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(54) LIQUID PREPARATION FOR CONTACT LENSES

(57) Provided is a liquid preparation for disinfecting a contact lens, which can advantageously be produced by a process employing filtration sterilization and is excellent in stability, and further, provided is a method of industrially advantageously producing the liquid preparation for disinfecting a contact lens, which has such excellent characteristics. A cationic polypeptide antimicrobial agent and Hypromellose 2910 as a thickening agent are used together, dissolved in an aqueous medium, and the kinematic viscosity at 25°C is adjusted to 0.8 mm^2/s to 15 mm^2/s to obtain a liquid preparation for disinfecting a contact lens.

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Description

TECHNICAL FIELD

[0001] The present invention relates to a liquid preparation for a contact lens, and particularly to a liquid preparation for a contact lens, which is suitably used as a composition for disinfecting a contact lens, easily produced and excellent in stability.

BACKGROUND ART

[0002] Antimicrobial agent-containing liquid preparations which have hitherto been used for disinfection and the like of contact lenses are generally produced as sterile preparations, and a process of achieving sterilization thereof is usually performed by sterilization by filtration, sterilization by an autoclave or a combination thereof.

[0003] Of these, however, the autoclave sterilization employs a process of performing cooling after heating at 121 °C or more. Accordingly, in the case of the liquid preparation which contains a component having low thermal stability, the autoclave sterilization cannot be employed. Further, a heat-resistant and pressure-resistant production line and cooling equipment become necessary, so that there is also an inherent demerit that the production time becomes longer due to the heating and cooling process.

[0004] In contrast, sterile processing by the filtration sterilization makes it possible to produce the liquid preparations at ordinary temperature, and has more advantages in production of the liquid preparations than the autoclave sterilization, when the liquid preparations have no problems with filterability and effects on a filter. Further, there is an advantage that foreign matter with which the liquid preparations are contaminated from raw materials and the production line can also be removed by the filter. Therefore, employment of the process of achieving sterilization by the filtration sterilization is usually studied as the first option. When some raw materials providing the liquid preparations have problems with filterability and the like in the sterile processing by the filtration sterilization, there is no choice but to employ a system in which only the components having poor filterability are subjected to the autoclave sterilization and the other components which are separately subjected to the filtration sterilization are aseptically mixed therewith, or a production system in which all components are mixed and subjected to the autoclave sterilization.

[0005] On the other hand, in the liquid preparations for contact lenses, attempts have been made to blend various kinds of thickening agents in order to impart slipperiness at the time of scrubbing the lenses, a cushion effect at the time of wearing on the eyes, and a wetting action due to components adhered to surfaces of the lenses, for example. However, it has been known that such thickening agents are raw materials (components) which largely affect the filterability, stability and the like, giving rise to problems such as deterioration of the filterability and reduction of the long-term stability, depending on the kind thereof. Therefore, in selecting the thickening agent, it also becomes an important factor to judge from the viewpoints of not only feeling and an effect of the wetting action but also an influence on the stability and production cost of the liquid preparations.

[0006] Generally, in the liquid preparations for disinfecting contact lenses, as the thickening agents, there are mainly used cellulose-based, guar gum-based, PVA-based and PVP-based ones, for example. However, at present, the thickening agents which can be processed by the filtration sterilization while imparting a certain degree of thickening effect to the liquid preparations are limited to the PVA-based thickening agents and some cellulose-based thickening agents (substitution type: HPMC 2910). Of these, the PVA-based thickening agents are extremely excellent in filterability. However, there is a problem that when the liquid preparations containing the PVA-based thickening agents are stored for a long period of time, acetic acid esters of unsaponified portions thereof are hydrolyzed, thereby causing a gradual decrease in the pH of the liquid preparations. Accordingly, in multi-purpose solutions which come into direct contact with the eye, there is an inherent problem that such a decrease in the pH causes eye irritation. From such a situation, in the production of the liquid preparations considering employment of the filtration sterilization processing process, the cellulose-based thickening agent (HPMC 2910) is considered to be the first option as the thickening agent.

[0007] Further, as the liquid preparations for disinfecting contact lenses, one-liquid type multi-purpose solutions in which cationic disinfectants requiring no neutralization are blended at low concentrations have become the mainstream, instead of hydrogen peroxide-based disinfectants requiring neutralization. As the cationic disinfectants used in the multi-purpose solutions, two kinds of disinfectants are mainly intended: PHMB (polyhexamethylene biguanide) as a disinfectant of a biguanide-based polymer, and Polyquad as a disinfectant of a quaternary ammonium salt-based polymer. Of these, Polyquad is reported to have a low disinfection effect to fungi and amebas, so that it is considered that a low-molecular disinfectant having a high disinfection effect to fungi and amebas is used together with Polyquad. However, the low-molecular disinfectant has a problem of high toxicity. Furthermore, a problem caused by accumulation in the inside of lenses or the like is also a concern. On the other hand, PHMB has a high disinfection effect not only to bacteria but also to fungi and amebas, and is a well-balanced disinfectant, so that it has been used in many multi-purpose solutions.

[0008] From such a situation, it is considered that when PHMB is used as the disinfectant and the cellulose-based

thickening agent having high filterability is used as the thickening agent, it is possible to realize liquid preparation composition which can be subjected to the filtration sterilization. Unfortunately, however, when such a PHMB disinfectant is combined with the cellulose-based thickening agent (substitution type: HPMC 2910), some kind of reaction occurs therebetween to pose a problem in stability of a disinfection action by PHMB, resulting in a problem of decreasing the disinfection effect with time.

