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(54) OPHTHALMIC INSERTS

(71) We, MERCK & CO. INC., a corporation duly organised 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 usual treatment of various eye conditions consists of applying doses of appropriate medicaments in aqueous suspensions, solutions or ointments. While such treatments are satisfactory for treating eye conditions where only one or a few applications of the medicinal agents are necessary, certain eye conditions require more frequent doses and the treatment is inconvenient to the patient. Recently, it has been proposed to apply the ophthalmically active medicinal agents in a solid form on an inert matrix (see for example U.S. Patent 3,710,795). This method has the disadvantage that the inert matrix must be removed after the drug has been completely released from the matrix. More recently, Loucas et al. [J. of Pharm. Sci., Vol. 61, page 985 (June 1972)] found that the alginic acid salt of pilocarpine, when administered as a solid-state ophthalmic insert, provides a greater miotic response than could be obtained by the administration of conventional pilocarpine solutions in the rabbit eye.

In accordance with this invention, there is provided a water-soluble solid medicianl insert comprising from 0.1 to 35% of an ophthalmic medicament, from 65 to 99.9% of hydroxypropyl cellulose and from 0 to 30% of a plasticizer, the percentages being by weight. Suitable inserts which can be prepared in various ways as will hereinafter be described produce ophthalmic preparations having prolonged activity on administration, thus minimizing the frequency of doses necessary in the treatment of various eye conditions. Egress of the drug from the ophthalmic insert in the lacrimal fluids is accompanied by the gelation and finally by the dissolution of the matrix in the lacrimal fluid, thereby eliminating any need to remove the drug-depleted matrix before administering a further dose.

Hydroxypropyl cellulose is a non-ionic water soluble cellulose ether having properties which are uniquely suitable for use in the preparation of ophthalmic inserts. Thus, it is water soluble and hence dissolves in the aqueous lacrimal fluids. In addition, it is thermoplastic and can therefore be advantageously combined with the ophthalmic drug using conventional plastic processing procedures such as compression molding, injection molding and extrusion prior to unit dose subdivision. Hydroxypropyl cellulose is available in several polymeric forms, all of which are suitable in the preparation of the ophthalmic inserts of the present invention. Thus, the products sold by Hercules Incorporated of Wilmington, Delaware under the name 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 new inserts of this invention.

The compositions of this invention can be prepared by various methods. Thus, the drug and the hydroxypropyl cellulose can be dissolved in a suitable solvent and the solution evaporated to afford a thin film comprising the hydroxypropyl cellulose and the drug which can then be subdivided to prepare suitable inserts containing the desired amount of the medicament. Alternatively, and in

accordance with a preferred embodiment of the invention, the inserts can be prepared most conveniently using the thermoplastic properties of the hydroxypropyl cellulose. For example, the medicament and the hydroxypropyl cellulose can be warmed together at temperatures between about 150°F. and 400°F. and the resulting mixture moulded to form a thin film. It is generally preferred to prepare the inserts by moulding or extrusion in accordance with well known procedures. The moulded or extruded product can then be subdivided to afford inserts of suitable size for administration in the eye. For example, castings or compression-moulded films having a thickness of 0.5 mm. to 1.5 mm. can be subdivided to obtain suitable inserts, e.g. in the form of squares, rectangles, circles or semi-circles, containing the desired amount of active ingredient. Rectangular segments of the cast or compressed film having a thickness in the range 0.5 to 1.5 mm. can be cut to afford shapes such as rectangular plates of 4 x 5-15 mm. or ovals of comparable size. Similarly, extruded rods having a diameter in the range 0.5 to 1.5 mm. can be cut into suitable sections to provide the desired dosage of medicament. For example, rods 1.0 to 1.5 mm. in diameter and about 10 mm. long are found to be satisfactory. The inserts may also be directly formed by injection moulding. All of the ophthalmic inserts prepared in accordance with the present invention should be formed so that they do not have any sharp edges or corners, which could cause damage to the eye.

