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(54) OPTHALMIC COMPOSITION INCLUDING A CATIONIC GLYCOSIDE AND AN ANIONIC THERAPEUTIC AGENT

OPHTHALMISCHE ARZNEIZUBEREITUNG ENTHALTEND EIN KATIONISCHES GLYCOSID UND EIN ANIONISCHES ARZNEIMITTEL

COMPOSITIONS OPHTALMIQUES A GLYCOSIDE CATIONIQUE ET AGENT THERAPEUTIQUE ANIONIQUE

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(56) References cited:
EP-A- 0 584 692
WO-A-95/00615
DE-A- 4 327 699

EP-A- 0 590 655
WO-A-97/23131
US-A- 4 913 743

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The present invention relates to ophthalmic compositions containing a cationic glycoside in combination with a therapeutic agent. In particular, the cationic glycoside can be used to improve the efficacy of an anionic therapeutic agent or an anionic polymer delivery vehicle in combination with a therapeutic agent. The present composition can be applied to the eye or to a silicone-containing contact lens.

In administering therapeutic agents to the eye, a variety of factors, including consistency and accuracy of dosage, type and time of vision interference, ease of administration, and timing of delivery can be important. Prior ophthalmic delivery vehicles have suffered drawbacks in one or more respects and, in any case, improvement in performance is always desirable. New topical ophthalmic delivery systems for controlled, sustained release of therapeutic agents are, therefore, continually being developed. It is especially challenging to find an ophthalmic delivery vehicle that is safe and effective for human use and that does not have undesirable side effects or cause undesirable interactions between components in a solution, particularly when limited to use in buffered solutions having osmolality values most common for in-eye solutions (typically from 270 to 330 mOsmols/kg).
SUMMARY OF THE INVENTION

[0009] The present invention provides a means for prolonging the association of a therapeutic agent with the surface of the eye and/or a contact lens in the eye, thereby increasing the beneficial effect offered by the therapeutic agent. In particular, the present invention utilizes quaternary nitrogen-containing ethoxylated glycosides to tether a therapeutic agent to the surface of the eye or to a contact lens. In one embodiment of the invention, the glycoside is used in combination with an anionic therapeutic agent. In a second embodiment of the invention, the glycoside is used in combination with both an anionic polymer and a therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

[0010] As indicated above, the present invention is directed to ophthalmic compositions and their use for the treatment of eyes with therapeutic agents. The invention utilizes a cationic glycoside which is believed to act as a cationic tether, holding an anionic therapeutic agent, or an anionic delivery vehicle for a therapeutic agent, in association with the surface of the eye and/or a contact lens that is worn in the eye. The subject glycoside is non-polymeric and soluble in buffered aqueous solutions when combined with the subject anionic compounds, as described below.

[0011] The cationic glycosides employed in the present invention are described in detail in US Patent No. 5,405,878. These glycosides can be described as quaternary nitrogen-containing ethoxylated glycosides represented. A particularly preferred class of compounds is by Formula (I):

\[
\begin{align*}
R_1 & \quad O \\
(CH_2)_wO(CH_2CH_2O)_xR_3 & \\
R_2(OCH_2CH_2)wO & \\
O(CH_2CH_2O)_yR_4 & \\
O(CH_2CH_2O)_zR_5 &
\end{align*}
\]

wherein \( R_1 \) is alkyl, preferably \( C_1-C_{18} \); the average sum of \( w, x, y, \) and \( z \) per mole of compound is within the range of about 1 to about 200, preferably about 4 to about 20; \( n \) is 0 or 1; \( R_2, R_3, R_4, \) and \( R_5 \) are individually hydrogen or quaternary nitrogen-containing groups; provided that at least one of \( R_2, R_3, R_4, \) or \( R_5 \) is a quaternary nitrogen-containing group and that at least one of \( R_2, R_3, R_4, \) or \( R_5 \) is hydrogen. Representative quaternary nitrogen-containing groups for \( R_2, R_3, R_4, \) and \( R_5 \) are represented by Formula (II):

\[
\begin{align*}
R_7 & \\
CH_2R_6 & \\
N^+R_8X^- & \\
R_9 &
\end{align*}
\]

wherein \( R_6 \) is a \( C_1-C_4 \) hydroxyalkylene; \( R_7, R_8, \) and \( R_9 \) are an alkyl from \( C_1-C_{16} \); and \( X \) is an anion, preferably a halide. Especially preferred compounds of Formula (I) include compounds wherein \( R_1 \) is methyl, each of \( R_2, R_3, \) and \( R_4 \) is individually hydrogen or quaternary nitrogen-containing group and that at least one of \( R_2, R_3, R_4, \) or \( R_5 \) is hydrogen. Representative quaternary nitrogen-containing groups for \( R_2, R_3, R_4, \) and \( R_5 \) are represented by Formula (II).

[0012] Such quaternary nitrogen-containing ethoxylated glycosides are commercially available or can be prepared by methods known in the art, such as the methods described in US Patent No. 5,138,043 to Polovsky et al. An especially preferred material is available under the CTFA designation lauryl methyl gluceth-10 hydroxypropylidonium chloride, including the product commercially available under the tradename Glucquat-100® (from Amerchol Corp., Edison, NJ).

[0013] The cationic glycoside of the present invention may be employed in the subject compositions at about 0.001 to about 10 weight percent, and preferably at about 0.001 to about 0.5 weight percent.

