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(54) Title: OPHTHALMIC SOLUTION AND METHOD OF USE

(57) Abstract

The present invention is a solution containing dermatan sulfate and is particularly useful as a contact lens washing and storing solution. The present invention is also useful as an eye wash during eye surgery and also includes an eye shield for corneal surgery.

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OPHTHALMIC SOLUTION AND METHOD OF USE

Technical Field

The present invention relates to methods and compositions which are useful in a wide variety of ocular applications. In particular, the present invention is a solution containing dermatan sulfate and is particularly useful as a contact lens washing and storing solution. The present invention is also useful as an eye wash during eye surgery and also includes an eye shield for corneal surgery.

Background of the Invention

In the normal course of wearing contact lenses, tear film and debris consisting of proteinaceous, oily, sebaceous, and related organic matter have a tendency to deposit and build up on lens surfaces. As part of the routine care regimen, contact lenses must be cleaned to remove these tear film deposits and debris. If these deposits are not properly removed, both the wetability and optical clarity of the lenses is substantially reduced causing discomfort for the wearer.

Further, contact lenses, especially those made from hydrophilic materials, must be continuously disinfected to kill any harmful microorganisms that may be present or grow on the lenses. A number of methods for disinfecting contact lenses have been used such as the use of high temperatures, the use of oxidative chemicals, and the use of antimicrobial agents. However, current

disinfecting solutions do not exhibit significant cleaning ability for the removal of proteinaceous material.

Conventionally, the cleaning of contact lenses is accomplished with one or both of two general classes of cleaners. Surfactant cleaners, generally known as "daily cleaners" because of their recommended daily use, are effective for the removal of most carbohydrate and lipid derived matter. However, they are not as effective for the removal of proteinaceous matter such as lysozyme. Typically, proteolytic enzymes derived from plant, animal, and microbial sources are used to remove the proteinaceous deposits. These "enzyme" cleaners are recommended for weekly use and are conventionally employed by dissolving enzyme tablets in suitable aqueous solutions. The process of cleaning and disinfecting contact lenses with enzyme cleaners (as well as daily cleaners) involves two steps. The first step consists of the cleaning phase whereby lenses are conventionally soaked in an enzyme cleaning solution at ambient temperature conditions, i.e., cold soaking for a period of up to 12 hours, to achieve effective removal of proteinaceous deposits. At the conclusion of the cleaning step, the lenses are separately disinfected. Disinfection involves contacting the lenses with a solution containing either an oxidative chemical or an antimicrobial agent at ambient temperatures or exposing the lenses to elevated temperatures for specified periods of time. The latter disinfection technique requires specific electrical disinfecting apparatus.

Generally, contact lenses fall into two categories: the hard or rigid corneal type lenses formed from materials prepared by polymerization of acrylic esters, such as polymethyl methacrylate (PMMA), and gel, hydrogel or soft type lenses made of polymerized hydrophilic or hydrophobic monomers, such as 2-hydroxyethyl methacrylate (HEMA). Soft type contact lenses and certain of the gas permeable hard contact lenses also have a tendency to bind and concentrate significantly more fluids, environmental pollutants, water impurities as well as antimicrobial

agents and other active ingredients commonly found in lens care solutions. In most instances, the low levels of the ingredients in lens care solutions do not lead to eye tissue irritation when used properly. Nevertheless, because of the inherent binding action of protein deposits, disinfecting agents and preservatives, deposits tend to build up on lens surfaces and become concentrated to potentially hazardous levels, such that, when released, can cause corneal inflammation and other eye tissue irritation.

Previous efforts to alleviate the problem of binding and concentrating disinfectants and preservatives onto contact lens surfaces, and reducing the potential for eye tissue irritation, have not been totally satisfactory. For example, in spite of low toxicity levels, not all disinfectants are compatible for use with all types of contact lenses. Many lens disinfecting and preservative solutions contain benzalkonium chloride or chlorobutanol. Although they are effective antibacterial agents, their use can result in a loss of lens hydrophilic properties, cause solution restability or may even lack compatibility with certain types of hard lenses, e.g., high silicon content.

Other antibacterial agents were found to be more compatible with contact lenses and exhibit less binding on lens surfaces. In one case, it was found that chlorhexidine, a biguanide, binds to soft lens material seven times less than benzalkonium chloride, but the presence of proteinaceous oily tear-film deposits can double the amount of chlorhexidine absorbed over that of clean tissue. U.S. Pat. No. 4,354,952 discloses very dilute disinfecting and cleaning solutions containing chlorhexidine or its salts in combination with certain amphoteric and non-ionic surfactants. These solutions were found to reduce the amount of binding of chlorhexidine on hydrophilic soft contact lenses. Currently, other disinfecting and preservative agents that are being used for contact lenses include polyaminopropyl biguanide, Onomer M, hydrogen peroxide and sorbic acid.

