OPHTHALMIC SOLUTION COMPRISING GLYCOGEN

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This invention relates to a humectant and lubricant solution for ophthalmic use based on a glycogen polysaccharide.

It is known that the instillation of humectant and lubricant solutions into the eye is indicated in some circumstances. These solutions are all the more useful if they mimic the functions of natural tear fluid.

This type of humectant and lubricant solution has therefore been given the name of "artificial tears", even when the capacity to mimic natural tear fluid is not entirely satisfactory.

Artificial tears are used, for example, to alleviate the symptoms of dry keratoconjunctivitis, exposure-induced keratopathies and other situations resulting in dry eye syndrome. In addition to this artificial tears are useful to wearers of contact lenses, particularly in the case of hard lenses.

One of the properties required from artificial tears is that they should produce a sensation of well-being and freshness which lasts for a sufficient length of time.

In the past it was considered that in order to achieve this objective artificial tears should have a high viscosity, and this was achieved by adding polymers such as cellulose esters, polyethylene glycol, polystyrene sulphonate or polyvinyl acid.

However, such artificial tears do not satisfactorily mimic the properties of natural tear fluid which, as is known, has a rather low viscosity (between 1 and 6 cP) [J.M. Tiffany, "International Ophthalmology", 15, 371-376, 1991; H. Botner, T. Waaler and O. Wik, "Drug Development and Industrial Pharmacy", 16(5), 755-768, 1990].

In addition to this it has been shown that a viscosity greater than 20 cP is generally regarded as being uncomfortable on account of eyelid movement (J.I. Greaves, O. Olejnik and C. G. Wilson, "Pharma.

Sciences", 2(1), 13-33, 1992). Also, viscosities in excess of 40-50 cP can cause occlusion of the tear duct and give the patient a continual sensation of having a foreign body in the eye (M. Amorosa, "Principi di Tecnica Farmaceutica", (Principles of pharmaceutical technology), 399, 1983).

US patent 4 039 662 proposes that this disadvantage should be overcome through a low viscosity ophthalmic solution containing dextran or arabinogalactan together with benzylalkonium chloride. In particular, the abovementioned patent specifies that the polysaccharide component alone without benzylalkonium chloride is incapable of remaining adsorbed onto the cornea for a sufficiently long period (column 3, lines 9-13). In explanation of this behaviour it is hypothesised that the polysaccharide particles described in the aforesaid patent combine in solution with the benzylalkonium chloride by electrostatic attraction. This seems to form a complex having an electron charge which causes the macromolecule to be adsorbed onto the surface of the cornea (column 3, lines 19-37).

Furthermore, it is known from the literature that aqueous solutions of dextran have an oncotic pressure which is much greater than that of natural tears (F.J. Holly and E.D. Esquivel "Colloid Osmotic Pressure of Artificial Tears", Journal of Ocular Pharmacology, 1, 327-336, 1985). Despite the fact that this contrasts with the principle according to which the physical properties of artificial tears should be as similar as possible to those of natural tears, Holly et al. specifically attribute the greater acceptance of dextran-based artificial tears by patients to the said greater oncotic pressure.

Now it has been surprisingly found that glycogen polysaccharides provide an ophthalmic solution of low viscosity and low oncotic pressure and exert a pleasing refreshing, lubricating and humectant

effect on the cornea even in the absence of benzylalkonium chloride (Table I).

Therefore, it is an object of this invention to provide an ophthalmic solution characterized in that it comprises a sterile aqueous solution of a glycogen polysaccharide.

Preferably the glycogen polysaccharide is that described in patent EP-B-0 654 048.

It has also been found that, in addition to being characterized by a long residence time in the eye, aqueous solutions of glycogen polysaccharides can be filtered to 0.2 microns, and can thus provide sterile solutions up to a concentration of 12% (w/v). In addition to this, these solutions have a low viscosity and a low oncotic pressure.

Typically the quantity of glycogen polysaccharide in the ophthalmic solution according to this invention is of from 0.1 to 12% (w/v). Preferably it is of from 1 to 6% (w/v). Even more preferably it is of from 2 to 4% (w/v).

Typically the ophthalmic solution according to this invention has a viscosity of between 1 and 9 cP. Preferably it has a viscosity between 2 and 7 cP. Even more preferably, it has a viscosity between 2 and 6 cP.

Typically, the ophthalmic solution according to this invention has an oncotic pressure of less than 5 mmHg. Preferably it has an oncotic pressure of less than 3 mmHg.

