

Oct. 29, 1974

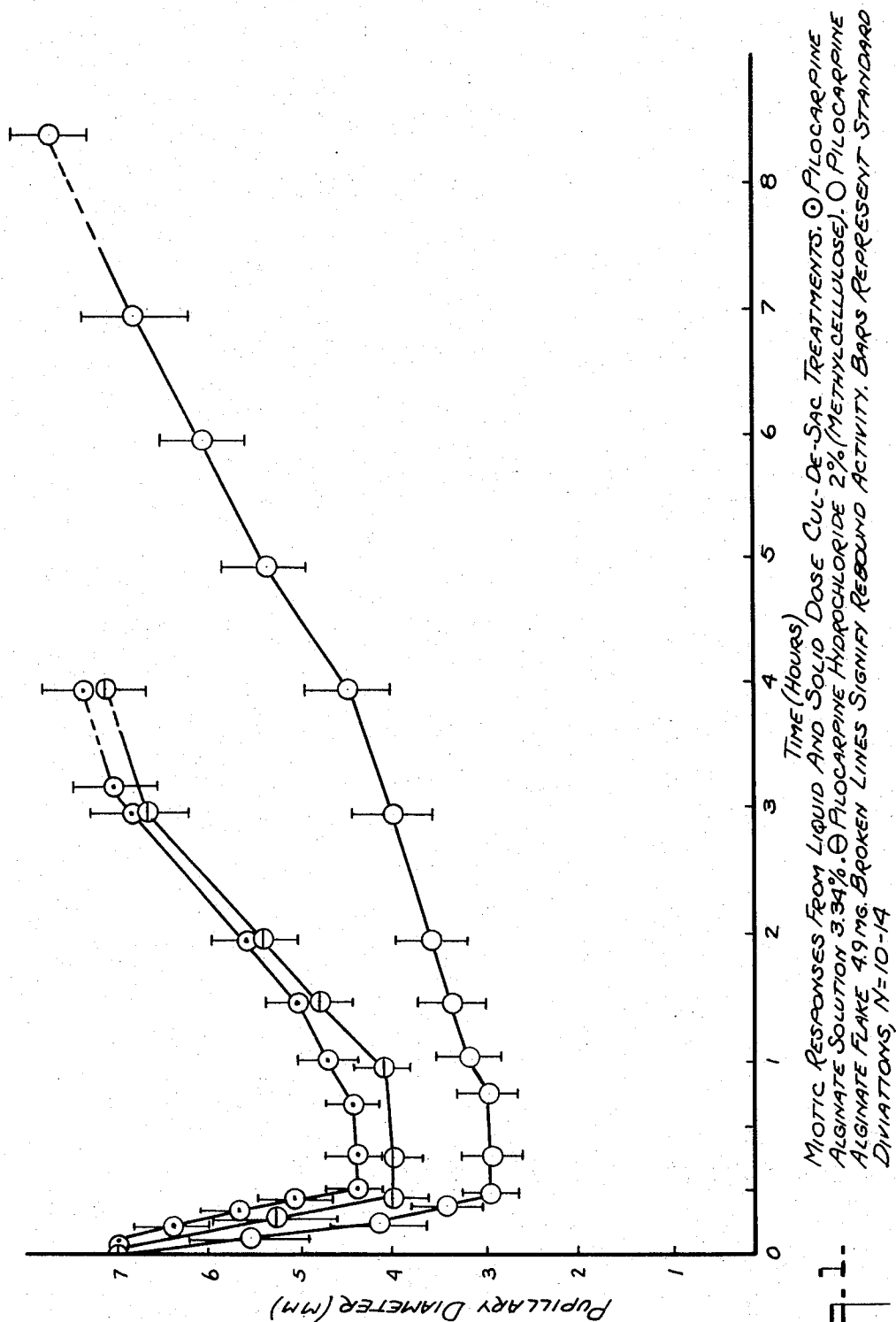
H. M. HADDAD ET AL

3,845,201

SOLID STATE OPHTHALMIC MEDICATION DELIVERY METHOD

Filed April 24, 1972

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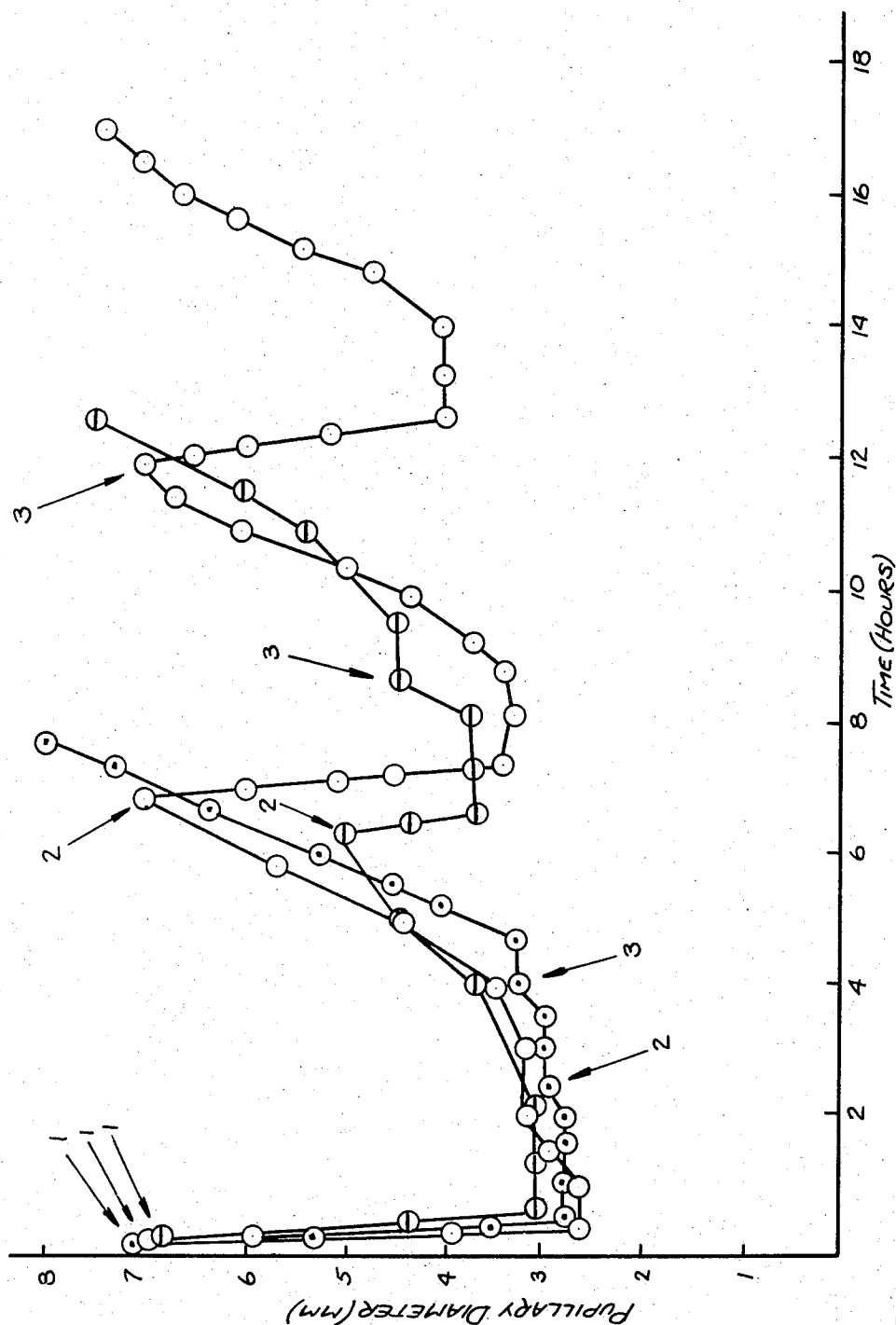
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REPETITIVE Pilocarpine Alginate Flake Treatment At 100% PUPILARY RECOVERY. ARROWS INDICATE DOSE NUMBER DEPOSITED IN RABBIT CUL-DE-SAC AT RESPECTIVE PUPILARY PLATEAU. 5.1 MG DOSE AT EACH POINT.

Fig. 2.