Other efforts to reduce or eliminate lens binding have led to the use of anti-binding or detoxifying agents, like polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA). However, these polymers alone were found to be ineffective, for the most part, in reducing lens binding and eye tissue irritation.

Other ophthalmic solutions include eye rewetting and lubrication drops, eye washes, eye ointments, eye shields, dissolvable eye inserts and interocular eye gels or fluids. The solutions are all designed to provide comfort and/or protection for the eye. Ophthalmic drug products that have been approved for over-the-counter human use are summarized in the final monograph under 21 CFR Part 349 which is incorporated herein by reference.

U.S. Patent No. 5,141,928 discloses the use of glycosaminoglycan polysulfates with a molecular weight of between 5,000 and 20,000 daltons for ophthalmic medications in the prevention and treatment of eye injuries. However, there are certain disadvantages to using glycosaminoglycans of this molecular weight. These compounds tend to be relatively unstable. They do not withstand heat sterilization and will break down in the presence of oxidants such as hydrogen peroxide. In addition, glycosaminoglycans of this molecular weight, which include hyaluronic acid, are difficult to sterilize by filtration.

Accordingly, there is a need for improved disinfective and preservative solutions which are compatible for use with all types of contact lenses while maintaining both a high level of antibacterial activity and low order of toxicity to eye tissue with little or no binding or concentrating of the disinfecting agent onto lens surfaces.

There is further a need for solutions that are not toxic and are not irritating to tissue in and surrounding the eye, i.e., the eye itself, the upper eyelid, the lower eyelid, etc. In addition, the solution should have lubricating qualities that reduce eye irritation and provide increased comfort after application of the solution to

the eye. The lubricating components in the solutions should be resistant to breakdown during sterilization and should be resistant to breakdown in the presence of disinfecting agents.

Summary of the Invention

The present invention provides for improved solutions and methods for disinfecting, storing and/or inserting contact lenses into the eye. The solutions and methods are compatible with both hard and soft type lenses, both tinted and untinted, and are adaptable for use with virtually any of the commonly known disinfecting techniques, including "cold" soaking under ambient temperature conditions, as well as with high temperature disinfecting methods. The present invention also includes solutions and compositions which can be used for a wide variety of ophthamic uses such as eye rewetting drops, lubrication drops, eye washes, eye ointments, eye shields, dissolvable eye insets and interocular eye gels or fluids.

The present invention includes solutions which contain dermatan sulfate or glycosaminoglycans with physical properties similar to dermatan sulfate. The preferred concentration of dermatan sulfate in the wash and soaking solutions is between approximately 0.01% and 5% by weight. The molecular weight range of dermatan sulfate is between 5,000 and 100,000 daltons with the preferred molecular weight of the dermatan sulfate being between approximately 25,000 and 60,000 daltons.

The present invention also includes saline wash solutions for contact lenses which contain dermatan sulfate. These solutions can optionally contain surfactants which will enhance the cleaning activity of the solution. Because of the presence of the dermatan sulfate in the solution, the cleaning solution has lubricating properties and the ability to reduce ocular irritation.

The present invention also includes eye drops that contain dermatan sulfate. These eye drops can optionally include antihistamines, vasoconstrictors and/or other active ingredients. The drops can be used to soothe eye strain or can be used to

alleviate strain or irritation due to the presence of contact lenses. Eye drops containing dermatan sulfate according to the present invention have a lubricating quality that makes the drops ideal for treating dry eyes. The drops made and used according to the present invention reduce irritation due to allergens or medications.

Another embodiment of the present invention is the addition of dermatan sulfate to over-the-counter eye drops and prescription eye drops. The addition of dermatan sulfate to these products increases the product's effectiveness in providing eye comfort. With irritating active ingredients in many pharmaceutical formulations, dermatan sulfate provides reduced irritation to the eyes and better overall tolerance.

Because dermatan sulfate solutions can be sterilized by autoclaving or filtration, a wide variety of single and multi-use products containing dermatan sulfate are contemplated as being included in the present invention. In addition, disinfecting components such as hydrogen peroxide can be added to the solution providing a disinfecting solution which has desirable lubricating properties.

