United States Patent

[11] 3,630,200

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[73] Assignee **ALZA Corporation**

[54] **OCULAR INSERT**
22 Claims, 2 Drawing Figs.

[52] **U.S. Cl.** **128/260**
[51] **Int. Cl.** **A61m 31/00**
[50] **Field of Search** 128/260, 268, 296, 156; 424/12; 206/63.2, 84

[56] **References Cited**

UNITED STATES PATENTS

3,006,338	10/1961	Davies	128/156
3,220,960	11/1965	Wichterle	260/2.5
3,301,257	1/1967	Crowe, Jr. et al.	128/156 X
3,416,530	12/1968	Ness	128/260
3,490,454	1/1970	Goldfarb et al.	128/260 X
3,520,949	7/1970	Shepherd et al.	128/156 UX

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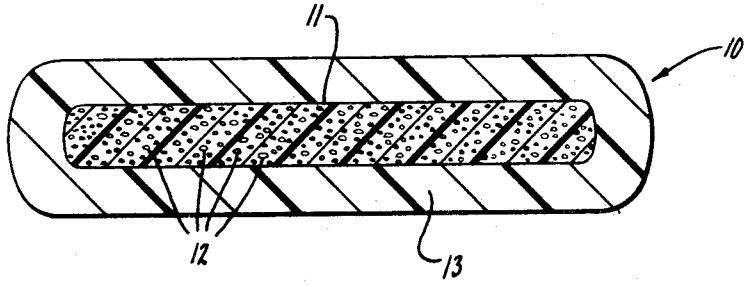
ABSTRACT: Drug dispensing ocular insert for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid to dispense drug to the eye over a prolonged period of time is rendered more compatible with the eye and surrounding tissues by fabricating the insert of an inner core containing the drug and a soft hydrophilic outer layer.



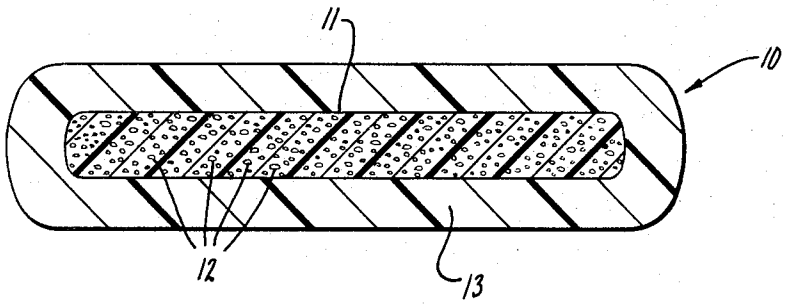


Fig. 1

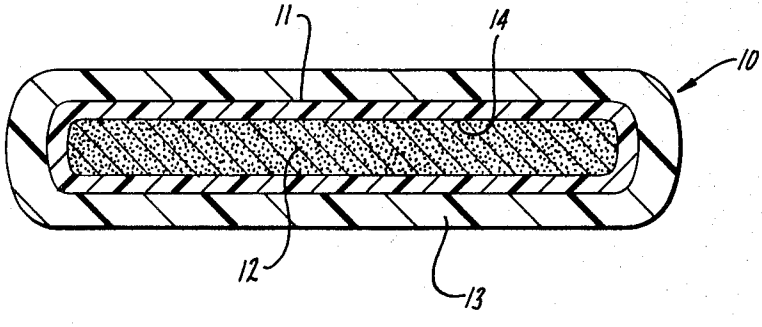


Fig. 2

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OCULAR INSERT

BACKGROUND OF THE INVENTION

This invention relates to an ocular insert for dispensing drugs to the eye and, more especially, to an ocular insert having improved compatibility with the eye and surrounding tissues.

At the present time, diseases of the eye are treated by applying ophthalmic drugs in liquid or ointment form. To be effective in many cases, the application of drug should be substantially continuous. Such continuous delivery of drug is not obtained through the use of liquid or ointment dosage forms, even though they be applied at intervals during the day and night. Periodic application of these dosage forms results in the eye receiving a massive, but unpredictable, amount of drug at the time of application but the drug is washed away rapidly by tears, leaving the eye without medication until the next application. Ointment dosage forms are presently available only in unsterilized form and this too presents a problem.

