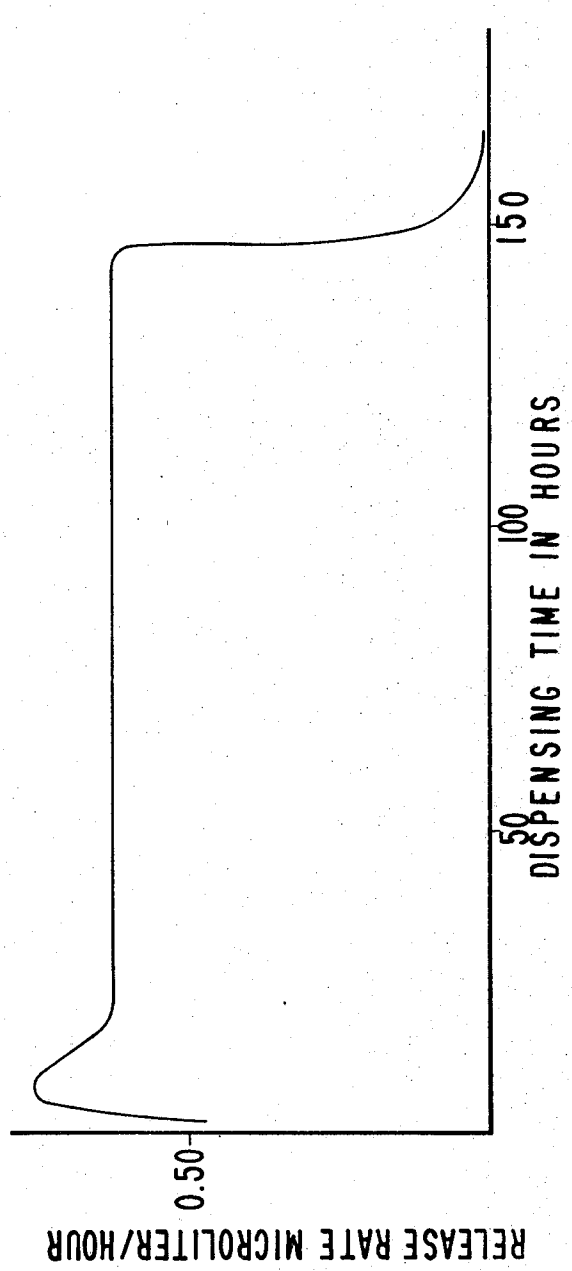
RELEASE RATE MICROLITER/HOUR
0.50
50
100
150
DISPENSING TIME IN HOURS

FIG.5

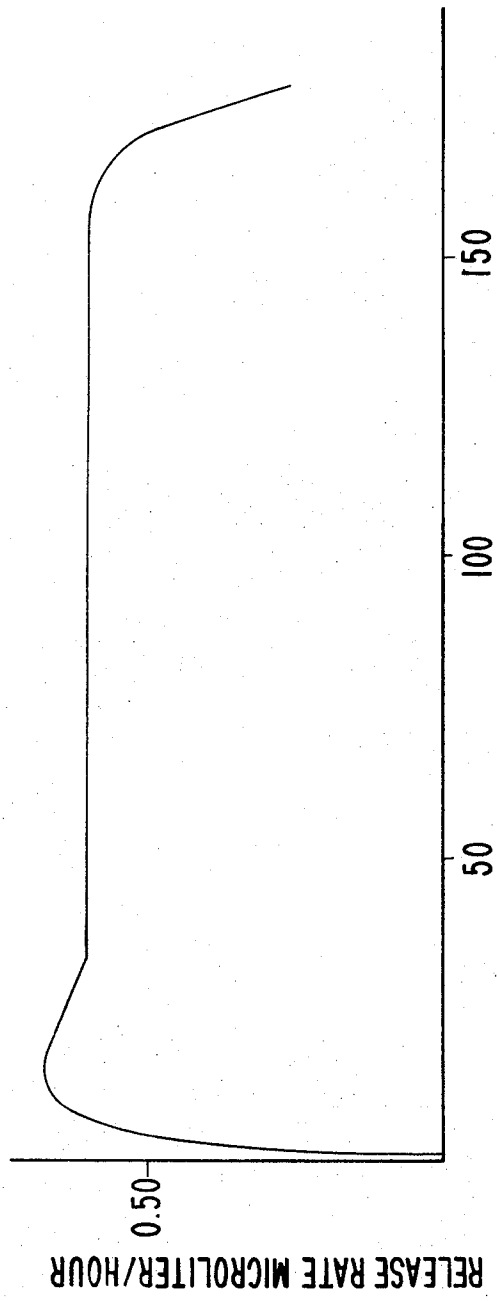
RELEASE RATE MICROLITER/HOUR
0.50
50
100
150
DISPENSING TIME IN HOURS

