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(54) **COMPOSITION ANTISEPTIQUE**
(54) **ANTISEPTIC COMPOSITION**

(57) Cette invention concerne une composition antiseptique à base d'eau, ayant un effet antiseptique constant et suffisant et comprenant une solution aqueuse contenant au moins un constituant choisi dans le groupe composé d'acide hyaluronique, d'acide cromoglycique, de dinucléotide d'adénine de flavine et de sels de ceux-ci et de gluconate de chlorhexidine, le gluconate étant contenu dans la solution aqueuse avec une concentration telle qu'il ne forme pas de composite insoluble avec les autres constituants mentionnés ci-dessus et par conséquent préserve l'effet antiseptique.

(57) A water-base antiseptic composition having a consistent and sufficient antiseptic effect and comprising an aqueous solution contaiing at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavin adenine dinucleotide and salts thereof and chlorhexidine gluconate, wherein the gluconate has such a concentration in the aqueous solution that it does not form any insoluble composite with the other components mentioned above and thus maintains the antiseptic effect.

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(54)Title: **ANTISEPTIC COMPOSITION**

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(57) Abstract

A water-base antiseptic composition having a consistent and sufficient antiseptic effect and comprising an aqueous solution contaiing at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavin adenine dinucleotide and salts thereof and chlorhexidine gluconate, wherein the gluconate has such a concentration in the aqueous solution that it does not form any insoluble composite with the other components mentioned above and thus maintains the antiseptic effect.

PCT/JP98/02210

SPECIFICATION

ANTISEPTIC COMPOSITION

FIELD OF THE INVENTION

The present invention relates to a composition made antiseptic by mixing chlorhexidine gluconate with a water-soluble liquid or an aqueous composition containing a pharmaceutical formulation that contains at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof, a method for producing the same, and a method of making antiseptic.

BACKGROUND ART

One or more components selected from the group of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof is useful as a pharmaceutical agent. For example, an aqueous eye drop formulation of hyaluronic acid and/or a salt thereof, especially sodium hyaluronate, is used, for example, in the field of ophthalmology for treatment and prevention of injuries on an eye tissue surface, for treatment of keratitis sicca, and as an intraocular infusion solution in inserting an intraocular lens in a cataract operation. In surgical areas, aqueous formulations of sodium hyaluronate are known to be effective for treatment of osteoarthritis of the knee and periarthritis of shoulder, and these formulations are commercially available. Use of these is disclosed in US Patent No. 4141973, US Patent No. 4328803, JP-A- 60-84225, JP-A-60-31390, JP-A-61-28503, JP-A-01-800044, JP-A-01-246227 etc.

Sodium cromoglycate is also used as a pharmaceutical agent for treatment of allergic asthma or rhinitis. Flavine-adenine dinucleotide is used as eye drops for

treatment of keratitis or blepharitis at the time of vitamin B_2 deficiency.

However, these pharmaceutical agents are liable to be contaminated and to degenerate in an aqueous formulation.

On the other hand, chlorhexidine gluconate has been used as a preservative for aqueous formulations, especially as an antiseptic for aqueous formulations for local use. However, if it is added into an aqueous solution of the above-mentioned pharmaceutical agent, an insoluble complex is produced generating turbidity in the solution. Having thus been regarded as a case of incompatibility, chlorhexidine gluconate is not mixed with these pharmaceutical agents. If it is mixed, an antiseptic effect of chlorhexidine gluconate is considered to be inhibited.

DISCLOSURE OF THE INVENTION

The present invention aims at providing a safe and useful aqueous formulation which contains at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof, and which has a stable and sufficient antiseptic effect while avoiding the incompatibility.

In an effort to solve the above-mentioned problems, the inventors of the present invention conducted a diligent study and found that a stable and safe aqueous formulation having a sufficient antiseptic effect can be obtained by mixing chlorhexidine gluconate, which was usually considered as a case of incompatibility, at an amount that does not produce an insoluble complex, and made a further study to complete the invention.