[0014] As mentioned above, the subject glycoside-containing compositions may be used in the treatment of the eye with a therapeutic agent, including both ophthalmic drugs and dry-eye agents. In particular, the subject glycosides are especially effective in prolonging the effect of anionic therapeutic agents that adhere to, or associate with, the eye and/
or a contact lens by means of the subject cationic glycosides. Examples of preferred anionic therapeutic agents are anionic polysaccharides, including glycosaminoglycans such as hyaluronic acid and derivatives thereof, chondroitin sulfate, carboxymethylcellulose (CMC), and algin. Various glycosaminoglycans are listed in U.S. patent no. 5,358,706. Hyaluronic acid is an anionic biopolymer that has been identified as useful in the treatment of the symptoms of dry eye. Synthetic anionic polymers for the treatment of dry eye can also be used in combination with the above-described glycoside, including the carboxy vinyl polymers known as Carbopol®, commercially available from B.F. Goodrich, as described in U.S. Patent No. 5,209,927 to Gressel et al.

[0015] The glycoside and the anionic therapeutic agent used in the present composition are soluble in buffered aqueous solutions which have osmolality values in the range of about 250 to about 350 mOsmols/kg.

[0016] Compositions of the present invention typically include from about 0.0001 to about 5 weight percent, and preferably from 0.01 to 2.0 weight percent, based on the total weight of the composition of at least one therapeutic agent. The ratio of the glycoside to the therapeutic agent may vary widely. Generally, an effective amount, which is defined as the amount of the glycoside sufficient to provide substantivity to a contact lens and/or the mucosal surface of the eye. In general, the relative weight ratio of glycoside to therapeutic agent may range from 0.01:1 to about 200:1.

[0017] In still another embodiment of the invention, a cationic glycoside may be combined with an anionic polymeric carrier or delivery vehicle that promotes a sustained or delayed release of an ophthalmic drug. Such anionic polymers include carboxy containing polymers, for example, as disclosed in U.S. Patent No. 5,192,535 to Davis et al. and U.S. Patent No. 5,461,081 to Ali et al. Preferred anionic polymeric carrier are the carboxy vinyl polymers available from B. F. Goodrich under the product name Carbopol®. Such polymers may be used in combination with oppositely charged electrolytes as disclosed in U.S. Patent No. 5,521,222. Combinations of polymers may be employed, as disclosed in U.S. Patent No. 5,077,033. The composition may be in the form of a solution or gel.

[0018] The amount of the anionic polymer in the composition may also vary widely. Typically, the amount of the polymer is at least about 0.0005 weight percent, preferably from about 0.00025 to about 20.0 weight percent, and most preferably from about 0.005 to 10 weight percent. The amount, however, will depend on whether other polymers are included and whether the composition is in the form of a gel or solution and the specific method of topical application to the eye.

[0019] The present invention may be practiced in a number of different embodiments. In one embodiment, a composition according to the present invention is applied to a contact lens, either before or after the lens is placed in the eye. In particular, the present invention is suitable for application to a silicone-containing lens, either a rigid gas permeable (RGP) lens or a high Dk (extended wear) silicone-containing hydrogel lens. An example of a silicone-containing hydrogel material is disclosed in U.S. Patent No. 5,260,000.

[0020] The composition may be applied to a lens before the lens is placed in the eye. Optionally, the lens can be first contacted with an aqueous solution of the subject cationic glycosides to form a thin cationic coating on the lens surface and subsequently contacted with an aqueous solution of one or more anionic therapeutic agents, or an anionic delivery vehicle in combination with one or more therapeutic agents, thus forming an outer anionic coating on the lens surface. Alternatively, a contact lens can be treated with an aqueous composition comprising a mixture of a cationic glycoside and one or more anionic therapeutic agents or a mixture of a cationic glycoside, an anionic delivery vehicle, and one or more therapeutic agents. Such compositions may, of course, include other conventional or monographed constituents such as thickeners, comfort agents, and stabilizers, including polyols such as glycerin.

[0021] Contact lenses may be contacted or treated with the subject compositions in the form of an aqueous solution, for example, by storing or soaking the contact lens in the solution or by spraying the lens with the solution for sufficient time to wet the surfaces thereof. The treated lens can be placed directly in the eye or, alternately, the lens can be first rinsed before being placed in the eye. Drops of subject solution can be placed on the lens surface and the treated lens placed in the eye, or the subject composition may be directly applied to the eye in the form of eye-drops while the contact lens is being worn. The specific lens care regimen used may depend on the other compounds or ingredients present in the solution, as will be appreciated by those skilled in the art.

[0022] In another embodiment of the invention, a composition according to the present invention is placed or instilled directly in the eye, for example, by means of eye drops independent, or in the absence, of contact lenses. In this embodiment, the anionic surface of the eye, especially the cornea, is the target for adherence of the cationic glycoside.