The ocular inserts prepared in accordance with this invention can also contain plasticizers to make the ophthalmic inserts more pliable. Plasticizers suitable for this purpose must, of course, also be completely soluble in the lacrimal fluids of the eye. Examples of suitable plasticizers are water, polyethylene glycol, propylene glycol, glycerine, trimetylol propane, di and tripropylene glycol and hydroxypropyl sucrose. Such plasticizers can be present in the ophthalmic insert in an amount ranging from 0% to 30% by weight. A particularly preferred plasticizer is water which is present in amounts of at least about 5% and preferably at least about 10%. In actual practice, a water content of from 10% to 20% by weight is preferred since it may be easily accomplished and adds the desired softness and pliability to the insert.

The solid medicinal product may be plasticized with water by contacting it with air having a relative humidity of at least about 40% until the product picks up at least 5% water and becomes softer and more pliable. The relative humidity of the air is preferably from 60% to 99%.

Suitable drugs that can be administered by the inserts of the present invention include antibacterial substances such as β-lcatam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, gentamycin, kanomycin and nitrofurazones; antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline and antazoline; anti-inflammatories such as cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone and indomethacin; miotics and anti-cholinesterases such as echothiophate, pilocarpine, physostigmine salicylate and diisopropylfluorophosphate; and mydriatics such as atropine, homatropine, scopolamine and hydroxyamphetamine.

These drugs or derivatives thereof such as salts, covalent derivatives, for example, esters or amides, or other therapeutically active forms can be admixed with the plasticizer and hydroxypropyl cellulose in the form of the water soluble inserts prepared as described above for the treatment of various eye diseases. These forms are especially advantageous for the treatment of conditions where prolonged drug administration is indicated, for example, in eye diseases or eye disorders such as uveitis, glaucoma, diseases of the cornea such as, for example, purulent keratitis, herpes simplex keratitis, herpes zoster, acne rosacea and interstitial keratitis, diseases of the orbit such as exophthalmos and periostitis and diseases of the conjunctiva such as mucopurulent conjunctivitis and ophthalmia. Also, this method of the administration of ophthalmically active drugs can be used when post-operative treatment is needed after retinal or cataract surgery.

The method of administering drugs as a water soluble insert is especially useful in the administration of pilocarpine to treat glaucoma, a condition characterized by an increase in intraocular pressure. The present treatment of this condition involves the use of solutions of pilocarpine acid salts which are administered to the eye in the form of drops at frequent intervals. By inserting the ophthalmic inserts of the present invention, a miotic response of up to 9—10 hours may be obtained in rabbits compared to the short response of 2—4 hours obtained by the administration of drops. The pilocarpine can be administered preferably in

the form of acid addition salts of this drug such as the hydrochloride, alginate and pamoate. Dipilocarpinium pamoate is claimed *per se* in the specification of our co-pending application No. 7147/77, (Serial No. 1,485,150). The ophthalmic inserts of the present invention can contain 0.1 to 35% by weight of pilocarpine to afford a dose of up to 1—6 mgs. of pilocarpine per insert.

The following examples describe specific methods of preparing the novel ophthalmic inserts of our invention and are provided to illustrate specific embodiments of our invention. Mesh sizes are U.S. standards, 'Carver' is a Trade Mark.

EXAMPLE 1.

The following aqueous solutions were prepared:

Solution A	
Pilocarpine base	208 g.
Alginic acid	2.42 g.
Hydroxypropyl cellulose (KLUCEL GF)	0.45 g.
Water	30 ml.
Solution B	
Pilocarpine base	2.08 g.
Alginic acid	2.42 g.
Hydroxypropyl cellulose (KLUCEL HF)	0.45 g.
Water	30 ml.
Solution C	
Pilocarpine base	2.08 g.
Alginic acid	2.42 g.
Hydroxypropyl cellulose (KLUCEL JF)	0.45 g.
Water	30 ml.

