

[54] OSMOTIC DISPENSER

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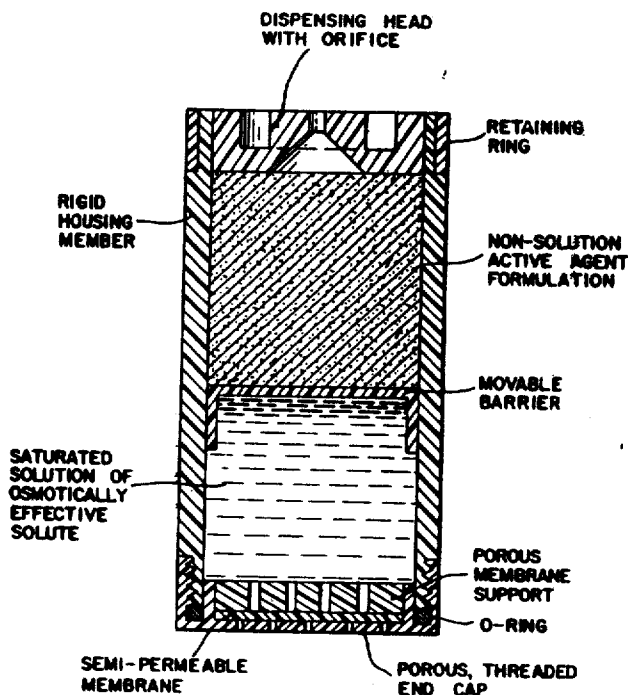
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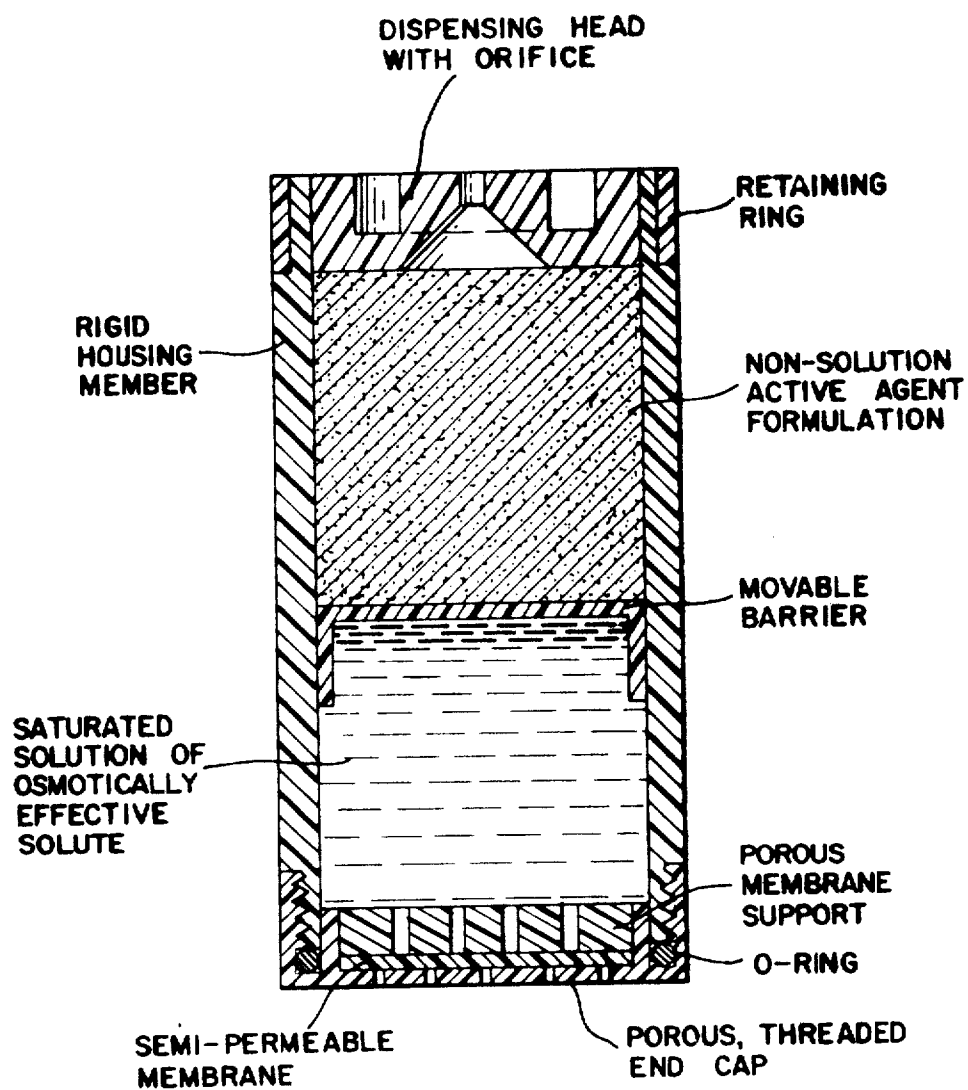
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ABSTRACT

