United States Patent

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[54] **EMULSION OF PILOCARPINE FOR OPHTHALMIC USE**

5 Claims, 3 Drawing Figs.

[52] **U.S. Cl.** **424/168,** 424/273
[51] **Int. Cl.** **A61k 27/00**
[50] **Field of Search** 424/273, 168

[56] **References Cited**

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ABSTRACT: An easy to apply, stable and effective form of pilocarpine is provided by an oil-in-water emulsion of pilocarpine.

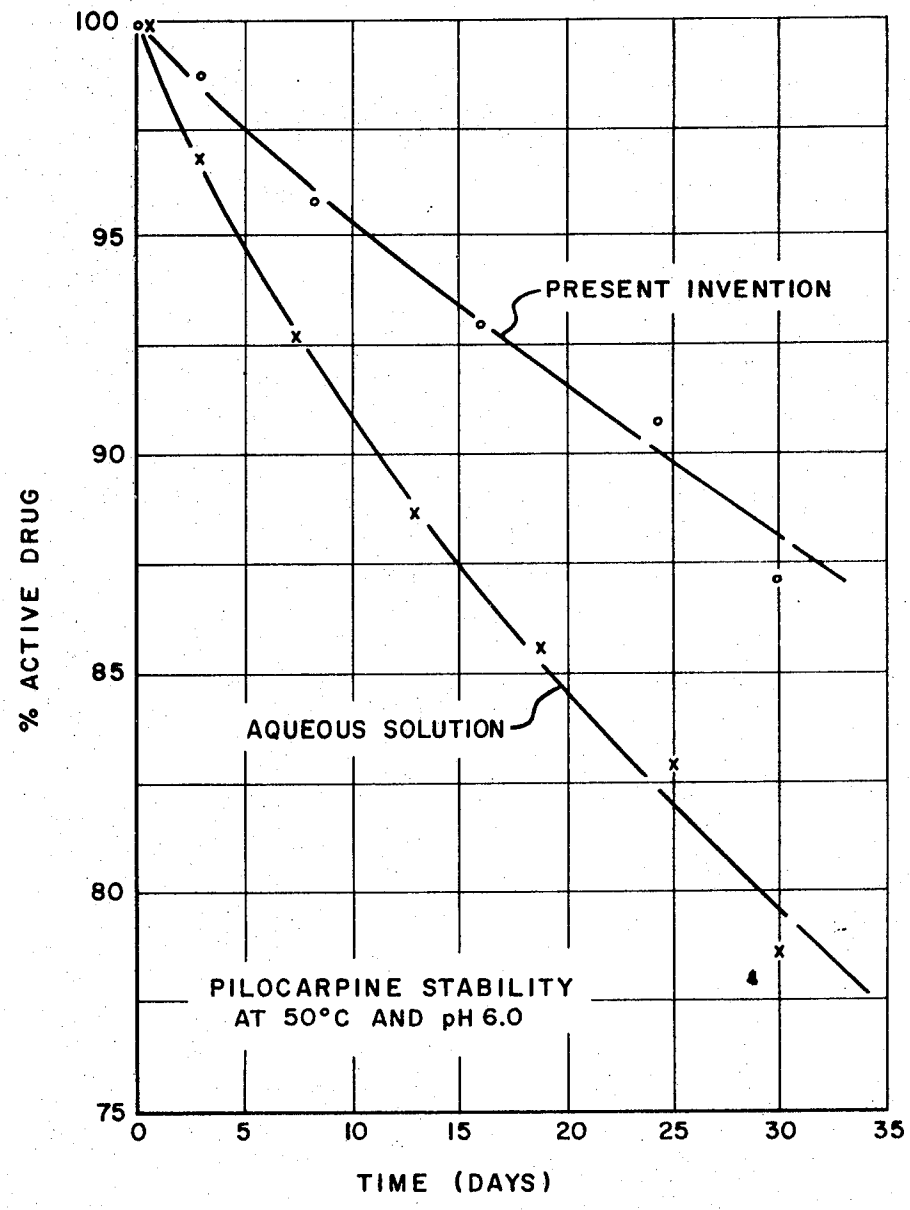

FIG-1

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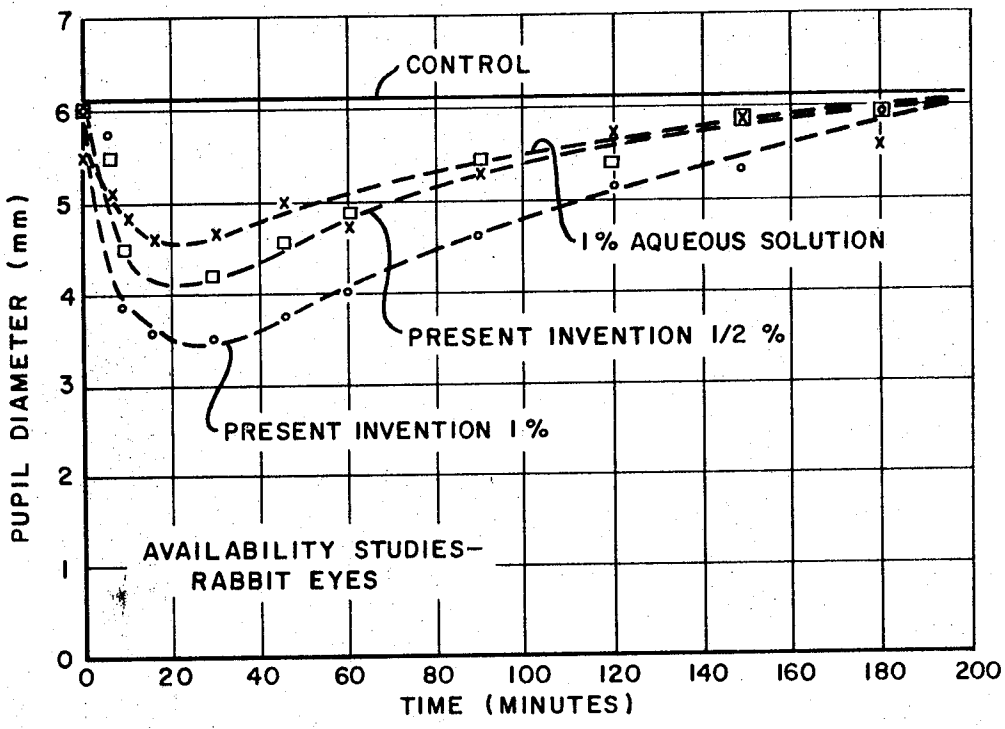

