

[54] **HELICAL OSMOTIC DISPENSER WITH NON-PLANAR MEMBRANE**

[75] Inventor: **Harold M. Leeper**, Lawrence, Kans.

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

[22] Filed: **Jan. 13, 1971**

[21] Appl. No.: **106,132**

[52] **U.S. Cl.**..... **128/260, 128/130, 222/386**

[51] **Int. Cl.**..... **A61m 31/00, A61f 5/46**

[58] **Field of Search**..... **128/260, 127-131, 128/172, 213, 261, 272, 271; 222/193, 389, 386.5, 386, 130, 105, 106, 94, 95, 97; 210/23**

[56] **References Cited**

UNITED STATES PATENTS

3,382,869	5/1968	Rigney et al.	128/130
3,604,417	9/1971	Stolzenberg	128/213
3,446,435	5/1969	Hager	222/389 X
2,962,023	11/1960	Chappaz et al.	128/260
2,880,913	4/1959	Peyron	222/389 X
3,104,663	9/1963	Laws	128/224

OTHER PUBLICATIONS

Govidan and Sourirajan, "Reverse Osmosis Separation of Some Inorganic Salts ...-Using...Membranes;" I & EC Process Design and Development, Vol. 5, No. 4, Oct. 1966; p. 422-429.

Primary Examiner—Richard A. Gaudet

Assistant Examiner—J. C. McGowan

Attorney—Steven D. Goldby and Paul L. Sabatine

[57]

ABSTRACT

An osmotic active agent dispenser is comprised of: (1) a first helical compartment of relatively impervious material containing an active agent and provided with a dispensing head for releasing active agent to the exterior of the dispenser; (2) a second helical compartment of controlled permeability to water containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water, the second compartment being interconnected with said first compartment to define a continuous helix therewith; and (3) a movable barrier member separating the first from the second compartment. The barrier member is slidably responsive to an increase in volume in the second compartment via absorption of water by osmosis therein; whereby as water flows into the compartment (2) of the dispenser in a tendency towards osmotic equilibrium with its environment, corresponding pressure is exerted behind the barrier (3) driving it into and diminishing the volume of the compartment (1), in turn continuously ejecting active agent thereout at an osmotically controlled rate over a prolonged period of time.

