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(54) Title: EYEWASH INTENDED IN PARTICULAR FOR THE TREATMENT OF THE DRY EYE SYNDROME

(57) Abrégé/Abstract:
The present invention relates to a ready-for-use eyewash intended in particular for the treatment of the dry eye syndrome comprising, in aqueous solution: - a gelifying polyanionic polymer; - a buffer in an amount sufficient to reduce the viscosity of the eyewash to a value of 10 to 60 mPa·s and - a polyvinylpyrrolidone in an amount sufficient for the eyewash to be clear.

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Eyewash intended in particular for the treatment of the dry eye syndrome

ABSTRACT

The present invention relates to a ready-for-use eyewash intended in particular for the treatment of the dry eye syndrome comprising, in aqueous solution:

- a gelifying polyanionic polymer
- a buffer in an amount sufficient to reduce the viscosity of the eyewash to a value of 10 to 60 mPa·s and
- a polyvinylpyrrolidone in an amount sufficient for the eyewash to be clear.

Fig. : none

EYEWASH INTENDED IN PARTICULAR FOR THE TREATMENT OF THE DRY EYE SYNDROME

The present invention relates to an eyewash intended in particular for the treatment of the dry eye syndrome.

Compositions intended for the treatment of the dry eye syndrome have already been described in WO 84/04 680 and WO 84/04 681. These compositions are composed of gels or very viscous solutions containing polyanionic polymers, such as products sold under the trade mark Carbopol® which are acrylic acid polymers crosslinked by allyl sucrose or allylpentaerythritol.

Thus, WO 84/04 681 describes, for example, a flowable gel which comprises 0.2% by weight of Carbopol® 940. This gel has a viscosity of 12,400-12,600 mPa·s.

Such gels are, however, difficult to use and can result in feelings of stricking of the eyelids.

Moreover, it is known (BF Goodrich, Carbopol® - Resins soluble in aqueous medium, 1981, bulletin GC-67) that the addition of soluble salts, such as sodium chloride or calcium chloride, to media containing Carbopols decreases the viscosity of these media.

Moreover, WO 95/05 804 has provided ophthalmic compositions containing 0.1 to 10% by weight of polyanionic polymers, such as acrylic acid polymers and in particular Carbopols, and from 0.01 to 1.0% by weight of electrolytes supplying cations, such as Na^+, Zn^{2+} or Al^{3+}.

These compositions have lower viscosities which allow instillation to be carried out.

The Applicant has, however, found that such compositions are opalescent and can obscure the vision during installation.

Moreover, it has been asserted, in a communication of Oechsver and Keipert, Proc. 1st Wold Meeting APGI/APV, Budapest 9-11 May 1995, p.

16-17, that the addition of polyvinylpyrrolidone decresed the viscosity of aqueous formulations based on Carbopol 980 and that the addition of sodium hydroxide rendered these formulations clear.

As will be shown subsequently, these results cannot be reproduced.

The present invention is targeted at providing ophthalmic compositions intended in particular for the treatment of dry eyes which exhibit low viscosities and which are clear.

The present invention relates to a ready-for use eyewash intended in particular for the treatment of the dry eye syndrome comprising, in aqueous solution

– a gelifying polyanionic polymer,

– a buffer in an amount sufficient to reduce the viscosity of the eyewash to a value of 10 to 60 mPa·s, preferably of 10 to 30 mPa·s, and

– a water soluble polyvinylpyrrolidone in an amount sufficient for the eyewash to be clear.

The present invention relates also to is a process for rendering clear an opalescent composition containing a gelifying polyanionic polymer and a buffer in an amount sufficient to reduce the viscosity of the composition to a value of 10 to 60 mPa·s, which comprises the addition of a sufficient amount of polyvinyl-pyrrolidone to render the composition clear.

The gelifying polyanionic polymer can be in particular a crosslinked acrylic acid polymer and in particular a crosslinked acrylic acid homopolymer. These polymers are in particular those sold under the trade mark Carbopol® and which are crosslinked by allyl sucrose or allylpentaerythritol, such as Carbopol 934, Carbopol 940 or Carbopol 980. These polymers can be present in particular at concentrations of 0.1 to 1% by weight.