An osmotic dispenser is described which is capable of releasing to its outside environment concentrations of active agent at an osmotically controlled rate over a prolonged period of time, and the active agent content of which dispenser is formulated in a form other than wholly in solution, namely, the active agent is formulated as a dispersion, suspension, emulsion, cream, gel, paste, slurry, or the like, and most preferably all of the above are characterized by the consistency of either the semisolid or solid state.

9 Claims, 1 Drawing Figure





OSMOTIC DISPENSER

This is a continuation of application Ser. No. 349,774, filed Apr. 10, 1973, and now abandoned.

CROSS REFERENCE TO RELATED APPLICATIONS

Takeru Higuchi copending application, Ser. No. 106,131, now U.S. Pat. No. 3,760,805 filed Jan. 13, 1971, assigned to the assignee of the present invention;

Takeru Higuchi and Harold M. Leeper copending application, Ser. No. 106130, now U.S. Pat. No. 3,732,865, filed Jan. 13, 1971, also assigned to the assignee of the present invention;

Harold M. Leeper copending application, Ser. No. 106132, now U.S. Pat. No. 3,768,066 filed Jan. 13, 1971, also assigned to the assignee of the present invention; and

Takeru Higuchi and Harold M. Leeper copending application, Ser. No. 106161, now abandoned, filed Jan. 13, 1971, also assigned to the assignee of the present invention.

PRIOR ART

Rose and Nelson, *Austral. J. exp. Biol.*, 33 pp. 415 - 420 (1955); Rose and Nelson, *Austral. J. exp. Biol.*, 33 pp. 411 - 414 (1955).

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 subtracting, 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, or at least for the water permeable membrane component thereof, 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.

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; sulfonamide, 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 demecarium 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, ethinyl 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-malarials 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 antihypotensive 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, amide, 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.

BACKGROUND OF THE INVENTION

Osmotic dispensers have heretofore been proposed, each of which is capable of dispensing concentrations of active agent at an osmotically controlled rate over a prolonged period of time.

Typically, these osmotic dispensers are comprised of a first compartment of relatively impervious material containing an active agent and a second compartment or chamber of controlled permeability to water containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water. Such devices are so constructed that, when placed in or functionally exposed to* a hypotonic aqueous environment, water is absorbed therefrom by osmosis and diffuses into the solution contained in the second compartment. As the water flows into the second compartment, the solution contained therein and in certain instances the compartment itself increase in volume, thus generating, either directly or indirectly, mechanical pressure or force on the active agent containing first compartment. The said first compartment is provided with any suitable dispensing head for releasing its active agent content to the exterior of the dispenser and individually is of a construction that its active volume is inversely responsive to the pressure thus exerted, i.e., is of such construction that, in use, the volume of same diminishes in a direct proportion to and as a consequence of increase in volume in the said second compartment. Hence, the rate and amount of release of the active agent are directly proportional to the change in volume in the second compartment, but inversely proportional to the volume change in the first. That is, as the water flows into the device, the second compartment increases in volume generating corresponding pressure for force on the first, either directly or indirectly, as by transmitting pressure against a separate or common wall member thereof, which wall member is yielding to such pressure, or by biasing a movable barrier into or against the first compartment or a wall member defining the same. The volume of said first compartment is thus constantly diminished and active agent is correspondingly continuously squeezed thereout at an osmotically controlled rate over a prolonged period of time.

*By "functionally exposed to" it is intended that, for example, such devices may be provided with their own self-contained water supply or separate water compartment, as in the first mentioned Rose and Nelson publication supra.

