

INTERNATIONAL PATENT APPLICATION
FOR

**OPHTHALMIC FORMULATIONS COMPRISING MAGNESIUM ASCORBYL
PHOSPHATE**

BY

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[001] The present disclosure is related to ophthalmic formulations comprising magnesium ascorbyl phosphate (MAP). The present disclosure also provides methods of treating, improving, and/or ameliorating oxidative stress, symptoms thereof, or ocular diseases associated therewith, including ocular surface inflammation and dry eye disease, comprising administering to a subject a formulation comprising MAP. In some embodiments, the formulations and methods provide for cleansing, cleaning, conditioning, moisturizing, lubricating, hydrating, nourishing, soothing, calming, and/or refreshing ocular surface tissues.

[002] The formulations of the present disclosure may rebuild and/or nurture the homeostasis of the ocular surface and may provide essential antioxidants to an imbalanced eye to reduce oxidative stress.

[003] Metabolic reactions in the eye provide cellular energy necessary for its cellular activities. The metabolic reactions also result in by-products, commonly known as reactive oxidative species (ROS). ROS include radical and nonradical oxygen derivatives, such as hydrogen peroxide (H₂O₂), superoxide anion (O₂⁻), and hydroxy (OH) radicals. These ROS can damage components of the cell including lipids, proteins, and nucleic acids.

[004] Cells have an antioxidant system to counter the effects of ROS. However, an imbalance between the generation of ROS and the ability of natural antioxidants to neutralize the generated ROS sometimes occurs. This imbalance is known as oxidative stress. Oxidative stress has been reported to play an important role in a variety of ocular diseases including ocular surface inflammation and dry eye disease.

[005] Dry eye is defined by the DEWS Definition and Classification Subcommittee as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. (Ubels et al., *Curr. Eye Res.*, 28:437-444, 2002). Dry eye is a disorder of the ocular surface due to tear deficiency, excessive tear evaporation, or incorrect composition of tears.

[006] For most patients with mild oxidative stress or symptoms thereof, over-the-counter eye drops (OTC-DED) are the first line of therapy. These products offer temporary relief by providing replacement of naturally produced tears in patients with aqueous tear deficiency, acting as lubricants, diluting pro-inflammatory substances, and/or protecting against osmotic

stress. Some drops may contain antioxidants to counter the effects of ROS. Known antioxidants for ophthalmic formulations include erythritol.

[007] Ascorbic acid is a known antioxidant, used heavily in skin care products. However, it is not typically used in ophthalmic formulations because it causes strong stinging, burning, or irritation of the eye. In the present disclosure, magnesium ascorbyl phosphate (MAP) has been found to provide good antioxidant activity in the eye, but is also gentle on the eye, thereby eliminating stinging, burning, and/or irritation. MAP has also been found to be surprisingly stable at a physiological pH. Thereby, the ophthalmic formulations of the present disclosure supplement the naturally occurring antioxidants of the eye to treat, improve, and/or ameliorate oxidative stress.

BRIEF DESCRIPTION OF FIGURES

[008] In order to provide an understanding of the embodiments of the present disclosure, reference is made to the appended figures. The figures are exemplary and should not be construed as limiting the disclosure.

[009] Figure 1(A-C) are graphs showing metabolic activity and ROS production of a transformed human corneal epithelial cell line (Riken-HCEC) after 3.5 hours exposure to 0.5 mU GOx and various antioxidants, including MAP. Fig. 1B shows ROS production response over time. Two-way ANOVA with Dunnett's multiple comparisons showed a significantly higher (* $p < 0.05$) or lower (** $p < 0.05$) difference in metabolic activity after antioxidant exposure versus no GOx control (Fig. 1A) and AUC of ROS production after antioxidant exposure versus no GOx control and 0.5 mU GOx only control (Fig. 1C).

[0010] Figure 2(A-C) are graphs showing metabolic activity and ROS production of Riken-HCEC cells after 3.5 hours exposure to 0.25 mU GOx and various MAP concentrations. Fig. 2B shows ROS production response over time. Two-way ANOVA with Dunnett's multiple comparisons showed a significantly higher (* $p < 0.05$) or lower (** $p < 0.05$) difference in metabolic activity after antioxidant exposure versus no GOx control (Fig. 2A) and AUC of ROS production after antioxidant exposure versus no GOx control and 0.25 mU GOx only control (Fig. 2C).

[0011] Figure 3(A-D) are graphs showing metabolic activity and ROS production of Riken-HCEC cells after 3.5 hours exposure to 0.25 mU GOx and various MAP concentrations or an

over-the-counter (OTC) Nourishing Drop. Fig. 3C shows ROS production response over time. Two-way ANOVA with Dunnett's multiple comparisons showed a significantly higher (* $p < 0.05$) or lower (** $p < 0.05$) difference in metabolic activity after antioxidant/OTC drop exposure versus no GOx control (Fig. 3A) and no antioxidant control (Fig. 3B) and AUC of ROS production after antioxidant/OTC drop exposure versus no GOx control and 0.25 mU GOx only control (Fig. 3D).

[0012] The present disclosure will now be described more fully. However, the disclosure may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein.

[0013] Definitions of certain terms as used in this application are provided below. Unless defined otherwise, all technical and scientific terms used herein have the normal and common meaning that would be commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0014] As used herein, “a,” “an,” and “the” refer to one or more (*i.e.*, to at least one) of the grammatical object of the article.

[0015] The terms “patient,” “subject,” “individual,” and the like, as used herein, are interchangeable and all refer to any animal, which may be a human or a non-human animal.