Finally, by cross-linking the dermatan sulfate with cross-linking agents such as cyanuric chloride, glutaraldehyde, hexamethylene diisocyanate or hexanoic anhydride, an ocular shield can be made which is useful in ocular surgery. The ocular shield is made up of between 80% and 100% crosslinked dermatan sulfate. The cross-linked dermatan sulfate can also be used to deliver drugs to eye tissues. The cross-linked dermatan sulfate can be impregnated with a desired drug, such as an anti-glaucoma drug, and then placed under the eyelid thereby delivering the drug to the eye over a period of time.

Accordingly, it is an object of the present invention to provide an improved ocular solution for use as eye drops, contact lens cleaning solution and contact lens storage solution.

It is another object of the present invention to provide a lubricating solution that can be sterilized by methods including, but not limited to, heat, filtration, or radiation.

It is another object of the present invention to provide a contact lens disinfecting solution that has lubricating qualities.

It is yet another object of the present invention to provide a single solution that can be used both for storing contact lenses and for inserting the contact lenses in the eye.

It is another object of the present invention to provide a contact lens solution that is capable of lubricating the lenses and also containing a disinfecting component such as hydrogen peroxide.

It is yet another object of the present invention to provide a contact lens solution that will inhibit the adherence of protein on the lenses.

It is another object of the present invention to provide an ocular shield for use in ocular surgery.

It is yet another object of the present invention to provide an antimicrobial fluid for use in surgery to reduce the risk of infection by microorganisms.

It is another object of the present invention to provide a cream or ointment that can be applied to eye tissues to promote healing of eye injuries.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

Detailed Description

The present invention comprises a wide variety of solutions, ointments and creams for use in ocular applications. The

present invention includes solutions, ointments and creams that contain dermatan sulfate. The solutions and compositions can include other active components such as antibiotics, disinfectants, vasoconstrictors and/or antihistamines.

The present invention also includes solutions which can be used with contact lenses. These solutions are useful with either hard contact lenses, gas permeable contact lenses or soft contact lenses. These solutions include, but are not limited to, solutions for washing contact lenses, solutions for disinfecting contact lenses, and solutions for inserting the contact lenses into the eye. Another embodiment of the present invention is the incorporation of dermatan sulfate into an aqueous based gel, salve or ointment. The gel can also be nonaqueous based. The gel or ointment can then be applied to the eye or to eye tissues.

Dermatan sulfate (α-L-iduronosyl-(1-3)-ß-D-N-acytylgalactosamine 4-sulfate) is classified as a glycosaminoglycan sulfate. Dermatan sulfate consists of repeating disaccharide units of iduronosyl and acetylgalactosamine. It can be isolated from various tissues including blood vessel walls, lungs and skin. There are minor differences in the structure of dermatan sulfate depending upon from which tissue the compound is isolated. These differences in structure are primarily attributed to differences in the degree of sulfation. It is to be understood that the present invention includes dermatan sulfates from all sources, including natural sources or from recombinant methods. Dermatan compounds generally are weak anticoagulants. The preferred form of dermatan sulfate is highly sulfated. The silver, copper or zinc salts of dermatan sulfate can be used to impart microbiocidal activity to the dermatan sulfate solutions.

An important aspect of the present invention is the molecular weight of the dermatan sulfate. Dermatan sulfate is a polymer and is therefore made up of a population of molecules of different sizes having an overall average molecular weight. The present invention includes various solutions with dermatan sulfate

that has a molecular weight of between approximately 5,000 to 100,000 with a preferred molecular weight of between 25,000 and 60,000 daltons. The most preferred molecular weight of dermatan sulfate is between approximately 30,000 and 45,000 daltons.

Pharmaceutically acceptable vehicles that can carry the dermatan sulfate at the preferred concentrations include, but are not limited to, aqueous and nonaqueous solutions, gels, ointments, suspensions, and aerosols. The solutions may by isotonic, hypotonic, or hypertonic and can include a variety of pharmaceutically acceptable salts, including but not limited to, NaCl, KCl and $CaCl_2$. The vehicle may also contain surfactants, chelating agents, such as EDTA, and a variety of buffers well known to those of ordinary skill in the art.

One embodiment of the present invention is an aqueous solution of dermatan sulfate. The optimal concentration of dermatan sulfate will depend upon the application that is contemplated. For example, for the saline solution for use as eye drops, the preferred concentration of dermatan sulfate in saline is between approximately 0.01% to 3% with the most preferred concentration of dermatan sulfate in saline of between approximately 0.05% to 1%. Although saline (a solution of sodium chloride, containing 0.9% by weight of sodium chloride in 1000 cc of water) is the preferred medium for the eyedrops, other solutions, either isotonic or not isotonic can be used in preparing the eye drops according to the present invention. Dermatan sulfate is not toxic to the sensitive tissues that make up the eye. In addition, dermatan sulfate has unique wetting and lubricating qualities that make it particularly useful in inserting and wearing contact lenses.

