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(54) **USE OF ANTIMICROBIAL PEPTIDES AS PRESERVATIVES IN OPHTHALMIC PREPARATIONS, INCLUDING SOLUTIONS, EMULSIONS, AND SUSPENSIONS**

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(57) **ABSTRACT**

Methods for preserving ophthalmic compositions are disclosed. In one embodiment, such compositions include a liquid medium and an antimicrobial component which is preferably substantially non-oxidative. Compositions which include a liquid medium and antimicrobial peptide magainins, present in an amount effective as a preservative, are also disclosed. Preserved compositions useful for administering a therapeutic component to the eyes or caring for contact lenses are also included within the scope of the present invention.

22 Claims, No Drawings

USE OF ANTIMICROBIAL PEPTIDES AS PRESERVATIVES IN OPHTHALMIC PREPARATIONS, INCLUDING SOLUTIONS, EMULSIONS, AND SUSPENSIONS

BACKGROUND OF THE INVENTION

This invention relates to preserved ophthalmic compositions. More particularly, the present invention relates to preserved ophthalmic compositions, for example, useful in administering a therapeutic component to the eyes, and for example, to care for contact lenses, which include one or more peptides and/or peptide derivatives as antimicrobial agents.

Various compositions, such as solutions, emulsions and suspensions are used in association with administering therapeutic components to the eyes. For example, an oil-in-water emulsion may be used as a carrier for a therapeutic component to be administered to the eyes.

At present, no safe effective preservative exists for an oil-in-water emulsion product. This is because the most acceptable preservative, benzalkonium chloride, loses its effectiveness due to partitioning into the oil phase. As a result only single dose containers of oil-in-water emulsion ophthalmic compositions can be marketed up to this time.

Use of single dose containers to store ophthalmic compositions prevents contamination and growth of microorganisms. However, single dose containers are inconvenient to use and are expensive for the consumer. Appropriate use of an effective preservative will allow for production of multidose containers of preserved ophthalmic compositions such as oil-in-water emulsions.

Various compositions are used in association with contact lenses to ensure that the lenses may be safely, comfortably and conveniently worn. Contact lens care compositions, for example, cleaning compositions, wetting compositions, conditioning compositions and the like, often utilize at least one preservative, depending on the type of composition, for preserving the lens care composition itself.

A preserved contact lens care composition has sufficient antimicrobial activity so that when the composition is contacted with a contact lens substantially no increase in the microorganism population on the lens or in the composition is obtained. A preserved contact lens care composition may be termed a microbiostatic composition. Contact lens care compositions are often preserved to prevent any substantial increase in, or to gradually decrease, the population of contaminating microorganisms in the compositions and, thereby, to extend their shelf life.

Various compounds are known for use as preserving agents in preserved ophthalmic compositions. Examples include thimerosal, benzalkonium chloride and chlorhexidine. However, these preserving agents are known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. Further, a soft contact lens, a rigid gas permeable contact lens (RGP) or a hard contact lens can absorb or adsorb these compounds. This causes the contact lens to retain the irritating compound and contributes to the eye irritation and eye sensitivity which may result.

Thus, it is readily apparent that a continuing need exists

SUMMARY OF THE INVENTION

New preserved compositions and methods employing such compositions, particularly compositions and methods directed to eye care and contact lens care, have been discovered. The present compositions include effective preservatives to protect against growth of contaminating microorganisms. Importantly, such preserving activities are achieved using the present compositions with little or no risk of eye irritation or sensitivity.

In one embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. Also included in the compositions is a therapeutic component. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK (SEQ ID NO: 4). The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions exist in various forms. For example, the compositions may be an oil-in-water emulsion, a solution or a suspension. Also, provided is for a sole preservative to be used in accordance with the invention.

The compositions may be applied onto or into the eyes. For example, the compositions may be used as a surgical irrigant.

In another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. In this embodiment, a sole preservative is used in the compositions. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK (SEQ ID NO: 4). The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions exist in various forms. For example, the compositions may be an oil-in-water emulsion, a solution or a suspension.

