(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/01959 A1

(51) International Patent Classification[7]: A61K 9/06, A61P 31/04, 31/10, 29/00, 9/10

(21) International Application Number: PCT/EP00/06062

(22) International Filing Date: 29 June 2000 (29.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001453 1 July 1999 (01.07.1999) IT

(71) Applicant *(for all designated States except US)*: **FARMILA FARMACEUTICI MILANO S.P.A.** [IT/IT]; Via E. Fermi, 50, I-20019 Settimo Milanese (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SANSO', Marco** [IT/IT]; Via E. Fermi, 50, I-20019 Settimo Milanese (IT). **SEBBEN, Renato** [IT/IT]; Via E. Fermi, 50, I-20019 Settimo Milanese (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/01959 A1

(54) Title: OPHTHALMIC COMPOSITIONS IN FORM OF AQUEOUS GELS

(57) Abstract: Ophthalmic preparations are described in form of aqueous gels with a viscosity range between 400 and 800 cps including: at least one active principle; a gelling agent and at least 2 co-solubilising/co-gelling agents.

OPHTHALMIC COMPOSITIONS IN FORM OF AQUEOUS GELS

The present invention relates to ophthalmic compositions in form of aqueous gels.

The pharmacological therapy of ocular pathologies by topical administration may appear as a simple problem if many peculiar elements of the ocular structure, which make it of pharmaceutically difficult treatment, are not considered.

Not considering the pathology and, therefore, the adequate active principle, the mostly influencing variables to optimise this kind of therapy are the following:

- physiological/anatomical aspects; the administered quantity of active principle in the form of homogeneous aqueous solution or suspension (conventional eye drops) quickly leaves the interested area either by blinking and/or lacrimal drainage.

Just a small percentage of the administered preparation is retained in the corneal region, and can develop, after absorption, a pharmacological action.

- "barrier" effect to absorption, induced by different tissues/components (cornea, conjunctiva, tear film etc.) influencing the active principle distribution in the different compartments of the anterior section of the eye.

In the last years, to solve the above mentioned problems, many strategies have been carried out , based on:

1) the chemical structure of the active principle (more addressed to hydrophilic/lipophilic ratio), therefore trying to increase absorption - in the cornea, conjunctiva etc. – of the slight residual quantity, after blinking;

2) the weight increase of the active principle in the formulations, with consequent higher risk of adverse effects;

3) the increase of the daily posology (up to 6/8 daily administrations) with reduction of patient compliance;

4) the change of the vehicle used in the pharmaceutical preparations.

As far as the latter point is concerned, the rational of different approaches, made up to now, consists in the hypothesis that an increase of residence time in the ocular milieu (cornea, conjunctiva) of the blinking-resistant residual dose should lead to an increase of therapeutical efficacy, due to high potential availability of the active principle absorption.

To reach this target different strategies have been adopted: i) use of solid devices with slow releasing effects to be placed in the cul-de-sac (scarcely accepted by the patient); ii) use of formulations characterised by a more or less high viscosity (mostly used approach).

Disregarding the use of eye ointments based on fat vehicles, whose limited compliance is well-known , the approach to viscous formulations can be divided into: i) use of preformed aqueous vehicles of appropriate viscosity, to be administered as such; ii) use of suitable solutions, gelling in contact with ocular surface (for example by variation of temperature, pH or ionic strength).

US3,920,810 (18/11/1975), to Burton Parson & Co., claims low viscosity ophthalmic solutions, using polyacrylamide as first agent and, optionally, polyethylene glycol as wetting and plasticizer agent.

These solutions can be used as artificial tears or as cleaning and hydrating liquids for contact lenses, or as vehicles for chemically alkaline or neutral active substances. In this latter case, the following additives are suggested but, are not considered essential: - water-soluble cellulose derivatives, like hydroxymethylcellulose as buffer agents and viscosity stabilising agents; polyvinylpirrolidone, as "detoxicant" of lacrimal film and spreading agent; biocides etc.

The viscosity of these solutions ranges between 10 and 200 cps, while the high residence time, compared with that of conventional eye drops, seems to be triplicated (even quadruplicated); the comparison between a pilocarpine preparation and one in the form of traditional eye drops leads to similar therapeutic results, with a slightly

reduction of the dosage (3 adm./day vs 4 adm./day).

