

The present invention relates to solutions for cleaning or preserving a soft contact lens, comprising a surfactant which also serves as a solution preservative.

A number of contact lens cleaner solutions are already known. Generally, such solutions contain sorbic acid, thimerosal, chlorhexidine, a polyquaternary germicide, a synthetic antibiotic or a conventional quaternary germicide, such as benzalkonium chloride, as a preservative agent. However, these conventional preservatives have drawbacks that restrict their use. For example, sorbic acid customarily contains formaldehyde residues; thimerosal in some patients acts as an allergy sensitizer; chlorhexidine is relatively toxic; and benzalkonium chloride, over a period of time, will tend to accumulate in soft hydrophilic contact lens materials and be released to the cornea to cause eye irritation.

US-PS 4,046,706 discloses the use of certain amphoteric imidazole surfactants in lens-cleaning solutions. Such solutions normally also require the presence of a germicidal preservative agent of the type discussed above.

Surprisingly and unexpectedly, it has now been found that, while the amphoteric surfactants to be used according to the invention contain a quaternary nitrogen, they do not appreciably accumulate in conventional hydrophilic soft contact lenses. This is in clear contrast to conventional quaternary germicides, such as benzalkonium chlorides (i.e. alkyl-substituted dimethylbenzylammonium chloride wherein alkyl is a mixture of C₈ to C₁₈ alkyl moieties), cetylpyridinium chloride and dodecyltriethanolamine hydrochloride, which tend to accumulate in hydrophilic soft contact lens materials. Moreover, the amphoteric surfactants according to the

invention do not tend to accumulate in the eye and are customarily less irritating than the conventional quaternary germicides.

Compounds such as the amphoteric surfactants used in accordance with the invention have already been disclosed by Riedhammer (US-A-4,354,952) as a constituent of solutions for disinfecting and preserving contact lenses. However, those solutions necessarily contain chlorhexidine or a salt thereof. Although, according to Riedhammer, relatively small amounts of chlorhexidine are sufficient, that is only true when specific, low-dose combinations of three different constituents are used as anti-microbial agent, namely chlorhexidine, amphoteric surfactant and nonionic surfactant. By contrast, according to the present invention a preservative agent such as chlorhexidine is not used, since, surprisingly, certain amphoteric surfactants on their own are suitable as preservative agents.

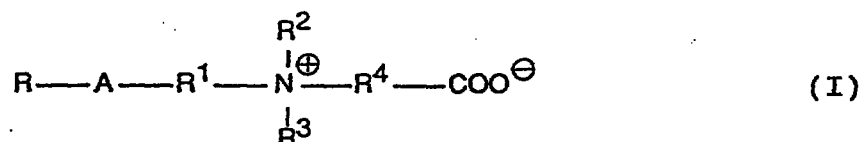
It is therefore an object of the present invention to overcome the various drawbacks associated with the use of the soft contact lens cleaning solutions hitherto known.

It is a further object of the present invention to provide a method of cleaning and preserving soft hydrophilic contact lenses using an amount of the amphoteric surfactants according to the invention that is effective in view of the desired properties.

It is yet a further object of the present invention to provide compositions useful in such methods, and processes for their preparation.

The present invention therefore relates to an aqueous self-preserving soft contact lens cleaning or preserving

solution comprising, as its only preservative agent, an effective surfactant and solution-preserving amount of a water-soluble amphoteric surfactant of the formula I



wherein R is alkyl, alkenyl or alkanedienyl of 6 to 18 carbon atoms, each of those radicals being unsubstituted or substituted by halo, hydroxy or amino; A is -O-, -S-, -C(O)O- or -C(O)NR'- where R' is hydrogen or lower alkyl; R¹ is alkylene of 2 to 6 carbon atoms which is unsubstituted or substituted by hydroxy; R² and R³ are independently hydrogen or lower alkyl which is unsubstituted or substituted by carboxy or by one or two hydroxyls, one of which may be esterified with phosphoric or sulfuric acid; and R⁴ is alkylene of up to 3 carbon atoms which is unsubstituted or substituted by hydroxy; or an ophthalmologically acceptable salt thereof, as well as an ophthalmologically acceptable water-soluble salt which is compatible with ocular tissue, in such an amount to provide a solution salt content equivalent in tonicity to about 0.5 to about 2 % by weight sodium chloride.

