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Abraham

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[54] **GRADUAL RELEASE MEDICINE CARRIER**

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[52] **U.S. Cl.** **128/260,** 424/19

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

[58] **Field of Search** 128/260, 268, 261, 249, 128/248, 172.1; 424/19, 21, 22

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[57] **ABSTRACT**

A medicament carried within a perforate or semipermeable shell is gradually released, as by dissolution into body fluids, to provide effective therapy with reduced concentration and dosage. The medicament may be in dry powdered form. For treatment of the eye, the carrier comprises a capsule less than 1 millimeter in diameter which is placed in the conjunctival sac or mounted in a contact lens. The capsule may be colored for easy location and removal, may be absorbable by the body, or may gradually swell to allow washout by the tears. For glaucoma treatment, less than 1 milligram of pilocarpine or phospholine in a single sustained release capsule may be an adequate daily dosage. In another embodiment a soft contact lens itself may serve as the medicine containing carrier.

For burn, ulcer, or wound treatment, the carrier may be of planar configuration or incorporated in a film forming spray comprising many minute particles or capsules each containing a medicament. The resultant film will protect the tissue from exposure, will provide sustained release medication, and may be absorbable to eliminate the need for removal with concomitant damage to newly formed granulation tissue.

5 Claims, 6 Drawing Figures

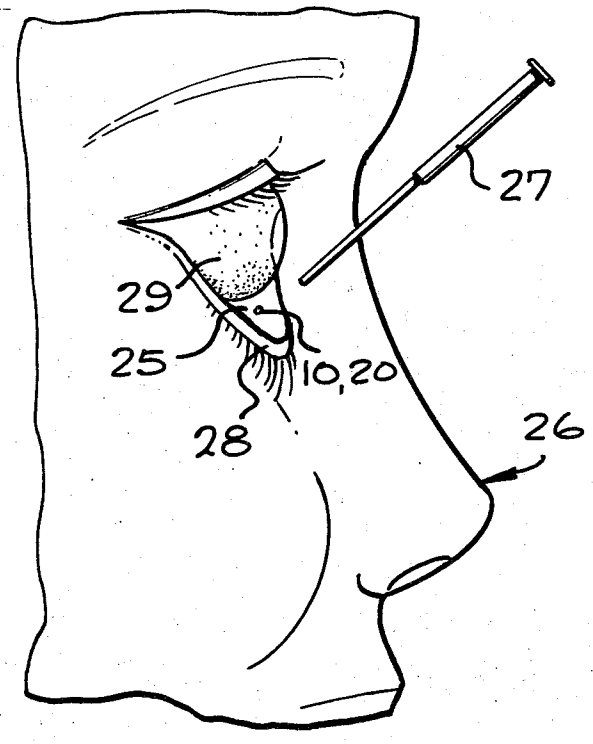


Fig. 1

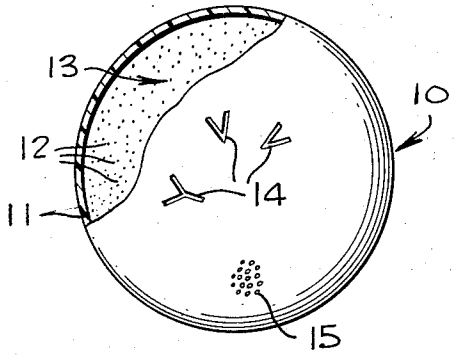


Fig. 2

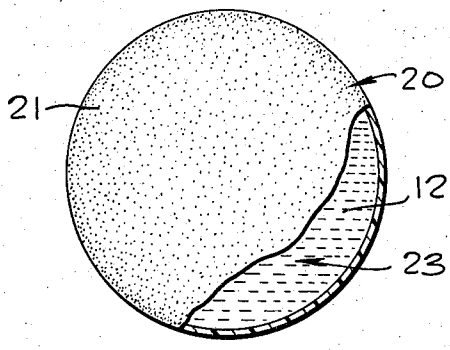


Fig. 3

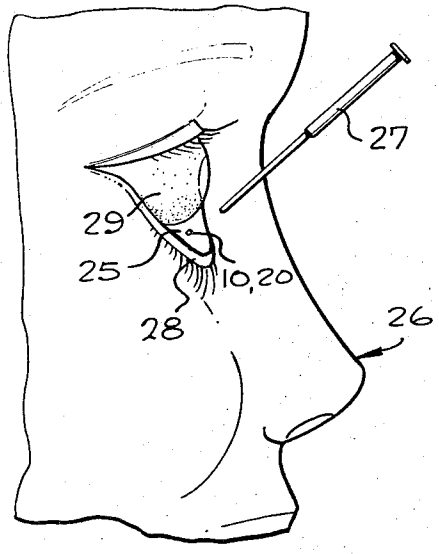


Fig. 4

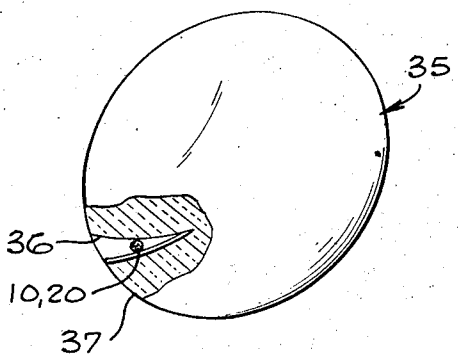


Fig. 5

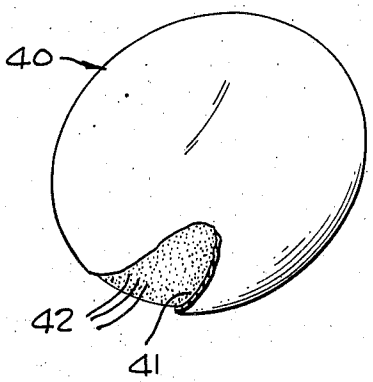
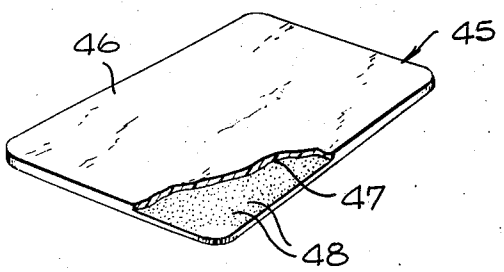


Fig. 6



GRADUAL RELEASE MEDICINE CARRIER

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to gradual release medicine carriers and particularly to a capsular medicament carrier useful for prolonged release therapy of the eye and adapted for placement in the conjunctival sac and to other carriers for treatment of superficial body areas.