At a very early time, drugs were dissolved or dispersed in a water soluble gel of glycerinated gelatin that was shaped to the form of a lamella or eye disk. These lamellae were applied to the inner surface of the eyelid to supply drug to the eye. In use, the glycerinated gelatin vehicle dissolved rapidly in tear liquid, producing the same type of effect as liquid dosage forms. Lamellae were not a sustained release dosage form. To my knowledge, they are not used in this country, although they may be used to a small extent in Europe. Further information on these water soluble dosage forms can be found in *Remington's Pharmaceutical Sciences, XIII*, pages 547–8 (Mack Publishing Co., Easton, Pa. 1965); Fishburn, *An Introduction to Pharmaceutical Formulation*, page 116 (Pergamon Press Ltd., New York City, N.Y. 1965); and U.S. Pat. No. 273,410, Mar. 6, 1883.

U.S. Pat. No. 3,416,530, granted Dec. 17, 1968, and assigned to the assignee of this invention, is directed to the invention of a drug dispensing ocular insert that truly acts as a depot or drug reservoir, retaining and slowly releasing drug to the eye for prolonged periods of time. Such ocular inserts are fabricated of flexible polymeric materials that are biologically inert, nonallergenic, and insoluble in tear liquid. To initiate the therapeutic program, the ocular insert is placed in the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid. Since the polymeric material from which the ocular insert is formed is insoluble in tear liquid it retains its integrity and remains intact during the course of therapy, acting as a reservoir to continuously release drug to the eye and surrounding tissues at a rate which is not affected by dissolution or erosion of the polymeric material. On termination of the therapeutic program, the ocular insert is removed from the cul-de-sac. Thus, a single such ocular insert provides the complete ophthalmic dosage regime for a particular time period, on the order of 24 hours or longer. Frequent repeated applications, as is necessary with liquids, ointments, or water soluble lamellae, often requiring awakening the patient during the night, are avoided.

The necessary characteristics for the material used to fabricate the ocular insert and obtain the desired drug metering effect are dependent on the particular drug used. With many drugs, hydrophobic polymeric materials having a relatively high affinity for the drug should be used in forming the ocular insert. Otherwise, the drug will be rapidly released from the ocular insert and the objective of continuous and sustained release defeated. However, many hydrophobic polymers having the desired drug retention and release characteristics tend to be irritating to the eye and surrounding tissues. To provide compatibility with the eye and surrounding tissues, it has been found that the surface of the ocular insert in contact with the eye and surrounding tissues should be soft and hydrophilic. Since hydrophilic materials do not have the drug retention characteristics needed for many drugs, it has been necessary at times in the past to select materials which compromise the desired comfort and tissue compatibility with the desired retention and release characteristics for the drug.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide an improved ocular insert that is compatible with and nonirritating to the eye and surrounding tissues.

Another object of this invention is to provide an improved ocular insert which can retain and slowly release a wide variety of drugs to the eye.

In attaining the objects of this invention, one feature resides in a drug dispensing ocular insert comprising a flexible body containing a drug and adapted for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid to dispense drug to the eye over a prolonged period of time. The ocular insert is rendered more compatible with the eye and surrounding tissues by comprising it of an inner core containing the drug and having an affinity therefor and a soft, hydrophilic outer layer.

Another feature of this invention resides in the ocular insert described above wherein the inner core is a hydrophobic polymer having an affinity for drugs and capable of slowly releasing such drugs to the eye over a prolonged period of time.

Other objects, features, and advantages of this invention will become more apparent from the following description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings

FIG. **1** is a cross-sectional view of the ocular insert of this invention and

FIG. **2** is a cross-sectional view of a modified ocular insert of this invention.