14 Claims, 5 Drawing Figures

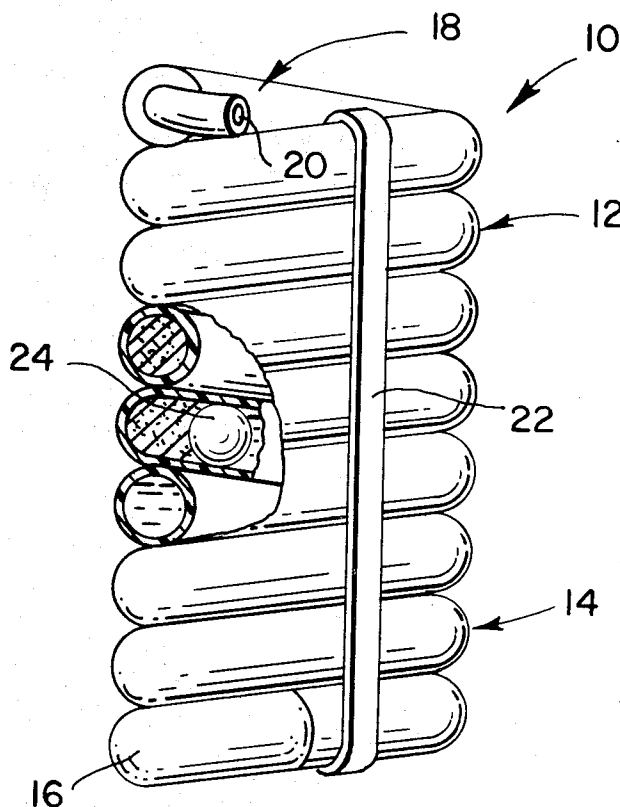


FIG. 1

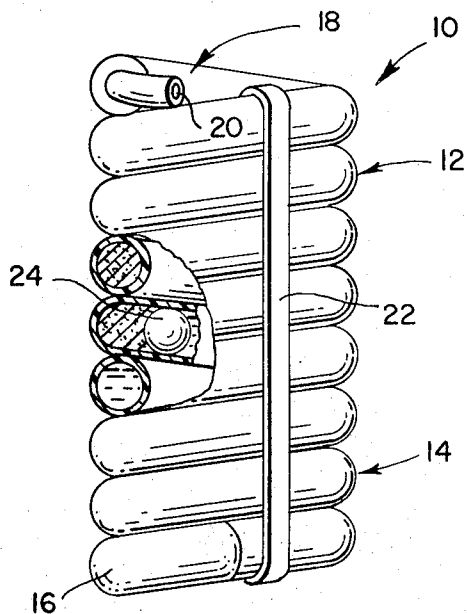


FIG. 2

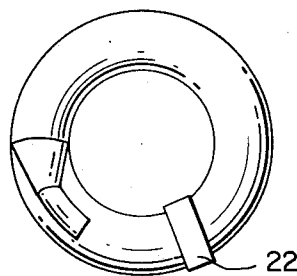


FIG. 3

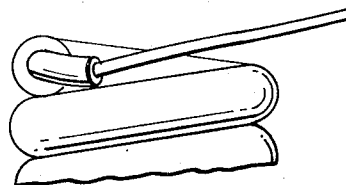


FIG. 3a

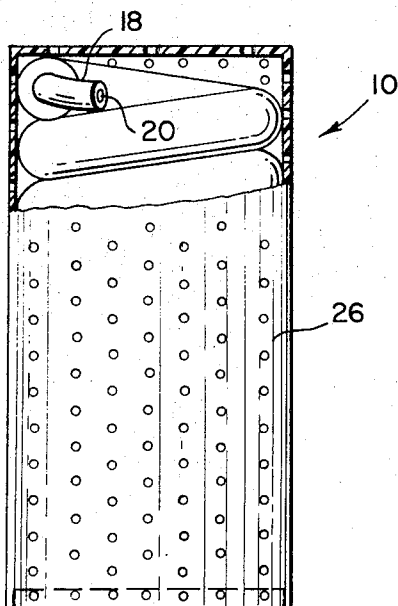
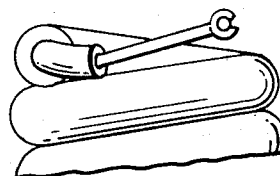


FIG. 4

INVENTOR

HAROLD M. LEEPER

BY

Steven D. Goldby
ATTORNEY

HELICAL OSMOTIC DISPENSER WITH NON-PLANAR MEMBRANE

CROSS REFERENCE TO RELATED APPLICATIONS

Takeru Higuchi copending application, Ser. No. 106,131, filed Jan. 13, 1971, assigned to the assignee of the present invention; and

Takeru Higuchi and Harold M. Leeper copending application, Ser. No. 106,130, filed Jan. 13, 1971, also assigned to the assignee of the present invention.

FIELD OF THE INVENTION

This invention relates to an osmotic dispenser, and, more especially, to an osmotic dispenser, simple in construction, capable of releasing to its outside environment concentrations of active agent at an osmotically controlled rate over a prolonged period of time.

DEFINITION OF TERMS

The expression "active agent" as used herein denotes any drug (as defined, *infra*); composition in any way affecting 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 substance having any other effect on any other environment, especially any aqueous environment.

Therefore, 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., vitamin compositions, sex sterilants, fertility inhibitors, fertility promoters, growth 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, modifying, repelling or retarding an animal or microorganism, such as food and non-food baits, attractants and lures, biocides, pesticides, algicides, parasiticides, rodenticides, insecticides, fungicides, and the like;

5. Preserving, disinfecting or sterilizing; and

6. Controlling or affecting generically an environment, as by introducing a catalyst or metering a reactant into a reacting chemical system, or by effecting any chemical process therein, such as a fermentation, including propagation and/or attenuation of a microorganism.

The terms "environment", "surroundings" and "habitat" as used hereinabove and herein denote any prospective situs for the osmotic dispenser of this invention which is comprised of or will provide sufficient water for absorption into the device to develop the needed osmotic pressure on which its motive force depends; and implicit in the foregoing definition of "active agent"—one that will develop its action in the

presence of such environment, surroundings or habitat, or one that will develop its action in a remote and/or another environment, which need not be aqueous, as hereinafter described and illustrated.