2. Description of the Prior Art

It is well known that the effectiveness of some medicinal agents is increased when the agent is released slowly into the host. This is particularly true of the eye, where the constant washing by tears tends to dilute and flush away a medicine dropped onto the cornea. A substantial portion of the actual medicament is lost, and the remaining therapeutic portion is present at the eye for a relatively short period of time.

Sustained release therapy, wherein a small amount of medicine is released over a prolonged period of time, significantly decreases both the concentration of medicament required and the total daily dosage. Such therapy is of value to patients who are sensitive either to the medication itself or to the preservative, vehicle or stabilizer used with the agent. For eye treatment, sustained release therapy is useful for continuous control of intraocular pressure or other ocular conditions (infections, etc.).

The reduced dosage and concentration achievable with sustained release therapy is illustrated by the pilocarpine treatment of open-angle glaucoma. To simulate gradual release of the medication, patients were administered 100 drops of pilocarpine over a 5 hour period. The results were compared with the response of patients given the conventional dosage of two or three drops per day of 1% to 4% pilocarpine. On a sustained release basis, the minimum effective dosage was found to be between 10 and 30 micrograms per hour, equivalent to a 24 hour dose of 240 to 720 micrograms. This is significantly less than the total dose of from 1500 micrograms per day for a patient receiving 1% pilocarpine three times daily to 6000 micrograms in a patient receiving 4% pilocarpine three times daily. The investigators reported that "If a suitable method of prolonged release pilocarpine therapy could be developed, most patients with wide-angle glaucoma would require a total 24-hour dose between 10 and 25 times less than that they are currently using." (See "Simulated Sustained Release Pilocarpine Therapy and Aqueous Humor Dynamics" by S. Lerman and B. Reininger, OPHTHALMOLOGY DIGEST, Sept., 1971.)