The compositions may be applied onto or into the eyes.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. In this embodiment, the composition is an oil and water emulsion. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK (SEQ ID NO: 4). The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions may be applied onto or into the eyes. For example, the compositions may be used as a surgical irrigant.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK (SEQ ID NO: 4) present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions may exist as a solution or a suspension.

The compositions may be applied onto or into the eyes.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. These compositions are applied onto or into the eyes. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. The compositions also may include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

Also provided for are methods of preserving ophthalmic compositions. One such method comprises contacting an ophthalmic composition with a magainin antimicrobial [illegible] in the composition. In one embodiment, the composition is an oil and water emulsion.

Also provided for are methods for treating an eye. One such method comprises contacting an eye with a liquid medium which includes magainin antimicrobial peptides, analogs of magainin antimicrobial peptides or mixtures thereof in an amount effective as a preservative. In one embodiment, the composition is an oil and water emulsion.

The invention also provides for ophthalmic compositions which comprise magainin antimicrobial peptides, analogs of magainin antimicrobial peptides or mixtures thereof in an amount effective as a preservative. In a particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK (SEQ ID NO: 4). Also in a preferred embodiment, the composition is an oil-in-water emulsion and the composition is provided in a multidose format.

Any and all features described herein and combinations of such features are included within the scope of the invention provided that such features of any such combination are not mutually exclusive.

These and other aspects and advantages of the present invention are apparent in the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is applicable to preserving ophthalmic compositions, such as eye care compositions and contact lens care compositions which are benefited from being preserved.

One important feature of the compositions of the present invention is the inclusion of one or more antimicrobial peptides in the compositions.

In one embodiment, the present compositions include a sufficient amount of an antimicrobial peptide to effectively preserve the compositions. In a preferred embodiment, the antimicrobial peptide is a magainin antimicrobial peptide.

The antimicrobial peptides useful according to the present invention include naturally occurring antimicrobial peptides, preferably cytolytic peptides, synthetic antimicrobial peptides, antimicrobial peptide mimetics and nanotubes. Such peptides may be the L-form, the D-form or combinations or mixtures of both forms. At least some of these antimicrobial peptides may be membrane active. One or more of these antimicrobial peptides may act by disrupting a cell membrane.

Among the antimicrobial peptides preferably employed are those selected from defensins, peptides related to defensins, cecropins, peptides related to cecropins, and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Particularly preferred antimicrobial peptides employed in the present invention are magainin antimicrobial peptides and peptides related to magainin antimicrobial peptides and mixtures thereof.

Magainin antimicrobial peptides were first reported in the literature in 1987 (Zasloff (1987) Proc. Natl. Acad. Sci. USA [illegible]

peptides, and are approximately 21 to 27 residues in length. It is believed that magainin antimicrobial peptides may exert their antimicrobial effect by disruption of cell membrane permeability.

Magainin antimicrobial peptides have numerous characteristics that make them a superior preservative for use in ophthalmic compositions. For example, magainin antimicrobial peptides are broad-spectrum antimicrobial agents which exhibit cidal activity against Gram-negative and Gram-positive bacteria, fungi and protozoa. Also, magainin antimicrobial peptides display a reduced eye irritation compared to existing preservatives for ophthalmic compositions. For example, benzalkonium chloride is known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. In addition, magainin antimicrobial peptides are highly water-soluble allowing effective antimicrobial action in an oil-in-water emulsion. This high water solubility also minimizes loss of effectiveness due to adsorption to plastic containers. Further, numerous magainin antimicrobial peptides and magainin antimicrobial peptide derivatives are available which increases the opportunities for avoiding incompatibilities with specific drugs or excipients in a particular formulation of a composition of the invention. Still further, magainin antimicrobial peptides have a low degree of bacterial resistance, are effective at very low concentrations and are easily produced by chemical synthesis or heterologous gene expression. Because of these and other factors magainin antimicrobial peptides are very well suited for use in the present invention.

