Title: THE PROCESS FOR PREPARING ISOTONIC TOPICAL ANTIBIOTIC OPHTHALMIC FORMULATION WITH IMPROVED THERAPEUTIC EFFECT

Abstract: Eye infections are responsible for ocular morbidity and mortality if not treated in time adequately. In countries like India, infections account for majority of corneal blindness. Because of this reason, there is constantly a search going on for better antibiotics to be available for ophthalmic use. The preferred antibiotic should have broad spectrum of action. It should achieve therapeutic concentration when applied topically. It is also preferable to maintain therapeutic concentration for as long as period as possible necessitating fewer application of the drug and improved compliance. The present invention relates to process of preparation of isotonic topical ophthalmic antibiotic formulation of Sparfloxacin in such a way that it is stable at room temperature, achieves higher concentration. It also has low MIC against pathogen and so achieves higher therapeutic index. This antibiotic formulation also achieves better therapeutic results.
1. THE PROCESS FOR PREPARING ISOTONIC TOPICAL ANTIBIOTIC OPHTHALMIC FORMULATION WITH IMPROVED THERAPEUTIC EFFECT.

2. Dr. Bakulesh Mafatlal Khamar, residing at 201 “Ashadha”, Vasundhara Colony, Gulbai Tekra, Ellisbridge, Ahmedabad 380 006, Gujarat, India, Nationality: Indian

3. The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.
FIELD OF INVENTION

The objective of the present invention is to prepare isotonic topical antibiotic ophthalmic formulation for treating eye infections, with improved therapeutic effect.

The further objective of present invention is to prepare isotonic topical antibiotic ophthalmic formulation in such a way that it is stable at room temperature for more than two years and maintains therapeutic concentrations in aqueous humor for more than 6 hours.

BACKGROUND OF THE INVENTION

Eye infections are responsible for ocular morbidity and mortality if not treated in time adequately. In country like India, infections account for majority of corneal blindness. Because of this reason, there is constantly a search going on for better antibiotics to be available for ophthalmic use. The preferred antibiotic should have broad spectrum of action. It should achieve therapeutic concentration when applied topically. It is also preferable to maintain therapeutic concentration for as long as period as possible necessitating fewer application of the drug and improved compliance.

Sparfloxacain is a newer fluoroquinolone with activity against a broad range of both gm +ve as well as gm –ve organisms, atypical pathogens like Chlamydia tracomatis. It is indicated for the treatment of lower respiratory tract infections as well as acute exacerbations of COPD. Oral Sparfloxacain is a good therapeutic option in the treatment of respiratory tract infections, on account of its efficacy, once daily dosage, lack of side effects and no significant drug interactions.
Sparfloxacin acts on susceptible organisms by inhibiting the enzyme, DNA gyrase. Like other quinolones, it displays a postantibiotic effect in vitro. Sparfloxacin is bactericidal at concentrations similar to or twice that of the MICs for susceptible pathogens.

Sparfloxacin provides good coverage against common bacterial pathogens responsible for external ocular infections e.g. conjunctivitis and corneal ulcer. It is active against Staph. aureus, Ps aeruginosa, N. gonorrhoeae, H. influenzae, M. catarrhalis, Staph. epidermidis, Strept. pneumoniae, Strept. viridians and Chlamydia species. The MIC$_{90}$ of Sparfloxacin for these organisms is in the range of 0.02 to 1.0 mcg/ml.

The penetration of Sparfloxacin into the acute humor after oral administration found to be 0.840 µg/mL.

It is desirable to have topical Sparfloxacin eye drops, since it does not achieve therapeutic concentration in aqueous following systemic administration. The preparation of Sparfloxacin for topical use is currently not available in the world. This may be due to problems associated with its formulation.

REFERENCES:


5. Treatment of acute bacterial conjunctivitis with topical lomefloxacin 0.3% compared to topical ofloxacin 0.3%. Eur J Ophthalmol 1999 Oct-Dec; 9(4):269-75.