In the aforementioned related applications, the disclosures of which are hereby incorporated by reference and are relied upon, there are described and claimed several osmotic active agent dispensers of the immediately above type.

For example, in Higuchi copending application, Ser. No. 106131, now U.S. Pat. No. 3760805 filed Jan. 13, 1971, osmotic dispenser is comprised of a water permeable housing member, advantageously rigid, confining a first flexible bag of relatively impervious material containing the active agent, advantageously a drug, preferably in a gel, paste or other semisolid state (albeit a solution or a concentrated solution of active agent will sometimes suffice), and a second bag of controlled permeability to moisture containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water. The said first and second bags are disposed within the said water permeable housing member or porous shell such that water permeates from the environment through the porous shell or housing and migrates by osmosis into the solution contained in the second bag. The solution in the second bag increases in volume, exerting mechanical force on the active agent containing first bag, which mechanical force in turn ejects the active agent out of the apparatus. For purposes of permitting the active agent to be

squeezed out of the said first flexible bag, same is provided with any suitable active agent release means or dispensing head to the exterior of the device, e.g., long plastic tubing extending through the porous shell, or ductlike fine tubule connections therethrough.

Higuchi and Leeper copending application, Ser. No. 106130, now U.S. Pat. No. 3732865, filed Jan. 13, 1971, relates to an osmotic dispenser comprised of a first compartment of relatively impervious material containing an active agent and a second compartment containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water. Separating the said first from the said second compartment, and defining a wall member common to each of said compartments, is a sliding or movable barrier of impervious material. 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 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 said 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 same, and which sliding barrier in turn ejects the active agent out of the apparatus at an osmotically controlled rate over a prolonged period of time. For purpose of permitting the active agent to be squeezed out of the first compartment, same also is provided with any suitable dispensing head or active agent release means to the exterior of the device, for example, capillary ducts therethrough. A further feature of this invention resides in an osmotic active agent dispenser comprised of a plurality of capsule half shells, similar in shape to pharmaceutical hard gelatin half shells, with a first and a second half shell being securely affixed in capsular configuration, and a third half shell frictionally disposed in such capsule but free to slidably move therein. The said capsule is thereby divided into the two compartments with the third half shell defining the wall member common to each of same.

And Leeper copending application Ser. No. 106132, now U.S. Pat. No. 37360806, filed Jan. 13, 1971, describes 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 capable of traversing the helix, 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 forgoing 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.

The osmotic active agent dispenser described in Higuchi and Leeper copending application, Ser. No. 106161, now abandoned, filed Jan. 13, 1971, is comprised of a chamber having controlled permeability to water and containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water, said chamber housing a flexible bag of relatively impervious material containing an active agent and provided with means or dispensing head for releasing said active agent to the exterior of the dispenser. The flexible bag is disposed within the said housing chamber such that as water permeates from the external environment through the permeable walls of the chamber and migrates or diffuses by osmosis into the solution contained therein, same increases in volume thereby generating mechanical compressing or deflating force on the flexible bag, which force in turn ejects the active agent out of the apparatus at an osmotically controlled rate over a prolonged period of time.

The osmotic dispenser proposed in the Rose and Nelson article, supra, too is capable of delivering drug solution at a relatively constant rate. This injection consists of three components 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 semi-permeable 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 water will move by osmosis into the Congo red solution, thus expanding the rubber compartment and providing the mechanical force to eject the drug out of the apparatus.

The compartment or chamber of the aforesaid osmotic active agent dispensers containing the solution of the osmotically effective solute, wherein the osmotic motive force of the respective devices is developed, is at least in part comprised of membrane which exhibits controlled permeability to water. Such membrane can

be formed from a 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. 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 membrane which typically are made of cellulose acetate; silicone rubbers, polyurethanes, natural rubber, and hydrolyzed ethylene/vinyl acetate polymers. Isotropic membranes have less water permeability than do the anisotropic membranes. Also, with both types of membranes, increasing the acetate content of the cellulose acetate polymer decreases the water permeability. In devices, the surface areas of the membranes of which are relatively limited, it will be preferred to use semi-permeable membranes allowing relatively rapid water transmission. Thus, in such embodiments the anisotropic membranes are the preferred. For drug depot applications as heretofore described, the membranes are also biologically inert, non-irritating to body tissues and non-allergenic. So too in such applications are the other materials from which the topic dispensers are fabricated. For best results, the membrane should be substantially impermeable to passage of the osmotically effective solute so as to prevent loss thereof.