Thin films were prepared by casting films from these solutions and then cutting the dried films into rectangular shapes, approximately 3 by 10 mm. The *in vivo* disappearance time and the total miotic action of these ophthalmic inserts were determined as follows:

Randomized series of six male and female New Zealand albino rabbits weighing 3—3.5 kg., approximately 4—5 months of age, were used. The animals were kept in restraint boxes in a room with a steady light of weak intensity. The naive animals were accustomed to the experimental conditions, including laboratory and restraint boxes, once before the time of testing. The same rabbits were re-used with at least 14 days rest between two testings; they were finally eliminated after five times. The animals were accustomed to the environment for 1 hour, and after initial measurements, the compounds to be studied were administered in various forms, *e.g.* solutions, rods, discs, and ointment, into the conjunctival sac of one eye and the other non-treated eye was the control. The pupil measurements were made 5, 30, 90, 210 and 360 minutes after treatment. The average pupil diameters and confidence limits for $P \leq 0.05$ of each series (6 rabbits) were given. The pupil diameter was measured with a LUNEAU and COFFIGNON puillometer whose principle of operation consists in superimposing the virtual image of a red light beam of variable diameter into the plane of the iris. With an adjustable diaphragm, one adjusts the diameter of the bundle of red light rays to coincide with that of the pupil. The diameter of the diaphragm is recorded directly in millimeters. The results of these tests are shown in the following table:

Preparation No.	Disappearance Time (minutes)	Mg. of Pilocarpine per Insert	Total Miotic Activity* Insert/ Total Miotic Activity* Solution
A	10<t<30	4.01	$\frac{23}{20.7} = 1.11$
B	120<t<240	4.56	$\frac{26.3}{16.8} = 1.56^{**}$
C	240<t<300	5.77	$\frac{34.1}{16.4} = 2.08^{**}$

*Total miotic activity is an equivalent term for total biologial response and is expressed as the area under the curve representing pupil size change from the time the dose was administered to the time for the pupil size to return to the control diameter. The area of the response curve is obtained from a plot of the pupil size versus time for the treated eye versus the control eye.

**Effect is significantly better than solution after 210 minutes.

EXAMPLE 2.

25 g. of 60 mesh dipilocarpinium pamoate and 75 g. of 60 mesh hydroxypropyl cellulose (KLUCEL HF) are mixed thoroughly using conventional dry powder mixing procedures such as mortar and pestle, twin shell blender and planetary mixer. The mixture is then passed through a 30-mesh screen and remixed. A small amount (2 to 5 g.) of the mixture is then placed in the centre of a clean dry aluminium sheet having a thickness of 0.2755 in., the surface of which is coated with a lubricant such as aerosolized lecithin and a thickness regulator (shim) of about 1 mm. is placed in each of the four corners of the aluminium sheet. A second lubricated 0.2755 in. thick aluminium sheet is placed over the first sheet and transferred to a hydraulic press, such as a Model B carver Press, between two 6 x 6 in. platens equipped for heating and cooling; the top and bottom platens having been previously preheated to a temperature of 200°F. The press is then closed and the material subjected to a pressure of 10,000 lbs. gauge while maintaining the platens at the same temperature. After 1 minute, cold water is circulated in the platens to cool the product while the pressure is being maintained. After about 2 minutes, the pressure is released and the product in the form of a wafer-thin sheet is removed. It is then cut into small rectangles approximately 10 mm. by 4 mm. having a thickness of about 0.8 mm. and containing 2 to 4 mg. of pilocarpine per unit dose.

The ophthalmic inserts so obtained were tested for miotic activity in rabbits using the procedures described in Example 1. At the same time, a conventional solution of pilocarpine comprising an equivalent dose of pilocarpine was administered to one group of rabbits. The results of these tests are shown in the following table:

Time (hrs.)	Mean Pupil Diameters — mm. Control	Conventional Pilocarpine Solution	Rectangular Pilocarpine Pamoate Inserts
0	7.5		
½	7.3	5.2	5.2
1½	7.3	5.6	4.8
3½	7.4	6.7	5.0
6	7.5	7.4	5.5
7	7.4	—	5.7
8	7.4	—	5.6
9	7.4	—	6.3
10	7.4	—	6.8

The above table shows the prolonged miotic effect obtained when the pilocarpine is administered in the form of the rectangular insert formed with the hydroxypropyl cellulose.