Exemplary magainin antimicrobial peptides include the peptides having the following amino acid sequences:

Magainin I
Gly Ile Gly Lys Phe Leu His Ser Ala (SEQ ID NO: 1)

Gly Lys Phe Gly Lys Ala Phe Val Gly

Glu Ile Met Lys Ser

Magainin II
Gly Ile Gly Lys Phe Leu His Ser Ala (SEQ ID NO: 2)

Lys Lys Phe Gly Lys Ala Phe Val Gly

Glu Ile Met Asn Ser

Exemplary magainin antimicrobial peptide analogs include the peptides having the following amino acid sequences:

MSI-78
Gly Ile Gly Lys Phe Leu Lys Lys Ala (SEQ ID NO: 3)

Lys Lys Phe Gly Lys Ala Phe Val Lys

Ile Leu Lys Lys-NH_2

MSI-344
Gly Ile Gly Lys Phe Leu Lys Lys Ala (SEQ ID NO:

-continued

Lys Lys Phe Gly Lys Ala Phe Val Lys

Ile Leu Lys Lys

Other useful magainin antimicrobial peptide analogs and derivatives include magainin antimicrobial peptides having N-terminal positively charged chain extensions (e.g., $(Lys)_{10}$-magainin which enhances the antimicrobial activity of the peptides).

Additional magainin antimicrobial peptides, magainin antimicrobial peptide analogs and derivatives which are contemplated for use according to the present invention are described in U.S. Pat. Nos. 5,912,231, 5,847,047, 5,792,831, and 5,643,876 and in the publications Zasloff et al., Proc. Natl. Acad. Sci. USA 85, 910–913 (February 1988); Zasloff, Proc. Natl. Acad. Sci. USA 84, 5449–5453 (August 1987); and Bessale et al, Antimicrobial Agents, Chemotherapy 36 (No. 2), 313–317 (February 1992), and Maloy and Kari, Biopolymers 37, 105–122 (1995) each of which is incorporated in its entirety herein by reference.

Cecropins useful according to the invention include the peptides having the following amino acid sequences:

cecropin A:

Lys Trp Lys Leu Phe Lys Lys Ile Glu (SEQ ID NO: 5)

Lys Val Gly Gln Asn Ile Arg Asp Gly

Ile Ile Lys Ala Gly Pro Ala Val Ala

Val Val Gly Gln Ala Thr Gln Ile Ala

Lys;

and cecropin B:

Lys Trp Lys Val Phe Lys Lys Ile Glu (SEQ ID NO: 6)

Lys Met Gly Arg Asn Ile Arg Asn Gly

Ile Val Lys Ala Gly Pro Ala Ile Ala

Val Leu Gly Glu Ala Lys Ala Leu Gly

Cecropin D can also be employed.

Cecropin derivatives having C-terminus modifications, substitutions, and/or truncations which either enhance or do not inhibit antimicrobial activity are also contemplated for use according to the present invention. Useful derivatives include cecropin A amide (CA—NH_2), and cecropin A with a C-terminal ethylenediamine-modified homoserine (CA-Hse-NH-Et-NH_2). The general sequence homology of the N-terminus portion of the cecropins is necessary for activity and is therefore less suitable for truncation, modification, or substitution. However, analogs resulting from substitution of amino acids with similar chemical characteristics to the original can be designed. Maintaining an amphipathic helical structure similar to the original peptide will result in

Met Pro Arg Trp Arg Leu Phe Arg Arg SEQ ID NO: 7)

Ile Asp Arg Val Gly Lys Gln Ile Lys

Gln Gly Ile Leu Arg Ala Gly Pro Ala

Ile Ala Leu Val Gly Asp Ala Arg Ala

Val Gly.

Shiva-1 and other cecropin substitution analogs having antimicrobial activity are contemplated as being useful according to the invention.

Defensins useful according to the invention include:

HNP-1 (human neutrophil peptide 1):
Ala Cys Tyr Cys Arg Ile Pro Ala Cys SEQ ID NO: 8)

Ile Ala Gly Glu Arg Arg Tyr Gly Thr

Cys Ile Tyr Gln Gly Arg Leu Trp Ala

Phe Cys Cys;

HNP-2:
Cys Tyr Cys Arg Ile Pro Ala Cys Ile (SEQ ID NO: 9)

Ala Gly Glu Arg Arg Tyr Gly Thr Cys

Ile Tyr Gln Gly Arg Leu Trp Ala Phe

Cys Cys;

HNP-3:
Asp Cys Tyr Cys Arg Ile Pro Ala Cys (SEQ ID NO: 10)