As illustrated in FIG. **1**, the ocular insert **10** of this invention is comprised of an inner core **11**, which is a matrix having drug **12** dispersed therethrough. Surrounding inner core **11** is an outer layer **13** of a soft hydrophilic material. Drug **12** gradually diffuses through or is leached from inner core **11** and passes through hydrophilic outer layer **13** to the eye and surrounding tissues.

In FIG. **2**, the modified ocular insert **10** of the invention has a hollow inner core **11** having an interior chamber **14** containing drug **12**. As with the other form of the ocular insert, drug **12** gradually diffuses through or is leached by tear liquid from the walls of inner core **11**, passes through outer layer **13** and contacts the eye and surrounding tissues.

DETAILED DESCRIPTION OF THE INVENTION

To use the ocular insert of the invention, it is inserted in the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid. While the ocular insert can be inserted under either the upper lid or the lower lid, placement of the ocular insert under the lower lid is preferred. The eye has a tendency to roll upwardly during sleeping, known as Bell's Phenomenon, which may cause discomfort to some persons if the ocular insert is under the upper lid. Once in place, the ocular insert functions as a drug reservoir gradually releasing drug to the eye and surrounding tissues. Drug leaving the ocular insert, whether by diffusion through the walls of the insert or as a result of the leaching action of tear liquid, is transported to the eyeball by the flow of tear liquid or by the blinking action of the eyelids.

By use of the ocular insert, the eye is continuously bathed with drug over a particular time span. Normally, the ocular insert will be retained in place for a period of **24** hours, thereby supplying the complete dosage regime for eye therapy over that period of time. Because the outer layer of the ocular insert is formed of a soft hydrophilic material, the device can remain in place for long periods of time without causing discomfort to the patient. This is achieved without sacrificing the necessary drug retention and release properties, since the inner core, which does not contact the eye and surrounding tissues, can be selected based on these properties.

The ocular insert can be fabricated in any convenient shape for comfortable retention in the cul-de-sac. Thus, the marginal outline of the ocular insert can be ellipsoid, beanshape, rectangular, etc. In cross section, it can be concavoconvex, rectangular, etc. As the ocular insert is flexible and, in use, will assume essentially the configuration of the cul-de-sac, the original shape of the device is not of controlling importance. Dimensions of the device can vary widely. The lower limit on the size of the device is governed by the amount of the particular drug to be supplied to the eye and surrounding tissues to elicit the desired pharmacologic response, as well as by the smallest sized device which conveniently can be inserted and removed from the eye. The upper limit on the size of the device is governed by the limited space within the cul-de-sac that conveniently and comfortably can be filled with an ocular insert. Typically, the ocular insert is 4 to 20 millimeters in length, 1 to 12 millimeters in width, and 0.1 to 1 millimeter in thickness.

Any of the drugs used to treat the eye and surrounding tissues can be incorporated in the ocular insert of this invention. Also, it is practical to use the eye and surrounding tissues as a point of entry for systemic drugs that enter circulation in the blood stream and produce a pharmacologic response at a site remote from the point of application of the ocular insert. Thus, drugs which will pass through the eye or the tissue surrounding the eye to the blood stream, but which are not used in therapy of the eye itself, can be incorporated in the ocular insert.

Suitable drugs for use in therapy of the eye with the ocular insert of this invention include, without limitation: Anti-infectives: such as antibiotics, including tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate; Antiallergenics such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and prophenpyridamine; Anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate; Decongestants such as phenylephrine, naphazoline, and tetrahydrazoline; Miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, diisopropyl fluorophosphate, phospholine iodide, and demecarium bromide; Mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; and Sympathomimetics such as epinefrine. Drugs can be in various forms, such as uncharged molecules, components of molecular complexes, or nonirritating, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, 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 ocular insert varies widely depending on the particular drug, the desired therapeutic effect, and the time span for which the ocular insert will be used. Since the ocular insert is intended to provide the complete dosage regime for eye therapy for but a particular time span, such as 24 hours, there is no critical upper limit on the amount of drug incorporated in the device. For when the device is removed and disposed of it makes little difference whether any drug remains in the device. The lower limit will depend on the activity of the drug and its capability of being released from the device. Thus it is not practical to define a range for the therapeutically effective amount of drug to be released by the device. However, typically, from 1 microgram to 1 milligram of drug is incorporated in the ocular insert.