BACKGROUND OF THE INVENTION

Many and varied compositions, products, appliances, depositors, applicators, dispensers, injectors and devices are well known in the art in which the timing or spacing of administration or absorption of an active agent is regulated by the structure or physical arrangement of elements so that a single administration provides a gradual but continuous or sustained feeding of the active agent to a system by slow or differential release. All of such prior art devices and the like, however, are characterized by at least one feature which adversely affects control over their rate of sustained or differential release or which detracts from the practical benefits attendant the long term continuous administration of various active agents both to humans, animals, and into other environments.

An osmotic dispenser too has been proposed which is capable of delivering drug solution at a relatively constant rate. See Rose and Nelson, *Austral. J. exp. Biol.*, 33 pp. 415-420 (1955). The Rose et al. injector consists of three compartments and a clamp to hold a semi-permeable membrane. The motive force of the injector depends on the osmotic pressure developed by a saturated aqueous solution of Congo red against water. This solution is contained in a partially collapsed rubber compartment and is separated from a second water compartment by the semipermeable cellophane membrane. The partially collapsed bag is placed in a glass ampoule, with the drug compartment of the device being defined by the space between the Congo red bag and the glass ampoule. The ampoule is also provided with drug release means and when the drug compartment is charged with a drug solution, by osmosis water will move into the Congo red solution thus expanding the rubber compartment and providing the mechanical force to eject the drug out of the apparatus.

The Rose et al. device, however, has substantial inherent disadvantages which has prevented its wide acceptance by the medical community. In the first place, the use of a solution as the drug vehicle 1. will not permit high concentration of drug to be embodied within the device; 2. such solutions exhibit the deleterious tendency to be released from the device by simple leaching, and 3. many chemical substances on prolonged storage in a dissolved state undergo chemical deterioration. The reference injector is moreover cumbersome in that it depends for its motive force on a separate water compartment rather than its environment. In addition, the Rose et al. device is essentially only a research or experimentation tool, is complex in construction and is at least literally restricted to a Congo red solution to produce the osmotic driving force and to a cellophane osmotic membrane. See also Rose and Nelson, *Austral. J. exp. Biol.*, 33 pp. 411-414 (1955).

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of this invention to provide an osmotic dispenser, simple in construction, which exhibits all of the practical benefits of long-term continuous administration of various active agents both to animals, humans, and into other environments.

Another object of this invention is to provide an improved osmotic dispenser which overcomes problems inherent in related devices heretofore proposed.

Another object of this invention is to provide an improved osmotic dispenser which will permit high concentrations of active agent to be embodied therein, and which high concentrations of active agent will not exhibit the tendency to be leached from the device, nor be decreased in potency by chemical breakdown.

Another object of this invention is to provide an osmotic active agent dispenser which depends for its motive force on its environment.

Still another object of this invention is to provide an osmotic dispenser, the osmotic membrane of which can be fabricated from many and varied suitable materials, and which is capable of using a variety of solutions of osmotically effective solutes to produce the osmotic driving force.

Yet another object of this invention is to provide an osmotic dispenser of simple design which will release active agent solution, or gel, or semisolid active agent formulation, at a controlled rate over a prolonged period of time.

In attaining the objects of this invention, one feature resides in an osmotic dispenser comprised of a first helical compartment of relatively impervious material containing an active agent and a second helical compartment containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water. The two helical compartments are interconnected so as to define a continuous helix. Separating the first helical compartment from the second helical compartment, and defining a wall member common to each of said compartments, is a sliding or movable barrier of impervious material, advantageously a plastic or glass ball separator. The enclosure, whether of integral construction or not, defining the remainder of the second compartment wherein the osmotic motive force of the dispenser is developed, is at least in part comprised of membrane material which exhibits controlled permeability to water. When placed in a hypotonic aqueous environment, water, by osmosis, is absorbed therefrom through the membrane and diffuses into the solution contained in the second compartment. As the water flows into the second compartment, the solution contained therein increases in volume exerting corresponding pressure behind the movable barrier divider. Such pressure serves to drive the said barrier forward and into the active agent compartment thus diminishing the volume of the same, and which sliding or rolling barrier in turn ejects the active agent out of the apparatus at an osmotically controlled rate over a prolonged period of time. For the purpose of permitting the active agent to be squeezed out of the first compartment, the same is provided at its terminal point with any suitable dispensing head or active agent release means to the exterior of the device, for example, a capillary duct therethrough.