In the past, some sustained release medicine carriers have been suggested, but none is useful for eye therapy. Typical is the polysiloxane (silicone rubber) implant shown in the U.S. Pat. No. 3,279,996 to D.M. Long, Jr. et al. That device comprises a tube about 1 centimeter in length, fabricated of certain silicone rubber material (typically dimethylpolysiloxane), and containing a drug which is soluble in and capable of diffusing through the silicone rubber at a constant rate. The carrier containing a relatively large supply of the medicament, is implanted in the living body. Drug molecules are removed from the polymer wall by body fluids and tissue absorption, this process continuing indefinitely or until the medicinal substance has been consumed completely. The agents used include anti-coagulants, anti-

infectives, anesthetics, and hormones. Sustained release drug application through polysiloxane implants also shows improved effectiveness over conventional therapy. For example, invivo experiments were performed with rats using the steroid hormonal preparation megestrol acetate. These experiments show that sustained release of the hormone through a polysiloxane implant is 6 to 25 times more effective than subcutaneous injections in producing comparable biological effect. (See C. Chang and F. Kinel, "Sustained Release Hormonal Preparations: Biologic Effectiveness of Megestrol Acetate" in STEROIDS, Vol. 12, No. 6, Dec., 1968.)

While effective therapeutically, silicone rubber implants are inapplicable for eye usage. An objective of the present invention is to provide a gradual release medicine carrier of sufficiently small size as to be placed in the conjunctival sac, or incorporated in a contact lens worn by the patient. Techniques for carrier insertion and disposal of the emptied capsule are set forth. Other embodiments for burn, ulcer, wound and implant therapy are discussed.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a sustained release medicine carrier comprising a capsule having a perforate or semipermeable shell and containing a medicament which is gradually released through the shell. Alternatively, the medicament may be impregnated in the capsule. For eye therapy, the capsule preferably is less than 1 millimeter in diameter, permitting deposit of the capsule in the conjunctival sac. The medicament, which may be in a dry, powdered form, dissolves in the tears to effectuate prolonged release into the eye. The capsule may be inert or have a pH matching that of the tears.

To facilitate insertion, one or more capsules may be prepackaged in a dropette. Coloring facilitates location of the emptied capsule for removal from the conjunctival sac. Alternatively, the capsule may be absorbable, or may swell so as to be washed from the eye by tears after some period of time.

In other embodiments, the sustained release medicine carrier may be inserted in a contact lens, or the corneoscleral lens itself may function as the medicament container. For burn, ulcer and wound treatment, very small medicament containing capsules or medicine-impregnated particles may be incorporated in a spray forming a film over the body area being treated. The film may be absorbable and applied in layers, with the rate of absorption controlling the medicament release rate. Preformed, absorbable, gradual release medicament containing structures such as thin pads or implants also are envisioned. Alternatively, the medicaments may be incorporated in linquets, pellets, microspansules, ointments, suppositories, or chewable tablets, each facilitating gradual release of the medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

A detailed description of the invention will be made with reference to the accompanying drawings wherein like numerals designate corresponding parts in the several figures. These drawings, unless described as diagrammatic or unless otherwise indicated, are to scale.

FIGS. 1 and 2 are greatly enlarged perspective views, partly broken away, of gradual release medicine carri-

ers for eye therapy and respectively using a perforate shell and a semipermeable membrane.

FIG. 3 is a pictorial view showing insertion of a gradual release medicine carrier into the conjunctival sac of the eye.

FIG. 4 is a perspective view of a prolonged release medicine carrier mounted in a contact lens.

FIG. 5 illustrates the manner in which a soft contact lens may be used as a medicament carrier.

FIG. 6 is a perspective view of a pad-shaped gradual release medicine carrier useful, e.g., for burn treatment.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following detailed description is of the best presently contemplated modes of carrying out the invention. This description is not to be taken in a limiting sense, but is made merely for the purpose of illustrating the general principles of the invention since the scope of the invention is best defined by the appended claims.

Structural and operational characteristics attributed to forms of the invention first described shall also be attributed to forms later described, unless such characteristics are obviously inapplicable or unless specific exception is made.

A gradual release medicine carrier **10** useful for eye therapy is shown in FIG. **1.** Referring thereto, the carrier or capsule **10** comprises a casing or shell **11** which may be, but is not necessarily spherical. Contained within the shell **11** is a medicament **12,** typically in dry, powdered form. The shell **11** is perforated to allow body fluids such as tears to enter the capsule interior **13.** The medicament **12** dissolves in such fluid and flows out through the perforated shell **11** in solution.

The medicine release rate is established by the size, shape and number of the shell **11** perforations. By way of example, a capsule **10** may have just a few relatively large openings **14** of V- or Y-shape. Such shape establishes a substantial flow area, but prohibits foreign bodies such as dust in tears from entering the capsule **10.** Alternatively, the shell **11** may be perforated by multiple tiny holes or micropores **15.** In another embodiment the medicament may be impregnated in the capsule shell or the capsule may be solid with the medicament impregnated throughout.