FR76358076 (Alcon Laboratories) discloses solutions used as artificial tears, for dry eye syndrome treatment; these solutions show low viscosity and contain polysaccharides such as dextrans or arabinogalactans and polyethylene glycols.

EP-B-227494 (02/10/1986, Laboratories Merk, Sharp & Dohme-Chibret) discloses polysaccharide liquid preparations which, under the effect of a ionic strength variation (ocular milieu salinity), undergo transition to high or low viscosity.

The used polysaccharide is a heteropolysaccharide produced by the Pseudomonas Elodea bacterium, known as gellan gum or its modifications.

The formulations are useful in the treatment of dry eye syndrome or as drug delivering systems.

Said formulations show a residence time about twice that obtained by a traditional aqueous preparation.

The comparison between two compositions, with the same concentration (0.25%) of timolol (a non-gelling commercial one and the other containing a vehicle described in EP-B-227494), shows that on checking times (30;60;120;180 minutes) the active principle concentration of the commercial preparation in the rabbit lacrimal fluid is 3 (30;60;120 minutes) to two times (180 min.) versus the disclosed composition.

A drawback could consists in the fact that the optimal active substances should be soluble in water, while the non soluble substances have to be used in suspensions or in emulsions.

WO 91/19481 (11/06/91 Allergan Inc.) discloses solutions reversibly gelling upon simultaneous variations of, at least, two physical parameters, such as temperature, pH or ionic strength.

These solutions, suitable for topical or sistemic formulations, consist of a methylcellulose and polyacrylic acid mixture in the presence or in the absence of inorganic salts.

These drug vehicles can carry active substances in solutions or in dispersion. The final, local values of lacrimal fluid viscosity, formed after gelling, should be very high, considering that initial values ranged from 3000 cP to 16,000 cP and more, even if they are defined easily flowing in drops.

The residence time and the distribution have been studied by the fluoresceine test or FITC-dextran test, with the following conclusions:

i) formation of a gelatinous deposit in the lower part of the cul-de-sac,

ii) formation of a regular-looking, thin film on the conjunctival-corneal region.

These results show that an important part of the composition remains in an ocular site of low absorption capacity, where, moreover, the elimination by lacrimal drainage is easier (the residence time in the eye has been evaluated of about 3 hours, whereas the one of the film would be twice longer).

WO 93/17664 (Alcon lab.) discloses ophthalmic preparations useful *per se* as drugs for the dry eye syndrome treatment (artificial tears) and as active substances delivery vehicles for different ocular pathologies; these preparations are combinations of aqueous mixtures of viscosity-increasing agents (i.e. carboxyvinyl polymers and non-carboxylated cellulose polymers), which result more viscous than the single component – preparations, the patent claims (but does not exemplify) the use of polyethylene glycol or polyvinyl alcohol only in the case of artificial tears.

Consequently it appears that, excluding the auto-gelling preparations, the viscosity increase can be desirable in artificial tears (dry eye syndrome treatment), but not in order to increase bioavailability of the active substance (and therefore the therapeutic efficacy of a preparation), due to the poor patient compliance towards vehicles with higher viscosity, and to the easier elimination of the drug by blinking or lacrimal drainage in the case of low viscosity vehicles.

Moreover, the higher costs of manufacturing are a negative element for the competition with conventional eye drops.

DISCLOSURE OF THE INVENTION.

It has been found that ophthalmic compositions in the form of aqueous gels, characterised by the presence of at least 3 components selected from gelling agents and co-solvents/co-gelling agents, are particularly effective and well tolerated.

Particularly, the compositions of the invention provide, under similar conditions, the same level of reduction of clinical symptoms, or of cure, obtained by conventional eye drops, even using:

- reduced concentrations of active principles;
- 50% to 70% reduced posology (for example from 4-6 adm./day to 2 adm./day).

These favourable effects cannot be explained only according to the theory of the residence time increase, related to a rise in vehicle viscosity.

The compositions of the invention provide the following advantages:

- a uniform distribution of the administered gel, expecially on the conjunctival region of the cornea, which is the most absorbing zone and, at the same time, an important depot for topically applied drugs. (Reddy I.K. et al. In "Ocular Therapeutic and Drug delivery" – I.K.Reddy Ed.-Technomic Publ., 1996,1-23);
- an optimal adhesion of the film to the corneal and bulbar conjunctival structures;
- a particularly high stabilisation of the above mentioned film, suitable to prevent its rupture and consequently its (partial or total) elimination by lacrimal drainage or its displacement in the lower cul-de-sac zone, where absorption for ocular therapeutical aims is reduced.