When A is -C(O)O- or -C(O)NR'-, the carbonyl group of that bivalent radical is preferably attached to the radical R.

Alkyl of 6 to 18 carbon atoms has preferably 8 to 18 carbon atoms and is e.g. octyl, decyl, undecyl, dodecyl, tridecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, or a mixture thereof.

Alkenyl of 6 to 18 carbon atoms has preferably 8 to 18

carbon atoms and is e.g. octenyl, decenyl, undecenyl or heptadecenyl, such as heptadec-8-enyl.

Accordingly, when A is $-C(O)NH-$, the partial structure R-A- of the compounds of formula I is represented e.g. by C_{11} - C_{17} alkylcarbonylamino or C_{17} alkenylcarbonylamino, such as lauroylamino, myristoylamino, palmitoylamino, stearoylamino, oleoylamino, or a mixture thereof, such as cocoylamino. The latter is also called cocoamido, is an extract from natural sources and has an average of 12 carbon atoms.

Halo is e.g. fluoro, iodo, or preferably chloro and bromo.

Lower alkyl has e.g. up to 7 carbon atoms, preferably up to 4 carbon atoms, and is e.g. methyl, ethyl, propyl, butyl or tert-butyl.

Alkylene of 2 to 6 carbon atoms is e.g. 1,2-ethylene, 1,3-propylene or 1,4-butylene. Those alkylene groups may be substituted by hydroxy, such that e.g. hydroxypropylene or hydroxybutylene results, preferably 2-hydroxy-1,3-propylene.

Preferably A is $-C(O)NH-$ and R^1 is alkylene of 2 to 3 carbon atoms.

R^2 and R^3 are preferably independently lower alkyl which is unsubstituted or mono- or di-substituted by hydroxy, one hydroxy of which may be esterified with phosphoric acid to form the corresponding mono-, di- or tri-organo-phosphate ester.

R^4 is preferably unsubstituted alkylene of up to 3 carbon atoms and, most preferably, is methylene, 1,2-ethylene,

1,1-ethylene, 1,3-propylene or 1,2-propylene. In an alternative preferred embodiment, R^4 is 2-hydroxy-1,3-propylene.

Preferred are solutions comprising, as their only preservative agent, a surfactant of formula I wherein R is alkyl or alkenyl of 11 to 17 carbon atoms, A is -O- or -C(O)NH-, the carbonyl group of which is attached to R, R^1 is alkylene of 2 or 3 carbon atoms which is unsubstituted or substituted by hydroxy, R^2 and R^3 are independently lower alkyl which is unsubstituted or monosubstituted by carboxy or mono- or di-substituted by hydroxy, one hydroxy of which may be esterified with phosphoric acid to form the corresponding triorganophosphate, and R^4 is alkylene of up to 3 carbon atoms, or an ophthalmologically acceptable salt thereof.

Especially preferred are solutions comprising, as their only preservative agent, a surfactant of formula I wherein R is alkyl of 11 to 17 carbon atoms or alkenyl of 17 carbon atoms, A is -C(O)NH-, the carbonyl group of which is attached to R, R^1 is alkylene of 2 or 3 carbon atoms, R^2 and R^3 are independently lower alkyl which is unsubstituted or monosubstituted by hydroxy, which may be esterified with phosphoric acid to form the corresponding triorganophosphate, and R^4 is alkylene of up to 3 carbon atoms, or an ophthalmologically acceptable salt thereof.

Another preferred group includes solutions comprising, as their only preservative agent, a surfactant of formula I wherein R is alkyl or alkenyl of 8 to 12 carbon atoms, A is -C(O)NH-, the carbonyl group of which is attached to R, R^1 is alkylene of 2 or 3 carbon atoms, R^2 and R^3 are independently lower alkyl, and R^4 is alkylene of up to 3 carbon atoms, or an ophthalmologically acceptable salt thereof.