FIG-2

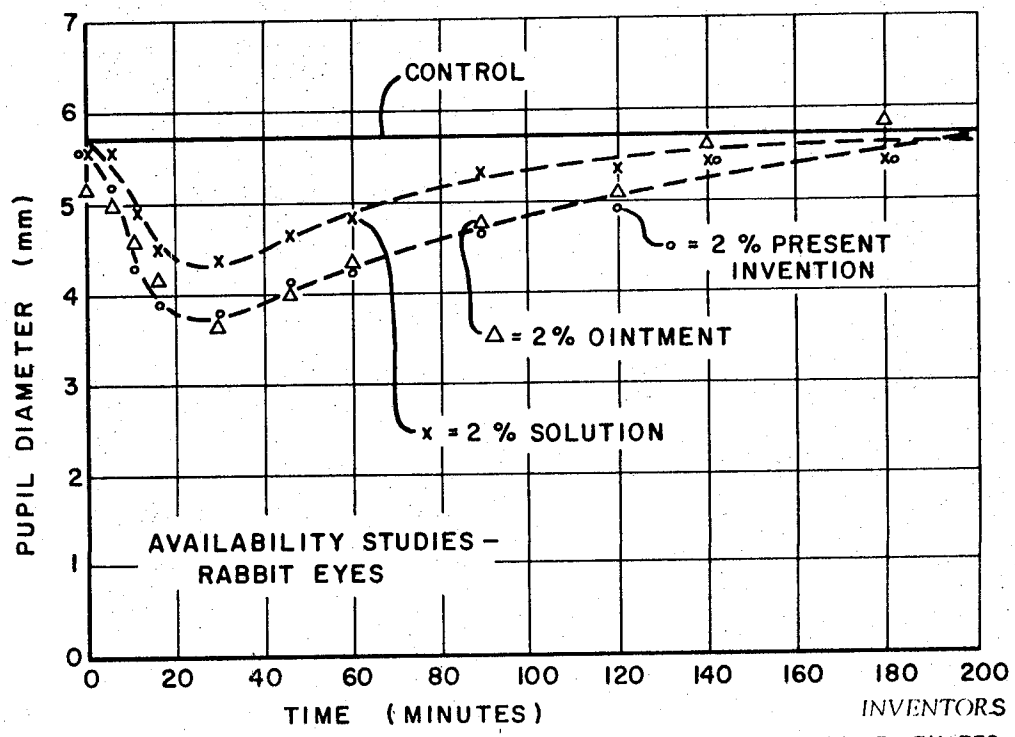

FIG-3

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EMULSION OF PILOCARPINE FOR OPHTHALMIC USE

SUMMARY OF THE INVENTION

Pilocarpine is used as an antiglaucoma agent over long periods of time. Generally the condition is such that it must be used for the rest of the patient's life. Since many of the users are old and infirm, they find great difficulty instilling medicine into the eye. The easiest form of application of this medicine is a liquid drop while the most effective form of medication previously known is an ointment of semisolid material. The ointment is more effective both from the depth and duration of clinically significant response. However, many patients have difficulty in applying an ointment and it also obscures the vision for prolonged period of time. It is also difficult for the patient to judge when he has instilled an effective amount of either the aqueous drop or the solid ointment in his eye since a drop may catch just the corner of the eye and be rinsed out by tear fluid while the ointment can obscure vision even though it is applied only to the eyelid and the eyelashes. For these reasons, ophthalmologists normally restrict the use of ointment to bedtime, if at all, despite the advantage of less frequent instillation and better effect.

In accordance with the present invention, a fluid emulsion is provided which combines the ease of administration of aqueous drops with the depth and duration of an ointment. With the emulsion of the present invention there is a brief obscuring of vision but this brief obscuring is actually an advantage because the patient can then judge whether he has instilled an effective amount of the medication on the surface of the eye itself.

It is surprising that the effectiveness of pilocarpine in the formulation of the present invention is virtually the same as the ointment since the pilocarpine is contained exclusively in the aqueous phase of the emulsion. Although the invention is not based on any theory of its operation, it is believed that this unexpected result comes from the effect of immobilizing the aqueous phase by the oil droplets, thereby permitting longer contact of the pilocarpine with the surface of the eye before it is normally drained.

Another advantage of the present invention is that the chemical decomposition of pilocarpine is retarded when in the emulsion of the present invention so that it can be formulated and have a substantial shelf life.

Further advantage of the present invention is that the emulsion can be produced in sterile form while ointments are not available as sterile products because of processing difficulties.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph comparing the stability of an emulsion formulated in accordance with the present invention with that of an aqueous solution. This is under accelerated aging conditions at 50° C.

