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(54) SOLID OPHTHALMIC INSERTS

(71) We, MERCK & CO INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:–

The treatment of dry eye syndrome has, in the past, been carried out by the use of ophthalmic preparations which served as wetting agents in the eye to keep the eye moist. These preparations have been of two general types: (1) aqueous solutions or suspensions or (2) ointment.

Historially, these ophthalmic preparations were isotonic aqueous solutions buffered to the required pH, were sterile and contained additives for improved viscosity and longer retention in the eye. However, with these solutions, there are problems of dosage, irritation to the eye, stability and, most important, brief duration of effect. In fact, these aqueous solutions are effective for, at the most, a few minutes or so. It was partly because of this very short retnetion time that ophthalmic solutions were used containing water-soluble polymers such as methylcellulose and other related cellulose derivatives as well as polyethylene oxide (see for example, US Patents 3,767,788, 3,767,789, emp, M.A., Int. Ophthal. Clin. *13* (No 4) page 145 (1973) and *13* (No 1) page 221 (1973), "External Eye Problems in the Elderly" by Frederick H. Theodore, M.D. Gereatrics 30: 71–77, April 1975 and Annals. of Ophthamology by Bach et al, Vol 4, pages 116–119 (1972) in an attempt to prolong the effectiveness of the preparation in the eye. The use of these polymers added to the viscosity of these ophthalmic solutions thereby affording a longer contact time of the medication with the eye. Nonetheless, these higher viscosity ophthalmic preparations are effective for no more than five to ten minutes and accordingly still require frequent applications to the eye to be effective.

The present invention is based on the unexpected discovery that a non-toxic water-soluble solid polymer inserted into the cul-de-sac of the eye is effective in relieving the symptoms of dry eye. It would not have been expected that such a polymer, which in the past had been used merely as a viscosity agent, could in a solid form act by itself to relieve such symptoms. It was also surprising to find that such a water-soluble polymer in solid form could uniformly dissolve in the eye and provide "artificial tear" for a period of at least several hours, particularly in patients with dry eye syndrome, since, with limited amount of water available in the eye of such a patient, it would not be expected that proper dissolution of the polymer would occur.

The present invention provides an ophthalmic insert comprising an unmedicated water-soluble solid polymer having a surface area of from 5 to 800 sq.mm., a maximum dimension of from 1–30 mm and the other two dimensions of from 0.2 mm to 30 mm.

The ophthalmic insert of the present invention serves as an artificial tear material and is useful for the treatment of dry eye. When inserted in the cul-de-sac of the eye, such inserts slowly dissolve, affording a continuous long-term release of artificial tears and thereby eliminating the need for frequent installation of eye drops or ointments.

The polymer used to form the inserts of this invention may be any water-soluble non-toxic polymer. For example, one may use water-soluble polymers of cellulose derivatives, e.g. (C_{1-6} alkyl)- celluloses such as methyl- cellulose, sodium carboxymethyl cellulose, (C_{1-6} hydroxy- alkyl)- celluloses such as hydroxyethyl cellulose, hydroxyp-

ropyl cellulose and hydroxy- propylmethyl cellulose; polyacrylates such as polyacrylic acid salts, polyethyl- acrylates and polyacryl- amides; nature products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar and acacia; the starch derivatives such as starch acetate, hydroxyethyl starch ethers and hydroxy-propyl starch, as well as other synthetic derivatives such as poly(vinyl alcohol), poly(vinyl- pyrrolidone), poly(vinyl methyl ether), poly- (ethylene oxide), neutralized Carbopol and xanthan gum, and mixtures of such polymers. (Carbopol is a trade mark).

