

[54] **OPHTHALMIC DOSAGE FORM, FOR
RELEASING MEDICATION OVER TIME**

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424/19; 424/20; 424/37

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[58] **Field of Search** 424/19-22,
424/32-38; 128/260, 272

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[57]

ABSTRACT

A dosage form for ophthalmic drugs is disclosed. The dosage form is a suspension of 10 to 300 micron particles in a liquid medium. The particles are made up of drug enclosed within a drug release rate-controlling material which bioerodes in the environment of the eye.

4 Claims, 4 Drawing Figures

FIG. 1

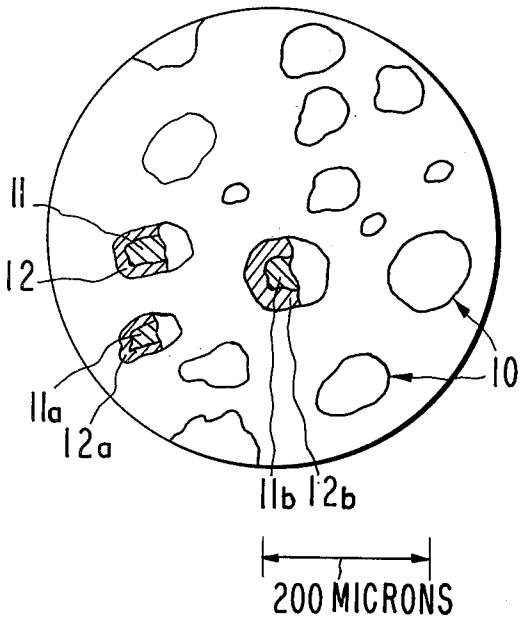


FIG. 3

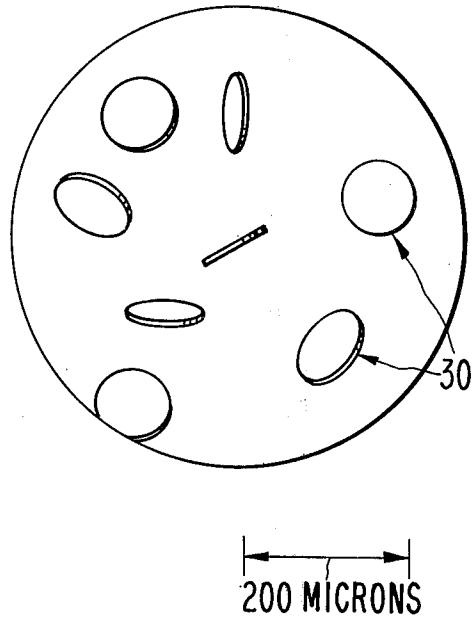


FIG. 2

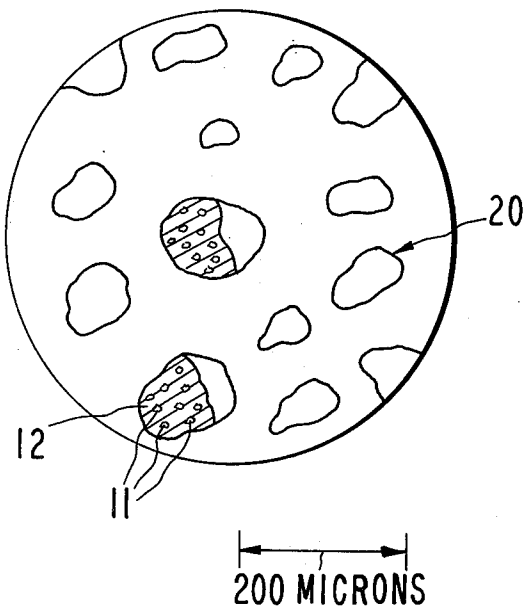
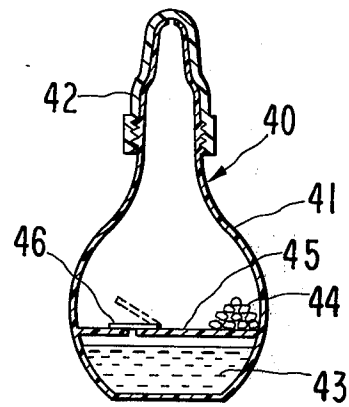


FIG. 4



OPHTHALMIC DOSAGE FORM, FOR RELEASING MEDICATION OVER TIME

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to an improved dosage form for ophthalmic drugs. More particularly it relates to a new ocular dosage form which is easy to use and which achieves a controlled release of drug to the eye over a prolonged period of time.