19. Treatment of acute bacterial conjunctivitis with topical lomefloxacan 0.3% compared to topical ofloxacan 0.3%. Eur J Ophthalmol 1999 Oct-Dec;9(4):269-75


24. Treatment of acute bacterial conjunctivitis with topical lomefloxacin 0.3% compared to topical ofloxacin 0.3%. Eur J Ophthalmol 1999 Oct-Dec;9(4):269-75.


Results:

The penetration of Sparfloxacain into the acute humor after oral administration found to be 0.840 μg/mL.


29. Relationship between the sensitivity of *Pseudomonas aeruginosa* and the post-antibiotic effect of *sparfloxacin* and *ciprofloxacin*

*Rev Esp Quimioter* 1998 Dec;11(4):333-8

Results:

The MIC of *sparfloxacin* and *ciprofloxacin* ranged from 0.25-256 mg/ml and from 0.25-128 mg/ml, respectively. PAE values ranged from 46.871 to 59.61 2.51 min and from 46.33 15.2 to 62.61 3.70 min, respectively.

**DESCRIPTION OF THE INVENTION**

According to present invention is described a method of preparing isotonic topical antibiotic formulation with improved therapeutic effect.

The objective of the present invention is to provide a broad spectrum antibiotic formulation for topical use with improved therapeutic effect.

The further objective of the present invention is to provide a topical antibiotic formulation which penetrates the cornea.

Another objective of the present invention is to provide an antibiotic formulation which achieves tissue concentration much more above MIC for majority of organisms.

Another objective of the present invention is to provide a topical formulation which maintains therapeutic concentrations for a longer period of time.

As per the present invention it is found that *Sparfloxacin* drops made as per the description meet the requirement.
As per the present invention it is observed that Sparfloxacain drops made as per the present invention achieves therapeutic concentration in the aqueous humor for more than 6 hours.

As per the present invention it is observed that preparation made as per the present invention achieves significantly higher tissue concentration compared to MIC. It is known that Sparfloxacain has effect on organism which is concentration dependent i.e. increasing tissue concentration is advantageous in killing of organisms.

It is also known that Sparfloxacain has significantly more post-antibiotic effect which prolongs the duration of action (pharmacodynamic effect).

It is also known that Sparfloxacain is not readily soluble.

As per the present invention it is found that: sparfloxacain eye drops has a better therapeutic effect due to low MIC, higher Cmax resulting into higher therapeutic index.

As per the present invention it is found that:
1. Sparfloxacain is soluble in lactic acid, ascorbic acid and lactobionic acid.
2. Amber coloured glass container is suitable for storage of Sparfloxacain.
3. The container is not to be stored in deep freeze.
4. The three reagents mentioned (lactic acid, ascorbic acid and lactobionic acid) can be used for solubilisation of Sparfloxacain.
5. Sparfloxacain is incompatable with potassium chloride and sodium chloride.
6. Propylene glycol and beta-cyclodextrin are to be used for formation of complex with sparfloxacain.
7. Mannitol and dextrose can be used for adjusting isotonicity.

The following is one of the examples for preparing Sparfloxacain isotonic topical ophthalmic formulation with improved therapeutic effect as per the present invention:
**EXAMPLE 1:**

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<th>No.</th>
<th>Ingredients</th>
<th>Quantity</th>
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<tr>
<td>1</td>
<td>Sparfloxacin</td>
<td>0.3%</td>
</tr>
<tr>
<td>2</td>
<td>Lactic acid 10%</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>Hydroxy propyl methyl cellulose</td>
<td>0.25%</td>
</tr>
<tr>
<td>4</td>
<td>Disodium EDTA</td>
<td>0.1%</td>
</tr>
<tr>
<td>5</td>
<td>Mannitol</td>
<td>5%</td>
</tr>
<tr>
<td>6</td>
<td>Beta-cyclodextrin</td>
<td>0.1%</td>
</tr>
<tr>
<td>7</td>
<td>Benzalkonium chloride</td>
<td>0.01%</td>
</tr>
<tr>
<td>8</td>
<td>Water for injection</td>
<td>q.s</td>
</tr>
</tbody>
</table>