The physiological combination of the vehicle (therefore of the active principle) and lacrimal film, without change of its capability to adhere to the cornea and bulbar conjunctiva, could be the basis of the above described advantages.

DETAILED DISCLOSURE OF THE INVENTION

The invention relates to ophthalmic compositions in the form of aqueous gels with a range of viscosity from 400 to 800 cps, containing:

- at least one active principle,
- a gelling agent,
- at least two co-solubilising/co-gelling agents.

Examples of active principles that can be adequately formulated according to the invention include: antibiotic/antibacterial agents (gentamicin, tobramycin and similar ones; chloramphenicol, etc.), antimicotics (miconazole, econazole and similar ones), steroidal and non-steroidal anti-inflammatories (budesonide, diclofenac, niflumic acid, betamethasone and others), beta-blocker such as timolol, etc.

Acrylic acid polymers, sodium carboxymethylcellulose, hydroxymethylcellulose, and/or these mixtures are preferably used as gelling agents.

Among the acrylic acid polymers, Carbomer 940 and 980 are preferably used.

The weight percentages of gelling agents in the final formulations are the following:

- acrylic acid polymers: from 0.1 to 0.7%, preferably from 0.2 to 0.3%;
- sodium carboxymethylcellulose: from 1.5 to 3%, preferably from 2 to 2.5%;
- hydroxymethylcellulose: from 0.5 to 3%, preferably from 1 to 1.5%.

The co-solubilising/co-gelling agents, according to the invention, are selected from: polyethylene glycol (molecular weight between 200 and 500 approx., preferably approx. 300: PEG 300), polyethoxylated hydrogenated castor oil derivatives (Cremophor RH®) and polyvinyl alcohol.

This latter is mainly a co-gelling agent; Cremophor RH is a co-solubilising agent, while PEGs can be considered both co-gelling and co-solubilising agents.

The weight percentages of co-gelling/co-solubilising agents on final formulations are the following ones:

- PEG, particularly for PEG 300, from 4 to 10%;
- Cremophor RH: from 0.5 to 20%, preferably from 2 to 10% and, more preferably, from 2 to 6%;
- polyvinyl alcohol: from 0.4% to 0.5%, preferably 0.4%.

Examples of formulations of this invention could include: i) PEG 300 as co-solubilising agent, Carbomer as gelling agent and PVA as co-gelling agent; ii) PEG 300 and Cremophor RH as co-solubilising/co-gelling agent and sodium carboxymethylcellulose as gelling agent; iii) PEG300 and Cremophor RH as co-solubilising/co-gelling agents and hydroxyethylcellulose as gelling agent.

The following examples show the details of this invention:

COMPOSITION NO. 1A (steroidal anti-inflammatory / antibiotic)

Active principles:

Betamethasone 21-phosphate	0.066 g
(equivalent to Betamethasone 0.05%)	
Chloramphenicol	0.250 g

Excipients:

Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.500 g
Carbomer *	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Carbopol 980

COMPOSITION N O. 1B (steroidal anti-inflammatory / antibiotic)

Active principles:

Betamethasone 21-phosphate	0.132 g
(equivalent to Betamethasone 0.1%)	

Chloramphenicol	0.250 g
Excipients:	
Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.500 g
Carbomer *	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Carbopol 980

COMPOSITION NO. 1C (steroidal anti-inflammatory / antibiotic)

Active principles:	
Betamethasone 21-phosphate	0.066 g
(equivalent to Betamethasone 0.05%)	
Chloramphenicol	0.250 g
Excipients:	
Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.400 g
Polyxil 40 hydrogenated castor oil [1)]	0.100 g
Carbomer [2)]	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

[1)] Cremophor RH40

[2)] Carbopol 980

COMPOSITION NO. 1D (steroidal anti-inflammatory / antibiotic)

Active principles:

Betamethasone 21-phosphate	0.132 g
(equivalent to Betamethasone 0.1%)	
Chloramphenicol	0.250 g

Excipients:

Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.400 g
Polyxil 40 hydrogenated castor oil [1)]	0.100 g
Carbomer [2)]	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