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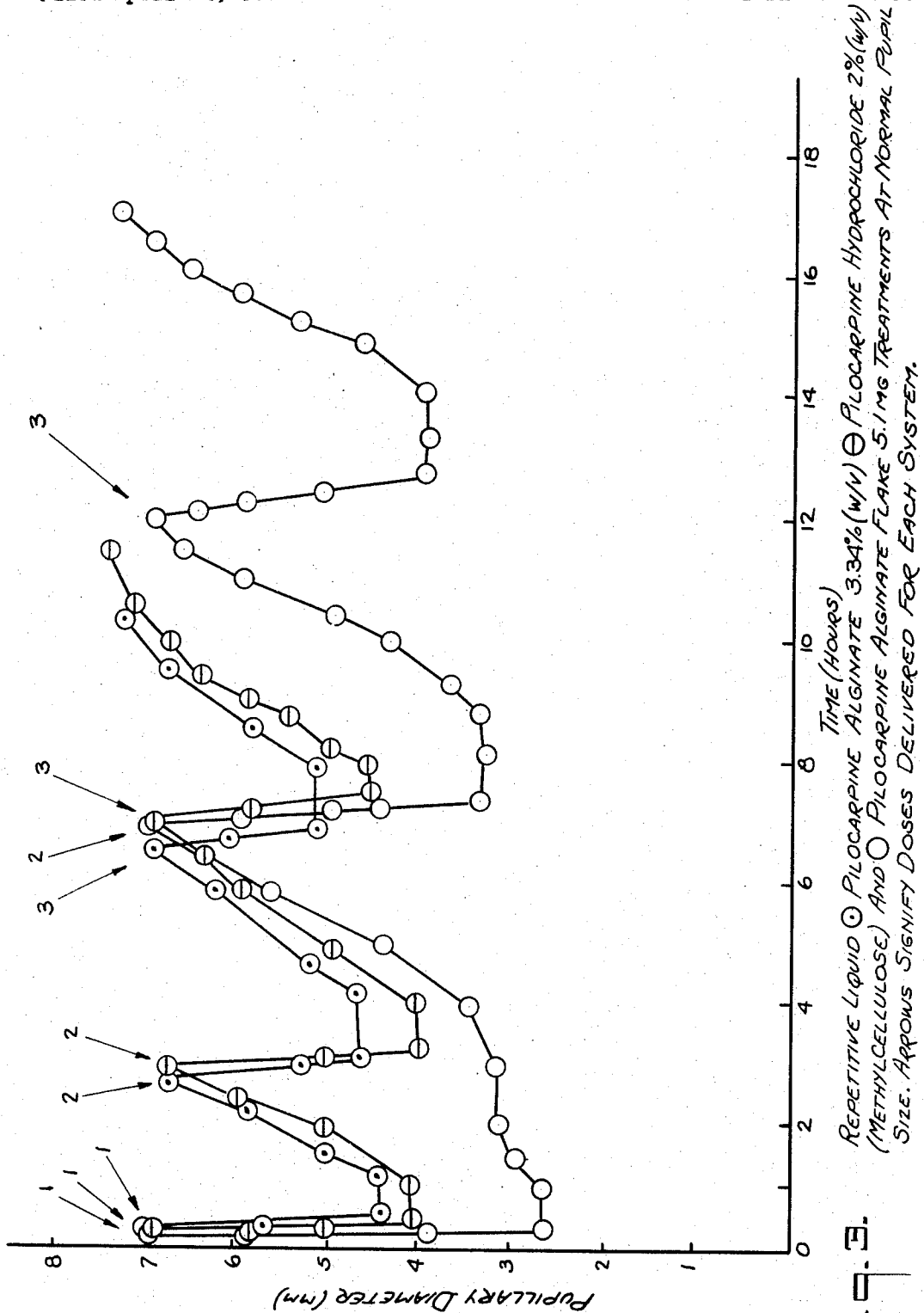
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SOLID STATE OPHTHALMIC MEDICATION DELIVERY METHOD

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16 Claims

ABSTRACT OF THE DISCLOSURE

A method of delivering a medicament to the eye in solid form is described. The duration of miotic, mydriatic or other pharmacological activity is prolonged by the direct insertion of solid dosage forms of pharmacologically active compounds in the cul-de-sac of the conjunctiva.

BACKGROUND OF THE INVENTION

This invention relates to a method of dispensing drugs to the eye over a prolonged period of time.