As described and illustrated above, the inner core of the ocular insert can be a matrix with the drug dispersed therethrough or can be a hollow capsule with the drug within its interior chamber. The inner core need not be a unitary member but can be made up of discrete particles or hollow capsules which release drug by diffusion or the leaching action of tear liquid. Since the function of the inner core is to act as the reservoir for the drug, it is fabricated, in each case, of a material that provides the optimal environment for the desired depot and release characteristics for the drug being used. No compromise between the retention and release characteristics and the compatibility with the eye and surrounding tissues must be made when designing the device of this invention since the outer layer is independently selected for its eye and tissue compatibility. Suitable materials for the inner core are those flexible materials through which the drug will diffuse or be leached by the action of tear liquid at a slow rate. Exemplary materials for fabricating the inner core of the device include hydrophobic polymers such as polyvinylchloride either unplasticized or plasticized with long chain fatty amides or other plasticizer, plasticized nylon, unplasticized soft nylon, silicone rubber, and polyethylene; and hydrophilic polymers such as the hydrophilic hydrogels of esters of acrylic and methacrylic acid (as described in U.S. Pats. Nos. 2,976,576 and 3,220,960 and Belgian Pat. No. 701,813), modified collagen, cross-linked hydrophilic polyether gels (as described in U.S. Pat. No. 3,419,006), cross-linked polyvinylalcohol, cross-linked partially hydrolyzed polyvinylacetate, cellulosic gels such as methylcellulose and hydroxyethylcellulose; and ion exchange resins, especially those with a low degree of cross-linkings. By using hydrophobic polymers as the core material, one obtains the maximum advantages from the present invention since this invention overcomes the disadvantages inherent in use of hydrophobic polymers in previously known ocular inserts.

Specific, but nonlimiting, examples of combinations of drugs and polymers for the inner core are:

1. chloramphenicol incorporated into polyethylene terephthalate plasticized with higher alcohols;
2. promethazine trichloroacetate incorporated into polyvinyl chloride plasticized with dioctylphthalate;
3. chloramphenicol dispersed throughout polydimethylsiloxane;
4. pilocarpine or pilocarpine perfluorobutyrate incorporated into polyvinyl chloride plasticized with dioctylseboate; and
5. dexamethasone incorporated into 6—6 nylon plasticized with higher alcohols.

In the ocular insert of this invention, the outer layer functions to render the device compatible with the eye and surrounding tissues and comfortable to the wearer. It should not provide a significant barrier to flow or passage of drug from the inner core to the eye and surrounding tissues. Materials used in fabricating the outer layer of the ocular insert are soft, flexible, hydrophilic, and insoluble in tear liquid. While these materials are hydrophilic and absorb water, they should not be substantially eroded or dissolved in the tear liquid. Exemplary materials include hydrophilic hydrogels of esters of acrylic and methacrylic acid (as described in U.S. Pats. Nos. 2,976,576 and 3,220,960, and Belgian Pat. No. 701,813), modified collagen, cross-linked hydrophilic polyether gels (as described in U.S. Pat. No. 3,419,006), cross-linked polyvinylalcohol, cross-linked partially hydrolyzed polyvinylacetate, and cellulosic gels such as methylcellulose and hydroxyethyl cellulose. Of course, the hydrophilic material used to form the outer layer will, in each case, have different characteristics than the material used to form the inner core of the particular ocular insert. Such hydrophilic materials are permeable to gases and liquids which is desirable in the eye since it permits free transfer of eye fluids, drugs, and oxygen. In a preferred embodiment of this invention, the inner core is also porous to liquid and gas flow to assist in the transfer of oxygen and eye fluids through the ocular insert.

The relative thickness of the inner core and the outer hydrophilic layer can vary widely and is not a limitation on the invention.