2. The Prior Art

Most ocular treatments call for the administration of medicaments topically to the tissues of the ocular cavity. These medicaments have, in the prior art, assumed a wide range of forms.

The most common dosage form for ophthalmic medicaments is liquid drops. Liquid drops may be found for example, in over-the-counter ocular decongestants, such as Murine, and Visine, and in anti-glaucoma solutions, such as ½ percent, 1 percent and 2 percent aqueous solutions of pilocarpine salts. The liquid drop dosage form is easy to use, but suffers from the disadvantage that the medication it contains is rapidly washed from the ocular cavity by tear flow, so that a continuous sustained level of medication is not achieved. Also, periodic application of eye drops results in the eye receiving a massive, but unpredictable, amount of medication at each time of application. The result of this intermittent administration and rapid washing is that the level of medication surges to a peak at the time the drops are applied — then the drug concentration drops rapidly. Thus, a plot of medication concentration in the eye versus time has the appearance of a series of peaks of drug level which may surpass the toxic threshold of the drug separated by extended valleys of drug level below the critical level needed to achieve the desired therapeutic effect.

Suspensions of particles of drug in liquids have been widely used as well; for example, hydrocortisone acetate and prednisolone acetate are typical of drugs presently marketed as suspensions. These suspensions usually contain preservatives, isotonicity adjusters, and suspending and dispersing agents. Present day suspensions present a variety of problems. First, they generally may only be made with relatively water-insoluble drugs, since soluble drugs form saturated solutions which have higher tonicities than the eye can easily adapt to. Also, the rate of release from the particles of the suspension is related to the rate of solubility of the drug so that one dosage rate along may be obtained with a given drug. In the majority of cases this one rate of delivery is not ideal.

Other dosage forms have been proposed, most on the basis that they give a more prolonged release of drug to the eye. These dosage forms include ointment; lamellae of glycerinated gelatin, such as described in U.S. Pat. No. 273,410 issued Mar. 6, 1883; and other similar dosage forms. These dosage forms give an only marginally more sustained drug release than do liquid drops and most particularly, do not give a constant release pattern; additionally they suffer the disadvantages of being difficult to sterilize and apply and often causing blurring of vision.

Recently developed ophthalmic drug delivery systems, such as described in U.S. Pat. No. 3,416,530 patented Dec. 17, 1968 and in U.S. Pat. No. 3,618,604 patented Nov. 9, 1971, do give true controlled deliver-

ies of drug. The ophthalmic drug delivery systems of these patents are unitary ocular inserts, several millimeters in size which are placed in the upper or lower sac of the eye to deliver a complete ophthalmic dosage regimen for a period of 24 hours or longer.

While these ocular inserts do deliver drug to the eye continuously and in a controlled manner, there remain improvements to be made. Many patients, especially the farsighted elderly have difficulty inserting or removing ocular inserts. Also the large unitary ocular inserts are at times accidentally ejected from the ocular cavity by the blinking action of the eyelids.

It would indeed be desirable to provide a dosage form which combined the ease of administration of liquid drops with the improved drug release characteristics of ocular inserts.

STATEMENT OF THE INVENTION

In accordance with the present invention, a new ophthalmic dosage form is provided which combines the ease of administration of liquid drops with the improved drug release characteristics of drug releasing ocular inserts. This new dosage form for ophthalmic drugs comprises a suspension of solid particles in a liquid medium, said particles comprising ophthalmic drug enclosed within a bioerodible drug release rate controlling material. These particles are from 10 to 300 microns in largest dimension.

In one embodiment, the particles each comprise a body of drug-impermeable bioerodible release rate-controlling material containing a drug dispersed throughout, which material bioerodes at a controlled rate over a prolonged period of time in response to the environment of the eye, thereby releasing the dispersed drug at a controlled rate over a prolonged period of time.

In another embodiment, the particles each comprise single depots of drug microencapsulated by a drug-impermeable bioerodible drug release rate controlling material which material bioerodes at a controlled rate over a prolonged period of time in response to the environment of the eye, thereby releasing the microencapsulated drug at a controlled rate over a prolonged period of time.

In yet other embodiments, the particles comprise either a drug-containing body or microcapsule made of a bioerodible material through which the drug is permeable at a controlled rate for a prolonged period of time.

Although the solid particles of the suspension are small enough to be passed from the ocular cavity through the punctum, this does not in fact happen. Instead the particles of the suspension painlessly disperse and lodge in the soft tissues which line the surfaces of the palpebral and bulbar conjunctiva.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawing contains four drawings.