At the present time, drugs of various kinds are frequently employed in ophthalmic practice for the treatment of eye diseases. Since these drugs are rapidly excreted from the body or diffuse from any site of local application, repeated or numerous administration of the drug during the crucial period is generally necessary. Therapeutic substances may be introduced into the eye by various methods. The methods generally used are instillation in the conjunctival sac, subconjunctival injection, iontophoresis, systemic administration and direct injection into the globe itself. The most common route is by instillation into the conjunctival sac in the form of drops or ointments. In this method, drugs enter the eye largely through the cornea but to be effective, in many cases, the application of the drug must be substantially continuous. At the present time, it is not possible to obtain continuous delivery of a given drug through the use of drops or ointments even though they are applied at intervals during a given period. Periodic application of such dosage forms generally results in the eye receiving a large but uncertain amount of the drug at the moment it is applied, but the drug is washed away rapidly by tears, thus leaving the eye without medication until the next application. For example, persons suffering from glaucoma, a symptomatic condition characterized by an increase in intra-ocular pressure, must use eyedrops in large quantities and at frequent intervals in order to maintain the base pressure below a reasonable level. Pilocarpine is generally used in the treatment of glaucoma, but frequent administration is required due to the fact that the hypotensive action of the drug is not of long duration. Thus, there still remains a need to find better methods of delivering drugs to the eye so as to obtain the maximum effect from the drug without the need for frequent administration.

One method which has been proposed for the treatment of acute glaucoma, for example, is to deliver the drug to the eye enclosed in a polyvinyl membrane. This method was proposed by Vropaeva & Indeikin in *Oftal. Zh.*, 24: 543 (No. 7) 1969. The membrane containing the drug is applied to the eyelid. However, it was found that the inclusion of the drug in a membrane did not increase the effectiveness of the drug in the general treatment of acute attacks of glaucoma. An additional drawback is the need to remove the membrane which contains the drug from the eye after each application.

U.S. Pat. No. 3,618,604 describes an ocular insert which is used to dispense drugs to the eye. The insert is comprised of a polymeric material which is insoluble in tear liquid, the body of which contains the drug. The drug

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is then dispensed to the eye by diffusion through the polymeric material. This method has an inherent disadvantage in that the insert must be removed from the eye each time after application of the drug. In addition, the polymeric insert must be so fashioned that it will not irritate the sensitive tissues of the eye.

U.S. Pat. No. 3,630,200 describes an ocular insert made up of an inner core having an affinity for a given drug and a soft hydrophilic outer layer. U.S. Pat. No. 3,626,940 also describes an ocular insert fabricated from polymeric materials, but the insert contains a magnetically attractable substance to permit insertion and removal of the insert by magnetic means. Thus, each of the drug dispensing methods described in the above patents requires removal of the insert after each application of the drug.

Other methods include the use of vehicles such as methylcellulose in the preparation of ophthalmic solutions because of the apparent ability of this compound to prolong the action of medicaments which have been dissolved in such solutions. Although the use of methylcellulose solutions prolongs the actions of the medication, frequent application of eyedrops made from such solutions is still required in order to bring a sufficient quantity of the drug in contact with the eye. Other agents have been added to ophthalmic solutions for the purpose of prolonging the effect of the drug, but each of these methods requires the use of solutions which must be placed in the eye at frequent intervals.

The object of the present invention is to provide a method of delivering a therapeutic drug to the eye in solid form which results in a continuous controlled release of the medicament and obviates the need for frequent administration of the drug.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to a method of treating diseases of the eye which comprises delivering a medicament in solid form to the eye. The drug, in the form of a disc, pellet, flake, wafer, etc. is placed in the cul-de-sac of the conjunctiva between the eyeball and the eyelid. While the disc can be inserted under either the upper lid or the lower lid, it is preferred to place the disc under the lower lid. Once the disc is in place, the drug disintegrates slowly causing it to be released into the tear fluids. The drug is transported to the eyeball by the flow of tear fluid or by the blinking action of the eyelids. A slow diffusional process controls the rate of loss of the drug from its solid matrix; thus, the drug is held in reserve and is available for prolonging the duration of a desired pupillary response. Due to the slow diffusional process, a means is thus provided for controlling the release of a given drug from its dosage form in which availability for absorption from the cul-de-sac is more uniform than is the case with ophthalmic solutions containing the drugs. Thus, a single disc can provide the complete ophthalmic dosage requirement for a particular time period depending upon the concentration of the drug in a given disc. Moreover, frequent repeated applications of the drug are unnecessary, which is not the case with solutions and ointments. For the purpose of lessening any irritation which may result from the initial contact of the solid with the eye, the solid may be dipped in an isotonic solution which causes the solid to assume a semi-plastic consistency. Generally, physiological salt solutions are suitable for this purpose.