Preferably the solid insert is prepared from cellulose derivatives such as methyl-cellulose, hydroxy- ethyl cellulose, hydroxy-propyl cellulose or hydroxy- propylmethyl cellulose or from other synthetic materials such as poly(vinyl alcohol, poly(vinyl- pyrrolidone), poly(ethylene oxide) or poly(vinyl methyl ether). Hydroxypropyl cellulose, one of the preferred polymers for the preparation of the insert of the invention, is available in several polymeric forms, all of which are suitable in the preparation of these inserts. Thus the products sold by Hercules. Inc. of Wilmington, Delaware under the Trade Mark KLUCEL such as KLUCEL HF, HWF, MF, GF, JF, LF and EF, which are intended for food or pharmaceutical use, are particularly useful in preparing the inserts of this invention. The molecular weight of these polymers useful for the purposes described herein may be at least 30,000 and may be as great as or greater than 1,000,000. Similarly, an ethylene oxide polymer having a molecular weight preferably from 100,000 to 5,000,000 can be used. Further, for example, POLYOX (registered Trade Mark) a polymer supplied by Union Carbide Co. may be used; this usually has a molecular weight of 50,000 to 5,000,000, preferably 3,000,000 to 4,000,000. Other specific polymers which are useful in this invention are poly(- vinyl-pyrrolidine) having a molecular weight of from 10,000 to 1,000,000, preferably up to 350,000 and especially 20,000 to 60,000; poly(vinyl alcohol) having a molecular weight of from 30,000 to 1,000,000, particularly 30,000 to 400,000 and especially 100,000 to 200,000; hydroxy- propylmethyl cellulose having a molecular weight of from 10,000 to 1,000,000, particularly 10,000 to 200,000 and especially 50,000 to 100,000; and CARBOPOL (carboxy- vinyl polymer) of B.F. Goodrich and Co. designated as grades 934, 940 and 941. It is clear that for the purpose of this invention the molecular weight of the polymer is not critical. Water-soluble polymers can be used having an average molecular weight that will afford dissolution of the polymer in any desired length of time. The inserts, therefore, can be prepared to allow for retention and accordingly effectiveness in the eye for any desired period.

The insert can be of any desired shape and size, subject to the dimensions specified hereinbefore, which in its outer limits can cover the entire globe of the eye including the cornea and sclera and extend from the inferior, superior, nasal and temporal limits to the conjunctival sac. Accordingly, the insert can be for example in the form of a film in the shape of a square, rectangle, oval, circle, doughnut, semi-circle or quarter-moon, preferably a doughnut, oval or quarter-moon, or in the form of a rod, which is another preferred form. The insert can be readily prepared, for example, by dissolving the polymer in a suitable solvent and evaporating the solution to afford a thin film of the polymer which can then be subdivided to prepare inserts of appropriate size. Alternatively the insert can be prepared by warming the polymer and then molding to form a thin film. Preferably, the inserts are prepared by known molding or extrusion procedures. The molded or extruded product can then be subdivided to afford inserts of suitable size for administration in the eye. In order to properly fit into the cul-de-sac of the eye without excessive irritation, and yet to be effective for its intended use, the insert should have a surface are of from 5 to 800 sq. mm. preferably 10–400 and especially 10–100 sq./mm., a maximum dimension of from 1–30 mm. and preferably 5–20 mm., the other two dimensions being from 0.2 mm. to 30 mm., preferably from 1–10 mm. and especially 1–5 mm. For example, castings or compression molded films having a thickness of 0.25 mm. to 15.0 mm. can be subdivided to obtain suitable inserts. Rectangular segments of the cast or compressed film having a thickness from 0.5 to 1.5 mm. can be cut to afford shapes such as rectangular plates of 4 × 5–20 mm. or ovals of comparable size. Similarly, extruded rods having a diameter of from 0.5 to 1.5 mm. can be cut into suitable sections to provide the desired amount of polymer. For example, rods of 1.0 to 1.5 mm. in diameter and about 20 mm. long are found to be satisfactory. The inserts may also be directly formed by injection molding. It is preferred that the ophthalmic inserts of the present invention be formed so that they are smooth and do not have any sharp edges or corners which could cause damage to the eye. Since the term smooth and sharp edges or corners are subjective terms, in this application these terms are used to indicate that excessive irritation of the eye will not result from the use of the insert.