[0009] JP-T-8-504346 (Patent Document 1) discloses a liquid preparation for a contact lens in which a polypeptide such as protamine, polyarginine or polylysine is contained in order to prevent adhesion of proteins, and exemplifies HPMC (hydroxypropyl methylcellulose) as one of barrier component coatings which constitute tablets. However, the kind of such HPMC is not disclosed at all therein, and a problem with the liquid preparation for a contact lens containing such HPMC is also not disclosed at all.

[0010] Further, Japanese Patent No. 3813133 (Patent Document 2), Japanese Patent No. 3693656 (Patent Document 3), Japanese Patent No. 3693657 (Patent Document 4), for example, disclose that polylysine is used as the disinfectant in a solution for disinfecting and storing a contact lens, and a POE lauryl ether type surfactant, a betaine type surfactant, sucrose laurate or the like is used together therewith in order to improve antimicrobial activity thereof. It is also disclosed therein to use HPMC as the thickening agent. However, the kind of HPMC which may be used is not disclosed at all. Similarly, Japanese Patent No. 4255839 (Patent Document 5) discloses that in a liquid preparation for a contact lens in which polylysine is contained as the disinfectant, the thickening agent such as cellulose or a derivative thereof represented by HPMC, PVA and PVP may be contained as one of further additives. However, the kind of HPMC which may be used is not disclosed at all therein.

PRIOR-ART DOCUMENTS

PATENT DOCUMENTS

[0011]

Patent Document 1: JP-T-8-504346
Patent Document 2: Japanese Patent No. 3813133
Patent Document 3: Japanese Patent No. 3693656
Patent Document 4: Japanese Patent No. 3693657
Patent Document 5: Japanese Patent No. 4255839

SUMMARY OF INVENTION

TECHNICAL PROBLEMS

[0012] The present invention has been made herein in the light of such situations. It is therefore a problem to be solved by the present invention to provide a liquid preparation for disinfecting a contact lens which preparation has excellent stability and can be advantageously produced by a process employing filtration sterilization. It is another problem to be solved by the present invention to provide a method of industrially advantageously producing the liquid preparation for disinfecting a contact lens which has such excellent characteristics.

SOLUTION TO PROBLEMS

[0013] In order to solve the problems, the present inventors have made intensive studies, and as a result, have found that in the production of the liquid preparation for disinfecting a contact lens, use of a cationic polypeptide as an antimicrobial agent and use of the specific substitution type hydroxypropyl methylcellulose (HPMC), Hypromellose 2910, selected from various types of known HPMCs as the thickening agent make it possible to maintain a high disinfection effect to fungi, Acanthamoeba and the like for a long period of time and to industrially produce the liquid preparation by filtration sterilization, thus being able to solve all the inherent problems of the conventional liquid preparations for disinfecting contact lenses.

[0014] The present invention has been completed on the basis of such findings, and the gist of the present invention is a liquid preparation for a contact lens comprising a cationic polypeptide antimicrobial agent and Hypromellose 2910 as a thickening agent, wherein a kinematic viscosity at 25°C thereof is adjusted to 0.8 mm^2/s to 15 mm^2/s.

[0015] In one preferred embodiment of the liquid preparation for a contact lens according to the present invention, the above-mentioned cationic polypeptide antimicrobial agent is selected from the group consisting of polylysine, protamine, cationic collagen, cationic keratin, cationic soybean protein and cationic silk.

[0016] Further, in the present invention, the cationic polypeptide antimicrobial agent is contained preferably at a ratio

of 0.1 ppm to 10,000 ppm.

[0017] Furthermore, in the liquid preparation for a contact lens according to the present invention, at least one of a tonicity agent, a chelating agent, a buffer and a surfactant may be contained as needed, in addition to the above-mentioned cationic polypeptide antimicrobial agent and Hypromellose 2910.

[0018] In addition, in the liquid preparation for a contact lens according to the present invention, a pH thereof is preferably adjusted to the range of 6 to 8.

[0019] It is also a gist of the present invention to employ a method of producing a liquid preparation for a contact lens comprising the steps of (a) preparing a solution by adding at least a cationic polypeptide antimicrobial agent and Hypromellose 2910 to an aqueous medium to be dissolved therein, and adjusting a kinematic viscosity of the solution at 25°C to 0.8 mm^2/s to 15 mm^2/s, and (b) sterilizing the resulting solution by filtering it using a membrane filter.

ADVANTAGEOUS EFFECTS OF INVENTION

[0020] As described above, in the liquid preparation for a contact lens according to the present invention, the specific substitution type HPMC, Hypromellose 2910, is combined as the thickening agent with the cationic polypeptide antimicrobial agent, and the liquid preparation is prepared so as to have the predetermined kinematic viscosity. Accordingly, the liquid preparation for a contact lens according to the present invention is characterized in that a high disinfection effect to fungi, Acanthamoeba and the like can be maintained over a long period of time, and the liquid pH can be stably maintained over a long period of time. Moreover, the filtration sterilization processing can be easily performed to the solution in which the cationic polypeptide antimicrobial agent and Hypromellose 2910 are dissolved and contained and which is adjusted to the predetermined kinematic viscosity, so that mass processing of the desired liquid preparation for a contact lens becomes possible, making it possible to perform the filtration sterilization processing advantageously in cost.