FIG.6

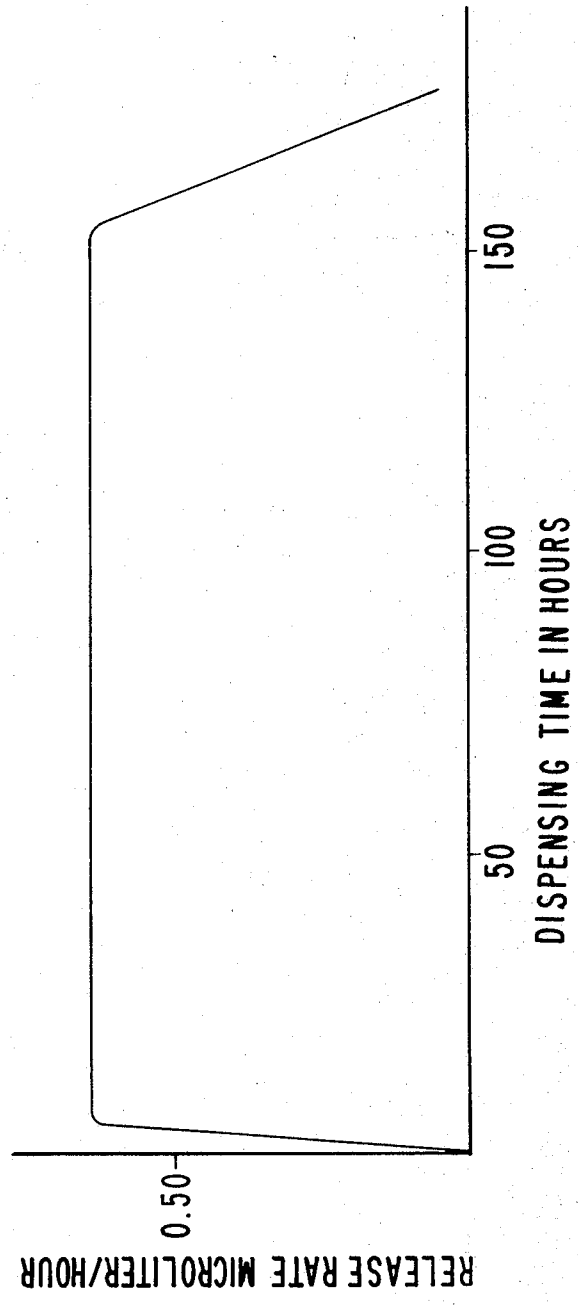
RELEASE RATE MICROLITER/HOUR
0.50
50
100
150
DISPENSING TIME IN HOURS

FIG. 7

OSMOTICALLY POWERED AGENT DISPENSING DEVICE WITH FILLING MEANS

AREA OF THE INVENTION

This invention pertains to both a novel and useful device for dispensing a useful agent. More particularly, the invention relates to a dispensing device for the controlled and continuous dispensing of an agent over a prolonged period of time to produce a desired result. Specifically, the invention concerns an osmotic dispenser manufactured with a minimum number of components wherein one of the components is a filling port with a means for self-closing the port to maintain the sterility and operability of the device after the device is charged with agent.

BACKGROUND OF THE INVENTION

Osmotic dispensing devices for the delivery of active agent are well known to the prior art. These devices are of assorted designs and generally have a plurality of similar structural components. For example, the devices usually have an external wall or housing for containing an internal collapsable chamber for containing an agent. The chamber in the device is surrounded by an osmotically effective solute that is capable of exhibiting a pressure gradient against an external fluid and increasing its volume as external fluid diffuses into the solute to generate a force that is exerted against the chamber causing it to collapse. As the chamber collapses, it ejects agent through a passageway that leads to the exterior of the device.

While these osmotic devices are useful for dispensing agent, they have certain disadvantages that restrict or tend to defeat their use for many applications. For example, the presently available devices are prefilled with a drug which often looses its sterility prior to use of the drug. Also, some drugs have a short shelf life and these drugs tend to deteriorate during storage and diminish the usefulness of the drug. Additionally, the prior art devices lacked a port for filling the chamber, and if they were filled by puncturing with a hollow needle, the device failed to function either because of osmotic pressure leakage at the puncture site or the device became contaminated resulting from mixing of solute and agent arising at the site the inner wall was pierced. Thus, it will be appreciated by those skilled in the art that while the prior art devices made a valuable contribution to the art, the above mentioned disadvantages tended to restrict their use to a few environments.

OBJECTS OF THE INVENTION

Accordingly, it is an immediate object of this invention to provide a novel dispensing device for the dispensing of agent to produce a beneficial effect, which device overcomes the aforesaid disadvantages associated with the prior art devices.