Because dermatan sulfate is resistant to breakdown by heat, solutions containing dermatan sulfate can be heat sterilized. These solutions can also be sterilized by filtration. This is a particular advantage over prior art preparations that use other glycosaminoglycans such as those disclosed in U.S. Patent No.

5,141,928. The glycosaminoglycans disclosed in the '928 patent cannot be sterilized by heat and are difficult to filter sterilize.

The present invention is particularly useful for the preparation of compositions or liquid baths for the storage of hard or soft contact lenses including the soft, hydratable, permeable contact lenses, contact lenses which are oxygen permeable, such as the hydroxy ethylmethacrylate contact lenses, and the non-hydrated or non-hydratable lenses, including the hydrophobic silicone lenses. It is believed that, because the dermatan sulfate has a net negative charge, it retards the adherence of protein from the eye on contact lenses. Thus, the dermatan sulfate solution according to the present invention reduces the adherence of protein and other substances on the lens thereby reducing the cloudy build-up on the lens. It is contemplated as part of the present invention that enzymes such as proteases can be added to the dermatan sulfate solution.

Another advantage of the contact lens solutions made according to the present invention is the capability of adding disinfecting agents to the solution. It has been determined that the dermatan sulfate in the solution according to the present invention is resistant to breakdown by disinfecting agents which may be required to disinfect the contact lenses. For example, a common disinfecting agent used to treat contact lenses is hydrogen peroxide. While a system utilizing hydrogen peroxide is effective in disinfecting contact lenses, the hydrogen peroxide also reacts with other components in the solution. Because the dermatan sulfate is resistant to breakdown by hydrogen peroxide, the disinfecting solution with the dermatan sulfate not only kills or inhibits microbial growth, but also has desirable lubricating qualities required of a contact lens solution. Other disinfecting agents used to treat contact lenses, such as peracetic acid, bendazac, chlorhexidine, hypochlorite, polyamino propyl biguanide, and chlorine dioxide are compatible with dermatan sulfate in the solution. Solutions prepared with dermatan sulfate

therein according to the present invention can also contain preservative agents such as EDTA and mercurial thimerosal.

The present invention also includes eye drops for alleviating eye strain, dry eye, allergies or for treating irritation due to allergies or medication. The preferred concentration of dermatan sulfate for these solutions is between approximately 0.05% to 5% by weight in saline. Other components such as demulcents, emollients, vasconstrictors and decongestants can be used with dermatan sulfate. Demulcents are soothing substances which relieve pain or irritation in mucus membranes. Demulcents which are suitable for use with dermatan sulfate in the ophthalmic solutions according to the present invention include, but are not limited to, cellulose derivatives such as sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose and methylcellulose. Other demulcents that can be used in the present invention are dextran, gelatin, polyols, glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate, propylene glycol, polyvinyl alcohol and povidone. Ophthalmic emollients that can be used with dermatan sulfate according to the present invention include, but are not limited to, lanolin, light mineral oil, paraffin, petrolatum, white ointment, white petrolatum, white wax or yellow wax. Ophthalmic vasoconstrictors that can be used with dermatan sulfate include, but are not limited to, ephedrine hydrochloride, phenylephrine hydrochloride, tetrahydroxoline hydrochloride. The present invention is particularly useful as an eyewash for eye strain or eye irritation because of the lubricating and wetting properties of the solution due to the presence of the dermatan sulfate.

Another embodiment of the present invention includes cross-linked dermatan sulfate for use as a corneal shield. The shield can also have active agents incorporated therein which will be slowly released as the shield breaks down. The shield can be 100% dermatan sulfate or can be a mixture of components such as a mixture of dermatan sulfate and collagen. The cross-linked

dermatan sulfate is acted upon by enzymes in the body fluids and gradually breaks down as the tissue heals.

Another use of the cross-linked dermatan sulfate is for delivering drugs. A drug, such as an anti-glaucoma drug, can be incorporated into the cross-linked dermatan sulfate and then shaped into a small plug or other appropriate shape. The dermatan sulfate plug can be placed under an eyelid and, as the plug breaks down, the drug is slowly delivered to the eye.

This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims.