Preferred compounds of formula I are, for example:

N-lauroylaminopropyl-N,N-dimethylglycine;
N-cocoylaminopropyl-N,N-dimethylglycine;
N-lauroylaminopropyl-N-carboxymethyl-N-hydroxyethyl-
glycine;
N-oleoylaminopropyl-N-carboxymethyl-N-hydroxyethyl-
glycine;
N-3-dodecyloxy-2-hydroxypropyl-N,N-dimethylglycine;
N-cocoylaminopropyl-N-hydroxyethyl-3-aminopropionic acid;
and
tris-[3-(N-cocoylaminoethyl-N-hydroxyethyl-N-carboxy-
methyl)amino-2-hydroxypropanol]phosphate.

Especially preferred are N-lauroylaminopropyl-N,N-
dimethylglycine; N-cocoylaminopropyl-N,N-dimethylglycine
and tris-[3-(N-cocoylaminoethyl-N-hydroxyethyl-N-carboxy-
methyl)amino-2-hydroxypropanol]phosphate.

Suitable ophthalmologically acceptable salts are salts
formed by the compounds of formula I e.g. with sodium
chloride, and also with potassium chloride, sodium
phosphate, sodium borate, sodium bicarbonate, carbonic
acid, boric acid, diethanolamine and analogous inorganic
and organic acids, bases and salts conventionally
employed in lens-care solutions. As is known, where
salts such as sodium chloride are employed, the zwitter-
ionic internal salt form may be in equilibrium with the
corresponding double salt form.

If the solution of the invention hereinbefore or herein-
after is defined as comprising a compound of formula I or
a salt thereof, this definition is understood to include
solutions comprising two or more compounds of formula I,
two or more salts thereof, or a mixture of one or more

compounds of formula I and one or more of the salts thereof.

A first embodiment of this invention relates to aqueous self-preserving soft contact lens cleaning solutions. These may contain, in addition to the compound of formula I, other conventional additives and adjuvants. For example, suitable self-preserving cleaning solutions comprise, based on the total solution weight:

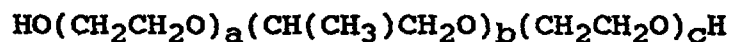
- a) between about 0.005 and about 2.0 % by weight of a compound of formula I;
- b) between 0 and about 5 % by weight of a substantially nonionic surfactant;
- c) between 0 and about 5 % by weight of a thickener;
- d) between 0 and about 1 % by weight of a chelating agent;
- e) between 0 and about 2 % by weight of a buffer;
- f) between 0.5 and about 2 % by weight of a water-soluble salt compatible with ocular tissue; and
- g) the remainder water.

Preferably, the compositions of the present invention contain between about 0.01 and about 0.5 % by weight, most preferably between about 0.02 and about 0.2 % by weight, of a compound of formula I.

When present, each of the components b) to f) is advantageously present in a minimum amount of about 0.01 % by weight, based on the total solution weight.

Suitable substantially nonionic surfactants for use as component b) advantageously include those nonionic surfactants which are known to be generally compatible with ocular tissue, and include physiologically acceptable poly(oxyethylene)-poly(oxypropylene) block copoly-

mers, such as those sold under the trademark PLURONIC® by Wyandotte Chemical Corporation, which may be represented empirically by the formula:



where a and c are statistically equal, the average molecular weight ranges between 2000 and 16 000, and the polyoxyethylene units constitute between about 10 and 80 % by weight of the molecule.

Also suitable are polyethoxylated alkylphenols, for example, wherein the alkyl moiety contains between about 6 and 12 carbon atoms and there are between about 3 and about 50 polyoxyethylene units per molecule, as well as the corresponding alkylated methylene bis-phenols which are polyethoxylated, such as that sold under the name TYLOXAPOL® by Ruger Chemical Company.

Also suitable are polyethoxylated fatty alcohols, fatty acids and fatty amines, e.g. those wherein the alkyl moiety contains between 6 and 18 carbon atoms and the molecule contains an average of between about 3 and about 50 polyoxyethylene units. Preferably, the compositions comprise between 0 and about 0.5 % by weight of component b).