[0016] As will be understood by one of ordinary skill in the art, when disclosed herein, each range includes all possible subranges as well as individual numerical values within that range. For example, a range of “1.0 to 5.0” includes and would be understood to specifically disclose subranges such as “1.0 to 3.0,” “1.5 to 3.7,” “2.1 to 4.3,” etc., as well as all individual numbers within the disclosed range, for example, 1.0, 1.1, 1.2, 1.3, etc.

[0017] As used herein, a formulation is “stable” if there is no visible appearance of flocculation and/or phase separation.

[0018] As used herein, a formulation is “shelf stable” if, after being stored at 20-25°C for 24 months, there is no visible appearance of flocculation and/or phase separation.

[0019] As noted above, the present disclosure is related to ophthalmic formulations comprising magnesium ascorbyl phosphate (MAP). The formulations may be useful for treating, improving, and/or ameliorating oxidative stress and symptoms thereof. In some

embodiments, the formulations and methods provide for conditioning, soothing, calming, and/or refreshing ocular surface tissues.

[0020] In some embodiments, the ophthalmic formulations disclosed herein comprise at least one natural humectant. In some embodiments, the at least one natural humectant is chosen from glycerin, trehalose, sucrose, and sodium hyaluronate. In some embodiments, ophthalmic formulations comprise glycerin. In some embodiments, the ophthalmic formulations comprise trehalose. In some embodiments, the ophthalmic formulations comprise glycerin and trehalose.

[0021] In some embodiments, the ophthalmic formulations disclosed herein comprise at least one amino acid chosen from arginine, leucine, taurine, proline, lysine, and methionine. In some embodiments, the ophthalmic formulation comprises arginine, leucine, and taurine.

[0022] In some embodiments, the ophthalmic formulations disclosed herein comprise at least one vitamin chosen from vitamin C and vitamin B₁₂. In some embodiments, the formulation comprises vitamin C and vitamin B₁₂.

[0023] In some embodiments, the ophthalmic formulations disclosed herein comprise at least one natural humectant and at least one amino acid. In some embodiments, the ophthalmic formulations disclosed herein comprise at least one natural humectant and at least one vitamin. In some embodiments, the ophthalmic formulations disclosed herein comprise at least one natural humectant, at least one amino acid, and at least one vitamin.

[0024] In some embodiments, the ophthalmic formulations disclosed herein are in the form of eye drops, eye sprays, aqueous solutions, suspensions, microemulsions, ointments, conjunctival inserts, gels, or other suitable medicinal or cosmetic preparations. In some embodiments, the ophthalmic formulations disclosed herein are eye drops, eye sprays, or aqueous solutions. In some embodiments the aqueous solutions are packaging solutions. In some embodiments, the packaging solutions are solutions for contact lenses or other ophthalmic medical or cosmetic devices.

[0025] In some embodiments the pH of the ophthalmic formulation is in a range of 6 to 8. In some embodiments the pH of the formulation is in a range of 6 to 7. In some embodiments the pH of the ophthalmic formulation is in a range of 7 to 8. In some embodiments the pH of the ophthalmic formulation is 6.0. In some embodiments the pH of the ophthalmic

formulation is 6.5. In some embodiments the pH of the ophthalmic formulation is 7.0. In some embodiments the pH of the ophthalmic formulation is 7.5. In some embodiments the pH of the ophthalmic formulation is 8.0.

[0026] In some embodiments, the ophthalmic formulations disclosed herein are stable. In some embodiments, the ophthalmic formulations are shelf-stable.

[0027] In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.75 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.6 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.5 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.4 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.3 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.25 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.2 pH units. In some embodiments, after being stored at 20-25°C for 24 months, the pH of the ophthalmic formulation does not drop more than 0.1 pH units.

[0028] In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 50 mOsm. In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 40 mOsm. In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 30 mOsm. In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 25 mOsm. In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 20 mOsm. In some embodiments, after being stored at 20-25°C for 24 months, the osmolality of the ophthalmic formulation does not increase more than 15 mOsm.

[0029] In some embodiments, the ophthalmic formulation is packaged in a sealed package. In some embodiments, the ophthalmic formulation is sealed in a plastic bottle. In some

embodiments, the plastic bottle is made of polyethylene. In some embodiments, the plastic bottle is made of polypropylene. In some embodiments, the plastic bottle is made of polyethylene terephthalate (PET).

[0030] Accordingly, in some embodiments, MAP is used as a stabilizing agent for ophthalmic formulations. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.01-1%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.1-0.9%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.25-0.75%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.4-0.6%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.01-0.5%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.02-0.2%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.05-0.15%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.01%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.02%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.025%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.05%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.1%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.15%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.2%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.25%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.3%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.35%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.4%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.45%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.5%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.55%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.6%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.65%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.7%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.75%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.8%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.85%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 0.9%. In some embodiments, the concentration of MAP in an

ophthalmic formulation is 0.95%. In some embodiments, the concentration of MAP in an ophthalmic formulation is 1%.

[0031] In some embodiments, the ophthalmic formulation disclosed herein is sterilized by filtration, autoclaving, gamma irradiation and/or electron-beam. In some embodiments, the ophthalmic formulation is sterilized by filtration. In some embodiments, the ophthalmic formulation is sterilized by autoclaving. In some embodiments, the ophthalmic formulation is sterilized by filtration and autoclaving. In some embodiments, the ophthalmic formulation is sterilized by gamma irradiation. In some embodiments, the ophthalmic formulation is sterilized by electron-beam.

[0032] The ophthalmic formulations disclosed herein may be prepared according to any known method for the manufacture of cosmetic formulations or preparations. As will be appreciated by those of ordinary skill in the art, a number of methods are known.

