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(54) **BORATE-POLYOL MIXTURES AS A BUFFERING SYSTEM**

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(57) **ABSTRACT**

A buffering system having a pKa which may be selected based on the environment in which the solution is designed to be used. Solutions containing the buffering system according to the present invention include borate-polyol complexes as the primary buffering agents, and may include one or more of the following: an aqueous liquid medium; an antimicrobial component; a surfactant component; a viscosity-inducing component; and/or a tonicity component. The borate-polyol buffering system may be formulated to have a lower pKa than traditional systems.

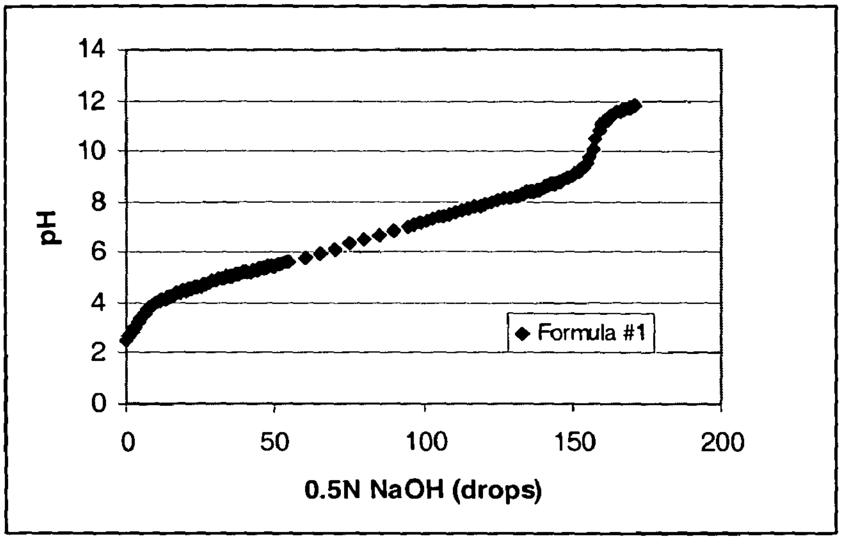


Figure 1

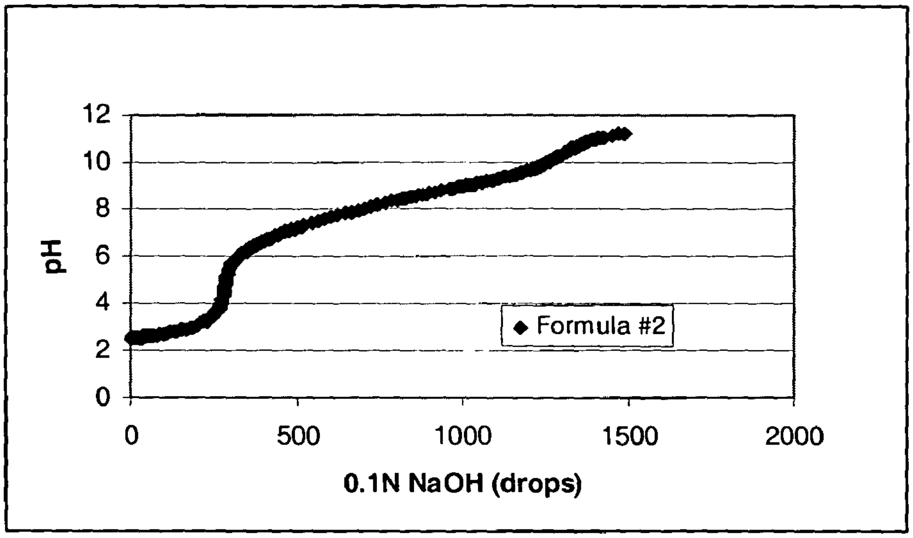
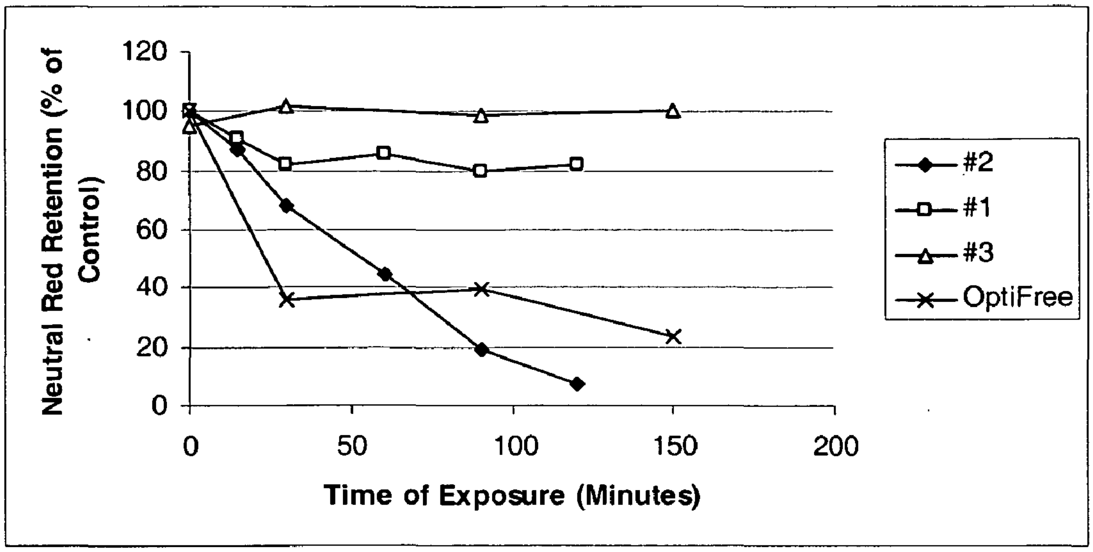