Any drug normally used to treat diseases of the eye and the surrounding tissues can be employed which is a solid or can be made into a solid derivative. Also, within the contemplation of the present invention is the use of drugs which will pass through the eye or the tissue sur-

rounding the eye into the bloodstream, but which may not be used in treatment of the eye itself.

Some examples of drugs used in ophthalmic therapy which may be employed in the present invention are: anti-infectives: such as antibiotics, including tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gram-
icidin, oxytetracycline, chloramphenicol, and erythro-
mycin; sulfonamides, including sulfacetamide, sulfamethizole, and sulfisoxazole; antivirals, including idoxuri-
dine; and other anti-infectives including nitrofurazone
and sodium propionate; antiallergenics such as antazo-
line, methapyrilene, chlorpheniramine, pyrilamine and
propenpyridamine; anti-inflammatories such as hydro-
cortisone, hydrocortisone acetate, dexamethasone, dex-
amethasone 21-phosphate, fluocinolone, medrysone, pred-
nisolone, prednisolone 21-phosphate and prednisolone
acetate; decongestants such as phenylephrine, naphazo-
line, and tetrahydrazoline; miotics and anticholinesterases
such as pilocarpine, eserine salicylate, carbachol, diiso-
propyl fluorophosphate, phospholine iodide, and dema-
carium bromide; mydriatics such as atropine sulfate,
cyclopentolate, homatropine, scopolamine, tropicamide,
eucatropine, and hydroxyamphetamine and sympathomi-
metics such as epinephrine. The drugs can be in various
forms such as uncharged molecules, components of
molecular complexes, or nonirritating, pharmacologically
acceptable salts, such as the hydrochloride, hydrobromide,
sulfate, phosphate, nitrate, borate, acetate, maleate,
tartrate, salicylate, salts of polyuronic acids such as
alginic acid, galacturonic acid and glucuronic acid, and
salts prepared from carboxymethylcellulose. Further-
more, 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 used to make up the solid dosage form will vary
widely depending upon the particular drug, the desired
therapeutic effect, and the time span for which the solid
dosage form will be used. There is no critical upper limit
on the amount of the drug used since the solid dosage is
intended to provide the complete dosage requirement for
a given period. The lower limit will depend on the activity
of a given drug and its rate of diffusion in the tear fluids.
Therefore, it is not practical to define a particular range
for a therapeutically effective amount to be used to make
up the solid dosage. However, generally about 1-50 mg.
will be employed in the usual solid form, depending upon
the particular drug employed. The preferred range is
from about 1-10 mg.

The solid dosage form can be prepared by any conventional method used to prepare discs, pellets, wafers, etc. from solids. One method, for example, involves dissolving the medicament in a solvent such as water, placing the solution in a suitable container or vessel and removing the solvent by evaporation. Where desired, the semi-solid mass left upon partial evaporation can be sectioned into the desired shape by means of various size cutting tools. The solid is then dried to ensure the removal of all of the solvent. In this manner, it is possible to vary the dimensions of a respective dose by simple replacing the size of the cutting tool or changing the volume of the liquid used in preparation of the disc. The disc can be fabricated in any convenient shape, keeping in mind that it must be comfortably retained in the cul-de-sac of the eye. The shape, however, must not have sharp, jagged or rough edges which may irritate the sensitive tissues of the eye. The actual shape used presents little problem to eye tissue since the initial form is changed upon coming into contact with the eye fluids. The solid form of the drug may be a disc, pellet, flake, etc.; it can be concave, convex, rectangular, etc. The original shape of the solid drug form is not of critical importance. The actual size of the solid dosage form will vary widely. The lower limit will be governed by the amount of the particular drug to be applied to the eye to obtain the desired ophthalmic

response. The upper limit will be governed by the smallest sized solid which can be conveniently inserted into the cul-de-sac. Generally, the solid form will be about 1-8 mm. in length, about 1-4 mm. in width, having a thickness of about 0.2-1 mm. The preferred shape is a disc having a thickness of about 0.3 mm., a diameter of 3-7 mm., and a weight of about 3.0-8 mg.

Although the duration of the pharmacological effect of the drug in the eye will depend upon the particular drug employed and the amount used, solid form delivery of the drug generally results in a pupillary response of up to 7-8 hours in the animal and longer in humans.