[0033] In some embodiments, the ophthalmic formulations disclosed herein are useful for cleansing, cleaning, conditioning, moisturizing, lubricating, hydrating, nourishing, soothing, calming, and/or refreshing, ocular surface tissues. In some embodiments, formulations disclosed herein improve and/or ameliorate oxidative stress, symptoms thereof, or ocular diseases associated therewith, including ocular surface inflammation and dry eye disease. In some embodiments, formulations disclosed herein are suitable for adults, children, and contact-lens wearers.

[0034] Accordingly, provided herein are methods of cleansing, cleaning, conditioning, moisturizing, lubricating, hydrating, nourishing, soothing, calming, and/or refreshing ocular surface tissues, comprising applying to said ocular surface tissues an ophthalmic formulation as disclosed herein. In some embodiments, provided herein are methods of improving, and/or ameliorating oxidative stress, symptoms thereof, or ocular diseases associated therewith, including ocular surface inflammation and dry eye disease. The methods disclosed herein comprise applying to ocular surface tissues an ophthalmic formulation as disclosed herein.

[0035] Descriptions of the disclosed embodiments are not exhaustive and are not limited to the precise forms or exemplary embodiments disclosed. Modifications and adaptations of the exemplary embodiments will be apparent from consideration of the specification and practice of the disclosed embodiments.

[0036] Without limitation, some embodiments of the disclosure include:

[0037] Exemplary Formulations

[0038] Embodiment A: An ophthalmic formulation comprising magnesium ascorbyl phosphate (MAP).

[0039] Embodiment B: The ophthalmic formulation according to Embodiment A, wherein the concentration of MAP in the formulation is 0.01-1%, for example, 0.1-0.9%, 0.25-0.75%, 0.4-0.6%, 0.01-0.5%, 0.02-0.2%, 0.05-0.15%, 0.01%, 0.02%, 0.025%, 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, or 1%.

[0040] Embodiment C: The ophthalmic formulation according to any of Embodiments A-B, wherein the concentration of MAP in the formulation is 0.01-0.5%, for example, 0.02-0.2%, 0.05-0.15%, or 0.1%.

[0041] Embodiment D: The ophthalmic formulation according to any of Embodiments A-C, wherein the concentration of MAP in the formulation is 0.02-0.2%, for example, 0.05-0.15% or 0.1%.

[0042] Embodiment E: The ophthalmic formulation according to any of Embodiments A-D, wherein the formulation further comprises at least one natural humectant, for example, glycerin, trehalose, sucrose, sodium hyaluronate, or a combination thereof.

[0043] Embodiment F: The ophthalmic formulation according to any of Embodiments A-E, wherein the formulation further comprises at least one amino acid, for example, arginine, leucine, taurine, proline, lysine, methionine, or a combination thereof, and at least one vitamin, for example, vitamin C, vitamin B₁₂, or a combination thereof.

[0044] Embodiment G: The ophthalmic formulation according to any of Embodiments A-F, wherein the pH of the formulation is in a range of 6 to 8, for example, the pH of the formulation is in a range of 6 to 7 or 7 to 8 or the pH of the formulation is 6.0, 6.5, 7.0, 7.5, or 8.0.

[0045] Embodiment H: The ophthalmic formulation according to any of Embodiments A-G, wherein the formulation is stable.

[0046] Embodiment I: The ophthalmic formulation according to any of Embodiments A-H, wherein the formulation counteracts reactive oxidative species (ROS).

[0047] Embodiment J: The ophthalmic formulation according to any of Embodiments A-I, wherein the formulation does not cause stinging of the eye, burning of the eye, irritation of the eye, or a combination thereof.

[0048] Embodiment K: The ophthalmic formulation according to any of Embodiments A-J, wherein the formulation treats, improves, and/or ameliorates oxidative stress and symptoms thereof.

[0049] Embodiment L: The ophthalmic formulation according to any of Embodiments A-K, wherein the formulation treats, improves, and/or ameliorates dry eye disease.

[0050] Embodiment M: The ophthalmic formulation according to any of Embodiments A-L, wherein the formulation comprises glycerin, trehalose, L-arginine, L-taurine, and/or L-leucine.

[0051] Embodiment N: The ophthalmic formulation according to any of Embodiments A-M, wherein the formulation is a product selected from eye drops, eye sprays, aqueous solutions, suspensions, microemulsions, ointments, conjunctival inserts, gels, and other suitable medicinal or cosmetic preparations.

[0052] Embodiment O: The ophthalmic formulation according to any of Embodiments A-N, wherein the formulation is a product selected from eye drops, eye sprays, and aqueous solutions.

[0053] Embodiment P: The ophthalmic formulation according to any of Embodiments A-O, wherein the aqueous solutions are packaging solutions.

[0054] Embodiment Q: The ophthalmic formulation according to any of Embodiments A-P, wherein the packaging solutions are solutions for contact lenses or other ophthalmic medical or cosmetic devices.

[0055] Exemplary Methods

[0056] Embodiment AA: A method of stabilizing an ophthalmic formulation comprising including MAP in said formulation.

[0057] Embodiment BB: The method according to Embodiment AA, wherein the concentration of MAP in the formulation is 0.01-1%, for example, 0.1-0.9%, 0.25-0.75%, 0.4-0.6%, 0.01-0.5%, 0.02-0.2%, 0.05-0.15%, 0.01%, 0.02%, 0.025%, 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, or 1%.

[0058] Embodiment CC: The method according to any of Embodiments AA-BB, wherein the concentration of MAP in the formulation is 0.01-0.5%, for example, 0.02-0.2%, 0.05-0.15%, or 0.1%.