A further feature of this invention resides in an osmotic active agent dispenser comprised of a dispenser according to the foregoing description enveloped by a relatively rigid, highly permeable housing member. The housing member serves both as a protective means for the dispenser and also to restrict expansion of the dispenser due to internal pressure. Alternatively, such expansion may be in and of itself restricted by means of any suitable band or tie member.

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

In the drawings:

FIG. 1 is a fragmentary cross-sectional view of an osmotic dispenser of this invention;

FIG. 2 is a top view of FIG. 1;

FIG. 3 is a fragmentary cross-sectional view of a modification in the dispensing head of the osmotic dispenser of FIG. 1;

FIG. 3a is a fragmentary cross-sectional view of another modification in the dispensing head of the osmotic dispenser of FIG. 1; and

FIG. 4 is a fragmentary cross-sectional view of an osmotic dispenser of this invention having a rigid housing member.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment in accordance with this invention, as illustrated in FIG. 1, an osmotic dispenser 10 is comprised of two helically shaped compartments, a first compartment designated generally by reference numeral 12 and the second compartment designated by reference numeral 14. Each of the helical compartments is formed by coiling a relatively flexible tubular material, the former essentially being a continuation of the latter, although, as hereinafter described, there are significant differences in the types and properties of the tubular material used to fabricate each of the helical compartments 12 and 14. The lower end or terminal point of compartment 14 is sealed off, as, for example, by curved plug member 16 of a rigid impervious material such as refractory plastic. Optionally, plug member 16 may be fabricated from metal or similar heavy material to additionally serve as a ballast member for adjusting the specific gravity of the dispenser. The terminal point of helical compartment 12 is provided with a short continuation in the form of tubing 18 having a capillary duct or opening 20 approximately 0.5 millimeters in diameter. Joints between the respective components may be press-fits or may involve use of an adhesive system. The device is preferably provided with one or more bands or ties 22 which bind together each of the coils in the helix and act as restraining means to prevent spreading of the coils due to internal pressures developed in the dispenser. A sliding barrier plug 24 of impermeable material compartmentalizes the helix and thus defines the exact boundaries of the helical compartments 12 and 14.

The first compartment 12 contains the active agent, advantageously a drug, in a gel, paste or other semisolid state (albeit a solution or concentrated solution of active agent will sometimes suffice), and the active agent, if a drug, is preferably normally carried in an oil phase, such as cocoa butter. Compartment 12 is thus fabricated from a material which is impermeable both to the drug contained therein and also to all components of the dispenser environment.

The second compartment 14 contains a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water; and the sliding barrier plug 24 is so constructed as to movably provide and maintain a tight barrier between the active agent

phase in the first compartment and the osmotic fluid in the second compartment. Advantageously, and as illustrated, the barrier is a plastic or glass ball separator. Without this tight barrier, undesirable contamination could take place. Compartment 14 is fabricated at least in part from a material which exhibits controlled permeability to water, preferably a semi-permeable membrane of the type used in reverse osmosis water desalination, e.g., isotropic or anisotropic cellulose acetate. Obviously, the tubing used to fabricate compartment 14 must be impermeable to the osmotically active solute contained therein.

The capillary tube or active agent release means 18 provides communication from the interior of the compartment 12 to the exterior of the device 10, in this instance the said means being comprised of capillary duct 20 formed at the terminal point of the active agent containing helical compartment 12. See also FIG. 2. The plug 24 is frictionally disposed but is free to move within the device by sliding while at the same time maintaining an impenetrable or contamination preventing barrier between the active agent phase and the osmotic fluid. Thus, an oil/water or other interface can be said to exist at the point of the plug in the device.

To use the osmotic active agent dispenser of FIG. 1, the device, when the active agent is a drug or other agent for treating, etc., a living organism, is either physically inserted or surgically implanted in the body of the organism, typically a mammal, or is administered via the gastrointestinal tract. Once in place, water will be absorbed therein from either body tissues or body fluids through the water permeable walls of compartment 14 in an effort to reach osmotic equilibrium, i.e., a transition from hypertonicity to isotonicity. As the water flows into the compartment 14 tending to increase the volume of same corresponding pressure is built up behind the sliding barrier plug 24. Such pressure serves to drive the said barrier plug 24 forward at a constant rate thus forcing the drug through the tube 18 and capillary duct 20 at an osmotically controlled and constant rate into the external environment. 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. Moreover, the use of any semisolid drug vehicle will reduce the tendency to release the drug, or any other active agent for that matter, by leaching and will permit high concentrations thereof to be embodied within the device.

