Title: COMPOSITION FOR STABILIZING POLY (CARBOXYLIC ACIDS)

Abstract: The invention concerns compositions and methods for reducing the decomposition rate of poly(carboxylic acids), such as hyaluronic acid. The compositions include at least one strong, stable chelating agent, preferably an organophosphorous compound such as diethylene triamine penta(methylene phosphonic acid). These bio compatible compositions are especially useful in the ophthalmic field. Also disclosed is a method of performing surgery on an eye including employing a hyaluronic acid material utilizing the inventive composition of the present invention.
Composition for stabilizing poly (carboxylic acids)

The present invention provides compositions and methods for reducing the decomposition rate of poly (carboxylic acids) at concentrations above 0.3%. The compositions include at least one strong, stable chelating agent, preferably an organophosphorous compound such as diethylene triamine penta(methylene phosphonic acid). These biocompatible compositions are especially useful in the ophthalmic field.

BACKGROUND OF THE INVENTION

Field of the Invention
This invention relates broadly to compositions and method for stabilizing poly (carboxylic acids) or the salts thereof at concentrations above 0.3%. In a preferred embodiment, the invention relates to stabilization of sodium hyaluronate in ophthalmic compositions.

Description of the Related Art
Poly (carboxylic acids) and the salts thereof are known to be useful in eye drops for managing dry eye syndrome. For example, hyaluronic acid is used in ophthalmic solutions or mixtures for this purpose. An example of a commercially available sodium hyaluronate is BS5111 available from Fermentech.

Typically, poly (carboxylic acids) such as sodium hyaluronate decompose, or are otherwise altered, during extended storage periods. For example, as hyaluronate is degraded, the distribution of molecular weight of the polymer decreases. The decomposition of this ingredient reduces the effectiveness of the composition, eventually to a point at which the composition is no longer deemed sufficiently effective for its intended use. Thus, there exist shelf-life problems with compositions, most notably buffered ophthalmic compositions that include poly (carboxylic acids). Accordingly, there is a need to reduce the rate of decomposition of poly (carboxylic acids), and to increase the shelf life of compositions including these materials.

U.S. Patent No. 5,576,028 to Martin, et al. teaches reducing the decomposition rate of hydrogen peroxide. The compositions include at least one strong, stable chelating agent, preferably an organophosphorous compound such as diethylene triamine penta(methylene
phosphoric acid). These biocompatible compositions are disclosed as being especially useful in the ophthalmic field. While stabilized hydrogen peroxide solutions containing a poly (carboxylic acids) at concentrations much less than 0.3% are disclosed, there is no teaching or suggestion of poly (carboxylic acids) at 0.3% or greater nor that such poly (carboxylic acids) are stabilized.

U.S. Patent No. 5,858,996 to Tsao teaches reducing the decomposition rate of viscosity enhancers, such as poly(acrylic acids) – but not poly (carboxylic acids). The compositions include at least one strong, stable chelating agent, preferably an organophosphorous compound such as diethylene triamine penta(methylene phosphonic acid). These biocompatible compositions are disclosed as being especially useful in the ophthalmic field.

Three commercially available hyaluronates for use in ophthalmic surgery are as follows:

a.  HEALON® – each ml of HEALON contains 10 mg of sodium hyaluronate, 8.5 mg of sodium chloride, 0.28 mg of disodium dihydrogen phosphate dihydrate, 0.04 mg of sodium dihydrogen phosphate hydrate and q.s. water for injection USP.

b. AMVISC® – each ml of AMVISC contains 10 mg of sodium hyaluronate adjusted to yield approximately 40,000 centistokes, 9.0 mg of sodium chloride and sterile water for injection USPQS.

c. VISCOAT® – each 1 ml of VISCOAT solution contains not more than 40 mg of sodium chondroitin sulfate, 30 mg sodium hyaluronate, 0.45 mg sodium dihydrogen phosphate hydrate, 2.00 mg disodium hydrogen phosphate, 4.3 mg sodium chloride (with water for injection USP grade, qs).

None of these three products contains a stabilizer, in particular a strong chelating agent. Without these stabilizers, there is the potential for degradation of the hyaluronic acid, and the subsequent loss of protective efficacy.
SUMMARY OF THE INVENTION

One embodiment of the invention is a stabilized buffered composition, which includes at least one poly (carboxylic acid) or salt thereof at a concentration greater than 0.3%, and at least one strong chelating agent (e.g., a phosphonic acid-containing chelating agent) capable of complexing with trace amounts of free catalytic metal ions. The chelating agent is believed to complex with trace amounts of metal ions, thereby reducing the free metal ion concentration. This reduction in free metal ion concentration reduces the decomposition rate of the poly (carboxylic acid). The compositions, which are especially useful in the ophthalmic field, exhibit increased shelf life.