Still another object of the invention is to provide a novel osmotic dispensing device for dispensing an agent at a controlled rate for a prolonged period of time.

Yet still another object of this invention is to provide a novel and useful osmotic dispensing device that is simple in construction, designed with a minimum number of parts, easy to use, and in operation is practical and useful for the controlled, continuous, long-term administration of an agent.

Still another object of the invention is to provide an osmotic dispensing device that has a separate port for filling the device which is self closing to maintain the integrity of the device.

Yet still another object of the invention is to provide an osmotic dispensing device that can be filled with agent when needed from a separate source through a self closing port integral in the device.

Still a further object of the invention is to provide an osmotic dispensing device that is empty until charged and then can administer a complete pharmaceutical dosage regimen for a period of time, the use of which requires intervention only for initiation and termination of the regimen.

Yet another immediate object of this invention is to provide a dispensing device that can be filled with drug at the time of use for administering a drug to produce a locally acting or systemically acting drug to produce a physiologic or pharmacologic effect which device can release the drug at a rate that does not vary with time.

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

SUMMARY OF THE INVENTION

The invention concerns a device comprised of an outer wall surrounding an inner wall that defines a compartment as a means for containing an agent. A layer of an osmotically effective solute capable of exhibiting an osmotic pressure gradient against an external fluid is housed between th outer and inner wall. A dispensing passageway leads from the compartment to the exterior of the device for releasing agent from the device. A filling passageway leads from the exterior of the device to the compartment and it houses a means for closing the passageway. The outer wall of the device is formed of a material having shape retaining properties and it is permeable to an external fluid and substantially impermeable to solute. The inner wall is formed of a material essentially impermeable to external fluid and solute and collapsable when force is exerted thereon. In operation, external fluid permeates at a rate controlled by the wall permeability, wall dimensions, and osmotic pressure gradient into the solute causing it to increase in volume. The increased volume generates a mechanical or hydrostatic compressing or deflating pressure on the collapsable wall, which pressure, negligible to the equilibrium in osmotic pressure of the fluid, in turn ejects the active agent out of the chamber at an osmotic-permeation controlled rate over a prolonged and continuous period of time.

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. 1 is an elevated illustration of an osmotic dispenser of the invention.

FIG. 2 is a cross-sectional view of FIG. 1 through 2—2 illustrating the structure of the device of FIG. 1.

FIG. 3 is a perspective, top view of a dispensing device of the invention illustrating another embodiment of the invention.

FIGS. 4 through 7 represent a graphic illustration of osmotic pumps showing their release rate from the devices over a prolonged period of time.

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

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various delivery devices of the invention, and which examples are not to be construed as limiting, one embodiment of a novel osmotic delivery device is indicated in FIG. 1 by the number **10.** Delivery device **10** is comprised of a body portion **11,** a discharge passageway **12** and a filling passageway **13** integrally formed with device **10.** A means **14** for self closing filling passageway **13** is seen in broken lines in passageway **13.**

Device **10** of FIG. 1 is seen in FIG. 2 in open section through 2—2 of FIG. 1. In FIG. 2, device **10** is comprised of a body **11** formed of an inner wall **15** formed of a flexible material collapsable in response to pressure and relatively impervious to fluid as osmotic solute, the wall surrounds and forms a compartment **16** defined by wall **15**'s inner surface. Compartment **16** is a means for containing an active agent and it is pro-Vided with a means **17** for dispensing the agent to the exterior of device **10.** COmpartment **16** is further provided with a means **18** for filling compartment **16.** Means **18,** also referred to as filling port or filling passageway is Provided with a means **14** for self closing passageway **18.** Closing means **14** is made from a material that is essentially impermeable and inert to agent and pierceable by a filling needle and self closes after the needle is removed therefrom. Distant from inner wall **15** is positioned outer wall **20.** Wall **20** is formed in at least a part of a material permeable to the passage of external fluid. Wall **20** can be of unit construction, or composite construction with a section of a semi-permeable membrane either formed integral in wall **20** or optionally lined or laminated to wall **20.** Wall **20** can be formed of a semi-permeable material that has uniform properties across all its dimensions, that is, it is substantially imperforate or substantially homogenous, or wall **20** can be formed of a material that is microporous.

In FIG. 2, positioned between wall **20** and wall **15** is a layer **21** of an osmotically effective solute that exhibits an osmotic pressure gradient against an external fluid, when the device is positioned in the environment of use. In operation, these solutes osmotically attract fluid through the semi-permeable membrane **20** to produce a solution of the solute which increases in volume while simultaneously generating mechanical or hydrostatic force that is exerted against wall **15** to cause it to correspondingly collapse. As wall **15** collapses it ejects active agent out of chamber **16** through dispensing passageway **17** to the exterior of device **10** at an osmotically membrane controlled rate over a prolonged period of time.