The ocular inserts of this invention can also contain plasticizers, buffering agents and preservatives. The invention is there-

fore also directed to compositions containing these materials along withe the water-soluble polymer. Plasticizers suitable for this purpose must, of course, alsi be completely soluble in the lachrymal fluids of the eye. Examples of suitable plasticizers that might be mentioned are water, polyethylene glycol, propylene glycol, glycerine, trimethylol propane, di and tripropylene glycol and hydroxy- propyl sucrose. Typically, such plasticizers can be present in the ophthalmic insert in an amount ranging from 1 to 40% by weight. A particularly preferred plasticizer is water, which is present in amounts of from 5% to 40%., preferably 10% to 20%, since this content may be easily accomplished and adds the desired softness and pliability to the insert.

When plasticizing the solid product with water, the product is contacted with air having a relative humidity of at least 40% until said product picks up at least 5% water and becomes softer and more pliable. In a preferred embodiment, the relative humidity of the air is from 60% to 99% and the contacting is continued until the water is present in the product in amounts of from 10% to 20%.

Suitable water-soluble preservatives for the insert are sodium bisulfate, sodium thiosulfate, ascorbate, bensalkanium chloride, chloro- butanol, thimerosal, phenyl- mercuric acetate, phenyl- mercuric borate, parabens, benzyl alcohol and phenyl- ethanol. These agents may be present in amounts of from 0.001 to 5% by weight of solid insert, and preferably 0.1 to 2%.

Suitable water-soluble buffering agents are alkali metal and alkaline-earth metal carbonates, phosphates, bicarbonates, citrates and borates, such as sodium phosphate, citrate, borate, acetate, bicarbonate and carbonate. These agents may be present in amounts sufficient to obtain a pH of the system of from 5.5 to 8.0 and especially 7 to 8; usually up to 2% by weight of polymer.

The water-soluble polymer inserts when applied to the eye of a patient having dry eye syndrome with at least one symptom of corneal pathology, photophobia, burning, foreign body sensations and instantaneous or near instantaneous break up time measurements, significantly improves patient comfort for at least several hours, prolongs the break up time and thickens the precorneal tear film for at least several hours compared to little or no improvement with commercially available liquid artificial tears. Accordingly, this invention also provides a method of treating the eye of a non-human animal exhibiting the symptoms of dry eye by means of an insert in accordance with the present invention.

The ophthalmic insert may contain any convenient weight of polymer. As a practical matter, too little polymer will lead to dissolution over too short a period of time while too much may make the insert too bulky. Accordingly, it is preferred that the insert contain from 1 mg to 1000 mg of water-soluble polymer, more particularly from 5 to 300 mg and especially from 5 to 100 mg. The time of dissolution of the insert is dependent upon each patient's natural supply of tears as well as the particular polymer. Usually the time of dissolution is from 4 hours to 7 days, and preferably 6 to 24 hours.

This invention also provides a process for the preparation of these ocular inserts which comprises dissolving the water soluble polymer and if desired the plasticizer, buffering agent and/or preservative in a suitable solvent and evaporating the solution to afford a thin film of the polymer, which is then subdivided to prepare suitable inserts. Alternatively, the inserts can be prepared most conveniently using the thermoplastic properties of the polymer. For example, the polymer can be warmed at temperatures between 150°F and 400°F and then molded to form a thin film. It is generally preferred to prepare the inserts by molding or extrusion in accordance with well known procedures.

The following examples are given by way of illustration.

EXAMPLE 1

Hydroxy- propyl Cellulose Inserts

Cylindrical rod-shaped ophthalmic inserts are prepared by an injection molding procedure as described below:

The powdered hydroxy- propyl cellulose (KLUCEL GF) is heated in a cup to 200°C. When the powder is melted and begins to flow, the valve at the outlet of the cup is opened and the molten mass is forced into a mold under the action of both pressure and the elastic melt extruder effect. The mold is then removed from the machine and opened. The specimen is removed from the mold and has a diameter of 1.25 mm. The specimen is cut into lengths of 10 mm. having a weight of about 12 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

Similar inserts are prepared having a diameter of 1.0 and 1.5 mm. and a length of 15, 20 and 23 mm.