[0023] By the term “therapeutic agents” herein is broadly meant ingredients which treat, diagnose, or prevent disorders or diseases of the eye. Therapeutic agents include agents such as lubricants or humectants that can treat or alleviate the symptoms of dry eye, as well as ophthalmic drugs. Ophthalmic drugs that may be used in compositions according to the present invention include known or conventional anti-inflammatory agents, anti-infection agents, glaucoma agents, imaging agents, and wound-healing agents. Illustrative anionic drugs that can be combined with the subject glycoside include, as listed in U.S. Patent No. 5,358,706 to Marlin et al., anti-inflammotary agents such as prostaglandins and derivatives, salicylic acid, propionic acid, fenemates such as anthranilic acid derivatives and cro- moly; anti-infective agents such as beta lactam antibiotics, glaucoma agents such as carbonic anhydrase inhibitors, imaging agents such as fluorescein and derivatives, and wound healing agents such as peptide growth factors. In
embodiments employing an anionic delivery vehicle, it is not necessary to limit the therapeutic agent to anionic compounds and illustrative drugs include antibiotics, antivirals, steroids, aminosubstituted steroids, polypeptides, cardiotonics, antihypertensives, anti-allergies, alpha- and beta-adrenergic blocking agents, anti-cataract agents, anti-glaucoma agents, anti-inflammatory agents, and anesthetic agents. Examples of specific drugs are listed in U.S. Patent No. 5,192,535 to Davis et al. Therapeutic agents or their pharmaceutically acceptable salt may be used.

[0024] Yet another aspect of the present invention is directed to a method for treating dry eye comprising topically administering to the eye of a patient suffering from dry eye a composition comprising a therapeutically effective amount of a sterile, aqueous composition comprising 0.001 to 10 percent by weight of the composition of a quaternary nitrogen-containing ethoxylated glycoside in combination with an effective amount of an anionic polymer that is a therapeutic agent effective in treating dry eye or keratoconjunctivitis sicca. The method preferably involves applying a solution or gel of the composition directly to the eye, preferably in the form of eye drops, either in the presence or the absence of a contact lens in the eye. Alternatively, a contact lens may be contacted with the composition before the contact lens is placed in the eye. The anionic polymer may be a polysaccharide, preferably a glycosaminoglycan such as hyaluronic acid, xanthan gum, or derivatives and/or salts of the foregoing. Alternatively, the anionic polymer may be a suitable synthetic polymer selected from the group consisting of carboxomers and polyacrylic acids. Examples of such therapeutic agents can be found, for example, in U.S. Patent No. 5,106,615 to Dickstein et al. and numerous other patents and literature references. Examples of polysaccharides may be found, for example, in IL FARMACO, 50 (9), 633-642 (1995), in the article by Albasini, Marco et al.

[0025] Compositions of the present invention may include additional constituents. For example, typical compositions include buffering agents for buffering or adjusting the pH of the composition, and/or tonicity adjusting agents for adjusting the tonicity (osmolality) of the composition. Preferably, the pH of compositions according to the present invention, which may be in the form of a solution or gel, should be maintained within the range of 5.0 to 8.0, more preferably 6.0 to 8.0, most preferably 6.5 to 7.8. Representative buffering agents include alkali metal salts such as potassium or sodium carbonates, acetates, borates, phosphates, citrates, and hydroxides; and weak acids such as acetic, boric, and phosphoric acids. Representative tonicity adjusting agents include sodium and potassium chloride, and those materials listed as buffering agents. Generally, buffers will be present in amounts ranging from about 0.05 to 2.5 percent by weight of the composition, preferably from 0.1 to 1.5 percent. The tonicity agents may be employed in an amount effective to adjust the osmotic value of the final composition to a desired value, typically from about 250 to about 350 mOsmols/kg, in order to approximate the osmotic pressure of normal lacrimal fluids which is equivalent to a 0.9 percent solution of sodium chloride. Generally, the buffering agents and/or tonicity adjusting agents may be included up to about 10 weight percent.

[0026] In some embodiments, an antimicrobial agent is included in the composition in an antimicrobially effective amount, i.e., an amount which is effective to at least inhibit growth of microorganisms in the composition. The composition can be used to also disinfect a contact lens treated therewith. Various antimicrobial agents are known in the art as useful in contact lens solutions, including chlorhexidine (1,1’-hexamethylene-bis[5-(p-chlorophenyl)biguanide]) or water soluble salts thereof, such as chlorhexidine gluconate; polyhexamethylene biguanide (a polymer of hexamethylene biguanide, also referred to as polyaminopropyl biguanide) or water-soluble salts thereof, such as the polyhexamethylene biguanide hydrochloride available under the trade name Cosmocil CQ (ICI Americas Inc.): benzalkonium chloride; and polymeric quaternary ammonium salts. When present, the antimicrobial agent may be included at about 5 weight percent, depending on the specific agent.

[0027] The compositions may further include a sequestering agent (or chelating agent) which can be present up to about 2.0 weight percent. Examples of preferred sequestering agents include ethylenediaminetetraacetic acid (EDTA) and its salts, with the disodium salt (disodium edetate) being especially preferred.

[0028] In order that those skilled in the art can more fully appreciate the aspects of the invention, the following examples are set forth, which examples are given solely for purposes of illustration, and should not be considered as expressing limitations unless so set forth in the appended claims.