FIG. 3 illustrates another embodiment of the invention. In FIG. 3, device **10** is illustrated comprised of a body **11** having a pair of ports **22** each distant from the other. Ports **22** can be optionally used as filling ports or discharge ports and each houses a material **14** for closing the port after penetrated by a needle. Additionally, either port can be equipped with a needle for discharging agent from device **10.**

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of the present invention, it has now been found that the osmotic delivery device of the invention provides many important advantages over previously known osmotically operated delivery devices. One advantage of the device is the ease of construction of the drug delivery device by standard manufacturing techniques into devices of various shapes and forms for delivering agent to recipient or environment. A more important advantage of the claimed delivery device is that it can be manufactured comprised of a minimum number of parts.

Another important advantage for osmotic delivery device **10** is the device and its agent can be separately stored and the device charged with agent at the time of use. This feature prevents or substantially reduces deterioration of the agent since agents susceptible to deterioration can be stored in glass containers and charged into the device at the time of use. Yet another important advantage for the devices of this invention resides in the users option to formulate special agents or compositions of agents that can be charged into the compartment at the time of use and at the environment of use. Another important advantage for the device resides in the device entering the commerical stream uncharged with agent in a simple sterile package. The feature enhances the utility of the device and simultaneously makes it possible to design special devices for special application that can be charged with agent at the environment of use. These features and other advantages are made available to the art by the invention providing the device with a filling port generally positioned distant from the discharge port. The filling port is equipped with a self sealing or self closing stopper or bung that fills the internal space of the filling port and can be repeatedly penetrated and closed following withdrawal by a penetrating instrument. The filling port housing the bung is constructed with the wall in intimate contact with the bung by shrinking the wall to the bung during fabrication of the device. This unique feature of the device also makes it possible to fill the device with agent without developing air pockets in the compartment and without penetrating the device's walls which could lead to a loss of osmotic pressure and leakage. Additionally, another advantage for the novel osmotic pump is that pumps made with a long and narrow catheter which could not be filled heretofore can now be filled by entering the chamber through filling port equipped with the bung.

Wall **20** of the device is a material that is semipermeable, for example a material that is permeable to an external fluid such as water and the like while essentially impermeable to a selected product or to other compounds in the device. The material forming the wall can be non-erodible or bioerodible after a predetermined period of time and in each instance it is semipermeable to external fluid but not to solute and is suitable through its shape retaining properties during its useful life for construction of the osmotic powered device. Typical materials for forming the wall include membranes known to the art as osmosis and reverse osmosis membranes such as commercially available unplasticized cellulose acetate, plasticized cellulose acetate, reinforced cellulose acetate, cellulose nitrate with

11 percent nitrogen, cellulose diacetate, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose acetate propionate, cellulose acetate p-toluene sulfonate, triacetate of locust gum bean, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylene-vinylacetate, cellulose acetate butyrate having a viscosity of from about 10 seconds to about 50 seconds, cellulose acetate butyrate containing about 17 percent of combined butyryl and about 29.5 percent acetyl permselective, aromatic nitrogen-containing polymeric membranes that exhibit water permeability and essentially no solute passage, osmosis membranes made from polymeric epoxides, osmosis membranes made from copolymers of an alkylene oxide and alkyl glycidyl ether, semi-permeable polyurethanes, semi-permeable polyglycolic or polylactic acid and derivatives thereof, thin film membranes as disclosed by Loeb and Sourirajan in U. S. Pat. No. 3,133,132, the membranes of ionically associated polyelectrolytes, the polymers formed by the coprecipitation of polycation and a polyanion as described in U. S. Pat. Nos. 3,276,586; 3,541,005; 3,541,006; 3,546,142; 3,173,876; derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly(vinylbenzyltrimethylammonium chloride), and the like. Generally, membranes having a fluid permeability of 0.01 to 10 cc/cm^2/hour or day or higher at atmosphere pressure against a saturated product solution or saturated solute solution to a changing concentration at the temperature of use while simultaneously possessing a high degree of impermeability to the product or solute are useful and within the spirit of the invention.