1. Sterile environment is maintained throughout the process. Exposure to light is avoided during the process.

2. The weight of all the ingredients are checked as per the formulation sheet.

3. Sparfloxacin is micronized.

4. Uniform suspension of Sparfloxacin is maintained in sufficient amount of water for injection.

5. Lactic acid is added in drops to get a clear solution.

6. The above solution is checked for pH.

7. HPMC, disodium EDTA and beta-cyclodextrin are added separately and dissolved in water for injection.

8. Mannitol is added to make solution isotonic.
The formulation, prepared as per the present invention, is a light yellow coloured clear solution, with pH between 3.5 to 5.5.

The formulation so prepared is isotonic and well tolerated in animal studies.

The formulation is also stable over a period of more than 2 years.

The formulation prepared as per the present invention was subjected to pharmacokinetic studies.

Ocular penetration of the formulation has been studied following instillation of 1 drops of 0.3% eye drops in the conjunctival sac over a period of 6-hours. After 15 minutes, Sparfloxacin levels in aqueous humor was found to be 1.4 mcg / ml. Maximum concentrations of 3.7 mcg / ml was found at 1 hour and the levels were maintained above 1 mcg / ml for upto 4-hours. Elimination half-life of the drug in the aqueous humor was 1.84 hours (see figure).

The topical ophthalmic antibiotic formulation made as per the present invention, has better ocular penetration. Cmax of sparfloxacin is 3.7 mcg/ml which is 2.51 times than ofloxacin, 10.57 times than ciprofloxacin. Such a high Cmax of sparfloxacin due to better ocular penetration gives it an advantage over other quinolones.

**Cmax OF VARIOUS FLUROQUINOLONES**

<table>
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<tr>
<th>S.No.</th>
<th>Fluoroquinolones</th>
<th>Value (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ciprofloxacin</td>
<td>0.35</td>
</tr>
<tr>
<td>2.</td>
<td>Ofloxacin</td>
<td>1.43</td>
</tr>
<tr>
<td>3.</td>
<td>Norfloxacin</td>
<td>0.057</td>
</tr>
<tr>
<td>4.</td>
<td>Sparfloxacin</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Therapeutic efficacy of antibiotic depends on its therapeutic index along with other factors. Sparfloxacin has therapeutic index which is more than 20 times for Staph. aureus compared to other quinolones. Staphylococcus is the commonest pathogen for external ocular disease. The comparison also reveals that sparfloxacin has therapeutic index which is higher (significantly) than any other antibiotic.

\[
\text{C}_{\text{max}} /\text{MIC} \quad \text{(Therapeutic Index)}
\]

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Ciprofloxacin</th>
<th>Ofloxacin</th>
<th>Norfloxacin</th>
<th>Sparfloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. aureus</td>
<td>0.57</td>
<td>1.43</td>
<td>0.19</td>
<td>29.6</td>
</tr>
<tr>
<td>S. Epidermidis</td>
<td>0.71</td>
<td>1.43</td>
<td>0.11</td>
<td>7.4</td>
</tr>
<tr>
<td>Strepto pneumoniae</td>
<td>0.17</td>
<td>0.35</td>
<td>1.9</td>
<td>7.4</td>
</tr>
<tr>
<td>Haemo. influenzae</td>
<td>11.66</td>
<td>22.5</td>
<td>0.013</td>
<td>61.66</td>
</tr>
<tr>
<td>Pseu. aeruginosa</td>
<td>0.47</td>
<td>0.71</td>
<td>0.057</td>
<td>3.7</td>
</tr>
<tr>
<td>Kleb. pneumoniae</td>
<td>1.45</td>
<td>10.8</td>
<td>0.45</td>
<td>14.8</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>3.8</td>
<td>0.05</td>
<td>0.95</td>
<td>46.25</td>
</tr>
</tbody>
</table>

Thus, the topical preparation of Sparfloxacin made as per the present invention provides preparation with better therapeutic efficacy.