The pH of the eyewash is advantageously from 6.0 to 8.0 and in particular in the region of 7.0. It can be adjusted with sodium hydroxide.

The buffers which make it possible to reduce the eyewash viscosity can be buffers such as potassium phosphate buffer (pH 7.0), borate buffer (pH 7.0), citrate buffer (pH 7.0) and sodium phosphate buffer (pH 7.0), the sodium or potassium phosphate buffers being preferred.

The amounts of buffer to be added increase with the concentration of polyanionic polymers.

The amounts of buffer to be added can be easily determined by viscosity measurements.

The viscosity shown is that measured by using a Haake VT500*rotational viscometer with NV coaxial cylinders comprising an inner cylinder with radii of 17.85-20.1 mm and a height of 60 mm and an outer cylinder with radii of 17.5-20.5 mm and a width of 0.35 mm. The viscosity shown is that measured at 1200 s^{-1} at a temperature of 22°C ± 1°C.

The polyvinylpyrrolidones used in the invention are water-soluble polyvinylpyrrolidones which advantageously have weight-average molecular masses of 25,000 to 100,000, such as the polyvidone PVP K30 (weight-average molecular mass 45,000).

The amounts of polyvinylpyrrolidones to be added can easily be determined by estimations of the clarity. Generally, the amounts of polyvinylpyrrolidones to be added increase with the amounts of polyanionic polymer. For percentages of polyanionic polymer of the order of 0.2% by weight, percentages of 1% by weight of polyvinylpyrrolidone are suitable.

A preferred eyewash comprises, in aqueous solution:

0.2% of Carbopol 980,
1% of polyvinylpyrrolidone K30,
sodium phosphate buffer in an amount sufficient to produce a viscosity of 10 to 30 mPa·s.

* trademark

The eyewash according to the invention can in addition contain conventional eyewash adjuvants, such as sodium edetate, which acts as preservative (and which partly contributes to decreasing the viscosity), anti-microbial preservatives, such as benzalkonium chloride or sodium mercurothiolate, and isotonicity agents, such as sorbitol or mannitol.

Examples of eyewashes according to the invention which simultaneously have a low viscosity and are clear will be given below.

EXAMPLE 1

Carbopol 934 : 0.200 g

Sodium edetate	:	0.050 g
Sodium hydroxide	:	0.078 g
70% Crystallizable sorbitol	:	6.630 g
Polyvidone PVP K30	:	1.000 g
Potassium dihydrogenphosphate	:	0.074 g
Potassium hydrogenphosphate	:	0.200 g
Purified water, q.s. for	:	100.000 g
Viscosity (at 1200 s^{-1})	:	11.4 mPa·s

EXAMPLE 2

Carbopol 980	:	0.500 g
Sodium hydroxide	:	0.195 g
Polyvidone PVP K30	:	2.000 g
Sodium dihydrogenphosphate dihydrate	:	0.540 g
Sodium hydrogenphosphate dodecahydrate	:	2.260 g
Purified water, q.s. for	:	100.000 g
Viscosity (at 1200 s^{-1})	:	30.0 mPa·s

EXAMPLE 3

Carbopol 980	:	0.750 g
Sodium hydroxide	:	0.292 g
Polyvidone PVP K30	:	2.550 g
Sodium dihydrogenphosphate dihydrate	:	1.250 g
Sodium hydrogenphosphate dodecahydrate	:	5.200 g
Purified water, q.s. for	:	100.000 g
Viscosity (at 1200 s^{-1})	:	27.7 mPa·s

EXAMPLE 4

Carbopol 980	:	0.200 g
Benzalkonium chloride solution for ophthalmic use	:	0.010 g
Sodium edetate	:	0.050 g
Polyvidone PVP K30	:	1.000 g
Sodium hydroxide	:	0.078 g
Sodium dihydrogenphosphate dihydrate	:	0.052 g
Sodium hydrogenphosphate dodecahydrate	:	0.217 g
70% Crystallizable sorbitol	:	6.360 g
Purified water, q.s. for	:	100.000 g
Viscosity (at 1200 s^{-1})	:	15.0 mPa·s

The results of a study on rabbits of the persistence of eyewashes according to the invention on the eye, compared with that of a gel containing the same concentration of Carbopol (0.2% by weight), will be given below.