Wall **15**, or the inner wall of the device that defines the compartment and is in intimate contact with bung **14** is a heat shrinkable, polymeric material that collapses on the application of force thereto and simultaneously maintains the self sealing bung in the filling port. The polymeric membrane is selected from the class of heat shrinkable polymeric films in the form of tubes, spheres, ellipsoids, envelopes, films, laminates, and other geometric shapes and fabricated structures is in one embodiment a material that has been prepared by inducing strong molecular orientation by uni-axially or bi-axially stretching of the film, which operation, preferably, can be preceded by the introduction of inter-molecular primary valence cross-linkage by chemical or radiation processes. The degree of cross-linking, when employed, should be sufficient to impart to the film a thermoset character, which can be conveniently defined as the ability to exhibit a minimum tensile strength of about 50 lbs./in.^{2} at a temperature of 300°F. By "heat shrinkable" is meant in this embodiment that the film can contract by at least 10 percent and typically from about 25 percent tO 75 percent of its stretched dimension in one or more directions upon heating. The material is expanded or stretched mechanically, hydraulically, or pneumatically, either uniaxially or bi-axially, at room temperature or elevated temperatures, and then is set or fixed, or "frozen", into this expanded, high energy state. Procedures for accomplishing this are well known in the polymer fabrication art. For example, in the manufacture of bi-axially oriented, heat shrinkable flim, the film is prepared by extrusion through a shaping die with a long, narrow horizontal slit of such width as to give the desired film thickness. As the hot ribbon of polymeric material issues from the die, it is gripped along its two edges by tenter hooks which tend to stretch the film along its width and to stretch it in a forward direction at the same time. This operation imparts bi-axial orientation and yields a film with equal shrinkage along both axes. Typically, such a film will have a potential shrinkage of 50 percent in both directions. Not only is the rate of stretching important in achieving this result, but the rate of cooling and the temperature profile during the stretching are important. As described here, this operation is done in-line with extrusion, but it can also be done on preformed film by heating and stretching the film.

In the manufacture of one type of heat shrinkable tubing for use in the present invention, the polymer is first prepared in tubular shape, preferably by extrusion through a die of the desired cross-sectional configuration. The tubing can then be subjected to ionizing radiation consisting of a stream of high energy electrons as delivered by a van de Graaff generator or other electron accelerating equipment. Or the tubing can be treated with gamma rays as emanating from cobalt-60. The dosage delivered can vary, depending upon the polymer system, from 0.5 to 100 megarads to achieve the desired degree of intermolecular cross-linkage. The tubing is then subjected to uni-axial molecular orientation by drawing it, optimally in a warm or heated condition, over an appropriately shaped mandrel, which increases the cross-sectional area by a factor of 2 to 16. The polymer, having been selected from classes which tned to have high intermolecular attraction, will tend to remain in the high energy, stretched state until heated above a temperature at which these intermolecular attractions are melted or released. The "memory" or tendency to recover back to the unstretched state is encouraged by the cross-linkage which was introduced by the earlier radiation treatment.

Polymeric membranes preferably are cross-linked prior to stretching and using to form the inner wall. The chemical cross-linking of these polymers can be achieved by incorporation of various cross-linking agents such as peroxides, sulfur, metallic oxides, selenium, tellerium, diamines, diisocyanates, alkyl phenol disulfides, p-quinone dioxime, tetra-chloro-p-benzoquinone, tetra alkyl thiuram disulfides, 4,4'-dithiomorpholine, sulfur dichloride, and the like, into the polymer followed by a period of heating. Alternatively, cross-linking or vulcanization can be achieved by use of high energy electron-beam radiation such as is provided by a van de Graaff generator or other types of electron accelerators, or by gamma ray emitters, or by X-ray generators.

In another embodiment pre-oriented shrinkable materials suitable for forming the chamber and housing the self sealing bung by engaging the bung when the film is exposed to heat comprise oriented film of vinyl chloride polymer which has a Young's modulus of elasticity in both directions of at least 200,000 p.s.i. (14,000 kg/cm^2) at 23°C, a shrinkage of at most 35 percent at 150 p.s.i. (10.5 kg/cm^2) at any temperature. The films preferably have shrink tensions not exceed-

ing 100 p.s.i. (7 kg/cm²) at any temperature. The most preferred film is a rigid (i.e. unplasticized) polyvinyl chloride film which is 0.01 to 0.95 mm thick and has been bi-axially oriented so that it has a shrinkage in both directions of at most about 20 percent, especially 15 to 20 percent, e.g. about 20 percent. Films having low degrees of orientation or shrink in one direction only, such as are produced directly by some extrusion methods, can be used in accordance with the invention, but require the use of rather high film temperatures, near the melting point of the polymer, in order sufficiently to shrink the film. Accordingly it is preferred to use films which have been bi-axially oriented so that they have percent shrinkages at 100°C in both directions of 5 to 35 percent, especially 15 to 25 percent, particularly 15 to 20 percent, and have shrink tensions not exceeding 150 p.s.i. (10.5 kg/cm²) and preferably not exceeding 100 p.s.i. (7.0 kg/cm²) at any temperature; such films are believed to be novel. They can be very satisfactorily used in shrink packaging procedures in which the film only has to reach a maximum temperature of 120°C and for regular objects 100°C or even less.