EXAMPLE 2

Hydroxy- propyl Cellulose Inserts

Ophthalmic inserts are prepared by the compression molding procedure as described below:

Compression-molded films are prepared on a Hydraulic Press by subjecting hydroxy-propyl cellulose (KLUCEL HF) to a compressional force of 12,000 lbs. (gauge) at

300°F for one to two minutes. The film is cooled under pressure by having cold water circulate in the platen. Film thickness is controlled by placing shims between the upper and lower compression plates holding the hydroxy- propyl cellulose. Ophthalmic inserts are then individually cut from the film with a rectangular shaped punch, to afford individual inserts having a thickness of 0.55 mm., width of 2 mm., length of 12.5 mm. and a weight of about 12.5 mg.

EXAMPLE 3

Hydroxy- propyl Cellulose Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of hydroxypropyl cellulose (KLUCEL JF) is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with an oval shaped punch. The final insert has a maximum diameter of 1.0 mm., length of 10 mm. and a weight of 7.0 mg.

EXAMPLE 4

Hydroxy- propyl Cellulose Inserts

Cylindrical rod-shaped ophthalmic inserts are prepared by the extrusion procedure as described below:

The hydroxy- propyl cellulose (KLUCEL HF) is fed into a screw extruder whose barrel is heated to 400 → 450°F. The hydroxypropyl cellulose is melted and then extruded through an orifice (0.04 inch to 0.065 inch). The extrudate while hot is then sized to form a monodiameter filament, which is then cut into 12 mm. lengths having a diameter of 1.0 mm. and a weight of 12.0 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

In a similar fashion, rod-shaped inserts are prepared having the following dimensions: length 12.0 mm., diameter 1.25 and 1.50 mm. and weight of about 15 and 21 mg., respectively.

EXAMPLE 5

Polyvinyl alcohol Inserts

Cylindrical rod-shaped ophthalmic inserts are prepared by the injection molding procedure as described below:

The powdered poly vinyl alcohol of average molecular weight 125,000 is heated in a cup at 190–200°C. When the powder is melted and begins to flow, the valve at the outlet of the cup is opened and the molten mass is forced into a mold under the action of both pressure and the elastic melt extruder effect. The mold is then removed from the machine and opened. The specimen that is removed from the mold is cut into lengths of 10 mm. having a diameter of 1.25 mm. and weight of 12 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

In a similar fashion, rod-shaped inserts are prepared having lengths of 10 mm. and 10 mm., diameters of 1.0 mm. and 1.5 mm. and weights of 8 mg and 18 mg., respectively.

EXAMPLE 6

Hydroxy- propyl- methyl Cellulose Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of hydroxypropyl cellulose sold under the trade mark (Methocel HG 60) is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a rectangular shaped punch to afford rectangular inserts having a length of 12.5 mm., thickness of 0.55 mm., width of 2 mm. and weight of 14 mg.

Methocel HG 60 is a commercial methyl cellulose product manufactured by the Dow Chemical Company and has a methoxyl percentage of 28–30%, a hydroxy- propyl percentage of 7–12%, is soluble in H_2O and organic solvents, has a normal gel temperature of 60°F and demonstrates an average viscosity of 50 centipoises (range 40–60, 2% aqueous solution).

EXAMPLE 7

Methyl Cellulose Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of methyl cellulose (average molecular weight 75,000) is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The insert is a rod having a diameter of 1 mm., a length of 8 mm. and weight of 6 mg.

EXAMPLE 8

Hydroxy- propyl Cellulose 90%
Propylene Glycol 10%

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 0.1% (w/v) aqueous solution of hydroxy- propyl cellulose (KLUCEL HF) containing 0.1% by weight propylene glycol is poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evapo-

rate.

The resulting film is removed from the glass and ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts are cylindrical and have a diameter of 0.9 mm. and weight of 22 mg.