Accordingly, in one aspect, the present invention relates to a stabilized solution, comprising: (a) greater than about 0.3 weight percent of at least one polymer selected from the group consisting of poly(carboxylic acids) and salts thereof and mixtures thereof; and (b) at least one strong and stable chelating agent having at least one phosphonic acid group in an amount of from 0.0001 to 0.1 weight percent; and (c) water.

Another embodiment of the invention is a method of stabilizing a poly (carboxylic acid) at a concentration greater than 0.3%. The method involves providing an ophthalmically compatible composition including a poly (carboxylic acid), adding a strong (e.g., a phosphonic acid-containing) chelating agent to the composition, and allowing the chelating agent to complex with free catalytic metal ions in the composition. The composition exhibits a decomposition rate that is less than the decomposition rate of a composition that does not include a strong chelating agent. Therefore, the resultant composition has an improved shelf life.

Thus, in another aspect, the present invention relates to a method of stabilizing a hyaluronic acid composition, comprising the step of preparing said hyaluronic acid composition including about 1 to 10 weight percent of hyaluronic acid or salts or mixture thereof and at least one strong and stable amino tri(alkylene phosphonic acid) chelating agent in an amount of from 0.0001 to 0.1 weight percent, wherein said chelating agent is capable of complexing with free catalytic metal ions to produce a composition with metal ion complexes and whereby reducing the decomposition rate of the hyaluronic acid in said composition.
Yet a further embodiment of the present invention is a composition having a free metal ion concentration less than an amount that will cause substantial poly (carboxylic acid) decomposition over a one-year storage period at room temperature.
Yet a further embodiment of the present invention is a method of performing surgery on an eye including employing the hyaluronic acid composition of the present invention during the performance of said surgery.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The solutions of the present invention include a poly (carboxylic acid) at a concentration greater than 0.3%, a buffer, and a stabilizer. Preferably, the concentration of the poly (carboxylic acid) is greater than 0.8%. A preferred group of solutions are those which are ophthalmically acceptable, i.e., those which do not produce substantial irritation or damage when contacted with the eye, ocular tissue, or surrounding fluids. The preferred ophthalmic solutions are those that are aqueous.

“Molecular weight” of a polymeric material, as used herein, refers to the number-average molecular weight unless otherwise specifically noted or unless testing conditions indicate otherwise.

Preferred stabilizers of the present invention are a group of chelating agents having phosphonic acid or phosphonate groups. A preferred group of chelating agents is organophosphonates, particularly amino tri (lower alkylene phosphonic acids). A variety of such chelating agents are commercially available from Monsanto Company, St. Louis, Mo., and are sold under the trademark DEQUEST®. Examples of such compounds include, without limitation, diethylene triamine penta(methylene phosphonic acid); hexamethylene-diaminetetra (methylene phosphonic acid); ethylenediaminetetra (methylene phosphonic acid); and aminotrimethylene phosphonates. A particularly preferred chelating agent is diethylene triamine penta(methylene phosphonic acid), sold under the trademark DEQUEST® 2060.

The poly (carboxylic acids) of the present invention are preferably selected from the group consisting of hyaluronic acids, preferably the salts thereof, and most preferably sodium hyaluronate.
Hyaluronic acid (HA) is a typical and important representative of a class of biological macromolecules known as glycosaminoglycans (mucopoly-saccharides). HA is a biological polymer that is present, with identical molecular structure, in all connective tissues of vertebrate organisms, where it plays a structural and biological role, in the sense that its local levels are strictly correlated with the tonus, trophism and tissue repair in case of injury. A review on the physiological role of these biological substances was given in Phys. Rev. (Comper, Laurent: Physiological Function Of Connective Tissue Polysaccharides, Phys. Rev., 58, (1), 255-315, 1978). The chemical-physical nature of HA is that of a saccharide biopolymer (D-glucuronic acid and N-acetylglucosamine), polymerized in alternation, forming long, unbranched molecular chains varying in molecular weight to a maximum of 8,000,000 Daltons (Meyer; Chemical Structure of Hyaluronic Acid. Fed. Proceed. 17, 1075, 1958; Laurent; Chemistry and Molecular Biology of Intracellular Matrix, 703-732, Academic Press N. Y., 1970). The behaviour of this biopolymer in aqueous solution guarantees a particular viscosity, called viscoelasticity, which is typical of some biological fluids, such as synovial fluid and vitreous fluid, where HA is present at a concentration of 0.12 - 0.24% (Balzas, et al.: Hyaluronic acid and replacement of vitreous and aqueous humor. Mod. Probl. Ophthal., 10, 3-21, 1972). Also aqueous humor, of human origin, was found to contain HA in an average concentration of 1.14 mg/g (Laurent: Hyaluronate In Human Aqueous Humor, Arch. Ophthalmol., 101, 129-130, 1983).