In some instances, the dispenser is 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 the device, such as the metal plug 16 in FIG. 1. Suitable weights comprise steel plugs, iron plugs, brass plugs, ceramic plugs, or the like.

When the active agent is other than a drug or similar agent, or is intended for use other than in a living organism, the device is introduced into the desired aqueous environment to produce the desired affect exactly as would be any of the known means for accomplishing a like result. 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 an aqueous reaction medium.

If desired, long flexible tubing of polythene or the like can be extended from the dispensing head of the device of FIG. 1. In such a configuration, as illustrated in FIG. 3, the device can be deposited at a site remote from the desired point of application and still release its active agent contents through the dispensing head and then through the tube directly to said point. This permits placement of the dispenser in an aqueous environment and release of the active agent into another environment which need not be aqueous. The dispensing head can also be provided with a check valve, for example, a one way ball valve (see FIG. 3a), to prevent backflow of active agent or other materials from the external environment into the device.

The design of a device in accordance with the present invention is moreover unique in that it provides a simple means to control the amount of surface area available for osmotic penetration. Thus, for example, by decreasing the diameter of the tubing used to manufacture the helical coils, or by increasing the number of turns in the helix of compartment 14 a significant increase in the surface area of the water-permeable material results, whereby such a design provides for ready attainment of large exposure areas of the water permeable membrane and thus takes advantage of the availability of a far greater number of water-permeable materials than the semi-permeable, anisotropic cellulose acetate membrane of the type used in reverse osmosis water desalination. Isotropic membranes have less water permeability than do the anisotropic membranes. Use of the latter type of material, however, permits significant decreases in the size of helical compartment 14.

In FIG. 4 there is depicted an osmotic active agent dispenser generally of the type illustrated in FIG. 1, except that the same is enveloped by a relatively rigid permeable housing member 26. The porosity of the housing member readily permits contact of water from the environment with the dispensing device, while at the same time its relatively rigid characteristics afford a high degree of protection from damage or puncturing to the dispenser. Moreover, the housing member advantageously serves as a restraining means to prevent spreading of the coils, etc., in the device due to internal pressure, especially when a housing member having both ends capped is provided for this purpose; and serves the further purpose of facilitating emplacement in a given host or environment.

Another salient feature of the osmotic active agent dispenser of this invention resides in its simple means of construction, and correlatively in the simple manner thereby provided for controlling the dosage rate in a given dispenser device. In contradistinction to other known types of active agent dispensing devices wherein a device of different size is required for each dosage level to be contained therein, the instant dispensing device may be designed to contain and administer any desired quantity of active agent to contain and administer any desired quantity of active agent by merely increasing or decreasing the length of tubing which constitutes the active agent containing helical compartment 12.

Moreover, a device according to this invention is admirably suited for the continuous administration of the antibiotic oxytetracycline to beef cattle from the rumen. This because such devices can easily be fabricated of a size, weight and shape as to be retained in the rumen of polygastric animals to release drug or similar

agents thereto at a carefully controlled rate. Other variations of the basic theme would be readily apparent to the skilled artisan. Although particular configurations may be designed for specific body uses, each of these configurations is applicable to use in other environments.