**CLINICAL EVALUATION OF PRESENT INVENTION:**

Topical ophthalmic antibiotic made as per the present invention, was clinically evaluated in patients with corneal ulcers, keratitis and conjunctivitis.

**CONJUNCTIVITIS:**

**Total No. of Eyes with bacterial Conjunctivitis : 76 eyes, 50 patients**

<table>
<thead>
<tr>
<th></th>
<th>Bilateral</th>
<th>Unilateral</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

**Bacteriological Profile :** Of 76 eyes 66 grew staphylococci, 8 grew pneumococci, and 2 had diplococci.
Clinical Response: Out of 76 eyes (50 patients), 75 (49 patients) (98.6%) responded to Sparfloxacin therapy and were cured clinically as well as microbiologically. One patient did not show any signs of improvement after ten days therapy and was shifted over to other therapy. The organism isolated was Staphylococcus. It was found resistant to all antibiotics tested like Cephalexin, Penicillin, Bactrim, Cefotaxime, Ampicillin, Cefadroxil, Amoxicillin, Lincomycin and Cloxacillin.

KERATITIS: (Total - 17 Patients)

Biological Profile: Of 17 eyes 12 grew staphylococci, 3 grew pneumococci and 2 had mixed infection.

Clinical Response:

One Patient withdrawn due to allergic reaction on 1st day of therapy.

All 16 patients (100%) (excluding the patient who discontinued) who completed the trial responded to the therapy and got cured. The Mean Cure Period was found to be 2.84 days.

CORNEAL ULCER: (Total - 46 Patients)

Biological Profile: Of 46 patients with corneal ulcer 33 grew staphylococci, 2 grew pneumococci, 3 had mixed infection and 8 grew no organism.

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient</th>
<th>Healed with Sparfloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypopyon Corneal Ulcer</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Simple Corneal Ulcer</td>
<td>09</td>
<td>09</td>
</tr>
</tbody>
</table>
Clinical Response:

All 46 patients (100%) (excluding the patient who diagnosed as fungal ulcer) who completed the trial responded to the therapy. The Mean Cure Period was found to be 7.12 days.

Comparative Efficacy of various fluoroquinolones:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conjunctivitis</th>
<th>Keratitis</th>
<th>Corneal Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>88%-96%</td>
<td>68%-82%</td>
<td>70%-91%</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>82%-89.%</td>
<td>80%-96%</td>
<td>80-82%</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>62%-75%</td>
<td>75%-88%</td>
<td>85%-93%</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>98.60%</td>
<td>100.0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The 98.68% cure rate with the present invention compares favourably with other antibiotics and is better than cure rate obtained with other quinolones (Table above).

Keratitis:

The cure rate of 100% is a much desirable and was achieved in this trial of Sparfloxacin. This is much better than those obtained with other quinolones (Table above).

Corneal ulcer:

The bacteriological profile comprised mainly Staph. aureus. The 100% cure rate is a much desired outcome and is much better than success rate with other quinolones e.g. 70-92% for ciprofloxacin, 80-80% for norfloxacin and 85-93% for ofloxacin (Table above).

Such a high success rate (better therapeutic effect) seen with Sparfloxacin eye drops as per the present invention is desirable but has not been described for any other topical ophthalmic antibiotic.
I claim:

1. The process for preparing isotonic topical antibiotic ophthalmic formulation, with improved therapeutic effect, comprising steps of:
   a) making uniform suspension of the antibiotic in sufficient amount of water,
   b) adding solvent to get a clear solution,
   c) checking the pH of the above solution,
   d) adding the excipients,
   e) adding tonicity agent to adjust the tonicity of the solution,
   f) filtering the bulk through 0.2 μm membrane filter.

2. The process as claimed in claim 1 wherein the antibiotic is Sparfloxac in.

3. The process as claimed in claims 1 to 2 wherein the solvent used can be lactic acid, ascorbic acid, lactobionic acid and the like.