Suitable thickeners c) include those conventionally employed in ophthalmic formulations, for example hydroxyethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol and the like. Preferably, a thickener is present in an amount between 0 and about 2 % by weight, more preferably between 0 and about 1.5 % by weight.

Suitable chelating agents d) include conventional

chelating agents such as ethylenediaminetetraacetic acid (EDTA) and the alkali metal salts, e.g. the di- and tri-sodium salts, thereof, and tri(hydroxymethyl)amino-methane. Preferably, the chelating agent is present in an amount between 0 and about 0.7 % by weight.

Suitable buffers e) include alkali metal phosphates, citrates, borates, tartrates, acetates, carbonates, bicarbonates and the corresponding mixtures thereof with acids, such as phosphoric acid, citric acid, boric acid, tartaric acid, and mixtures thereof. Preferably, buffers are present in an amount between 0 and about 1 % by weight.

Suitable water-soluble salts f) compatible with ocular tissue include especially those salts conventionally employed in preparing solutions having a salt content equivalent to up to about 0.9 % sodium chloride. Preferred salts are alkali metal halides, sulfates, nitrates and phosphates, especially sodium chloride, potassium chloride and mixtures thereof.

Another embodiment of the invention relates to aqueous self-preserving soft contact lens preserving solutions. These also contain a solution-preserving amount of the compound of formula I and a sufficient amount of a water-soluble salt which is compatible with ocular tissue to provide a solution salt content equivalent in tonicity to about 0.5 to about 2 % by weight sodium chloride.

In this embodiment, it is preferred to have a salt content which provides a solution salt content equivalent in tonicity to between about 0.7 and about 1.8 % by weight, and most preferably between about 0.7 and about 1.0 % by weight, sodium chloride.

Suitable salts which may be employed in adjusting the tonicity include alkali metal halides, sulfates, nitrates, phosphates and the like, especially the sodium and potassium salts thereof and most preferably sodium chloride, potassium chloride and mixtures thereof.

The lens preserving and storing solutions may in principle comprise the same additives and adjuvants in the same amounts as mentioned above in connection with the self-preserving contact lens cleaning solutions, except that the lens preserving and storing solutions advantageously comprise a sufficient amount of component f) to provide a solution salt content equivalent in tonicity to between about 0.7 and about 1.8 % by weight sodium chloride.

The solutions according to the invention are suitable for cleaning proteinaceous, lipid and other non-proteinaceous deposits which normally accumulate on conventional hydrophilic soft contact lenses. These deposits, which are derived from mucus, oils, cosmetics, protein from tear fluid, and the like, unless removed, will tend to accumulate on the lenses, reducing their life and their optical clarity. The present compositions are highly useful in removing and dissolving such deposits, while at the same time being physiologically tolerable and self-preserving.

Furthermore, the preferred lens storing and preserving solutions according to the invention are additionally advantageous in that the tonicity of such compositions, coupled with the non-irritating nature of the compounds of formula I to the eye, and their reduced tendency to accumulate in soft hydrophilic contact lens materials, makes such compositions highly suitable as a medium for preserving lenses, from which a lens can be placed

directly into the eye without rinsing with a conventional saline solution.

The compositions of the present invention are prepared from materials known per se. Thus, the compounds of formula I belong to a known class of amphoteric surfactants. The compositions may be prepared by conventionally mixing the ingredients.

It is a further object of the invention to provide a method of cleaning a soft contact lens comprising intimately contacting said soft contact lens with an aqueous solution comprising an effective surfactant and solution-preserving amount of a water-soluble surfactant of formula I. A convenient method of cleaning contact lenses according to the invention is e.g. to place the lens in the palm of the hand, place a few drops of solution on each lens surface, rub the lens surfaces with the forefinger or between the thumb and forefinger, and rinse with additional solution.

It is another object of the invention to provide a method of preserving a soft contact lens by storing said lens in a solution comprising a solution-preserving amount of the compound of formula I and a sufficient amount of a water-soluble salt which is compatible with ocular tissue to provide a solution salt content equivalent in tonicity to about 0.5 to about 2 % by weight sodium chloride.

The following Examples are for illustrative purposes only and are not intended to limit the scope of the invention. All percentages and parts are by weight unless otherwise specified.