EXAMPLES

[0029] In the following examples, blanks of a commercial fluorosilicone rigid gas permeable contact lens material (Boston RXD® available from Polymer Technology Corporation of Wilmington, MA) were formulated without wetting agents. These blanks were cut into wafers and both sides were polished to an optical finish. The wafers were then soaked in deionized water overnight, and subsequently treated with various aqueous solutions as described below. After each treatment with a solution, dynamic contact angle and surface tension measurements were taken using a Cahn Instrument DCA 322. The results are provided below. A baseline aqueous buffer solution used in each of the examples below consisted of a phosphate buffer prepared comprising 0.280% sodium phosphate (dibasic), 0.055% potassium phosphate (monobasic), 0.780% sodium chloride, 0.170% potassium chloride, 0.050% disodium edetate, and a sufficient amount of deionized water to bring the total percent to 100. All percentages are weight percent, unless
otherwise indicated. The abbreviations used in the Tables below have the following meanings:

S.T. = Surface Tension (dynes/cm).
Adv = Advancing contact angle in degrees.
Rec = Receding contact angle in degrees.
Adv-Rec = Difference between advancing and receding contact angles.

EXAMPLE 1

This example illustrates the ability of a cationic glycoside to tether an anionic polymer (xanthan gum) to the surface of a contact-lens material. Xanthan gum is useful either as a vehicle for an ophthalmic drug or as a therapeutic agent for the treatment of the symptoms of dry eye. The following three solutions were prepared by adding a sufficient amount of the indicated constituent to the baseline phosphate buffer (described above) in order to achieve the final percentage indicated: (1) 0.015% Glucquat® 100 glycoside; (2) 0.015% xanthan gum; and (3) a mixture of 0.015% Glucquat® 100 glycoside and 0.015% xanthan gum. (Glucquat® 100 is a registered trademark of Amerchol for lauryl methyl gluceth-10 hydroxypropyldimonium chloride.) The above-described wafers were sequentially dipped within the solutions indicated in the Tables 1-1 through 1-4. After being treated with each solution, contact angle measurements were taken, the results of which are also provided in the Tables below.

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.T.</td>
<td>73.4</td>
<td>43.1</td>
<td>72.8</td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td>102</td>
<td>76</td>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>Rec</td>
<td>58</td>
<td>20</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Adv-Rec</td>
<td>44</td>
<td>56</td>
<td>47</td>
<td>50</td>
</tr>
</tbody>
</table>

It is evident from the lowering of the surface tension that the Glucquat® 100 glycoside is very surface active. Furthermore, lens treatment with Glucquat® 100 dramatically lowered both the advancing and receding contact angles of the treated wafers (see Condition 2). However, the adsorbed Glucquat® on the wafer surface is almost entirely removed during the first and second desorption processes (i.e. dipping the wafer in fresh buffer solutions) in that the wafer surface returns to baseline values (see Conditions 3 and 4 as compared to Condition 1 in Table 1-1).

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.T.</td>
<td>73.4</td>
<td>72.3</td>
<td>72.8</td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td>103</td>
<td>100</td>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>Rec</td>
<td>59</td>
<td>48</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Adv-Rec</td>
<td>44</td>
<td>52</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

As evident from Table 1-2 above, the surface tension of the xanthan gum solution is very close to that of the baseline phosphate buffer solution. Furthermore, the xanthan solution did not significantly lower advancing angles and had only a minor reducing effect on the receding contact angles. Given the data of Table 1-2, it would appear that the xanthan solution had little affinity for the wafer surface.
As indicated in Table 1-3 above, while the Glucquat 100® glycoside is very surface active, once the Glucquat® has been adsorbed onto the surface, exposure to an xanthan gum solution (Condition 3) appears to result in the formation of a complex on the surface wherein the receding angle is raised due to the presence of the xanthan gum polymer. The advancing/receding angles are significantly lowered in both cycles of desorption process, indicating that this surface complex is very tenacious (Conditions 4 and 5 in Table 1-3 above).

As indicated in Table 1-4 above, combining the Glucquat® glycoside and xanthan gum in the same solution produces a complex that exhibits surface activity as evidenced by the low surface-tension values. This complex adsorbs onto the wafer surface and lowers both the advancing and receding angles (Condition 2). This surface complex is very tenacious, and the receding angles in both cycles of the desorption process are stable (Condition 3 and 4).

EXAMPLE 2

This example illustrates the ability of a cationic glycoside to tether an anionic polymer (a carboxy vinyl polymer) to the surface of a contact lens material. Such polymers are useful either as a vehicle for an ophthalmic drug or as a therapeutic agent for the treatment of the symptoms of dry eye. The following three solutions were prepared by adding a sufficient amount of the indicated constituent to the baseline phosphate buffer (described above) in order to achieve the final percentage indicated: (1) 0.015% Carbopol® 971P polymer, (2) 0.015% Glucquat® 100 glycoside, and (3) a mixture of 0.015% Glucquat® 100 and 0.015% Carbopol® 971P. (Carbopol® is a trademark of B.F. Goodrich for carboxyl methacrylate copolymer that is a homopolymer of acrylic acid crosslinked with an allyl ether of pentaerythritol or an allyl ether of sucrose.)

The above-described wafers were sequentially dipped within the solutions indicated in the Tables 2-1 through 2-3 below in the same manner described with respect to Example 1. After being treated with each solution, contact angle measurements were taken, the results of which are also provided in the Tables below.

As indicated in Table 2-1 above, the surface tension of the 0.015% Carbopol® 971P carboxy polymer solution is very...
close to that of the baseline phosphate buffer solution. A concentration of 0.015% carbomer did not lower the advancing and the receding contact angles of the wafers (Condition 2 in Table 2-1). This data suggest that there was only slight or no affinity of the carbomer to the non-wetting wafer surfaces. Also both the first and the second desorption process exhibit close to baseline conditions (Conditions 3 and 4).