A body of published evidence has accumulated showing that the local supply of exogenous HA has distinct therapeutic and protective benefits in a great variety of pathological conditions of connective and epithelial tissues, such as:

- impaired tissue regeneration in non-healing skin ulcers;
- arthrosic degeneration of articular connective tissue;
- ocular surgery.

Particularly appreciated is the possibility, provided by the visco-elastic nature of HA, to coat the tissues exposed to risk of damage during surgical manipulation. According to all the surgeons who have used HA, the presence of a viscous layer of exogenous HA on the tissues which are most exposed to traumatizing accidental contacts, such as the cornea,
exerts an efficient protective influence, which is reflected to a very positive degree in the successful outcome of the operation.


Exogenous hyaluronic acid introduced in the anterior or posterior chamber of the eye does not exert any negative effect on post surgical intraocular pressure, nor does it trigger any inflammatory sequelae in the intraocular environment. In addition, as opposed to other viscoelastic products, hyaluronic acid may be left in the eye as it is rapidly eliminated by physiological mechanisms. This property is very useful, especially during perforating keratoplasty or other eye lesions, where the removal of the injected substance is technically impracticable.

However, hyaluronic acid will typically decompose, or otherwise become altered, during extended storage periods, particularly at higher concentrations. One effect of the decomposition of HA is a marked reduction in molecular weight. The molecular weight of a particular fraction of HA is of special clinical importance in the uses contemplated. The biological activity of HA solutions depends generally on a combination of the molecular weight and conformation of the HA molecules and the concentration of these molecules in solution. There is an inverse relationship between HA molecular weight and concentration, such that higher concentrations of smaller HA molecules are required to achieve a given level of biological activity. Furthermore, reduction in molecular weight leads to a lower
viscosity of the composition, eventually to a point at which the composition is no longer deemed sufficiently effective for such uses as ophthalmic surgery.

In order to have therapeutic activity, the concentration of HA in a therapeutically active solution should be at least the same magnitude as that which is found in normal tissue fluids, namely 0.1 - 0.3%. However, it is preferable that the concentration of HA in the therapeutic solution be higher than in normal tissue fluids, i.e., greater than about 0.3%, more preferably greater than about 0.5%, and most preferably greater than about 0.8%. The preferred composition according to the invention is a HA molecular weight of at least about 750,000, preferably at least about 1,200,000 and a concentration greater than about 1%; more preferably greater than about 1.5%.

The composition of the present invention is buffered. The buffer maintains the pH preferably 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 5.5 to about 8. The buffer is selected from inorganic or organic bases, preferably basic acetates, phosphates, borates, citrates, nitrates, sulfates, tartrates, lactates, carbonates, bicarbonates and mixtures thereof, more preferably basic phosphates, borates, citrates, tartrates, carbonates, bicarbonates and mixtures thereof. Typically, it is present in an amount of 0.001% to 2%, preferably 0.01% to 1%; most preferably from about 0.05% to about 0.30%.

The buffer component preferably includes one or more phosphate buffers, for example, combinations of monobasic phosphates, dibasic phosphates, and the like. Particularly useful phosphate buffers are those selected from phosphate salts of alkali and/or alkaline earth metals. Examples of suitable phosphate buffers include one or more of sodium dibasic phosphate (Na$_2$HPO$_4$), sodium monobasic phosphate (NaH$_2$PO$_4$), and potassium monobasic phosphate (KH$_2$PO$_4$).