[1)] Cremophor RH40

[2)] Carbopol 980

COMPOSITION NO. 2A (non steroidal anti-inflammatory)

Active principle:

Diclofenac Sodium	0.050 g

Excipients:

Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.500 g
Carbomer *	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Carbopol 980

COMPOSITION NO. 2B (non steroidal anti-inflammatory)

Active principle:

Diclofenac Sodium	0.100 g

Excipients:

Polyethylene Glycol 300	6.500 g
Polyvinyl Alcohol	0.500 g
Carbomer *	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Carbopol 980

COMPOSITION NO. 2C (non steroidal anti-inflammatory)

Active principle:

Diclofenac Sodium	0.050 g

Excipients:

Polyethylene Glycol 300	6.400 g
Polyxil 40 hydrogenated castor oil [1)]	0.100 g
Polyvinyl Alcohol	0.500 g
Carbomer [2)]	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

[1)] Cremophor RH40

[2)] Carbopol 980

COMPOSITION NO. 2D (non steroidal anti-inflammatory)

Active principle:

Diclofenac Sodium	0.100 g

Excipients:

Polyethylene Glycol 300	6.400 g
Polyxil 40 hydrogenated castor oil [1)]	0.100 g
Polyvinyl Alcohol	0.500 g
Carbomer [2)]	0.290 g
Sodium Edetate	0.100 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

[1)] Cremophor RH40

[2)] Carbopol 980

COMPOSITION NO. 3A (non steroidal anti-inflammatory)

Active principle:

Niflumic Acid	0.500 g

Excipients:

polyethylene Glycol 300	6.500 g
Sodium Carboxymethylcellulose	2.500 g
Sodium Chloride	0.570 g
Polyxil 40 hydrogenated castor oil*	0.500 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s.	100.000 g

* Cremophor RH-40

COMPOSITION NO. 3B (non steroidal anti-inflammatory)

Active principle:	
Niflumic Acid	1.000 g
Excipients:	
Polyethylene Glycol 300	6.500 g
Sodium Carboxymethylcellulose	2.500 g
Sodium Chloride	0.570 g
Polyxil 40 hydrogenated castor oil *	0.500 g
Sodium Merthiolate	0.002 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH-40

COMPOSITION NO. 4A (Antifungal)

Active principle:	
Miconazole	0.300 g
Excipients:	
Polyethylene Glycol 300	10.000 g
Polyoxil 40 hydrogenated castor oil *	6.000 g
Sodium Carboxymethylcellulose	2.500 g
Gluconic Acid	0.150 g
Cetrimide	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH-40

COMPOSITION NO. 4B (Antifungal)

Active principle:	
Miconazole	0.500 g

Excipients:

Polyethylene Glycol 300	10.000 g
Polyoxil 40 hydrogenated castor oil*	6.000 g
Sodium Carboxymethylcellulose	2.500 g
Gluconic Acid	0.250 g
Cetrimide	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 5A (Anti-glaucoma)

Active principle:

Timolol maleate	0.342 g
(equivalent to Timolol 0.25 %)	

Excipients:

Polyethylene Glycol 300	3.000 g
Sodium Carboxymethylcellulose	2.000 g
Polyoxil 40 hydrogenated castor oil *	2.000 g
Sodium Chloride	0.165 g
Sodium Edetate	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 5B (Anti-glaucoma)

Active principle:

Timolol maleate	0.684 g
(equivalent to Timolol 0.50 %)	

Excipients:

Polyethylene Glycol 300	3.000 g
Sodium Carboxymethylcellulose	2.000 g
Polyoxil 40 hydrogenated castor oil *	2.000 g
Sodium Chloride	0.165 g
Sodium Edetate	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 6 (Antibiotic / non steroidal anti-inflammatory)

Active principles:

Diclofenac Sodium	0.100 g
Tobramycin	0.300 g

Excipients:

Polyethylene Glycol 300	4.000 g
Polyoxil 40 hydrogenated castor oil *	2.000 g
Cellulose Hydroxyethyl	1.500 g
Sodium Chloride	0.800 g
Cetrimide	0.010 g
Hydrogen Chloride q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 7A (Antibiotic)

Active principle:

Gentamicin Sulphate	0.250 g
(equivalent to Gentamicin 0.15%)	

