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(54) **VEHICULE OPHTALMIQUE A BASE DE GEL PROTEIQUE**

(54) **PROTEIN GEL OPHTHALMIC VEHICLE**

(57) The present invention relates to a liquid ophthalmic composition, characterized in that it comprises at least one active principle and a sulphated polysaccharide or sulphated polysaccharide derivative in aqueous solution which undergoes a liquid-gel phase transition on interaction of the said sulphated polysaccharide or one of its derivatives with the proteins of the lachrymal fluid. The present invention also relates to a process for preparing the said composition.

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LIQUID AQUEOUS OPHTHALMIC COMPOSITION UNDERGOING
LIQUID-GEL PHASE TRANSITION

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ABSTRACT

15 The present invention relates to a liquid
ophthalmic composition, characterized in that it
comprises at least one active principle and a sulphated
polysaccharide or sulphated polysaccharide derivative in
aqueous solution which undergoes a liquid-gel phase
transition on interaction of the said sulphated
20 polysaccharide or one of its derivatives with the
proteins of the lachrymal fluid.

The present invention also relates to a process
for preparing the said composition.

LIQUID AQUEOUS OPHTHALMIC COMPOSITION UNDERGOING
LIQUID-GEL PHASE TRANSITION

5 The present invention relates to a liquid
ophthalmic composition undergoing liquid-gel phase
transition.

10 In many known ophthalmic compositions, a large
proportion of the active principle administered in the
eye is removed by lachrymal drainage. The effective
therapeutic action of such compositions is consequently
limited to a very short time. To overcome this
disadvantage, the use of compositions of the gel, solid
implant or ointment type have been proposed. However,
these dosage forms find patient resistance; liquid forms
better tolerated.

15 Thus, in order to solve this problem, liquid
dosage forms which gel in situ through the effect of a pH
change (US 4,136,173) or a temperature rise (US
4,188,373, US 4,474,751) have been proposed.

20 The major drawback of the above formulations
is, in the first case, a non-physiological and hence
poorly tolerated pH value, and in the second case, the
risk of the formulation gelling before its
administration, that is to say on storage, through the
effect of a temperature rise.

25 The object of the present invention is to
propose an ophthalmic composition having a sustained
activity over a period of time and not possessing these
drawbacks.

30 More specifically, the present invention
relates to a liquid ophthalmic composition, characterized
in that it comprises at least one active principle and a
sulphate polysaccharide or sulphate polysaccharide
derivative in aqueous solution which undergoes a liquid-
gel phase transition on interaction of the said sulphate

polysaccharide or sulphate polysaccharide derivative with the proteins of the lachrymal fluid.

5 According to the invention, the liquid-gel phase transition undergone by the ophthalmic composition is a consequence of the interaction of the sulphate polysaccharides in aqueous solution with tear proteins.

The presence of electrolytes further improves the rheological properties of the gels obtained.

10 This phase transition undergone by the ophthalmic composition increases the contact time of the said composition with the eye, and accordingly enables a sustained or delayed diffusion of the active principle contained in this composition to be obtained.

15 In addition, it is found that the composition according to the invention leads to larger contents of active principle in the eye as soon as the composition is applied.

20 Such an ophthalmic composition also possesses the advantages of not spontaneously gelling through the effect of a temperature rise and of possessing a pH close to physiological pH, that is to say of the order of 7.

The sulphate polysaccharides used according to the invention will preferably be chosen from kappa-carrageenan, iota-carrageenan and mixtures thereof.

25 According to a preferred embodiment of the invention, iota-carrageenan will be used.

The sulphate polysaccharide or sulphate polysaccharide derivative is preferably used at a concentration of the order of 0.1 to 5% by weight.

30 The said composition contains at least one active principle in solution or in suspension in an aqueous medium.

It is possible to use a wide diversity of active principles. The latter may be chosen, in particular, from the following pharmaceutical compounds:

- 5 - antibacterial substances such as beta-lactum antibiotics, for example cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin cefazolin, cefaloridine, chibrorifamycin, gramicidin, bacitracin and
10 sulphonamides;
aminoglycoside antibiotics such as gentamicin, kanamycin, amikacin, sisomicin and tobramycin;
nalidixic acid and its analogues such as norfloxacin and the antimicrobial combination of
15 fluoroalanine/pentizidone, nitrofurazones and their analogues;
- anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methyl-
20 prednisolone, medrysone, fluorometholone, prednisolone, triamcinolone, idomethacin, sulindac, its salts and corresponding sulphides, and their analogues;
- miotics and anticholinergics such as echothiopate, pilocarpine, physostigmine salicylate, diisopropyl
25 fluorophosphate, epinephrine, dipivalylepinephrine, neostigmine, echothiopate iodide, demecarium bromide, carbamoylcholine chloride, methacholine, bethanechol and their analogues;
- mydriatics such as atropine, homatropine, scopolamine,
30 hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine and their analogues.
- Other drugs used in the treatment of eye conditions and lesions, such as:

- antiglaucoma drugs, for example timolol and R-timolol and a combination of timolol or R-timolol with pilocarpine, and also many other adrenergic agonists and/or antagonists; epinephrines and a complex of epinephrine or prodrugs, and dipivefrin derivatives and hyperosmotic agents such as glycerol, mannitol and urea;
- 5 antiparasitic compounds and/or antiprotozoal compounds such as ivermectin; phrimethamine, trisulphapyrimidine, clindamycin and corticosteroid preparations;
- 10 compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, and interferon and interferon-inducing agents such as polyI.polyC, carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-
- 15 hydroxyphenyl)thio-5-thiophenesulphonamide, 6-hydroxy-2-benzothiazolesulphonamide, 6-pivaloyloxy-2-benzothiazole-sulphonamide, MK 927 and MK 417;
- antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole;
- 20 anaesthetic agents such as etidocaine, cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine,
- 25 mepivacaine and prilocaine;
- Ophthalmic diagnostic agents such as:
- a) those which are used for examining the retina, such as fluorescein sodium;
- b) those which are used for examining the conjunctiva,
- 30 cornea and lachrymal apparatus, such as fluorescein and rose bengal; and
- c) those which are used for examining abnormal responses of the pupil, such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine;

- Ophthalmic agents such as ethylenediaminetetraacetic acid (EDTA) and deferoxamine;
- Immunosuppressants and antimetabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine; and antibiotic/anti-inflammatory combinations such as the combination neomycin sulphate/dexamethasone sodium phosphate, and combinations concomitantly treating glaucoma, for example a timolol maleate/aceclidine combination.

10 The ophthalmic composition according to the invention must naturally fulfil the criteria for use in this field, in particular it should preferably be isotonic and have a pH lying between 5.0 and 8.0. Thus, it may incorporate other components such as tonicity
15 regulators, preservatives and buffer systems.

 The present invention also relates to a process for preparing the said composition, characterized in that the active principle and, optionally, the other components are mixed with stirring in an aqueous solution
20 in the presence of sulphated polysaccharide or sulphated polysaccharide derivative, so as to obtain the said composition.

 The examples given below will enable other advantages and features of the present invention to be
25 demonstrated.

EXAMPLE 1 Formulation of an ophthalmic composition

	Timolol maleate	0.342 g
	(corresponds to 0.25 g of timolol base)	
	Aubygel	1.500 g
5	Tromethamine	0.240 g
	Maleic acid	qs pH 7.0
	Mannitol	3.800 g
	Benzalkonium chloride	0.0075 g
	Water	qs 100.00 g

10 Timolol maleate is the active principle,
Aubygel X52TA marketed by Meso-Rousselot-Satia is iota-
carrageenen, the tromethamine/maleic acid combination
represents a buffer system, mannitol is a tonicity
regulator and benzalkonium chloride a preservative.

15 Aubygel is a trade-mark.

EXAMPLE 2

 The composition of Example 1 is tested in vitro
according to a gelation test.

20 In this test, gelation is induced by adding 0.5
ml of the said composition to 1 ml of artificial tears,
the composition of which is given in Table I. The
formation of this gel is assessed after 30 seconds;
incubation at 34°C followed by filtration, by weighing
25 the residue deposited on the filter.

 The results are given in Table II.

 In protein-free artificial tears, gel formation
is small, and may be attributed to an interaction between
the carrageenan and the electrolytes present in the
30 artificial tears. The same test carried out on
artificial tears containing proteins (lysozyme/bovine
albumin fraction V), on the other hand, gives good
results. The formation of an opalescent gel having low

cohesion is observed. the formation of this gel is, moreover increased by moderate agitation.

5 EXAMPLE 3

In order to demonstrate the sustained presence in the eye of the active principle contained in the ophthalmic composition according to the invention, an in vivo study was carried out.

10 An ophthalmic composition according to the invention and Timoptol, used by way of comparison, were subjected to a test of ocular penetration of timolol in albino rabbits. (Timoptol is a trade-mark.)

15 For this purpose, instillations of 50 μ l of each of the test solutions were carried out inside the conjunctival sac of living albino rabbits. Following the administration, groups of six animals were then sacrificed at times 10 minutes, 30 minutes, one hour, two hours and four hours, and the timolol assayed in the
20 cornea, aqueous humor and iris.

The timolol concentrations thus assayed are shown, respectively, in Table III for the cornea, Table IV for the aqueous humor and in Table V for the iris and the ciliary bodies.

25 The results demonstrate that an ophthalmic composition according to the invention gives higher concentrations of active principle in the different tissues than the comparative product Timoptol 0.25%, this being the case both at the beginning of the application
30 and after 4 hours.