FIG. 2 shows the effect on pupil dilation of 0.5 percent and 1 percent formulations made in accordance with the present invention compared with a 1 percent aqueous solution of the prior art.

FIG. 3 is similar to FIG. 2, showing the availability of 2 percent formulation of the present invention, of an ointment, and of a solution.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In its simplest form the formulation of the present invention includes pilocarpine, water, a physiologically acceptable oil and a physiologically acceptable emulsifying agent. Other materials are advantageously added to adjust the pH, to act as buffering agents and to render the emulsion isotonic. Fungicidal and sterilizing agents as well as a chelating agent may also be employed.

The formulation of the present invention contains from 0.25 to 8 percent pilocarpine and from 10 to 80 percent of oil. The balance of the formulation is water plus any of the minor ingredients mentioned above. Normally the pH is adjusted in the range of 4.5 to 7 and preferably is about 6.

Pilocarpine can be employed as the base material itself or its salts such as pilocarpine hydrochloride, pilocarpine borate or pilocarpine nitrate can be employed. Preferably the salts are employed because of their greater stability.

Various oils can be used such as mineral oil, U.S.P., silicone oils or vegetable oils such as corn oil, peanut oil, olive oil or the like. Preferably mineral oil is employed because of its acceptance by the medical profession, superior stability and low cost.

In preparing the formulations of the present invention, the emulsifying agent or agents are added to the oil and the mixture is then heated to about 60° C. This warm mixture is added with rapid stirring to water which also is about 60° C. and which contains the pilocarpine as well as any of the minor ingredients mentioned above. The resulting oil-in-water emulsion is then allowed to cool slowly to room temperature while it is slowly stirred. The formulation is then ready for use.

A large number of emulsifying agents are suitable for use with the present invention. The requirements are that the material form oil-in-water emulsions and that it be nontoxic in the concentration employed. Thus suitable materials include carbohydrates such as acacia, gum tragacanth and methylcellulose; alcohols and esters of alcohol such as lecithin and cholesterol and its esters; polyoxyethylene derivatives such as polyoxyethylene (40 units) sterate, polyoxyethylene cetyl ether, ethylene oxide reaction product of wool fat, and polyethylene oxide sorbitan reaction product of wool fat as well as sorbitan and sorbide derivatives such as sorbitan trioleate and polyoxyethylene (20) sorbitan trioleate.

As been mentioned above, various additional materials can be added. These include sodium acid phosphate, disodium acid phosphate as buffering agents, benzalkonium chloride as a fungicide and sterilizing agent, chelating such as sodium ethylene diamine tetra-acetic acid and salts such as sodium chloride or sodium nitrate to render the emulsion isotonic.