The present invention provides a water-soluble antiseptic composition containing at least one component selected from the group consisting of hyaluronic acid,

cromoglycic acid, flavine-adenine dinucleotide, and salts thereof and chlorhexidine gluconate; an aqueous antiseptic composition comprising an aqueous solution containing the above-mentioned component and chlorhexidine gluconate, wherein the chlorhexidine gluconate in the aqueous solution has such a concentration that it does not form an insoluble complex with the component while maintaining an antiseptic effect; and a process of making an aqueous composition containing the above-mentioned component antiseptic characterized in that the aqueous composition is mixed with chlorhexidine gluconate.

The concentration of the chlorhexidine gluconate in the composition of the present invention is 0.001 to 0.05 wt%, preferably 0.001 to 0.01 wt%, more preferably around 0.005 wt%, if it is administered to a mucous membrane as eye drops, ear drops, or nose drops, though the concentration depends on the type and form of a main pharmaceutical agent and administration site.

The concentration of one or more components selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof in the composition of the present invention is determined in accordance with the intended use of the composition. The concentration is typically 0.001 to 5 wt%, preferably 0.005 to 3 wt%, more preferably 0.005 to 1 wt%.

The composition of the present invention can be administered in the form of various oral or non-oral liquid, preferably as a local external liquid, more preferably as eye drops, ear drops, or nose drops.

The composition of the present invention may contain another main pharmaceutical agent and/or a component that produces a different type of pharmaceutical effect as long as it does not spoil the purpose of the present invention.

Various additives that are usually used, such as a pH adjuster, a gelling agent, a

stabilizer, a solubilizer, a surfactant, a sweetener, a buffering agent, a flavor, a suspending agent, an absorption promoter, a colorant, an isotonicity agent, an emulsifier, a thickening agent, a forming agent, a dispersing agent, a preservative, an aromatizing agent, a dissolving agent, a dissolving auxiliary, and a solvent may be used as appropriate into these formulations as long as the purpose of the present invention can be achieved.

The composition of the present invention maintains a sufficient antiseptic effect that satisfies the standard of microorganism test as defined in United States Pharmacopoeia (USP) 23, <51> ANTIMICROBIAL PRESERVATIVES-EFFECTIVENESS.

Examples of the antiseptic test are as follows.

Prescription	Rp. 1	Rp. 2
Sodium hyaluronate	0.15 g	0.15 g
Sodium chloride	0.75	0.75
Potassium chloride	0.16	0.16
Disodium hydrogenphosphate	0.08	0.08
Sodium dihydrogenphosphate	In appropriate amount	In appropriate amount
Benzalkonium chloride	0.005	-
Chlorhexidine gluconate	-	0.005
Sterile purified water	In appropriate amount	In appropriate amount
		Total Amount 100 ml
		(pH 7.0)

Rp. 1 is a comparative using benzalkonium chloride as a preservative. Rp. 2 is a preparation of the present invention.

The above-mentioned two preparations were subjected to an antiseptic effect

test according to the provisions of the United States Pharmacopoeia after being filtered with a 0.45 μm filter.

As to sodium hyaluronate, the one manufactured by Shiseido Co., Ltd. and having a molecular weight of 2,000,000 was used. The following results were obtained by the test that extended over four weeks.

(Rp. 1)

microorganism	Number of formed colonies				
	Start time	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks
S. aureus	6	n.d.	n.d.	n.d.	n.d.
E. coli.	6	n.d.	n.d.	n.d.	n.d.
P. aeruginosa	6	4	5	4	4
C. albicans	5	1	1	1	1
A. niger	5	2	1	1	1

Unit: logCFU/ml

(Rp. 2)

microorganism	Number of formed colonies				
	Start time	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks
S. aureus	6	1	n.d.	n.d.	n.d.
E. coli.	6	2	2	2	2
P. aeruginosa	6	1	1	1	n.d.
C. albicans	5	2	2	2	1
A. niger	5	4	4	4	4

Unit: logCFU/ml

As will be apparent from the above, the preparation using benzalkonium

chloride (Rp. 1) does not meet the USP standard, and the preparation using chlorhexidine gluconate (Rp. 2) has been found to meet the USP standard.

Examples

The present invention will now be illustrated in detail by way of examples, but these are not to be understood to limit the present invention.

Example 1 Eye Drops

Sodium hyaluronate	0.1 g
Allantoin	0.1 g
Boric acid	1.8 g
Sodium Citrate	0.2 g
Chlorhexidine gluconate	0.0015 g
Borax	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml
	(pH 7.0)

The above components are dissolved in an ordinary manner to prepare an aqueous formulation.