In the osmotic dispenser proposed by Rose and Nelson, *supra*, the active agent is employed in the form of a solution. Consequently, there result several disadvantages as regards the handling of such osmotic devices, e.g., spillage and loss of active ingredient, as well as in their storage capabilities since drug containing solutions generally have a relatively short shelf life, and many chemical substances on prolonged storage in a dissolved state undergo chemical deterioration. Furthermore, the use of solutions in osmotic devices places an absolute upper limit on the concentration of active agent that can be administered from a given volume of composition. This latter limitation is of great importance when overall size limitations of such devices are considered. Moreover, drug or other active agent solutions exhibit the deleterious tendency to be released from an osmotic device by simple leaching.

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 handling and storage problems inherent in related devices heretofore proposed.

Another object of the invention resides in the provision of an improved osmotic dispenser which enables high concentrations of active agent to be administered therefrom, 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.

In attaining the objects of this invention, one feature resides in an osmotic active agent dispenser, the active agent of which is formulated in a form other than wholly in liquid solution. That is to say, the active agent is formulated in the form of for example a dispersion, a suspension, an emulsion, a cream, a gel, a paste, a slurry, or any other physical or chemical form which

does not wholly involve solvation of the active agent molecules. In a preferred embodiment, the active agent formulation is in the form of a paste, cream, gel or other at least semisolid. Optionally, there may be incorporated into the active agent formulation one or more additional ingredients, such as surfactants, antioxidants, preservatives, and/or dispersed inert particulate solid fillers or gellants.

Other objects, features and advantages of this invention will become more apparent from the following description.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention, it has been discovered that significant advantages are obtained by employing in the subject osmotic dispensers an active agent formulated in a form other than wholly in liquid solution form. Thus, the active agent formulation may comprise an active agent dispersed, suspended, emulsified, etc., in a carrier which is typically but not necessarily liquid at the storage temperatures of the subject devices, advantageously room temperature. Active agent formulations of the invention may take on the physical characteristics of a solid, semi-solid or a thickened liquid; however, it is preferred that the formulations exhibit the characteristics of a semi-solid and only somewhat less preferably those characteristics of a liquid of relatively high viscosity, e.g., a liquid having a viscosity of at least 1,000 centipoises at 20°C. Liquid active agent formulations having lower viscosities are of course feasible but less advantageous in certain contemplated applications of the subject devices. By employing the topic active agent formulations, the dispensers of the invention are characterized by improved handling convenience because there is little or no possibility for spillage or loss of active ingredient from the devices, thereby assuring uniformity of dosage at all times subsequent to fabrication of the same. Moreover, in active agent formulations wherein the active agent is not wholly in solution, the tendency for chemical breakdown of the active agent is markedly decreased, and also such non-solution formulations are characterized by storage stability greatly improved as compared with liquid solution active agent formulations which typically have a relatively short shelf life. In another aspect, by removing the solubility limitations inherent in active agent formulations of the solution type, higher concentrations of active agent can be administered from the same volume of composition in accordance with the active agent formulations of the present invention, and there is considerably less tendency for the active agent formulated in solid, semi-solid or high viscosity formulations to be leached from the topic devices. Thus, the devices of this invention are capable of administering a wide range of active agent dosages while at the same time conforming to inherent overall size limitations.

Active agent formulations containing an active agent formulated other than wholly in solution form may consist of active agent compounds or compositions *per se* provided that such compounds or compositions are capable of being forced out of the device as a result of the osmotic pressure developed therein. More typically, however, the active agent formulation comprises an active agent in combination with a carrier. Any suitable carrier for the active agent may in general be employed in the device of this invention; however, when use of the subject devices for drug depot applica-

tions is contemplated, the carrier must be biologically inert, non-irritating to body tissues and non-allergenic. A multitude of such carriers are available, including such liquids as water, alcohols such as ethanol, propylene glycol, glycerine, polyethylene glycols of various molecular weights, etc., mineral oil, vegetable oils such as corn oil, peanut oil, cottonseed oil, etc., and solids which are converted to liquids at the temperature of the prospective situs of the device, i.e., body temperature in the case of drug depot applications, such as those disclosed in copending Nakano, Higuchi and Hussain application Ser. No. 106133, now abandoned filed Jan. 13, 1971.