Example I

A solution for use as eye drops or as a solution for storing contact lenses is prepared by dissolving 1 gram of dermatan sulfate isolated from porcine lung (Scientific Protein Labs, Waunakee, WS) is dissolved in 1 liter of saline. The solution is then sterilized at 121°C for 30 minutes. The solution is then applied to the eyes of a patient to reduce irritation in the eye.

When used as a contact lens soaking solution, the contact lenses are immersed and stored in the solution until use.

Example II

A solution for use as eye drops for treating irritated red eyes. The eye drop solution has the following components:

Component	Amount
Saline	1000 g
Dermatan Sulfate	10 g
Polysorbate	1% by weight

The eye drops are applied to the eye every four hours until the eyes are normal.

Example III

A solution for use as eye drops for treating irritated red eyes. The eye drop solution has the following components:

Component	Amount
Saline	1000 g
Dermatan Sulfate	10 g
Ephedrine hydrochloride	0.1% by weight

The eye drops are applied to the eye every four hours until the eyes are normal.

Example IV

A solution for disinfecting contact lenses having biguanide as the disinfecting agent. The use of Polyaminopropyl biguanide as a disinfectant is described in U.S. Patent No. 4,836,986, which is incorporated herein by reference. The solution has the following components:

Component	Amount
Saline	1000 g
Dermatan Sulfate	5 g
Polyaminopropyl biguanide	0.03 g

The contact lenses are soaked in the solution for 12 hours after use.

It should be understood, of course, that the foregoing relates only to a preferred embodiment of the present invention and that numerous modifications or alterations may be made therein

without departing from the spirit and the scope of the invention as set forth in the appended claims.

CLAIMS

1. An ophthalmic solution comprising an effective amount of dermatan sulfate dissolved in a pharmaceutically acceptable carrier.

2. The solution of Claim 1, wherein the dermatan sulfate has a molecular weight of between 25,000 and 60,000 daltons.

3. The solution of Claim 2, wherein the dermatan sulfate has a molecular weight of between 30,000 and 45,000 daltons.

4. The solution of Claim 1, wherein the pharmaceutically acceptable carrier is saline.

5. The solution of Claim 1, wherein the solution further comprises a demulcent.

6. The solution of Claim 5, wherein the demulcent is selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, methylcellulose dextran, gelatin, polyols, glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate, propylene glycol, polyvinyl alcohol, povidone and mixtures thereof.

7. The solution of Claim 1, wherein the solution further comprises an emollient.

8. The solution of Claim 7, wherein the emollient is selected from the group consisting of lanolin, light mineral oil, paraffin, petrolatum, white ointment, white petrolatum, white wax and yellow wax.

9. A solution for disinfecting contact lenses comprising an effective amount of dermatan sulfate and an effective amount of a disinfectant dissolved in a pharmaceutically acceptable carrier.

10. The solution of Claim 9, wherein the disinfectant is selected from the group consisting of polyaminopropyle biguanide, onomer M, hydrogen peroxide, and sorbic acid.

11. The solution of Claim 9, wherein the dermatan sulfate has a molecular weight of between 25,000 and 60,000 daltons.

12. The solution of Claim 11, wherein the dermatan sulfate has a molecular weight of between 30,000 and 45,000 daltons.

13. A method for treating irritated eyes comprising the step of administering to the eyes of a human or animal with irritated eyes an effective amount of dermatan sulfate dissolved in a pharmaceutically acceptable carrier.

14. The method of Claim 13, wherein the dermatan sulfate has a molecular weight of between 25,000 and 60,000 daltons.

15. The method of Claim 14, wherein the dermatan sulfate has a molecular weight of between 30,000 and 45,000 daltons.

16. The method of Claim 13, wherein the pharmaceutically acceptable carrier is saline.

17. The method of Claim 13, wherein the solution further comprises a demulcent.

18. The method of Claim 17, wherein the demulcent is selected from the group consisting of sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, methylcellulose dextran, gelatin, polyols, glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate, propylene glycol, polyvinyl alcohol, povidone and mixtures thereof.

19. The method of Claim 13, wherein the solution further comprises an emollient.

20. The method of Claim 19, wherein the emollient is selected from the group consisting of lanolin, light mineral oil, paraffin, petrolatum, white ointment, white petrolatum, white wax and yellow wax.

INTERNATIONAL SEARCH REPORT

Inte. .tional application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/715
US CL :514/54,912
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54,912

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A, 5,141,928 (Goldman) 25 August 1992, entire document.	1 1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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