The tubing employed to fabricate the osmotic solution containing compartment 14 can be formed from the wide variety of materials permeable or semi-permeable to solvent (water) but not to solute, i.e., those suitable for the construction of an osmotic cell. For best results, the material should be substantially impermeable to passage of the osmotically effective solute so as to prevent losses thereof. Same is also insoluble and chemically compatible with the salt solution in the compartment 14. Typical membranes are isotropic membranes such as unplasticized cellulose acetate, plasticized cellulose acetate, reinforced cellulose acetate, cellulose di- and triacetate, ethyl cellulose; anisotropic reverse osmosis membranes which typically are made of cellulose acetate; silicone rubbers, polyurethanes, natural rubber, and hydrolyzed ethylene/vinyl acetate copolymers. Isotropic membranes such as above have less water permeability than do the anisotropic membranes. Also, with both types of materials, increasing the acetate content of the cellulose acetate polymer decreases the water permeability. Since, as previously described, the surface area available for osmotic transfer may be widely varied, the devices of this invention are not limited to any one class of water permeable material, i.e., both those exhibiting high permeability as well as those of lower permeability may be employed. Thus, a cellulose acetate membrane suitable for a device designed with limited surface area available for osmotic transfer is Eastman Chemical Products Type RO 97, which is rated to be permeable to 1.5 to 2 cc/cm²/day at atmospheric pressure, against a saturated solution of K₂SO₄ at 39° C. When the compartment is fabricated from an anisotropic reverse osmosis type of membrane it is possible to obtain a delivery rate of from 20 to 10,000 mg of active agent per day. In general, the unplasticized membranes of whatever type provide for a far greater rate of release per day than do the plasticized membranes. The device of the above specific embodiment, having a specific gravity of at least 1.5, is moreover well suited for administration to the rumen of beef cattle, whereat it is retained, via the gastrointestinal tract; and this is an excellent way of treating, for example, a 500 pound calf with anti-biotic. For drug depot applications as heretofore described, the membranes are also biologically inert, non-irritating to body tissues and non-allergenic. One specific embodiment of a dispenser fabricated in accordance with the design illustrated in FIG. 1, having compartment 14 fabricated of cellulose diacetate tubing (degree of acetyl substitution = 2.4) and compartment 12 formed of polyethylene tubing, and having the following dimensions:

	Compartment 14	Compartment 12
Outer diameter of tubing	1.000 cm	0.976 cm
Wall thickness	0.012 cm	0.050 cm
Inner diameter of tubing	0.976 cm	0.876 cm
Outer diameter of helix	3 cm	3 cm
Number of turns	4	3
Uncoiled length	25.1 cm	18.8 cm
Initial volume		
Osmotic Solution ¹	18.75 cc	

¹ Saturated aqueous solution of NaCl containing sufficient excess solute in solid form to maintain solution saturated over period of intended use.

	Compartment 14	Compartment 12
Initial volume drug ²		11.3 cc
Effective surface area	78.9 cm ²	
Final volume osmotic solution	30.0 cc	
Final volume drum		0.00 cc
Overall size of device:		
Diameter	3.2 cm	
Height	7.5 cm	

² Approximately 55 percent oxytetracycline hydrochloride in 45 percent cocoa butter medium.

is capable of delivering 20 to 300 mg of drug per day.

The impermeable plastic material used to fabricate compartment 12 of the device too is insoluble, is chemically compatible with the active agent contained therein, and can be formed of polystyrene, polyethylene, polypropylene, polyethylene terephthalate, polyvinyl chloride, reinforced epoxy resin, polymethylmethacrylate, etc., metal foil polyethylene laminate, neoprene rubber, natural gum rubber, rubber hydrochloride, sheet metal, galvanized pipe, or styrene/acrylonitrile copolymer. It is of course intended that such casing or shell act as a barrier to the transport of water. Again, for drug depot applications, the same are advantageously biologically inert, non-irritating to body tissues and non-allergenic. The barrier plug 24 can be formed of materials identical to those used for fabricating the impervious active agent containing compartment 12, and additionally can be formed of glass. Likewise with respect to the rigid housing member 26 of FIG. 4, except in this instance the materials would be highly porous since it is not intended that the housing member in any way act as a barrier to or restrict the transport of water.

Many other materials including those which are biologically acceptable 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 have previously been described as being insoluble under the conditions and 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 situs 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.

It is further within the scope of the invention to optionally provide the subject dispenser with a self-contained water supply or separate water compartment, as in the first mentioned Rose and Nelson publication, supra.

The relative wall thicknesses of the various types of tubing comprising the two compartments of the dispensers of the invention can vary widely and are not limitations on the invention. Typically, however, the impermeable tubing of compartment 12 has a wall thickness of 0.5 to 50 mils, preferably of 5 to 50 mils, and the water permeable tubing of compartment 14 has a wall thickness of 1 to 10 mils.

Any of the drugs used to treat the body, both topical and systemic, can be compartmentalized as the active agent in any of the osmotic dispensers of this invention. "Drug" is used herein in its broadest sense as including any composition of substance that will produce a pharmacological or biological response.