[0021] Further, in the method of producing a liquid preparation for a contact lens according to the present invention, the filtration sterilization process can be employed. Therefore, mass processing becomes possible, and the filtering cost for removing foreign matter and the degerming cost to fungi, Acanthamoeba and the like can be advantageously reduced, thereby being able to largely contribute to a reduction of product cost. Thus, an industrially advantageous production method has been established.

MODES FOR CARRYING OUT THE INVENTION

[0022] A liquid preparation for a contact lens according to the present invention has a major characteristic in that the preparation is mainly composed of an aqueous medium in which a cationic polypeptide antimicrobial agent and Hypromellose 2910 as a thickening agent are contained, and adjusted to a predetermined kinematic viscosity.

[0023] Specifically, the cationic polypeptide antimicrobial agent used as an essential component in the present invention is known as a relatively high-molecular-weight disinfectant in a liquid preparation for disinfecting a contact lens, and components such as polylysine, protamine, cationic collagen, cationic keratin, cationic soybean protein and cationic silk are appropriately selected and used.

[0024] In order to effectively exhibit an antimicrobial action to the contact lens thereby, the cationic polypeptide antimicrobial agent is generally contained in the liquid preparation for a contact lens at a ratio of 0.1 ppm to 10,000 ppm, and more preferably at a ratio of 1 ppm to 1,000 ppm. There is a risk that excessive inclusion of the antimicrobial agent causes a harmful action to the eye, so that it is desirable to avoid the excessive inclusion thereof.

[0025] Further, Hypromellose 2910 which is another essential component of the liquid preparation for a contact lens according to the present invention is used as the thickening agent, and is one substitution type of a cellulose-based compound (hydroxypropyl methylcellulose: HPMC) having a structure in which hydrogen atoms of hydroxyl groups of cellulose are partially substituted with methyl groups ($-CH_3$) or hydroxypropyl groups ($-CH_2CHOHCH_3$). Namely, Hypromellose 2910 used in the present invention contains methoxy groups in an amount of 28.0% to 30.0% and hydroxypropoxy groups in an amount of 7.0% to 12.0%, on the weight basis. Hypromellose 2910 has a high degree of safety against living organisms, and is ophthalmologically sufficiently allowable, while having no influence on the shape and physical properties of the contact lens.

[0026] In the liquid preparation for a contact lens in which such Hypromellose 2910 is contained together with the cationic polypeptide antimicrobial agent, the kinematic viscosity thereof at 25°C is adjusted to 0.8 mm^2/s to 15 mm^2/s. When the kinematic viscosity excessively decreases, inconvenience occurs in use of the liquid preparation for a contact lens, because of an insufficient thickening effect thereof. On the other hand, when the kinematic viscosity excessively increases, it becomes difficult to perform the filtration sterilization processing of the liquid preparation. The kinematic viscosity is preferably within the range of 1 mm^2/s to 10 mm^2/s.

[0027] In order to give the kinematic viscosity within such a range, the content of Hypromellose 2910 is appropriately adjusted depending on the viscosity grade used. In general, Hypromellose 2910 is added and contained within the range

of about 0.01 % to 10%, preferably about 0.1 % to 5%, on the weight basis.

[0028] As described above, the liquid preparation for a contact lens according to the present invention is obtained by using the cationic polypeptide antimicrobial agent and the specific cellulose-based compound, Hypromellose 2910, as the thickening agent combined therewith, adding these two components to an appropriate aqueous medium to be dissolved therein in the same manner as the conventional liquid preparation for a contact lens, and adjusting the kinematic viscosity to the specific value. However, in the present invention, one, two or more of additive components described later, such as a tonicity agent, a chelating agent, a buffer and a surfactant which have been used in a common liquid preparation for a contact lens, may be appropriately selected and added at an ordinary addition ratio as needed, in addition to the two contained components of the cationic polypeptide antimicrobial agent and Hypromellose 2910. It is preferable that the additive components have a high degree of safety against living organisms, and are ophthalmologically sufficiently allowable, while having no influence on the shape and physical properties of the contact lens. It is desirable that the additive components are used within a quantitative range satisfying such requirements. This makes it possible to advantageously impart various functions depending on the additive components to the liquid preparation for a contact lens, without impairing the effects of the present invention in any way.

[0029] For example, as the tonicity agent which is contained in the liquid preparation for a contact lens according to the present invention and used for adjustment of the osmotic pressure thereof, there are generally used at least one or more compounds selected from the group consisting of sodium chloride, potassium chloride, a saccharide, a sugar alcohol and a polyol, or an ether or an ester thereof. Specific compounds thereof include glycerol, propylene glycol, polyethylene glycol, mannitol, sorbitol, dextrin, dextran and the like, in addition to the above-mentioned alkali metal chlorides. It is preferred that the osmotic pressure of the liquid preparation for a contact lens is generally adjusted to about 200 mOsm/kg to 400 mOsm/kg, using such a tonicity agent.