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Buffer</td>
<td>0.015% Glycoside</td>
<td>0.015% Carbomer</td>
<td>1st Desorption in Buffer</td>
<td>2nd Desorption in Buffer</td>
<td></td>
</tr>
<tr>
<td>S.T.</td>
<td>73.2</td>
<td>43.1</td>
<td>72.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td>103</td>
<td>75</td>
<td>84</td>
<td>90</td>
<td>91</td>
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<tr>
<td>Rec</td>
<td>53</td>
<td>21</td>
<td>33</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Adv-Rec</td>
<td>50</td>
<td>56</td>
<td>51</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

As indicated in Table 2-2 above, once the glycoside (Glucquat® 100) has been adsorbed on the surface, exposure to the carbomer (Carbopol® 971P) solution indicates the formation of a complex on the surface in that both the advancing and the receding angles are raised due to the presence of the carbomer polymer (Condition 3). In the desorption process, both cycles, indicated that the surface complex is very tenacious in that the advancing/receding angles are stable (Conditions 4 and 5).

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Buffer</td>
<td>0.015% Glycoside plus 0.015% Carbomer</td>
<td>1st Desorption in Buffer</td>
<td>2nd Desorption in Buffer</td>
<td></td>
</tr>
<tr>
<td>S.T.</td>
<td>73.2</td>
<td>45.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td>103</td>
<td>25</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Rec</td>
<td>54</td>
<td>22</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Adv-Rec</td>
<td>49</td>
<td>3</td>
<td>56</td>
<td>59</td>
</tr>
</tbody>
</table>

As indicated in Table 2-3 above, combining a glycoside (Glucquat® 100) and a carbomer (Carbopol® 971P) in the same solution produces a complex that exhibits surface activity as evidenced by the low surface tension. The complex adsorbs onto the non-wetting wafer surface as evidenced by the low advancing and receding angles (Condition 2). The complex desorbs very slowly from the wafer surface (Conditions 3 and 4).

EXAMPLE 3

This example illustrates the ability of a cationic glycoside to tether an anionic polymer (hyaluronic acid) to the surface of a contact lens material. Such polymers are particularly useful as a therapeutic agent for the treatment of the symptoms of dry eye. The following three solutions were prepared by adding a sufficient amount of the indicated constituent to the baseline phosphate buffer (described above) in order to achieve the final percentage indicated: (1) 0.015% hyaluronic acid, (2) 0.015% Glucquat® 100 glycoside, and (3) a mixture of 0.015% Glucquat® 100 and 0.015% hyaluronic acid.

The above-described wafers were sequentially dipped within the solutions indicated in the Tables 3-1 through 3-3 below in the same manner as described with respect to Example 1. After being treated with each solution, contact angle measurements were taken, the results of which are also provided in the Tables below.

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Buffer</td>
<td>0.015% Hyaluronic acid</td>
<td>1st Desorption in Buffer</td>
<td>2nd Desorption in Buffer</td>
<td></td>
</tr>
<tr>
<td>S.T.</td>
<td>73.4</td>
<td>72.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As indicated in Table 3-1 above, the surface tension of the 0.015% hyaluronic acid solution is very close to that of the baseline phosphate buffer solution. A concentration of 0.015% hyaluronic acid did not lower the advancing and the receding contact angles of the wafers (Condition 2). This suggests that there was only slight or no affinity of hyaluronic acid to the non-wetting wafer surfaces. Also both the first and the second desorption process exhibit close to baseline conditions (Conditions 3 and 4).

As indicated in Table 3-2 above, once the glycoside (Glucquat® 100) has been adsorbed on the surface of the lens material wafer, exposure to a hyaluronic acid solution indicates the formation of a complex on the surface in that both the advancing and the receding angles are raised due to the presence of the hyaluronic acid (Condition 3 in the Table). In the desorption process, both cycles indicated that the surface complex is very tenacious in that the advancing/receding angles are stable (Conditions 4 and 5).

As indicated in Table 3-3 above, combining a glycoside (Glucquat®100) with hyaluronic acid in the same solution produces a complex that exhibits surface activity as evidenced by the low surface tension. The complex adsorbs onto the non-wetting wafer surface as evidenced by the low advancing and receding angles (Condition 2 in the Table). The complex desorbs very slowly from the wafer surface (Conditions 3 and 4).

EXAMPLE 4

This example illustrates the preparation of formulations for the treatment of the symptoms of dry eye. Three formulations (Test Solutions 1-3) were prepared using the ingredients listed below in Table 4. Boston® IV and Boston RXD® lenses were soaked overnight in these test solutions. The lenses were subsequently worn by patients who were then examined by a clinician using a biomicroscope. The solutions were all found to provide a conditioned lens surface which exhibited excellent ocular compatibility. The tear film wetted the entire surface of the lenses and was even in nature. Furthermore, the relative thickness of tear film was increased, indicating that the test solutions could be used...
for treating or relieving the symptoms of dry eye or to provide an artificial tear.