FIG. 1 is a magnified view of ophthalmic suspension in accord with this invention showing in partial cross-sectional view one type of useful particle.

FIG. 2 is a view like FIG. 1 showing in partial cross-sectional view another type of useful particle.

FIG. 3 is a view like FIG. 1 showing in perspective view yet another type of useful particle.

FIG. 4 is a cross-sectional view of a container for mixing and administering the suspensions of this invention.

DETAILED DESCRIPTION OF THE INVENTION

In its simplest form, the present dosage form includes a liquid medium and a substantial plurality of 10 to 300 micron sized particles containing drug and a drug release rate-controlling substance. The liquid medium employed in the present suspension dosage form may be an aqueous or non-aqueous ophthalmically acceptable sterile liquid. Suitable non-aqueous liquid media include the physiologically acceptable oils such as silicone oil, USP mineral oil, white oil, and vegetable oils, for example corn oil, peanut oil, or the like. An aqueous medium is generally preferred.

The dosage form optionally contains a variety of other materials to adjust pH, render the medium isotonic, preserve the dosage form and the like. Preservative agents include benzalkonium chloride in a concentration of from 1:15,000 to 1:30,000; chlorobutanol, in a concentration of from 0.3 percent to 0.8 percent; thimerosal, in a concentration of from 0.001 percent to 0.003 percent; and phenyl mercuric nitrate, in a concentration range of from 1:60,000 to 1:80,000. Agents may be added to increase viscosity, promote suspension and/or improve ocular compatibility, such as methyl cellulose in an amount of from 0.1 percent to 0.7 percent or poly(vinyl alcohol) in an amount of from 0.4 percent to 2 percent. These and other additive materials are known in the art and are generally described in the book *Contact Lens Practice* by Robert B. Mandell (Charles C. Thomas, 1965) at pages 159-165, which description is herein incorporated by reference.

The particles which are suspended in the liquid medium contain at minimum, drug surrounded by a bioerodible drug release rate-controlling material. As used herein, a "drug release rate-controlling material" is defined to be a material which, when fully surrounding a particle of physiologically active drug, prevents the drug from exhibiting its physiological activity or limits the rate at which the drug may diffuse into the ocular environment. Only when the surrounding drug release rate-controlling material is disrupted or when the drug diffuses through the rate-controlling material may the enclosed drug be released. As used herein the term "drug release rate-controlling material" is intended to include only those materials which truly function as just set forth. Fillers, binders and the like, known to the art are not included within these materials. If the particles are to painlessly lodge in the ocular tissues and to deliver drugs at a controlled rate they must be of a size of from 10 microns to 300 microns in largest dimension, preferably from 20 microns to 200 microns in largest dimension. The particles should also be sized such that a substantial plurality of particles (such as 100 or more) are delivered with each administration, to ensure a uniform delivery.

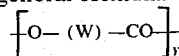
The drug release rate-controlling material must be bioerodible, that is, it must innocuously disintegrate or break down from a unit structure or enclosure over a prolonged period of time in response to the environment of the eye by one or more physical or chemical degradative processes, for example, enzymatic action, hydrolysis, ion exchange, or dissolution by solubilization, emulsion formation or micelle formation.

Likewise the term "bioerode" is defined as the method by which such disintegration takes place. Bioerosion of the release rate-controlling material serves two purposes, not only may it release enclosed drug at a controlled rate but also it prevents a build-up of particles in the tissues of the ocular cavity.

In the particles of the suspensions of this invention are employed bioerodible materials which are non-toxic and compatible with the drug used, and which are capable of forming films which wholly surround and enclose drug particles. Exemplary of the materials which can be employed are:

1. Polyesters

Polyesters of the general formula:



and mixtures thereof, wherein:

W is a radical of the formula $-\text{CH}_2-$; or



Y has a value such that the molecular weight of the polymer is from about 4,000 to 100,000 may be employed as release rate-controlling materials.