[0030] Further, the chelating agent is added for the purpose of inhibiting polyvalent metal ions such as calcium from depositing on or being adsorbed by the contact lens, or improving stability of the liquid preparation to advantageously intend long-term storage thereof, and various known agents are appropriately selected and used. Specifically, there can be used ethylenediamine tetraacetic acid (EDTA) and salts thereof such as disodium ethylenediamine tetraacetate (EDTA·2Na), trisodium ethylenediamine tetraacetate (EDTA·3Na), for example.

[0031] Furthermore, various known surfactants may be added to the liquid preparation for a contact lens according to the present invention to be contained therein for the purpose of enhancing cleaning properties of the contact lens, or in the case where the liquid preparation component to be contained is insoluble in water, for the purpose of stably dissolving (solubilizing) the component in the aqueous medium. As such surfactants, there may be employed all of conventionally known anionic surfactants, nonionic surfactants, amphoteric surfactants and cationic surfactants, as long as they have a high degree of safety against living organisms and have no influence on the contact lens. The surfactants are advantageously added and contained at a concentration not impairing the functions and effects of the present invention.

[0032] As specific examples of such surfactants, there are advantageously used, for example, polyoxyethylene-polyoxypropylene block copolymers and derivatives thereof, polyethylene glycol derivatives such as polyoxyethylene alkyl phenyl ether-formaldehyde condensates, such as tyloxapol, sorbitan fatty acid esters such as sorbitan sesquioleate, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monooleate (for example, Polysorbate 80), glycerin fatty acid esters such as glyceryl monostearate, polyethylene glycol fatty acid esters such as polyethylene glycol monostearate, polyoxyethylene alkyl ethers such as polyoxyethylene lauryl ether, polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether carboxylic acids and salts thereof, and sucrose fatty acid esters. Among these, it is desirable to use in particular, Pluronic, Pluronic R, Tetronic and Tetronic R (the above are manufactured by BASF SE, Germany), which are polyoxyethylene-polyoxypropylene block copolymers and commercially available as nonionic surfactants, specifically, Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 338, Poloxamer 407, Tetronic 904, Tetronic 908, Tetronic 1304, Tetronic 1107, Polysorbate 80 which is polyoxyethylene sorbitan monooleate, polyoxyethylene hydrogenated castor oil, for example.

[0033] In addition, in the liquid preparation for a contact lens according to the present invention, when the pH value or osmotic pressure thereof becomes too high or conversely too low, there is a risk of giving a stimulus to the eye or causing eye troubles. It is therefore generally desirable to adjust the pH value of the liquid preparation for a contact lens to about 6 to 8 and especially to around 7.0 by addition of an appropriate pH adjusting agent or buffer.

[0034] As the pH adjusting agent used for such pH adjustment, there is used sodium hydroxide, hydrochloric acid, for example. On the other hand, the buffer for keeping the pH of the liquid preparation effectively within the above-mentioned range and within a range safe to the eye is appropriately selected from conventionally known various ones and used. Specific examples thereof include acids such as phosphoric acid, boric acid, carboxylic acid, oxycarboxylic acid, and salts thereof (for example, sodium salts and the like), and further, Good-Buffer, tris(hydroxymethyl)aminomethane (TRIS), bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane (Bis-Tris), sodium hydrogen carbonate and the like, because they are safe to the eye, and moreover, influences thereof on the contact lens can be decreased.

[0035] The liquid preparation for a contact lens according to the present invention is prepared by using the specific combination of the cationic polypeptide antimicrobial agent with Hypromellose 2910 as the thickening agent as described

above, thereby being able to exhibit excellent characteristics as the liquid preparation for disinfecting a contact lens. However, it is also possible to add a thickening agent or thickener other than Hypromellose 2910 within a quantitative range not impairing the effect owing to the use of the specific thickening agent. Such thickening agent includes, for example, various gums such as polysaccharides, mucopolysaccharides and heteropolysaccharides, such as condroitin sulfuric acid, hyaluronic acid, gluconic acid and salts thereof; synthetic organic high-molecular compounds such as polyvinyl alcohol, poly-N-vinylpyrrolidone, polyethylene glycol, polypropylene glycol and polyacrylamide; cellulose derivatives such as hydroxyethylcellulose, carboxymethylcellulose and methylcellulose; and starch derivatives.

[0036] Further, in addition to the above-described components, it is possible to appropriately add pharmaceutical components similar to the conventional ones, such as an anti-inflammatory agent for reducing intraocular inflammation caused by stress or by wearing the contact lens, a refrigerant for the purpose of releasing an irritating or itching sensation at the time of wearing the contact lens, and further various vitamins and amino acids, to the liquid preparation for a contact lens according to the present invention depending on the intended application thereof.

[0037] The liquid preparation for a contact lens according to the present invention is prepared by adding the above-described components in respective proper amounts to an appropriate aqueous medium to be contained therein, in the same manner as the conventional one. It goes without saying that it is also possible to utilize as the aqueous medium, an isotonic sodium chloride solution or a sodium chloride-containing aqueous solution, a known liquid preparation for a contact lens or the like, in addition to water itself such as tap water, purified water or distilled water, as long as it is a solution mainly composed of water.