Example 2 Eye Drops

Sodium hyaluronate	0.05 g
Aminoethylsulfonic acid	0.5 g
Boric acid	1.5 g
Chlorhexidine gluconate	0.0025 g
Borax	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100ml
	(pH 6.5)

The above components are dissolved in an ordinary manner to prepare an aqueous formulation.

Example 3 Eye Drops

Sodium hyaluronate	0.35 g
Boric acid	1.25 g
Sodium chloride	0.3 g
Chlorhexidine gluconate	0.0025 g
Sodium hydroxide	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml
	(pH 6.0)

The above components are dissolved in an ordinary manner to prepare an aqueous formulation.

Example 4 Eye Drops

Sodium hyaluronate	0.005 g
Naphazoline hydrochloride	0.003 g
Diphenhydramine hydrochloride	0.1 g
Pyridoxine hydrochloride	0.05 g
Boric acid	1.8 g
Sodium edetate	0.02 g
Chlorhexidine gluconate	0.002 g
Sodium hydroxide	In appropriate amount
Hydrochloric acid	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml

(pH 6.1)

The above components are dissolved in an ordinary manner to prepare an aqueous formulation.

Example 5 Nose drops

Sodium hyaluronate	0.01 g
Naphazoline hydrochloride	0.05 g
Chlorpheniramine maleate	0.05 g
Chlorhexidine gluconate	0.005 g
Sodium citrate	0.2 g
Concentrated glycerin	2.1 g
Sodium hydroxide	In appropriate amount
Hydrochloric acid	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml
	(pH 6.0)

The above components are dissolved in an ordinary manner to prepare nose drops.

Example 6 Eye drops

Sodium hyaluronate	0.01 g
Flavine-adenine dinucleotide	0.01 g
ε-aminocaproic acid	0.1 g
Boric acid	1.8 g
Chlorhexidine gluconate	0.005 g
Sodium hydroxide	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml
	(pH 7.5)

The above components are dissolved in an ordinary manner to prepare eye drops.

Example 7 Nose drops

Sodium hyaluronate	0.01 g
Sodium cromoglycate	1.0 g
Chlorhexidine gluconate	0.002 g
Hydrochloric acid	In appropriate amount
Sterile purified water	In appropriate amount
	Total amount 100 ml
	(pH 5.0)

The above components are dissolved in an ordinary manner to prepare nose

drops.

Each of the formulations obtained in the above-mentioned embodiments were a colorless transparent liquid at the time of preparation and even after being preserved at room temperature for three months.

According to the present invention, there is provided an antiseptic composition that overcomes the incompatibility problem and meets the United States Pharmacopoeia by mixing chlorhexidine gluconate with a water-soluble or aqueous composition containing hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, or salts thereof.

CLAIMS

1. A water-soluble antiseptic composition containing at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof and chlorhexidine gluconate, wherein the gluconate has such a concentration that it does not form an insoluble complex with said component in an aqueous solution.

2. The antiseptic composition of claim 1, wherein at least one component is hyaluronic acid and/or a salt thereof.

3. An aqueous antiseptic composition comprising an aqueous solution containing at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof and chlorhexidine gluconate, wherein the chlorhexidine gluconate in the aqueous solution has such a concentration that it does not form an insoluble complex with said component while maintaining an antiseptic effect.

4. The composition of claim 3, wherein at least one component is hyaluronic acid and/or a salt thereof.

5. The composition of claim 3 or 4, wherein the concentration of the chlorhexidine gluconate is 0.05 to 0.0001 wt%.

6. A process for producing an aqueous antiseptic composition characterized in that at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof is dissolved in water and mixed with chlorhexidine gluconate at such a concentration that it does not form an insoluble complex with said component in an aqueous solution while maintaining an antiseptic effect.

7. The producing process of claim 6, wherein at least one component is hyaluronic

acid and/or a salt thereof.

8. A process of making antiseptic an aqueous composition containing at least one component selected from the group consisting of hyaluronic acid, cromoglycic acid, flavine-adenine dinucleotide, and salts thereof, characterized in that the aqueous composition is mixed with chlorhexidine gluconate.

9. The process of claim 8, wherein at least one component is hyaluronic acid and/or a salt thereof.