Those compounds which are normally solids may be delivered in the form of a disc or pellet, etc. without the aid of an additive. Those compounds which are normally liquid may be used in the form of a pharmacologically acceptable solid derivative. Also contemplated is the use of a diluent or vehicle in conjunction with the solid dosage form. Suitable vehicles include, for example, methylcellulose, hydroxypropylmethylcellulose, diethylaminoethylcellulose, polyvinylpyrrolidone and pharmacologically acceptable cationic or anionic resins.

The treatment of eye diseases by delivering the medication directly to the cul-de-sac of the eye in solid form has general application to various diseases of the eye. Any condition where prolonged drug administration is required may be treated in this manner. For example, it is possible to treat in this manner such eye disorders as uveitis, glaucoma, diseases of the cornea such as, for example, purulent keratitis, herpes simplex keratitis, herpes zoster, acne rosacea, interstitial keratitis, and the like, diseases of the orbit such as exophthalmos and periostitis and diseases of the conjunctiva such as mucopurulent conjunctivitis and ophthalmia. The present mode of drug delivery may also be used when postoperative treatment is required such as after retinal and cataract surgery.

An additional disadvantage related to the use of solutions of drugs in the treatment of diseases of the eye is the instability of most drugs in solution. Drug solutions generally contain a preservative to prevent bacterial growth. The pH of eye fluids is about 7.4 while the pH of commercial pilocarpine solutions is about 5.3-5.5. It is known that acidic solutions tend to cause discomfort to the eye. The administration of the drug in solid form, however, circumvents the problems relating to stability and eye discomfort since the drug in solid form is stable for an indefinite period.

In a specific example of the method of delivering a drug to the cul-de-sac in solid form, in accordance with the present invention, pilocarpine is prepared in the form of a disc and used to treat the symptoms of glaucoma. Glaucoma is a clinical condition which is characterized by an increase in intra-ocular pressure. The tension which is associated with chronic simple glaucoma requires careful study and repeated observation. In cases of chronic simple glaucoma, miotic treatment is generally instituted. The most commonly used miotic is pilocarpine which is administered several times a day. A solution of about 0.5-4% is used in early cases, but stronger solutions are used when necessary to control the condition. Eserine can be used generally in an 0.025-1.0% solution if necessary and, in certain instances, stronger cholinergic drugs such as echothiophate iodide (phospholine iodide) may be employed.

In treating glaucoma, pilocarpine is generally administered in the form of an aqueous solution, but it may also be administered in the form of an ointment or by injection. The eye drops commonly used to make up the solution generally consist of an aqueous solution of pilocarpine hydrochloride. The present inventors have found that delivery of the drug, pilocarpine in the present example, to the cul-de-sac of the eye in the form of a solid disc provides a means for controlling the release of the drug from a given dosage form. The availability of the drug for absorption from the cul-de-sac is more uniform than

that obtained from inorganic salt type ophthalmic solutions.

The effectiveness of the administration of the drug in solid form is illustrated by the following example. The acid salts used in the example are prepared by conventional methods used to prepare acid addition salts from compounds containing a base nitrogen.

EXAMPLE 1

A. Preparation of ophthalmic solid dosage forms

(a) *Pilocarpine alginate*.—ophthalmic discs are prepared by dissolving pilocarpine alginate powder (7% w./v.) in a small quantity of sterile water with stirring. The solution is placed in a flat-bottom petri dish and evaporated under reduced pressure at 30° C. in a thermostatic water bath assembly. When the colloidal solution reaches a semi-solid consistency, the mass is sectioned into circular flakes (0.3 mm. thickness, 3–7 mm. diameter, 3.1–7.8 mg.) by means of various size trephines and the sections are dried to the point of solidification at 30° C. The solid is dried for an additional 24 hours at room temperature and the discs are removed and stored in light-resistant containers.

(b) *Pilocarpine hydrochloride*.—A disc was prepared in the same manner as in a) above using 14.7 mg. of pilocarpine hydrochloride and 100 mg. of methylcellulose 4000 cps. in sterile water for injection. A disc weighing 4.6 mg. was obtained.

(c) *Pilocarpine alginate*.—A disc was prepared in the same manner as in a) above using 22 mg. of pilocarpine alginate and 0.23 mg. of methylcellulose in sterile free water for injection. A disc weighing 22.23 mg. was obtained.

(d) *Pilocarpine*.—A disc was prepared as in a) above using 4 mg. of pilocarpine. A disc weighing 4 mg. was obtained.