[0059] Embodiment DD: The method according to any of Embodiments AA-CC, wherein the concentration of MAP in the formulation is 0.02-0.2%, for example, 0.05-0.15%, or 0.1%.

[0060] Embodiment EE: The method according to any of Embodiments AA-DD, wherein the formulation further comprises at least one natural humectant, for example, glycerin, trehalose, sucrose, sodium hyaluronate, or a combination thereof.

[0061] Embodiment FF: The method according to any of Embodiments AA-EE, wherein the formulation further comprises at least one amino acid, for example, arginine, leucine, taurine, proline, lysine, methionine, or a combination thereof, and at least one vitamin, for example, vitamin C, vitamin B₁₂, or a combination thereof.

[0062] Embodiment GG: The method according to any of Embodiments AA-FF, wherein the pH of the formulation is in a range of 6 to 8, for example, the pH of the formulation is in a range of 6 to 7 or 7 to 8 or the pH of the formulation is 6.0, 6.5, 7.0, 7.5, or 8.0.

[0063] Embodiment HH: The method according to any of Embodiments AA-GG, wherein the formulation is stable.

[0064] Embodiment II: The method according to any of Embodiments AA-HH, wherein the formulation counteracts reactive oxidative species (ROS).

[0065] Embodiment JJ: The method according to any of Embodiments AA-II, wherein the formulation does not cause stinging of the eye, burning of the eye, irritation of the eye, or a combination thereof.

[0066] Embodiment KK: The method according to any of Embodiments AA-JJ, wherein the formulation treats, improves, and/or ameliorates oxidative stress and symptoms thereof.

[0067] Embodiment LL: The method according to any of Embodiments AA-KK, wherein the formulation treats, improves, and/or ameliorates dry eye disease.

[0068] Embodiment MM: The method according to any of Embodiments AA-LL, wherein the formulation comprises glycerin, trehalose, L-arginine, L-taurine, and/or L-leucine.

[0069] Embodiment NN: The method according to any of Embodiments AA-MM, wherein the formulation is a product selected from eye drops, eye sprays, aqueous solutions, suspensions, microemulsions, ointments, conjunctival inserts, gels, and other suitable medicinal or cosmetic preparations.

[0070] Embodiment OO: The method according to any of Embodiments AA-NN, wherein the formulation is a product selected from eye drops, eye sprays, and aqueous solutions.

[0071] Embodiment PP: The method according to any of Embodiments AA-OO, wherein the aqueous solutions are packaging solutions.

[0072] Embodiment QQ: The method according to any of Embodiments AA-PP, wherein the packaging solutions are solutions for contact lenses or other ophthalmic medical or cosmetic devices.

[0073] Exemplary Uses

[0074] Embodiment AAA: Use of MAP as an antioxidant in an ophthalmic formulation.

[0075] Embodiment BBB: The use according to Embodiment AAA, wherein the concentration of MAP in the formulation is 0.01-1%, for example, 0.1-0.9%, 0.25-0.75%, 0.4-0.6%, 0.01-0.5%, 0.02-0.2%, 0.05-0.15%, 0.01%, 0.02%, 0.025%, 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, or 1%.

[0076] Embodiment CCC: The use according to any of Embodiments AAA-BBB, wherein the concentration of MAP in the formulation is 0.01-0.5%, for example, 0.02-0.2%, 0.05-0.15%, or 0.1%.

[0077] Embodiment DDD: The use according to any of Embodiments AAA-CCC, wherein the concentration of MAP in the formulation is 0.02-0.2%, for example, 0.05-0.15%, or 0.1%.

[0078] Embodiment EEE: The use according to any of Embodiments AAA-DDD, wherein the formulation further comprises at least one natural humectant, for example, glycerin, trehalose, sucrose, sodium hyaluronate, or a combination thereof.

[0079] Embodiment FFF: The use according to any of Embodiments AAA-EEE, wherein the formulation further comprises at least one amino acid, for example, arginine, leucine, taurine, proline, lysine, methionine, or a combination thereof, and at least one vitamin, for example, vitamin C, vitamin B₁₂, or a combination thereof.

[0080] Embodiment GGG: The use according to any of Embodiments AAA-FFF, wherein the pH of the formulation is in a range of 6 to 8, for example, the pH of the formulation is in a range of 6 to 7 or 7 to 8 or the pH of the formulation is 6.0, 6.5, 7.0, 7.5, or 8.0.

[0081] Embodiment HHH: The use according to any of Embodiments AAA-GGG, wherein the formulation is stable.

[0082] Embodiment III: The use according to any of Embodiments AAA-HHH, wherein the formulation counteracts reactive oxidative species (ROS).

[0083] Embodiment JJJ: The use according to any of Embodiments AAA-III, wherein the formulation does not cause stinging of the eye, burning of the eye, irritation of the eye, or a combination thereof.

[0084] Embodiment KKK: The use according to any of Embodiments AAA-JJJ, wherein the formulation treats, improves, and/or ameliorates oxidative stress and symptoms thereof.

[0085] Embodiment LLL: The use according to any of Embodiments AAA-KKK, wherein the formulation treats, improves, and/or ameliorates dry eye disease.

[0086] Embodiment MMM: The use according to any of Embodiments AAA-LLL, wherein the formulation comprises glycerin, trehalose, L-arginine, L-aurine, and/or L-leucine.

[0087] Embodiment NNN: The use according to any of Embodiments AAA-MMM, wherein the formulation is a product selected from eye drops, eye sprays, aqueous solutions,

suspensions, microemulsions, ointments, conjunctival inserts, gels, and other suitable medicinal or cosmetic preparations.