The vinyl chloride polymer shrinkable materials used herein include homopolymers and copolymers such as vinyl chloride and vinyl acetate, styrene, acrylonitrite, dialkyl fumarate or maleate, or alkyl acrylate or methacrylate, vinyl acetate and vinylidene chloride, blends of polyvinyl chloride with chlorinated polyethylene or terpolymer, and the like. Other heat shrinkable materials include vinylidene chloride, copolymers of vinylidene chloride of 20 to 80 percent vinylidene chloride, copolymers of vinylidene chloride and vinyl chloride and the like. Heat shrinkable materials are set forth in U.S. Pat. Nos. 3,022,543; 3,419,421; 3,459,582; 3,614,852; 3,627,116; and the like.

Various osmotically effective solutes including organic and inorganic compounds are advantageously used for coating on the exterior surface of the inner wall to act as a means for generating osmotic pressure. Suitable solutes exhibit an osmotic pressure gradient against an external fluid across the semi-permeable membrane which membrane is substantially impermeable to the passage of the osmotically effective solute to prevent loss thereof through the membrane. Various osmotically effective solutes include compounds such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium sulfate, potassium acid phosphate, calcium lactate, magnesium succinate, tartaric acid, soluble carbohydrates such as raffinose, glucose, mixtures thereof and the like.

Additionally, the solute can be used in a mixed form by mixing the compound with a binder. The solute in powdered, granular, piece and the like form, is homogenously or heterogenously dispersed in the binder which binder is soluble or insoluble but will release the solute on contact with wall material. Typical binders include polyethylene glycol, gelatin, agar, carboxycellulose, ethylmethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, soluble starch derivatives and the like. Typical binders that can comprise about 1 to 50 percent of the composition include cellulose acetate, polyurethane, epoxides, and other binders that permit the free movement of fluid into the solute of the layered structure to permit the solute to increase in volume and generate osmotic pressure.

The stopper or bung, as confined in the filling passageway, is comprised of naturally occurring or synthetic material that possesses self closing or self sealing properties following the withdrawal therefrom of a piercing instrument. These materials are generally known to the art as elastomers, and they include the commercially available carboxylated butadiene acrylonitrile copolymers, butadiene vinylpyridine copolymers, polychloroprene, isoprene, copolymerized with piperylene, polyisoprene, poly(butadiene-co-styrene), poly(butadiene-co-acrylonitrile), natural rubber, poly(isobutylene-co-isoprene), silicones, fluroelastomers, butyl rubber, halogenated butyl rubber, poly(butadiene-styrene-vinylpyridine) acrylic rubbers, butadiene:acrylonitrite 80/20, 73/27, 68/32, 61/39, free radical cross-linked silicone elastomers, and the like.

The phrase "active agent" and the term "agents" as used throughout the specification and the accompanying claims comprises any compound, or mixture of compounds, composition of matter or mixture thereof that can be dispensed from the device to produce a predetermined beneficial and useful result. The active agents include pesticides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, antioxidants, plant growth promoters, plant growth inhibitors, preservating agents, surfactants, disinfectants, sterilization agents, catalysts, chemical reactants, fermentation agents, cosmetics, foods, nutrients, food supplements, drugs, vitamins, sex sterilants, fertility inhibitors, fertility promotors, air purifiers, microorganism attenuators, and other like agents that benefit the environment, surroundings, and habitat including animals, mammals, man, valuable farm animals, household animals, sport animals, and the like.

In a presently preferred embodiment the active agent is a drug that will produce a local or systemic physiologic or pharmacologic response when administered to animals, including humans, avians, and the like. Suitable drugs that are dispensed in conventional, standard dosage amounts as known to the art comprise desensitizing agents such as ragweed pollen antigens, hay fever pollen antigens, dust antigen and milk antigen; vaccines such as small pox, yellow fever, distemper, hog cholera, fowl pox, antivenom, scarlet fever, diphtheria toxoid, tetanus toxoid, pigeon pox, whooping cough, influenzae, rabies, mumps, measles, poliomyelitis, Newcastle disease, etc; anti-infectives, such as antibiotics, including penicillin, tetracycline, chlortetracycline, bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethizole, sulfamethazine, sulfadiazine, sulfamerazine, and sulfisoxazole; anti-virals including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate; anti-allergenics such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and prophenpyridamine; anti-inflammatories such as hydrocortisone, cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate,fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate; decongestants such as phenylephrine, naphazoline, and tetrahydrozoline; miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phospholine

