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(54) Title: OPHTHALMIC GEL COMPOSITION AND METHOD OF TREATING EYE INFECTIONS

(57) Abstract

An ophthalmic gel composition for human and veterinary use comprising 0.5-4% w/v of fusidic acid suspended in an aqueous vehicle containing 0.2-2% w/v of a polyanionic polymer.
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Ophthalmic gel composition and method of treating eye infections

The present invention relates to an ophthalmic gel composition for human and veterinary use comprising an ophthalmic drug and a vehicle based on a polyanionic polymer.

One of the major problems of topical ophthalmic therapy is to maintain an adequate concentration of the ophthalmic drug at the desired site of action for a prolonged period of time. Thus, only a small volume of preparation can be contained in the fornix inferior and the preparation applied tends to be diluted by the tears and to be drained through the nasolacrimal duct.


These gel compositions exhibit a duration of action which is about twice that of a conventional ophthalmic drug preparation.

Surprisingly, it has now been found that eye infections can be combated very effectively with a composition comprising fusidic acid suspended in a gel of the above mentioned type.

The composition of the invention comprises from 0.1 to 4% w/v of fusidic acid suspended in an aqueous vehicle containing from 0.2 to 2% w/v of polyanionic polymer.

The surprising efficiency of the composition of the invention is evidenced by the fact that the duration of action is about 10 times that of a preparation based on fusidic acid and a conventional gelling agent, cf. the example below.

The very substantial prolongment of the action of fusidic acid is particularly surprising, since hitherto it was believed that the prolonged action of the prior art compositions is based on an interaction of a positively charged drug with the negatively charged polymer. Thus, it might be expected that a drug, such as fusidic
acid, which is negatively charged at the pH value of the eye, i.e. about 7.4, would be unable to interact with the polyanionic polymer and to provide a prolonged action.

The composition of the invention is particularly useful for the local treatment of eye infections. Thus, whereas conventional ophthalmic preparations, such as chloramphenicol eye drops, have to be applied 5-6 times daily or even more, it is sufficient to apply preparations based on the composition of the invention 1-2 times daily.

The composition of the invention preferably contains about 1% w/v of fusidic acid in the form of particles having a particle size not exceeding 10 μm and preferably between 2 and 5 μm.

A polyanionic polymer is preferably a carboxyvinyl polymer having a molecular weight of from about 400,000 to about 6 million.

The viscous solutions which are formed during the preparation of the ophthalmic polymer suspension have a viscosity of from 10 to about 20,000 cps at 25°C measured on a RVT Brookfield Viscosimeter.

The polyanionic polymer is preferably of the type which is commercially available under the trade name "Carbopol" (B.F. Goodrich Company). A particularly preferred polyanionic polymer is "Carbopol 934". The "Carbopol" polymers do not blur the normal vision because the gel structure breaks down shortly after application to the eye under the influence of ions contained in the lacrimal fluid.

The pH value of the composition of the invention is preferably from 5.0 to 6.5 and more preferably about 5.8.

The adjustment of the pH value is preferably effected with a pharmaceutically and physiologically acceptable base, such as sodium hydroxide.

A preparation based on the composition of the invention may contain auxiliary agents, such as preservatives, stabilizing agents and bacteriostatic agents.

Preparations based on the composition of the invention are preferably used in dosages of from 5 to 100 mg and more preferably from 20 to 50 mg when the preparation is applied into the fornix inferior of an infected eye.

The frequency of dosing varies dependant upon the severity of the infection. However, as mentioned above an application twice
a day ordinarily suffices.

The invention also relates to a method of treating eye infections, said method comprising applying an effective amount of a preparation based on the composition of the invention into the fornix inferior of the infected eye.

The invention will be described in detail with reference to the following non-limiting example:

Example

An eye preparation having the following composition per ml was prepared:

**Preparation A:**

- Fusidic acid, micronized, sterile: 10 mg
- "Carbopol 934": 5 mg
- Sodium hydroxide, 5N, q.s. for pH 5-6.0
- Mannitol: 50 mg
- Benzalkonium chloride: 0.1 mg
- Tetracemin disodium: 0.5 mg
- Water, sterile, to make 1 ml.

Benzalkonium chloride, tetracemin disodium and mannitol are dissolved in sterile water.

The "Carbopol 934" is suspended aseptically in the solution and sterilized by autoclaving at 120°C for 20 minutes. The suspension is cooled and the sterile fusidic acid is suspended therein. Finally, the suspension is neutralized by addition of sterile sodium hydroxide solution.

The preparation (in the following called Preparation A) thus prepared was compared with a preparation of fusidic acid suspended in a vehicle based on a conventional gel forming agent and further containing preservatives, tonicity agents and a buffer. This preparation (in the following called Preparation B) had the following composition per ml:
Preparation B:
Fusidic acid, micronized, sterile 10 mg
Hydroxyethylcellulose 4 mg
Methyl cellulose 0.2 mg
Sodium acetate 1 mg
Glacial acetic acid, q.s. for pH 5-6.0
Sodium chloride 9 mg
Phenethanol 2.5 mg
Water, sterile, to make 1 ml.

The two preparations were compared in the following manner:

Five New Zealand white rabbits weighing about 3 kg were used in the studies. They were designated Nos. 1-5 and placed in restraining boxes during the first 6 hours of the investigation period and at the 24 hour sampling. Between the 6 hour and the 24 hour sampling, the animals were housed individually and given pelleted food and water ad libitum.