4. The process as claimed in claims 1 to 3 wherein the solvent is lactic acid.

5. The process as claimed in claim 1 wherein the excipients are HPMC, disodium EDTA and Beta-cyclodextrin.

6. The process as claimed in claims 1 to 4 wherein the pH of the solution is between 3.5-5.5.

7. The process as claimed in claim 1 to 6 wherein the tonicity agent is mannitol or dextrose.

8. The process as claimed in claim 1 and herein described in example 1.
AMENDED CLAIMS

[received by the International Bureau on 31 January 2002 (31.01.02); original claims 1-8 replaced by amended claims 1-9 (1 page)]

1. A clear topical aqueous ophthalmic antibiotic preparation comprising sparfloxacin in the range of about 0.2% to about 0.8%.

2. The ophthalmic antibiotic preparation claimed in claim 1 having $C_{\text{max}}$ value in aqueous humor in range of about 2 mcg/ml to about 4.5 mcg/ml.

3. The ophthalmic antibiotic preparation claimed in claim 1 and 2 achieving more than double minimum inhibitory bactericidal concentration in aqueous humor against ocular pathogens.

4. The ocular pathogens claimed in claim 3 include Staphlococcus aureus, Staphlococcus epidermis, Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumoniae and Neisseria gonorrhoea and their like.

5. The ophthalmic antibiotic preparation claimed in claims 1-3 has pH of 3.5 – 5.5.

6. A preparation as claimed in claims 1-3 and 5 wherein sparfloxacin is solubilised using Lactic acid, Ascorbic acid, Lactobionic acid and like.

7. A preparation as claimed in claims 1-3 and 5 wherein the more preferable solubilizing agent is lactic acid.

8. A preparation as claimed in claims 1-3 and 5 wherein excipients are selected from Hydroxy propyl methyl cellulose, Disodium EDTA, and beta-cyclodextrin, singly or in combination.

9. A preparation as claimed in claim 1-3 and 5 wherein tonicity agent is mannitol or dextrose.
Figure:

CONCENTRATION IN AQUEOUS HUMOR

- Concentration of Sparfloxacin
- Staph. MIC
INTERNATIONAL SEARCH REPORT

CLASSIFICATION OF SUBJECT MATTER
IPC7: A61K 9/08, 31/4709, 31/501, A61P 31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, EPDOC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>Y</td>
<td>WO 98/19707 A1 (ALCON LABORATORIES, INC.) 14 May 1998 (14.05.98) page 2, lines 4-8; page 5, lines 1-6; claims 1, 2.</td>
<td>1-3</td>
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<td>Y</td>
<td>EP 0534860 A1 (RHONE-DPC EUROPE) 31 March 1993 (31.03.93) the whole document.</td>
<td>1-4, 6, 7</td>
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<td>Y</td>
<td>WO 00/01365 A1 (LEO PHARMACEUTICAL PRODUCTS LTD. A/S) 13 January 2000 (13.01.00) claim 1.</td>
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</table>

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* 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 application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"Y" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"V" 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

"D" document member of the same patent family

Date of the actual completion of the international search
29 October 2001 (29.10.2001)

Date of mailing of the international search report
6 December 2001 (06.12.2001)

Name and mailing address of the ISA/AT
Austrian Patent Office
Kohlmarkt 8-10; A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer
KRENN

Telephone No. 1/53424/435
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☒ Claims Nos.: 8
   because they relate to subject matter not required to be searched by this Authority, namely:
   Apart from its reference to the description (which is not allowed according to PCT-Rule 6.2.) claim 8 does not refer to any technical feature.

2. ☒ Claims Nos.: 1
   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:
   According to PCT-Article 6 claims should be (1) clear and concise and(2) be supported by the description. Although claim 1 does not correspond to said requirement, the search was carried out restricting the subject matter of claim 1 to the specifications made in claims 2 and 3. Moreover the term "...and the like." was not considered within the search.

3. ☐ Claims Nos.: 
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ 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 claims Nos.:

Remark on Protest  ☐ The additional search fees were accompanied by the applicant’s protest.
☐ No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
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<td></td>
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