The ophthalmic solution according to this invention may also contain other conventional ingredients such as: antioxidants, buffers, compounds to render the solution isotonic with tear fluid, stabilising agents, colouring agents and the like.

Typical examples of antioxidants are cysteine, ascorbic acid and taurine. The latter is also particularly preferred on account of its anti-free radical properties.

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The quantity of antioxidant in the ophthalmic solution according to this invention will vary widely according to the preselected composition. In the specific case of taurine, the quantity is preferably of from 0.1 to 0.6% (w/v) and, even more preferably, from 0.2 to 0.4% (w/v).

Typical examples of buffers are borate, bicarbonate, acetate and phosphate buffers, and their quantities will be selected so as to regulate the pH of the ophthalmic solution according to this invention between 5 and 8. Preferably the buffer will be a phosphate buffer and the pH of the ophthalmic solution according to the invention will be adjusted between 6.5 and 7.5.

Typical examples of compounds suitable for ensuring that the ophthalmic solution according to this invention is isotonic with natural tear fluid are glycerine, sodium chloride and mannitol.

The quantities of these in the ophthalmic solution according to this invention will vary widely according to the preselected composition. In the particular case of mannitol, the quantity is preferably of from 0.5 to 3% (w/v). Even more preferably it is of from 1.5% to 2% (w/v).

The composition according to this invention may also contain one or more preservatives selected from the group comprising benzylalkonium chloride, thimerosal, methyl parabenes, ethyl parabenes, propyl parabenes and butyl parabenes.

The glycogen polysaccharide used in the examples below was extracted from Mytilus edulis or Mytilus gallus provincialis using the method described in EP-B-0 654 048 and had the following characteristics:

C: 44.44%

N: absent [1]

reducing sugars[2]: absent

$[\alpha]_D^{20}$: 198 ± 1.0 (c = 1, water)

mean surface tension[3]:

3% aqueous solution at 25°C: 66.29 mN/m

6% aqueous solution at 25°C: 61.04 mN/m

3% aqueous solution at 37°C: 59.19 mN/m

6% aqueous solution at 37°C: 58.20 mN/m

contact angle with glass[4] at ambient temperature (the comparison test with water yielded a result of 42°):

3% aqueous solution: 32°

6% aqueous solution: 18°.

Notes:

[1] determined by the Kjeldahl method,

[2] determined in accordance with F.D. Snell and Snell, "Colorimetric Method of Analysis" N.Y., 1954, Vol. III, pag. 204,

[3] determined using a Lauda tensiometer,

[4] determined using a contact angle measuring device of the Face Contact Angle Meter, Kyowa Kaimenkagaki Co. Ltd., Nordtest type.

The following examples are intended to illustrate this invention without limiting it in any way.

EXAMPLE 1

Preparation of an ophthalmic solution containing a glycogen polysaccharide (Solution A)

Components	Quantity (g)
glycogen polysaccharide	3
D-mannitol	1.8
taurine	0.3
monobasic sodium phosphate H_2O	0.2
dibasic sodium phosphate 12 H_2O	1.5
distilled water q.s.p.	100 ml

The abovementioned ophthalmic solution was prepared by dissolving the abovementioned components in the prescribed quantity of water at

18-25°C. The product was then filtered using a 0.22 μm filter to sterilise the preparation.

The solution prepared in this way (Solution A) was subdivided into 0.4 ml doses in single-use phials having a capacity of 1 ml. The solution prepared in this way had the following properties:

pH	7.18
osmolarity[5]	272
density[6] (g/ml) at 25°C	1.024
density[6] (g/ml) at 37°C	1.016
viscosity[7] (cP)	5
oncotic pressure[8] (mmHg)	1.7
sterility	sterile
mean surface tension[3] (m/Nm)	
at 25°C	61.80
at 37°C	61.90

Notes:

[5] determined using the Knauer Automatic Osmometer apparatus,

[6] determined using the Ken Da-310 M Mettler - Toledo densimeter,

[7] determined using a Mettler Rheomat Rm-180 rheometer,

[8] determined using the Osmomat 050 Colloid Osmometer apparatus from the Gonotec company,

Under the same conditions the oncotic pressure of a 3% w/w solution of dextran was 16.4 mmHg.