In the alternative embodiment of FIG. **2,** the capsule **20** includes a shell **21** having the characteristics of a semipermeable membrane. Body fluid diffuses through the membrane **21** into the capsule interior **23** where it comes in contact with the dry, powdered medicament **12.** The medicine dissolves, and the solution flows back out through the shell **21** at a rate established by the membrane characteristics. Alternatively, a liquid medicament may be contained in the capsule **20,** and the semipermeable membrane selected for preferred outward diffusion of the medicine. The shell **21** may comprise a dialysis membrane.

Preferably the diameter of each capsule **10, 20** is sufficiently small so that there is no irritation or discomfort when the carrier is situated in the conjunctival sac of the eye. A diameter of less than about 1 millimeter is satisfactory. The shell **11, 21** may be inert or may have a pH of about 7.2, equal to that of a tear, and should be non-allergenic.

FIG. **3** illustrates delivery of the capsule **10, 20** to the conjunctival sac **25** of a patient **26.** Many of the capsules **10, 20** may be packaged in a bottle, in a saline or antiseptic solution. The capsules may be colored for ease of visability. An eyedropper is used to remove one or two capsules from the bottle for deposit into the sac **25.** Since the capsules **10, 20** are small, it may be difficult to pick up only one or two in a dropper. This problem is alieviated by prepackaging a very small number (i.e., one or two) capsules **10, 20** in an individual, disposable dropette **27** or ampoule-like dropper. In use, the dropette **27** is opened and the contents deposited into the conjunctival sac **25** as the lid **28** (FIG. **3**) is held away from the eye **29.**

While the capsule **10, 20** is within the conjunctival sac **25,** the medicament **12** will dissolve in the patient's tears and flow onto the eye **29.** Prolonged release of the medicine is achieved, so that the amount of medicament **12** employed may be very small. For example, in the treatment of glaucoma the medicament **12** may comprise powdered crystals of pilocarpine or phospholine. When gradually released from the carrier **10, 20,** less than 1 milligram of such powder may constitute a day's supply. As discussed earlier, this is significantly less than the amount required for effective therapy using the conventional liquid drop application. Moreover, as the pilocarpine or phospholine is maintained in dry powder form, no preservative is required, eliminating the chance of allergic reaction to such preservatives. Similarly, no preservative may be required if the medicament is impregnated in the capsule.

When all of the medicament **12** has been released to the eye **29,** the capsule **10, 20** is removed from the sac **25** by flushing the eye with water, or by use of a cue tip. If the shell **11, 21** is colored, the capsule readily can be located for removal.

The need to remove the emptied capsule **10, 20** from the sac **25** can be eliminated by making the shell **11, 21** of a material absorbed by the body. For example, the perforated shell **11** may be made of a synthetic polyglycolic acid polymer which hydrolyzes in the human body. Sutures made of such synthetic material are sold commercially by the Lederle Laboratories, Pearl River, N.Y., under the trademark DEXON. Certain colloidal materials such as collagen fibrils may be formed into a shell **11** absorbably in the body. Alternatively, the semipermeable shell **21** may comprise absorbable gut of the type used for dialysis membranes. Such material is absorbed in the body by proteolysis, a protein cleavage process.

An alternative approach to the capsule removal problem is to form the shell **11, 21** of a material which will swell when immersed in tears. In the course of a day, as the medicament **12** is dispensed, the shell will swell sufficiently so as to be washed from the eye by the tears present in the sac **25.** A swelling gelatin material satisfactory for use at the eye is described in the Mar., 1968 issue of ARCH OPHTHAL, on page 289. This gelatin is absorbed by the body, but only after periods much longer than a day.

Rather than placing the gradual release medicine carrier in the conjunctival sac, the capsule **10, 20** may be situated in a contact lens. Thus (FIG. **4**) a contact lens **35** may include a capsule receiving notch or recess **36** in a peripheral edge **37** of the lens. A capsule **10, 20** is injected into the recess **36.** When the lens **35** is placed on the eye, tears will enter the recess **36;** the medica-

ment **12** will dissolve in the tears and flow onto the eye **29** as before.