These polymers are polymerization condensation products of monobasic hydroxy acids of the formula:



wherein n has a value of 1 or 2, especially lactic acid and glycolic acid. Also included are copolymers derived from mixtures of these acids. The preparation of polymers of the formula I per se forms no part of the present invention. Several procedures are available and reported by Filachione, et al, *Industrial and Engineering Chemistry*, Vol. 36, No. 3, pp.223-228, (March 1944; Tsuruta, et al, *Macromol. Chem.*, Vol 75, pp.211-214 (1964) and in U.S. Pat. Nos. 2,703,316; 2,668,162; 3,297,033; and 2,676,945. These polymers are hydrophobic and substantially impermeable to most drugs. Thus, they function best in particles which release encapsulated drug by an erosion mechanism. This application is related to copending U.S. application Ser. No. 248,168 filed on Apr. 27, 1972, now U.S. Pat. No. 3,867,519 issued on Feb. 18, 1975 and assigned to the same assignee as this application. Application Ser. No. 248,168 disclosed bioerodible ocular devices of polylactic acid microencapsulated chloramphenicol which erode in the eye. 2. Cross-Linked Gelatin

Gelatin is obtained by the selective hydrolysis of collagen, as is well known, and comprises a complex mixture of high molecular weight water soluble proteins. As used herein, the term cross-linked gelatin means the reaction product of gelatin or a gelatin derivative with a cross-linking agent which is reactive with either the hydroxyl, carboxyl or amino functional groups of the gelatin molecule but is substantially unreactive with the peptide linkages of the gelatin molecule. The product of cross-linking reaction preferably has an average molecular weight of from 20 to 50,000 between cross-links, while higher values can also be employed. These reaction products bioerode in the environment of the eye over a prolonged period of time.

Cross-linked gelatin materials and their preparations are well known. The degree of gelatin cross-linking is dependent upon the processing conditions employed and markedly affects the gelatin's bioerodibility. This

application is related to copending U.S. application Ser. No. 179,129 filed on Sept. 9, 1971 which application is assigned to the same assignee as this application and discloses ocular devices made of cross-linked gelatin. Application Ser. No. 179,129 is cross-referenced in U.S. Pat. No. 3,867,519.

Exemplary cross-linking agents are: aldehydes, such as monoaldehydes, e.g. C₁ - C₄ aldehydes, dialdehydes, epoxides, para-benzene quinone, and aqueous peroxydisulfate.

Aldehydes and ketones, especially the 1 to 4 carbon aldehydes and ketones are preferred, with formaldehyde being a most preferred across linking agent.

Irradiation is another suitable method for cross-linking gelatin; see for example Y. Tomoda and M. Tsuda, *J. Poly. Sci.*, 54,321 (1961).

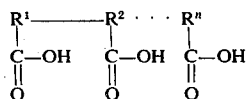
The reactive hydroxyl, carboxyl and amino groups are respectively present in gelatin in the appropriate amounts of 100, 75 and 50 meq per 100 grams. These quantities may serve as a general guide in determining the amount of cross-linking agent to be used.

Cross-linked gelatin is relatively permeable to ocular fluid so that diffusion of drug through gelatin may take place to some extent. Thus, cross-linked gelatin is a good example of a release rate-controlling material which releases drug by a diffusion mechanism.

3. Polyacids

A third typical group of drug release rate-controlling materials is made up of a certain class of poly(carboxylic acids). These polyacids are characterized as being hydrophobic when unionized and compatible with the tissues of the eye and as having a specified proportion of carboxylic hydrogens.

Suitable poly(carboxylic acids) are the hydrophobic polyacids which are represented by the general formula:



wherein: the R's are organic radicals independently selected to provide an average of from 8 to 22 total carbon atoms for each carboxylic hydrogen. Variations of this ratio within this range can vary the bioerosion and drug release rates of drug particles prepared from these polymeric acids. Organic radicals represented by R¹, R², . . . Rⁿ may be selected from hydrocarbon radicals and hetero-atom containing organic radicals. Suitable hetero-atoms for employment in R¹, R², . . . Rⁿ can include oxygen, nitrogen, sulfur and phosphorous as well as other hetero-atoms so long as the required hydrophobicity and carbon to carboxylic hydrogen average ratio is maintained. The value of n and hence the average molecular weight of the polymer is not critical and may vary over a wide range. Suitable molecular weights, for example, range from about 10,000 to about 800,000. Materials within this range bioerode to products which may be easily and innocuously passed from the environment of the eye. Preferred molecular weights are from about 15,000 to about 500,000. These poly(carboxylic acids) materials and their preparation and fabrication are more fully described in U.S. patent application Ser. No. 318,891 of Heller and Baker, filed Dec. 27, 1972, and now U.S. Pat. No. 3,811,444 dated

May 21, 1974 which application is herein incorporated by reference. U.S. Pat. No. 3,811,444 and this application Ser. No. 369,916 are assigned to the same assignee. The patent pertains to ocular inserts containing different ocular drugs in varying amounts, with the insert having varying dimensions and prepared from many reagents. The patent discloses the in vivo erosion rates for inserts and the examples numbers in the Table below correspond to the example numbers in the patent. In the Table, number 1 through 5 are alkanol half esters of maleic acid. Examples 7 through 14 are the alkanol half esters of poly(vinyl methyl ether maleic acid). The patent also discloses other inserts prepared from different reagents with the erosion rates measured in vitro and in simulated ocular environments. These examples are incorporated herein by reference.

