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(54) Title: SALT FREE HYALURONATE OPHTHALMIC SOLUTION

(57) Abstract: The present invention is directed to an ophthalmic composition in the form of a topical aqueous solution consisting essentially of an ophthalmologically active agent, an ion sensitive, hydrophilic polymer in an amount a of 0.004 to 1.5% by weight, at least one salt selected from the group of inorganic salts and buffers in a total amount of from 0.01 to 2.0% by weight, a wetting agent in an amount of 0 to 3.0% by weight, a preservative in an amount of 0 to 0.02% by weight, water, and optionally a pH regulating agent in an amount sufficient to give a pH of 4.0 to 8.0 to the composition, the ratio between salt and polymer components being such that the solution exhibits a viscosity of less than 1000 mPas. The composition contains a sufficient amount of polymer to provide for a controlled absorption of the drug into the eye, its viscosity having been reduced to provide for better handling characteristics.

SALT FREE HYALURONATE OPHTHALMIC SOLUTION

BACKGROUND OF THE INVENTION

The present invention relates to an ophthalmic composition in the form of a topical aqueous solution for human and veterinary use.

It is well known to use polymers alone or in combination with other polymers for the preparation of ophthalmic pharmaceuticals and artificial tear compositions. The inclusion of the polymer aims at increasing the viscosity of the composition so as to provide for a longer contact time with the cornea of the eye, and, for example, in connection with ophthalmic drugs, to provide for a sustained release of the drug into the eye.

For example, the U.S. Pat. Nos. 5,710,182 and 5,795,913 relate to ophthalmic compositions having decreased viscosity while still maintaining high polymer concentration. The prior art teaches the use of inorganic salts and buffers to obtain desirable viscosity and maintain pH during storage and use. We have discovered certain salt and buffer free formulations have desirable viscosity and pH stability during storage.

SUMMARY OF THE INVENTION

The present invention thus provides a salt and buffer free ophthalmological composition in a liquid, easy-to-use form which contains a sufficient amount of polymer to provide for both an increased and prolonged absorption of active agent into the eye.

More specifically, provided is a stabilized, topical ophthalmic Levofloxacin composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic Taurine composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic

Chloramphenicol composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic Chondroitin Sulfate composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic Dexamethasone and Neomycin composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic Naphazoline and Chlorpheniramine composition, wherein the improvement comprises a salt and buffer free composition.

In yet another embodiment, provided is a stabilized, topical ophthalmic Acyclovir composition, wherein the improvement comprises a salt and buffer free composition.

BRIEF DESCRIPTION OF THE DRAWINGS

None

DETAILED DESCRIPTION OF THE INVENTION

The ion-sensitive hydrophilic polymer to be used according to the invention is typically hyaluronic acid. Other ion sensitive polymers such as the polyacrylate elastomers commercially available as Carbopol would also be suitable according to the invention herein. Other suitable ion sensitive polymers would be obvious to those of ordinary skill in the art.

The polymer is preferably used in an amount of 0.01 to 0.8, more preferably 0.01 to 0.4, and advantageously 0.04 to 0.4% by weight.

The pH of the composition is suitably from 5.0 to 8, preferably from 6.5 to 8.0. When using a base as the active agent, the pH of the composition can be regulated by the

amounts used of acidic polymer and basic active agent respectively. However, if necessary, the pH of the composition may be adjusted also by adding an additional base or an acid, as the case may be, such as an alkali metal hydroxide, especially sodium hydroxide, or ammonium hydroxide, or e.g. hydrochloric acid.

The ophthalmologically active agent is advantageously an antibiotic agent, anti-viral agent, anti-retroviral agent, antiglaucoma agent, nutrients, mucopolysaccharides, a sympathomimetic agent, a sympatholytic agent, such as a beta-blocker, a carbonic anhydrase inhibitor, antiinflammatory, adrenergic, antiallergic agent, etc., or a combination thereof.

The amount of active agent in the final composition may vary, such as between 0.001 to 7% by weight, usually however between 0.01 to 0.5% by weight, and typically between 0.1 and 0.5% by weight.

According to an advantageous embodiment of the invention, the composition contains in addition, in order to enhance the wetting effect thereof, a wetting agent, preferably a polyhydric alcohol, such as glycerol. The amount of wetting agent is generally at the most 3.0%, such as of the order of 0.5 to 3.0% by weight.

As preservatives, e.g. benzalkonium bromide, benzalkonium chloride, benzyl alcohol, mercury salts, thimerosal, chlorhexidine or the like, as such or in combination. The amount of preservative usually lies in the range of 0 to 0.03% by weight.

The following examples illustrate the invention in more detail, without limiting the same. As used herein the following abbreviations have the given meanings:

EDTA	Ethylenediamine tetraacetic acid
BAB	Benzalkonium Bromide
BAK	Benzalkonium Chloride
Borax	Sodium borate
RT-6mos.	20° C. six month stability testing

Viscosity was determined according to the method set forth in the 2005 Chinese Pharmacopeia using an Ostwald-type Viscometer.