EXAMPLE 9

Hydroxy- propyl Cellulose (HF) 90%
Glycerine 10%

Cylindrical rod-shaped ophthalmic inserts are prepared by an extrusion procedure as described below:

The hydroxy- propyl cellulose/glycerine mixture is fed into a 3/4" single screw extruder whose barrel is heated to 300–350°F. The mixture is melted and then extruded through an orifice (0.04 inch to 0.065 inch). The extrudate while hot is then sized to form a mono-diameter filament, which is then cut into lengths of 6 mm. having a diameter of 1.5 mm. and a weight of 11 mg.

EXAMPLE 10

Poly ethylene oxide Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of poly ethylene oxide having an average molecular weight of 1,000,000 is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and cylindrical ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts have a diameter of 1 mm., a length of 6 mm. and a weight of 9 mg.

EXAMPLE 11

Benzal- konium Chloride 0.02%
Hydroxy- propyl Cellulose 9.98

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of hydroxy-propyl cellulose (KLUCEL GF) containing 0.02% by weight benzal- konium chloride is poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The diameter of the insert is 1.25 mm., the length is 6 mm. and the weight is 7 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

EXAMPLE 12

Carboxy- polymethylene Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of carboxy-polymethylene (average molecular weight 3 million) is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a rectangular shaped punch. The insert has a length of 12.5 mm., a thickness of 0.7 mm., width of 2 mm. and weight of 18 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

EXAMPLE 13

Sodium Carbonate (anhydrous) 0.25%
Hydroxy- propyl Cellulose (KLUCEL GF) 9.75

Ophthalmic inserts can be prepared by a compression molding procedure as described below:

Compression molded films are prepared on a Carver Press by subjecting the hydroxy- propyl cellulose/sodium carbonate (anhydrous) mixture to a compressional force of 12,000 lbs. (gauge) at 300°F for one to two minutes. The film is cooled under pressure by having cold water circulate in the platen. Film thickness is controlled by placing shims between the upper and lower compression plates holding the hydroxy-propyl cellulose. Cylindrical ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts have a diameter of 1.25 mm., a length of 10 mm. and weight of 12 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

WHAT WE CLAIM IS:–

1. An ophthalmic insert comprising an unmedicated water-soluble solid polymer having a surface area of from 5 to 800 sq. mm., a maximum dimension of from 1–30 mm. and the other two dimensions of from 0.2 mm. to 30 mm.

2. An insert as claimed in claim 1 in which the polymer is a (C_{1-6} hydroxy- alkyl)-cellulose, polyvinyl alcohol, (C_{1-6} alkyl)- cellulose, poly- (vinyl- pyrrolidone) or poly-(ethylene oxide).

3. An insert as claimed in claim 1 or 2 in which the surface area is from 10 to 100 mm., the maximum dimension is from 5 to 20 mm. and the other two dimensions are from 1 to 5 mm.

4. An insert as claimed in claim 3 in which the polymer is hydroxy- propyl cellulose.

5. An insert as claimed in claim 3 or 4 in the form of a rod.

6. An insert as claimed in any one of

rate.

The resulting film is removed from the glass and ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts are cylindrical and have a diameter of 0.9 mm. and weight of 22 mg.

EXAMPLE 9

Hydroxy- propyl Cellulose (HF) 90%
Glycerine 10%

Cylindrical rod-shaped ophthalmic inserts are prepared by an extrusion procedure as described below:

The hydroxy- propyl cellulose/glycerine mixture is fed into a 3/4" single screw extruder whose barrel is heated to 300–350°F. The mixture is melted and then extruded through an orifice (0.04 inch to 0.065 inch). The extrudate while hot is then sized to form a mono-diameter filament, which is then cut into lengths of 6 mm. having a diameter of 1.5 mm. and a weight of 11 mg.

EXAMPLE 10

Poly ethylene oxide Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of poly ethylene oxide having an average molecular weight of 1,000,000 is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and cylindrical ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts have a diameter of 1 mm., a length of 6 mm. and a weight of 9 mg.