The persistence of the compositions at the surface of the eye was determined by studying the kinetics of the artificially induced increase in the lacrimal volume, in comparison with the effect of an ophthalmic solution not containing polymers.

The experiments were carried out on male New Zealand albino rabbits weighing from 2.3 kg to 3.6 kg, sourced from the breeder Charles River France (St Aubin-les-Elbeuf, 76410, CLEON), acclimatized for a minimum of 5 days in the animal house (temperature 19±2°C, relative humidity: 55±10%, lighting: 12 hours of artificial lighting - 12 hours of night).

The eyewashes tested had the following composition:

	A	B	C
Carbopol 980	0.20 g	0.20 g	-
Sodium edetate	0.05 g	0.05 g	0.05 g
Crystallizable sorbitol (70%)	6.82 g	6.36 g	6.36 g
Benzalkonium chloride	0.01 g	0.01 g	0.01 g
Sodium dihydrogen-phosphate dihydrate	0.018 g	0.052 g	0.052 g
Sodium hydrogen-phosphate dodecahydrate	0.077 g	0.217 g	0.217 g
Polyvidone PVP K30	1.00 g	1.00 g	1.00 g
Sodium hydroxide	0.078 g	0.078 g	q.s. pH 7
Purified water, q.s. for	100.0 g	100.0 g	100.0 g
pH			7

The lacrimal volume was measured according to a technique for diluting a fluorescein solution similar to the methods used by Mishima et al. (Invest. Ophthalmol., 5(3), 264-276, 1966) and Göbbels et al. (Graefe's Arch. Clin. Exp. Ophthalmol., 229, 147-149, 1991) in man. The general principle of this method is as follows: a fluorescein solution of known concentration is instilled, in the smallest possible volume, in order to avoid the lacrimal reflex, and then immediately distributed homogeneously in the lacrimal film by successive blinkings. A sample of tears is taken immediately afterwards; the fluorescence of this sample is determined by fluorimetry. The lacrimal volume is calculated according to the equation:

$$V = \frac{Vs.\ Qi}{Qs} - Vi$$

V : lacrimal volume

Vs : volume of the sample of tears taken

Qi : amount of fluorescein instilled

Qs : amount of fluorescein in the sample of tears taken

Vi : volume of the fluorescein solution instilled.

The animals are anaesthetized by intramuscular administration of a ketamine (35 mg/kg)/xylazine (5 mg/kg) mixture in order to facilitate the taking of the sample of tears and to render the measurement of the lacrimal volume more reliable; indeed, in the conscious animal, a great deal of blinking is observed on approach of the microcapillary.

Ten minutes after injection of the anaesthetic, 1 µl of a 1% aqueous fluorescein solution was instilled in the lower conjunctival cul-de-sac using a microcapillary. The eyelids were manually closed twice while avoiding any pressure on the eyeball. Five seconds after the fluorescein installation, 1 µl of tears was removed by capillarity from the lower meniscus while avoiding any contact of the microcapillary with the lower eyelid and the surface of the eye.

The sample of tears taken was diluted in 4 ml of pH 7.4 isotonic phosphate buffer (NaH_2PO_4: 32 mM, Na_2HPO_4: 104 mM). The fluorescence of these samples was measured at room temperature with a spectrofluorimeter (excitation wavelength: 496 nm; emission wavelength: 506 nm) in comparison with that of a reference solution containing 1.6 µg of fluorescein in 4 ml of phosphate buffer (100% fluorescence). The 0 was adjusted with the phosphate buffer alone.

The amount of fluorescein contained in the sample of tears taken (Qs) was calculated from the relative percentage of fluorescence of the sample (x) according to the formula:

$$Qs\ (\mu g) = \frac{x\ (\%)\ \times\ 1.6\ \mu g}{100}$$

The lacrimal volume, expressed in µl, was calculated according to the equation given above in which:

Vi = 1 µl Qi = 10 µg Vs = 1 µl

Prior controls made it possible to confirm that the quantitative determination method was linear in this range of concentrations of the samples tested in this study and that the addition of tears or of the formulae tested did not modify the intensity of fluorescence of reference fluorescein solutions.