Suitable drugs for use in therapy with the dispenser of the invention include without limitation:

1. Protein drugs such as insulin;
2. Desensitizing agents such as ragweed pollen antigens, hay fever pollen antigens, dust antigen and milk antigen;
3. 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.;
4. 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;
5. Anti-allergens such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and propenpyridamine;
6. Anti-inflammatories such as hydrocortisone; cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate;
7. Decongestants such as phenylephrine, naphazoline, and tetrahydrozoline;
8. Miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phospholine iodide, and demercurium bromide;
9. Mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine;
10. Sympathomimetics such as epinephrine;
11. Sedatives and Hypnotics such as pentobarbital sodium, phenobarbital, secobarbital sodium, codeine, (α -bromoisovaleryl) urea, carbromal;
12. Psychic Energizers such as 3-(2-aminopropyl) indole acetate and 3-(2-aminobutyl) indole acetate;
13. Tranquilizers such as reserpine, chlorpromazine, and thiopropazate;
14. Androgenic steroids such as methyltestosterone and fluoxymesterone;
15. Estrogens such as estrone, 17 β estradiol, and diethyl stilbesterol;
16. Progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-nor-progesterone, norethindrone, medroxyprogesterone and 17 α -hydroxy-progesterone;
17. Humoral agents such as the prostaglandins, for example, PGE₁, PGE₂, and PGF₂;
18. Antipyretics such as aspirin, sodium salicylate, and salicylamide;
19. Antispasmodics such as atropine, methantheline, papaverine, and methscopolamine bromide;
20. Anti-materials such as the 4-aminoquinolines, 8-aminoquinolines, chloroquine, and pyrimethamine;
21. Antihistamines such as diphenhydramine, dimenhydrinate, tripeleminamine, perphenazine, and carphenazine;
22. Cardioactive agents such as hydrochlorothiazide, flumethiazide, chlorothiazide, and trolnitrate;
23. Nutritional agents such as vitamins, essential amino acids and essential fats;

24. Anti-Parkinsonism agents such as L-dopa, (L-3,4-dihydroxyphenylalanine);

25. Investigative antihypertensive agents such as dopamine 4-(2-aminoethyl) pyrocatechol.

Other drugs 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 dispensed with equal facility as with single component systems.

Drugs can be in various forms, such as uncharged molecules, components of molecular complexes, or non-irritating pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulphate, phosphate, nitrate, borate, acetate, maleate, tartrate, salicylate, etc. For acidic drugs, salts of metals, amines, or organic cations (e.g., quaternary ammonium) can be employed. Furthermore, simple derivatives of the drugs (such as ethers, esters, amides, etc.) which have desirable retention and release characteristics but which are easily hydrolyzed by body pH, enzymes, etc., can be employed.

The amount of drug incorporated in the osmotic dispenser varies widely depending on the particular drug, the desired therapeutic effect, and the time span for which it takes the drug to be released. Since a variety of dispensers in a variety of sizes and shapes are intended to provide complete dosage regimes 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.

The motive force of the dispenser of this invention depends on the osmotic pressure generated by the solution of the osmotically effective solute contained in the compartment 14, which solution exhibits an osmotic pressure gradient against water. Said solution is most preferably a saturated aqueous salt solution. To maintain the solution saturated and therefore to achieve a constant osmotic pressure throughout operation of the dispenser, the compartment containing the solution also contains excess solute in solid form. Various osmotically effective solutes can be used. These include magnesium sulphate, magnesium chloride, sodium chloride, potassium sulphate, sodium carbonate, sodium sulphite, sodium sulphate, sodium bicarbonate, potassium acid phthalate, calcium bicarbonate, potassium acid phosphate, raffinose, tartaric acid, succinic acid, calcium succinate, calcium lactate, and magnesium succinate. The excess solid solute can be in the form of dispersed particles or preferably in the form of a pellet. The solution can initially be a solution of the same or of a osmotically effective solute different than the solid excess solute.

The osmotic dispenser can be fabricated in any convenient shape for either physical insertion or implantation in the body, or for administration via the gastrointestinal tract, or for introduction into any 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 dosage unit takes, for example, in

cases of specific body uses, implantate, bolus, IUD, IVD, vaginal ring, uterine capsule for fertility suppression, artificial gland, pessary, prosthesis, suppository, and the like. Likewise with respect to the upper limit on the size of the device. In one specific embodiment, the dispenser can be of such size as to deliver 1 to 2 cc of drug formulation per day and to deliver a total of 5 to 10 cc of drug formulation over a 5 to 10 day period. With alternate choice of slower permeation materials, the pump can deliver drug more slowly up to and in excess of one year. It is preferred that the construction of the several compartments and of the active agent release means be such that the osmotic driving pressure developed is at least 10 times greater than the back pressure generated by the active agent formulation.

