Aqueous pharmaceutical compositions containing a synergistic combination of a quinolone and a polystyrene sulfonic acid polymer are described, wherein the compositions are clear solutions which are comfortable and have sustained release. Methods for use of the compositions are also disclosed. This type of formulation is particularly useful with ciprofloxacin-type quinolones by greatly increasing the solubility of these quinolones, making it feasible to have aqueous solutions containing such quinolones at or near physiological pH.
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COMPOSITIONS CONTAINING QUINOLONE ANTIBIOTICS AND SULFONATE OF POLYSTYROL

Background of the Invention

The present invention relates to pharmaceutical compositions comprising a synergistic combination of a quinolone and a polystyrene sulfonic acid polymer. In particular, the present invention relates to aqueous preparations containing a quinolone and a polystyrene sulfonic acid polymer, wherein the quinolone is solubilized by the polystyrene sulfonic acid polymer. These preparations are particularly well-suited for ophthalmic or otic use in the treatment of bacterial infections.

A number of quinolones have previously been used to treat bacterial infections through a variety of methods, including topical administration. Representative quinolones and antibacterial compositions thereof are: the norfloxacin-type quinolones, disclosed in U.S. Patents Nos. 4,146,719 (Irikura) and 4,292,317 (Pesson); the ofloxacin-type quinolones, disclosed in U.S. Patent No. 4,382,892 (Hayakawa, et al.); and the ciprofloxacin-type quinolones, disclosed in U.S. Patent No. 4,670,444 (Grohe, et al.). The ciprofloxacin-type quinolones generally have a broader spectrum of antibacterial activity than either of the other types of quinolones listed above. Because of the poor solubility of these quinolones at physiological or higher pH, the ciprofloxacin-type quinolone formulations were developed at acidic pH and/or as suspensions; however, when these formulations were administered topically to the eye, they were uncomfortable.

Summary of the Invention

The present invention provides aqueous pharmaceutical compositions and methods for the treatment of bacterial infections using these compositions. The compositions are particularly well-suited for ocular or otic use. The compositions of the present invention are formulated such that the solubility of quinolones and/or quinolone analogues at higher pH
is increased by the use of an ionic polymer (namely, polystyrene sulfonic acid polymer) which binds the quinolone to the polymer. The binding between the polymer and the quinolone additionally provides both initial and continual comfort upon instillation to the eye, as there is less free drug to irritate the tissues of the eye. Another added benefit to the compositions of the present invention is that there is sustained release of the quinolone.

**Detailed Description of the Invention**

The pharmaceutical compositions of the present invention contain a synergistic combination of a quinolone and/or quinolone analogue having antibacterial activity and a polystyrene sulfonic acid polymer, preferably at physiological or near-physiological pH. For purposes of this specification, quinolones and/or quinolone analogues shall hereinafter be collectively referred to as "quinolone" or "quinolones" unless otherwise stated. These compositions are especially useful in the eye, as the compositions are comfortable upon topical administration to the eye and provide sustained release of the quinolone.

The polystyrene sulfonic acid polymers (and their salts) which are used in the formulations of the present invention have the following formula:

![Chemical Structure](image)

wherein,

- $R = H$ or $\text{CH}_3$; and
- $X = \text{an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.}$
In the preferred polystyrene sulfonic acid of the above formula, R=H and the molecular weight is between about 500,000 to about 1,000,000, preferably about 600,000. The polystyrene sulfonic acid polymers are used in the formulas of the present invention at a concentration less than about 8.0 by weight (wt%), preferably less than about 5.0 wt%.

All quinolones having antibacterial activity and which are ophthalmically acceptable are useful in the compositions of the present invention, including, but not limited to the quinolones disclosed in U.S. Patents Nos. 4,146,719 (Kyorin), 4,292,317 (Bellon), 4,382,892 (Daiichi), 4,670,444 (Grohe, et al.). The entire contents of these patents are hereby incorporated by reference herein.