The solutions of the present invention preferably include an effective amount of a tonicity component to provide the liquid medium with the desired tonicity. Such tonicity components may be present in the solution and/or may be introduced into the solution. Among the suitable tonicity adjusting components that may be employed are those conventionally used in contact lens care products, such as various inorganic salts. Sodium chloride and/or
potassium chloride and the like are very useful tonicity components. The amount of tonicity component included is effective to provide the desired degree of tonicity to the solution. Such amount may, for example, be in the range of about 0.4% to about 1.5% (w/v). If a combination of sodium chloride and potassium chloride is employed, it is preferred that the weight ratio of sodium chloride to potassium chloride be in the range of about 3 to about 6 or about 8. The preferred tonicity component is sodium chloride present in the range of 0.50% to 0.90%.

Typical tonicity builders for use in the invention include suitable water soluble salts compatible with ocular tissue, preferably alkali or alkali earth metal halide, sulfates, nitrates, carbonates, borates, and phosphates, more preferably sodium or potassium chloride. The tonicity builder is present in an amount sufficient to provide a tonicity of the dosage regimen of 50 to 400 mosmol/kg, most preferably 250 to 350 mosmol/kg.

Thus, in a particularly preferred embodiment, the ophthalmic solution is a buffered saline solution comprising:

(a) greater than about 1 weight percent of hyaluronic acid; and
(b) about 0.0001 to 0.1 weight percent of a chelating agent having at least one phosphonic acid group.

The present method of stabilizing a buffered poly (carboxylic acid) solution at a concentration of 0.3 or higher, generally includes providing a buffered ophthalmically compatible composition including a poly (carboxylic acid); adding at least one strong, stable chelating agent, preferably including at least one phosphonic acid group, to the solution; and allowing the chelating agent to complex with the free metal ions present in the solution, which free metal ions may degrade the poly (carboxylic acid), i.e., "catalytic metal ions". This method is believed to allow for the formation of a metal ion complex and poly (carboxylic acid) formulation that has a decomposition rate that is less than the decomposition rate of the solution containing trace amounts of free catalytic metal ions.

The order of mixing the components is not believed to be critical. Thus, each of the components of the ophthalmic solution may be, separately and serially, added to a vessel containing water, or all the components may be added simultaneously. Preferably, the
components are added separately, with dispersion or dissolution of each separate component being achieved prior to addition of the next component. However, the present stabilization method is not limited by the order of addition or contact of the components. Because the solutions of the present invention are contemplated to be used, inter alia, in ophthalmic surgery, it is important in such cases, that the compositions be non-irritating to the internal environment of the eye. Thus, it is preferred that the compositions of the present invention be substantially free of hydrogen peroxide or compounds that generate hydrogen peroxide, such as sodium perborate.

Furthermore, the composition of the present invention may include a pharmaceutically active agent. For clarity of presentation, and not by way of limitation, the pharmaceutically active agents suitable for use in the present invention are divided into the following sections: (1) miotic agents; (2) mydriatic agents; and (3) anesthetic agents.

Suitable miotic agents include, but are not limited to, pilocarpine, isopilocarpine, pilocarpine hydrochloride, pilocarpine nitrate, isopilocarpine hydrochloride, isopilocarpine nitrate, carbachol, physostigmine, physostigmine sulfate, physostigmine sulfite, demecarium bromide, ecothiophate iodide and acetylcholine chloride. Preferred miotic agents are members of the pilocarpine and isopilocarpine family of compounds.

Suitable mydriatic agents include, but are not limited to, atropine, atropine sulfate, atropine hydrochloride, atropine methylbromide, atropine methylnitrate, atropine hyperdural, atropine N-oxide, phenylephrine, phenylephrine hydrochloride, hydroxyamphetamine, hydroxyamphetamine hydrobromide, hydroxy-amphetamine hydrochloride, hydroxyamphetamine iodide, cyclopentolate, cyclopentolate hydrochloride, homatropine, homatropine hydrobromide, homatropine hydrochloride, homatropine methylbromide, scopolamine, scopolamine hydrobromide, scopolamine hydrochloride, scopolamine methylbromide, scopolamine methylnitrate, scopolamine N-oxide, tropicamide, tropicamide hydrobromide, and tropicamide hydrochloride. Preferred mydriatic agents are members of the atropine family and phenylephrine family of compounds.