iodide, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; sympathomimetics such as epinephrine; sedatimes and hypnotics such as pentobarbital sodium, phenobarbital, secobarbital sodium, codeine, (α-bromo-isovaleryl) urea, carbromal; psychic energizers such as 3-(2-aminopropyl) indole acetate and 3-(2-aminobutyl) indole acetate; tranquilizers such as reserpine, chlorpromazine, and thiopropazate; androgenic steroids such as methyltestosterone and fluoxymesterone; estrogens such as estrone, 17 β-estradiol, ethinyl estradiol, and diethyl stilbesterol; progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-norprogesterone, norethindrone, medroxyprogesterone and 17 α-hydroxyprogesterone; humoral agents such as the prostaglandins, for example PGE_1, PGE_2, and PFD_2; antipyretics such as aspirin, sodium salicylate, and salicylamide; anti-spasmodics such as atropine, methantheline, papaverine, and methscopolamine bromide; anti-malarials such as the 4-aminoquinolines, 8-aminoquinolines, chloroquine, and pyrimethamine; antihistamines such as diphenhydramine, dimehydrinate, tripelennamine, perphenazine, and carphenazine; cardioactive agents such as hydrochlorothiazide, flumethiazide, chlorothiazide, and trolnitrate; nutritional agents such as vitamins, essential amino acids and essential fats; anti-Parkinsonism agents such as L-dopa, (L-3,4-dihydroxyphenylalanine); investigative antihypotensive agents such as dopamine, 4-(2-aminoethyl) pyrocatechol. Other agents having the same or different physiological activity as those recited above can be employed in osmotic dispensers within the scope of the present invention. Suitable mixtures of drugs can, of course, be explained with equal facility as with single component systems.

The agent can be in various forms, such as unchanged molecules, components of molecular complexes, or non-irritating pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulphate, phosphate, nitrate, borate, acetate, maleate, tartrate, salicylate, and the like. For acidic drugs, salts of metals, amines, or organic cations, for example, quaternary ammonium can be employed. Furthermore, simple derivatives of the drugs such as ethers, esters, amides, and the like which have desirable retention and release characteristics but which are easily hydrolyzed by body pH, enzymes and the like can be employed. The amount of agent incorporated in the osmotic dispenser varies widely depending on the particular agent, the desired therapeutic effect, and the time span for which it takes the agent to be released. Since a variety of dispensers in a variety of sizes and shapes are intended 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 dispenser. The lower limit too will depend on the activity of the drug and the time span of its release from the dispenser. Thus it is not practical to define a range for the therapeutically effective amount of drug to be released by the dispenser. Thus, the amount dispensed for active agents such as drug will be the standard amount as described in *Pharmacology in Medicine*, edited by DiPalma, J.R.., 1965, McGraw-Hill Book Company, New York; *The Pharmacological Basis of Therapeutics*, Fourth Edition, by Goodman, L.S. and Gilman, A., 1970, The Macmillian Co., New York; *Remington's Pharmaceutical Sciences*, Fourteenth Edition, 1970, Mack Publishing Company, Easton, Penn.; and the like. Additionally, the drug can be charged into the device in known forms such as solution, dispersion, cream, emulsion, suspensions, fine powders, and the like. Generally, the device will contain about 0.01 to 90 percent or higher of an agent or a mixture of agent and carriers based on the weight of the agent or agent carriers composition solute to the volume of the device, and the like. Typically, the device can be of such size and shape to release 0.01 cc to 5 cc or higher of agent, usually contained in a pharmaceutical carrier, per hour, day or longer, such as 1 cc to 10 cc of agent composition for 1 to 10 days, and the like.

The expressions "passageway" and "passageway communicating with" as used herein are comprised of those means and methods suitable for releasing the product from the device under the pumping rate of the device. The expression includes an aperture, orifice, bore, stainless steel needles, hollow cellulose acetate tubes, polyolefin tubes, capillary tubes suitable for passing the agent, tubes and conduits of various inside diameters, closed passageways containing a bioerodible material that erodes in the environment of use to produce an open passageway. Typical bioerodible materials include erodible polyglycolic and polylactic fibers, erodible gelatinous filaments, polyvinyl alcohol, and the like.

The following 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.

An osmotic dispensing device for the continuous release of active agent and having a diameter volume of 100 microliters was manufactured as follows: first, a section of commerically available heat shrinkable poly(olefine) such as poly(vinylidene chloride) having an internal diameter three thirty-seconds inches was cut into a 5 cm section. Next, a plug of commerically available Silastic silicone rubber was cut from a rod, with the plug having the following dimensions 3 mm long × 3 mm O.D. wherein O.D. is outside diameter. Then, the plug was inserted into the heat shrinkable tubing and held in position between two solid steel rods. One rod entered the tubing from each of its entrances. The unit was heated at 100°C in water and pulled longitudinally until the gap between the plug and the rod was 2 mm longer than a mold cavity used for the pulling step. The mold cavity was 7 mm long.