EXAMPLE 2

Preparation of Solution B

Working in a manner similar to that described in Example 1 above, a second solution was prepared and comprised:

Components	Quantity (g)
glycogen polysaccharide	3
mannitol	1.8

sodium chloride	0.070
phosphate buffer	pH 7, 1-7.4
distilled water q.s.p.	100 ml

The solution prepared in this way had the following characteristics:

sterility	sterile
oncotic pressure[8] (mmHg)	1.7
mean surface tension[3] m/Nm	
at 25°C	61.43
at 37°C	60.02

Notes:

[3] determined as in note [3] above.

[8] determined as in note [8] above.

EXAMPLE 3

Preparation of an ophthalmic solution containing a glycogen polysaccharide (Solution C)

Operating in a manner similar to that described in Example 1 above a third solution was prepared and comprised:

Components	Quantity (g)
glycogen polysaccharide	3
D-mannitol	1.8
taurine	0.3
monobasic sodium phosphate H_2O	0.2
dibasic sodium phosphate 12 H_2O	1.5
distilled water q.s.p.	50 ml

The solution prepared in this way (Solution C) had the following characteristics:

pH	7.30
density[6] (g/ml) at 20°C	1.02252
sterility	sterile
mean surface tension[3] (m/Nm)	

at 25°C	72.81 ± 1.86
at 37°C	69.97 ± 0.39

contact angle at 25°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
12.3 ± 1.9	60.9 ± 4.1	45.3 ± 5.7	94.3 ± 8.5	58.2 ± 6.0	40.1 ± 13.0

contact angle at 37°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
16.1 ± 3.3	60.2 ± 1.9	57.5 ± 7.0	95.6 ± 4.0	65.3 ± 7.5	38.8 ± 12.9

Notes:

[3] determined by the method of Ferguson and Kenney (1932) [Tiffany J.M., Winter N., Bliss G., "Curr. Eye Res.", 8, 507-515, 1989],

[4] determined by the procedure of Tiffany (1990) [Tiffany J.M., "Acta Ophtalmol", 68, 182-187, 1990],

[6] determined using the Ken Da-310 M Mettler-Toledo densimeter.

EXAMPLE 4

Preparation of solution E

Operating in a manner similar to that described in Example 1 above a fourth solution was prepared and comprised:

Components	Quantity (g)
glycogen polysaccharide	1
D-mannitol	1.8
taurine	0.3
monobasic sodium phosphate H_2O	0.2
dibasic sodium phosphate 12 H_2O	1.5
distilled water q.s.p.	50 ml

The solution prepared in this way (Solution C) had the following characteristics:

pH	7.32

density[6] (g/ml) at 20°C	1.01602
sterility	sterile
mean surface tension[3] (m/Nm)	
at 25°C	72.94 ± 0.61
at 37°C	70.08 ± 0.22

contact angle at 25°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
11.3 ± 2.3	44.3 ± 10.7	55.6 ± 4.3	78.4 ± 2.6	67.9 ± 4.0	43.4 ± 14.2

contact angle at 37°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
13.9 ± 4.0	51.3 ± 7.9	39.3 ± 5.8	88.7 ± 7.5	60.2 ± 12.9	19.8 ± 7.7

Notes:

[3] determined by the method of Ferguson and Kenney (1932) [Tiffany J.M., Winter N., Bliss G., "Curr. Eye Res.", 8, 507-515, 1989],

[4] determined by the procedure of Tiffany (1990) [Tiffany J.M., "Acta Ophtalmol", 68, 182-187, 1990],

[6] determined using the Ken Da-310 M Mettler-Toledo densimeter.

EXAMPLE 5

Preparation of Solution F

Operating in a manner similar to that described in Example 1 above a fifth solution was prepared and comprised:

Components	Quantity (g)
glycogen polysaccharide	6
D-mannitol	1.8
taurine	0.3
monobasic sodium phosphate H_2O	0.2
dibasic sodium phosphate 12 H_2O	1.5
distilled water q.s.p.	50 ml

The solution prepared in this way (Solution F) had the following characteristics:

pH	7.38
density[6] (g/ml) at 20°C	1.03173
sterility	sterile
mean surface tension[3] (m/Nm)	
at 25°C	73.76 ± 0.91
at 37°C	73.66 ± 0.74

contact angle at 25°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
10.7 ± 2.1	60.4 ± 4.9	65.6 ± 6.9	99.9 ± 5.2	80.7 ± 6.7	98.9 ± 7.6

contact angle at 37°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
17.6 ± 3.7	66.8 ± 2.7	52.8 ± 4.1	95.3 ± 3.6	81.7 ± 11.2	28.8 ± 10.8

Notes:

[3] determined by the method of Ferguson and Kenney (1932) [Tiffany J.M., Winter N., Bliss G., "Curr. Eye Res.", 8, 507-515, 1989],

[4] determined by the procedure of Tiffany (1990) [Tiffany J.M., "Acta Ophtalmol", 68, 182-187, 1990],

[6] determined using the Ken Da-310 M Mettler-Toledo densimeter.