Pilocarpine and its salts, like many drugs, are chemically unstable in aqueous solution and will therefore lose potency with time. The loss of pilocarpine nitrate from a conventional solution and the product of the present invention when both samples were stored under identical accelerated conditions, is shown in FIG. 1. As can be seen, a higher concentration of the therapeutically effective form of the drug is always present in the emulsion than is in an equivalent conventional dosage from. At the end of 30 days the emulsion has 88 active drug as compared to 79.5 percent in the aqueous solution. These results are since in both samples, of the drug was contained in the water.

An accepted method of comparing the biological availability of a drug from various dosage forms is to compare the areas under their biological and neither the disadvantages solution and human efficacy formulations of response versus time plots. Applying this method to the data in FIGS. 2 and 3, it is found that the emulsion of the present invention has more than twice the biological availability or activity of an equivalent conventional dosage form. The release or availability of the drug from the emulsion is as good as from an ointment but the emulsion has the advantages of a solution and neither the disadvantages of a solution or an ointment. The availability results shown in FIGS. 2 and 3 are surprising in view of the fact that the drug is present in the water in both dosage forms. Assay has shown that none of the drug in the emulsion is present in the oil phase of the preparation. Although this particular work was done with rabbits, pilocarpine is an old drug and the correlation in pupil response between rabbits and human beings is well established. Further, tests on human beings have been made and have established the efficacy and safety of the formulations of the present invention.

The following nonlimiting examples illustrated preferred embodiments of the invention. All percentages are being weight.

EXAMPLE I

	%
Pilocarpine nitrate	3.0
Mineral Oil (U.S.P.)	30.0
Tween-40 (a)	2.52
Arlacel-40 (b)	5.48
$NaH_2PO_4.H_2O$	0.26
Na_2HPO_4	0.045
Benzalkonium chloride	0.004
EDTA (c)	0.02
NaCl	0.26
Water to make	100.0
pH 5.5	

EXAMPLE II

	%
Pilocarpine (free base)	1.0
Silicone Oil 100 c.p.s.	10.0
Polawax (d)	2.4
$NaH_2PO_4.H_2O$ qs. pH	6
Thimerosal (e)	0.01
NaCl	0.26
Water to make	100.0

EXAMPLE III

	%
Pilocarpine nitrate	4.0
Mineral Oil (U.S.P.)	30.0
Polawax	2.1
$NaH_2PO_4.H_2O$	0.04
Na_2HPO_4	0.04
PMA (Phenylmercuric acetate)	0.004
Sodium nitrate	0.38
Water to make	100.0
pH 6.0	

EXAMPLE IV

	%
Pilocarpine nitrate	2.0
Corn Oil	50.0
Polawax	1.8
$NaH_2PO_4.H_2O$	0.19
Na_2HPO_4	0.46
Thimerosal	0.01
NaCl	0.26

Water to make	100.0
pH 7.0	

EXAMPLE V

	%
Mineral Oil (U.S.P.)	30.0
Polyoxyethylene (40) Stearate	2.4
Pilocarpine nitrate	8.0
Water to make	100.0

EXAMPLE VI

	%
Mineral Oil (U.S.P)	80.0
Polyoxyethylene (20) Sorbitan Monolaurate	7.5
Pilocarpine (hydrochloride)	0.25
Water to make	100.0

a. Tween 40 is Polyoxyethylene Sorbitan Monopalmitate
b. Arlacel 40 is Sorbitan Monopalmitate
c. Ethylenediaminetetraacetate sodium
d. Polawax is Polyoxyethylene Stearate
e. Thimerosal is Sodium Ethylmercurithiosalicylate

We claim:

1. An oil-in-water emulsion of a pilocarpine useful in the treatment of glaucoma containing on a weight basis from about 0.25 to 8 percent of a pilocarpine selected from the group consisting of pilocarpine hydrochloride, pilocarpine borate and pilocarpine nitrate, from about 10 to 80 percent of a physiologically acceptable oil selected from the group consisting of mineral oil, silicone oil and a vegetable oil, an emulsifying amount of a physiologically acceptable emulsifier selected from the group consisting of acacia, gum tragacanth, methyl cellulose, lecithin, cholesterol, polyoxyethylene (40 units) stearate, polyoxyethylene cetyl ether, sorbitan, sorbitan trioleate and polyoxyethylene (20) sorbitan trioleate and the balance of the composition being essentially water.

2. The composition of claim 1 wherein the oil is mineral oil.

3. The composition of claim 1 wherein pilocarpine nitrate is employed.

4. The composition of claim 1 wherein the pH of the aqueous phase of the emulsion is from 4.5 to 7.

5. The composition of claim 4 wherein the pH is about 6.