Samples for microbiologic determination were taken by placing 6.0 mm AA discs (Whatman) in the fornix inferior, closing the eye lids for approximately 10 seconds and removing the discs with forceps. The discs were placed on the surface of inoculated agar dishes, 14 cm in diameter, together with discs which has been pre-treated with standard solutions for 10 seconds.

The petri dishes were incubated for 16-18 hours at the optimum temperature for the test organisms in question. The inhibition zones of the samples were measured and interpolated on the standard curve which was established as the best response line from the inhibition zones for the standard solutions.

Prior to each investigation the lacrimal fluid of each rabbit was tested for the absence of substances which are inhibitory to the test organisms.

One drop of each preparation was instilled in the fornix inferior of the left eye of each of the five rabbits. Samples were taken at 1, 2, 4, 6 and 24 hours following treatment.

There was a period of at least 72 hours between treatments with different preparations.

The results are presented in the table which shows that fusidic acid is present in measurable concentrations 24 hours after
the treatment.

However, the concentration of fusidic acid in the 24 hour samples is approximately ten times higher for preparation A than for preparation B.

<table>
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<th>Animal No.</th>
<th>mcg fusidic acid per ml lacrimal fluid</th>
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<tr>
<td></td>
<td>Hours after treatment</td>
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<tr>
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<td>0</td>
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<tr>
<td>Preparation A</td>
<td></td>
</tr>
<tr>
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<td>4</td>
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<tr>
<td>5</td>
<td>-</td>
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<tr>
<td>Preparation B</td>
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-- indicates a value lower than the detection limit of 0.02 mcg fusidic acid per ml.
Patent Claims

1. An ophthalmic gel composition for human and veterinary use comprising an ophthalmic drug and a vehicle based on a polyanionic polymer, said composition comprising 0.1 to 4% w/v of fusidic acid suspended in an aqueous vehicle containing from 0.2 to 2% w/v of polyanionic polymer.

2. An ophthalmic gel composition according to claim 1, said composition comprising about 1% w/v of fusidic acid in the form of particles having a particle size not exceeding 10 \( \mu \)m.

3. An ophthalmic gel composition according to claim 2, wherein the particle size of the suspended particles of fusidic acid is between 2 and 5 \( \mu \)m.

4. An ophthalmic gel composition according to claim 1, said composition having a pH value of from 5.0 to 6.5.

5. An ophthalmic preparation comprising a gel composition according to claim 1 and an auxiliary agent selected from the group consisting of preservatives, stabilizers and bacteriostatic agents.

6. An ophthalmic preparation according to claim 5, said preparation comprising

\[
\begin{align*}
\text{Fusidic acid} & \quad \text{about 1} \quad \% \quad \text{w/v} \\
\text{"Carbopol 934"} & \quad \text{about 0.5} \quad \% \quad \text{w/v} \\
\text{Mannitol} & \quad \text{about 5} \quad \% \quad \text{w/v} \\
\text{Benzalkonium chloride} & \quad \text{about 0.01} \quad \% \quad \text{w/v} \\
\text{Tracemium disodium} & \quad \text{about 0.05} \quad \% \quad \text{w/v,}
\end{align*}
\]

said preparation having a pH value of approximately 5.8.

7. A method of treating eye infections, comprising applying an effective amount of a preparation according to claim 5 into the fornix inferior of the infected eye.

8. A method according to claim 7, wherein the preparation is used in dosages of from 5 to 100 mg.

9. A method according to claim 8, wherein the preparation is used in dosages of from 20 to 50 mg.

10. A method according to claim 9, wherein the preparation is applied 1-2 times daily.
### I. CLASSIFICATION OF SUBJECT MATTER

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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched.

### III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Y</td>
<td>EP, A, 0 020 794 (TOKYO YAKUHIN KOGYO KABUSHIKI KAISHA) 7 January 1981 See claims</td>
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<td>FR, A, 2 407 214 (TOKYO YAKUHIN KOGYO KABUSHIKI KAISHA) 1 June 1979 See page 1, lines 25-32, page 6, line 36--page 7, line 13, claims. &amp; BE, 871615 GB, 2007646 NL, 7810758 DE, 2846713 JP, 54070297 AU, 41073/78 US, 4259333 SE, 7811148</td>
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<td>Y</td>
<td>DK, B, 135 267 (WERNER-LAMBERT COMPANY) 28 March 1977 See claims</td>
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* Special categories of cited documents:
  - **A**: document defining the general state of the art which is not considered to be of particular relevance
  - **E**: earlier document but published on or after the international filing date
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  - **O**: document referring to an oral disclosure, use, exhibition or other means
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  - **X**: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
  - **Y**: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - **A**: document member of the same patent family

### IV. CERTIFICATION

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International Searching Authority: Swedish Patent Office

Signature of Authorized Officer: Agnete Tannerfeldt

Form PCT/ISA/210 (second sheet) (January 1985)
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 7-10, because they relate to subject matter not required to be searched by this Authority, namely:

   Methods for treatment of the human or animal body by therapy (Rule 39.1.iv)

2. [ ] Claim numbers .........., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers .........., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.
### III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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<td>GB, A, 2 013 084 (ALCON LABORATORIES INC.) 3 August 1979 &amp; FR, 2415459 DE, 2902863 JP, 54110312 US, 4271143 CA, 1108053 CH, 640737</td>
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