The above ophthalmic inserts are placed in a cabinet and contacted for 2 days with air at room temperature and a relative humidity of 88%. The ophthalmic inserts having an initial weight of about 18 mgs. increase to a weight of 20 mgs. In the two-day period showing a pickup of 2 mgs. of water or about 11% based on the total weight of the insert. The plasticizing effect of the water makes the insert much softer and pliable.

EXAMPLE 3.

The mixture of dipilocarpinium pamoate and hydroxypropyl cellulose prepared as described in Example 2 is used for the preparation of an extruded filament in conventional extrusion equipment in the following manner.

The heater control of a Custom Scientific Instrument Mini-Max Molder (Model CS—183) is set at 200°C. After the apparatus is sufficiently heated, the drive switch for the rotor is turned on and approximately 0.5 g. of the bulk powdered mixture is fed into the cup. A filament of the desired diameter (less than 1 mm. to 2 mm.) is obtained by drawing the extrudate with steady pulling; the force exerted on the hot extrudate determining the diameter of the filament. Filaments in the form of rods prepared in this way are cut in lengths of about 10 mm. having a pilocarpine content of 1.9 mg. These are tested for miotic response in the rabbit eye using the test procedure described in Example 1 with the results shown in the following table:

Time (hrs.)	Mean Pupil Diameter — mm. Control	Extruded Filament
0	7.5	
½	7.4	5.3
1½	7.3	5.3
3½	7.4	5.9
6	7.4	5.5
7	7.5	5.7
8	7.5	6.0
9	7.6	6.2

The above ophthalmic inserts are placed in a cabinet and contacted for 2 days with air at room temperature and a relative humidity of 88%. The ophthalmic inserts having an initial weight of about 18 mgs. increase to a weight of 20 mgs. in the two-day period showing a pickup of 2 mgs. of water or about 11% based on the total weight of the insert. The plasticizing effect of the water makes the insert much softer and pliable.

The ophthalmic inserts can also be injection molded using the same equipment and a single or multi-cavity mould.

EXAMPLE 4.

16.25 parts by weight of 60-mesh pilocarpine nitrate and 83.8 parts by weight parts of propylene glycol in a higher shear mixer. A small amount of resulting mixture is then compressed using the procedures described in Example 2 to form a mixture is then compressed using the procedures described in Example 2 to form a thin solid sheet of the mixture which is cut into rectangular shaped inserts about 10 mm. by 4 mm. having a thickness of about 0.8 mm. The ophthalmic inserts containing 3.4 mg. of pilocarpine so obtained were tested in the rabbit eye for miotic response with the following results:

	Mean Pupil Diameter — mm.	
Time (hrs.)	Control	Rectangular Insert
0	7.3	
½	7.2	4.7
1½	7.2	4.6
3½	7.3	4.6
6	7.3	5.9
7	7.3	5.9
8	7.3	6.2
9	7.3	6.4
10	7.3	6.9

EXAMPLE 5.

17.5 parts by weight of pilocarpine alginate, 74.25 parts by weight of hydroxypropyl cellulose (KLUCEL HF), and 8.25 parts by weight of propylene glycol are mixed following the procedures described in Example 4. The resulting mixture is compressed following the procedures described in Example 2 to obtain a thin film which is cut to form rectangular inserts 10 × 4 mm. and about 0.8 mm. thick. These inserts containing about 2.2 mg. of pilocarpine are tested in the rabbit eye by the test procedure described in Example 1 with the following results:

	Mean Pupil Diameter — mm.	
Time (hrs.)	Control	Rectangular Insert
0	7.3	
½	7.3	4.3
1½	7.3	4.5
3½	7.3	4.8
6	7.3	5.3
7	7.5	6.2
8	7.7	6.9
9	7.5	6.9

Comparative Data.