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TABLE I:

. Lysozyme	: -	0.15%
. Bovine albumin, fraction V	: -	0.55%
. Sodium chloride	: 0.67%	0.67%
. Potassium chloride	: 0.11%	0.11%
. Sodium bicarbonate	: 0.20%	0.20%
. Calcium chloride	: 0.008%	0.008%
. Hydrochloric acid	: qs pH 7.4	qs pH 7.4
. Demineralized water	: qs 100.00%	qs 100.00%

TABLE II:
Gellation test

	<u>Weight of</u> <u>the residue</u>	<u>Standard</u> <u>deviation</u>
. Protein-free artificial tears	0.219 mg	0.033 mg
. Artificial tears with proteins	0.514 mg	0.055 mg
. Artificial tears with proteins and agitation	0.969 mg	0.075 mg

The results are expressed on a mean of 12 measurements

TABLE III
Timolol concentrations in the cornea of albino rabbits after instillation
of formulations containing 0.25% of timolol

µg of timolol/ml

Time after administration	10 mins	0.5 hr	1 hr	2 hr	4 hr
TIMOPTOL	17.4 ± 5.5	9.2 ± 3.4	8.1 ± 3.6	2.6 ± 0.8	1.3 ± 0.7
Ophthalmic composition according to the invention (Example 1)	60.0 ± 14.8*	64.0 ± 22.0*	41.9 ± 14.5*	15.6 ± 9.5*	2.9 ± 1.9*

Each result represents the mean ± the standard deviation of measurements carried out on 12 eyes

* Values significantly different (p < 0.005) from those obtained with Timoptol

(Student's t test)

TABLE IV

Timolol concentrations in the aqueous humor of albino rabbits after instillation of formulations containing 0.25% of timolol

μg of timolol/ml

Time after administration	10 mins	0.5 hr	1 hr	2 hr	4 hr
TIMOPTOL	0.5 ± 0.2	0.7 ± 0.2	0.8 ± 0.5	0.3 ± 0.1	0.1 ± 0.1
Ophthalmic composition according to the invention (Example 1)	0.9 ± 0.4*	3.1 ± 0.9*	3.5 ± 0.9*	1.5 ± 0.5*	0.2 ± 0.1

Each result represents the mean ± the standard deviation of measurements carried out on 12 eyes

* Values significantly different (p < 0.005) from those obtained with Timoptol (Student's t test)

TABLE V

Timolol concentrations in the iris and the ciliary bodies of albino rabbits after instillation of formulations containing 0.25% of timolol

μg of timolol/ml

Time after administration	10 mins	0.5 hr	1 hr	2 hr	4 hr
TIMOPTOL	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	0.4 ± 0.2	0.2 ± 0.1
Ophthalmic composition according to the invention (Example 1)	3.8 ± 1.6*	4.1 ± 0.9*	4.0 ± 1.6*	1.7 ± 0.8*	< 0.4

Each result represents the mean ± the standard deviation of measurements carried out on 12 eyes

* Values significantly different (p < 0.005) from those obtained with Timoptol (Student's t test)

CLAIMS:

1. A liquid ophthalmic composition,
characterized in that it comprises at least one active
5 principle and 0.1 to 5% by weight of a sulphated
polysaccharide selected from kappa-carrageenan, iota-
carrageenan and mixtures thereof, in aqueous solution
which undergoes a liquid-gel phase transition on
interaction of said sulphated polysaccharide with the
10 proteins of the lachrymal fluid.

2. An ophthalmic composition according to
Claim 1, characterized in that it has a pH close to
physiological pH.
15

3. An ophthalmic composition according to
Claim 1 or 2, characterized in that the sulphated
polysaccharide is iota-carrageenan.

4. An ophthalmic composition according to any
one of Claims 1 to 3, characterized in that it contains
other compounds chosen from tonicity regulators,
20 preservatives and buffer systems.

5. An ophthalmic composition according to any
one of Claims 1 to 4, characterized in that the active
principle is chosen from antiglaucoma agents, antibiotics
and antiviral agents.
25

6. An ophthalmic composition according to any
one of Claims 1 to 5, characterized in that the active
principle is tamolol.
30

7. A process for preparing an ophthalmic composition according to any one of Claims 1 to 6, characterized in that the active principle is mixed with stirring in an aqueous solution in the presence of 0.1 to 5% by weight of a sulphated polysaccharide selected from kappa-carrageenan, iota-carrageenan and mixtures thereof, so as to obtain the said composition.

8. A process according to Claim 7, characterized in that the active principle and other compounds chosen from tonicity regulators, preservatives and buffer systems, are mixed with stirring in an aqueous solution in the presence of 0.1 to 5% by weight of a sulphated polysaccharide selected from kappa-carrageenan, iota-carrageenan and mixtures thereof, so as to obtain the said composition.