The animals were treated in a single eye by an instillation in the lower conjunctival cul-de-sac of 25 µl of the preparation tested, at different times before measuring the lacrimal volume. The eyelids were then manually closed once.

For each formula tested and each time, a batch of animals receiving, under the same conditions, 25 µl of an isotonic sorbitol solution was included as control (70% sorbitol at 7.5% w/w).

When different treatments (different formulations or pretreatment times) were tested in the same animals, a minimum interval of 3 days was complied with between the experiments.

The lacrimal volume is expressed in mean ± standard deviation form.

In very rare cases, insufficient anaesthesia or poor homogenization of the fluorescein solution after manually closing the eyelids was observed. The corresponding measurements were not taken into account in calculating the means.

The mean values obtained in each batch (control and treated) were compared using the Mann-Whitney U-test.

Statistical analysis was carried out using Statworks software. The difference is regarded as significant when p is less than or equal to 0.05.

Eyewashes A and B are eyewashes according to the invention whereas Eyewash C does not contain Carbopol.

The composition of the comparison gel was as follows:

Carbopol 940	: 0.2000 g
Benzalkonium chloride	: 0.0100 g
Sodium hydroxide	: 0.0660 g
70% Crystallizable sorbitol	: 5.7143 g
Purified water, q.s. for	: 100.0000 g

The viscosities of the compositions were measured with a Carri-Med CSL 100* device

· Rotor: stainless steel cone/plate for the gel with a diameter of 4 cm, angle : 2°, gap = 56

cone/plate for the other compositions with a diameter of 6 cm, angle : 2° and gap 67.

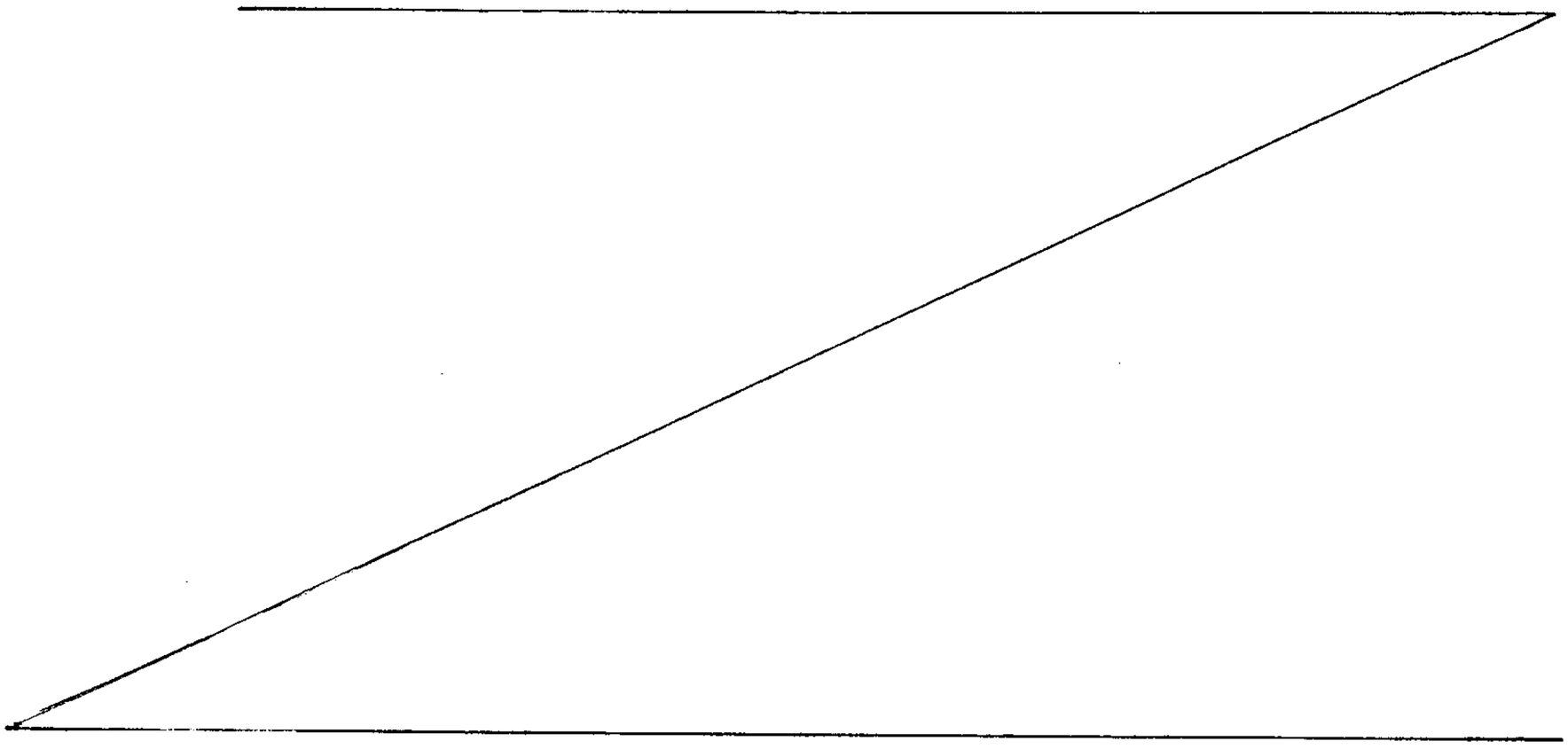
The rate gradient is from 0 to 1200 s^{-1} over 3 minutes at a temperature of 34.0 ± 1°C.

