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(54) Title: ZINC PRESERVATIVE COMPOSITION AND METHOD OF USE

(57) Abstract: The present invention is a composition comprising a preservative-effective amount of a zinc compound and less than a preservative-effective amount of a primary preservative agent--preferably no primary preservative agent. In one aspect of the present invention, there is a method of enhancing an ophthalmic composition, process for making a composition and a method of treating a patient using one or more compositions according to the present invention.

## ZINC PRESERVATIVE COMPOSITION AND METHOD OF USE

### FIELD OF THE INVENTION

The present invention relates to the methods and/or compositions, particularly ophthalmic compositions such as eye drop and contact lens treating solutions.

### BACKGROUND

The contact of eye tissue with bacteria may lead to various eye infections, such as microbial keratitis. The contact of eye tissue with bacteria may result when an ophthalmic solution contaminated with bacteria is instilled directly in the eye. Examples of such ophthalmic solutions instilled directly in the eye are eye drop solutions (for example, for treating dry eye) or contact lens drop solutions (for example, for conditioning a contact lens while worn). Additionally, eye tissue may be contacted with bacteria by placing a contact lens on the eye where the contact lens is contaminated with bacteria. The risk of eye infection is increased when bacteria is adhered to a contact lens, since the bacteria may remain in contact with eye tissue for a prolonged period of time.

For this reason, ophthalmic compositions, such as eye drop and contact lens treating solutions, conventionally include a preservative agent that acts to inhibit growth of bacteria and/or fungi, as well as other infectious organisms, in case the solution becomes contaminated with such organisms. For contact lens treating solutions, the preservative agents used to preserve the solution may also serve to disinfect contact lenses when rinsed or soaked with the solution. Alternately, ophthalmic compositions may include no preservative, but in such cases, the compositions are packaged in a special container that prevents contamination of the container contents, an example being single unit-dose packages where each dosage of solution is separately packaged.

Various preservative agents are known for use in ophthalmic compositions. Such preservative agents should have a broad spectrum of preservative activity and be non-irritating to the eye. However, many preservative agents have a tendency to irritate eye tissue, especially at higher concentrations. Therefore, it is generally advantageous to employ as low as possible concentration of preservative agent to avoid the risk of eye irritation.

U.S. Patent Nos. 6,323,165 and 6,274,133 disclose compositions and methods for blocking protein and/or lipid deposits on hydrophilic contact lenses with polyquaternium polymers or cationic cellulose polymers that bind to lenses and block the deposits from binding.

U.S. Patent No. 4,443,429 discloses the use in a contact lens disinfecting solution of a dimethyldiallylammonium chloride homopolymer commercially known as Merquat™ 100 (i.e., which has a molecular weight of about 10,000 to about 1,000,000). Preferred disinfecting solution concentrations were recited therein as 0.0004 wt.% to about 0.02 wt.% (4 ppm to 200 ppm).

WO 02/34308 discloses inhibiting adhesion of bacteria to the surface of a biomedical device, such as a contact lens, by binding a cationic polysaccharide to the surface of the device.

Pending U.S. Ser. Nos. 10/427,056 filed April 30, 2003, and 10/427,084 filed April 30, 2003, disclose the use of polycations such as Polymer JR (Polyquaternium-10) as a preservative-enhancing additive. Polymer JR was less of an irritant than traditional preservatives but enhanced the performance of the traditional preservative. U.S. Patent No. 5,460,834 discloses a physiological tear composition that may contain a zinc compound at a concentration having a minimum of about 0.005 and/or a maximum of about 0.015 mmol/L in addition to other salts known to be present in tears.

U.S. Patent No. 2,230,748 discloses an impregnating solution that prevents rot fungus in textiles or other organic materials. The impregnating solution includes sugar or sachcariferous substances. Soluble salts of zinc and copper are disclosed as ingredients in the solution.

A National Eye Institute Study entitled, NEI Study: Antioxidants and Zinc May Reduce AMD Risk, Review of Optometry, pp. 138-49, volume 6(1) (November 15, 2001), concluded that high levels of antioxidants and zinc was believed to significantly reduce the risk of advanced age related macular degeneration. Zinc was administered orally in the study.

Grahn, B.H. et al., Zinc and the Eye, Journal of the American College of Nutrition, vol. 20 (2) pp. 106-118 (April 2001) indicated that zinc played an important role in maintaining normal ocular function. Zinc was administered orally to patients.

It would be desirable to provide an ophthalmic composition with enhanced preservative efficacy that is safe, convenient and economical to use and non-irritating to eye tissue. The present invention addresses these and other problems encountered in the art.

### **SUMMARY OF THE INVENTION**

The present invention relates to a composition that includes a preservative-effective amount of a soluble zinc compound and has less than a preservative-effective amount of a primary preservative agent, preferably no primary preservative agent. The composition has the benefit of being adequately preserved without having a harsh physiological effect such as irritation or discomfort caused by at least some traditional preservative agents. The present invention relates to processes for manufacture, methods of enhancing compositions, and methods of use of the composition related to the above composition.

According to another embodiment, the composition further comprises a polycationic material including but not limited to a cationic cellulosic Polymer such as, for example, Polymer JR.

According to one embodiment, the composition is an ophthalmic solution that optionally includes at least one component selected from the group consisting of tonicity adjusting agents, buffering agents, chelating agents, pH adjusting agents, viscosity modifying agents, and therapeutic agents.

In one embodiment, the composition is an eye drop solution. In another embodiment, the composition is a contact lens treating solution. Typically, the composition is suitable for direct instillation in the eye without irritation to eye tissue.

### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to a composition that includes a preservative-effective amount of a soluble zinc compound and has less than a preservative-effective

amount of a primary preservative agent, preferably no primary preservative agent. The composition has the benefit of being adequately preserved without having a harsh physiological effect such as irritation or discomfort caused by at least some traditional preservative agents. Likewise in another embodiment, there is an ophthalmic composition comprising a preservative-effective amount of a zinc compound. The ophthalmic composition comprises a less than a preservative-effective amount of a primary antimicrobial compound—preferably no primary preservative agent.

The term “preservative” or like terms denotes agents included in the ophthalmic compositions for the purpose of inhibiting the growth of microorganisms in the product, thereby helping to maintain sterility of the composition. The term “preservative agent” denotes the specific active agent, which provides the preservative efficacy. As mentioned, the composition has less than a preservative-effective amount of a primary preservative agent. Primary preservative agents are defined as non-zinc containing compounds that derive their preservative activity through a chemical or physiochemical interaction with the microbial organisms.

A “preservative-effective amount” is defined as an amount sufficient to reduce the cell population by three log orders of the five following microorganisms, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Eschrechia coli*, *Candida albicans* and *Aspergillus niger*. The phrase, “a preservative-effective amount,” as it pertains to an amount of a primary preservative agent in a subject composition containing zinc, is defined as the amount of the primary preservative agent that would be required to reduce the cell population by three log orders of the five following microorganisms, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Eschrechia coli*, *Candida albicans*, and *Aspergillus niger* in a comparative composition that is the same as the subject composition except that all zinc containing compounds are removed from the comparative compound.

The term “soluble amount” as it pertains to a zinc compound is defined as an amount of a zinc compound that either dissolves completely in the composition or exceeds the saturation level by an amount that is not noticeable to the patient when the composition is applied to the patient’s eye. Preferably, the zinc compound is completely dissolved.

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