<table>
<thead>
<tr>
<th>CONSTITUENT</th>
<th>Test Solution 1</th>
<th>Test Solution 2</th>
<th>Test Solution 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbomer (Carbopol® 971P)</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyaluronic acid</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>xanthan</td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>sodium chloride</td>
<td>0.45</td>
<td>0.45</td>
<td>0.85</td>
</tr>
<tr>
<td>sodium borate</td>
<td>0.90</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>boric acid</td>
<td>0.10</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>polyhexamethylene biguanide</td>
<td>15 (ppm)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>sodium phosphate, dibasic</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>potassium phosphate, monobasic</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>deionized water (Q.S.)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Based upon the foregoing, it should be apparent to those skilled in the art that the present invention is not limited by the examples set forth above and that the use of specific compositions can be determined from the specification without departing from the invention as herein disclosed and described.

Claims

1. An ophthalmic aqueous composition comprising:

   (a) 0.001 to 10 percent by weight of the composition of a quaternary nitrogen-containing ethoxylated glycoside;
   (b) an effective amount of an anionic therapeutic agent; and
   (c) an effective amount of a buffering agent to maintain the pH between 6 and 8 and an effective amount of a
tonicity adjusting agent to obtain an osmolality between 250 and 350 mOsmols/kg.

2. A composition as claimed in Claim 1 wherein the anionic therapeutic agent is an anionic polysaccharide or a
carboxy-containing polymer.

3. A composition as claimed in Claim 2 wherein the anionic polymer is a glycosaminoglycan.

4. A composition as claimed in any preceding claim wherein the anionic polymer is a biopolymer selected from hy-
aluronic acid, xanthan gum, and derivatives and salts thereof.

5. A composition as claimed in Claim 2 wherein the anionic polymer is a synthetic polymer selected from carbomers
and polyacrylic acids.

6. An ophthalmic aqueous composition comprising:

   (a) 0.001 to 10 percent by weight of the composition of a quaternary nitrogen-containing ethoxylated glycoside;
   (b) an effective amount of a delivery vehicle comprising an anionic polymer;
   (c) an effective amount of a therapeutic agent; and
   (c) an effective amount of a buffering agent to maintain the pH between 6 and 8 and an effective amount of a
tonicity adjusting agent to obtain an osmolality between 250 and 350 mOsmols/kg.

7. A composition as claimed in Claim 6 wherein said anionic polymer is a carboxy-containing polymer.

8. A composition as claimed in Claim 6 or Claim 7 in which the anionic polymer is present in an amount of from
9. A composition as claimed in any preceding claim wherein said glycoside is represented by the formula:

\[
\begin{align*}
R_1O &- O(CH_2)_{n}(O(CH_2CH_2O)_{y}R_2 \quad R_5 \\
R_2(OCH_2CH_2)_{w}O &- O(CH_2CH_2O)_{x}R_4 \\
O(CH_2CH_2O)_{y}R_3 &
\end{align*}
\]

wherein \( R_1 \) is an alkyl; the average sum of \( w, x, y, \) and \( z \) per mole of compound is within the range of about 1 to about 200; \( n \) is 0 or 1; \( R_2, R_3, R_5 \) are individually hydrogen or quaternary nitrogen-containing groups; provided that at least one of \( R_2, R_3, R_4, \) or \( R_5 \) is a quaternary nitrogen-containing group and that at least one of \( R_2, R_3, R_4, \) or \( R_5 \) is hydrogen.

10. A composition as claimed in any preceding claim in which the anionic therapeutic agent is present in an amount in the range 0.0001 to 5% by weight of the composition.

11. A composition as claimed in any preceding claim in which the buffering agent is present in an amount in the range 0.05 to 2.5% by weight of the composition.

12. A composition as claimed in any preceding claim in the form of a solution or gel.

13. Use of a composition comprising:

(a) 0.001 to 10 percent by weight of the composition of a quaternary nitrogen-containing ethoxylated glycoside,

(b) an effective amount of an anionic therapeutic agent for the manufacture of a medicament for therapeutic application to the eye.

14. Use of a composition comprising:

(a) 0.001 to 10 percent by weight of the composition of a quaternary nitrogen-containing ethoxylated glycoside;

(b) an effective amount of a delivery vehicle comprising an anionic polymer; and

(c) an effective amount of a therapeutic agent for the manufacture of a medicament for therapeutic application to the eye.

15. Use as claimed in Claim 13 or Claim 14 in which the composition is as defined in any one of Claims 1 to 12.

16. Use as claimed in any one of Claims 13 to 15 for the manufacture of a medicament in the form of a solution or gel for therapeutic applications directly to the eyes.

17. Use as claimed in any one of Claims 13 to 15 for the manufacture of a medicament for therapeutic applications by contacting the composition with a contact lens and thereafter placing the contact lens in the eye.

18. Use as claimed in Claim 17 wherein a contact lens is contacted with said composition by sequentially contacting the lens with a solution of the glycoside and a solution of the therapeutic agent, thereafter the contact lens is placed in the eye.

**Patentansprüche**

1. Wässrige ophthalmische Zusammensetzung, umfassend

(a) 0.001 bis 10 Gew.-% eines quaternären Stickstoff enthaltenden ethoxyierten Glycosids, bezogen auf die
Zusammensetzung:

(b) eine wirksame Menge eines anionischen therapeutischen Mittels; und

(c) eine wirksame Menge eines Puffers, um den pH zwischen 6 und 8 zu halten, und eine wirksame Menge eines die T onizität einstellenden Mittels, um eine Osmolalität zwischen 250 und 350 m0smol/kg zu erhalten.