The preferred quinolones useful in the compositions of the present invention are the type disclosed in U.S. Patent No. 4,670,444 referenced above. The quinolones described therein are generally described as 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline- and -naphthyridine-3-carboxylic acids of the formula:

\[
\text{R}^1, \text{R}^2, \text{Z}, \text{N}, \text{A}, \text{COOH}
\]

or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

in which A represents a nitrogen atom or CR$_3$,

wherein R$_3$ denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group, and

Z represents a nitrogen atom or C-H, and A and Z cannot simultaneously be nitrogen atoms, and R$_1$ and R$_2$ are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkynyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from
hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in each alkyl radical, alkoxy carbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl, or furthermore represents a cycloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxy carbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

More preferred are the 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acids of the formula:

\[(\text{II})\]

or salts and/or hydrates thereof, in which R denotes hydrogen, methyl, ethyl or β-hydroxyethyl.

Most preferred is ciprofloxacin, which has the following structure:

The chemical name for ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

Methods of preparation for the preferred quinolones are described in U.S. 4,670,444. The quinolone component of the pharmaceutical compositions
of the present invention generally contain less than about 1.0 wt% of the total composition, preferably between about 0.1 wt% to about 0.75 wt%. The most preferred quinolone concentration is between about 0.2 to about 0.4 wt%.

The compositions of the present invention are prepared by combining the quinolone with polystyrene sulfonic acid polymer in aqueous media and adjusting the pH, if necessary. The compositions of the present invention may also include one or more ingredients conventionally found in ophthalmic or otic formulations, such as preservatives (e.g., benzalkonium chloride or thimerosal), viscosity-impacting agents (e.g., polyvinyl alcohol or hydroxypropomethylcellulose) and tonicity agents (e.g., sodium chloride or mannitol). The compositions will also normally include buffering agents, such as phosphates and citrates, to maintain the pH within the range of physiological pH (pH between 6.0 and 7.5) and tonicity agents, such as mannitol. Hydrochloric acid or sodium hydroxide will typically be used to adjust the pH of the resultant composition.

The following example is presented to illustrate further certain preferred embodiments of the present invention and should not be interpreted as limiting the scope of the invention in any way.

**EXAMPLE**

The following represents a preferred embodiment of the compositions of the present invention.

<table>
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<tr>
<th>Ingredient</th>
<th>Amount (wt%)</th>
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<tbody>
<tr>
<td>Ciprofloxacin HCl, Monohydrate</td>
<td>0.35*</td>
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<tr>
<td>PSSA</td>
<td>50 ml**</td>
</tr>
<tr>
<td>Mannitol</td>
<td>3.75</td>
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<tr>
<td>Benzalkonium chloride</td>
<td>0.01</td>
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<tr>
<td>NaOH and/or HCl</td>
<td>to pH 7.0</td>
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<td>Purified Water</td>
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*Equivalent to 0.3% as base
**2% PSSA solution in water
The 2% PSSA solution was filtered through a 0.6 micron filter, 50 milliliters (mL) of the filtered solution added to a first beaker, and the contents stirred. To a second beaker were added 15 mL of water and the ciprofloxacin and the mixture stirred until the ciprofloxacin was completely dissolved, at which point the mannitol and benzalkonium chloride were added and the contents stirred again, until a homogeneous solution was achieved. Then the contents of the second beaker were slowly added to the contents of the first beaker, while stirring. The pH was then adjusted to pH 7.0 using NaOH and water was added to bring the volume of the final solution to 100 mL.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.
What is Claimed is:

1. An aqueous pharmaceutical composition useful in the treatment of bacterial infections which comprises a quinolone and a polystyrene sulfonic acid polymer.

2. The composition of claim 1, wherein the quinolone has the following formula:

```
  O
 /\  
 N  
 /\  
 N  
 /\  
 A  
 /\  
 R
```

or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

in which A represents a nitrogen atom or CR₃;

wherein R₃ denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group; and

Z represents a nitrogen atom or C-H, and A and Z cannot simultaneously be nitrogen atoms, and R₁ and R₂ are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkinyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in alkyl radical, alkoxy carbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or by-cyclic carbocyclic ary1, or furthermore represents a cycloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxy carbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic ary1.
3. The aqueous pharmaceutical composition of claim 1, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.