[0088] Embodiment OOO: The use according to any of Embodiments AAA-NNN, wherein the formulation is a product selected from eye drops, eye sprays, and aqueous solutions.

[0089] Embodiment PPP: The use according to any of Embodiments AAA-OOO, wherein the aqueous solutions are packaging solutions.

[0090] Embodiment QQQ: The use according to any of Embodiments AAA-PPP, wherein the packaging solutions are solutions for contact lenses or other ophthalmic medical or cosmetic devices.

EXAMPLES

EXAMPLE 1: Exemplary formulation

[0091] Ophthalmic formulations of the present disclosure can be prepared with ingredients as listed in **Table 1** below.

Table 1

Ingredient	% w/w
Glycerin	0.750
Trehalose	0.500 (13 mmol/L)
Sodium hyaluronate	0.240
Sodium chloride	0.300
Potassium chloride	0.140 (18.8 mmol/L)
Magnesium ascorbyl phosphate	0.100 (3.2 mmol/L)
Sodium citrate	0.060 (2 mmol/L)
L-Arginine	0.050 (2.9 mmol/L)
Citric acid	0.024 (1.4 mmol/L)
L-Taurine	0.020 (1.6 mmol/L)
L-Leucine	0.020 (1.6 mmol/L)
Calcium chloride	0.020 (1.36 mmol/L)
Sodium bicarbonate	0.005 (1.8 mmol/L)
Cyanocobalamin (B ₁₂)	0.004
Purified water	Q.S. to 100 % volume

[0092] Formulations with the ingredients listed above can be prepared by mixing the recited ingredients, for example according to the proposed manufacturing process below:

1. In an appropriate mixing vessel, add volume of water equivalent to 80 % of the total batch weight.
2. Sprinkle in sodium hyaluronate while mixing, until the polymer is fully hydrated, NLT 1 hour to ensure homogenous dispersing.
3. Slowly add batch quantities of the remaining ingredients to the solution. Mix NLT 30 minutes to ensure complete dissolution. For example, one order of addition could be: glycerin, trehalose, sodium chloride, potassium chloride, calcium chloride, magnesium ascorbyl phosphate, sodium citrate, citric acid, sodium bicarbonate, amino acids, and vitamin B₁₂ (cyanocobalamin).
4. Q.S. to 100% batch weight with purified water.
5. Sterile filter the formulation with an appropriate sterilizing filter (0.2 µm PES).

[0093] The pH, osmolality, and color of the formulations are assessed.

[0094] A pH adjuster could be added. For example, sodium hydroxide and/or hydrochloric acid may be added to adjust pH. As a non-limiting example, 1N sodium hydroxide could be added to obtain a pH of 7.5.

[0095] Other key ingredients could be added. For example, at least one amino acid chosen from L-proline, L-lysine, and L-methionine, or combinations thereof. Propylene glycol could also be used as an additional humectant, and sucrose could be used as an alternative saccharide. Copper and/or zinc could be added as an additional nutritional component. These metals are added to vitamin supplements and operate as vitamin co-factors. For example, copper could be added in an amount of about 5 ppm and zinc could be added at higher levels.

EXAMPLE 2: A study to test the effects of antioxidants on metabolic activity and ROS production in Riken human corneal epithelial cells

[0096] Purpose: To determine the cell metabolic activity and ROS production of Riken-HCEC exposed to MAP in glucose oxidase (GOx).

[0097] Methods: Riken-HCEC were seeded in a 96 well plate. After culture for 72h in Dulbecco's Modified Eagles Medium/Hams-F12 (DMEM/F12), cell medium was changed, and cells were incubated for an additional 24 h. Cells were pre-exposed to 5 µM CellROX Green (CRG) for 30 minutes with erythritol, glycerin, or MAP. The CRG solution was removed, and cells were then exposed to 0.5 mU or 0.25 mU GOx with erythritol, glycerin,

and/or MAP as shown in **Table 2** below. OTC Nourishing Drop, having a formulation as defined in **Table 1** above, was also tested with GOx. GOx-initiated ROS production measured by CRG fluorescence was read every 30 minutes for 3.5 hours. After 3.5 hours, the cells were exposed to alamarBlue™ for metabolic activity determination.

Table 2: Experimental Design

Experimental Formulation
Control (no GOx)
0.5 mU GOx
0.5 mU GOX + 0.9% Erythritol
0.5 mU GOX + 0.9% Glycerin
0.5 mU GOX + 0.9% Erythritol + 0.9% Glycerin
0.5 mU GOX + 0.1% MAP
0.25 mU GOx
0.25 mU GOx + 0.9% Erythritol + 0.9% Glycerin
0.25 mU GOx + 0.025% MAP
0.25 mU GOx + 0.05% MAP
0.25 mU GOx + 0.1% MAP
0.25 mU GOx+ 50% Nourishing Drop

[0098] ROS Analysis: GOx initiated ROS production was measured by CRG fluorescence every 30 minutes for 3.5 hours.

[0099] Metabolic Activity Analysis: Riken-HCEC lines were assessed for metabolic activity, using alamarBlue™. In brief, cells were washed 1X with 0.2 ml/well Dulbecco's Modified Eagle's medium (DMEM). The alamarBlue™ solution was diluted in DMEM at 10% v/v, and then pre-warmed in a water bath, and 0.1 ml solution was added per well. Each plate was incubated for 3 hours at 37 °C, 5% CO₂, and 95% relative humidity. Each plate was read on a fluorescent microplate reader and results were assayed using relative fluorescence units (RFUs).