2. Zusammensetzung nach Anspruch 1, in der das anionische therapeutische Mittel ein anionisches Polysaccharid oder ein Carboxy-containing Polymer ist.

3. Zusammensetzung nach Anspruch 2, in der das anionische Polymer ein Glycosaminoglycan ist.

4. Zusammensetzung nach einem der vorangehenden Ansprüche, in der das anionische Polymer ein Biopolymer, ausgewählt unter Hyaluronsäure, Xanthangummi und Derivaten und Salzen davon, ist.

5. Zusammensetzung nach Anspruch 2, in der das anionische Polymer ein synthetisches Polymer ist, das unter Carbomeren und Polyacrylsäuren ausgewählt ist.

6. Wässrige ophthalmische Zusammensetzung, umfassend

(a) 0,001 bis 10 Gew.-% eines quaternären Stickstoff enthaltenden ethoxylierten Glycosids. bezogen auf die Zusammensetzung;

(b) eine wirksame Menge eines Zuführungsträgers, der ein anionisches Polymer umfasst;

(c) eine wirksame Menge eines therapeutischen Mittels; und

(d) eine wirksame Menge eines Puffers, um den pH zwischen 6 und 8 zu halten, und eine wirksame Menge eines die T onizität einstellenden Mittels, um eine Osmolalität zwischen 250 und 350 m0smol/kg zu erhalten.

7. Zusammensetzung nach Anspruch 6, in der das anionische Polymer ein Carboxy-containing Polymer ist.

8. Zusammensetzung nach Anspruch 6 oder Anspruch 7, in der das anionische Polymer In einer Menge von 0,00025 bis 20 Gew.-%, bezogen auf die Zusammensetzung, vorliegt.

9. Zusammensetzung nach einem der vorangehenden Ansprüche, in der das Glycosid durch die Formel:

\[
\begin{align*}
R_1 & \quad \text{Alkyl ist; die durchschnittliche Summe von w, x, y und z pro Mol Verbindung im Bereich von etwa 1 bis etwa 200 liegt; n 0 oder 1 ist; R_2, R_3, R_4 einzeln Wasserstoff oder quaternären Stickstoff enthaltende Gruppen sind, mit der Maßgabe, dass mindestens einer der Reste R_2, R_3, R_4 oder R_5 eine quaternären Stickstoff enthaltende Gruppe ist und dass mindestens einer der Reste R_2, R_3, R_4 oder R_5 Wasserstoff ist.}
\end{align*}
\]

dargestellt wird, worin R_1 ein Alkyl ist; die durchschnittliche Summe von w, x, y und z pro Mol Verbindung im Bereich von etwa 1 bis etwa 200 liegt; n 0 oder 1 ist; R_2, R_3, R_4 einzeln Wasserstoff oder quaternären Stickstoff enthaltende Gruppen sind, mit der Maßgabe, dass mindestens einer der Reste R_2, R_3, R_4 oder R_5 eine quaternären Stickstoff enthaltende Gruppe ist und dass mindestens einer der Reste R_2, R_3, R_4 oder R_5 Wasserstoff ist.

10. Zusammensetzung nach einem der vorangehenden Ansprüche, in der das anionische therapeutische Mittel in einer Menge im Bereich von 0,0001 bis 5 Gew.-%, bezogen auf die Zusammensetzung, vorhanden ist.

11. Zusammensetzung nach einem der vorangehenden Ansprüche, in der der Puffer in einer Menge im Bereich von 0,05 bis 2,5 Gew.-%, bezogen auf die Zusammensetzung, vorhanden ist.

12. Zusammensetzung nach einem der vorangehenden Ansprüche In Form einer Lösung oder eines Gels.
13. Verwendung einer Zusammensetzung, umfassend:
   (a) 0,001 bis 10 Gew.-% eines quatemären Stickstoff enthaltenden ethoxylierten Glycosids, bezogen auf die 
   Zusammensetzung;
   (b) eine wirksame Menge eines anionischen therapeutischen Mittels für die Herstellung eines Arzneimittels 
   für die therapeutische Anwendung auf das Auge.

14. Verwendung einer Zusammensetzung, umfassend:
   (a) 0,001 bis 10 Gew.-% eines quatemären Stickstoff enthaltenden ethoxylierten Glycosids, bezogen auf die 
   Zusammensetzung;
   (b) eine wirksame Menge eines Zuführungsträgers, der ein anionisches Polymer umfasst; und
   (c) eine wirksame Menge eines therapeutischen Mittels zur Herstellung eines Arzneimittels für die therapeuti- 
   sche Anwendung auf das Auge.

15. Verwendung nach Anspruch 13 oder Anspruch 14, wobei die Zusammensetzung so wie in einern der Ansprüche 
   1 bis 12 definiert ist.

16. Verwendung nach einem der Ansprüche 13 bis 15 zur Herstellung eines Arzneimittels in Form einer Lösung oder 
   eines Gels für therapeutische Anwendungen direkt auf die Augen.

17. Verwendung nach einem der Ansprüche 13 bis 15 zur Herstellung eines Arzneimittels für therapeutische Anwen- 
   dungen, bei denen die Zusammensetzung mit einer Kontaktlinse in Kontakt gebracht wird und die Kontaktlinse 
   danach In das Auge eingesetzt wird.