Figure 2



Neutral Red Retention (% of Control)
120
100
80
60
40
20
0
0
50
100
150
200
Time of Exposure (Minutes)
#2
#1
#3
OptiFree

Figure 3

BORATE-POLYOL MIXTURES AS A BUFFERING SYSTEM

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention relates to compositions and methods for formulating and using the same, and more particularly to compositions containing borate-polyol mixtures as the primary buffering agents.

[0003] 2. Description of Related Art

[0004] Contact lenses must be disinfected and cleaned to kill harmful microorganisms that may be present or grow on the lenses, and to remove any buildup that may have accumulated on the lenses. Some of the most popular products for disinfecting lenses are multi-purpose solutions that can be used to clean, disinfect and wet contact lenses, followed by direct insertion (placement on the eye) without rinsing.

[0005] The ability to use a single solution for contact lens care is an advantage to many users. Such a solution must be strong enough to kill harmful microorganisms that may be present or grow on the lenses. It must also be particularly gentle to the eye, since at least some of the solution will be on the lens when inserted and will come into contact with the eye. Such a solution must also be compatible with all contact lens materials, particularly the silicone hydrogel materials, which represent the state-of-the-art contact lens materials.

[0006] A significant challenge to improving the disinfecting efficacy of a solution is to simultaneously improve or maintain its contact lens material compatibility and comfort. One important component of ophthalmic compositions is the buffer, which helps to maintain the pH of the composition within an acceptable physiological range.

[0007] Conventional buffers which are typically used in ophthalmic compositions suffer either from the problems of the interaction with quaternary ammonium based antimicrobial, which reduces its antimicrobial efficacy (such as phosphate butter) or from the problem that their pKa values (the ability of an ionizable group to donate a proton in an aqueous media) typically fall outside of acceptable physiological range. For example, borate buffers have a pKa of 9.0. This is clearly outside the desired ophthalmic pH range of 7.0-7.8. While this may be overcome by increasing the concentration of said buffer, this increase in concentration may not be desirable to users from a physiological viewpoint.

[0008] Similar problems are present with lens rewetting solutions and artificial tears.