[00100] Antioxidant activity was assessed by comparing AUC of RFUs for each Riken-HCEC test group to the GOx-only control. Specifically, integrated responses of the

change in RFUs from ROS production were analyzed by calculating the areas under the curve (AUC) for each test well over the time course using the trapezoidal rule, which is defined by the following equation:

$$\Sigma (\text{Time (Hr)} \cdot n - (n-1)) \times (\text{ROS production (RFUs)} \cdot n + n-1) / 2 = \text{RFUs} \cdot \text{Hr}$$

[00101] Results

[00102] Metabolic Activity: For cells treated with 0.25 and 0.5 mU, GOx, metabolic activity was significantly decreased by addition of GOx versus no GOx control (see **Fig. 1A** and **Fig. 2A**). Moreover, metabolic activity was significantly decreased in cells receiving GOx with MAP antioxidant versus GOx only (see **Fig. 3A** and **Fig. 3B**).

[00103] ROS Production: For cells treated with 0.25 and 0.5 mU GOx, ROS production was reduced by the addition of erythritol and/or glycerin and MAP, with MAP having the greatest reduction relative to the no GOx control (see **Fig. 1B** and **Fig. 2B**).

[00104] For cells treated with 0.5 mU GOx, AUC indicated that all GOx exposures were significantly higher versus the no GOx control. AUC also indicated that all exposures, except 0.9% erythritol, were significantly reduced versus 0.5 mU GOx only. MAP exposure resulted in the greatest AUC reduction (see **Fig. 1C**).

[00105] For cells treated with 0.25 mU GOx, AUC similarly indicated that all GOx exposures were significantly higher versus the no GOx control. Likewise, all exposures to 0.9% erythritol + 0.9% glycerin and each of 0.025%, 0.05%, and 0.1% MAP were significantly reduced versus 0.25 mU GOx only, with each of the MAP exposures resulting in the greatest AUC reduction (see **Fig. 2C**). Exposure to 50% OTC Nourishing Drop similarly exhibited significant reduction in AUC versus 0.25 mU GOx only. However, MAP exposures resulted in greater reductions than the OTC Nourishing Drop (see **Fig. 3C** and **Fig. 3D**).

EXAMPLE 3: A study to test the effects of MAP on ocular irritation

[00106] Purpose: To evaluate the ocular irritation of MAP in citrate borate solution packaged in PET bottle, following topical ocular administration to New Zealand white rabbits up to 3 times daily for up to 6 days.

[00107] Formulations: The Test Articles employed are illustrated in Table 3 below.

Table 3

Ingredient	Test Article A	Test Article B
Magnesium ascorbyl phosphate	1% w/w	5% w/w
Citric Acid	0.18% w/w	0.18% w/w
Sodium Borate	0.6% w/w	0.6% w/w
Hydrochloric Acid (6N)	Q.S. to pH 7.45	--
Sodium Hydroxide (2N)	--	Q.S. to pH 7.4

[00108] Methods: Dosing occurred in a stepwise manner beginning on Day 1 with Test Article A (low dose – 1% MAP in citrate borate solution). Because macroscopic ocular examinations after each dose of Test Article A did not yield results indicative of a positive irritation response, animals were dosed with Test Article B (high dose – 5% MAP in citrate borate solution) for Days 2-6. Test Articles were instilled into the right eye of each animal via micropipette. Instillation was made in the cup formed after the lower eyelid (conjunctival sac) was gently pulled away from the globe (eyeball). Lids were held together for approximately one second after instillation. The left eye remained untreated as a control. Animals were dosed 100 µL three times per day (TID).

[00109] On Day 1 prior to the first dose administration, all eyes were examined microscopically via slit lamp with fluorescein stain. Eyes were also examined macroscopically using the Draize scoring system. Both examinations confirmed that all animals had clinically normal eyes prior to initiation of dosing.

[00110] The animals' eyes were examined four times daily using the Draize Method. Scoring was performed just prior to the first dose instillation and 30±15 minutes after each dose administration. Positive or negative irritation scores were as follows.

[00111] Positive irritation score: Scores of >1 for conjunctival redness, >1 for conjunctival chemosis, >0 for corneal opacity, and/or >0 for iris involvement. A positive irritation score was not considered clinically significant.

[00112] Negative irritation score: Scores of ≤1 for conjunctival redness, ≤1 for conjunctival chemosis, 0 for corneal opacity, and/or 0 for iris involvement.

[00113] On Day 6, after a minimum of 10 minutes after the last dose instillation, the animals were examined microscopically using slit lamp with fluorescein stain as previously described.

[00114] Results

[00115] All results indicate that MAP in a citrate borate solution did not elicit a positive irritation response. There were no scores for irritation observed in either the right (test) or left (control) eyes at any observation point throughout the study.

Table 4: Individual Microscopic Ocular Examinations – McDonald Shadduck Scoring

Animal	Eye	Conjunctiva			Aqueous flare	Iris Involvement	Cornea			Lens (N or A)
		Congestion	Swelling	Discharge			Severity of Opacity	Area of Opacity	Pannus	
Pre-dose Observations										
1	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
2	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
3	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
4	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
5	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
Day 6, Post-dose										
1	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
2	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
3	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
4	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N
5	R	0	0	0	0	0	0	0	0	N
	L	0	0	0	0	0	0	0	0	N

N: Normal; A: Abnormal

[00116] The McDonald Shadduck score system is outlined below.

[00117] **Conjunctival Congestion**

0 = Normal. May appear blanched to reddish pink without perilimbal injection (except at 12:00 and 6:00 o'clock positions) with vessels of the palpebral and bulbar conjunctiva easily observed.