[0038] Further, when other additive components are added to and dissolved in the predetermined aqueous medium in addition to the essential components of the cationic polypeptide antimicrobial agent and Hypromellose 2910 which are used according to the present invention, no particular technique is required to be employed at all. Addition and dissolution of the additive components can be easily performed by dissolving the respective components in the aqueous medium in the same manner as in the case where an ordinary aqueous solution is prepared. In particular, in the present invention, it is easy to perform the filtration sterilization processing to the aqueous solution obtained by dissolving these respective components, thereby making it possible to perform mass processing. Thus, the liquid preparation for a contact lens according to the present invention can be industrially advantageously obtained with good productivity, and accordingly in low production cost. It is recommended that the filtration sterilization processing of the aqueous solution is generally performed by filtration using a membrane filter having a pore size of about 0.1 μm to 10 μm. Further, a degerming processing is effectively realized by this filtration sterilization processing, together with removal of foreign matter from the solution, resulting in that the desired aseptic liquid preparation for a contact lens is advantageously obtained.

[0039] The liquid preparation for a contact lens according to the present invention obtained as described above has a sufficient degree of safety to the eye and is easy to produce, whereby the productivity thereof is enhanced, and the liquid preparation is advantageously used as the liquid preparation for disinfecting a contact lens. The liquid preparation for a contact lens is advantageously used, for example, as a multi-purpose liquid preparation (multi-purpose solution: MPS) such as a cleaning-preservative solution, a cleaning-preservative-rinsing solution or a germicidal-cleaning solution, which can perform plural treatments with one kind of liquid preparation, as well as being able to be used as a germicidal or disinfecting solution for a contact lens, a cleaning solution for a contact lens, a preservative solution for a contact lens, a rinsing solution for a contact lens, for example.

[0040] The type of the contact lens to be treated with the liquid preparation for a contact lens according to the present invention is not limited in any way. The liquid preparation can be applied to soft contact lenses which are classified into all of non-water-content, low-water-content and high-water-content contact lenses, and hard contact lenses, for example. The material or the like of the contact lens does not become an issue in any way in the application of the present invention.

EXAMPLES

[0041] The present invention will be described more specifically showing some examples, but it goes without saying that the present invention is by no means restricted by descriptions of such examples. In addition to the following examples and further the above-mentioned specific descriptions, it should be understood that various changes, modifications and improvements may be made to the present invention, based on knowledge of those skilled in the art, without departing from the spirit and scope of the present invention.

[0042] First, in order to prepare many test liquids as liquid preparations for a contact lens according to the present invention, and as liquid preparations for a contact lens according to comparative examples, various disinfectants (polypeptides), various comparative disinfectants, various thickening agents, a chelating agent, a surfactant, a buffer and a tonicity agent shown in Table 1 were each obtained from the companies shown in Table 1.

[0043]

[TABLE 1]

Ingredients		Source
Disinfectant (Polypeptide)	ε-Polylysine	Chisso Corp.
	Protamine sulfate	Wako Pure Chemical Industries Ltd.
	Cationic hydrolyzed collagen (W42-CAQ)	Seiwa Kasei Co. Ltd.
	Cationic hydrolyzed keratin (WK-HCAQ)	
	Cationic hydrolyzed soybean protein (WS-HCAQ)	
	Cationic hydrolyzed silk (S-CAQ)	
Comparative Disinfectant	Polybiguanide PHMB (Cosmocil CQ)	Arch Chemicals Inc.
	Polyquaternary ammonium P-4 (L-200)	National Starch and Chemical Co.
	Polyquaternary ammonium P-10 (SC-230M)	Kao Corp.
	Cationic guar gum (C-14S)	Sansho Co., Ltd.
	Cationic dextran (CDC-L)	Meito Sangyo Co., Ltd.
	Cationic trehalose	Hayashibara Co., Ltd.
Thickening Agent	Hypromellose 2910, viscosity G=4000 (60SH-4000)	Shin-Etsu Chemical Co., Ltd.
	Hypromellose 2910, viscosity G=50 (60SH-50)	
	Hypromellose 2910, viscosity G=3 (TC-5E)	
	Hypromellose 2906, viscosity G=4000 (65SH-4000)	
	Hypromellose 2208, viscosity G=4000 (90SH-4000)	
	Methylcellulose, viscosity G=4000 (SM-4000)	
	Hydroxyethylcellulose (SE-400)	Daicel Corp.
	PVP (Kollidon K-90)	BASF SE
	PVA (Gohsenol EG-40)	Nippon Synthetic Chemical Industry Co., Ltd.
Chelating Agent	EDTA·2Na	Nagase Chemtex Corp.
Surfactant	Poloxamer 407	BASF SE
Buffer	Boric acid	Tomiyama Pure Chemical Industries, Ltd.
Tonicity Agent	Propylene glycol	Asahi Glass Co., Ltd.

[0044] -Preparation of Liquid Preparations for Contact Lens (Test Liquids)-Predetermined ingredients were each added to sterilized purified water at various ratios shown in the following Tables 2 to 5, thereby preparing various test liquids (Nos. 1 to 24), respectively, adjusted to an initial pH of 7.4.

[0045] Then, for each of the obtained various test liquids (Nos. 1 to 24), the disinfection effect (4 hours), filterability and kinematic viscosity (25 °C) were examined according to the following disinfection test method of bacteria (*Pseudomonas aeruginosa)* and fungi (*Candida*), disinfection test method of amebas, measuring method of kinematic viscosity and evaluation method of filterability. The results thereof are shown together in the following Tables 2 to 5.