18. Verwendung nach Anspruch 17, wobei eine Kontaktlinse mit der Zusammensetzung in Kontakt gebracht wird, 
   indem die Linse nacheinander mit einer Lösung des Glycosids und einer Lösung des therapeutischen Mittels in 
   Kontakt gebracht werden und die Kontaktlinse danach in das Auge eingesetzt wird.

Revendications

1. Composition aqueuse ophtalmique comprenant:
   (a) 0,001 à 10% en poids de la composition d’un glycoside éthoxylé contenant de l’azote quaternaire:
   (b) une quantité efficace d’un agent thérapeutique anionique; et
   (c) une quantité efficace d’un agent tampon pour maintenir le pH entre 6 et 8 et une quantité efficace d’un 
   agent d’ajustement de la tonicité pour obtenir une osmolalité entre 250 et 350 mOsmoles/kg.

2. Composition suivant la revendication 1, dans laquelle l’agent thérapeutique anionique est un polysaccharide anio- 
   nique ou un polymère contenant du carboxy.

3. Composition suivant la revendication 2, dans laquelle le polymère anionique est un glycosaminoglycane.

4. Composition suivant l’une quelconque des revendications précédentes, dans laquelle le polymère anionique est 
   un biopolymère choisi parmi l’acide hyaluronique, la gomme de xanthane et leurs dérivés et sels.

5. Composition suivant la revendication 2, dans laquelle le polymère anionique est un polymère synthétique choisi 
   parmi les carbomères et les acides polyacryliques.

6. Composition aqueuse ophtalmique comprenant:
   (a) 0,001 à 10% en poids de la composition d’un glycoside éthoxylé contenant de l’azote quaternaire; 
   (b) une quantité efficace d’un véhicule de distribution comprenant un polymère anionique; 
   (c) une quantité efficace d’un agent thérapeutique; et
(d) une quantité efficace d'un agent tampon pour maintenir le pH entre 6 et 8 et une quantité efficace d'un agent d'ajustement de la tonicité pour obtenir une osmolalité entre 250 et 350 mOsmoles/kg.

7. Composition suivant la revendication 6, dans laquelle le polymère anionique est un polymère contenant du carboxy.

8. Composition suivant l'une ou l'autre des revendications 6 et 7, dans laquelle le polymère anionique est présent en une quantité de 0,00025 à 20% en poids de la composition.

9. Composition suivant l'une quelconque des revendications précédentes, dans laquelle le glycoside précité est représenté par la formule :

\[
\begin{align*}
R_1 O & \quad \{(CH_2)_{2n}(CH_2CH_2O)_{2m}R_2 \quad (CH_3)_{2n}(CH_2CH_2O)_{2m}R_4 \quad (CH_2CH_2O)_{2m}R_5 \\
O & \quad (CH_2CH_2O)_{2m}R_3
\end{align*}
\]

dans laquelle \( R_1 \) est un groupe alkyle, la somme moyenne de \( w, x, \ y \) et \( z \) par mole de composé se situe dans la gamme d'environ 1 à environ 200, \( n \) est égal à 0 ou 1, \( R_2, R_3, R_5 \) représentent individuellement de l'hydrogène ou des groupes contenant de l'azote quaternaire, pour autant qu'au moins l'un des \( R_2, R_3, R_4 \) et \( R_5 \) soit un groupe contenant de l'azote quaternaire et qu'au moins l'un des \( R_2, R_3, R_4 \) et \( R_5 \) soit de l'hydrogène.

10. Composition suivant l'une quelconque des revendications précédentes, dans laquelle l'agent thérapeutique anionique est présent en une quantité allant de 0,0001 à 5% en poids de la composition.

11. Composition suivant l'une quelconque des revendications précédentes, dans laquelle l'agent tampon est présent en une quantité allant de 0,05 à 2,5% en poids de la composition.

12. Composition suivant l'une quelconque des revendications précédentes, sous la forme d'une solution ou d'un gel.

13. Utilisation d'une composition comprenant :

(a) 0,001 à 10% en poids de la composition d'un glycoside éthoxylé contenant de l'azote quaternaire; 
(b) une quantité efficace d'un agent thérapeutique anionique pour la fabrication d'un médicament pour une application thérapeutique à l'œil.

14. Utilisation d'une composition comprenant :

(a) 0,001 à 10% en poids de la composition d'un glycoside éthoxylé contenant de l'azote quaternaire; 
(b) une quantité efficace d'un véhicule de distribution comprenant un polymère anionique; et 
(c) une quantité efficace d'un agent thérapeutique pour la fabrication d'un médicament pour une application thérapeutique à l'œil.

15. Utilisation suivant l'une ou l'autre des revendications 13 et 14, dans laquelle le composition est telle que définie dans l'une quelconque des revendications 1 à 12.

16. Utilisation suivant l'une quelconque des revendications 13 à 15, pour la fabrication d'un médicament sous la forme d'une solution ou d'un gel pour des applications thérapeutiques directement aux yeux.

17. Utilisation suivant l'une quelconque des revendications 13 à 15, pour la fabrication d'un médicament pour des applications thérapeutiques par la mise en contact de la composition avec une lentille de contact et ensuite le placement de la lentille de contact dans l'œil.

18. Utilisation suivant la revendication 17, dans laquelle une lentille de contact est mise en contact avec la composition précédée en mettant en contact successivement la lentille avec une solution du glycoside et une solution de l'agent thérapeutique, la lentille de contact étant ensuite placée dans l'œil.