Excipients:	
Polyethylene Glycol 300	4.000 g
Cellulose Hydroxyethyl	1.500 g
Sodium Phosphate Dibasic	0.630 g
Polyoxil 40 hydrogenated castor oil *	0.500 g
Sodium Chloride	0.500 g
Sodium Phosphate Monobasic	0.170 g
Sodium Edetate	0.100 g
Sodium Metabisulfite	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 7B (Antibiotic)

Active principle:	
Gentamicin Sulphate	0.500 g
(equivalent to Gentamicin 0.3%)	
Excipients:	
Polyethylene Glycol 300	4.000 g
Cellulose Hydroxyethyl	1.500 g
Sodium Phosphate Dibasic	0.630 g
Polyoxil 40 hydrogenated castor oil *	0.500 g
Sodium Chloride	0.500 g
Sodium Phosphate Monobasic	0.170 g
Sodium Edetate	0.100 g
Sodium Metabisulfite	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	

Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 8A (Anti-glaucoma)

Active principle:

Timolol maleate	0.342 g
(equivalent to Timolol 0.25 %)	

Excipients:

Polyethylene Glycol 300	3.000 g
Polyoxil 40 hydrogenated castor oil *	2.000 g
Cellulose Hydroxyethyl	1.200 g
Sodium Chloride	0.280 g
Sodium Edetate	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	
Purified water q.s. to	100.000 g

* Cremophor RH40

COMPOSITION NO. 8B (Anti-glaucoma)

Active principle:

Timolol maleate	0.684 g
(equivalent to Timolol 0.50 %)	

Excipients:

Polyethylene Glycol 300	3.000 g
Polyoxil 40 hydrogenated castor oil *	2.000 g
Cellulose Hydroxyethyl	1.200 g
Sodium Chloride	0.280 g
Sodium Edetate	0.100 g
Benzalkonium Chloride	0.010 g
Sodium Hydroxide q.s. to pH 7.0	

Purified water q.s. to	100.000 g

* Cremophor RH40

CLAIMS

1. Ophthalmic compositions in the form of aqueous gel with a viscosity range between 400 and 800 cps, comprising:

- one active principle;
- a gelling agent and at least two co-solubilising/co-gelling agents.

2. Compositions as claimed in claim 1, wherein the gelling agent is selected from acrylic acid polymers, sodium carboxymethylcellulose, hydroxyethilcellulose.

3. Compositions as claimed in claim 1 or 2, wherein the co-solubilising/co-gelling agent is selected from a polyethylene glycol with molecular weight ranging from 200 to 500, polyethoxylated derivatives of hydrogenated castor oil (Cremophor RH40), polyvinyl alcohol.

4. Compositions as claimed in any one of the above claims wherein the acrylic acid polymer is Carbomer 980.

5. Compositions as claimed in any one of the above claims wherein one of the two co-solubilising/co-gelling agents is PEG300.

6. Compositions as claimed in claim 5 wherein the other co-solubilising/co-gelling agents is Cremophor RH40.

7. Compositions as claimed in claim 6 wherein the other co-solubilising/co-gelling is polyvinyl alcohol.

8. Compositions as claimed in any one of the above claims, containing an ophthalmically useful active principle selected from antibiotics, antibacterials, antimicotics, steroidal or non steroidal anti-inflammatories, beta-blockers.

INTERNATIONAL SEARCH REPORT

Inte..ional Application No
PCT/EP 00/06062

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/06 A61P31/04 A61P31/10 A61P29/00 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 188 826 A (REENTS MARGARET J ET AL) 23 February 1993 (1993-02-23) column 1, line 20 - line 32 column 3, line 60 -column 5, line 55 column 8, line 10 -column 9, line 24 column 12; example 3 claims 1,2,9-11	1-3
X	FR 2 462 160 A (LION CORP) 13 February 1981 (1981-02-13) page 1, line 4 - line 31 page 12, line 24 -page 13, line 4 page 36, line 36 -page 37, line 13; example 24	1,2,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Muller, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ..onal Application No
PCT/EP 00/06062