B. Preparation of ophthalmic solutions

(a) *Pilocarpine alginate* (3.34% w./v.) solution was prepared from sterile Sørensen phosphate buffer stock solutions mixed in varying proportions to give a final pH of 6.14. The solution was adjusted for toxicity with sodium chloride.

(b) *Pilocarpine hydrochloride solution* (2.00% w./v.) in the presence of methylcellulose 4000 cps. required to adjust the viscosity to that of the alginate in a) above (72 cps., Brookfield viscosimeter, model LVT, 25° C.) was prepared from sterile Sørensen phosphate buffer stock solutions mixed in varying proportions to give a final pH of 6.14 and adjusted for toxicity with sodium chloride.

PREPARATION A

1. *Pilocarpine alginate*.—Pilocarpine free base (5 g.) and alginic acid powder (5 g.) are mixed together in 50 ml. of sterile, distilled water with stirring. The mixture is heated in a water bath at 50° C. and the stirring is continued for 1 hour. The resulting gel is cooled to room temperature and the stirring is continued for 24 hours under reduced light. The mixture is then diluted to 100 ml. with distilled water and the resulting solution is stirred for 12 hours at room temperature. The solution is then transferred to a dessicator-water bath assembly and evaporated to dryness under reduced pressure at 30° C. The dry powder left upon removal of the water is used directly to prepare the disc and the solution of pilocarpine alginate.

Albino male rabbits are allowed to equilibrate under constant conditions of illumination for twenty-four hours prior to treatment with liquid and solid dosages of pilocarpine.

Each solution is delivered from a micrometer syringe (0.075 ml.) into the lower cul-de-sac of one eye. Aqueous alginic acid or aqueous hydrochloric acid is placed in the other eye as a control. The disc is soaked in isotonic sodium chloride solution and then deposited into the lower cul-de-sac with the aid of forceps. The alginic acid and

methylcellulose disc is used as a control. The size of each pupil is measured just before the test drug is applied by means of an Optiker Ryer pupillary gauge fixed at a distance of six inches from the globe. During measurement, the animals are confined in a wooden box which provides free head and neck motion. Prior to taking measurements, a waiting period of one minute is exercised from the time the gauge is brought within the above distance. At specified time intervals, at least six pupillary diameter readings are made at each point.

Pupillary responses indicate (FIG. 1) that, in the liquid state, pilocarpine alginate exhibits essentially comparable miotic activity as pilocarpine hydrochloride following single dose treatment. No pupillary constriction is noted in both liquid and solid dose control eyes. The results derived from solid pilocarpine alginate deposition show the magnitude of maximum pupil size constriction to be enhanced, with duration of miosis significantly increased over that of both liquid dosage systems. Restoration of normal pupillary diameter for the solid state dose is observed to occur between 7 and 8 hours in contrast to 3–3½ hours for the ophthalmic solutions.

In FIG. 2, data for repetitive pilocarpine alginate disc application are given. In this study phase, miotic activity is monitored after repeating the dose at maximum pupil constriction, 50% and 100% recovery of pupillary diameter. Repeating the treatment at 50% pupil recovery gives about a two-fold increase in miotic duration relative to both single dose deposition and normal pupillary diameter and multiple treatments at the points of maximum constriction. When a second and third disc is applied at recovery (7 mm.), the behavior is additive with restoration of pupil size being reached after seven, twelve and about seventeen hours.

Overall duration of miosis in the case of triplicate liquid treatments (FIG. 3) at recovery shows that activity derived from solutions of pilocarpine alginate and pilocarpine hydrochloride methylcellulose is essentially equal. Recovery from the first, second and third drop instillations is reached at about four, seven and ten hours, respectively.

The availability of the medicament in the cul-de-sac from solid form doses appears to be more uniform as a consequence of diminished diffusion through the gel matrix where the drug is held in reserve in contrast to liquid dosage forms when the dose is immediately released in the conjunctival fluids. Although the rate of diffusion of the solid drug will depend on the given drug employed, the concentration of a given disc can be controlled so as to allow maximum dosage over a given period once the rate of diffusion of a given drug is known. The use of solid ophthalmic dosages in the treatment of diseases of the eye is more effective than conventional methods and requires less frequent administration of the drug to produce prolonged physiological activity.