The amount of active agent incorporated in the active agent formulation varies widely depending upon the particular active agent, the particular vehicle employed and the desired dosage to be administered by the dispenser. Thus, there is no lower limit on the amount of active agent to be combined with the carrier, and likewise, there is no upper limit save for the physical limitation of a given carrier material. Accordingly, it is not practical to define a range for the amount of active agent to be incorporated in the inert carrier; however, in a typical active agent formulation the carrier contains from about 5 to about 80 percent by weight of active agent, preferably from about 35 to about 75 percent.

Typically, a surfactant is advantageously included in the active agent formulation to enhance its physical stability. The surfactant must be inert to the active agent as well as biologically inert, and accordingly non-ionic surfactants are preferred. Exemplary non-ionic surfactants include sorbitan monostearate, sorbitan monooleate, polyoxyethylene (20) sorbitan monooleate, and polyoxyethylene (40) stearate. Several active agent surfactant combinations have been found to be particularly effective, for example, sorbitan monostearate has been found effective to stabilize suspensions of tetracycline, while polyoxyethylene sorbitan monooleate has likewise been found suitable for use with chloramphenicol. A preferred range for the surfactant is typically between about 0.1 and 1.0 percent by weight of the total mixture.

Optionally, the active agent formulations of the invention may include an anti-oxidant to prevent degradation during prolonged periods of storage, usually in an amount of from about 0.01 to about 2 percent by weight of the active agent. Any of the food-approved anti-oxidants may be employed in this capacity, with the following being merely illustrative in this regard: tertiary butyl-4-methoxyphenol (mixture of 2- and 3-isomers), 2,6-ditertiary butyl-p-cresol, propyl gallate, 6-ethoxy-1,2-dihydroxy-2,2,4-trimethylquinoline (ethoxyquin), nordihydroguaiaretic acid (NDGA) and ascorbyl palmitate. Use of other preservatives such as methylparaben, propylparaben, sorbic acid, etc., are likewise contemplated in the active agent formulations of the invention.

Similarly, there is contemplated the optional inclusion of a dispersed inert particulate solid to the active agent formulations of the invention. These particulate solids are included typically in amounts from about 0.5 to 5 percent by weight of the active agent to enhance the stability of the product by providing a high solids content. Thus, when low concentrations of drug or other active agent are employed as inert solid such as fumed silica, bentonite, etc., may be added as a gellant

to prevent the formulation from settling out upon prolonged storage of the device.

To further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that the same are intended merely as illustrative and in no wise limitative:

EXAMPLE 1

40 grams of polyethylene glycol 600 containing 8 milligrams of butylated hydroxytoluene are admixed with 60 grams of tetracycline hydrochloride. The resulting paste is mixed well and then milled on an ointment mill to provide a uniform active agent formulation of a viscous paste or cream-like consistency. 10 cc of the active agent formulation are then placed in the active agent compartment of an osmotic dispenser constructed in accordance with FIG. 4 of Higuchi and Leeper application, Ser. No. 106130, now U.S. Pat. No. 3732865 filed Jan. 13, 1971. In the FIGURE of drawing there is illustrated the device of this example.

EXAMPLE 2

1200 milligrams of tetracycline hydrochloride and 800 milligrams of polyethylene glycol 600 - polyethylene glycol 1000 mixture (6:4) containing 8 milligrams of sorbitan monostearate and 0.16 milligrams of 2,6-ditertiary butyl-p-cresol are mixed at 39°C. whereat the glycol mixture is a clear viscous liquid. Thereafter, the mixture is milled twice in an Asra mill, reheated and poured into the active agent compartment of an osmotic dispenser constructed in accordance with the device of the FIGURE of drawing. The active agent formulation is then allowed to cool to room temperature whereupon it solidifies to a storage-stable state. The osmotic dispenser is then placed in an aqueous solution at approximately 38°C., and the active agent formulation again melts to a liquid form and is forced out of the device through the dispensing head by the osmotic pressure developed in the osmotically effective solute compartment as a result of water from the environment permeating by osmosis thereinto.