EXAMPLE 6

Preparation of Solution G

Operating in a manner similar to that described in Example 1 above a sixth solution was prepared and comprised:

Components	Quantity (g)
glycogen polysaccharide	9
D-mannitol	1.8
taurine	0.3

monobasic sodium phosphate H_2O	0.2
dibasic sodium phosphate 12 H_2O	1.5
distilled water q.s.p.	50 ml

The solution prepared in this way (Solution G) had the following characteristics:

pH	7.27
density[6] (g/ml) at 20°C	1.04122
sterility	sterile
mean surface tension[3] (m/Nm)	
at 25°C	74.37 ± 0.26
at 37°C	72.63 ± 0.95

contact angle at 25°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
12.8 ± 2.2	55.8 ± 4.1	54.3 ± 5.2	100.3 ± 3.0	87.3 ± 1.9	35.5 ± 9.9

contact angle at 37°C[4]:

glass	methyl-acrylate	polyethylene	paraffin wax	teflon	rabbit cornea
15.2 ± 3.3	54.0 ± 3.1	59.8 ± 4.6	94.4 ± 1.5	76.3 ± 4.6	20.7 ± 4.3

Notes:

[3] determined by the method of Ferguson and Kenney (1932) [Tiffany J.M., Winter N., Bliss G., "Curr. Eye Res.", 8, 507-515, 1989],

[4] determined by the procedure of Tiffany (1990) [Tiffany J.M., "Acta Ophtalmol", 68, 182-187, 1990],

[6] determined using the Ken Da-310 M Mettler-Toledo densimeter.

TEST 1

A double blind experiment was performed with Solution A, using the ophthalmic solution Dacriosol™ from the Alcon company (Solution D), containing dextran (0.1%) and hydroxypropylmethylcellulose (0.3%) as active ingredients, as the comparison preparation.

The experiment was performed on 11 healthy subjects of which 2 were affected by mild reddening of both eyes as a result of frequent computer use, while 1 had reddening, again of both eyes, as a result of incipient rhinitis of an allergic nature.

One drop (equal to approximately 0.05 ml) of Solution A was instilled into the left eye of each individual and one drop of Solution D into the right eye.

10-15 minutes after application the individuals were asked to describe their sensations on a card, putting a cross on a continuous 90 mm line which started from a beginning (0 - total absence of feeling) to an end (maximum or marked feeling). The distance of the cross from the start expressed in millimetres constituted the score for that sensation.

The following parameters were taken into consideration:

a) sensation of wellbeing in the eyes,
b) sensation of freshness in the eyes,
c) sensation of wetness,
d) viscosity,
e) burning,
f) pain,
g) lachrymation,
h) sensation of the presence of a foreign body,
i) blurred vision, and
j) reddening of the conjunctiva.

It will be noted from Tables I and II that both the solutions are well tolerated and that after an initial stage in which no individual reported any differences in sensation, after some 5-10 minutes Solution A proved to induce a greater sensation of wellbeing, freshness and wetness and a lesser sensation of viscosity and lachrymation with a consequent lesser sensation of the presence of a foreign body and

blurring. This subjective assessment was confirmed in measurements of the viscosities of the two preparations (2.02 cP for Solution A and 7.6 cP for Solution D). The three individuals affected by reddening of the eyes manifested a more marked reduction in this reddening in the case of Solution A.

The above experiment was extended to a further 23 individuals. Here again the following parameters were taken into consideration:

a) sensation of wellbeing in the eyes,

b) sensation of freshness in the eyes,

c) sensation of wetness,

d) viscosity,

e) burning,

f) pain,

g) lachrymation,

h) sensation of the presence of a foreign body,

i) blurred vision, and

j) reddening of the conjunctiva.

This experiment yielded results similar to Tables I and II.