While a preferred embodiment of the present invention has been described, it is apparent that numerous variations and additions may be made to the invention without departing from the spirit thereof. It is the intention, therefore, to be limited only by the scope of the following claims:

What is claimed is:

1. In the method of obtaining the ophthalmic pharmacological effect of a medicament comprising inserting a complete ophthalmic dosage of medicament in solid form into the cul-de-sac of the eye between the eyeball and the lid to dispense the medicament to the eye over a prolonged period of time, the improvement by means of which the cul-de-sac is left free of tear insoluble residue after said medicament is dispensed, which comprises employing a solid matrix of a non-irritating pharmacologically acceptable polyuronic acid or carboxymethylcellulose salt of said medicament, free from tear insoluble carriers, said matrix adapted to form a gel-matrix after insertion into the cul-de-sac and to dissolve completely for slow release of said dosage.

2. The method of claim 1 wherein the medicament is employed in the form of a disc capable of assuming essentially the configuration of the curvature between the eyeball and the lid.

3. The method of claim 1 wherein the medicament employed is in the form of a salt of a polyuronic acid.

4. The method of claim 3 wherein the polyuronic acid is alginic acid.

5. The method of claim 1 wherein the medicament is a miotic.

6. The method of claim 5 wherein the miotic is selected from the group consisting of pilocarpine, eserine and carbachol.

7. The method of claim 1 wherein a vehicle is additionally present, said vehicle being selected from methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, diethylaminoethylcellulose, polyvinylpyrrolidone and pharmacologically acceptable cationic and anionic resins.

8. The method of obtaining the ophthalmic pharmacological effect of a medicament for treating glaucoma comprising inserting a complete ophthalmic dosage of medicament in solid form into the cul-de-sac of the eye between the eyeball and the lid to dispense the medicament to the eye over a prolonged period of time, the improvement by means of which the cul-de-sac is left free of tear insoluble residue after said medicament is dispensed, which comprises employing a solid matrix of a non-irritating pharmacologically acceptable polyuronic acid or carboxymethylcellulose salt of said medicament, free from tear insoluble carriers, said matrix adapted to form a gel-matrix after insertion into the cul-de-sac and to dissolve completely for slow release of said dosage.

9. The method of claim 8 wherein the medicament is employed in the form of a disc capable of assuming essentially the configuration of the curvature between the eyeball and the lid.

10. The method of claim 9 wherein the medicament is in the form of a disc having a thickness of about .3 mm., a diameter of about 3-7 mm., and a weight of about 3-8 mg.

11. The method of claim 9 wherein the medicament is present in the form of a salt of a polyuronic acid.

12. The method of claim 9 wherein the polyuronic acid is selected from the group consisting of alginic acid, galactouronic acid and glucouronic acid.

13. The method of claim 8 wherein the medicament is selected from the group consisting of pilocarpine, eserine, carbachol and pharmacologically acceptable salts thereof.

14. The method of claim 12 wherein the pharmacologically acceptable salt is pilocarpine alginate.

15. The method of claim 8 wherein a vehicle is additionally present, said vehicle being selected from the group consisting of methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, diethylaminoethylcellulose,

polyvinylpyrrolidone, and pharmacologically acceptable cationic and anionic resins.

16. In the method of obtaining the ophthalmic pharmacological effect of a medicament which comprises insertion of a complete ophthalmic dosage requirement, said medicament being in solid disc, pellet or wafer form, for inserting into the cul-de-sac of the eye between the eyeball and the lid, to dispense the medicament to the eye over a prolonged period of time, the improvement which comprises a complete ophthalmic dosage requirement of said medicament formulated as a non-irritating pharmacologically acceptable polyuronic acid or carboxymethylcellulose salt gel-matrix with slow diffusional drug release and availability for absorption from the cul-de-sac, said salt form of a complete ophthalmic dosage requirement of said medicament being tear-fluid diffusible in solid form, without the aid of an additive, diluent or vehicle, and further being free from any solid carrier insoluble in tear fluid and free from the drawback of the need of removal of any solid carrier insoluble in tear fluid after each application, said solid complete ophthalmic dosage being adapted for deposition into the cul-de-sac of the eye after assuming a semi-plastic consistency upon being presoaked in isotonic sodium chloride solution and being adapted to be completely controllably released after insertion.

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SHEP K. ROSE, Primary Examiner

U.S. Cl. X.R.

128—260; 424—19, 180, 273