The miotic effect of a standard solution of pilocarpine and a solid pilocarpine alginate insert prepared as described by Loucas et al. are compared using the rabbit test procedure described in Example 1. In these tests dosages of 9.7 mg. of pilocarpine are used. The miotic responses are shown in the following table:

Time (hrs.)	Mean Pupil Diameter — mm.		
	Control	Equivalent Dose of Pilocarpine Solution	Pilocarpine Alginate
0	7.5		
½	7.5	4.6	4.8
1½	7.5	4.9	4.8
3½	7.5	7.2	5.3
6	7.5	7.4	6.6
7	7.5	—	7.2

WHAT WE CLAIM IS:—

1. A water-soluble solid ophthalmic medicinal insert comprising from 0.1 to 35% of an ophthalmic medicament, from 65 to 99.9% of hydroxypropyl cellulose and from 0 to 30% of a plasticizer, the percentages being by weight.
2. An insert as claimed in claim 1, in which the plasticizer is propylene glycol.
3. An insert as claimed in claim 1, in which the plasticizer is water.
4. An insert as claimed in any one of claims 1 to 3, in which the medicinal agent is pilocarpine or a salt thereof.
5. An insert as claimed in claim 4, in which the medicinal agent is pilocarpine.
6. An insert as claimed in claim 4, in which the medicinal agent is an acid addition salt of pilocarpine.
7. An insert as claimed in claim 6, in which the pilocarpine acid addition salt is pilocarpine nitrate.
8. An insert as claimed in claim 6, in which the acid addition salt is pilocarpine alginate.
9. An insert as claimed in claim 6, in which the acid salt is dipilocarpinium pamoate.
10. An insert as claimed in any one of claims 1 to 3, in which the medicinal agent is an antiinflammatory agent.
11. An insert as claimed in claim 10, in which the antiinflammatory agent is dexamethasone or a salt or covalent derivative thereof.
12. An insert as claimed in claim 10, in which the antiinflammatory agent is indomethacin or a salt or covalent derivative thereof.
13. A method of preparing an ophthalmic medicinal insert as claimed in claim 1 that comprises forming a solid medicinal insert from a mixture of ingredients as specified in claim 1.
14. A method of preparing an ophthalmic medicinal insert as claimed in claim 3 that comprises forming a solid medicinal insert from a mixture of 0.1 to 30 parts by weight of an ophthalmic medicament and 65 to 94.9 parts by weight of hydroxypropyl cellulose and contacting the said insert with air having a relative humidity of at least 40% until the product picks up from 5 to 30 parts by weight of water and becomes softer and more pliable.
15. A method as claimed in claim 14, in which the air has a relative humidity of 60 to 99%.
16. A method as claimed in claim 14 or 15, carried out so that the final product has a water content of at least 10% by weight.
17. A method as claimed in claim 16, carried out so that the final product has a water content of 10 to 20% by weight.
18. A method as claimed in any one of claims 13 to 17, in which the mixture is moulded and solid dosage forms are prepared from the cooled mixture.

Comparative Data.

The miotic effect of a standard solution of pilocarpine and a solid pilocarpine alginate insert prepared as described by Loucas et al. are compared using the rabbit test procedure described in Example 1. In these tests dosages of 9.7 mg. of pilocarpine are used. The miotic responses are shown in the following table:

Time (hrs.)	Mean Pupil Diameter — mm.		
	Control	Equivalent Dose of Pilocarpine Solution	Pilocarpine Alginate
0	7.5		
½	7.5	4.6	4.8
1½	7.5	4.9	4.8
3½	7.5	7.2	5.3
6	7.5	7.4	6.6
7	7.5	—	7.2

WHAT WE CLAIM IS:—

1. A water-soluble solid ophthalmic medicinal insert comprising from 0.1 to 35% of an ophthalmic medicament, from 65 to 99.9% of hydroxypropyl cellulose and from 0 to 30% of a plasticizer, the percentages being by weight.