1 = A flushed, reddish color predominately confined to the palpebral conjunctiva with some perilimbal injection but primarily confined to the lower and upper parts of the eye from the 4:00 and 7:00 and 11:00 to 1:00 o'clock positions.

2 = Bright red color of the palpebral conjunctiva with accompanying perilimbal injection covering at least 75% of the circumference of the perilimbal region.

3 = Dark, beefy red color with congestion of both the bulbar and the palpebral conjunctiva along with pronounced perilimbal injection and the presence of petechia on the conjunctiva. The petechia generally predominate along the nictitating membrane.

[00118] **Conjunctival Swelling**

0 = Normal or no swelling of the conjunctival tissue.

1 = Swelling above normal without eversion of the lids (can be easily ascertained by noting that the upper and lower eyelids are positioned as in the normal eye); swelling generally starts in the lower cul-de-sac near the inner canthus, which needs slit-lamp examination.

2 = Swelling with misalignment of the normal approximation of the lower and upper eyelids; primarily confined to the upper eyelid so that in the initial stages the misapproximation of the eyelids begins by partial eversion of the upper eyelid. In this stage, swelling is confined generally to the upper eyelid, although it exists in the lower cul-de-sac (observed best with the slit-lamp).

3 = Definite swelling with partial eversion of the upper and lower eyelids essentially equivalent. This can be easily ascertained by looking at the animal

head-on and noticing the positioning of the eyelids; if the eye margins do not meet, eversion has occurred.

4 = Eversion of the upper eyelids is pronounced with less pronounced eversion of the lower eyelid. It is difficult to retract the lids and observe the perilimbal region.

[00119] Conjunctival Discharge

[00120] Discharge is defined as a whitish, gray precipitate, which should not be confused with the small amount of clear, inspissated, mucoid material that can be formed in the medial canthus of a substantial number of rabbit eyes.

0 = Normal. No discharge.

1 = Discharge above normal and present on the inner portion of the eye but not on the lids or hairs of the eyelids. One can ignore the small amount that is in the inner and outer canthus.

2 = Discharge is abundant, easily observed, and has collected on the lids and around the hairs of the eyelids.

3 = Discharge has been flowing over the eyelids so as to wet the hairs substantially on the skin around the eye.

[00121] Aqueous Flare

[00122] The intensity of the Tyndall phenomenon is scored by comparing the normal Tyndall effect observed when the slit-lamp beam passes through the lens with that seen in the anterior chamber. The presence of aqueous flare is presumptive evidence of breakdown of the blood-aqueous barrier.

0 = The absence of visible light beam light in the anterior chamber (no Tyndall effect).

1 = The Tyndall effect is barely discernible. The intensity of the light beam in the anterior chamber is less than the intensity of the slit beam as it passes through the lens.

2 = The Tyndall beam in the anterior chamber is easily discernible and is equal in intensity to the slit beam as it passes through the lens.

3 = The Tyndall beam in the anterior chamber is easily discernible; its intensity is greater than the intensity of the slit beam as it passes through the lens.

[00123] Iris Involvement

[00124] In the following definitions the primary, secondary, and tertiary vessels are utilized as an aid to determining a subjective ocular score for iris involvement. The assumption is made that the greater the hyperemia of the vessels and the more the secondary and tertiary vessels are involved, the greater the intensity of iris involvement.

0 = Normal iris without any hyperemia of the iris vessels. Occasionally around the 12:00 to 1:00 o'clock position near the pupillary border and the 6:00 to 7:00 o'clock position near the pupillary border there is a small area around 1-3 mm in diameter in which both the secondary and tertiary vessels are slightly hyperemic.

1 = Minimal injection of secondary vessels but not tertiary. Generally, it is uniform, but may be of greater intensity at the 1:00 or 6:00 o'clock position. If it is confined to the 1:00 or 6:00 o'clock position, the tertiary vessels must be substantially hyperemic.

2 = Minimal injection of tertiary vessels and minimal to moderate injection of the secondary vessels.

3 = Moderate injection of the secondary and tertiary vessels with slight swelling of the iris stroma (this gives the iris surface a slightly rugose appearance, which is usually most prominent near the 3:00 and 9:00 o'clock positions).

4 = Marked injection of the secondary and tertiary vessels with marked swelling of the iris stroma. The iris appears rugose; may be accompanied by hemorrhage (hyphema) in the anterior chamber.

[00125] Cornea

[00126] The scoring scheme measures the severity of corneal cloudiness and the area of the cornea involved. Severity of corneal cloudiness is graded as follows:

0 = Normal cornea. Appears with the slit-lamp as having a bright gray line on the epithelial surface and a bright gray line on the endothelial surface with a marble-like gray appearance of the stroma.

1 = Some loss of transparency. Only the anterior half of the stroma is involved as observed with an optical section of the slit-lamp. The underlying structures are clearly visible with diffuse illumination, although some cloudiness can be readily apparent with diffuse illumination.

2 = Moderate loss of transparency. In addition to involving the anterior stroma, the cloudiness extends all the way to the endothelium. The stroma has lost its marble-like appearance and is homogeneously white. With diffuse illumination, underlying structures are clearly visible.

3 = Involvement of the entire thickness of the stroma. With optical section, the endothelial surface is still visible. However, with diffuse illumination the underlying structures are just barely visible (to the extent that the observer is still able to grade flare, iritis, observe for pupillary response, and note lenticular changes).

4 = Involvement of the entire thickness of the stroma. With the optical section, cannot clearly visualize the endothelium. With diffuse illumination, the underlying structures cannot be seen. Cloudiness removes the capability for judging and grading aqueous flare, iritis, lenticular changes, and pupillary response.