Drug can be incorporated in the inner core in many ways. When the inner core is a hollow capsule, any of the encapsulation techniques conventionally used can be employed. When the inner core is a solid matrix with the drug dispersed therethrough, the inner core can be fabricated by adding the drug to the monomers prior to polymerization; adding the drug to the polymer in liquid form, molding, and curing; or by impregnating the inner core with the drug. Thereafter, the inner core, containing the drug, can be coated with or laminated to the hydrophilic outer layer. When lamination is employed to fabricate the insert, the device may comprise a sheet of inner core material sandwiched between two sheets of outer layer material. To enhance adhesion between the layers, the inner core can be perforated or embossed.

In a specific example of the manufacture of a device of the invention, liquid polydimethylsiloxane (Dow Corning Silastic) is mixed with chloramphenicol antibiotic. After uniformly mixing the antibiotic with the unvulcanized layers, the inner core can be perforated or embossed.

In a specific example of the manufacture of a device of the invention, liquid polydimethylsiloxane (Dow Corning Silastic) is mixed with chloramphenicol antibiotic. After uniformly mixing the antibiotic with the unvulcanized silicone rubber, stannous octoate catalyst (0.5 percent by weight) is added and the mixture is poured into a mold having a cavity 8×2×0.2 mm. to cure the silicone rubber at room temperature. The resulting silicone rubber body contains 0.5 milligram of chloramphenicol. 2-hydroxyethyl methacrylate 100 parts by weight) is mixed with tertiary butyl peroctoate (0.2 part by weight) and ethylene glycol dimethacrylate (0.2 by weight) to provide a casting syrup which is coated onto the foregoing silicone rubber body in a mold and cured at 70° C. The dimensions of the resulting ocular insert are 10×4×0.8 mm. Immediately prior to use, the outer surface of the ocular insert is wet with water which softens the hydrophilic poly (hydroxyethyl methacrylate) outer layer forming a hydrogel thereof. When inserted in the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid, the ocular insert is effective to deliver to the eye the dose of chloramphenicol antibiotic required for 24 hours of treatment of infection. The soft hydrophilic outer layer is compatible with the eye and surrounding tissues and produces no irritation or discomfort.

Thus, the improved ocular insert of this invention offers many advantages. The inner core material, which functions as the drug reservoir to retain and release the drug, can be chosen so as to produce the optimum environment for the drug. In selecting this material, one need not consider its compatibility with the eye and surrounding tissues since the ocular insert includes an external layer that is soft, flexible, hydrophilic, and compatible with the eye and surrounding tissues.

While there have been shown and described and pointed out the fundamental novel features of the invention as applied to the preferred embodiment, those skilled in the art will appreciate that various modifications, changes, and omissions in the ocular insert illustrated and described can be made without departing from the spirit of the invention. It is the intention, therefore, to be limited only by the scope of the following claims.

What is claimed is:

1. In a drug dispensing ocular insert comprising a flexible body containing a drug and adapted for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid to dispense said drug to the eye over a prolonged period of time, the improvement for rendering the ocular insert more compatible with the eye and the surrounding tissues comprising (1) an inner core comprised of a hydrophobic polymer, said inner core containing the drug and permeable to passage of the drug and (2) a soft flexible

2. The ocular insert of claim 1 wherein said inner core is porous to permit passage of gases and liquids therethrough.

3. The ocular insert of claim 1 wherein said inner core is a matrix of a hydrophobic polymer permeable to passage of the drug, to meter the passage of drug from the inner core to and through the hydrophilic outer layer.

4. The ocular insert of claim 3 wherein said hydrophilic outer layer is a hydrophilic hydrogel.

5. The ocular insert of claim 3 wherein said hydrophilic outer layer is a hydrophilic hydrogel of a polymer of an ester of acrylic acid or methacrylic acid.

6. The ocular insert of claim 1 wherein said inner core is comprised of a plurality of drug-containing particles.

7. The ocular insert of claim 1 wherein said inner core is a capsule of a hydrophobic polymer, having the drug in the interior chamber thereof, the walls of said capsule being permeable to passage of the drug, to meter the flow of drug from said interior chamber to and through the hydrophilic outer layer.