TABLE

Example	Ester	Time to complete erosion in eye, hrs
1	n-hexyl	175
2	n-butyl	10 - 15
3	n-pentyl	30
4	n-heptyl	90
5	n-octyl	550
6	—	—
7	n-pentyl	20
8	ethyl	3
9	isopropyl	4
10	butyl	8
11	butyl	8
12	butyl	8
13	n-pentyl	1
14	2-pentyl	60

A preferred group of polyacid release rate-controlling materials comprise hydrophobic polymers of an acid selected from acrylic acid, lower alkyl acrylic acids of from 4 to 6 carbon atoms per monomeric unit, and maleic acid either alone or copolymerized with up to about 2 moles, per mole of acid, of a copolymerizable olefinically unsaturated group such as ethylene or lower (1 to 4 carbon) alkyl vinyl ethers wherein from about 20 percent to 90 percent of the acid groups have been esterified with an alkanol of from 1 to about 10 carbon atoms and wherein the ratio of total carbon atoms to acidic carboxylic hydrogens is in the range of from about 9:1 to about 20:1.

An even more preferred group of poly(carboxylic acids) comprise the hydrophobic partially esterified copolymers of acrylic acid, methacrylic acid or maleic acid with from 0.2 to 1.5 moles, per mole of acid, of ethylene or lower (1-4 carbon) alkyl vinyl ether having from about 35 percent to about 70 percent of their total carboxylic groups esterified with lower alkanol of from about 3 to about 10 carbon atoms, said copolymers having a carbon to acidic carboxylic hydrogen ratio of from about 10:1 to about 15:1.

A group of poly(carboxylic acids) most preferred for use as rate controlling materials in accord with the present invention comprise hydrophobic copolymers of maleic acid with about one mole, per mole of maleic acid, of ethylene or methyl vinyl ether, said copolymer having about half of its total carboxyl groups esterified with a lower monoalkanol of from 4 to 8 carbon atoms, wherein the carbon to acidic carboxylic hydrogen ratio has a value of from about 10:1 to about 14:1. These poly(carboxylic acids) are generally drug-impermeable and thus are another example of a material which releases drug at a controlled rate by erosion.

These materials are considered illustrative. Any bioerodible material which is compatible with the drug, non-toxic and which has the desired encapsulation, diffusion and erosion properties might also be used. The polyesters, cross-linked gelatins and polyacids set forth herein are preferred as release rate-controlling materials.

Drugs suitable for incorporation in the particles of the suspension, consistent with their known dosages and uses, are without limitation solid ophthalmic drugs including: antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, and erythromycin; antibacterials such as sulfonamides, sulfacetamide, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; and other antibacterial agents such as nitrofurazone and sodium propionate; anti-allergens such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and prophenpyridamine; anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, medrysone, prednisolone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluorometholone, betamethasone and triamcinolone; decongestants such as phenylephrine, naphazoline, and tetrahydrazoline, miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phospholine iodide, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; and sympathomimetics such as epinephrine.

The solid drug and drug release rate-controlling material are combined in any fashion which enables small (10 to 300 micron) particles of enclosed drug to be formed which have the predominant portion of the drug fully enclosed within rate-controlling material.

One suitable manner for combining drug and rate-controlling material is illustrated in FIG. 1. FIG. 1 is a magnification of a suspension containing particles 10 in a liquid medium not expressly shown. Particles 10, when cut away, can be seen to comprise drug 11 microencapsulated within drug release rate-controlling material 12. As the figure illustrates, the particles 10 are of variable size. Also, it should be noted that the thickness of the coatings of drug release rate-controlling material varies (compare coating 12 with coatings 12a and 12b). This variation in erodible coating substantially prolongs the release of drug. Light coatings will erode through rapidly, while heavier coatings will take longer. By varying the relative proportions of various coating thicknesses a variable release rate may be achieved as well. Also, by varying the coating material among a group of differently eroding materials, some rapid — some slow, a controlled prolonged release may be obtained. It can also be seen, how, by adjusting the proportions of coated particles, a constant rate of drug release could be obtained, that is, a release rate having a zero order dependence on time.