2. An insert as claimed in claim 1, in which the plasticizer is propylene glycol.

3. An insert as claimed in claim 1, in which the plasticizer is water.

4. An insert as claimed in any one of claims 1 to 3, in which the medicinal agent is pilocarpine or a salt thereof.

5. An insert as claimed in claim 4, in which the medicinal agent is pilocarpine.

6. An insert as claimed in claim 4, in which the medicinal agent is an acid addition salt of pilocarpine.

7. An insert as claimed in claim 6, in which the pilocarpine acid addition salt is pilocarpine nitrate.

8. An insert as claimed in claim 6, in which the acid addition salt is pilocarpine alginate.

9. An insert as claimed in claim 6, in which the acid salt is dipilocarpinium pamoate.

10. An insert as claimed in any one of claims 1 to 3, in which the medicinal agent is an antiinflammatory agent.

11. An insert as claimed in claim 10, in which the antiinflammatory agent is dexamethasone or a salt or covalent derivative thereof.

12. An insert as claimed in claim 10, in which the antiinflammatory agent is indomethacin or a salt or covalent derivative thereof.

13. A method of preparing an ophthalmic medicinal insert as claimed in claim 1 that comprises forming a solid medicinal insert from a mixture of ingredients as specified in claim 1.

14. A method of preparing an ophthalmic medicinal insert as claimed in claim 3 that comprises forming a solid medicinal insert from a mixture of 0.1 to 30 parts by weight of an ophthalmic medicament and 65 to 94.9 parts by weight of hydroxypropyl cellulose and contacting the said insert with air having a relative humidity of at least 40% until the product picks up from 5 to 30 parts by weight of water and becomes softer and more pliable.

15. A method as claimed in claim 14, in which the air has a relative humidity of 60 to 99%.

16. A method as claimed in claim 14 or 15, carried out so that the final product has a water content of at least 10% by weight.

17. A method as claimed in claim 16, carried out so that the final product has a water content of 10 to 20% by weight.

18. A method as claimed in any one of claims 13 to 17, in which the mixture is moulded and solid dosage forms are prepared from the cooled mixture.

* C L M S *

19. A method as claimed in any one of claims 13 to 17, in which the mixture is extruded and solid dosage forms are prepared from the extruded mixture.

20. A method as claimed in any one of claims 13 to 17, in which a solution of the mixture is evaporated to form a thin solid and the latter is subdivided to obtain inserts.

21. A method as claimed in any one of claims 13 to 20, in which the ophthalmic medicament is a miotic.

22. A method as claimed in any one of claims 13 to 20, in which the ophthalmic medicament is pilocarpine.

23. A method as claimed in any one of claims 13 to 20, in which the ophthalmic medicament is an acid addition salt of pilocarpine.

24. A method as claimed in any one of claims 13 to 20, in which the ophthalmic medicament is an antiinflammatory agent.

25. A method as claimed in claim 23, which the ophthalmic medicament is dipilocarpinium pamoate, pilocarpine nitrate, pilocarpine alginate or pilocarpine nitrate.

26. A method of applying medicaments to the eye of a non-human animal that comprises inserting a solid mixture of an ophthalmically active agent, hydroxypropyl cellulose and, optionally a plasticizing agent in the cul-de-sac of the conjunctiva to dispense the active agent to the eye over a prolonged period of time.

27. A method as claimed in claim 26, in which the ophthalmically active agent is a miotic.

28. A method as claimed in claim 27, in which the miotic is a pilocarpine acid addition salt.

29. A method as claimed in claim 26, in which the ophthalmically active agent is an antiinflammatory drug.

30. A method as claimed in claim 27, in which the antiinflammatory drug is dexamethasone.

31. A method of preparing ophthalmic inserts substantially as described in the foregoing Examples.

32. A water-soluble solid ophthalmic medicinal insert comprising from 0.1 to 35% of an ophthalmic medicament, from 65 to 99.9% of hydroxypropyl cellulose and up to 30% of a plasticizer, the percentages being by weight, when prepared by a method as claimed in any one of claims 13 to 25 and 31.

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