The surface area of the cornea relative to the area of cloudiness is divided into five grades from 0 to 4.

0 = Normal cornea with no area of cloudiness.

1 = 1-25% area of stromal cloudiness.

2 = 26-50% area of stromal cloudiness.

3 = 51-75% area of stromal cloudiness.

4 = 76-100% area of stromal cloudiness.

[00127] Pannus

[00128] Pannus is vascularization or the penetration of new blood vessels into the corneal stroma. The vessels are derived from the limbal vascular loops. Pannus is divided into three grades.

0 = No pannus.

1 = Vascularization is present but vessels have not invaded the entire corneal circumference. Where localized vessel invasion has occurred, they have not penetrated beyond 2 mm.

2 = Vessels have invaded 2 mm or more around the entire corneal circumference.

[00129] Fluorescein

[00130] The use of fluorescein is a valuable aid in defining epithelial damage. The area of staining can be judged on a 0 to 4 scale using the same terminology as for corneal cloudiness.

0 = Absence of fluorescein staining.

1 = Slight fluorescein staining confined to a small focus. With diffuse illumination the underlying structures are easily visible. (The outline of the pupillary margin is as if there were no fluorescein staining.)

2 = Moderate fluorescein staining confined to a small focus. With diffuse illumination the underlying structures are clearly visible, although there is some loss of detail.

3 = Marked fluorescein staining. Staining may involve a larger portion of the cornea. With diffuse illumination the underlying structures are barely visible but are not completely obliterated.

4 = Extreme fluorescein staining. With diffuse illumination the underlying structures cannot be observed.

[00131] Lens

[00132] The lens should be evaluated routinely during ocular evaluations and graded as either normal (N) or abnormal (A).

Table 5: Individual Macroscopic Ocular Examinations – Gross Ocular Observations (Draize)

Day 1, Pre-dose (Test Article A – 1%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 1, Post-dose #1 (Test Article A – 1%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 1, Post-dose #2 (Test Article A – 1%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 1, Post-dose #3 (Test Article A – 1%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 2, Pre-dose (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Day 2, Post-dose #1 (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 2, Post-dose #2 (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 2, Post-dose #3 (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 3, Pre-dose (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Day 3, Post-dose #1 (Test Article B – 5%)																			
Animal	Cornea						Iris				Conjunctiva								Total Score
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Day 3, Post-dose #2 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 3, Post-dose #3 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 4, Pre-dose (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 4, Post-dose #1 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 4, Post-dose #2 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Day 4, Post-dose #3 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 5, Pre-dose (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 5, Post-dose #1 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 5, Post-dose #2 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 5, Post-dose #3 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Day 6, Pre-dose (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 6, Post-dose #1 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 6, Post-dose #2 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Day 6, Post-dose #3 (Test Article B – 5%)																				
Animal	Cornea						Iris				Conjunctiva								Total Score	
	Opacity (A)		Area (B)		Subtotal AxBx5=		Score (A)		Subtotal Ax5=		Redness (A)		Chemosis (B)		Discharge (B)		Subtotal (A+B+C)x2			
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

What is claimed:

1. An ophthalmic formulation comprising magnesium ascorbyl phosphate (MAP).
2. The ophthalmic formulation according to claim 1, wherein the concentration of MAP in the formulation is 0.01-1%.
3. The ophthalmic formulation according to claim 1 or 2, wherein the concentration of MAP in the formulation is 0.01-0.5%.
4. The ophthalmic formulation according to any one of claims 1-3, wherein the concentration of MAP in the formulation is 0.02-0.2%.
5. The ophthalmic formulation according to any one of claims 1-4, wherein the formulation further comprises at least one natural humectant.
6. The ophthalmic formulation according to any one of claims 1-5, wherein the formulation further comprises at least one amino acid and at least one vitamin.
7. The ophthalmic formulation according to any one of claims 1-6, wherein the pH of the formulation is in a range of 6 to 8.
8. The ophthalmic formulation according to any one of claims 1-7, wherein the formulation is stable.
9. The ophthalmic formulation according to any one of claims 1-8, wherein the formulation counteracts reactive oxidative species (ROS).
10. The ophthalmic formulation according to any one of claims 1-9, wherein the formulation does not cause stinging of the eye, burning of the eye, irritation of the eye, or a combination thereof.
11. The ophthalmic formulation according to any one of claims 1-10, wherein the formulation treats, improves, and/or ameliorates oxidative stress and symptoms thereof.
12. The ophthalmic formulation according to any one of claims 1-11, wherein the formulation treats, improves, and/or ameliorates ocular surface inflammation.

13. The ophthalmic formulation according to any one of claims 1-12, wherein the formulation treats, improves, and/or ameliorates dry eye disease.
14. The ophthalmic formulation according to any one of claims 1-13, wherein the formulation comprises glycerin, trehalose, L-arginine, L-aurine, and L-leucine.
15. The ophthalmic formulation according to any one of claims 1-14, wherein the formulation is a product selected from eye drops, eye sprays, aqueous solutions, suspensions, microemulsions, ointments, conjunctival inserts, gels, and other suitable medicinal or cosmetic preparations.
16. The ophthalmic formulation according to any one of claims 1-15, wherein the formulation is a product selected from eye drops, eye sprays, and aqueous solutions.
17. The ophthalmic formulation according to claim 16, wherein the aqueous solutions are packaging solutions.
18. The ophthalmic formulation according to claim 17, wherein the packaging solutions are for solutions for contact lenses or other ophthalmic medical or cosmetic devices.
19. A method of stabilizing an ophthalmic formulation comprising including MAP in said formulation.
20. Use of MAP as an antioxidant in an ophthalmic formulation.