Composition	Apparent viscosity* (mPa·s)
A	30.4 ± 0.3**
B	15.0 ± 0.1
Gel	256.5 ± 3.4

* Shear rate: 1200 s^{-1}

** Mean ± standard deviation (3 measurements)

The results obtained with the gel are as follows:



* trademark

Time (min)	Lacrimal volume (µl)	
	Control	Gel
10	4.82 ± 0.23 (4)	13.45 ± 5.28** (11)
20	4.59 ± 0.96 (4)	9.69 ± 2.62** (12)
40	3.77 ± 0.26 (4)	7.47 ± 2.28** (11)
60	4.09 ± 0.78 (4)	5.92 ± 1.43* (12)
120	4.46 ± 0.37 (4)	5.03 ± 1.06 (12)

* p < 0.05; ** p < 0.01 in comparison with the control batch

Number of animals in brackets

The results obtained with Eyewash A according to the invention are as follows:

Time (min)	Lacrimal volume (µl)	
	Control	Eyewash A
10	4.16 ± 0.52 (5)	13.59 ± 6.22** (11)
20	4.07 ± 0.68 (5)	10.04 ± 2.06** (11)
40	4.64 ± 0.56 (5)	7.52 ± 1.90** (11)
60	4.25 ± 0.38 (5)	4.92 ± 0.82 (8)
120	5.16 ± 0.78 (5)	5.18 ± 0.60 (10)

** $p < 0.01$ in comparison with the control batch
Number of animals in brackets

The results obtained with Eyewash B (according to the invention) are as follows:

Time (min)	Lacrimal volume (µl)	
	Control	Eyewash B
10	4.56 ± 0.84 (5)	12.42 ± 3.40** (11)
20	4.72 ± 0.64 (4)	10.51 ± 2.46** (11)
40	4.84 ± 0.75 (5)	7.80 ± 1.91** (11)
60	4.33 ± 1.06 (5)	5.54 ± 1.63 (11)
120	4.98 ± 1.12 (5)	5.28 ± 1.03 (7)

** $p < 0.01$ in comparison with the control batch
Number of animals in brackets

The results obtained with Eyewash C (comparative example) are as follows:

Time (min)	Lacrimal volume (µl)	
	Control	Eyewash C
5	8.08 ± 1.75 (6)	12.51 ± 3.16** (10)
10	5.85 ± 1.36 (6)	7.12 ± 2.53 (9)
20	5.30 ± 1.22 (6)	6.02 ± 1.47 (10)

** p < 0.01 in comparison with the control batch
Number of animals in brackets

These results demonstrate a persistence on the eye with Eyewashes A and B according to the invention which is virtually comparable with that of the gel. On the other hand, Eyewash C, which contains polyvinylpyrrolidone but which does not contain Carbopol, only has an effect of very limited duration.