Suitable anesthetic agents include those that are cationic in charge (cationic amine salts) or potentially cationic in charge (uncharged amino groups), such agents comprising lidocaine, proparacaine, tetracaine, phenacaine, naepaine, lidocaine, cocaine, betoxycaine,
bupivacaine, butacaine, butanillicaine, butoxycaaine, carticaine, cyclomethycaine, dibucaine, 
dimethocaine, etidocaine, formcaine, hexylcaine, hydroxytetracaine, leucinocaine, 
mepricaine, meprylcaine, metatobutocaine, myrtecaine, octacaine, orthocaine, 
oxethazine, parethoxycaine, piperocaine, piridocaine, piflocaine, procaine, propanocaine, 
propocaine, propoxycaine, pseudocaine, pyrrocaaine, ropivacaine, tollycaine, tricaine and 
trimocaine. Preferred anesthetic agents are lidocaine, proparacene and tetracaine. The 
anesthetic agents of the invention may be used in their neutral, uncharged form or their 
charged, cationic form.

While the ideal concentration of the pharmaceutically active agent will depend on a number 
of factors, the concentration will generally fall within 0.001 and 10 weight percent. 
Preferably, the pharmaceutically active agent is present in an amount from about 0.01 to 
2.0 weight percent. More preferably, the concentration of pharmaceutically active agent is 
about 0.1 to 1.5 weight percent. The preferred pharmaceutically active agent is an 
anesthetic; most preferably, lidocaine.

The previous disclosure will enable one having ordinary skill in the art to practice the 
invention. In order to better enable the reader to understand specific embodiments and the 
advantages thereof, reference to the following non-limiting examples is suggested.

Example 1
A solution was prepared by adding BS5111 sodium hyaluronate (Fermentech Medical 
Limited, Lot #4916) to purified water in amounts sufficient to produce a 1% sodium 
hyaluronate solution. The pH of the solution was 7.384.

Example 2
A solution was prepared in the same manner as in Example 1, but with 180 ppm of 
DEQUEST 2060. The pH of the solution was 7.451.

Example 3
A solution was prepared by adding BS5111 sodium hyaluronate to purified water in 
amounts sufficient to produce a 0.8% sodium hyaluronate solution. The pH of the solution 
was 7.190.
Example 4
A solution was prepared in the same manner as in Example 3, but with 120 ppm of DEQUEST 2060. The pH of the solution was 7.289.

Example 5
For all solutions, the viscosity of the sodium hyaluronate solution was measured initially and after exposure to a temperature of about 100 °C for about 4 hours to calculate a relative recovery of sodium hyaluronate after heating. An elevated temperature is used in order to accelerate the stability testing. The results are shown in Table 1 below and demonstrate the effectiveness of the DEQUEST in stabilizing the sodium hyaluronate.

<table>
<thead>
<tr>
<th>Sample (with/without DEQUEST)</th>
<th>Viscosity before heated (cps)</th>
<th>Viscosity after heated (cps)</th>
<th>The viscosity recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1 (without)</td>
<td>29180</td>
<td>5222, 5376</td>
<td>18.2</td>
</tr>
<tr>
<td>Example 2 (with)</td>
<td>26420</td>
<td>9676</td>
<td>36.6</td>
</tr>
<tr>
<td>Example 3 (without)</td>
<td>14590</td>
<td>1075</td>
<td>7.36</td>
</tr>
<tr>
<td>Example 4 (with)</td>
<td>11830, 11980</td>
<td>4608</td>
<td>38.7</td>
</tr>
</tbody>
</table>

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.
Claims:

1. A stabilized solution, comprising:
   (a) greater than about 0.3 weight percent of at least one polymer selected from the group consisting of poly(carboxylic acids) and salts thereof and mixtures thereof; and
   (b) at least one strong and stable chelating agent having at least one phosphonic acid group in an amount of from 0.0001 to 0.1 weight percent; and
   (c) water.

2. A composition of Claim 1, wherein said composition is ophthalmically compatible.

3. A composition of Claim 2, wherein said poly(carboxylic acids) is selected from the group consisting of hyaluronic acid and salts thereof.

4. A composition of Claim 1, wherein said solution is substantially free of hydrogen peroxide and sources of hydrogen peroxide.

5. A composition of Claim 1, wherein the concentration of said poly(carboxylic acid) is at least 0.8%.

6. A composition of Claim 1, wherein the concentration of said poly(carboxylic acid) is at least 1%.

7. A composition of Claim 3, wherein said chelating agent is selected from the group consisting of diethylene triamine penta(methylene phosphonic acid); hexamethylene-diaminetetra (methylene phosphonic acid); ethylenediaminetetra (methylene phosphonic acid); aminotrimethylene phosphonates; and mixtures thereof.