4. The aqueous pharmaceutical composition of claim 3, wherein the quinolone is present at a concentration between about 0.1 wt% to about 0.75 wt%.

5. The aqueous pharmaceutical composition of claim 4, wherein the quinolone is present at a concentration between about 0.2 to about 0.4 wt%.

6. The aqueous pharmaceutical composition of claim 5, wherein the quinolone is present at a concentration of about 0.3 wt%.

7. The aqueous pharmaceutical composition of claim 1, wherein the polystyrene sulfonic acid polymer has the following formula:

\[
\begin{array}{c}
\text{OH} \\
\text{R} \\
\text{X}
\end{array}
\]

wherein: R = H or CH₃; and X = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

8. The aqueous pharmaceutical composition of claim 7, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 8.0 wt%.

9. The aqueous pharmaceutical composition of claim 7, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 5.0 wt%.
10. An aqueous pharmaceutical composition useful in the treatment of bacterial infections consisting essentially of a quinolone of formula:

![Chemical structure](image)

or salts and/or hydrates thereof, in which R denotes hydrogen, methyl, ethyl or β-hydroxyethyl; and a polystyrene sulfonic acid polymer.

11. The aqueous pharmaceutical composition of claim 10, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.

12. The aqueous pharmaceutical composition of claim 11, wherein the quinolone is present at a concentration between about 0.1 wt% to about 0.75 wt%.

13. The aqueous pharmaceutical composition of claim 12, wherein the quinolone is present at a concentration between about 0.2 to about 0.4 wt%.

14. The aqueous pharmaceutical composition of claim 13, wherein the quinolone is present at a concentration of about 0.3 wt%.

15. The aqueous pharmaceutical composition of claim 12, wherein the quinolone is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piprazinyl)-3-quinoline carboxylic acid.
16. The aqueous pharmaceutical composition of claim 10, wherein the polystyrene sulfonic acid polymer has the following formula:

\[
\text{[Diagram of chemical structure]}
\]

wherein: \( R = \text{H or CH}_3 \); and \( X = \) an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

17. The aqueous pharmaceutical composition of claim 16, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 8.0 wt%.

18. The aqueous pharmaceutical composition of claim 16, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 5.0 wt%.

19. The aqueous pharmaceutical composition of claim 10, wherein the quinolone is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piprazinyl)-3-quinoline carboxylic acid.

20. A method for the treatment of bacterial infections which comprises the topical administration of an aqueous pharmaceutical composition which comprises a quinolone and a polystyrene sulfonic acid polymer.
21. The method of claim 20, wherein the quinolone has the following formula:

\[ \text{R}^1_A \text{R}^2 \text{N} \text{Z} \text{N} \text{COOH} \]

or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

wherein \( R^3 \) denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group; and

\( Z \) represents a nitrogen atom or \( C-H \), and \( A \) and \( Z \) cannot simultaneously be nitrogen atoms, and \( R^1 \) and \( R^2 \) are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkynyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in alkyl radical, alkoxyalkyl with 1 to 4 carbon atoms in the alcohol part, and mono- or by-cyclic carbocyclic aryl, or furthermore represents a cycloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of \( N, O \) and \( S \) form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxyalkyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

22. The method of claim 20, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.
23. The method of claim 20, wherein the polystyrene sulfonic acid polymer has the following formula:

\[
\begin{array}{c}
\text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 \\
\end{array}
\]

wherein: \( R = \text{H} \) or \( \text{CH}_3 \); and \( X \) = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

24. The method of claim 23, wherein the concentration of the polystyrene sulfonic acid polymer is less than about 8.0 wt%.
### INTERNATIONAL SEARCH REPORT

**International Application No.** PCT/US 92/07744

#### I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K47/48

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  - "I" 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
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* "I" 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

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* "A" document member of the same patent family

#### IV. CERTIFICATION

**Date of the Actual Completion of the International Search**

23 NOVEMBER 1992

**Date of Mailing of this International Search Report**

07.12.92

**International Searching Authority**

EUROPEAN PATENT OFFICE

**Signature of Authorized Officer**

SCARPONI U.
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/11/92

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82