Example 1: 0.5 ml of an aqueous solution comprising 30 percent by weight N-cocoylaminopropyl-N,N-dimethylglycine (Monateric[®] CAB by Mona Industries, Inc.) is combined with 2.613 g of sodium chloride, 1.25 g of sodium tetraborate, 1.75 g of boric acid, 1.0 ml of tyloxapol, 3.5 g of hydroxyethylcellulose and 2.5 g of disodium edetate. Water is added to a total solution volume of 500 ml, with stirring. The resulting solution is sterile-filtered using ultrafiltration to obtain a solution having a pH of 7.2 and an osmolarity of 304.

Example 2: 0.5 ml of an aqueous solution comprising 30 percent by weight N-lauroylaminopropyl-N,N-dimethylglycine (Monateric[®] LMAB) is combined with 2.685 g of sodium chloride, 1.25 g of tyloxapol, 3.5 g of hydroxyethylcellulose and 2.5 g of disodium edetate. Water is added to a total solution volume of 500 ml, with stirring. The resulting solution is sterile-filtered using ultrafiltration to obtain a solution having a pH of 7.2 and an osmolarity of 298.

Example 3: 0.5 ml of an aqueous solution comprising 30 percent by weight N-cocoylaminopropyl-N,N-dimethylglycine is combined with 3.45 g of sodium chloride, 0.7 g of sodium tetraborate, 2.7 g of boric acid and 1.0 g of disodium edetate. Water is added to a total solution volume of 500 ml, with stirring. The resulting solution is sterile-filtered using ultrafiltration to obtain a solution having a pH of 7.2 and an osmolarity of 306.

Example 4: 0.5 ml of an aqueous solution comprising 30 percent by weight N-lauroylaminopropyl-N,N-dimethylglycine is combined with 3.18 g of sodium chloride, 0.7 g of sodium tetraborate, 2.7 g of boric acid and 1.0 g of disodium edetate. Water is added to a total solution volume of 500 ml, with stirring. The resulting solution

is sterile-filtered using ultrafiltration to obtain a solution having a pH of 7.21 and an osmolarity of 310.

Example 5: 0.3 g of an aqueous solution comprising 30 percent by weight tris-[3-(N-cocoylaminoethyl-N-hydroxyethyl-N-carboxymethyl)amino-2-hydroxypropanol]-phosphate (Monaquat P-TL by Mona Industries, Inc.) is combined with 0.24 g of tris(hydroxymethyl)aminomethane, 1.0 g of boric acid and 0.36 g of sodium chloride and diluted with sufficient water to obtain a total solution volume of 100 ml.

Example 6: 1.5 g of an aqueous solution comprising 30 percent by weight N-lauroylaminopropyl-N,N-dimethylglycine are combined with 2.685 g of sodium chloride, 1.25 g of sodium tetraborate, 1.75 g of boric acid, 1.0 g of tyloxapol, 3.5 g of hydroxyethylcellulose and 2.5 g of disodium edetate. Sufficient water is added with stirring to obtain a total solution volume of 500 ml. The pH of the solution is 7.43, which is adjusted with 0.5N HCl to a pH of 7.23.

Example 7: The procedure of Example 6 is repeated and identical amounts of ingredients are used, except that 2.5 g of an aqueous solution comprising 30 percent by weight N-lauroylaminopropyl-N,N-dimethylglycine is employed. Upon dilution to 500 ml with water, the pH is 7.4, which is adjusted with 0.5N HCl to a pH of 7.20.

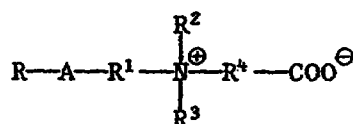
Example 8: 1.5 g of an aqueous solution comprising 30 percent by weight N-lauroylaminopropyl-N,N-dimethylglycine are combined with 1 g of disodium edetate, 2.7 g of boric acid, 0.70 g of sodium borate and 3.15 g of sodium chloride and diluted with sufficient water, with stirring, to make a total solution volume of 500 ml. The solution has a pH of 7.22 and an osmolarity of 319.