Thus, the invention provides, in an osmotic dispenser, a reliable means for releasing effective concentrations of active agent contained therein to the body of a living organism, or to any other environment, at an osmotically controlled rate and over a prolonged period of time. In addition, prime advantages of the dispenser of the invention are that it is simple in construction and exhibits all of the practical advantages of the long-term continuous administration of various active agents both to humans, animals, and into other environments, and that the active agent contained therein will not exhibit the tendency to be leached therefrom.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various modifications, changes, omissions, and substitutions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention be limited only by the scope of the following claims.

What is claimed is:

1. An osmotic active agent dispenser comprising, (1) a first helical compartment of relatively impervious material containing an active agent and provided with means for releasing said active agent to the exterior of the dispenser; (2) a second helical compartment comprised of membrane material having controlled permeability to water, being at least in part non-planar in configuration, and containing an osmotically effective solute which, in solution, exhibits an osmotic pressure gradient against water, said second compartment being interconnected with said first compartment to define a continuous helix therewith; means to restrict substantial expansion of the helix due to internal pressure and (3) a movable barrier member separating the said first from the said second compartment and movably responsive to an increase in volume in the said second compartment via absorption of water by osmosis therein; whereby as water flows into the compartment (2) of the dispenser in a tendency towards osmotic equilibrium with its environment, corresponding pressure is exerted behind the barrier (3) driving same into and diminishing the volume of the compartment (1), in turn continuously ejecting active agent thereout at an osmotically controlled rate over a prolonged period of time.

2. The osmotic dispenser as defined by claim 1, wherein the barrier (3) defines a wall member common

to each of said compartments (1) and (2).

3. The osmotic dispenser as defined by claim 1, wherein the active agent is selected from the group consisting of a drug and a bio-affecting composition.

4. The osmotic dispenser as defined by claim 1, wherein the active agent contained therein is in the form of a semisolid formulation.

5. The osmotic dispenser as defined by claim 1, wherein the solution exhibiting an osmotic pressure gradient against water is a saturated aqueous salt solution.

6. The osmotic dispenser as defined by claim 5, wherein the saturated salt solution contains excess solute in solid form.

7. The osmotic dispenser as defined by claim 1, wherein the first helical compartment (1) is comprised of a member selected from the group consisting of polyethylene, metal-foil polyethylene laminate, neoprene rubber, rubber hydrochloride, polystyrene, polypropylene, polyethylene terephthalate, polyvinyl chloride, polymethylmethacrylate, sheet metal, galvanized pipe, reinforced epoxy resin, natural gum rubber, and styreneacrylonitrile copolymer.

8. The osmotic dispenser as defined by claim 1, wherein the second helical compartment (2) is comprised of a member selected from the group consisting of cellulose acetate, silicone rubber, polyurethane, natural rubber and hydrolyzed ethylene/vinyl acetate copolymer.

9. The osmotic dispenser as defined by claim 1, wherein the active ingredient release means comprises a capillary tube forming an extension of helical compartment (1).

10. The osmotic dispenser as defined by claim 1, wherein the restricting means comprises a relatively rigid permeable housing member enveloping the device.

11. The osmotic dispenser as defined by claim 10, wherein the housing member is comprised of a member selected from the group consisting of perforated polystyrene, perforated polyethylene, perforated polypropylene, perforated polyethylene terephthalate, perforated polyvinyl chloride, perforated polymethylmethacrylate, perforated sheet metal, perforated reinforced epoxy resin, perforated galvanized pipe, porous sintered brass tubing, porous styrene/acrylonitrile polymer, and porous sintered polyethylene.

12. The osmotic dispenser as defined by claim 1, wherein the movable impervious barrier is a spherical body comprised of glass or plastic.

13. The osmotic dispenser as defined by claim 1, further comprising a ballast member to regulate the weight thereof.

14. The osmotic dispenser as defined by claim 1, wherein the osmotically effective solute is selected from the group consisting of magnesium sulphate, magnesium chloride, sodium chloride, potassium sulphate, sodium carbonate, sodium sulfite, sodium sulphate, sodium bicarbonate, potassium acid phthalate, calcium bicarbonate, potassium acid phosphate, raffinose, tartaric acid, succinic acid, calcium succinate, calcium lactate, magnesium succinate and mixtures thereof.

* * * * *