[0009] It is known in the art to use borate-polyol complexes as antimicrobial agents. By way of example, this is taught by Chowhan et al., U.S. Pat. No. 6,849,253. However, this reference does not teach a buffering system having a pKa that may be selected for physiological compatibility based on the use for which the resulting solution will be used.

[0010] Thus, it would be desirable to develop a buffering system which may be designed to have a pKa that is tailored [illegible] having a pKa that provides a pH buffering capacity within the normal physiological range of approximately 7.0 to 7.8. Such system may be used in any composition in which a buffer having a pH buffering capacity within that range may be employed including, but not limited to, for example, multi-purpose contact-lens solutions, rewetters and artificial tears.

DETAILED DESCRIPTION

[0011] A borate-polyol buffering system which may be designed to have a pKa that is significantly lower than that of boric/borate. Associated compositions and methods employing this buffering system according to the present invention provide improved, physiologically acceptable solutions and treatments, and for ease in formulating the same solutions and treatments.

[0012] The pKa of the buffering system according to the present invention may be selected based on the environment in which the solution is designed to be used. As a general statement, the larger the molar ratio of the polyol to boric acid, the higher the complexation. Since the buffering capacity is provided by the boric-polyol complex, the amount of the complex in solution affects the overall pKa value. That is, the larger the amount of complexes, the lower the pKa value. Similarly, the smaller the amount of the complex, the higher pKa value. Therefore the pKa value can be adjusted by changing the amount and the ratio of the boric acid and polyol. Therefore the buffer according to the present invention is unique in that it can provide a wide range of buffering capacities around physiological pH from 6-9.

[0013] As used herein, a polyol is an organic compound having two or more hydroxyl (—OH) group adjacent to each other.

[0014] As used herein, the term 'boric acid' is used to mean boric acid (H_3BO_3), metal salts of boric acid (MH_2BO_3), and borate ($M_2B_4O_7$), all of which will complex with polyols. Sodium salt of boric acid is one example of a metal salt of boric acid. Sodium borate is one example of borate. When the boric acid is complexed with the polyol, it is a borate-polyol complex. The concentration of borate-polyol complex in solutions according to the present invention ranges from about 0.005 to about 2% w/w, preferably from about 0.01% to about 0.5% w/w, and most preferably from about 0.04% to about 0.4% w/w.

[0015] The buffer component is present in an amount effective to maintain the pH of the composition or solution in the desired range, for example, in a physiologically acceptable range of about 4 or about 5 or about 6 to about 8 or about 9 or about 10. In particular, the solution preferably has a pH in the range of about 6 to about 8.

[0016] The present compositions preferably further comprise effective amounts of one or more additional components, such as one or more antimicrobial agent(s); detergent or surfactant component; a viscosity inducing or thickening component; a surfactant; a chelating or sequestering component; a tonicity component; and the like and mixtures thereof. Compositions according to the present invention may also include beneficial. amino acids. The additional component or components may be selected from materials [illegible] desired effect or benefit. When an additional component is included, it is preferably compatible under typical use and storage conditions with the other components of the composition. For instance, the aforesaid additional component or components preferably are substantially stable in the presence of the antimicrobial and buffer components described herein.

[0017] The compositions and methods of the present invention may be used to achieve stand-alone disinfection standards against four of the five FDA contact lens disinfection panel organisms (*P. aeruginosa, S. aureus, S. marcescens* and *F. solani*) and regimen disinfection against the fifth organism, *C. albicans*.

[0018] Antimicrobial components which may be used in association with the buffering system according to the present invention include chemicals which derive their antimicrobial activity from chemical or physiochemical interaction with microbes or microorganisms such as those contaminating a contact lens. Suitable additional antimicrobial components include, but are not limited to, those generally employed in ophthalmic applications such as quaternary ammonium salts such as poly [dimethylimino-2-butene-1,4-diyl] chloride, alpha-[4-tris(2-hydroxyethyl) ammonium]-dichloride (chemical registry number 75345-27-6, available under, the trademark Polyquatemium 1® from Onyx Corporation), benzalkonium halides, and biguanides, such as salts of alexidine, alexidine-free base, salts of chlorhexidine, hexamethylene biguanides and their polymers, and salts thereof, antimicrobial polypeptides, chlorine dioxide precursors, and the like and mixtures thereof. Generally, the hexamethylene biguanide polymers (PHMB), also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in Ogunbiyi et al, U.S. Pat. No. 4,759,595, the disclosure of which is hereby incorporated in its entirety by reference herein.