Moreover, results intended to show the influence of the addition of polyvinylpyrrolidone and buffers to aqueous Carbopol-based compositions on the viscosity and clarity will be given below. These results are combined in the following table:

	Formula 1	Formula 2	Formula 3	Formula 4	Formula 5
Carbopol 980	0.2 g	Id.	Id.	Id.	Id.
EDTA	0.05 g	Id.	Id.	Id.	Id.
Sodium hydroxide	q.s. pH=7	Id.	Id.	Id.	Id.
Sorbitol	q.s. isotonicity	Id.	Id.	Id.	Id.
PVP K 30	-	1 g	6 g	-	1 g
$NaH_2PO_4 \cdot 2H_2O$	-	-	-	0.052 g	0.052 g
$NaH_2PO_4 \cdot 12H_2O$	-	-	-	0.217 g	0.217 g
Water	q.s. for 100 ml	Id.	Id.	Id.	Id.
Appearance	clear	clear	opalescent	opalescent	clear
Viscosity in mPa·s (at 1400 s^{-1})	100	130	95	16	19

These results show that, in contrast to what was announced in the article of Oechsver and Keipert

mentioned above, the addition of polyvinylpyrrolidone does not significantly modify the viscosity of Carbopol-base compositions, either at concentrations of 1% or of 6%, and that, moreover, the addition of 6% of polyvinyl-pyrrolidone induces an opalescence (which cannot be masked by the addition of sodium hydroxide since neutrality cannot be exceeded). Only the addition of buffer makes it possible to decrease the viscosity (Formulae 4 and 5) and the opalescence is removed by addition of polyvinylpyrrolidone (Formula 5). The addition of a polyvinylpyrrolidone K25, as taught in the communication, instead of polyvinylpyrrolidone K30 gives the same results.

Finally, results showing that it is easy to determine the amount of buffer to be added in order to achieve the desired viscosity will be given.

Increasing amounts of sodium phosphate buffer were added to a composition identical to that of Example 4 but without buffer and without preservative, the sodium phosphate buffer having the composition:

$NaH_2PO_4 \cdot 2H_2O$	0.87 g
$NaH_2PO_4 \cdot 12H_2O$	3.62 g
H_2O, q.s. for	100 ml.

The viscosities as a function of the amounts of buffer are as follows:

Volume of buffer present in the formula	0	0.25 ml	0.5 ml	1 ml	2 ml	4 ml	6 ml	8 ml	10 ml
Viscosity (mPa·s)	100	53	44	35	29	26	21	18	16

CLAIMS

1. Ready-for-use eyewash comprising, in aqueous solution:

– a gelifying polyanionic polymer

– a buffer in an amount sufficient to reduce the viscosity of the eyewash to a value of 10 to 60 mPa·s and

– a water-soluble polyvinylpyrrolidone in an amount sufficient for the eyewash to be clear.

2. Eyewash according to claim 1, in which the gelifying polyanionic polymer is a crosslinked acrylic acid polymer.

3. Eyewash according to claim 2, in which the crosslinked acrylic acid polymer is a Carbopol®.

4. Eyewash according to claim 2 or 3, in which the crosslinked acrylic acid polymer is present at a concentration of 0.1 to 1% by weight.

5. Eyewash according to any one of claims 1 to 4, in which the buffer is selected from the group consisting of potassium phosphate buffer and sodium phosphate buffer.

6. Eyewash according to any one of claims 1 to 5, in which the polyvinylpyrrolidone is polyvinylpyrrolidone K30.

7. Eyewash according to any one of claims 1 to 6, comprising 0.2% by weight of the gelifying polyanionic polymer and 1% by weight of polyvinylpyrrolidone.

8. Eyewash according to any one of claims 1 to 7, comprising, in aqueous solution:

0.2% of Carbopol® 980,

1% of polyvinylpyrrolidone K30,

sodium phosphate buffer in an amount sufficient to produce a viscosity of 10 to 30 mPa·s.

9. Use of the eyewash according to any one of claims 1 to 8, for the treatment of the dry eye syndrome.

10. Process for rendering clear an opalescent composition containing a gelifying polyanionic polymer and a buffer in an amount sufficient to reduce the viscosity of the composition to a value of 10 to 60 mPa·s, which comprises the addition of a sufficient amount of polyvinylpyrrolidone to render the composition clear.