EXAMPLE 3

6000 milligrams of chloramphenicol, 5000 milligrams of cocoa butter and 44 milligrams of Tween 80 (polyoxyethylene 20 sorbitan monooleate USP) are mixed at 39°C., milled twice in the Asra mill, reheated and poured into the active agent compartment of an osmotic device constructed in accordance with the design illustrated in FIG. 1 of Higuchi application, Ser. No. 106131, now U.S. Pat., No. 3760805, filed Jan. 13, 1971. The active agent formulation is again a solid at room temperature, and is readily dispensed through the dispensing head of the device in response to an osmotic pressure developed therein when the device is placed in an aqueous environment at approximately 36°C.

EXAMPLE 4

An active agent formulation containing 13,000 milligrams tetracycline base (vacuum dried), 13,000 milligrams of cocoa butter and 104 milligrams of Span 60 (sorbitan monostearate USP) is prepared according to the procedure of Example 3 and poured into the active agent compartment of an osmotic dispenser constructed in accordance with FIG. 1 of Higuchi and Leeper application, Ser. No. 106130, now U.S. Pat. No. 3732865 filed Jan. 13, 1971. The resulting formulation is again solid at room temperature, storage stable

thereat and again an easily dispensible liquid at approximately 38°C.

EXAMPLE 5

An active agent formulation containing 1000 milligrams of cocoa butter, 1200 milligrams of sulfisoxazole, 8.8 milligrams of Span 60 (sorbitan monostearate), and 0.2 milligrams of 2,6-ditertiary-butyl-p-cresol is prepared according to the procedure of Example 3, and poured into the active agent compartment of a device identical to that employed in Example 3. Results essentially identical to the foregoing Examples 2 to 4 are obtained.

The osmotic dispenser can be fabricated in any conventional 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 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.

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, by providing an active agent formulation wherein the active agent is formulated in a form other than wholly in solution, e.g., dispersion, suspension, emulsion, etc., and preferably in the form of a solid, semi-solid, for example, a gel, paste, or cream, or a highly viscous liquid, the active agent formulation will not be decreased in potency by chemical breakdown and exhibits enhanced storage stability and handling characteristics as well as advantageous high concentrations of the active ingredient itself, and the same will exhibit a decreased tendency to be leached from the device.

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 comprised of a first compartment of relatively impervious material containing an active agent and provided with means for releasing the active agent to the exterior of the dispenser, and a second compartment of controlled permeability to water containing a solution of an osmotically effective solute which exhibits an osmotic pressure gradient against water, the said first and second compartments having a barrier member such that the said first compartment diminishes in volume in response to an increase in volume of the solution in the said second compartment via absorption of water by osmosis therein and defining a means for establishing a substantially zero order rate of release as water flows into the dispenser in a tendency towards osmotic equilibrium with its environment, so that the active agent is continuously squeezed thereout at an osmotically controlled rate over a prolonged period of time; said active agent being formulated in a form other than wholly in liquid solution, and characterized by a consistency at least as firm as that of the semisolid state, whereby the uniformity of dosage of the said active agent over the said prolonged period of time is assured.

2. The osmotic dispenser as defined in claim 1, wherein the active agent formulation is a semisolid.

3. The osmotic dispenser as defined in claim 1, wherein the active agent formulation is a solid.

4. The osmotic dispenser as defined by claim 1, wherein the active agent formulation is a thickened liquid having a viscosity of at least 1,000 centipoises at 20°C.

5. The osmotic dispenser as defined in claim 1, wherein the active agent formulation further comprises a nonionic surfactant.

6. The osmotic dispenser as defined in claim 5, wherein the surfactant is selected from the group consisting of sorbitan mono-stearate, sorbitan monooleate, polyoxyethylene (20) sorbitan monooleate, and polyoxyethylene 40 stearate.

7. The osmotic dispenser as defined in claim 1, wherein the active agent formulation further comprises an anti-oxidant.

8. The osmotic dispenser as defined in claim 7, wherein the anti-oxidant is selected from the group consisting of 2,6-ditertiary-butyl-p-cresol, propyl galate, tertiary butyl-4-methoxyphenol, ethoxyquin and nordihydroguaiaretic acid.

9. The osmotic dispenser as defined by claim 1, wherein the active agent formulation further comprises an inert particulate solid filler.

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