The use of the invention with soft contact lenses is of particular interest. The hydrophilic corneoscleral lens, composed of a cross-linked hydrophilic polymer of 2-hydroxyethyl methacrylic acid has the known disadvantage that bacteria tend to grow in the interstices of the plastic. As a result, such lenses normally must be boiled in saline each day for sterilization, or kept in a sterilizing solution overnight with questionable results. Such daily sterilization could be eliminated by mounting in the lens a capsule **10, 20** containing an antibacterial agent instead of or in addition to a medicament.

Another disadvantage of soft contact lenses is that ocular preservatives such as benzalkonium chloride and chlorbutanol drops might concentrate within the interstices of the lens. This problem is completely eliminated by the use of a carrier **10, 20** which contains the medicament without any preservative.

As the cost of soft contact lenses is reduced, it is likely that disposable lenses will become available. The medicament carrier **10, 20** could be mounted in such a disposable lens at the time of manufacture. The user would purchase the daily disposable lenses by prescription specifying the appropriate medication.

In yet another embodiment, a disposable, soft contact lens itself may serve as the medicament shell. Thus in FIG. **5**, the soft contact lens **40** contains a chamber **41** containing the medicament **12**, injected during manufacture. The region **41** is perforated, as for example, by micropores **42** analogous to the openings **15** in the embodiment of FIG. **1**. Controlled release of the medicine is achieved directly from the lens **40.**

For the treatment of burns, ulcers and wounds, the carrier **45** (FIG. **6**) may comprise a pad of minimal thickness but relatively large length and width. The casing **46** of the pad **45** is analogous in composition and function to the shell **11** or **12** described above, and surrounds a hollow interior **47** containing a medicament **48.** Preferably the casing **46** is of absorbable material. When placed on a burn or open wound the medicament **48** slowly will be released. Eventually the casing **46** itself will be absorbed. The slow release of medication provides the benefits of lowered dosage and concentration, while the absorbability feature eliminates the pain usually associated with bandage removal. The pad need not be hollow, but may have the medicament impregnated throughout.

By making the capsules **10, 20** of very small size, they may be combined with a film forming plastic material and applied to a wound area in the form of a spray. Alternatively the spray may comprise small particles of a film forming material impregnated with the medicament. Such particles may consist of a polyglycolic acid intermediary, a colloidal protein, collagen fibrils or other absorbable material.

The film thus formed in situ will be conformal with the wound, and will have the desirable gradual medicine release characteristics described above. In addition, the film will protect the tissue from exposure, decreasing pain and reducing the chance of toxic reactions. The medicament may include an antiseptic to prevent infection.

Additional benefits result from using an absorbable film forming material. The rate of medicament release may be determined by the absorption rate. Additional layers may be sprayed on to affect the dosage and replenish the medication. Further, use of such an absorbable film eliminates the problem, associated with removal of conventional wound coverings, of pulling off newly formed granulation tissue.

Suitably packaged forms of the invention, for example linguets or suppositories, can be placed in the mucus membrane of the eye, oral or nasal cavity, vagina or rectum to achieve gradual release of medicament.

Intending to claim all novel, useful and unobvious features is shown or disclosed, the applicant claims:

1. For sustained release medicinal therapy of the eye:

a sealed, disposable, ampoule-like dropper prepackaged to contain a very small number of gradual release medicine carriers in a saline or antiseptic solution, each carrier having a hollow casing containing a medicament in dry powdered form, said casing being non-allergenic, having a tear-equivalent pH, and being perforated by orifices to allow the entry of tear fluids, the number and size of said orifices establishing the gradual release rate of said medicament by dissolution into said tear fluids, each carrier having no dimension greater than about 1 millimeter to permit non-irritating disposition of said carrier in the conjunctival sac of the eye, said ampoule-like dropper facilitating delivery of said carriers into said conjunctival sac for intimate tear fluid exchanging delivery of said medicament to the eye.

2. A prepackaged ampoule-like dropper according to claim **1** wherein said casing is absorbable by tissue of said conjunctival sac over a time duration commensurate with or greater than the total release period of said medicament.

3. A prepackaged ampoule-like dropper according to claim **1** wherein said carrier is colored to aid finding the emptied casing for removal from said conjunctival sac.

4. A prepackaged ampoule-like dropper according to claim **1** wherein said casing gradually swells in the presence of tears to a size sufficient to be washed from said conjunctival sac by said tears.

5. A prepackaged ampoule-like dropper according to claim **1** wherein said medicament comprises less than 1 milligram of pilocarpine or phospholine, said medicament being a sufficient daily dosage for the sustained release treatment of glaucoma.

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