EXAMPLE 1

The following compositions were made:

API & Excipients	w/o Borax	w/ Borax
	w/w (%)	w/w (%)
Taurine	5.00	5.00
Sodium Hyaluronate	0.10	0.10
EDTA	0.01	0.01
BAB	0.003	0.003
1 Mol/L NaOH	0.45	0.45
Borax	-----	0.100
Viscosity (RT-6 mos.)	5.65-6.32 mm^2/s	6.94 mm^2/s

EXAMPLE 2

The following compositions were made:

API & Excipients	w/ Borax	w/o Borax	w/ Borax
	w/w (%)	w/w (%)	w/w (%)
Taurine	5.15	5.15	5.15
Sodium Hyaluronate	0.10	0.10	0.10
EDTA	0.01	0.01	0.01
Benzalkonium Bromide	-	-	0.003
Ethylparaben	0.03	0.03	-
Polysorbate-80	-	-	0.10
1 Mol/L NaOH	-	0.45 ml	-
Borax	0.08	-	0.08
pH at 0 time	6.92	7.03	6.99
pH at 1 month	6.95	6.97	6.87
pH at 3 month	6.87	6.90	6.73
pH at 6 month	6.84	6.86	6.61

EXAMPLE 3

The following compositions were made:

API & Excipients	w/o Borax	w/ Borax
	w/w (%)	w/w (%)
Taurine	7.00	7.00
Sodium Hyaluronate	0.10	0.10
EDTA	0.01	0.01
BAB	0.003	0.003
1 Mol/L NaOH	0.45	0.45
Borax	-----	0.100

EXAMPLE 4

The following compositions were made:

API & Excipients	w/o Borax	w/ Borax
	w/w (%)	w/w (%)
Taurine	5.00	5.00
Sodium Hyaluronate	0.10	0.10
EDTA	0.01	0.01
BAK	0.003	0.003
4% NaOH	0.45	0.45
Borax	----	0.080
Viscosity (RT-6 mos.)	5.65-6.32 mm^2/s	6.95 mm^2/s

EXAMPLE 5

The following compositions were made:

		w/o Borax	w/o Borax	w/ Borax
Levofloxacin HCl%		0.30	0.30	0.30
Glycerin%		2.35	2.35	2.35
EDTA%		0.02	0.02	0.02
Borax%		----	----	0.08
Sodium Hyaluronate %		0.12	0.12	0.12
BAB %		0.0035	0.0035	0.0035
4% NaOH % (ml)		0.6	0.6	----
Day 0	Viscosity/pH (mm^2/s)	15.52/6.52	17.09/6.56	18.24/6.15
3 month RT	Viscosity (mm^2/s)	16.09/6.45	16.28/6.44	18.25/6.06
6 month RT	Viscosity (mm^2/s)	15.24/6.43	11.14/6.43	14.50/6.04
12 month RT	Viscosity (mm^2/s)	15.37/6.38	13.08/6.37	16.52/6.00

EXAMPLE 6

The following compositions were made:

		w/o Borax	w/o Borax	w/ Borax
Levofloxacin HCl%		0.40	0.40	0.40
Glycerin%		2.35	2.35	2.35
EDTA%		0.02	0.02	0.02
Borax%		----	----	0.08
Sodium Hyaluronate %		0.12	0.12	0.12
BAB %		0.0035	0.0035	0.0035
4% NaOH % (ml)		0.6	0.6	----
Day 0	Viscosity (mm^2/s)	15.52	17.09	18.24
1 month RT	Viscosity (mm^2/s)	16.33	17.31	17.97
2month RT	Viscosity (mm^2/s)	16.51	17.07	18.02

EXAMPLE 7

The following compositions were made:

FORMULATION -5 (40°C)

Lot No.		w/o Borax	w/o Borax	w/ Borax
Levofloxacin HCl%		0.30	0.30	0.30
Glycerin%		2.35	2.35	2.35
EDTA%		0.02	0.02	0.02
Borax%		----	----	0.08
Sodium Hyaluronate%		0.12	0.12	0.12
BAB %		0.0035	0.0035	0.0035
4% NaOH % (ml)		0.6	0.6	----
Day 0	Viscosity/pH (mm^2/s)	15.52/6.52	17.09/6.56	18.24/6.15
1 month 40° C.	Viscosity/pH (mm^2/s)	15.03/6.66	15.52/6.67	16.38/6.10
2 month 40° C.	Viscosity/pH (mm^2/s)	14.84/6.46	14.44/6.46	14.78/6.10
6 month 40° C.	Viscosity/pH (mm^2/s)	10.56/6.44	10.67/6.43	8.51/6.03