Any of the standard encapsulation techniques known in the art can be used to prepare the microcapsule particles 10. The drug can be added to the drug release rate-controlling encapsulating material while it is in liquid or particle form, the mixture being reduced to fine microcapsules by grinding, or the like. Alternatively, fine particles of the drug can be coated such as by suspending dry particles of the drug in an air stream and

contacting that stream with a stream of rate-controlling material that coats the drug with a wall of rate-controlling material.

Another suitable microencapsulation method is the co-ascervation technique. The co-ascervation technique of fabrication consists essentially of the formation of three immiscible phases, a liquid manufacturing phase, a core material phase and a liquid coating phase. Liquid coating is deposited on the core material and rigidized usually by thermal, cross-linking or desolvation. Techniques for preparing microcapsules, such as the Bungenberg, de Jong and Kaas method are reported in *Biochem. Z.*, Vol. 232, (1931) pp. 338-345; and *J. Pharm. Sci.*, Vol. 59, No. 10 (1970) pp. 1367-1376.

A second typical configuration which particles may assume is illustrated in FIG. 2. There, a variety of particles 20 are illustrated which each contain a number of depots or drug 11 dispersed through a body 12 of rate-controlling material. As the rate-controlling material erodes, it gradually exposes and releases the drug from the depots.

These type of particles could be easily formed by admixing 0.5 to 5 micron drug particles and release rate-controlling material in a fluid phase and casting and settling a solid piece of drug and rate-controlling material. This piece could then be micronized, such as in a CRC Micromill, to give the desired 10 to 300 micron particles of rate-controlling material containing drug.

FIG. 3 illustrates an embodiment of the invention which can yield a more constant rate of release. The particles of the suspension of FIG. 3 are all flat discs, essentially having only two dimensions. That is, one of each disc's dimensions is less than 10 percent of either of its other dimension. While round discs are shown in FIG. 3, clearly other two dimensional shapes could also be used. These two dimensional particles present an essentially constant surface area throughout their period of bioerosion. The particles internally are similar to particles 20 of FIG. 2, that is, they contain a plurality of drug depots dispersed through a body of release rate-controlling material.

Another way to obtain a constant rate of drug release with an ophthalmic suspension in accord with this invention is to employ particles of the type shown in FIG. 1 (particles 10) having accurately controlled proportions of rate-controlling wall material. By providing an accurately graded range of thickness of rate-controlling material, a smooth flow of drug can be achieved.

The suspension dosage forms of this invention permit a uniform rate of ophthalmic drug delivery. Also, by their ability to prolong drug release, they permit the time periods between drop instillation to be greatly prolonged, such as to well over 4 hours, for example up to 4 to 5 days or even a week. Preferably suspensions are used to prolong drug release over periods of from 18 to 72 hours per instillation.

The suspension must therefore contain enough drug to satisfy the dosage requirements for these prolonged periods.

It is generally preferred to adjust the amount of drug in the suspensions so that from about 2 to 10 drops of suspension contains the required complete dosage regimen.

Typical dosages for drugs administered in the improved dosage form are:

Antibiotics, such as polymixin:	250 micrograms/day
Sulfonamides, such as sulfacetamide:	500 micrograms/day
Antivirals, such as idoxuridine:	5 micrograms/day
Anti-inflammatories, such as hydrocortisone acetate or prednisolone:	500 micrograms/day
Philocarpine:	25-500 micrograms/day

The proportion of drug and drug release rate-controlling material can range from about 8 parts drug to 1 part rate-controlling material to about 1 part drug to about 3 parts rate-controlling material. The particles shall contain sufficient drug for the entire dosage regimen. The proportion of drug-containing particles to liquid medium of the suspension can range from about 1 part particles to 100 parts liquid to about 1 part particles to about 2 parts liquid.