EXAMPLE 11

Benzal- konium Chloride 0.02%
Hydroxy- propyl Cellulose 9.98

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of hydroxypropyl cellulose (KLUCEL GF) containing 0.02% by weight benzal- konium chloride is poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The diameter of the insert is 1.25 mm., the length is 6 mm. and the weight is 7 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

EXAMPLE 12

Carboxy- polymethylene Inserts

Ophthalmic inserts are prepared by a film casting procedure as described below:

A 1% (w/v) aqueous solution of carboxypolymethylene (average molecular weight 3 million) is prepared and then poured onto a glass plate. The glass plate is then placed into a 50°C hot air cabinet for 16 hours and the water is allowed to evaporate.

The resulting film is removed from the glass plate and ophthalmic inserts are then individually cut from the film with a rectangular shaped punch. The insert has a length of 12.5 mm., a thickness of 0.7 mm., width of 2 mm. and weight of 18 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

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Hydroxy- propyl Cellulose (KLUCEL GF) 9.75

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Compression molded films are prepared on a Carver Press by subjecting the hydroxy- propyl cellulose/sodium carbonate (anhydrous) mixture to a compressional force of 12,000 lbs. (gauge) at 300°F for one to two minutes. The film is cooled under pressure by having cold water circulate in the platen. Film thickness is controlled by placing shims between the upper and lower compression plates holding the hydroxypropyl cellulose. Cylindrical ophthalmic inserts are then individually cut from the film with a hollow cylindrical punch. The inserts have a diameter of 1.25 mm., a length of 10 mm. and weight of 12 mg. The ophthalmic inserts are plasticized by placing them into an 88% relative humidity cabinet for two days where they pick up 10–15% moisture.

WHAT WE CLAIM IS:–

1. An ophthalmic insert comprising an unmedicated water-soluble solid polymer having a surface area of from 5 to 800 sq. mm., a maximum dimension of from 1–30 mm. and the other two dimensions of from 0.2 mm. to 30 mm.

2. An insert as claimed in claim 1 in which the polymer is a (C_{1-6} hydroxy- alkyl)-cellulose, polyvinyl alcohol, (C_{1-6} alkyl)- cellulose, poly- (vinyl- pyrrolidone) or poly-(ethylene oxide).

3. An insert as claimed in claim 1 or 2 in which the surface area is from 10 to 100 mm., the maximum dimension is from 5 to 20 mm. and the other two dimensions are from 1 to 5 mm.

4. An insert as claimed in claim 3 in which the polymer is hydroxy- propyl cellulose.

5. An insert as claimed in claim 3 or 4 in the form of a rod.

6. An insert as claimed in any one of

claims 1 to 5 having from 5 to 40% by weight of water as plasticizer.

7. An insert as claimed in claim 6 in which the water content is 10%–20%.

8. An insert as claimed in any one of claims 1 to 5 formed of a composition comprising an unmedicated solid water-soluble polymer containing a plasticizer, a buffering agent and a preservative, the amount of plasticizer not exceeding 40%, the amount of buffering agent not exceeding 2% and the amount of preservative not exceeding 5%, by weight based on the total composition.

9. An insert as claimed in claim 1 substantially as hereinbefore described in any one of Examples 1 to 13.

10. A method of treating dry eye syndrome in a non-human animal comprising placing in the eye a solid water-soluble polymer insert as claimed in Claim 1.

11. A method as claimed in claim 10 in which the polymer is as defined in claim 2.

12. A method as claimed in claim 11 in which the polymer is hydroxy- propyl cellulose.

13. A method as claimed in any one of claims 10 to 12 in which the polymer contains from 10 to 20% water.

14. A method as claimed in any one of claims 10 to 12 in which the polymer contains a plasticizer, a buffering agent and a preservative, the amount of plasticizer not exceeding 40%, the amount of buffering agent not exceeding 2% and the amount of preservative not exceeding 5%, by weight based on the total composition.

15. A method of making an insert as claimed in claim 1, comprising dissolving the water-soluble polymer and if desired the plasticizer, buffering agent and/or preservative in a suitable solvent and evaporating the solution to afford a thin film of the polymer, which is then subdivided into inserts of the stated dimensions.

16. A method of making an insert as claimed in claim 1, comprising molding or extruding the polymer and any other ingredients into inserts of the stated dimensions.

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