Ile Ala Gly Glu Arg Arg Tyr Gly Thr

Cys Ile Tyr Gln Gly Arg Leu Trp Ala

Phe Cys Cys;

NP-1 (rabbit neutrophil peptide 1):
Val Val Cys Ala Cys Arg Arg Ala Leu (SEQ ID NO: 11)

Cys Leu Pro Arg Glu Arg Arg Ala Gly

Phe Cys Arg Ile Arg Gly Arg Ile His

Pro Leu Cys Cys Arg Arg;

and the BNP-1 (bovine neutrophil peptide) sequence:

Arg Leu Cys Arg Val Val Ile Arg Val (SEQ ID NO: 12)

Cys Arg.

Other defensins and defensin analogs, such as those described in Selsted et al, J. Clin. Invest. 76, 1436–1439 (October 1985), and Kagan et al, Proc. Natl. Acad. Sci. USA 87, 210–214 (January 1990), each of which is incorporated in its entirety herein by reference, are also useful in the present invention.

Tachyplesins, such as tachyplesin I and II, and polyphemusins, such as polyphemusin I and II, are defensin-like peptides. See, e.g., Ohta et al, Antimicrobial Agents and Chemotherapy 36 (No. 7), 1460–1465 (July 1992), which is incorporated in its entirety herein by reference. These peptides and antimicrobially active derivatives thereof are also contemplated as being useful in the present invention.

Other peptides, such as hybrids (peptides comprised of

or more of the L-amino acids are replaced with other L-amino acids, can also be used with advantage provided that they retain sufficient antimicrobial activity.

Exemplary hybrid peptides include cecropin A-(1–8)-melittin-(1–18)-NH_2:

Lys Trp Lys Leu Phe Lys Lys Ile Gly (SEQ ID NO:13)

Ile Gly Ala Val Leu Lys Val Leu Thr

Thr Gly Leu Pro Ala Leu Ile Ser-NH_2;

and cecropin A-(1–3)-melittin-(1–13)-NH_2:

Lys Trp Lys Gly Ile Gly Ala Val Leu (SEQ ID NO:14)

Lys Val Leu Thr Thr Gly Leu-NH_2.

Melittin itself, however, is unsuitable for use due to its high toxicity.

Antimicrobial peptide mimetics are also contemplated for use with the present invention. Antimicrobial peptide mimetics may have a lower molecular weight than an average size antimicrobial peptide. These peptides may comprise components such as modified thiazole and/or oxazole moieties. Antimicrobial peptide mimetics may be membrane active molecules that function by disrupting cell membranes. At least one type of antimicrobial peptide mimetic can be obtained from Genaera Corp., Plymouth Meeting, Pa.

The antimicrobial agents must be compatible with the composition being preserved. The antimicrobial peptides should also be non-toxic to humans.

Antimicrobial agents useful according to the present invention can be prepared using techniques well known to those skilled in the art. For example, antimicrobial peptides can be prepared by solid-phase synthesis or using heterologous gene expression. Exemplary processes for preparing antimicrobial peptides are given in Wade et al, Proc. Natl. Acad. Sci. USA 87, 4761–4765 (June 1990), Bessale et al, FEBS Letters 274, No. 1,2, 151–155 (November 1990), and Biochem. Biophys. Res. Commun. 277(3) 675–580 (November 2000) each of which is incorporated herein by reference in its entirety.

A second antimicrobial component can be employed in the present invention that is other than the first antimicrobial component. This second antimicrobial component can be selected from substantially non-oxidative antimicrobial components and mixtures thereof.

As used herein, substantially non-oxidative antimicrobial components include effectively non-oxidative organic chemicals, for example, synthetic polymers, which derive their antimicrobial activity through a chemical or physiochemical interaction with the microbes or microorganisms. Suitable non-oxidative antimicrobial components include, but are not limited to, quaternary ammonium salts used in ophthalmic applications such as poly[dimethylimino-2-butene-1,4-diyl]chloride, alpha-[4-tris(2-hydroxyethyl) ammonium]-dichloride (chemical registry number 75345-27-6, available under the trademark polyquarternium 1® from ONYX Corporation), benzalkonium halides, and bigu-

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