- Disinfection Test Method of Bacteria *(Pseudomonas aeruginosa)* and Fungi (*Candida*)-

[0046] The following test was performed according to the guide line of ISO 14729 specifying the test method of a disinfection effect to contact lens-care products.

[0047] First, using the respective test liquids prepared as described above, 9.9 ml of each liquid was accommodated in a test tube, and 0.1 ml of a bacterial or fungi liquid containing *Pseudomonas aeruginosa (Pseudomonas aeruginosa* NBRC 13275) or *Candida albicans (Candida albicans* I FO 1594) at a ratio of 10^8 cfu/ml to 10^9 cfu/ml was added thereto, followed by stirring to prepare a bacterial or fungi suspension corresponding to each test liquid, finally containing 10^6 cfu/ml to 10^7 cfu/ml of bacteria or fungi. Thereafter, each suspension was allowed to stand at 23 °C for 4 hours, and then, 1 ml of the suspension was taken out. Using 20 ml of glucose-peptone agar medium, the viable cell count per ml of sample was measured by a plate dilution method. Then, from this viable cell count, the viable cell count per ml of each suspension was calculated, and thereafter, a logarithmic reduction (log reduction) of bacteria or fungi was determined according to the following equation:

Log reduction=log(viable cell count per ml of bacterial or fungi suspension immediately after preparation)-log(viable cell count per ml of bacterial or fungi suspension after standing)

The disinfection efficacy of the respective test liquids was evaluated from the value of the above-mentioned logarithmic reduction (log reduction) of bacteria or fungi. With respect to evaluation criteria thereof, the case where First Criteria (for germiciding) in ISO 14729 were satisfied was evaluated as ○, and the case where not satisfied was evaluated as x.

-Test Method of Amebas-

[0048] A pre-cultured vegetative hypha of Acanthamoeba (*Acanthamoeba castellanii* ATCC50370) was collected from a flask, and a suspension of 5×10^5 cells/ml was prepared using 1/4 Ringer's solution. On the other hand, 5 ml of each test liquid was accommodated in a test tube, and 50 μl of the above-mentioned Acanthamoeba suspension was added thereto, followed by stirring to prepare a suspension finally containing 5×10^3 cells/ml of amebas. Then, after each suspension was allowed to stand at 22°C for 4 hours, 20 μl of such ameba suspension was collected, and 10-fold serial dilution was appropriately performed by a method of mixing the suspension with 180 μl of lecithin polysorbate (LP)-added 1/4 Ringer's solution as a neutralizing agent. Then, 50 μl of a suspension of Escherichia coli prepared to 1×10^8 cfu was added to each test liquid subjected to the 10-fold serial dilution, followed by cultivation for 14 days. Then, the number of viable amebas was measured from the number of wells in which ameba multiplication was observed, and the log reduction value was calculated according to the following equation:

Log reduction=log(the number of viable amebas per ml of the sample immediately after preparation)-log(the number of viable amebas per ml of the sample after processing)

-Measuring Method of Kinematic Viscosity-

[0049] The kinematic viscosity of each test liquid was measured using an ubbelohde viscometer (manufactured by Shibata Scientific Technology, Ltd.). In that case, the ubbelohde viscometer having such a coefficient that the flow time in seconds becomes 200 to 1,000 seconds was selected. The measurement was conducted in a constant temperature bath at 25°C so as to have no change in temperature. Then, the kinematic viscosity (unit: mm^2/s) was determined by the product of the flow time in seconds of each test liquid, which was measured with the ubbelohde viscometer, and the coefficient of the ubbelohde viscometer.

-Evaluation Method of Filterability-

[0050] Using a membrane filter (manufactured by Nihon Pall Ltd., Supor EKV, pore size: 0.2 μm) having a diameter of 47 mm, after it was set to an inline stainless filter holder (manufactured by Nihon Millipore K.K., effective area: 13.8 cm^2) for a 47 mm disk, filtration was performed for the respective test liquids at a pressure of 1 kgf/cm^2, and the amounts of filtration after 3 hours were compared. The case where the amount of filtration after 3 hours was 2 litters or more was

evaluated as ◎, the case where it was 1 litter or more was evaluated as ○, the case where it was between 500 ml and 1 litter was evaluated as Δ, and the case where it was less than 500 ml was evaluated as x.

[0051]

[TABLE 2]

Test Liquid			1	2	3	4	5	6	7
Content (% by weight)	Disinfectant (Polypeptide)	ε-Polylysine	0.02	0.02	0.02	0.02	0.02	0.02	0.02
	Thickening Agent	Hypromellose 2910, viscosity G=4000	0.10	0.30	0.30	0.40	0.45	-	-
		Hypromellose 2910, viscosity G=50	-	-	-	-	-	1.00	-
		Hypromellose 2910, viscosity G=3	-	-	-	-	-	-	3.50
	Chelating Agent	EDTA·2Na	-	-	0.05	-	-	0.05	0.05
	Surfactant	Poloxamer 407	-	-	0.10	-	-	0.10	0.10
	Buffer	Boric acid	-	-	0.10	-	-	0.10	0.10
	Tonicity Agent	Propylene glycol	-	-	2.00	-	-	2.00	2.00
Disinfection Effect (4 hours)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
		Fungus (*C.albicans*)	>4.9	4.9	>4.9	>4.9	>4.9	>4.9	>4.9
		Ameba (*A.Casteranni*)	>2.8	>2.8	>2.8	>2.8	>2.8	>2.8	>2.8
Filterability			◎	◎	◎	○	×	◎	◎
Kinematic Viscosity (25°C)(mm^2/s)			2.1	7.8	8.0	13.2	17.5	4.5	5.7