Example 9: The compositions of Examples 6, 7 and 8 are evaluated in accordance with the modified Draize rabbit eye test (Food, Drug and Cosmetic Law Reports 233) in order to assess potential irritation. The three solutions are each determined to be "non-irritating" in this test.



Patent claims for all designated Contracting States
except AT and ES

1. An aqueous self-preserving soft contact lens cleaning or preserving solution comprising, as its only preservative agent, an effective surfactant and solution-preserving amount of a water-soluble amphoteric surfactant of the formula I



wherein R is alkyl, alkenyl or alkanedienyl of 6 to 18 carbon atoms, each of those radicals being unsubstituted or substituted by halo, hydroxy or amino; A is -O-, -S-, -C(O)O- or -C(O)NR'- where R' is hydrogen or lower alkyl; R¹ is alkylene of 2 to 6 carbon atoms which is unsubstituted or substituted by hydroxy; R² and R³ are independently hydrogen or lower alkyl which is unsubstituted or substituted by carboxy or by one or two hydroxyls, one of which may be esterified with phosphoric or sulfuric acid; and R⁴ is alkylene of up to 3 carbon atoms which is unsubstituted or substituted by hydroxy; or an ophthalmologically acceptable salt thereof, as well as an ophthalmologically acceptable water-soluble salt which is compatible with ocular tissue, in such an amount to provide a solution salt content equivalent in tonicity to about 0.5 to about 2 % by weight sodium chloride.

2. A solution according to claim 1 wherein R is alkyl or alkenyl of 11 to 17 carbon atoms, A is -O- or -C(O)NH-, the carbonyl group of which is attached to R, R¹ is alkylene of 2 or 3 carbon atoms which is unsubstituted or substituted by hydroxy, R² and R³ are independently lower alkyl which is unsubstituted or monosubstituted by



carboxy or mono- or di-substituted by hydroxy, one hydroxy of which may be esterified with phosphoric acid to form the corresponding triorganophosphate, and R^4 is alkylene of up to 3 carbon atoms.

3. A solution according to claim 1 wherein R is alkyl of 11 to 17 carbon atoms or alkenyl of 17 carbon atoms, A is $-C(O)NH-$, the carbonyl group of which is attached to R, R^1 is alkylene of 2 or 3 carbon atoms, R^2 and R^3 are independently lower alkyl which is unsubstituted or monosubstituted by hydroxy, which may be esterified with phosphoric acid to form the corresponding triorganophosphate, and R^4 is alkylene of up to 3 carbon atoms.

4. A solution according to claim 1 wherein R is alkyl or alkenyl of 8 to 12 carbon atoms, A is $-C(O)NH-$, the carbonyl group of which is attached to R, R^1 is alkylene of 2 or 3 carbon atoms, R^2 and R^3 are independently lower alkyl, and R^4 is alkylene of up to 3 carbon atoms.

5. A solution according to claim 1 wherein the compound of formula I is selected from the group consisting of N-lauroylaminopropyl-N,N-dimethylglycine; N-cocoylamino-propyl-N,N-dimethylglycine and tris-[3-(N-cocoylamino-ethyl-N-hydroxyethyl-N-carboxymethyl)amino-2-hydroxy-propanol]phosphate.

6. The solution of claim 1 comprising:

- a) between about 0.005 and about 2.0 % by weight of a compound of formula I;
- b) between 0 and about 5 % by weight of a substantially nonionic surfactant;
- c) between 0 and about 5 % by weight of a thickener;
- d) between 0 and about 1 % by weight of a chelating agent;
- e) between 0 and about 2 % by weight of a buffer;



f) between 0.5 and about 2 % by weight of a water-soluble salt compatible with ocular tissue; and
g) the remainder water.

7. The solution of claim 6 having a salt content equivalent to up to about 0.9 % sodium chloride.

8. The use of a solution according to claim 6 for preserving soft contact lenses.

9. The use of a solution according to claim 7 for cleaning soft contact lenses.

10. A method of cleaning or preserving a soft contact lens, comprising intimately contacting said soft contact lens with a solution according to claim 1.

11. A process for the manufacture of a solution according to claim 1 by conventionally mixing the ingredients.