In summary, the suspensions of this invention generally contain the following proportions of components:

Liquid medium	100 parts
Particles	1-50 parts
Drug	0.3-45 parts
Rate-controlling material	0.1 to 33 parts
Preservatives and the like	(as required)

When an aqueous medium is employed in the suspension, it is often desirable to take precautions to prevent undue erosion of the particles in the medium prior to use. This may be done chemically, for example, by saturating the medium with dissolved drug release rate-controlling material in cases where bioerosion proceeds through solubilization, or by adjusting the solution pH, in cases where the ratecontrolling material's erosion is pH dependent, to nonerodible ranges. It may also be done physically by separating the solid particles from the liquid medium until immediately prior to application of the suspension. In a most elementary fashion, this may be carried out by adding a few drops of liquid to the particles prior to use. A more accurate, more controlled addition of liquid can be carried out using a multi-chambered drug container such as shown in cross-sectional form in FIG. 4 as container 40. Container 40 grossly is in the form of a single dosage dropper bottle of the type often used for ophthalmic preparations. It has an outer wall 41, generally of flexible plastic. The top of wall 41 terminates in a small dropper tip having a hole. It may be a part of wall 41, as shown, or it may be as second separate insert plug. The latter configuration facilitates filling the container. The tip is equipped with a cover to keep dirt, germs, and the like out and maintain sterility of the contents of container 40. Container 40 contains a measured amount of 20 to 200 micron enclosed solid drug particles 44 in a second upper chamber. The two chambers are separated from one another by a barrier 45 carrying a valve 46. By squeezing the lower portion of device 40 the liquid there contained is forced upward through the valve into the upper chamber and mixed with particles 44. A variation of this configuration could employ a rupture disc between the two chambers. The resulting suspension would have an accurately determined composition and would be easily administered to a patient's eye via the dropper tip.

EXAMPLES I and II

Two ocular suspensions in accord with this invention are prepared.

A. First, a drug release rate-controlling material is prepared as follows: 126 grams (1.0 equivalents) of ethylene-maleic anhydride copolymer (Monsanto EMA, Grade 31) is stirred with 500 ml (4.0 moles) of n-hexyl alcohol at 120°-125° C for 7 hours. The solution is cooled to room temperature and methylene chloride is gradually added to the cloud point. Then more methylene chloride is added to precipitate the product (total volume 20l). The precipitate is thoroughly leached with the methylene chloride. The solvent is decanted and the product dissolved in 750 ml warm acetone. Methylene chloride is added to the cloud point. Then more methylene chloride is added to precipitate the product (total volume 15l). The precipitate is then thoroughly leached with methylene chloride. The solvent is decanted and the product dissolved in 750 ml acetone. The solution is transferred to a polypropylene container and solvent is removed under vacuum at 50°C to yield the drug release rate-controlling polymer product. The infrared spectrum of the polymer shows broad bands at 1680 and 1780 cm⁻¹ indicative of ester carboxyl. Titration with base shows that the hexyl half ester of maleic acid has been formed, and thus the ratio of total carbons to ionizable hydrogens on average is 12:1.

B. Preparation of hydrocortisone-containing particles. 1.8 Grams of the half ester polymer of part A is dissolved in 5 ml of acetone, with stirring at 25°C. 0.6 Grams of hydrocortisone acetate micronized to 4 to 10 microns are dispersed in the solution with stirring. The resulting viscous dispersion is cast on a polyethylene film. The casting is allowed to dry thoroughly to yield a dry film. The resulting film is removed from the polyethylene film by stripping, and is micronized and screened to a size of from 20 to 200 microns. 20 Mg of these particles containing 5 mg of hydrocortisone acetate suspended in 40 drops of sterile water (about 2 cc).

A 4 drop portion of this suspension is added to a small shaken vessel having a liquid volume and liquid turnover simulating a human eye. The rate of hydrocortisone acetate release is measured by infrared spectroscopy and compared with the rate of release of hydrocortisone acetate observed when 0.5 mg of 4 to 10 micron hydrocortisone acetate particles are placed in the same vessel under the same conditions. The coated particles present a release which is substantially more prolonged than that of the uncoated particles.

C. Alternative preparation. 30 Grams of hydrocortisone acetate are micronized to 5 micron average size and screened to separate out a 1 to 10 micron range of sizes. These separated particles are then microencapsulated in 50 grams of the poly(acid) of part A by dissolving the poly(acid) in 500 cc's of acetone and spraying the acetone solution using a Wurster air suspension technique. The spray coating varies from 5 to 40 microns in thickness. When these particles are suspended in an aqueous medium and tested in accord with part B of this example, they too give a sustained release of drug.

EXAMPLE III

Five hundred grams of chloramphenicol of a particle

size of from 20 to 40 microns is encapsulated with polylactic acid polymer of molecular weight 50,000, according to the following procedure: 250 grams of the polylactic acid is dissolved in 2 liters of chloroform. The chloramphenicol particles are coated with the polylactic acid using a Wurster air suspension technique. The coat thickness is determined to vary from 8 to 60 microns thick.