[0019] Generally, the antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration such that the user may remove the disinfected lens from the liquid aqueous medium and thereafter directly place the lens in the eye for safe and comfortable wear. Alternatively, the antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration and sufficient for maintaining preservative effectiveness. The additional antimicrobial components useful in the present invention preferably are present in the liquid aqueous medium in concentrations in the range of about 0.00001% to about 0.01% (w/w), and more preferably in concentrations in the range of about 0.00005% to about 0.001% (w/w) and most preferably in concentrations in the range of about 0.00005% to about 0.0005% (w/w).

[0020] Antimicrobial components suitable for inclusion in the present invention include chlorine dioxide precursors. Specific examples of chlorine dioxide precursors include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade sodium chlorite is a very useful chlorine dioxide precursor. Chlorine dioxide containing complexes such as complexes of chlorine dioxide [illegible] sors. The exact chemical composition of many chlorine dioxide precursors, for example, SCD and the chlorine dioxide complexes, is not completely understood. The manufacture or production of certain chlorine dioxide precursors is described in McNicholas, U.S. Pat. No. 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor® by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc.

[0021] The polyquaternium-1 that may be used in the present invention may come in the form of a pure liquid, a liquid concentrate, a salt, or a salt in aqueous solution. One particularly useful form of polyquaternium-1 is polyquaternium-1 chloride in aqueous solution. Likewise, the PHMB that may be used in the present invention may come in the form of a pure liquid, a liquid concentrate, a salt, or a salt in aqueous solution. One particularly useful form of PHMB is a hydrochloride salt in aqueous solution at between 1 and 20 w/w %.

[0022] If a chlorine dioxide precursor in included in the present compositions, it generally is present in an effective preservative or contact lens disinfecting amount. Such effective preservative or disinfecting concentrations usually are in the range of about 0.002 to about 0.06% (w/w) of the present compositions. The chlorine dioxide precursors may be used in combination with other antimicrobial components, such as biguanides, biguanide polymers, salts thereof and mixtures thereof.

[0023] In the event that chlorine dioxide precursors are employed as antimicrobial components, the compositions usually have an osmolality of at least about 200 mOsmol/kg and are buffered to maintain the pH within an acceptable physiological range, for example, a range of about 6 to about 10.

[0024] In one embodiment, the additional antimicrobial component is non-oxidative. It has been found that reduced amounts of non-oxidative antimicrobial components, for example, in a range of about 0.1 ppm to about 3 ppm or less than 5 ppm (w/w), in the present compositions are effective in disinfecting contact lenses and reduce the risk of such antimicrobial components causing ocular discomfort and/or irritation. Such reduced concentration of antimicrobial component is very useful when the antimicrobial component employed is selected from biguanides, biguanide polymers, salts thereof and mixtures thereof.

[0025] Cetylpyridinium chloride (CPC) is an example of an antimicrobial agent that may be used in conjunction with the buffer system according to the present invention. One of the present inventors previously discovered that cetylpyridinium chloride (CPC) at low concentrations, in combination with a non-ionic poly(oxypropylene)-poly(oxyethylene) block copolymer surfactant, can be efficacious as a contact lens disinfection agent. Such efficacy may be seen in concentrations ranging from as low as 0.1 ppm or 0.3 ppm to about 8 ppm, 9 ppm or 10 ppm. The benefits which may be achieved through the use of CPC are disclosed in U.S. patent application Ser. No. 10/820,486, to Zhi-Jian Yu et al., entitled "Cetylpyridinium Chloride as an Antimicrobial Agent" which is incorporated herein by reference.

[0026] [illegible]

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