EXAMPLE 8

The following compositions were made:

		w/o Borax	w/ Borax
Aminocaproic Acid %		0.15	0.15
Taurine %		0.105	0.105
Vitamin B_6 %		0.0105	0.0105
EDTA%		0.02	0.02
Borax%		----	0.024
4% NaOH % (ml)		0.6	----
PROPANEDIOL %		2.0	2.0
Tween-80%		0.1	0.1
Menthol %		0.001	0.001
Chlorhexidine Acetate %		0.02	0.02
Sodium Hyaluronate%		0.04	0.04
0 Day	Viscosity (mm^2/s)	15.52-17.09	18.24

EXAMPLE 9

The following compositions were made:

		w/o Borax	w/ Borax
Aminocaproic Acid %		0.20	0.20
Taurine %		0.10	0.10
Vitamin B_6 %		0.0105	0.0105
EDTA%		0.02	0.02
Borax%		----	0.024
4% NaOH % (ml)		0.6	----
PROPANEDIOL %		2.0	2.0
Tween-80%		0.1	0.1
Menthol %		0.001	0.001
Chlorhexidine Acetate %		0.02	0.02
Sodium Hyaluronate%		0.04	0.04
0 Day	Viscosity (mm^2/s)	15.52-17.09	18.24

EXAMPLE 10.

The following compositions were made:

Ingreident	w/Borax	w/Borax	w/o Borax	w/o Borax
Chloramphenicol%	0.287	0.287	0.287	0.287
EDTA %	0.02	0.02	0.02	0.02
Sodium Hyaluronate %	0.10	0.10	0.10	0.10
BAB %	0.003	0.003	0.003	0.003
Glycerin %	2.60	2.60	2.60	2.60
Borax	0.009	0.009	----	----
0.1 N NaOH	----	----	0.4 ml	0.4 ml

EXAMPLE 11.

The following composition was made:

Ingredient	w/ Borax	w/o Borax
Chondroitin Sulfate	3.0	3.0
Sodium Hyaluronate	0.1	0.1
Glycerin	2.45	2.45
Ethylparaben	0.03	0.03
EDTA	0.02	0.02
Borax	0.02	----
0.1 N NaOH	----	0.4 ml
Viscosity (mm^2/s) 6 month at 40 C.	5.19	5.09
pH at 0 time	6.02	6.03
pH at 1 month	5.95	5.85
pH at 3 month	5.83	5.80
pH at 6 month	5.50	5.48

EXAMPLE 12.

The following compositions were made:

Ingredient	w/ Borax	w/o Borax
Dexamethasone Sodium Phosphate %	0.105	0.105
Neomycin Sulfate	0.385	0.385
Glycerin	1.40	1.40
Ethylparaben	0.04	0.04
EDTA	0.04	0.04
Borax	0.65	----
Creatinine	0.10	0.10
Sodium bisulfite	0.32	0.32
Sodium hyaluronate	0.20	0.20
0.1 N NaOH	----	0.11%

EXAMPLE 13.

The following compositions were made:

Ingredient	w/ Borax	w/o Borax
Naphazoline HCl %	0.002	0.002
Chlorpheniramine Maleate	0.02	0.02
Glycerin	2.60	2.60
Vitamin B12	0.01	0.01
EDTA	0.03	0.03
Borax	0.0015	----
BAB	0.003	0.003
Polysorbate 80	0.05	0.05
Sodium hyaluronate	0.05	0.05
Menthol	0.01	0.01
0.1 N NaOH	----	0.0006 %
0 month pH	5.43	5.57
1 month pH	5.33	5.51
3 month pH	5.31	5.53
6 month pH	5.40	5.57
Viscosity at 6 month at 40 C. (mm^2/s)	3.27	3.78

EXAMPLE 14.

The following compositions were made:

Ingredient	w/ Borax	w/o Borax
Acyclovir %	0.10	0.002
Sodium hyaluronate	0.10	0.02
Glycerin	2.60	2.60
EDTA	0.01	0.03
Borax	0.05	----
BAB	0.003	0.003
1% NaOH	----	0.25 ml
0 month pH	8.03	8.15
1 month pH	7.91	7.67
3 month pH	7.83	7.51
6 month pH	7.81	7.45
Viscosity at 6 month at 40 C. (mm^2/s)	25.6	36.3

We claim:

1. A stabilized, topical ophthalmic Levofloxacin composition, wherein the improvement comprises a salt and buffer free composition.

2. A stabilized, topical ophthalmic Taurine composition, wherein the improvement comprises a salt and buffer free composition.

3. A stabilized, topical ophthalmic chlorhexidine composition, wherein the improvement comprises a salt and buffer free composition.

4. A topical ophthalmic active agent containing composition, wherein the improvement comprises a salt and buffer free composition and wherein the viscosity is less than 50 mm^2/s.

5. The composition of claim 4 wherein the active agent is selected from the group consisting of an antibiotic agent, anti-viral agent, anti-retroviral agent, antiglaucoma agent, nutrients, mucopolysaccharides, a sympathomimetic agent, a sympatholytic agent, such as a beta-blocker, a carbonic anhydrase inhibitor, antiinflammatory, adrenergic, antiallergic agent, etc., or a combination thereof.