Three grams of the chloramphenicol microcapsules are dispersed in 50 cc's of an aqueous medium containing preservatives and salts to achieve ocular isotonicity. When drops of this dispersion are placed in the eye, the poly (lactic acid) coated particles imbed in the soft tissues lining the eyelids. They gradually release their chloramphenicol over a prolonged (48 hour) period. After about 96 hours, no residual poly (lactic acid) is noted in the ocular cavity.

EXAMPLE IV

The procedures of Example III are repeated, substituting 250 grams of crystalline pilocarpine nitrate for the chloramphenicol. The pilocarpine has an average particle size of 15 to 30 microns. The polylactic acid coating has a thickness ranging from 10 to 50 microns. When 3 - 4 drops of the resulting liquid suspension are added each day for a week to a patient's ocular cavities, it is noted that the patient's ocular pressures are continuously reduced from their normal levels, indicative of a prolonged controlled release of pilocarpine. This release pattern is especially effective as it avoids periods where no drug is being delivered.

EXAMPLE V

A suspension of cross-linked gelatin particles containing hydrocortisone acetate for the treatment of eye inflammation is prepared as follows:

A phosphate buffer is prepared from one liter of distilled water, 7.1 grams of disodium hydrogen phosphate and 6.9 grams of sodium dihydrogen phosphate monohydrate. The pH of 6.8. 40 ml of the phosphate buffer and 0.15 grams chlorobutanol as combined with heating and stirring. Nine grams of gelatin (Atlantic Pharmacel 250 Bloom Type A USP) is added slowly with stirring to the 40 grams of buffer solution at 90°C. Alternatively, the gelatin can be added to the buffer solution after it is cooled to room temperature and the mixture then heated to 90°C until solution is complete.

3.1 Grams of micronized (10 micron) hydrocortisone and 10 microliters of Tween 80 (Atlas, USP grade) are ground together and suspended in 5 ml of phosphate buffer. The resultant mixture is added immediately to the stirred gelatin solution as it cools to approximately 50°C. The final mixture is stirred thoroughly for four minutes until the temperature falls to 40°C and poured onto a sheet of polyvinyl chloride. The resulting film is dried at room temperature for one day.

A solution of formaldehyde (1% by weight) is prepared by addition of 13.1 grams of 38 percent formal-

dehyde reagent to 487 grams phosphate buffer (pH 6.8). The gelatin films are submerged in this buffered formaldehyde solution for 20 minutes at room temperature, quickly rinsed with water and soaked in ice water for 2 hours. The films are removed from the ice water and dried overnight. The dried film is then micronized to a particle size of about 100 microns.

A liquid medium consisting of sterile distilled water, 1 percent w. poly(vinyl alcohol) and 0.004 percent benzalkonium chloride is prepared.

A suspension of about 2 parts particles in 100 parts liquid medium is prepared. When drops of this suspension are administered to the eye, the particles lodge in the linings of the ocular cavity. Ocular fluid permeates the gelatin of the particles and drug diffuse out through the ocular fluid at a controlled rate over a prolonged period of time. The gelatin erodes as well in the ocular environment.

I claim:

1. An ophthalmic dosage form comprising substantially dry solid particles of ophthalmic drug enclosed within a bioerodible release rate controlling material formed of a hydrophobic poly(carboxylic acid) having a molecular weight of about 10,000 to about 800,000 and containing 8 to 22 carbon atoms for each carboxylic hydrogen with the particles consisting of about 8 parts drug up to 1 part material to about 1 part drug up to about 3 parts material, said particles being from 10 to 300 microns in largest dimensions and forming a suspension of 1 part up to 50 parts when admixed prior to administration with up to 100 parts of an ophthalmically acceptable isotonic aqueous carrier having a pH acceptable to the eye, with drug released in the eye as the particles erode in response to the ocular environment in a controlled and continuous rate over a prolonged period of time.

2. An ophthalmic dosage form according to claim 1 wherein the ophthalmic drug is a member selected from the group consisting of idoxuridine, phenylephrine, pilocarpine and its acceptable salts, eserine, carbachol, phospholine iodine, demecarium bromide, cyclopentolate, homatropine, scopolamine and epinephrine.

3. An ophthalmic dosage form according to claim 1 wherein the drug is an ophthalmic steroid selected from the group consisting of hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, medrysone, prednisolone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluorometholone, betamethasone and triamcinolone.

4. An ophthalmic dosage form according to claim 1 wherein the drug is an ophthalmic antibiotic selected from the group consisting of tetracycline, chlorotetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin and erythromycin.

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