The tubing containing the plug was cooled to room temperature and clamped into a second mold with a milled cavity and a clamping means for confining the encapsulated silicone rubber. The mold was closed and heated at 100°C in water with pressure applied for 30 seconds through one opening of the tubing to expand the tubing to the dimensions of the cavity. The mold was next cooled and tubing housing the plug and having a cavity was removed from the mold.

Next, an osmotic solute slurry was prepared by mixing 500 grams of analytical reagent grade K_2SO_4 powder with 200 ml of 2 wt percent ethyl cellulose in ethanol in a Waring blender at the highest speed for about 2 minutes. The appropriate amount of solute was

deposited on 15 chambers by 5 dips in the cooled solute slurry with 15 minute intervals between dips. The slurry coated chambers were placed in a near zero humidity dry box to prevent water absorption during evaporation of solvent. A few of the chambers were optionally dipped in gelatin to smooth any pores and add strength to the solute deposit. When gelatin was applied, the gelatine dip was 15 g in 100 ml of distilled water at 60°C. All the coated chambers were dried at least 2 hours. The total solute coat thickness was measured at about 0.27 mm.

Next, the dry solute coated chambers were placed in a dipping box containing an acetone atmosphere for dipping in a freshly prepared cellulose acetate membrane solution comprised of 15 wt percent cellulose acetate and 85 wt percent acetone. The chambers were dippsed 14 times with 15 minute intervals between dips to deposit a membrane about 14 mils thick.

Four osmotic dispensing devices manufactured according to the above description were changed with a blue dye solution and the dye release rate measured and charted in accompanying FIGS. **4, 5, 6** and **7.** The osmotic pumps were placed in an environment of water which was an external fluid. The dispensed blue dye is measured volumetrically or by using standard otpical laboratory measuring instruments. The results obtained show that after a short start-up period, the osmotic devices uniformly dispense about 0.6 μl/hr. The prolonged and constant pumping rate is obtained to exhaustion of the chamber, or for about 150 hours, and the total volume dispensed from the devices was about 92 μl. The results for the devices measured as shown in FIGS. 4 – 7 are seen as evidencing the useful operability of the device for its application in industry and commence.

The novel, osmotic product delivery device of this invention employs a unique means which facilitates the obtainment of precisely conducted agent release rates in the environment of use. While there has been described and pointed out the fundamental novel features of the invention as applied to the presently preferred embodiments, those skilled in the art will appreciate that various modifications changes and omisslons in the osmotic agent devices illustrated and described can be made without departing from the spirit of the invention.

What is claimed is:

1. An osmotic dispenser for dispensing an active agent, wherein said dispenser comprises:

a. an inner wall formed of a fexible material essentially impermeable to solute and external fluid, the wall surrounding and forming,

b. a compartment defined by the inner surface of the wall as a means for housing an active agent,

c. a layer of an osmotically effective solute deposited on the inner wall's outer surface, said solute capable of exhibiting an oxmotic pressure gradient against an external fluid when the dispenser is positioned in the environment of use,

d. an outer wall surrounding the layer of solute, said outer wall formed of a material having shape retaining properties and at least a part of the wall is permeable to external fluid and impermeable to solute,

e. a dispensing passageway communicating with the compartment and the exterior of the device for dispensing an agent from the device,

f. a filling passageway communicating with the exterior of the device and the compartment as a means for charging agent into the compartment,

g. a means positioned in the filling passageway for closing the passageway, said means formed of a material that automatically closes after agent is charged into the compartment through the filling passageway.

2. An improved osmotic dispenser for dispensing an active agent according to claim **1** wherein the inner wall material is a heat shrinkable polymeric material.

3. An improved osmotic dispenser for dispensing an active agent according to claim **1** wherein the automatic closing material is an elastomeric material.

4. An improved osmotic dispenser for dispensing an active agent according to claim **1** wherein the filling passageway is formed of a heat shrinkable polymer in intimate contact with the automatic closing material formed of an elastomeric material.

5. An improved osmotic dispenser for dispensing an active agent according to claim **1** wherein in operation in the environment of use, agent is dispensed from the dispensor by external fluid permeating from the exterior through the permeable outer wall continuously dissolving the solute in a tendency toward osmotic equilibrium with the environment to continually increase the volume between the outer wall and the compartment generating a mechanical or hydrostatic force to cause the compartment to continuously collapse and dispense agent from the device at a controlled rate over a prolonged period of time through the dispensing passageway with essentially no agent dispensed through the filling passageway.

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