[0052]

[TABLE 3]

Test Liquid			8	9	10	11	12	13
Content (% by weight)	Disinfectant (Polypeptide)	ε-Polylysine	0.02	0.02	0.02	0.02	0.02	0.02
	Thickening Agent	Hypromellose 2906, viscosity G=4000	0.25	-	-	-	-	-
		Hypromellose 2208, viscosity G=4000	-	0.30	-	-	-	-
		Methylcellulose, viscosity G=4000	-	-	0.15	-	-	-
		Hydroxyethylcellulose	-	-	-	0.60	-	-
		PVP	-	-	-	-	2.00	-
		PVA	-	-	-	-	-	1.50
	Chelating Agent	EDTA·2Na	-	-	-	0.05	0.05	0.05
	Surfactant	Poloxamer 407	-	-	-	0.10	0.10	0.10
	Buffer	Boric acid	-	-	-	0.10	0.10	0.10
	Tonicity Agent	Propylene glycol	-	-	-	2.00	2.00	2.00
Disinfection Effect (4 hours)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
		Fungus (*C.albicans*)	>4.9	>4.9	>4.9	>4.9	>4.9	>4.9
		Ameba (*A.Casteranni*)	>2.8	>2.8	>2.8	>2.8	>2.8	>2.8
Filterability			×	×	×	×	×	◎
Kinematic Viscosity (25°C)(mm^2/s)			4.5	8.4	1.4	10.2	6.8	4.6

[0053]

[TABLE 4]

Test Liquid			14	15	16	17	18	19
Content (% by weight)	Disinfectant (Polypeptide)	Protamine sulfate	0.15	-	-	-	-	-
		Cationic hydrolyzed collagen	-	0.05	-	-	-	-
		Cationic hydrolyzed keratin	-	-	0.01	-	-	-
		Cationic hydrolyzed soybean protein	-	-	-	0.01	-	-
		Cationic hydrolyzed silk	-	-	-	-	0.01	-
	Comparative Disinfectant	Polybiguanide (PHMB)	-	-	-	-	-	0.005
	Thickening Agent	Hypromellose 2910, viscosity G=4000	0.30	0.30	0.30	0.30	0.30	0.30
	Chelating Agent	EDTA·2Na	0.05	0.05	-	-	-	0.05
	Surfactant	Poloxamer 407	0.10	0.10	-	-	-	0.10
	Buffer	Boric acid	0.10	0.10	-	-	-	0.10
	Tonicity Agent	Propylene glycol	2.00	2.00	-	-	-	2.00
Disinfection Effect (4 hours)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
		Fungus (*C.albicans*)	>4.9	>4.9	>4.9	>4.9	>4.9	>4.9
		Ameba (*A.Casteranni*)	2.4	1.8	2.5	1.4	>2.8	>2.8
Filterability			◎	◎	◎	◎	◎	◎
Kinematic Viscosity (25°C)(mm^2/s)			7.8	7.9	7.8	7.8	7.8	7.8

[0054]

[TABLE 5]

Test Liquid			20	21	22	23	24
Content (% by weight)	Comparative Disinfectant	Polyquaternary ammonium P-4	0.01	-	-	-	-
		Polyquaternary ammonium P-10	-	0.10	-	-	-
		Cationic guar gum (C-14S)	-	-	0.05	-	-
		Cationic dextran (CDC-L)	-	-	-	0.10	
		Cationic trehalose	-	-	-	-	0.10
	Thickening Agent	Hypromellose 2910, viscosity G=4000	0.30	0.30	0.30	0.30	0.30
Disinfection Effect (4 hours)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	0.2
		Fungus (*C.albicans*)	>4.9	0.6	4.3	0.8	-0.1
		Ameba (*A.Casteranni*)	2.5	0.2	2.6	0.1	0.0
Filterability			×	×	×	○	◎
Kinematic Viscosity (25°C)(mm^2/s)			7.9	14.1	8.4	8.1	7.9

[0055] As is apparent from the results of Tables 2 to 5, it has been observed that test liquid Nos. 1 to 4, 6, 7 and 14 to 18 obtained by combining the polypeptide disinfectants with Hypromellose 2910 and adjusted in kinematic viscosity (25°C) to 0.8 mm^2/s to 15 mm^2/s according to the present invention show excellent disinfection effect and filterability. In contrast, test liquid No. 5 adjusted in kinematic viscosity (25°C) to more than 15 mm^2/s has poor filterability, and a filtration sterilization operation cannot be advantageously performed. Further, even when the polypeptide disinfectant is used, it has been observed that test liquid Nos. 8 to 12 using Hypromellose 2906 or 2208 different from Hypromellose 2910 in substitution type, methylcellulose, hydroxyethylcellulose or PVP, have poor filterability, even when the kinematic viscosity (25°C) is lower than 15 mm^2/s. Further, it has been observed that test liquid Nos. 20 to 24 using the disinfectants (comparative disinfectants) other than the polypeptide disinfectant are insufficient in either the disinfection effect or filterability, and of no practical use.