8. A composition of Claim 7, wherein said chelating agent is diethylene triamine penta(methylene phosphonic acid).

9. A composition of Claim 1, further comprising up to about 2 weight percent of a buffer.
10. A composition of Claim 1, further comprising 0.6 to 1.2 weight percent of a tonicity enhancer.

11. A composition of Claim 3, wherein said hyaluronic acid has an average molecular weight of at least 750,000.

12. A composition of Claim 11, wherein said hyaluronic acid has an average molecular weight of at least 1,200,000.

13. A composition of Claim 1, further comprising a pharmaceutically active agent.

14. A composition of Claim 13, wherein said pharmaceutically active agent is selected from the group consisting of miotic agents; mydriatic agents; and anesthetic agents.

15. A composition of Claim 14, wherein said pharmaceutically active agent is a miotic agent selected from the group consisting of pilocarpine, isopilocarpine, pilocarpine hydrochloride, pilocarpine nitrate, isopilocarpine hydrochloride, isopilocarpine nitrate, carbachol, physostigmine, phsysostigmine sulfate, phsyostigmine sulfite, demecarium bromide, ecothiophate iodide and acetylcholine chloride.

16. A composition of Claim 15, wherein said miotic agent is selected from the group consisting of members of the pilocarpine and isopilocarpine family of compounds.

17. A composition of Claim 14, wherein said pharmaceutically active agent is a mydriatic agent selected from the group consisting of atropine, atropine sulfate, atropine hydrochloride, atropine methylbromide, atropine methylnitrate, atropine hyperdure, atropine N-oxide, phenylephrine, phenylephrine hydrochloride, hydroxyamphetamine, hydroxyamphetamine hydrobromide, hydroxy-amphetamine hydrochloride, hydroxyamphetamine iodide, cyclopentolate, cyclopentolate hydrochloride, homatropine, homatropine hydrobromide, homatropine hydrochloride, homatropine methylbromide, scopolamine, scopolamine hydrobromide, scopolamine hydrochloride, scopolamine methylbromide, scopolamine methylnitrate, scopolamine N-oxide, tropicamide, tropicamide hydrobromide, and tropicamide hydrochloride.
18. A composition of Claim 17, wherein said mydriatic agent is selected from the group consisting of members of the atropine family and phenylephrine family of compounds.

19. A composition of Claim 14, wherein said pharmaceutically active agent is an anesthetic agent selected from the group consisting of lidocaine, proraracaine, tetracaine, phenacaine, naepaine, lidocaine, cocaine, betoxycaine, bupivacaine, butacaine, butanillicaine, butoxycaine, carticaine, cyclomethycaine, dibucaine, dimethocaine, etidocaine, formcaine, hexylicaine, hydroxytetracaine, leucinocaine, mepivacaine, meprylcaine, metaboloxycaine, myrtcale, octacaine, orthocaine, oxethazine, paretroxycaine, piperocaine, piridocaine, pfilocaine, procaine, propanocaine, propipocaine, propoxycaine, pseudocaine, pyroccaine, ropivacaine, tolylcaine, tricaine and trimecaine.

20. A composition of Claim 19, wherein said anesthetic agent is selected from the group consisting of lidocaine, proraracaine and tetracaine.

21. A method of stabilizing a hyaluronic acid composition, comprising the step of preparing said hyaluronic acid composition including about 1 to 10 weight percent of hyaluronic acid or salts or mixture thereof and at least one strong and stable amino tri(lower alkylene phosphonic acid) chelating agent in an amount of from 0.0001 to 0.1 weight percent, wherein said chelating agent is capable of complexing with free catalytic metal ions to produce a composition with metal ion complexes and whereby reducing the decomposition rate of the hyaluronic acid in said composition.

22. A method of Claim 21, wherein said chelating agent is selected from the group consisting of diethylene triamine penta(methylene phosphonic acid); hexamethylene-diaminetetra (methyleneephosphonic acid); ethylenediaminetetra (methyleneephosphonic acid); aminotrimethylene phosphonates; and mixtures thereof.

23. A method of Claim 22, wherein said chelating agent is diethylene triamine penta(methylene phosphonic acid).

24. In a method of performing surgery on an eye including employing a hyaluronic acid material during the performance of said surgery, the improvement, which comprises utilizing the formulation of Claim 3 as said hyaluronic acid material.