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INTERNATIONAL SEARCH REPORT

For two-letters codes and other abbreviations, see “Guidance Note for Codes and Abbreviations” described in the front of each PCT gazette published periodically.

(54) Title: STABLE LIQUID PREPARATION

(57) Abstract: Provided is a liquid preparation of sitafloxacin excellent in a light stability, comprising an aqueous solution containing sitafloxacin and sodium chloride.

STABILIZED LIQUID PREPARATION

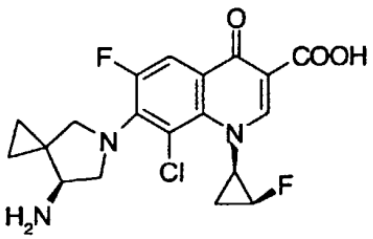
TECHNICAL FIELD

The present invention relates to a liquid preparation comprising an antimicrobial aqueous solution having an improved light stability and a process for producing the same.

BACKGROUND ART

Sitafloxacin (in this specification, the name according to International Nonproprietary Names (INN) is used) is a compound having the following chemical structure (Japanese Patent No. 2714597).

This compound exhibits a very high antimicrobial activity and a high safety and has been studied with an expectation for application as an excellent quinolone synthetic antimicrobial drug.



Sitafloxacin is a promising antimicrobial drug having potent antimicrobial activities, especially in the treatment of a serious infectious disease. Therefore, it is desirable that sitafloxacin be available in a parenteral formulation as well; and thus, inventors of the present invention investigated a liquid preparation comprising an aqueous sitafloxacin solution. As a result, it was found that sitafloxacin in aqueous solution lacks stability to a light. That is, it was found that sitafloxacin in aqueous solution undergoes decomposition when it is irradiated with a light, resulting in reduction in a sitafloxacin content, as well as lowering in pH and a light transmittance. Formation of sitafloxacin-related substances was also confirmed. That is, it was found that the light stability of an aqueous sitafloxacin solution needs to be improved in order to supply a liquid preparation comprising an aqueous sitafloxacin solution.

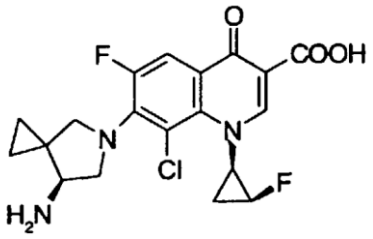
DISCLOSURE OF INVENTION

Under the situation as mentioned above, inventors of the present invention carried out an extensive investigation; and as a result, it was found that sitafloxacin in an aqueous solution can be prevented from decomposing upon irradiation in the presence of sodium chloride. That is, it was found that under the circumstance of the presence of sodium chloride in the aqueous solution, reduction in a sitafloxacin content, lowering in pH and a

light transmittance of the aqueous sitafloxacin solution, and formation of the related substances can be suppressed. The present invention could be completed on the basis of these findings.

That is, the present invention relates to a (antimicrobial) liquid preparation comprising an aqueous solution containing sitafloxacin and sodium chloride.

Also, the present invention relates to a liquid preparation comprising an aqueous solution containing a compound represented by the following formula and sodium chloride.



Further, the present invention relates to a liquid preparation comprising an aqueous solution containing (–)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-l-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and sodium chloride. The present invention also relates to the following embodiments:

The above-mentioned liquid preparation, wherein sodium chloride is present in an amount of 0.01 to 10% by weight.

The above-mentioned liquid preparation, wherein sodium chloride is present in an amount of 0.01 to 5% by weight.

The above-mentioned liquid preparation, wherein sodium chloride is present in an amount of 0.05 to 3% by weight.

The above-mentioned liquid preparation, wherein sodium chloride is present in an amount of 0.50 to 1% by weight.

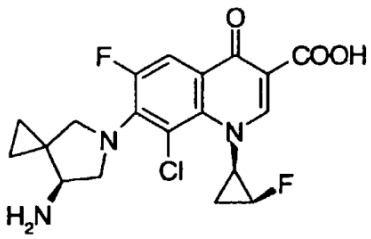
The above-mentioned liquid preparation, wherein pH of the aqueous solution is 3.5 to 4.5.

The above-mentioned liquid preparation, wherein pH of the aqueous solution is 3.8 to 4.2.

The present invention further relates to the following processes for preparing of the above-mentioned liquid preparation:

A process for preparing a liquid preparation comprising the steps of:
(1) preparing an acidic aqueous solution having dissolved therein sitafloxacin or a hydrate thereof and sodium chloride, and
(2) adjusting pH of the said acidic aqueous solution.

A process for preparing a liquid preparation comprising the steps of:
(1) preparing an acidic aqueous solution having dissolved therein a compound represented by the following formula or a hydrate thereof and sodium chloride, and
(2) adjusting pH of the said acidic aqueous solution.



A process for preparing a liquid preparation comprising the steps of:
(1) preparing an acidic aqueous solution having dissolved therein (−)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid or a hydrate thereof and sodium chloride, and
(2) adjusting pH of the said acidic aqueous solution.

The above-mentioned process for preparing a liquid preparation, wherein the acidic aqueous solution is an aqueous hydrochloric acid solution.

A process for preparing a liquid preparation comprising the steps of:
(1) preparing an aqueous solution having dissolved therein a sitafloxacin salt or a hydrate thereof and sodium chloride, and
(2) adjusting pH of the said aqueous solution.

The above-mentioned process for preparing a liquid preparation, wherein the sitafloxacin salt is a hydrochloride thereof, a nitrate thereof, a benzenesulfonate thereof, a methanesulfonate thereof or a toluenesulfonate thereof.

A process for preparing a liquid preparation comprising the steps of:
(1) preparing an aqueous solution having dissolved therein a salt of a compound

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