-Evaluation of Long-Term Stability-

[0056] Using test liquids 3, 6, 13 to 15 and 19 prepared in the above-indicated Tables 2 to 4, the long-term stability of the respective test liquids was examined.

[0057] Specifically, after each test liquid was stored at 45°C for 6 months, the disinfection effect was examined in the same manner as described above, and the pH value of each test liquid was measured. The results thereof are shown in Table 6, in which the disinfection effect is shown in comparison with the disinfection effect shown in the above-mentioned Tables 2 to 4, and the pH value is shown in comparison with the pH value immediately after the preparation of each test liquid.

[0058]

[TABLE 6]

Test Liquid			3	6	13	14	15	19
Content (% by weight)	Disinfectant (polypeptide)	ε-Polylysine	0.02	0.02	0.02	-	-	-
		Protamine sulfate	-	-	-	0.15	-	-
		Cationic hydrolyzed collagen	-	-	-	-	0.05	-
	Comparative Disinfectant	Polybiguanide (PHMB)	-	-	-	-	-	0.005
	Thickening Agent	HPMC 2910, viscosity G=4000	0.30	-	-	0.30	0.30	0.30
		HPMC 2910, viscosity G=50	-	1.00	-	-	-	-
		PVA	-	-	1.50	-	-	-
	Chelating Agent	EDTA·2Na	0.05	0.05	0.05	0.05	0.05	0.05
	Surfactant	Poloxamer 407	0.10	0.10	0.10	0.10	0.10	0.10
	Buffer	Boric acid	0.10	0.10	0.10	0.10	0.10	0.10
	Tonicity Agent	Propylene glycol	2.00	2.00	2.00	2.00	2.00	2.00
Disinfection Effect (4 hours)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
		Fungus (*C.albicans*)	>4.9	>4.9	>4.9	>4.9	>4.9	>4.9
		Ameba (*A.Casteranni*)	>2.8	>2.8	>2.8	2.4	1.8	>2.8
Disinfection Effect (45°C-after 6 months)		Bacteria (*P.aeruginosa*)	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
		Fungus (*C.albicans*)	>4.9	>4.9	>4.9	3.1	1.8	0.7
		Ameba (*A.Casteranni*)	>2.8	>2.8	>2.8	1.6	1.2	0.4
		Comprehensive Evaluation	◎	◎	◎	○	○	×
pH		Immediately after Preparation of Test Liquid	7.4	7.4	7.4	7.4	7.4	7.4
		After Storage at 45 °C for 6 Months	7.3	7.2	5.2	7.2	7.3	7.4
		Comprehensive Evaluation	○	○	×	○	○	○

[0059] As is apparent from the results of Table 6, it has been observed that test liquids 3, 6, 14 and 15 according to the present invention vary little in pH and also in the disinfection effect even after the storage at 45°C for 6 months, to exhibit the excellent disinfection effect. In contrast, it has become clear that test liquid 13 using PVA as the thickening agent is excellent in the disinfection effect, but its liquid pH is significantly decreased by the long-term storage, giving rise to a problem with long-term storage stability. Further, in the case of test liquid 19 using polybiguanide (PHMB) as the disinfectant, it has become clear that the disinfection effect is significantly decreased by the long-term storage.

Claims

1. A liquid preparation for a contact lens comprising a cationic polypeptide antimicrobial agent and Hypromellose 2910 as a thickening agent, wherein a kinematic viscosity at 25°C thereof is adjusted to 0.8 mm^2/s to 15 mm^2/s.

2. The liquid preparation for a contact lens according to claim 1, wherein the cationic polypeptide antimicrobial agent is selected from the group consisting of polylysine, protamine, cationic collagen, cationic keratin, cationic soybean protein and cationic silk.

3. The liquid preparation for a contact lens according to claim 1 or 2, wherein the cationic polypeptide antimicrobial agent is contained at a ratio of 0.1 ppm to 10,000 ppm.

4. The liquid preparation for a contact lens according to any one of claims 1 to 3, wherein at least one of a tonicity agent, a chelating agent, a buffer, a pH adjusting agent and a surfactant is further contained.

5. The liquid preparation for a contact lens according to any one of claims 1 to 4, wherein a pH thereof is from 6 to 8.

6. A method of producing the liquid preparation for a contact lens according to any one of claims 1 to 5 comprising the steps of:

   preparing a solution by adding at least a cationic polypeptide antimicrobial agent and Hypromellose 2910 to an aqueous medium to be dissolved therein, and adjusting a kinematic viscosity of the solution at 25°C to 0.8 mm^2/s to 15 mm^2/s; and
   sterilizing the resulting solution by filtering it using a membrane filter.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
A61L2/18(2006.01)i, *G02C13/00*(2006.01)i

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)
A61L2/18, G02C13/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2011
Kokai Jitsuyo Shinan Koho 1971-2011 Toroku Jitsuyo Shinan Koho 1994-2011

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2000/71175 A1 (LARGE SCALE BIOLOGY CORP.), 30 November 2000 (30.11.2000), claims 79 to 99 & US 6482799 B1 & AU 5166900 A	1-6
A	JP 2010-204597 A (Lion Corp.), 16 September 2010 (16.09.2010), claims; paragraphs [0020], [0026] (Family: none)	1-6

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

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Date of the actual completion of the international search	Date of mailing of the international search report
10 March, 2011 (10.03.11)	22 March, 2011 (22.03.11)
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