TABLE I

Effects of Solution A after a single application

No.	Eye	Wellbeing	Freshness	Wetness	Viscosity	Burning	Pain	Lachrymation	Foreign body	Blurring	Reddening	
1	L	2.5	5.1	3.0	0.5	0	0	0	0	0	0	
2	L	1.5	3.9	3.8	6.2	0	0	0	0	0	0	*
3	L	1.0	3.7	1.0	0	0	0	0	0	0	0	
4	L	2.8	2.8	2.8	0.5	0	0	0.4	0	0	0	
5	L	0.3	0.3	0	0.8	0	0	0	0	0	0	
6	L	7.7	7.7	7.9	0	0	0	0	0	0	0	*
7	L	7.3	7.3	7.2	0	0	0	0	0	0	0	
8	L	4.0	4.0	4.0	0	0	0	0	0	0	0	**
9	L	6.5	6.5	9.0	6.7	0	0	0	0	0	0	
10	L	6.0	6.1	5.5	0	0	0	0	0	0	0	
11	L	6.2	6.7	4.6	0	0	0	1.9	0			
	Mean	4.2	4.9	4.4	1.3	0.0	0.0	0.2	0.0	0.0	0.0	
	±	2.68	2.23	2.83	2.55	0.00	0.00	0.57	0.00	0.00	0.00	

* Slight reduction in pre-existing reddening

** Marked reduction in pre-existing reddening

TABLE II

Effects of Solution D after a single application

No.	Eye	Wellbeing	Freshness	Wetness	Viscosity	Burning	Pain	Lachrymation	Foreign body	Blurring	Reddening	
1	R	2.8	3.7	5.7	0.4	0	0	1.5	0	0	0	
2	R	4.5	4.6	4.6	1.8	0	0	0	0	0	0	*
3	R	1.0	1.9	0.9	6.8	0	0	0	0.5	2.8	0	
4	R	2.8	2.7	5.2	6.9	0	0	0.5	0	3	0	
5	R	1.7	1.5	0	0	0	0	0	0	0	0	
6	R	4.8	8.0	8.0	0	1.0	0	1.1	0	0	0	*
7	R	3.0	2.9	2.9	7.7	0	0	0	0	0	0	
8	R	4.0	1.7	0.9	0	0	0	0	0	0	0	*
9	R	6.5	1.5	0.0	1.6	0	0	0	0	0	0	
10	R	6.1	8.1	7.0	0.7	0.7	0.7	1.4	0.9	0.7	0	
11	R	1.1	1.1	2.8	1.3	6.7	0	1.7	2.7	0	0	
	Mean	3.5	3.4	3.5	2.5	0.8	0.1	0.6	0.4	0.6	0.0	
	±	1.88	2.51	2.83	3.07	2.00	0.21	0.71	0.83	1.16	0.00	

* Slight reduction in pre-existing reddening

CLAIMS

1. An ophthalmic solution characterized in that it comprises a sterile aqueous solution of a glycogen polysaccharide.
2. An ophthalmic solution according to Claim 1, characterized in that the quantity of glycogen polysaccharide is of from 0.1 to 12% (w/v).
3. An ophthalmic solution according to Claim 2, characterized in that the quantity of glycogen polysaccharide is of from 1 to 6% (w/v).
4. An ophthalmic solution according to Claim 3, characterized in that the quantity of glycogen polysaccharide is of from 2 to 4% (w/v).
5. An ophthalmic solution according to any one of the foregoing claims, characterized in that it further comprises an antioxidant.
6. An ophthalmic solution according to Claim 5, characterized in that the antioxidant is taurine.
7. An ophthalmic solution according to any one of the foregoing claims, characterized in that it further comprises an agent capable of regulating isotony.
8. An ophthalmic solution according to Claim 7, characterized in that the agent capable of regulating isotony is mannitol.
9. An ophthalmic solution according to any one of the foregoing claims, characterized in that it is buffered to a pH of between 5 and 8.
10. An ophthalmic solution according to Claim 9, characterized in that it is buffered to a pH of between 6.5 and 7.5.
11. An ophthalmic solution according to any one of the foregoing claims, characterized in that it has a viscosity of between 1 and 9 cP.
12. An ophthalmic solution according to any one of the foregoing claims, characterized in that it has an oncotic pressure of less than 5 mmHg.



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13. An ophthalmic solution according to Claim 12, characterized in that it has an oncotic pressure of less than 3 mmHg.
14. An ophthalmic solution according to any one of the foregoing claims, characterized in that it further comprises a preservative selected from the group comprising benzylalkonium chloride, thimerosal, methyl parabenes, ethyl parabenes, propyl parabenes and butyl parabenes.

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