8. The ocular insert of claim 7 wherein said hydrophilic outer layer is a hydrophilic hydrogel.

9. The ocular insert of claim 7 wherein said hydrophilic outer layer is a hydrophilic hydrogel of a polymer of an ester of acrylic or methacrylic acid.

10. The ocular insert of claim 1 wherein said hydrophilic outer layer is comprised of a polymer selected from the group consisting of hydrophilic hydrogel of an ester of acrylic or methacrylic acid, modified collagen, cross linked hydrophilic polyether gel, cross linked polyvinyl alcohol, cross-linked partially hydrolyzed polyvinyl acetate and cellulosic gel.

11. The ocular insert of claim 1 wherein said drug is an ophthalmic drug.

12. The ocular insert of claim 1 wherein said drug is a systematically active drug which will pass through the eye to the bloodstream and produce a pharmacologic response at a site remote from the eye.

13. The ocular insert of claim 1 wherein said drug is a systemically active drug which will pass through the tissue surrounding the eye to the bloodstream and produce a pharmacologic response at a site remote from the eye.

14. The ocular insert of claim 1 wherein from 1 microgram to 1 milligram of drug is incorporated in said tablet.

15. The ocular insert of claim 1 wherein same ranges from 4 to 20 millimeters in length, 1 to 12 millimeters in width, and 0.1 to 1 millimeter in thickness.

16. In a drug dispensing ocular insert comprising a flexible body containing a drug and adapted for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and the lid to dispense said drug to the eye over a prolonged period of time, the improvement for rendering the ocular insert more compatible with the eye and the surrounding tissues comprising (1) an inner core containing the drug and having an affinity therefor, and said inner core being comprised of material permeable to passage of the drug, which material is independently selected to provide the desired drug release rate, and (1) a soft flexible hydrophilic outer layer insoluble in tear liquid, said outer layer also being permeable to passage of the drug and being independently selected for its eye and tissue compatibility, but providing no significant barrier to flow or passage of the drug from the said inner core (1) to the eye and surrounding tissue, whereby there is no compromise in selection of material for the inner core (1) having the desired release rate for the drug therein by reason of the soft and flexible eye and surrounding tissue compatible outer layer (2).

17. The ocular insert of claim 16 wherein said inner core is comprised of a polymer selected from the group consisting of plasticized or unplasticized polyvinyl chloride, plasticized nylon, unplasticized soft nylon, silicone rubber, polyethylene, hydrophilic hydrogel of an ester of acrylic or methacrylic acid, modified collagen, cross linked hydrophilic polyether gel, cross linked polyvinyl alcohol, cross linked partially hydrolyzed polyvinyl acetate, cellulosic gel, ion-exchange resin and plasticized polyethylene terephthalate.

18. The ocular insert of claim 17 wherein the drug is chloramphenicol and the polymeric material of the inner core is polyethylene terephthalate.

19. The ocular insert of claim 17 wherein the drug is promethazine trichloroacetate and the polymeric material of the inner core is polyvinyl chloride.

20. The ocular insert of claim 17 wherein the drug is chloramphenicol and the polymeric material of the inner core is polydimethylsiloxane rubber.

21. The ocular insert of claim 17 wherein the drug is a member selected from the group consisting of pilocarpine and pilocarpine perfluorobutyrate and the polymeric material of the inner core is polyvinyl chloride.

22. The ocular insert of claim 17 wherein the drug is dexamethasone and the polymeric material of the inner core is nylon-66.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,630,200 Dated December 28, 1971

Inventor(s) Takeru Higuchi

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 5, lines 18 through 22 inclusive should be deleted.

Claim 1, line 73, after "flexible" add: --- hydrophilic outer layer insoluble in tear liquid, compatible with the eye and surrounding tissue and permeable to passage of the drug. --- .

Claim 12, lines 31 and 32, "systematically" should read --- systemically --- .

Claim 16, line 55, "(1)" should read --- (2) --- .

Signed and sealed this 26th day of September 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents

FORM PO-1050 (10-69)

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* U.S. GOVERNMENT PRINTING OFFICE : 1969 O—366-334