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 947 573 A (RANKIN BILLY F) 30 March 1976 (1976-03-30) column 1, line 11 -column 2, line 37 column 7, line 1 -column 8, line 68 claims 1,4,5,10,12	1,2,8
X	US 5 800 807 A (DENICK JOHN ET AL) 1 September 1998 (1998-09-01) column 2, line 46 -column 3, line 50 column 5; table 2 claims 1-3	1
A	US 5 676 949 A (MEYBECK ALAIN ET AL) 14 October 1997 (1997-10-14) column 11; example 11	1-8
A	US 4 409 205 A (SHIVELY CHARLES D) 11 October 1983 (1983-10-11) column 9; example 4	1-8

1

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte. ..ional Application No
PCT/EP 00/06062

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5188826 A	23-02-1993	US 5192535 A	09-03-1993
		AT 178476 T	15-04-1999
		AU 8184991 A	04-02-1992
		CA 2086120 A	07-01-1992
		DE 69131100 D	12-05-1999
		DE 69131100 T	12-08-1999
		DK 538313 T	18-10-1999
		EP 0538313 A	28-04-1993
		ES 2132088 T	16-08-1999
		GR 3030381 T	30-09-1999
		NZ 238850 A	25-11-1992
		WO 9200707 A	23-01-1992
		ZA 9105220 A	26-08-1992
		AT 91408 T	15-07-1993
		CA 1336500 A	01-08-1995
		DE 68907545 D	19-08-1993
		DE 68907545 T	28-10-1993
		DK 47793 A	27-04-1993
		DK 168727 B	30-05-1994
		DK 493689 A	01-12-1989
		EP 0362321 A	11-04-1990
		ES 2012634 A	01-04-1990
		IE 63392 B	19-04-1995
		JP 2503201 T	04-10-1990
		JP 2814637 B	27-10-1998
		NO 176696 B	06-02-1995
		WO 8906964 A	10-08-1989
		AT 112157 T	15-10-1994
		AT 181824 T	15-07-1999
		AU 639069 B	15-07-1993
		AU 7033191 A	31-05-1991
		BR 9007807 A	29-09-1992
		CA 2072148 A	01-05-1991
		DE 69012955 D	03-11-1994
		DE 69012955 T	09-02-1995
		DE 69033199 D	12-08-1999
		DE 69033199 T	28-10-1999
		DK 429156 T	16-01-1995
		DK 500807 T	07-02-2000
		EP 0429156 A	29-05-1991
		EP 0500807 A	02-09-1992
		ES 2059300 T	16-11-1994
		ES 2134769 T	16-10-1999
		FI 921932 A	29-04-1992
		GR 3031288 T	31-12-1999
		HU 68635 A	28-07-1995
		IE 62386 B	25-01-1995
		IL 96148 A	31-08-1995
		JP 2510052 B	26-06-1996
FR 2462160 A	13-02-1981	JP 1204249 C	25-04-1984
		JP 56022720 A	03-03-1981
		JP 58035965 B	05-08-1983
		JP 1210641 C	12-06-1984
		JP 56045407 A	25-04-1981
		JP 58046483 B	17-10-1983
		CA 1136991 A	07-12-1982
		DE 2940460 A	23-07-1981

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ..onal Application No
PCT/EP 00/06062

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2462160 A		GB 2055574 A,B	11-03-1981
		HK 72386 A	03-10-1986
		MY 66286 A	31-12-1986
		SE 8005321 A	01-02-1981
		US 4259316 A	31-03-1981
		US 4335102 A	15-06-1982
US 3947573 A	30-03-1976	US 3856919 A	24-12-1974
		CA 970687 A	08-07-1975
		DE 2051369 A	09-06-1971
		FR 2073437 A	01-10-1971
		GB 1340517 A	12-12-1973
		GB 1340515 A	12-12-1973
		GB 1340516 A	12-12-1973
		GB 1340518 A	12-12-1973
		JP 54021405 B	30-07-1979
		NL 7015332 A	03-06-1971
		US 3767788 A	23-10-1973
		CH 543278 A	14-12-1973
US 5800807 A	01-09-1998	AU 723024 B	17-08-2000
		AU 6253398 A	18-08-1998
		BR 9807117 A	25-04-2000
		EP 0969812 A	12-01-2000
		WO 9832421 A	30-07-1998
US 5676949 A	14-10-1997	FR 2699073 A	17-06-1994
		FR 2699081 A	17-06-1994
		EP 0673237 A	27-09-1995
		EP 0797982 A	01-10-1997
		WO 9413259 A	23-06-1994
		JP 8507289 T	06-08-1996
US 4409205 A	11-10-1983	NONE	